Design and Development of Efficient and Greener Strategies for Heterocycle Synthesis

A Thesis

Submitted for the Degree of

Doctor of Philosophy

By

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October- 2016

Declaration

I hereby declare that the entire work embodied in this thesis entitled "***Design and Development of Efficient and Greener Strategies for Heterocycle Synthesis***" is the result of investigations carried out by me in the *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru, India* under the guidance of **Prof. H. Ila**, and it has not been submitted elsewhere for any degree or diploma.

In keeping with general practice, due acknowledgements have been made wherever the work described is based on findings of other investigators. Any omissions that might have occurred due to oversight or error in judgment are regretted.

October, 2016 **S. Yugandar**

Bengaluru (Research Scholar)

Certificate

I hereby certify that the entire work embodied in this thesis entitled "***Design and Development of Efficient and Greener Strategies for Heterocycle Synthesis***" has been carried out by **Mr. S. Yugandar** under my supervision in the *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru, India* and that no part of it has been submitted elsewhere for any degree or diploma.

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Dedicated to…..

Dr. K. Vasudeva Reddy

Acknowledgement

*First and foremost, I would like to express my sincere gratitude to my research supervisor **Prof. H. Ila**, Synthetic Organic Chemistry Lab, New Chemistry Unit, JNCASR, for her continued support, motivation, patience and guidance throughout my PhD career. It has been a great privilege and honor to be associated with her.*

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S. Yugandar

Synopsis

Title of Thesis: "***Design and Development of Efficient and Greener Strategies for Heterocycle Synthesis***"

Submitted by: Mr. S. Yugandar, New Chemistry Unit, JNCASR, Bengaluru-560064, India

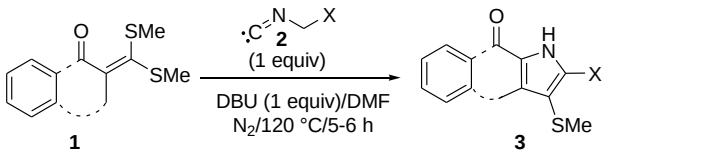
The above thesis is divided into six chapters:

Chapter 1: "*Efficient and greener approaches in organic synthesis: An Introduction"*

The present chapter gives a brief introduction of efficient and greener approaches in organic synthesis, i.e., domino reactions, multicomponent one-pot reactions, transition metal catalyzed coupling and atom economy reactions such as C-H activation.

Chapter 2: "*Reaction of Cyclic α-Oxoketene Dithioacetals with Activated Methylene Isocyanides: A Novel Pyrrole Annulation-Ring Expansion Domino Process*"

The chapter 2 of the thesis describes a novel domino process involving a base induced reaction of cyclic α-oxoketene dithioacetals **1** with activated methylene isocyanides **2** leading to the formation of a diverse range of annulated pyrroles **3** along with a highly regioselective one carbon ring expansion of cyclic ketones as the key step (Scheme 1). The method provides facile access to biologically important fused pyrroles with structures ranging from pyrrolonapthoquinones, angular and linear pyrroloquinolones, tetracyclic fused indoles and pyrrole annulated dibenzooxocinone and dibenzothiocinone derivatives (Scheme 1).

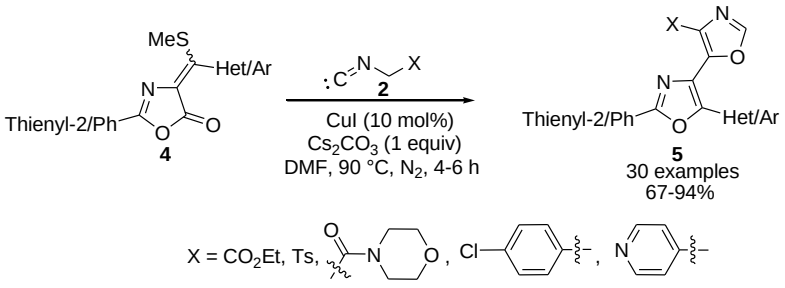


Scheme 1

Chapter 3: "*Synthesis of 2,5-Bis(hetero)aryl 4'-Substituted 4,5'-Bisoxazoles via Copper(I)-Catalyzed Domino Reactions of Activated Methylene Isocyanides with 2-(Het)aryl-4-[(het)aryl)(methylthio)methylene]oxazol-5(4H)ones*"

The chapter 3 of the thesis describes an efficient straightforward synthesis of 2,5,4'-trisubstituted- 4,5'-bisoxazoles **5** via copper(I) catalyzed domino reaction of 2-phenyl/(2-thienyl)-4-[(aryl/heteroaryl)-methylene]-5-oxazolones **4** with activated

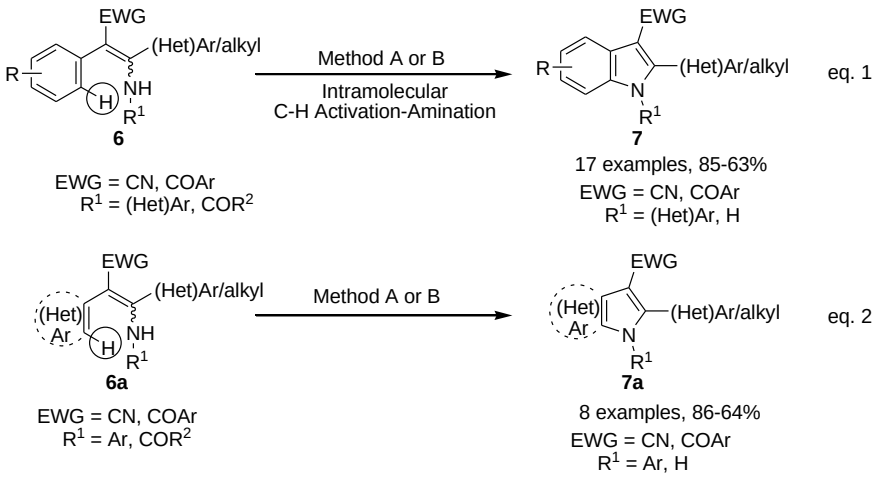
methylene isocyanides **2**. The overall domino process comprising of one C-C and two C-O bond formation, involves initial nucleophilic ring opening of oxazolones by cupriomethylene isocyanides followed by sequential construction of two oxazole rings in the presence of copper catalyst (Scheme 2).



Scheme 2

Chapter 4: "*Amine Directed Pd(II) Catalyzed C-H Activation-Intramolecular Amination of N-Het(aryl)/acyl Enaminonitriles and Enaminones: An Approach towards Multisubstituted Indoles and Hetero-Fused Pyrroles*"

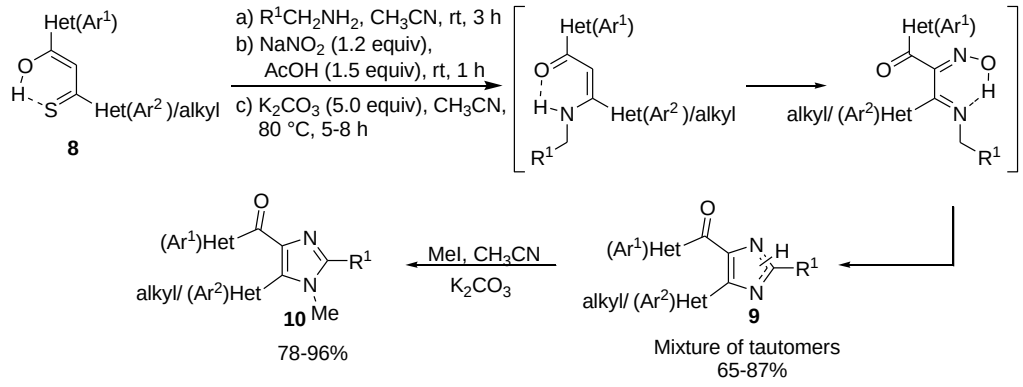
The chapter 4 of the thesis deals with an efficient route to multisubstituted indoles **7** through intramolecular oxidative C-H activation-amination of readily available 2-(het)aryl-3-(het)aryl/alkyl-3-(het)aryl/acylaminoacrylonitrile/enaminone precursors **6** in the presence of either palladium acetate/cupric acetate catalytic system under oxygen atmosphere or palladium acetate/silver carbonate in presence of pivalic acid as additive (Scheme 3, eq. 1). The versatility of this method was further demonstrated by elaborating it for the synthesis of hetero-fused pyrroles **7a** such as thieno[2,3-*b*]pyrroles, thieno[3,2-*b*]pyrroles, pyrrolo[2,3-*b*]indoles and pyrrolo[2,3-*b*]pyridines in good yields (Scheme 3, eq. 2).



Scheme 3

Chapter 5: "*One-Pot Three Component Synthesis of 2,4,5-Trisubstituted Imidazoles via [2+2+1] Cycloannulation of 1,3-Bishet(aryl)-monothio-1,3-diketones, α-Substituted Methylamines and Sodium Nitrite through α-Nitrosation of Enaminones*"

The chapter 5 of the thesis describes an efficient, highly regiocontrolled, sequential one-pot three component synthesis of a series of diversely functionalized trisubstituted 4(5)-het(aroyl)-2,5(4)-het(aryl)/alkylimidazoles **9**, from readily available precursors i.e., 1,3-bishet(aryl)monothio-1,3-diketones **8** , *α*-substituted methylamines and sodium nitrite and their subsequent alkylation to the corresponding *N*-methyl derivatives **10**. This novel sequential one-pot protocol involves the formation of three new carbon-nitrogen (C-N) in contiguous fashion. The method provides rapid access, especially to imidazoles with sterically demanding (het)aromatic groups on 2 and (4)5-positions, as well as to 4(5)- (2-hydroxyphenyl) imidazoles, which are known to be good coordinating ligands (Scheme 4).

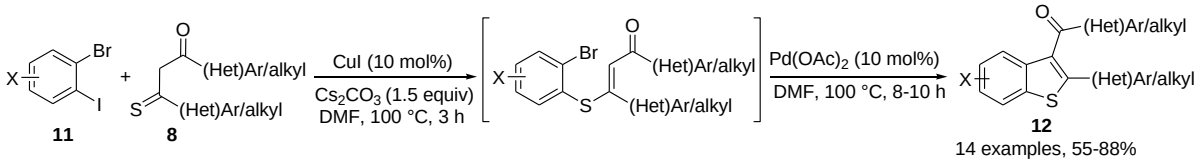


Scheme 4

Chapter 6: "*A Novel One-Pot, Two Step Synthesis of Multisubstituted Benzo[b]thiophenes via Sequential Copper Catalyzed C-S Bond Formation and Palladium Catalyzed Arene-Alkene Coupling via Intramolecular Heck Reaction*"

The chapter 6 of the thesis deals with a novel, convergent highly regioselective one-pot synthesis of substituted 2-(het)aryl/alkyl-3-acylbenzo[*b*]thiophenes **12** involving sequential intermolecular copper catalyzed C-S bond formation and an intramolecular palladium catalyzed Heck type arene-alkene coupling. Benzothiophene formation could be accomplished by employing a range of 1,3-monothioketones **8** and substituted *o*-

bromoiodobenzenes **11** as coupling partners under suitable optimized reaction conditions (Scheme 5).



(Het)Ar/alkyl= Ph, 4-$MeOC_6H_4$, 2-thienyl, 2-furyl, 2-(N-methylpyrrolyl), 3-(N-methylindolyl, 3-pyridyl, n-butyl, *t*-butyl,methyl, N-morphilino

X = F, Cl, CF_3, acetyl, CN

Scheme 5

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List of Abbreviations

NMR	:	Nuclear magnetic resonance
IR	:	Infrared spectroscopy
TMS	:	Tetramethylsilane
m.p.	:	Melting point
DMF	:	*N*,*N*-Dimethyl formamide
DMSO	:	Dimethyl sulfoxide
THF	:	Tetrahydrofuran
EtOAc	:	Ethyl acetate
DCM	:	Dichloromethane
DCE	:	Dichloroethane
DMA	:	*N*,*N*-Dimethylacetamide
CS_2	:	Carbon disulfide
NaH	:	Sodium hydride
LDA	:	Lithium diisopropylamide
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
PPA	:	Polyphosphoric acid
TFA	:	Trifluroacetic acid
m-CPBA	:	*m*-Chloroperbenzoic acid
NBS	:	N-Bromosuccinimide
TLC	:	Thin layer chromatography
Ts	:	Tosyl
Nu	:	Nucleophile
Bn	:	Benzyl

Equiv	:	Equivalent
rt	:	Room temperature
EWG	:	Electron withdrawing group
PMB	:	*p*-Methoxy benzyl
TBHP	:	*t*-Butyl hydroperoxide
DMEDA	:	*N,N′*-Dimethylethylenediamine
DIPEA	:	*N*,*N*-Diisopropylethylamine
TMSE	:	Trimethylsilylethyl
PIDA	:	Phenyliodine diacetate
$Pd(OAc)_2$	:	Palladium(II) acetate

:

Chapter 1

Introduction: Efficient and Greener Approaches in Organic Synthesis

In the last few decades, rapid progress has been made in synthetic organic chemistry, which has been explored in a dramatic way. A large number of several highly selective methods have been developed allowing the preparation of complex molecules in highly regio-, chemo-, diastereo- and enantioselective manner, and it has been possible to accomplish synthesis of highly complex naturally occurring compounds in several distinct steps. One of the most outstanding synthesis is that of palytoxin, reported by Kishi with 64 stereogenic centers in more than 100 steps (Chart 1).[1] However despite this great progress and its importance, the image of chemistry has been deteriorated in public. This is mainly due to the increasing consciousness regarding environmental issues in our society, which feels that chemistry and chemical production, are adversely affecting the ecological balance.

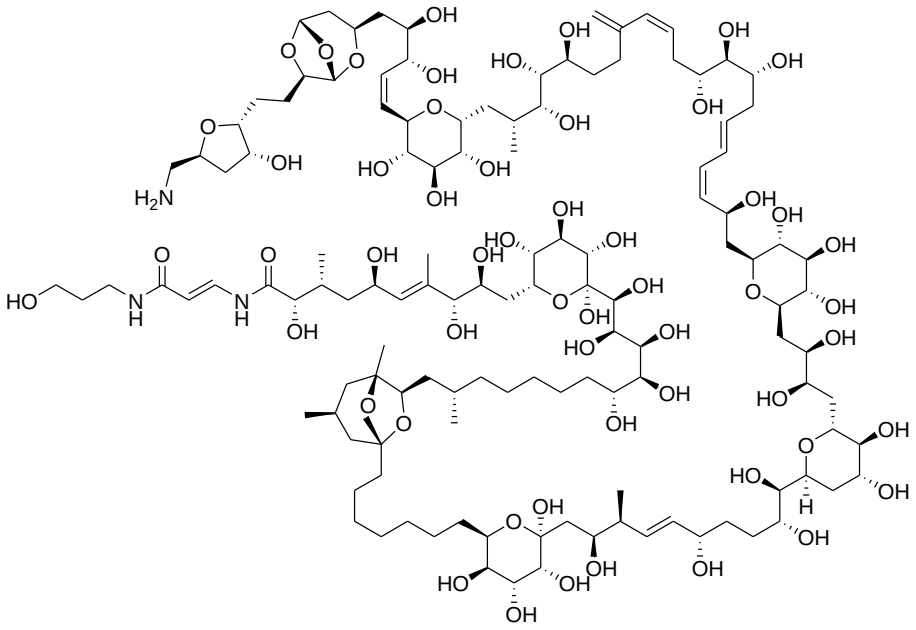


Chart 1. Palytoxin

Some of the important issues faced in the production of organic compounds are the search for environmentally benign methods, the preservation of resources, the handling of waste, and above all, the increase in efficiency.[2] Solving these problems would not only be beneficial for the environment, but also be economically useful by reducing the cost of production. Therefore, efficiency and environmental sustainability are central issues in the present contemporary organic synthesis. Both need to be addressed carefully, while synthesizing a valuable target molecules involving several distinct steps. Therefore the question today is not only the synthesis of particular compound for which there is no limit, but how to synthesize it. Consequently, synthetic organic chemists are faced with great challenge to discover concise, elegant and conceptually novel synthetic and environmentally benign routes, which has become a steadily increasing driving force both in academia and industry.

These issues have led to the development of an emerging new field called, 'Green Chemistry', which is defined as the design of chemical products and processes to reduce and eliminate the use and generation of hazardous substances.[3] 'Green Chemistry' has received widespread attention and interest in the past decades, due to its ability to harness chemical innovation to meet environmental and economic goals simultaneously and to strive to work

at the molecular level to achieve sustainability. 'Green Chemistry' has a framework of a cohesive set of twelve principles,[3a] which were introduced in 1998 by Paul Anastas and John Warner[4] and have been systematically surveyed in critical reviews. These principles are main guidelines for the design of new chemical products and processes,[3b-d] relevant to all aspects of the process life cycle from the raw material used, to the efficiency and safety of the transformation, the toxicity and biodegradability of products and reagents used. Some of the rules, which are directly concerned to synthetic organic chemists are:

1. Prevention: It is better to prevent waste than to treat or clean up waste after it is formed.

2. Catalysis: Use of catalytic reagents/methods (as selective as possible) are superior to stoichiometric reagents/processes.

3. Reduction of derivatization: Unnecessary derivatization (use of blocking group, protection/deprotection, temporary modification of physical/chemical process) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

4. Atom economy: Synthetic method should be designed to maximize the incorporation of all material used in to the process in the final product.

5. Design for Energy Efficient Processes: Energy requirement of the chemical process should be recognized for their environmental and economical impacts and should be minimized.

6. Depletion of resources: The raw/starting materials should be easily available and should be renewable if possible rather than depleting, whenever technically or economically practicable.

7. Use of less hazardous and non-toxic chemicals and solvents: Whenever practicable, synthetic methods should be designed so as to use safer non- toxic chemical and solvents, so as to pose little or no toxicity to human health and the environment.

However for a synthetic organic chemist, addressing all the issues such as simplicity, safety, brevity, selectivity, diversity, yield, availability of starting materials along with

environmental demand at the same time for designing a new reaction, in the sense of an ideal synthesis, is a highly daunting task. Therefore they have sought and devised fruitful strategies that inevitably tackle the very fundamental principles of efficacy and efficiency. Enhancing the efficiency of the synthesis of complex organic products constitutes one of most exciting challenges to the synthetic organic chemists.

Presently, the synthetic toolbox of organic chemists has been expanded by a significant number of novel and innovative reactions, discovered in the past decade, along with the already existing green reactions, that were discovered during past century. Some of the reactions based on cycloadditions, rearrangements, or multicomponent coupling reactions were already known in the literature, representing one category of efficient reactions. Domino, or cascade/tandem reactions, transition metal catalyzed coupling reactions, C-H activation, metathesis and enzymatic reactions are rather new approaches and constitute some of powerful examples of cleaner, more efficient synthetic tools available to organic chemists.

The research work presented in this thesis is based on design and development of novel synthetic strategies for heterocycles, which address some of above described important issues such as efficiency and environmentally benign design of organic reactions. In this chapter, we have given a short account of the various strategies developed in recent years for enhancing the efficiency of reactions, while designing a new synthesis, i.e., domino reactions, multicomponent one pot reactions, transition metal catalyzed coupling and atom economy reactions such as C-H activation. These reactions also indirectly address environmental issues by reducing the waste generation in short concise synthesis. This is not a comprehensive review, but main objective is to introduce these reactions to the readers.

1.1 Domino Reactions

Domino and multicomponent reactions have emerged as powerful tools in organic synthesis, where an inherent reactivity profile can be exploited in most favorable way for the construction of complex molecular framework in a one- pot fashion. According to Tietze's definition,[5] a 'domino reaction' or 'domino process' is the transformation of two or more bond forming reactions under identical conditions, in which the latter transformation takes place at the functionalities generated in the former bond forming reaction. Thus domino

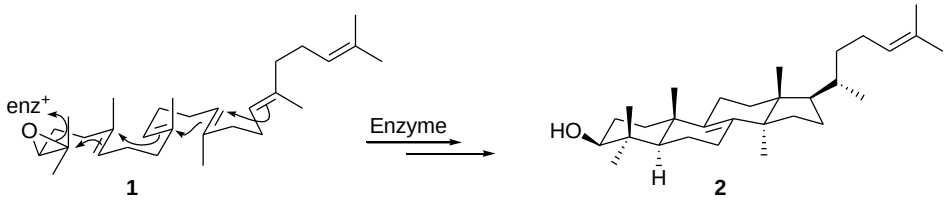
processes are time resolved transformations, an excellent example being that of domino stones, where one stone tips over the next, which tips the next.., such that they all fall down in turn. In the literature, the word 'tandem'[6] and 'cascade'[7] are often used for such type of reactions, however these terms do not fit with the time resolved aspects of domino reaction type, besides these terms are used in so many different connections i.e., 'tandem bicycle', 'photochemical cascade', 'biochemical cascade', 'electrochemical cascade' which makes database search more difficult. Several excellent reviews have been published on this subject.[8] Presently, domino reactions are regarded as sequences of uni- or bimolecular elementary reactions that proceed without intermediate isolation or work-up as a consequence of the reactive functionalities that has been formed in the previous step.

The efficiency of a domino reaction is usually evaluated firstly in terms of the number of bonds which are formed in one sequence, which is called as the 'bond-forming efficiency' (or bond-forming economy or sometimes called as 'step economy'),[8,19] secondly, the increase in structural complexity (structure economy), and, thirdly, to its viability for a general application. Another great advantage of the domino concept to our environment and our natural resources, is that it allows reduction in waste production compared to normal stepwise procedure, besides minimizing the amount of chemicals required for the preparation of product. This also makes them economically favorable, besides they also lead to decrease of the production time which altogether would reduce furthermore the costs of any product.

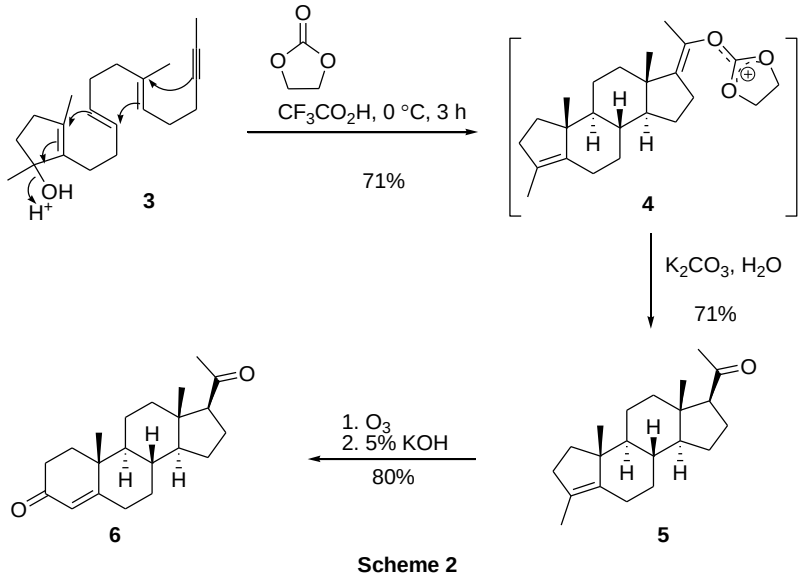
As a requirement for all domino reactions, the substrate used must have more than two functionalities of comparable reactivity. They can be located in one or two or more than two molecules in case of multicomponent reactions. For the design and performance of domino reactions, it is of paramount importance that the functionalities react in a fixed chronological order to allow the formation of defined molecules. Also, when designing a domino reaction, a careful adjustment of all factors is very important.

In nature, domino reactions are rather common, although a direct comparison to the reactions in a flask is not possible, because of the involvement of multienzymes, which can allow the catalysis of different steps. A beautiful example is the biosynthesis of steroids from squalene epoxide **1** which is transformed highly selectively into lanosterol **2** with the formation of four C-C bonds, four rings and six stereogenic centers (Scheme 1).[9] This scheme has been used by Johnson for the elegant chemical synthesis of progesterone **6** by an

acid-catalyzed domino cyclization of the monocyclic trieneyne **3** to give the tetracyclic intermediate **4** which is then converted to progesterone **6** via **5** (Scheme2).[10]



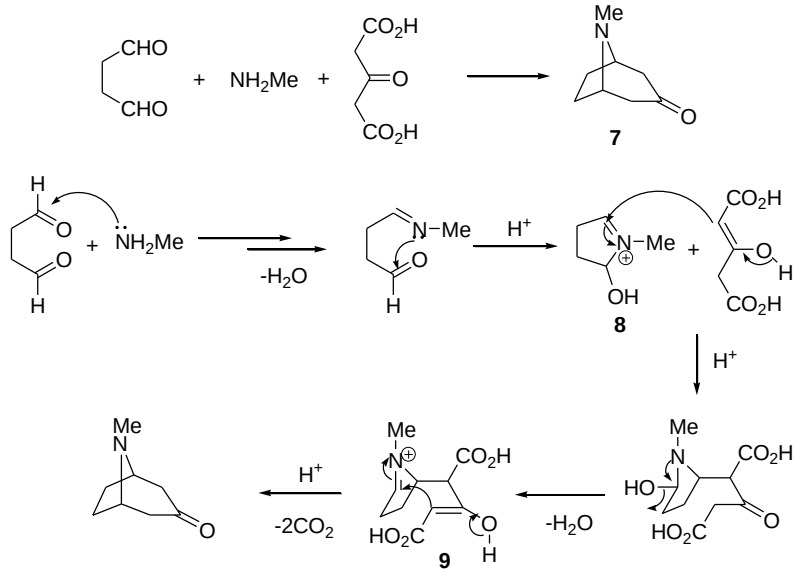
Scheme 1



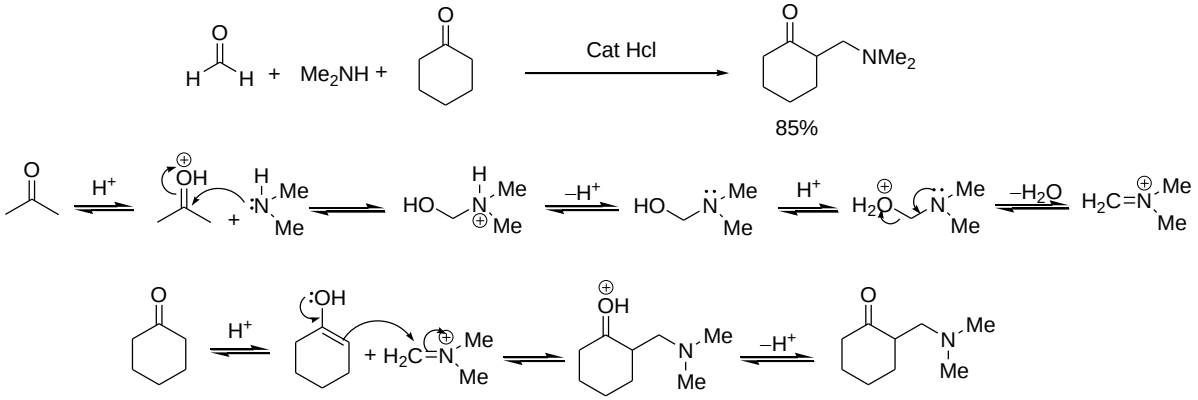
Scheme 2

Domino reactions are also involved in the biosynthesis of alkaloids, one of the most well known example is biosynthesis of tropinone **7**, which is structural component of several alkaloids such as cocaine and atropine. Interestingly, before disclosure of its biosynthesis,[11] a biomimetic one-pot synthesis of tropinone was developed by Robinson and Schopf, nearly 100 years ago, which is a landmark achievement in organic chemistry. Thus shortly after publication of Willstater's more than twenty step synthesis of tropinone,[12] Robinson and Schopf described a domino process by reacting succinaldehyde, methyl amine and acetone dicarboxylic acid to give tropinone in excellent yield without isolation of any intermediate (Scheme 3). The key step in this synthesis is a double Mannich reaction, involving iminium ions **8** and **9** as intermediates, which are trapped by enols of acetone dicarboxylic acids. However, even the normal Mannich reaction combining an aldehyde, generally formaldehyde, a ketone, and a secondary amine is also a domino reaction and presumably the

first domino reaction described in the literature (Scheme 4). In contrast, the well known Diels-Alder reaction may not be attributed as a domino reaction, although two bonds are usually formed in a sequence.



Scheme 3

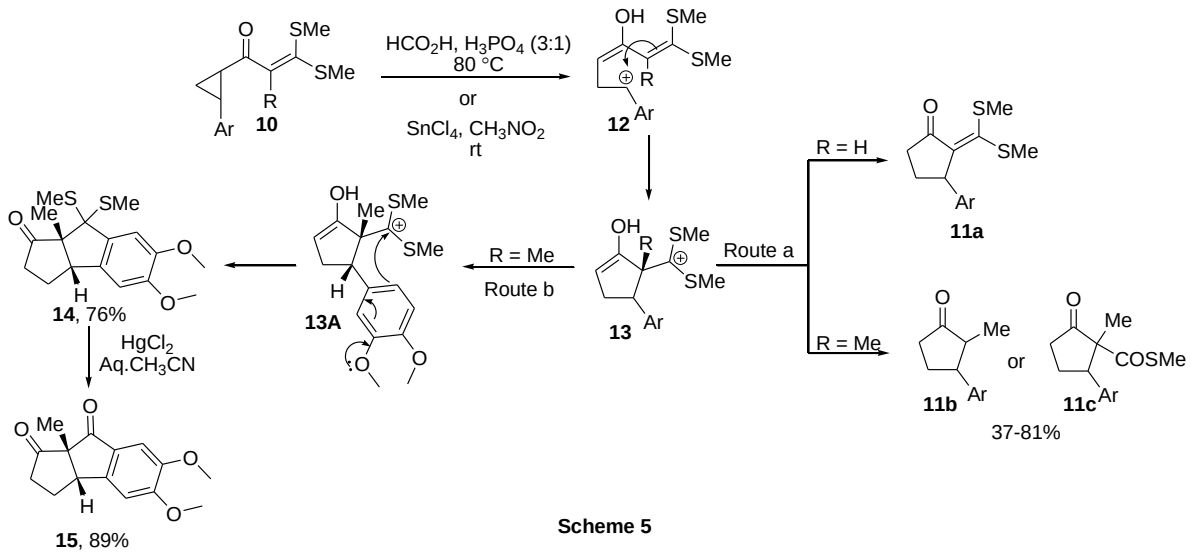


Scheme 4

Our research group has also been involved for several years in designing novel domino reactions of several push-pull cyclopropyl ketones (Schemes 5-10).[13,14]

Thus, a domino acid catalyzed rearrangement of α-bis(methylthio)methylene arylcyclopropyl ketones **10** to the corresponding substituted cyclopentanones **11a-c** was reported first by Deb et al from our research group as shown in the Scheme 5. The carbocationic intermediate **12** generated by electrophilic ring opening of cyclopropyl ketone **10** is trapped by mercapto double bond in a 5-*exo-trig* process to give cyclic carbocation **13**

which affords either ketene dithioacetal **11a**, cyclopentanone **11b**, or the thioester **11c** depending upon reaction conditions (route a)(Scheme 5).[13a-c]



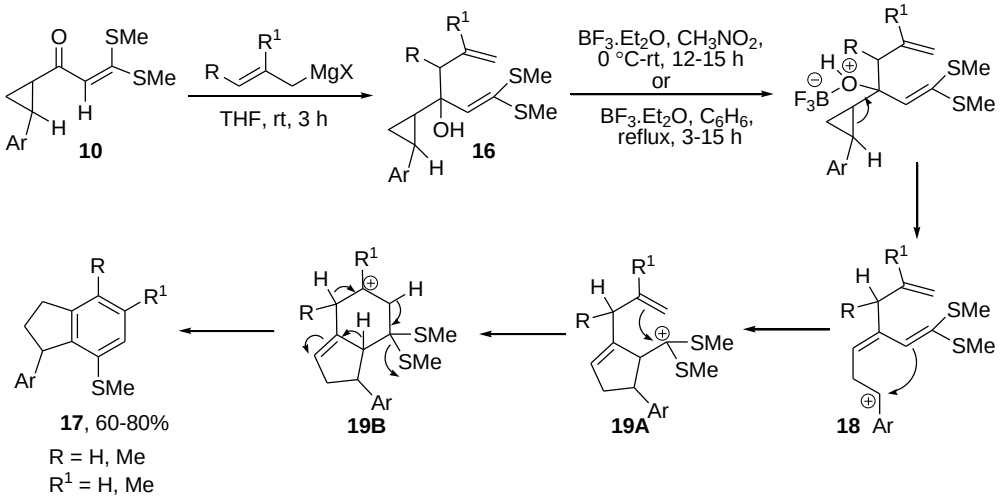
Scheme 5

Interestingly when the aryl group in the cyclopropyl ring carries a cation stabilizing group like methoxy etc at the *para* position, the intermediate **13A** with a pendant bismetylthiomethyl carbocation is further trapped by the aromatic ring to afford cyclopentano fused indanones **14** or **15** in good yields (Scheme 5, route b).[13c]

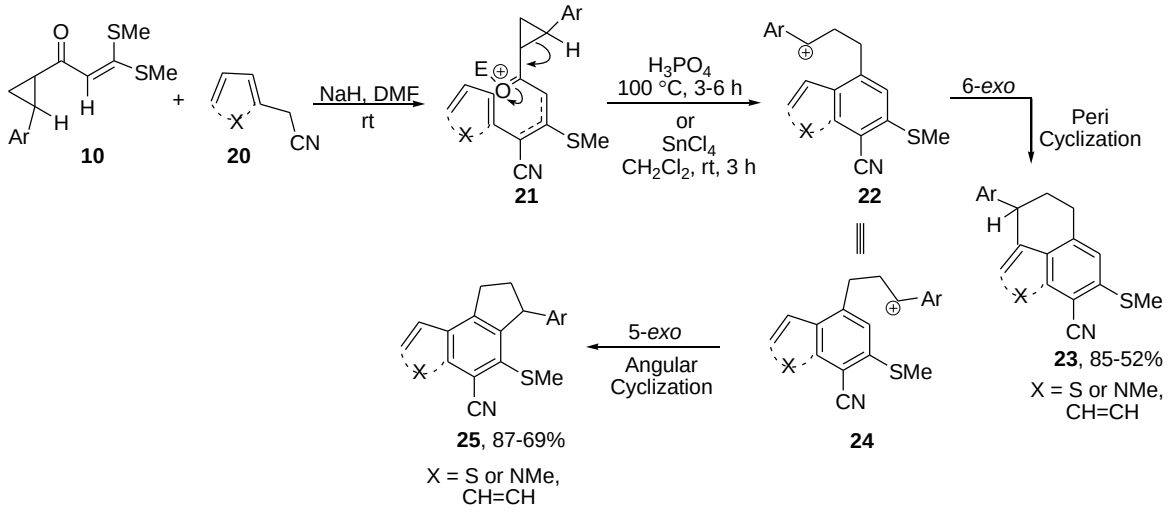
In continuation of these studies, our research group has further reported a new domino carbocationic rearrangement of α-[bis(methylthio)methylene]alkyl-2-aryl-cyclopropyl carbinols **16** (obtained by addition of allyl Grignard reagent to cyclopropyl ketones **10**) to 1-arylindanes **17** (Scheme 6).[13d] The overall mechanism of this transformation involves Lewis acid assisted ring opening of the cyclopropylcarbinol **16** to give the carbocationic intermediate **18**, which is trapped by (bismethylthio)methylene double bond, followed by concomitant attack of the allylic double bond on the newly generated carbocation **19A** through 6-*endo*-cyclization to afford the bicyclic carbocation intermediate **19B** followed by aromatization to give arylindanes **17** (Scheme 6).[13d]

Nandi et al from our research group have shown that cyclopropyl ketone adduct **21** undergo acid-induced domino carbocationic cyclization to yield a range of novel functionalized peri and angularly fused polycyclic aromatic and heteroaromatic frameworks **23** and **25** in high yields. The probable mechanism of this domino process involves stepwise

or concomitant acid-induced ring opening and intramolecular cyclocondensation of cyclopropylketone **21** to give benzo/heteroannelated arenes **24** or **22** with a pendant α-arylpropyl carbocationic side chain, which can be captured intramolecularly via 5- or 6-exo cyclization to yield either angularly fused indanes **25** or the novel pericyclized carbo- and heterocyclic ring systems **23** (Scheme 7).[13e]



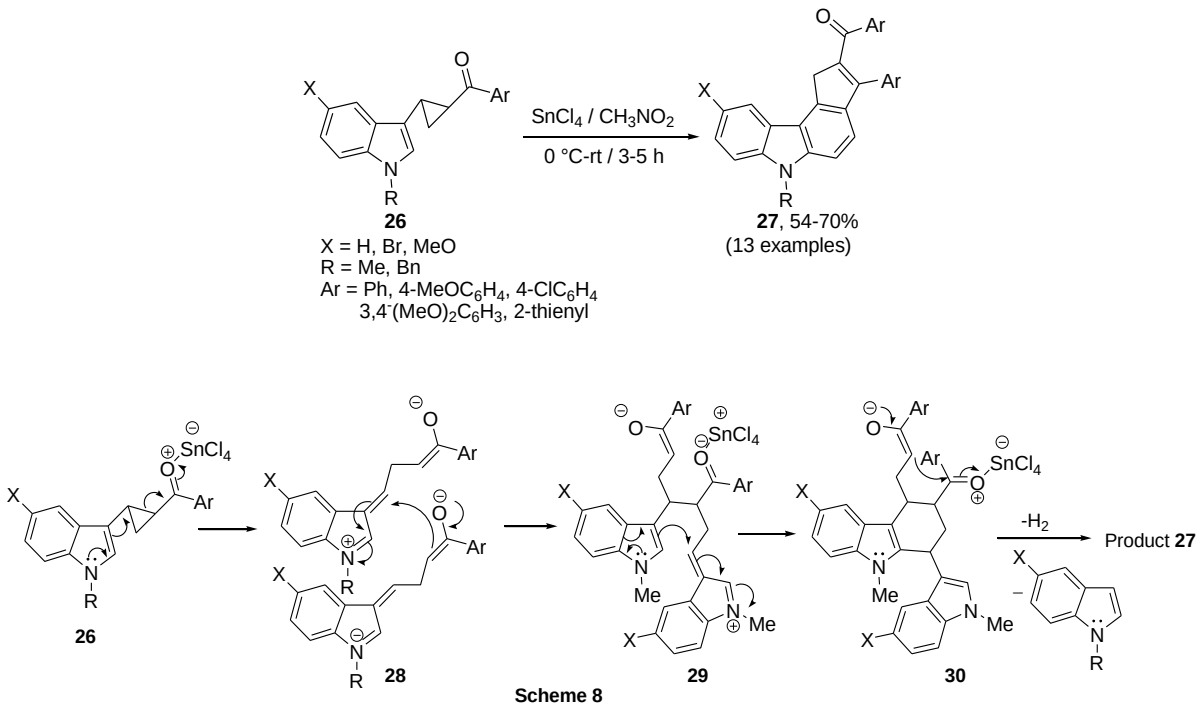
Scheme 6



Scheme 7

In an another parallel transformation, Venkatesh et al from our research group have shown that aryl-2-(*N*-methyl/benzyl-3-indolyl)cyclopropyl ketones **26** undergo an unexpected carbocationic rearrangement in presence of $SnCl_4/CH_3NO_2$ to afford 2-aroyl-3-aryl-1*H*-cyclopenta[*c*]carbazoles **27** in good yields (Scheme 8).[14a] The proposed probable

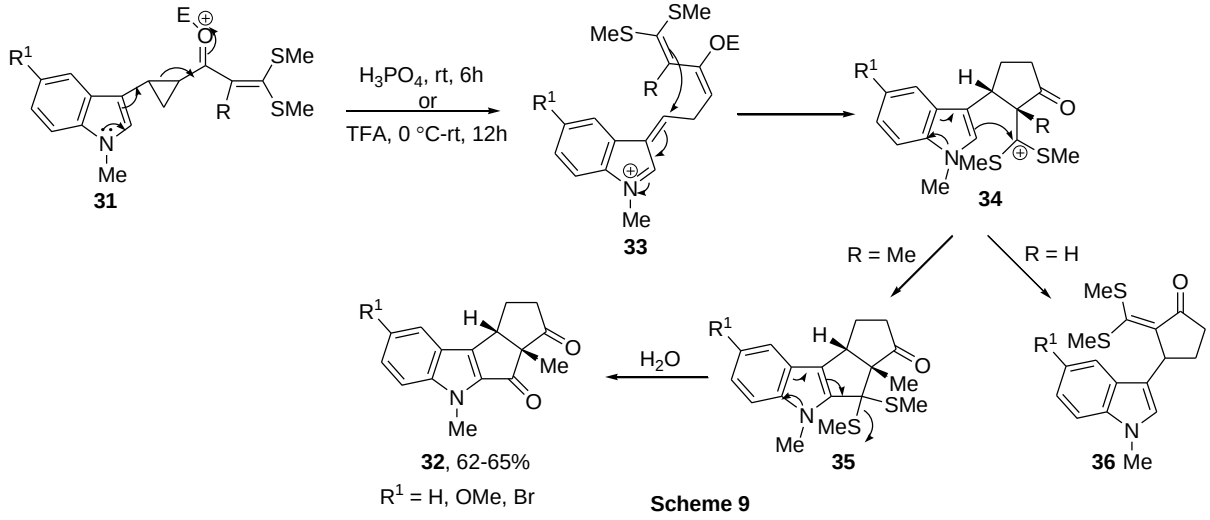
transformation for the formation of cyclopentanocarbazoles 27 involves dimerization of carbocationic species **28**, formed by electrophilic ring opening of cyclopropyl ketone **26**, followed by intramolecular cyclization with elimination of an indole moiety (through intermediates carbocations **29**-**30**), and subsequent intramolecular Aldol condensation in the intermediate **30** affords the cyclopenteno fused carbazoles **27** in good yields (Scheme 8).[14a]



Scheme 8

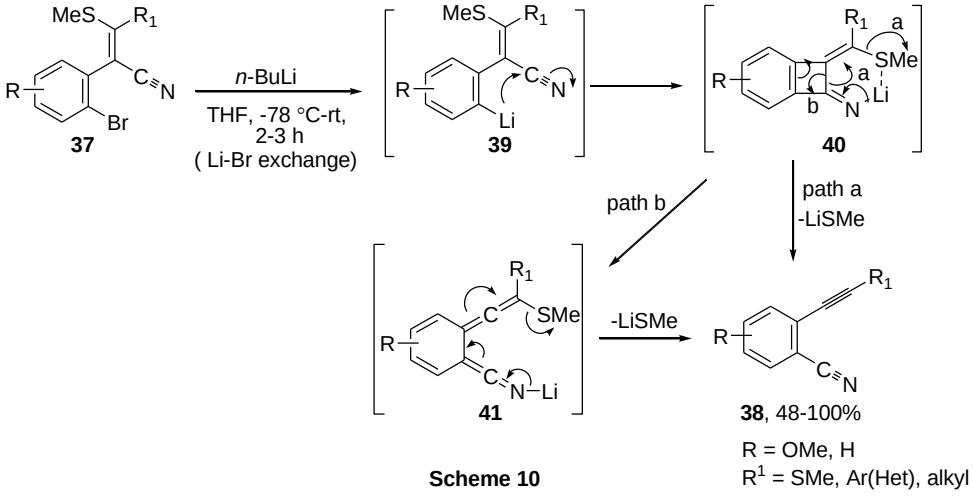
In a subsequent work, Yadav and Peruncheralathan from our research group reported a novel domino carbocationic rearrangement of α-[bis(methylthio)methylene]alkyl-2-(3-indolyl)cyclopropyl ketones **31** to pentaleno[*b*]indole diketones **32** in the presence of phosphoric or trifluoroacetic acid (Scheme 9).[14b] The overall transformation involves annulations of two cyclopentanone rings to indole in domino fashion, through initial electrophilic ring opening of cyclopropyl ketone **31**, followed by sequential trapping of carbocationic intermediates **33** and **34** by bismethylthiomethylene double bond as well as by indolyl 2- position respectively and subsequent in situ hydrolysis of bismethylthioketal moiety in the resulting biscyclopentano fused intermediate **35** leading to final products **32** (Scheme 9). This transformation for annulations of two cyclopentanone rings require presence of an α-methyl group on bis(methylthiomethylene) moiety in the cyclopropylketone **31** (R = Me), in the absence of a methyl group (R = H), the carbocationic intermediate **34** is

quenched by deprotonation to afford indolylcyclopentanone **36** with a bismethylthiomethylene moiety (Scheme 9) .



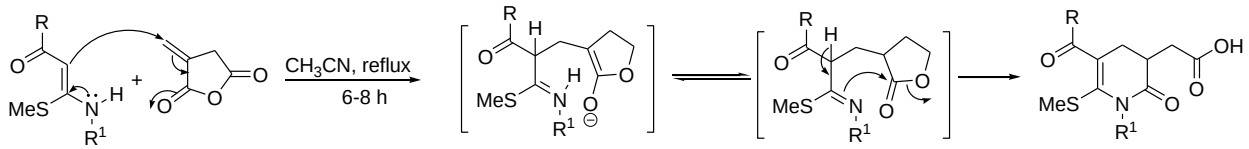
Scheme 9

Recently, our research group has reported, a novel unprecedented anionic domino rearrangement of 3,3-bis(methylthio)- or 3-(methylthio)-3-aryl/heteroaryl/alkyl-2-(*o*-bromoaryl)acrylonitriles **37** to *o*-cyanoarylacetylenes **38** in the presence of *n*-butyl lithium (Scheme10). The proposed mechanism involves lithium-halogen exchange, and intramolecular nucleophilic attack of aryllithio species on neighbouring nitrile group in the intermediate **39.** Subsequent cleavage of the resulting lithiobenzocyclobutanimine intermediate **40**, followed by concurrent or step-wise elimination (via intermediate **41**) of (methylthio) group, in the intermediates **40** respectively affords (*o*-cyanoaryl)acetylenes **38** in good yields (Scheme 10).[14c]



Scheme 10

Sriparna et al from our research group have also reported a novel domino process involving aza-annulation of polarized ketene-N,S- and N,N-acetals **42** with itaconic anhydride **43** providing an efficient and highly regioselective route toward substituted and fused 1,2,3,4-tetrahydro-2-pyridones **44** bearing an acetic acid side chain, in good yields (Scheme 11).[14d] The overall mechanism for the formation of pyridones **44** involves conjugate addition of N,S- or N,N- acetals (through β- carbon) on itaconic anhydride to give intermediate adduct **45A**, which undergoes intramolecular cyclization (through intermediate **45B**) via nucleophilic attack of amino group on lactone carbonyl group along with ring opening of the lactone ring to give tetrahydropyridones **44** bearing an acetic acid side chain at 5-position (Scheme 11).



Scheme 11

Chapter 2 of the present thesis describe novel domino reactions leading to formation of pyrrolo-fused complex structural frameworks through base mediated reaction of activated methylene isocyanides with cyclic oxoketene dithioacetals, whereas chapter 3 of the thesis reports a novel synthesis of substituted 2,5-bis(hetero)aryl 4'-substituted 4,5'-bisoxazoles via domino ring opening and cyclization of 2-(het)aryl-4-[(het)aryl)(methylthio)methylene]oxazol-5(4*H*)ones with activated methylene isocyanides in the presence of copper catalyst.

1.2 Multicomponent and One-Pot Reactions

The increasing demand for rapid syntheses of functional and biologically active molecules has inspired synthetic organic chemists to explore and design innovative strategies, that inevitably address the very fundamental principles of efficiency and efficacy. One very important aspects in modern drug discovery is the preparation of so called 'compound libraries', which are subjected to biological screening for selection of pharmaceutical lead structures for the treatment of different disease. An efficient approach

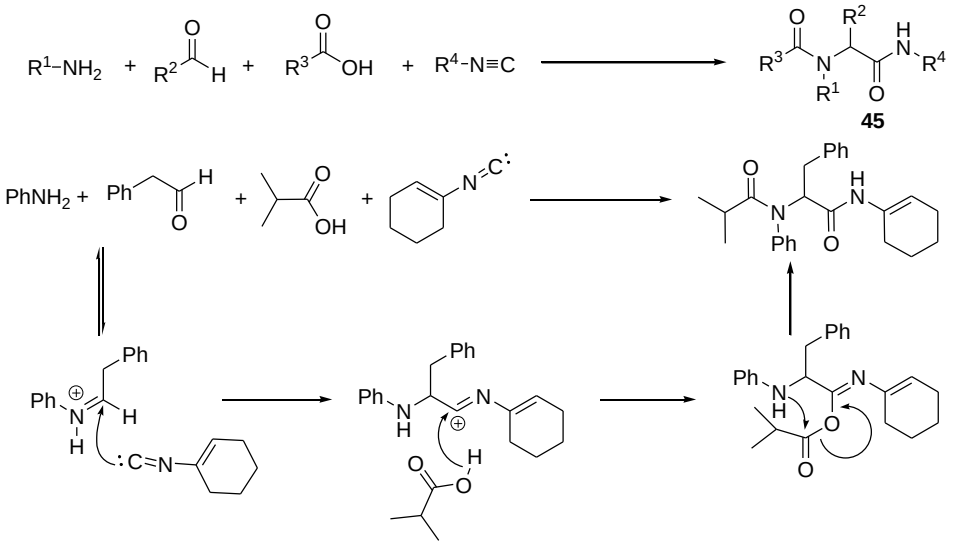
for the preparation of highly diversified libraries is the development of multicomponent reactions (MCR) and in the past two decades, the productive concept of multicomponent processes, and sequential transformations have considerably stimulated the synthetic and medicinal chemists.

A multicomponent reaction is a process, in which three or more reactants are reacted in a single chemical operation to furnish a compound that incorporates substantial portion of all starting materials.[15] They can be considered as subclass of domino processes, as they are usually performed employing all substrates in one single vessel, under similar reaction conditions, where the compounds undergo transformation in a time resolved mode, meaning, 'one after each other'. Since several substrates are reacted together, it is not only the molecular complexity that is built up very rapidly, indeed there is also possibility of generating diversity i.e., several analogs of target compound. Infact, a combination of diversity generation and creation of functionality has merged into the field of 'diversity oriented synthesis' which has found broad application in the discovery and development of pharmaceutical lead structures.[15] Because of this diversity and easy accessibility to a large number of starting materials, combined with high throughput screening techniques, MCR have emerged as a very important tool in modern drug discovery research. Also, because of its high convergence and enormous exploratory potential, MCR requires mastering an unusual combination of elementary organic reactions under similar conditions, providing organic chemists with major conceptual challenge in crafting novel type of sequences. Very recently, several excellent books and many highly informative reviews have been published on multicomponent transformations.[16]

One of the most widely used transformations of this type was described by Ugi and coworkers using an aldehyde, an amine, an acid and an isocyanide to prepare the peptide like compounds **45** (Scheme 12). The process could even be elaborated to an eight component reaction.[16a]

Some of the most popular well established multicomponent reactions such as Hantzsch synthesis of dihydropyridines **46** and Biginelli reaction for the synthesis of dihydropyrimidinones **47** are shown in Schemes 13 and 14.[17]

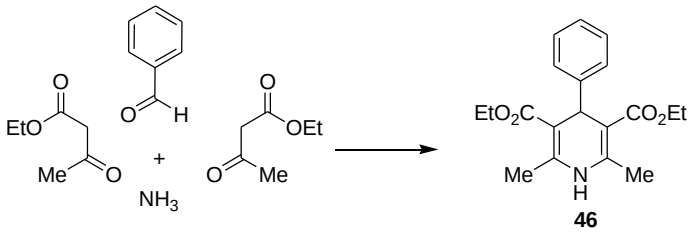
Ugi Reaction



45

Scheme 12

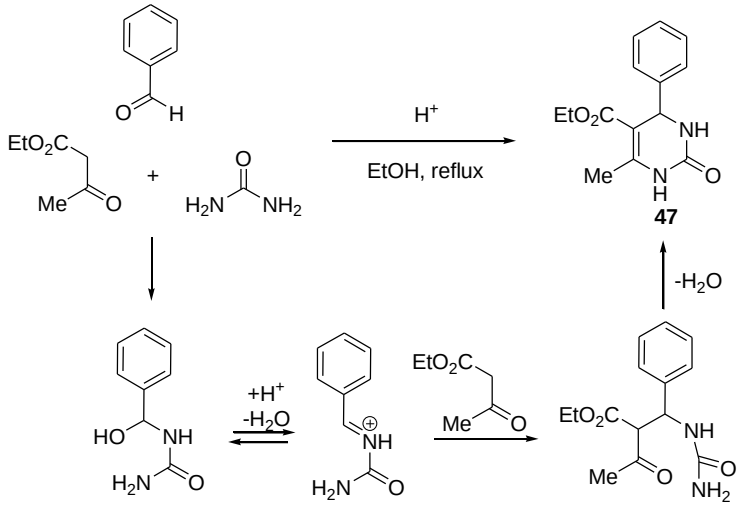
Hantzsch Reaction



46

Scheme 13

Biginelli Reaction



47

Scheme 14

In addition to the purist stand point, where all the ingredients of MCRs have to be present from very beginning of the process (MCRs in domino fashion), now a days, sequential (subsequent addition of reagents in a well defined order without the changing the conditions) and consecutive (subsequent addition of reagents with changing the conditions) one pot reactions are also included as well in the class of MCRs (Fig 1).[5a,18a-b] Muller and co-workers have developed a new consecutive one-pot multicomponent reaction for the synthesis of pyrimidines **48** via Sonogashira coupling of acetylenes and acid chloride to give acetylenic ketones **49** followed by their in situ cyclocondensation with amidinium salts (Scheme 15).[18c] In a subsequent work, these workers have also reported a sequential one pot four step synthesis of tetrasubstituted pyrazoles **50** through acetylenic ketones involving Sonogashira coupling, addition-cyclocondensation with methyl hydrazine, bromination of the resulting trisubstituted pyrazoles **51** followed and Suzuki coupling (Scheme 16).[18d]

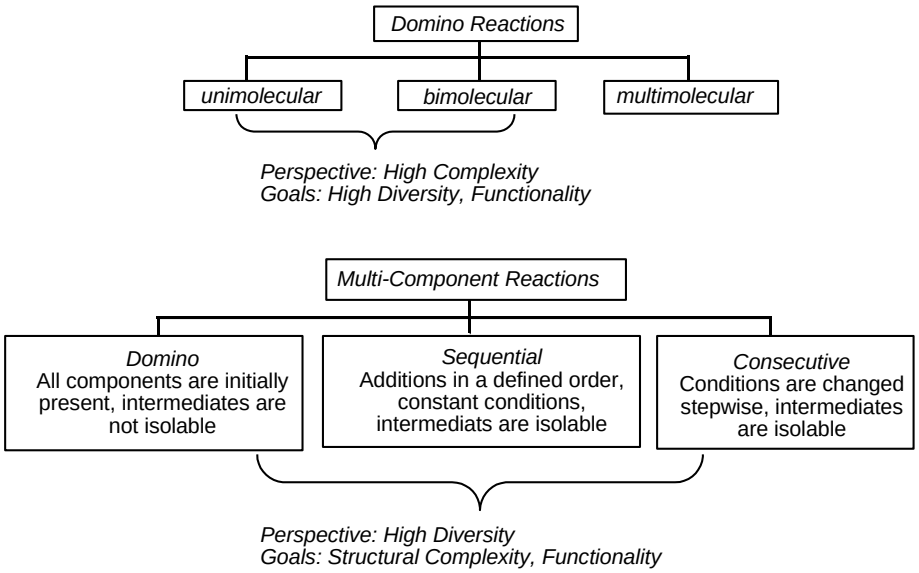
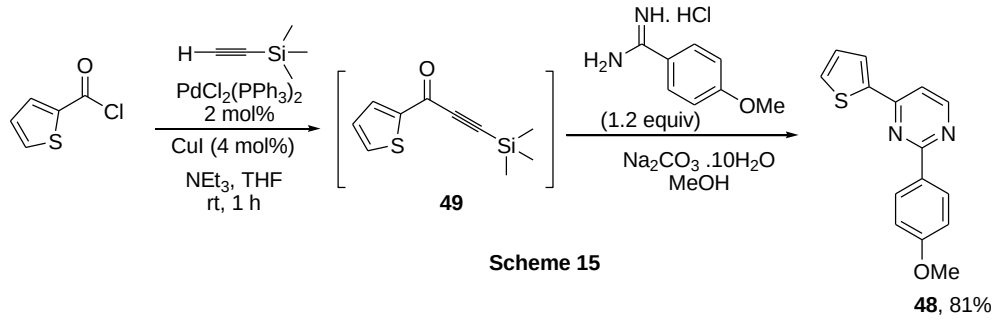
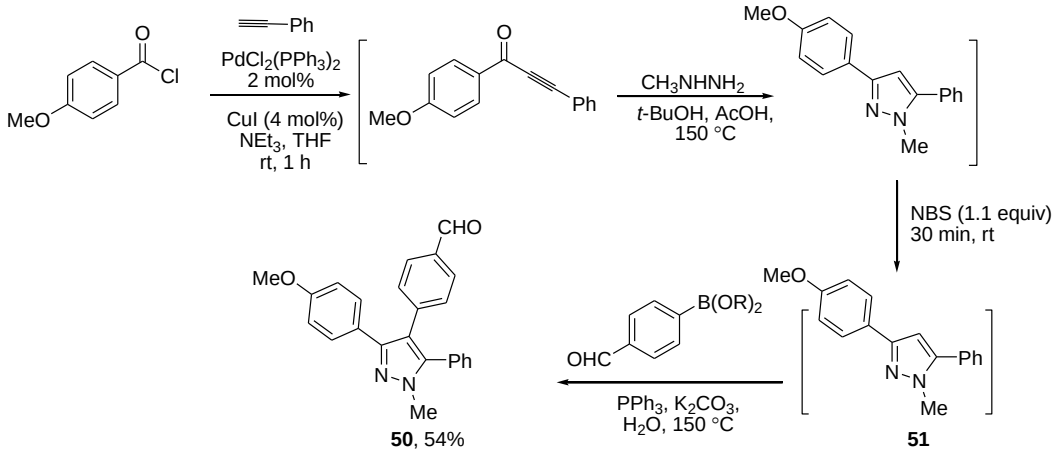


Fig 1: Multicomponent and domino reactions - enhancing synthetic efficiency



Scheme 15



Scheme 16

Our research group has also reported a novel highly regioselective sequential one- pot four component synthesis of 1,3,5-trisubstituted pyrazoles via in situ generation of 1,3-monothioketones by base mediated condensation of active methylene ketones with dithioesters followed by their S-methylation with methyl iodide and subsequent cyclocondensation of in situ generated β-(methylthio)-arylenones (Scheme 18, Chapter 5).

Similarly, Anand et al from our research group have developed a sequential three component synthesis of functionalized thiophenes via condensation of active methylene ketenones with dithioesters followed by their in situ S-alkylation with activated methylene halides and subsequent base mediation cyclocondensation of the resulting adducts (see, Scheme 19, Chapter 5).

These multistep multicomponent approaches are very often termed as 'one-pot' reactions.[19] Inspite of all these terminologies, a 'one- pot synthesis' is defined as a strategy to improve the efficiency of a chemical reaction, whereby a reactant (or more than one reactant) is subjected to successive chemical reactions in just one same vessel.[19] They are very effective procedures because several synthetic transformations can be carried out in a single pot, without isolation/purification of intermediates, while circumventing several purification procedures at the same time. A one-pot procedure can thus minimize chemical waste, amount of solvent, save time, labour and cost and simplify practical aspects. Infact, this approach has been used widely in synthetic organic chemistry for a long time. Hayashi and co-workers, in a recent review have termed it as 'pot economy',[19] wherein work-up and

isolation of intermediates is not always necessary, thus 'pot economy' is also important in synthesizing a target molecule in terms of 'greenness' and practicability of a synthetic sequence.

Chapter 5 of the thesis describes a novel sequential one-pot three component reaction for the synthesis of highly functionalized 2,4,5-trisubstituted imidazoles.

1.3 Catalytic Processes and Transition Metal Catalyzed Reactions

One of the fundamental considerations that should be addressed to make an organic synthesis more environmentally benign by design, is the stoichiometry of the process. In many cases, the formation of waste in a reaction is associated with the traditional use of a stoichiometric amount of reagents. Switching from stoichiometric to the catalytic process is considered as one major ways to improve the efficiency of synthetic toolbox. The catalysis can improve the efficiency of a reaction by lowering the energy input required, by avoiding the use of stoichiometric amount of reagents and by greater product selectivity thus implying less energy, less feedstock and less waste. Moreover it often opens door to innovative chemical reactions and leads to unconventional solutions to traditional chemical problems.

Besides efficiency, catalysis can allow for otherwise unfavorable reactions to be realized. This is very well illustrated by the metathesis reaction and development of Grubs catalyst.[20] Thus as demonstrated in Figure 2,[20d,e] the development of Grubs metathesis

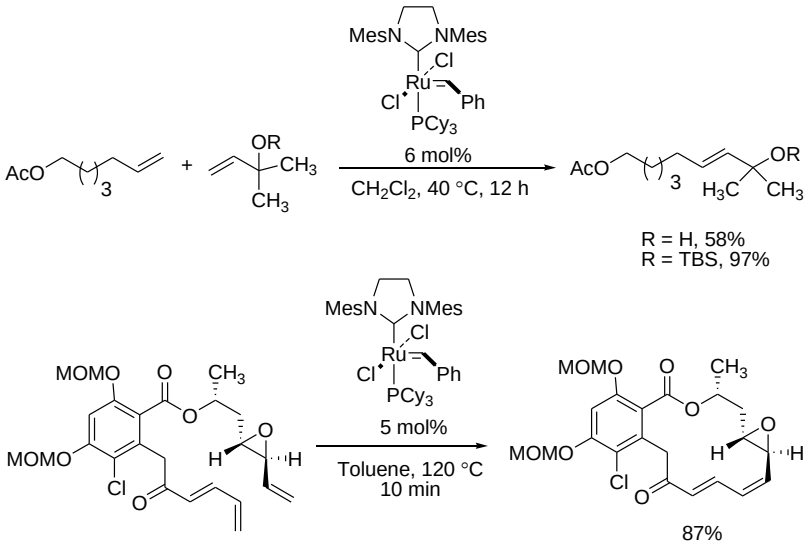
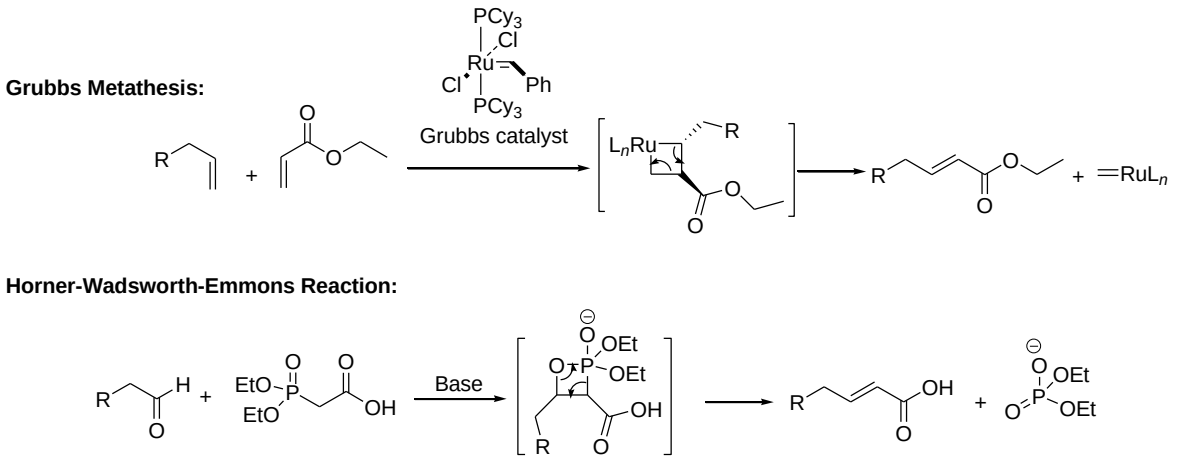


Figure 2

catalyst opened door for a breakthrough environmentally benign and innovative approach for the synthesis of unsaturated compounds. For example Grubbs catalyst, allows alkene metathesis through a mechanism similar to Wittig type reactions such as Horner-Wadsworth- Emmons reaction (formation of a four membered ring as reaction intermediate) (Scheme 17). However, unlike Wittig reaction, the metathesis reaction does not produce a large amount of waste such as the formation of phosphonium salts in the case of the Wittig reaction, which is unfortunately unavoidable since it is part of the design of the reaction and is the main driving force.

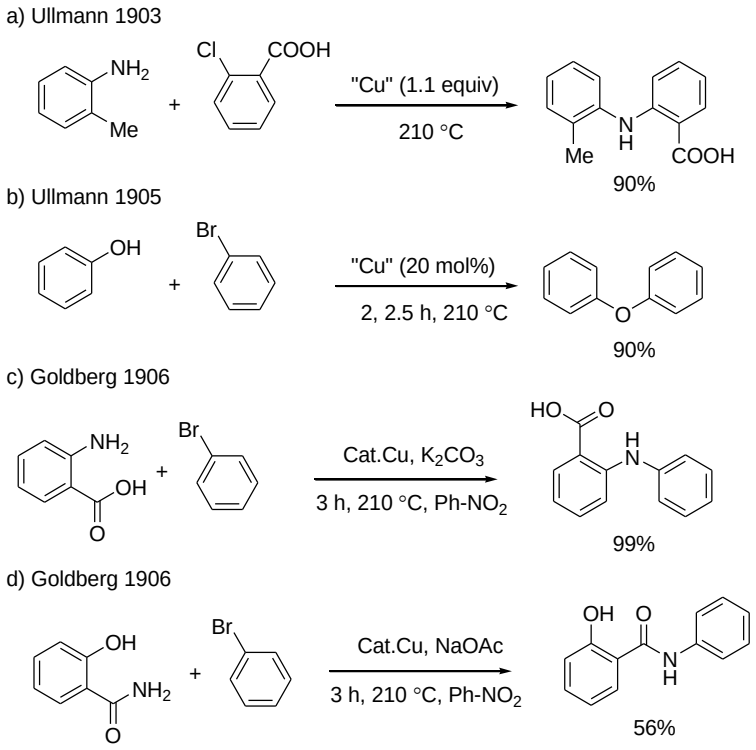


Scheme 17

` 1.3.1 Copper Catalyzed C-heteroatom Bond Formation

Another catalytic reactions worth mentioning are copper catalyzed C-N, C-O- and C-S- coupling reactions, which have been extensively investigated in past few years and constitute a powerful tool in organic synthesis and provide practical methods for the synthesis of aryl amines, aryl ethers and arylthioethers.[21a,b]

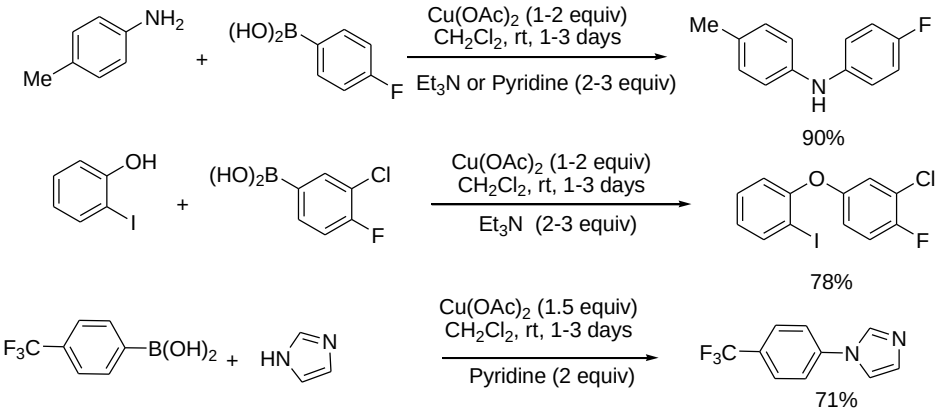
A few years after the discovery of Ullman reaction for biaryl synthesis, these workers also explored new ways to form aryl-N-, and aryl-O- bonds and developed method for synthesis of arylamines and aryl ethers (stoichiometric Cu) in 1903 and 1905 respectively and in 1906, first copper catalyzed synthesis of arylamide was reported by Irma Goldberg who also reported catalytic arylation of amines in the same year. These results represent a general breakthrough in the field of catalysis (Scheme 18).[21a,b]



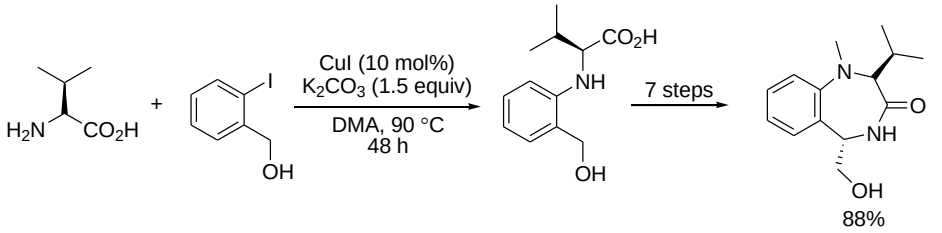
Scheme 18

Despite these early impressive examples, Cu-mediated reactions generally required harsh conditions (high temperature, strong bases, long reaction time and stoichiometric amounts of copper reagent), and electron-poor aromatic substrates and high-boiling polar solvents were often necessary. Moreover, problems related to the solubility of many Cu compounds were evident, hence excess amounts of Cu had often to be used. In addition, with the evolution of green chemistry, the necessity to use stochiometric amounts of the heavy metal copper in order to obtain satisfactory yields, has to be considered as a major drawback. A major breakthrough was certainly achieved 1998 by Chan, Evans, and Lam, who independently reported an applicable protocol for the transformation of arylboronic acids to arylamines under mild conditions (Scheme 19).[21c,d]

Ma and coworkers devised the first protocol for a mild copper catalyzed coupling of aryl bromide with chelating α-amino acid realizing that Goldberg amination reaction was successful with chelating nature of the substrate (Scheme 20).[21e]



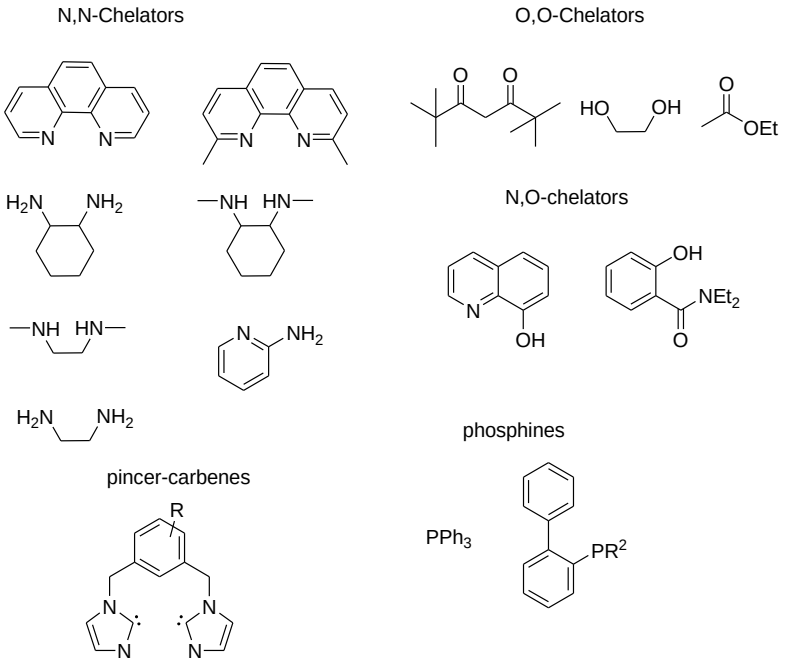
Scheme 19



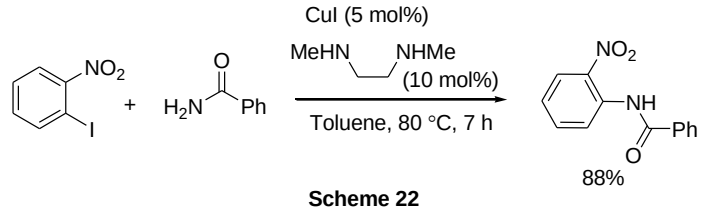
Scheme 20 Benzolactam V8

In the following years, the introduction of ligands in Ullmann type reactions led to much milder reaction conditions possible, and temperatures (usually 80–100 ºC) could be used achieving good results, and amounts of Cu source and ligand in the range 5-20% relative to the substrate were normally used. Subsequently, it was shown that different types of bidentate ligands, are much more efficient than monodentate ones. The ligands used in Ullmann-type reactions were generally N-donors or mixed N- and O-donors, while P-based ligands were generally found to be scarcely effective (Scheme 21). The understanding of solubilizing and accelerating effects exhibited by substrates and ligands initiated further developments originally on N-arylation of amines, amides, and nitrogen heterocycles.[21a,b]

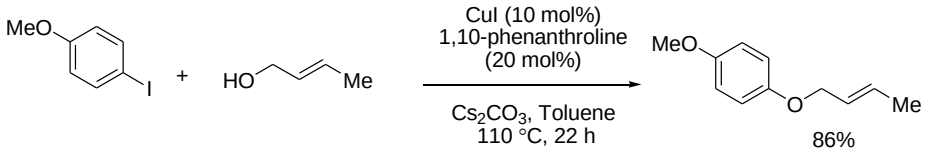
With the growing set of optimized protocols including mild reaction conditions and readily accessible ligands, high stability of the catalysts even under air and their low costs, the copper catalyzed C-heteroatom bond formation has emerged as a general and highly useful protocol for aryl-N, aryl-O and aryl-S bond formation (Schemes 22-24).[21f-h]



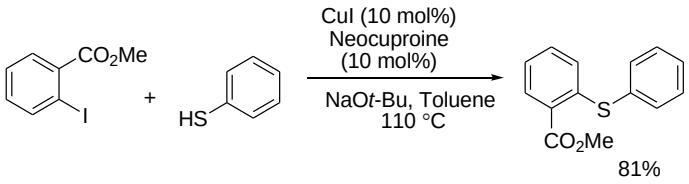
Scheme 21: Ligand toolbox for copper-catalyzed cross couplings



Scheme 22



Scheme 23

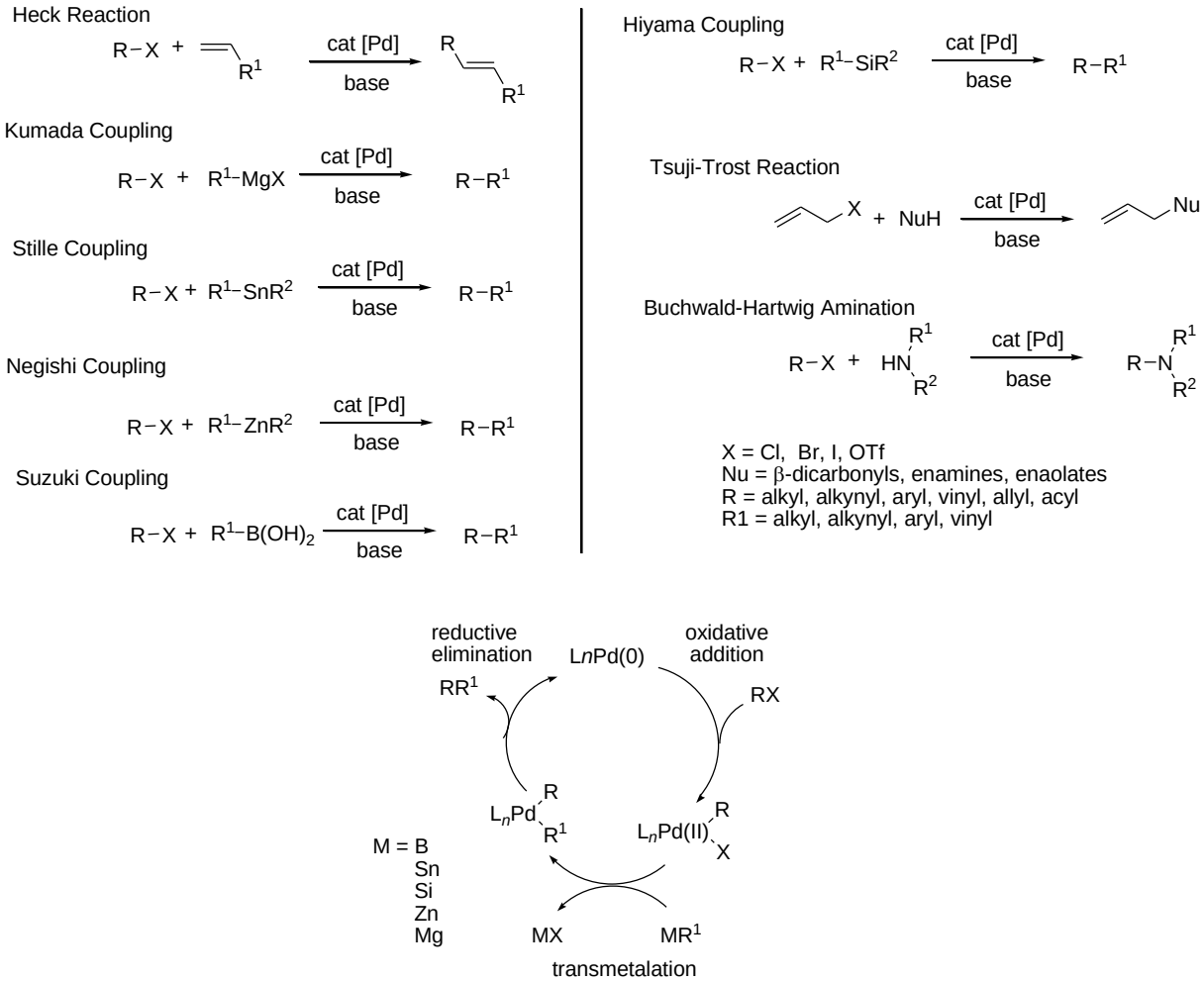


Scheme 24

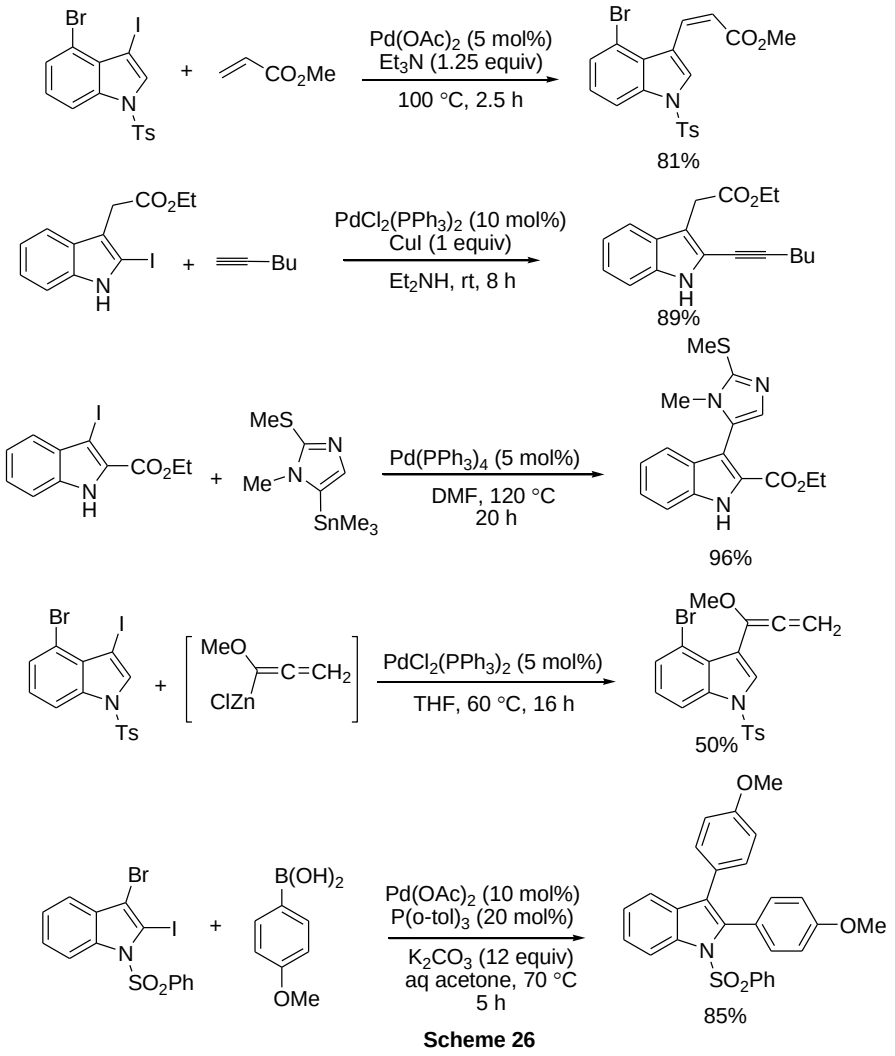
1.3.2 Transition Metal Catalyzed Cross-Coupling Reactions

In the past decades, transition metal-catalyzed synthetic transformations have been considered as one of the most powerful and reliable tools for a variety of bond connections, giving complex molecular structures to be prepared in an efficient and economical manner. Among the myriad of important transition metal catalyzed synthetic transformations,

palladium-catalyzed Heck coupling, cross-couplings (Kumada, Stille, Negishi, Suzuki–Miyaura, Hiyama), Tsuji–Trost allylation, and Buchwald–Hartwig amination[22-24] reactions involving reaction of organometallic nucleophiles with preactivated electrophiles such as aryl, vinyl or alkyl halides and other surrogates are particularly valuable tools in synthetic organic chemistry. A common and critical feature of these catalytic processes is the formation of aryl or alkyl palladium(II) intermediates which can be subsequently functionalized to form carbon–carbon and carbon–heteroatom bonds (Scheme 25). For instance, derivatization of indoles are most efficiently achieved by using 2- or 3-haloindoles to couple with alkenes[25a], alkynes,[25b] organostannanes,[25c] organozincs[25d] and aryl boronic acids[25e] (Scheme 26).



Scheme 25: Generalized mechanism for palladium-catalyzed croos-coupling reactions



Scheme 26

Chapter 6 of the thesis describes a novel synthesis of substituted benzo[*b*]thiophenes involving a sequential one-pot copper catalyzed C-S bond formation and an intramolecular C-C bond formation via a palladium catalyzed intramolecular Heck reaction through reaction of 1,3-monothioketones and 2-bromo-1-iodoarenes.

1.4 Atom Economy and C-H Activation

1.4.1 Atom Economy

In 1990, Barry Trost proposed the concept of 'Atom Economy' (AE) also called 'Atom Efficiency' for evaluation of synthetic efficiency of a reaction.[26] It deals with the concept of maximizing the use of starting materials, so that the final product incorporates the maximum number of atoms from the reactants. Thus, production of all kinds of organic

compounds must address synthetic efficiency not only in terms of selectivity (chemo-, regio-, diastereo-, and enantioselectivity) but also in terms of atom economy, that is, the final product should contain most of the atoms of starting compounds. Infact, an ideal reaction should incorporate all of the atoms of reactants. The 'Atom Economy', is the value to quickly assess the efficiency of a reaction, which can be calculated as the ratio of the molecular weight of the desired product over molecular weights of all reactants used in the reaction.[3a,26]

'Catalytic hydrogenation' can be considered as one of the oldest and ideal 'atom economy reaction'. Other processes such as hydroformylation, Ziegler-Natta polymerization, and hydrocyanation represent further examples of 'Atom Economy' reactions. The Diels-Alder reaction is an excellent example of an atom economical reaction. Its AE is 100%, since all the atoms from the reactant are incorporated into the final products. Diels-Alder reaction which is one of most useful reactions for C-C bond formation in highly regio-, diastereo- and enantioselective fashion, can be considered as one of the greenest type of reactions, as well as being atom economic. Surprisingly, few industrial processes make use of such a reaction, although it is an extremely important research tool for the synthesis of complex molecules. The multicomponent reactions are also very efficient and atom economic reaction, as 92% of original atoms present in the reactants are incorporated in the final products in most of these reactions.

1.4.2 C-H Activation

Despite the great progress, in the field of transition metal catalyzed cross-coupling reactions, the search for new reactions that proceed with similar efficiency and selectivity upon employing readily available non-preactivated starting materials such as aromatics and heteroaromatics themselves, still remains one of the important objectives in this area. The use of unnatural halogenated arene precursors, in these cross-coupling reactions, requires additional steps for the synthesis of these intermediates, which not only adds to the costs, but also releases the generated halogenated waste products, thus reducing the breadth of readily available starting materials.

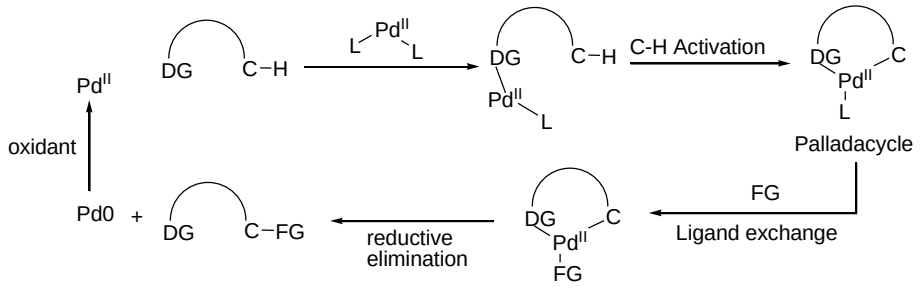
Recently, organic reactions involving direct functionalization of non-activated C-H bond have emerged as an attractive class of synthetic strategy and powerful tools for the construction of functionalized aromatic and heterocyclic compounds. These reactions have

received considerable attention because of their economic, sustainable and environmentally benign features, besides maximizing atom- and step-economy thus simplifying chemical synthesis.[27] This new strategy holds great promise for the future as it does not require prefunctionalization of the hetaryl group, it operates under ambient conditions, and broadens the substrate scope of the reactions by increasing the number of compatible functional groups. Also, this methodology allows the efficient installation of substituents at different positions in the target compounds, compared with previous methods, and it can be applied for the synthesis of complex heteroaromatic molecules.

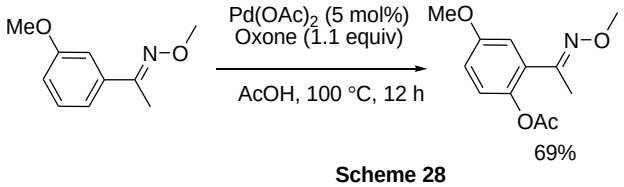
Over the last 20 years, the field of C–H activation has become one of the most rapidly developing areas of homogeneous catalysis, reshaping the landscape of both organometallic catalysis and synthetic organic chemistry and also being applied in natural product synthesis, pharmaceuticals and material science.[27] This methodology is becoming an increasingly viable alternative to traditional cross-coupling reactions with organometallic reagents. In particular, use of palladium,[27] ruthenium[28a] and rhodium[28b] catalysts have been reported for direct arylation of (hetero)arenes with challenging coupling partners-including electrophilic aryl chlorides and tosylates as well as simple arenes in cross-dehydrogenative arylations. Recently, less expensive copper,[29a,b] iron,[29c] and nickel[29d] catalysts have also been shown to be effective in direct arylation reactions. In recent years, practical aspects of the direct C–H bond functionalization strategy have also been increasingly investigated for their application in industrial processes, due to the advantages that no preactivation of heteroarenes is required and wasteful byproducts are minimized, as compared to the conventional double preactivation procedures.

Two fundamental challenges faced in direct C-H bond functionalization reactions are: (i) the inert nature of most carbon-hydrogen bonds and (ii) the necessity to control site selectivity in molecules containing diverse range of C-H groups. A number of studies have been carried out to address the first challenge by demonstrating that transition metals can react with C-H bonds to produce C-M bonds in a process known as "C-H activation".[30] The resulting C-M bonds are far more reactive than their C-H counterparts, and in many cases they can be converted to new functional groups under mild conditions.[30]

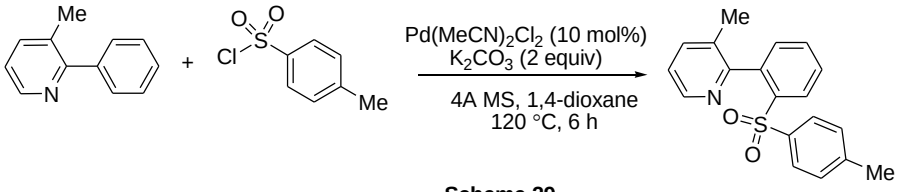
Several different strategies have been employed to address the second major challenge in achieving selective functionalization of a single C-H bond within a complex molecule. The most common involves the use of substrates that contain coordinating ligands.[31] These ligands (often termed "directing groups") bind to the metal center and selectively deliver the catalyst by direct ortho-funcionalization via a five or six membered metalla cycles to a proximal C-H bond. Many different transition metals, including Ru, Rh, Pt, and Pd, undergo stoichiometric ligand-directed C-H activation reactions (also known as cyclometalation) (Scheme 27).[31] A large variety of directing groups such as oxime ethers,[32a] pyridines,[32b] benzyl amines[32c] and benzoic acids[32d] have been used in such kind of ligand directed C-H activation processes (Schemes 28-31).



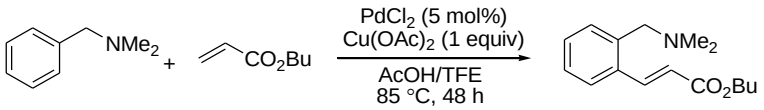
Scheme 27:Transition metal catalyzed ligand directed C-H activation/functionalization



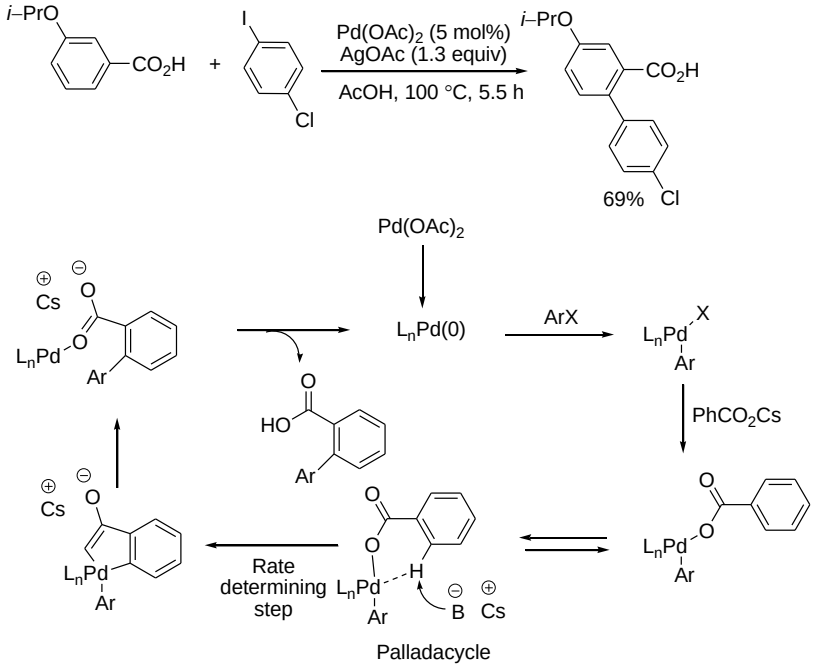
Scheme 28



Scheme 29



Scheme 30

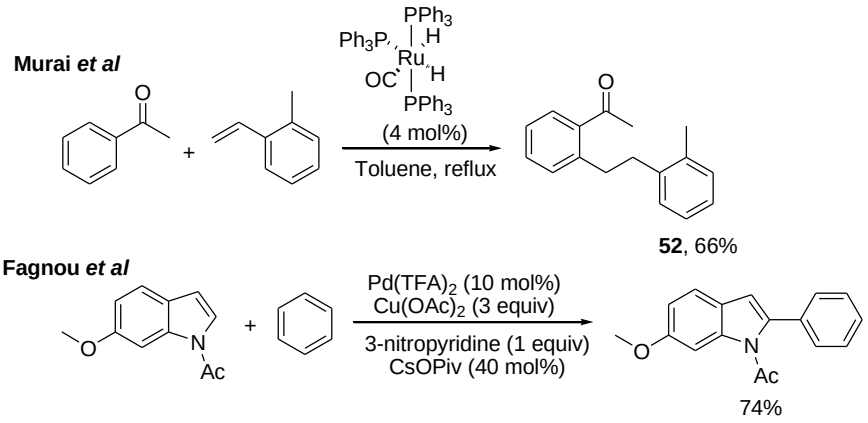


Scheme 31

Over the last 15 years, a variety of catalytic carbon-carbon bond-forming processes have been developed that involve cyclometalation as a key step.[30a-b,33] Palladium complexes are particularly attractive catalysts for such transformations for several reasons. First, ligand-directed C-H functionalization at Pd centers can be used to install many different types of bonds, including carbon-oxygen, carbon-halogen, carbon-nitrogen, carbon-sulfur, and carbon-carbon linkages. Few other catalysts allow such diverse bond constructions. Second, palladium participates in cyclometalation with a wide variety of directing groups and, unlike many other transition metals, readily promotes C-H activation at both $sp^2$and sp^3 C-H sites. Finally, the vast majority of Pd-catalyzed directed C-H functionalization reactions can be performed in the presence of ambient air and moisture, making them exceptionally practical for applications in organic synthesis.

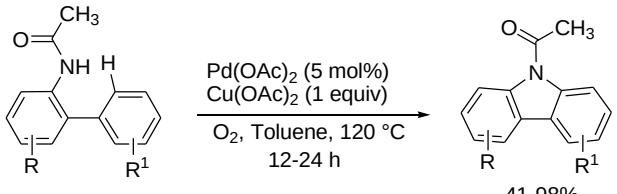
Some excellent reviews describing the functionalization of heteroarenes by transition metal catalyzed C-H functionalization are reported in recent years by several research group especially from Lautens et al,[33b] Seregin and Gevorgyan,[34a] Ackermann et al,[34b] Campeau and Fagnou,[27a] Bellina and Rossi,[34c] and Hirano and Miura[34d] they basically cover catalytic C–H bond functionalization of (hetero)arenes by employing preactivated organic as a coupling partner, as well as on ligand directed C-H activation-functionalization.[31]

The two famous examples of C-H activation were published in 1993 by Murai[35a] and in 2007 by Fagnou (Scheme 32).[35b] In the first case, Murai reported ruthenium catalyzed coupling of the inactivated substrate acetophenone and 2-methylstyrene to give product **52**. This work was one of the first examples of C-H activation and represents a milestone in the field. Fagnou and Stuart coupled two aromatic compounds selectively without the need for any activating or directing group through 'cross dehydrogenative coupling'. These examples demonstrate the power of C-H activation in advancing green chemistry.



Scheme 32

However, disadvantage of ligand directed C-H activation is that ligand should be removed after C-H functionalization since activating ligand is not always required in the final product. Buchwald and coworkers in their breakthrough publication in 2005, first time demonstrated in their synthesis of substituted carbazoles via intramolecular C-H activation/ C-N bond formation that participating coupling partner can act as both reacting group as well as directing group (Scheme 33).[36]



Scheme 33

Subsequently several research group has utilized this strategy especially for the synthesis of benzoheterocycles.

The 4th chapter of the thesis describes a novel synthesis of 1,2,3-multisubstituted indoles involving a palladium catalyzed C-H activation–intramolecular C-N bond formation of *N*-het(aryl)/acyl enaminonitriles and enaminones, in which the aryl amino group acts both as directing group and a coupling partner. A short literature survey highlighting application of C-H activation in benzoheterocycle synthesis has been described in chapter 4.

1.5 References

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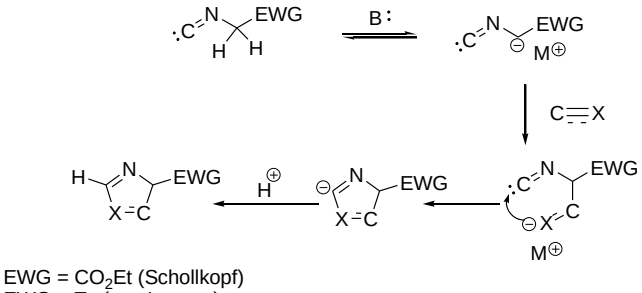
Chapter 2

*Reaction of Cyclic α-Oxoketene Dithioacetals with Activated Methylene Isocyanides: A Novel Pyrrole Annulation-Ring Expansion Domino Process**

2.1 Introduction

The rich chemistry of anionized α-isocyanoacetate and tosylmethyl isocyanide developed by Schollkopf[1a-b] and van Leusen[2] respectively is mainly due to the exploitation of nucleophilicity of the α-carbon atom, which can add to a variety of polar (hetero)multiple bonds, along with the electrophilicity of divalent carbon atom of the isonitrile functionality resulting in efficient construction of a C-C and C-X (X = N, O, S) bonds in a formal cycloaddition process to generate various heterocycles (Chart 1).

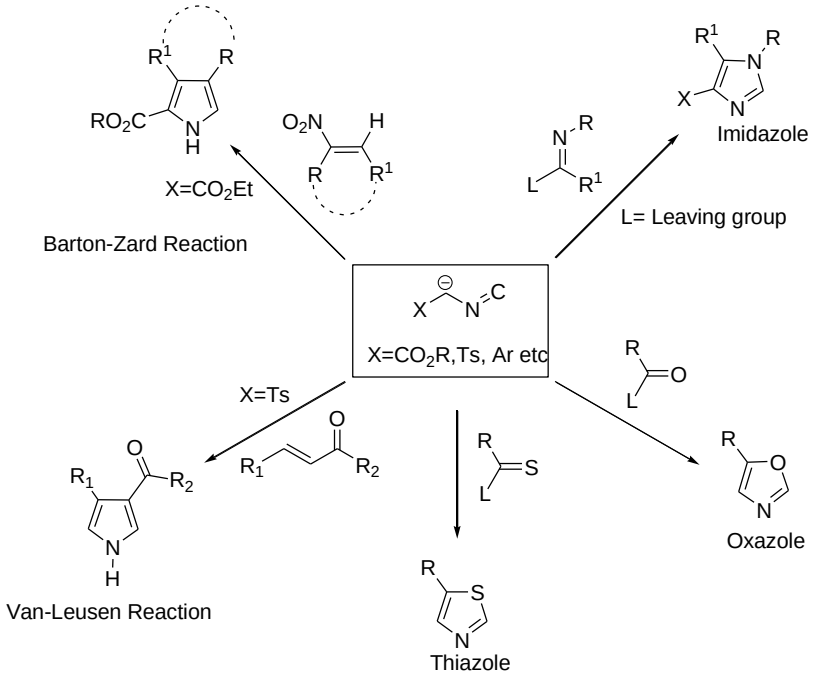


EWG = CO_2Et (Schollkopf)
EWG = Ts (van Leusen)

Chart 1

*The overall results of study described in this chapter have been published in *Org. Lett.* **2013**, *15*, 5250.

One of the useful and versatile methods for the synthesis of substituted and annulated pyrroles, involves base mediated formal cycloaddition of activated methylene isocyanides with various Michael acceptors.[3] Since the initial discovery by Schollkopf and Gerhart about 45 years ago,[1a] α-metalated isocyanides are shown to participate in various type of cocyclizations with a range of multiple bonds and other reactive species, leading to diverse array of nitrogen heterocycles (Scheme 1).[1b-d,4]



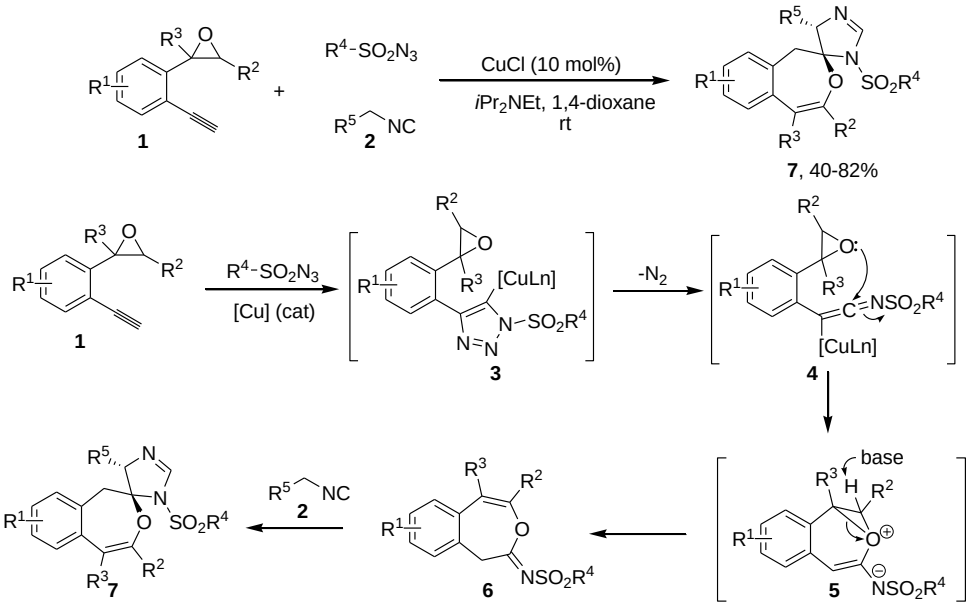
Scheme 1

In the present chapter we have disclosed a new domino process involving base induced rearrangement of cyclic *α*-oxoketene dithioacetals with activated methylene isocyanides leading to the formation of a diverse range of annulated pyrroles along with highly regioselective one carbon ring expansion of cyclic ketones (Scheme 23). Before presenting our results, a short review on domino reactions of activated methylene isocyanides for the synthesis of various heterocycles along with few recent synthesis of substituted pyrroles has been described in the following section. Since two reviews have appeared on reactions of activated methylene isocyanides in 2010, the present chapter highlights the literature after 2010.

2.2 Domino Reactions of Activated Methylene Isocyanides: A Short Recent Literature Survey

Domino reactions have attracted significant attention in organic synthesis, due to their high efficiency for multiple bond formation in a single operation without the need to isolate intermediates.[5]

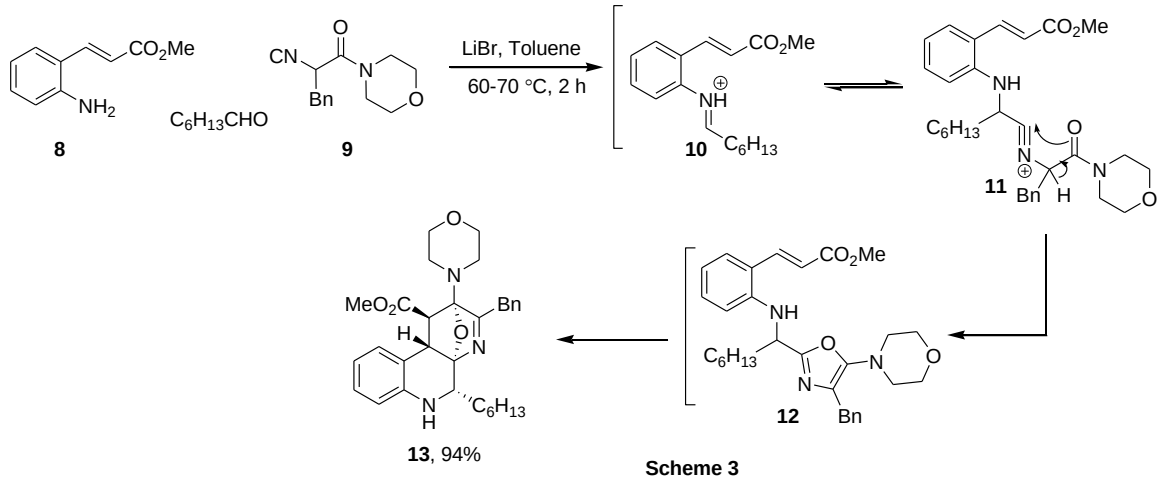
Thus, Wu and co-workers have reported a novel and straight forward synthetic protocol for the synthesis of 3',5'-dihydro-1*H*-spiro[benzo[*d*]oxepine-2,4'-imidazoles] **7** through a copper-catalyzed one-pot reaction between oxirane **1**, sulfonyl azide and isocyanoacetate **2** (Scheme 2). The reaction mechanism involves, copper catalyzed reaction of oxirane with sulfonyl azide providing the intermeadite **3**, which on release of nitrogen would give reactive ketenimine **4**. Now, an intramolecular nucleophilic attack of epoxide on to the **4**, affords the intermediate **5**, which would undergo intramolecular rearrangement to furnish **6**. Finally, [3+2] cycloaddition between compound **6** and isocyanoacetate **2** affords the product **7**. In this domino process, four new bonds and two rings are formed under mild reaction conditions (Scheme 2).[6]



Scheme 2

Zhu and co-workers have described a novel multicomponent domino process for the synthesis of oxa-bridged tetracyclic tetrahydroquinolines **13** starting from *ortho*-amino cinnamate **8**, aldehyde, and *α*-isocyanoacetamide **9** (Scheme 3). In this reaction one C-N,

one C-O and three C-C bonds are formed in one-pot process. The mechanism of the reaction involves, initial formation of iminium ion **10** via condensation of aldehyde with secondary amino group of **8** followed by addition of isonitrile **9** to **10** and subsequent intramolecular cyclization of the nitrilium intermediate **11** to oxazole intermediate **12**, which undergoes in situ intramolecular Diels Alder cycloaddition on activated double bond to furnish oxabridged tetracyclic tetrahydroquinoline **13** in good yield (Scheme 3).[7a]

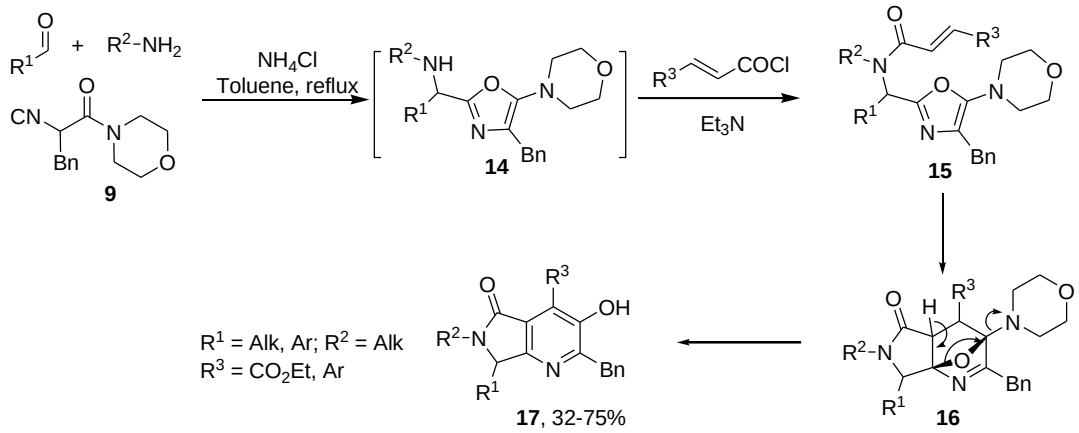


Scheme 3

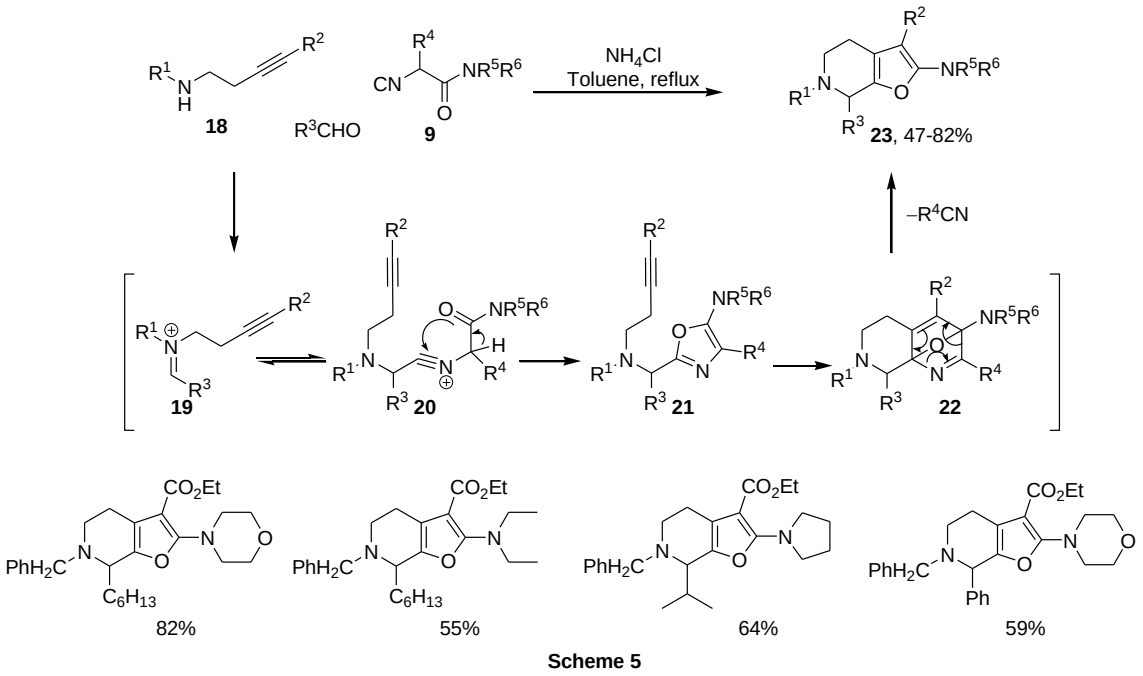
In a subsequent extension of this work, Zhu and co-workers have developed an efficient one-pot, four component domino process for the synthesis of pyrrolo[3,4-*b*]pyridine-5-ones **17**, involving intramolecular Diels Alder cycloaddition of in situ generated oxazole intermediate **15** and subsequent retro-Michael cycloreversion of the intermediate **16** (Scheme 4). The intermediate 5-aminooxazole **15** was generated in situ by condensation and cyclization of an aldehyde, amine and an *α*-isocyanoacetamide **9** followed by acylation of the resulting intermediate **14** with α,β-unsaturated acid chlorides (Scheme 4).[7b]

In a parallel process, Zhu and co-workers have also reported a novel three component domino process for the synthesis of tetrahydrofuro[2,3-*c*]pyridines **23** from readily available starting materials such as aminopentynoate **18**, aldehyde, and an *α*-isocyanoacetamide **9** (Scheme 5). The overall reaction involves initial condensation of aldehyde and aminopentynoate **18** leading to the imine **19**, which on reaction with isonitrile **9** affords the intermediate oxazole **21**, via intramolecular cyclization of the resulting nitrilium intermediate **20**. Subsequent in situ intramolecular Diels-Alder cycloaddition of the **21** with the tethered

acetylene furnishes the tetrahydrofuro[2,3-*c*]pyridine **23** through retro Diels-Alder fragmentation of the intermediate oxa-bridged adduct **22** (Scheme 5).[7c]



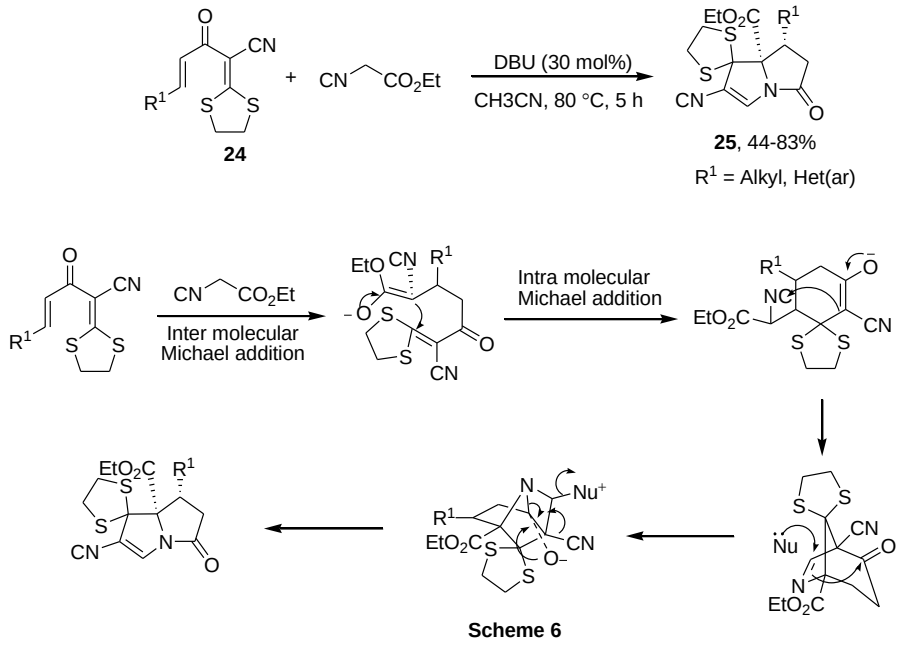
Scheme 4



Scheme 5

Liu and co-workers have described in a series of papers reaction of isocyanoacetate anions with alpha-alkenoylketenedithioacetals leading to a range of unexpected products via novel domino processes (Schemes 6-9).[8] Thus they have demonstrated that cyclic ketenedithioacetal **24** affords substituted pyrrolizidines **25** on reaction with ethyl isocyanoacetate in presence of 30 mol % DBU in acetonitrile solvent (Scheme 6). This single step process involves a novel tandem double-Michael addition/cyclization/1,3 acyl migration.

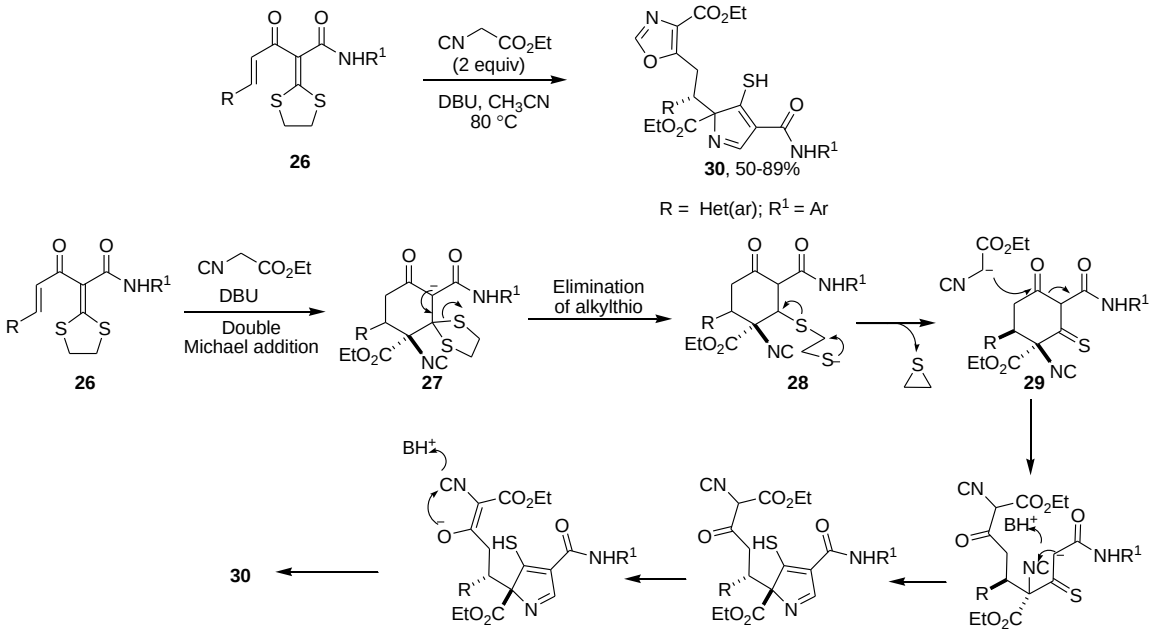
This domino reaction involves the formation of one C-N and three C-C bonds in a regio- and diastereoselective manner (Scheme 6).[8a]



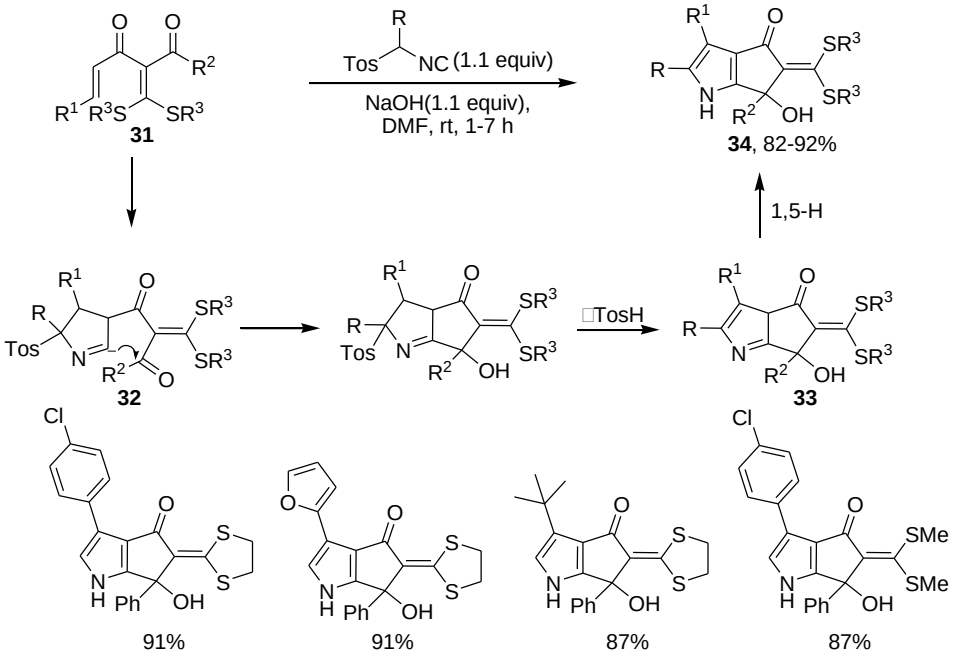
Scheme 6

In a parallel paper, Liu and co-workers have described a new strategy for the synthesis of C_2-tethered pyrrole/oxazole pairs **30** via base induced cyclization of α-alkenylketenedithioacetal amide **26** and ethyl isocyanoacetate (Scheme 7). The reaction mechanism involves (a) the diastereoselective double Michael addition of ethyl isocyanoacetate to 1,5-dielectrophile **26** to provide cyclohexanone intermediate **27**, (b) intramolecular elimination of a thiol group, followed by elimination of thiirane molecule from **28** provides thione intermediate **29**, (c) the preferential cleavage of the C-C bond of **29** upon nucleophilic attack by ethyl isocyanoacetate anion, followed by double isocyanide cyclization furnishes a pyrrole and oxazole rings **30** respectively (Scheme 7).[8b]

Liu and co-workers have reported a new method for the synthesis of fused pyrroles **34** from alkenoyl ketene dithioacetals **31** and tosylmethyl isocyanides (Scheme 8). The overall process involves, a formal [3+2] cycloaddition of TosMIC with Michael acceptor **31** under basic conditions to provide imidoyl anion intermediate **32**, which on intramolecular nucleophilic attack on tethered carbonyl group followed by elimination of tosylic acid affords the intermediate **33**. Finally intermediate **33**, undergoes 1,5-sigmatropic hydrogen shift to furnish cyclopenta[*b*]pyrroles **34** (Scheme 8).[8c]



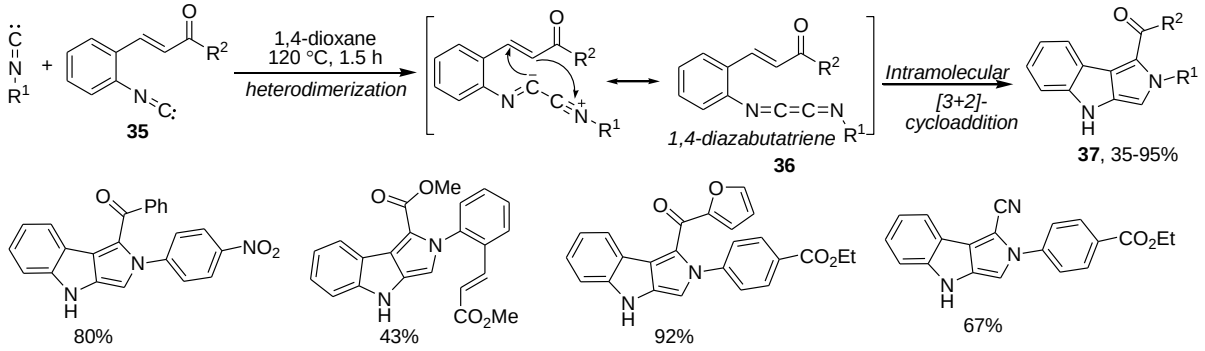
Scheme 7



Scheme 8

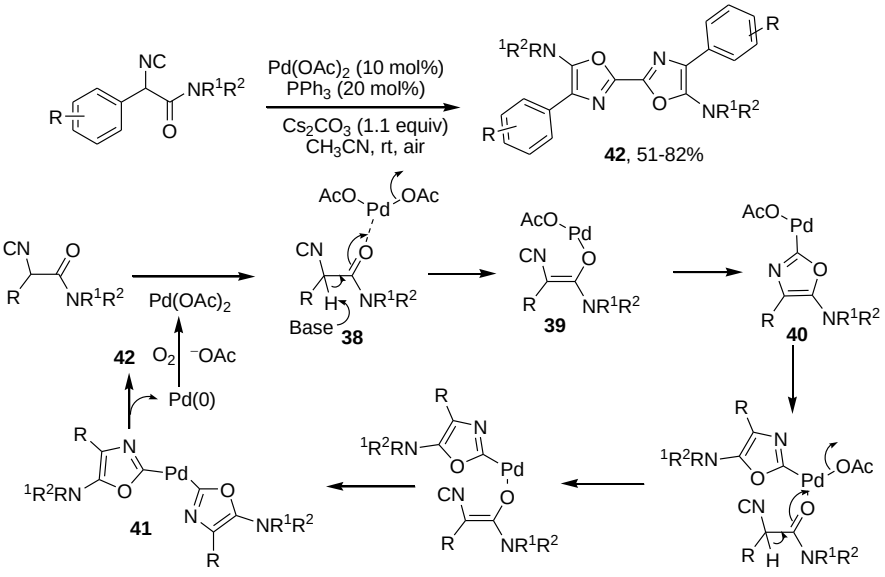
Recently, Liu and co-workers have reported a new method for the synthesis of pyrrolo[3,4-*b*]indoles **37** via cross-cycloaddition between isocyanides and 2-isocyanochalcones **35** under thermal conditions (Scheme 9). This domino reaction involves chemoselective hetero dimerization of two different isocyanides to form 1,4-diazabutatriene

intermediate **36**, which undergoes intramolecular [3+2] cycloaddition followed by 1,3-proton shift to furnish pyrrolo[3,4-*b*]indoles **37** (Scheme 9).[8d]



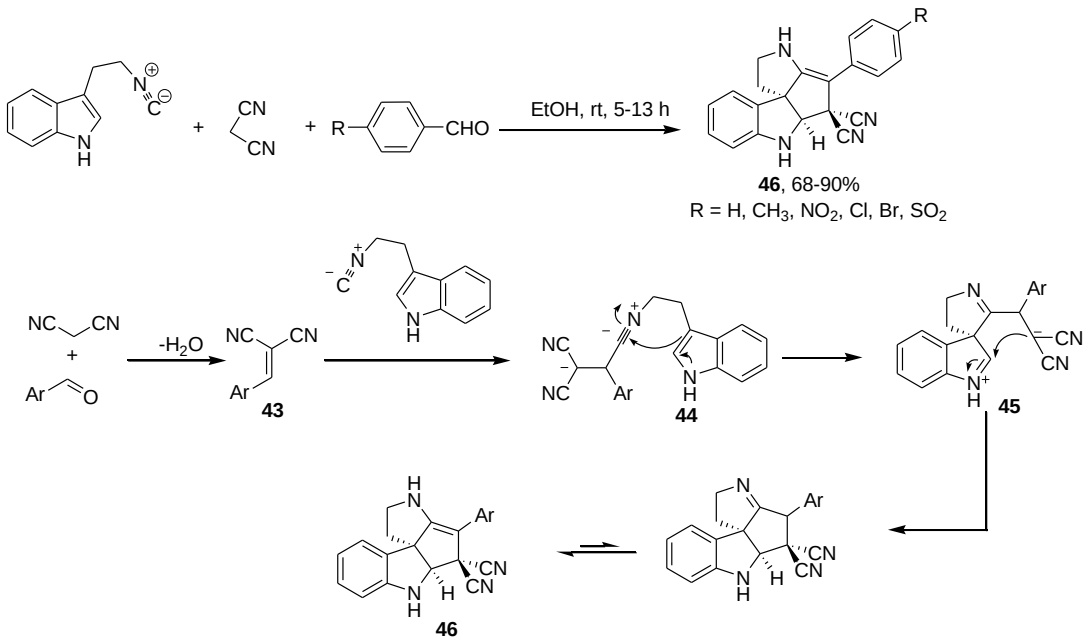
Scheme 9

Recently, Zhu and co-workers have reported a novel palladium catalyzed synthesis of 2,2'-bisoxazoles **42** from readily available *α*-isocyanoacetamides using air as an oxidant at room temperature (Scheme 10). The reaction mechanism involves, coordination of the carbonyl oxygen in *α*-isocyanoacetamide with $Pd(OAc)_2$ affording the intermediate **38**, which on deprotonation and the subsequent isocyanide insertion in the Pd-O bond of the resulting enolate Pd intermediate **39** affords oxazole Pd complex **40**. Repeating the same process yields the bisoxazole ligated palladium(II) intermediate **41**, which undergoes reductive elimination provides the homo-coupling bisoxazole **42** (Scheme 10). In this domino process two oxazole rings, two C-O bonds and one C-C bond are formed.[9]



Scheme 10

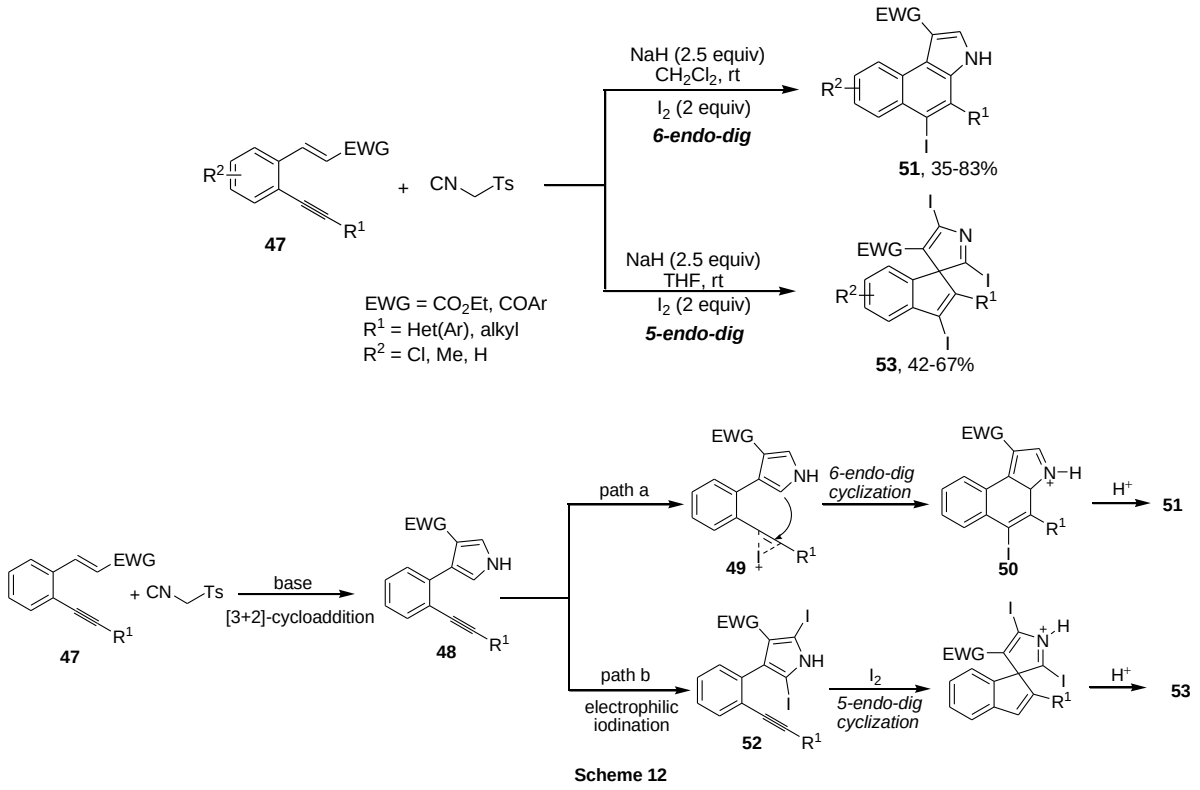
Ji and co-workers have developed a novel catalyst-free multicomponent reaction for the construction of polycyclic spiroindolines from 2-isocyanoethylindole, aromatic aldehydes and malononitrile (Scheme 11). The reaction mechanism involves Knoevenagel condensation of malononitrile with aromatic aldehyde to give benzylidenemalonodinitrile **43**, which reacts with isocyanide to provide the isonitrilium intermediate **44** followed by nucleophilic attack of the C3 carbon indole to afford the intermediate **45**. Subsequently, intramolecular nucleophilic addition of dicyanomethyl anion in the intermediate **45** affords the spiroindolines **46** (Scheme 11).[10]



Scheme 11

Recently, Xu and co-workers have described a solvent-dependent divergent domino one-pot synthesis of benz[*e*]indoles **51** and spiro[indene-1,3'-pyrroles] **53** via [3+2]-cycloaddition/iodocyclization of alkyne-tetherd chalcones/cinnamates **47** and tosylmethyl isocyanide (Scheme 12). In this reaction, two structurally distinct scaffolds are constructed with successive formation of four to six new bonds in one-pot. The mechanism of reaction involves, the formation of pyrrole intermediate **48** via formal [3+2] cycloaddition of cinnamate **47** with TosMIC, which undergoes two pathways to give the two different products. In path a, the carbon-carbon triple bond is activated by the coordination of I_2 to form the intermediate **49**, which would undergo intramolecular 6-*endo-dig* cyclization by attack of the α-position of pyrrole to the triple bond to give intermediate **50**, finally **50**

undergoes deprotonation and aromatization furnishing the **51**. In path b, an electrophilic bisiodination of pyrrole **48** occurs with elemental iodine to give **52**, which undergoes iodine promoted 5-*endo-dig* cyclization and deprotonation to afford the **53** (Scheme 12).[11]

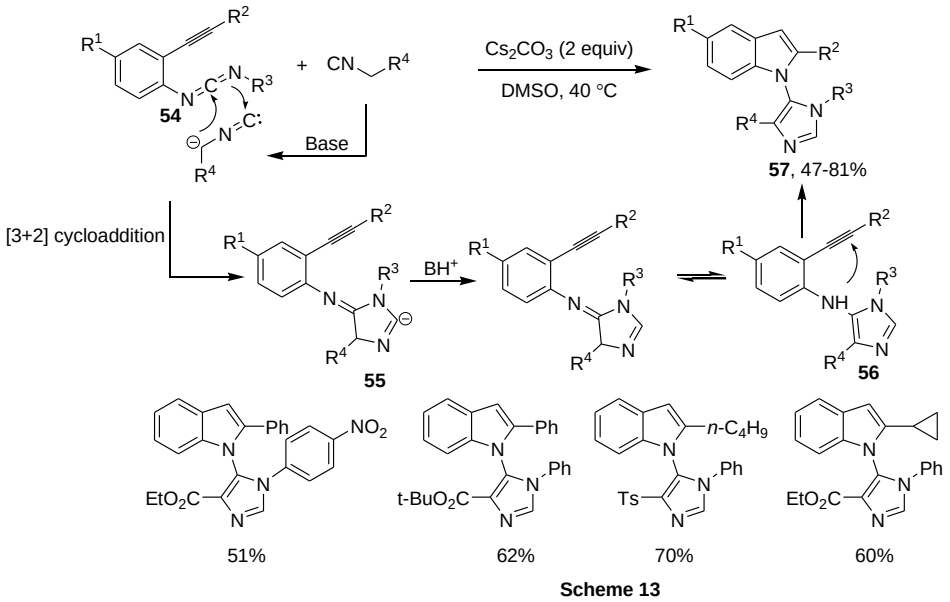


Scheme 12

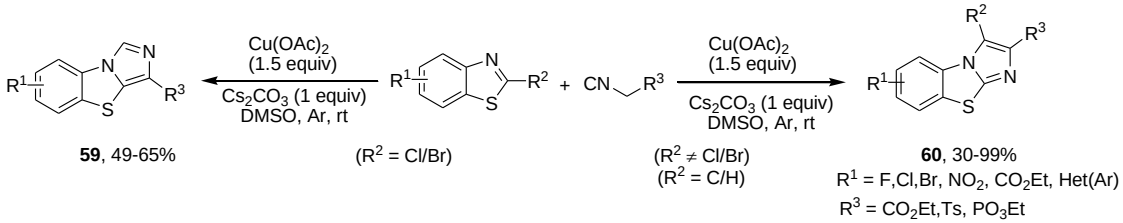
Cai and co-workers have reported an efficient route for the synthesis of indolyl imidazoles through a base-promoted tandem reaction of *N*-[2-(1-alkyl)phenyl]carbodiimide **57** with activated methylene isocyanides (Scheme 13). The reaction mechanism involves [3+2] cycloaddition of isocyanides to carbodiimide **54** providing the intermediate **55**, which undergoes protonolysis and isomerization to afford the aminoimidazolyl intermediate **56**. Finally intramolecular cyclization of intermediate **56** via nucleophilic attack of secondary amino group on acetylenic moiety yields the indolylimidazoles **57** (Scheme 13).[12]

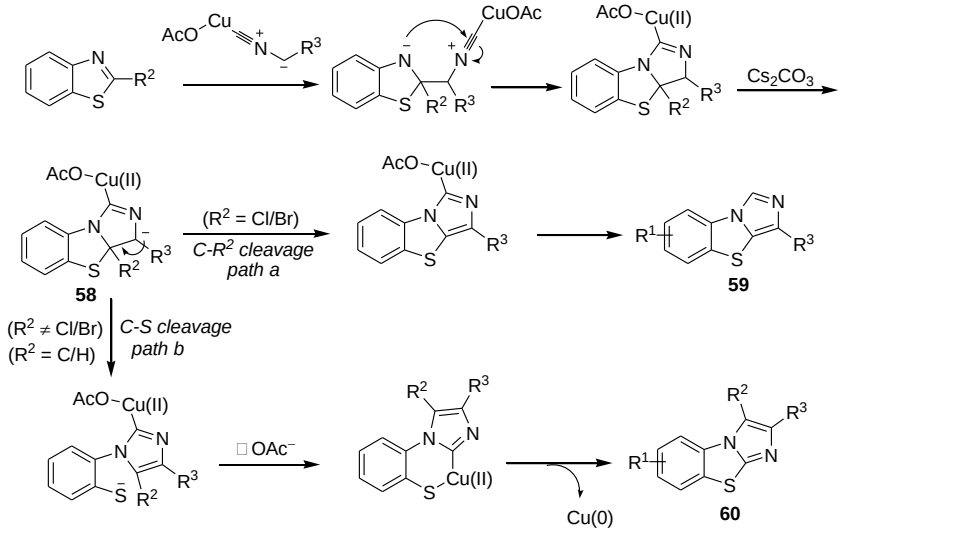
Recently, Zhu and co-workers have developed a tunable route to both isomers of benzo[*d*]imidazothiazole via copper-promoted cycloaddition of *α*-isocyanoacetate with benzothiazoles under mild reaction conditions (Scheme 14). The reaction mechanism involves copper catalyzed [3+2] cycloaddition of benzothiazoles and *α*-isocyanoacetate to give the intermediate **58**, which undergoes two different reaction pathways to afford the **59**

and **60**. When R^2 is Cl or Br the carbon-halogen bond breaks preferentially to give the benzo[*d*]imidazo[2,1-*b*]thiazoles **59** (path a), when R^2 is H or C, the corresponding C-H or C-C cleavage must overcome much higher energy barriers, and as a result, the weaker C-S bond cleaves to give the other isomeric benzo[*d*]imidazo[5,1-*b*]thiazoles **60** (path b) (Scheme 14).[13]



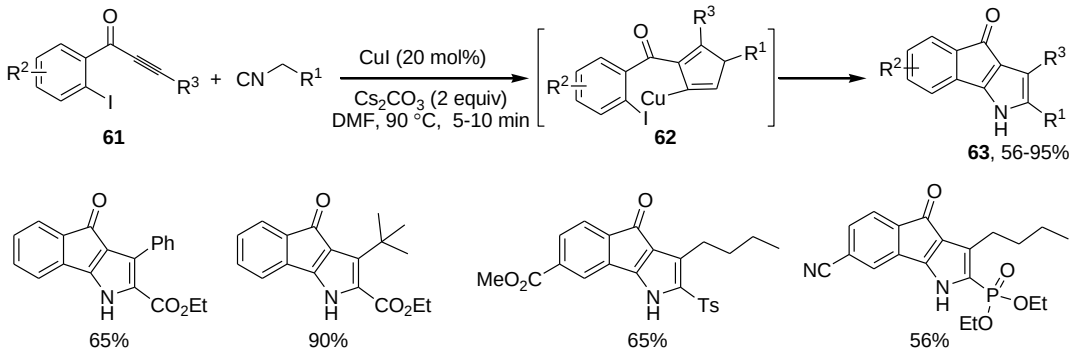
Scheme 13



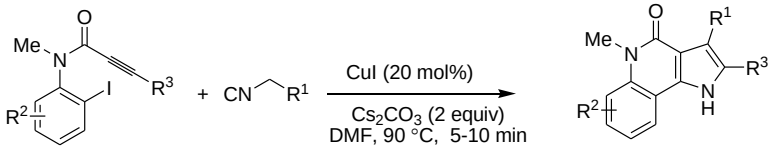


Scheme 14

Cai and co-workers have described a novel method for the synthesis of 4-oxo-indeno[1,2-*b*]pyrroles **63** via copper-catalyzed domino reaction of 1-(2-iodoaryl)-2-yn-1-ones **61** with isocyanides (Scheme 15A).[14a] In this reaction a highly active organocopper intermediate **62** is generated by the formal [3+2] cycloaddition of isocyanides to ynone moiety of **61**, which undergoes intramolecular insertion of Cu into the aryl C-I bond, followed by the tautomerization of the resulting intermediate affording the 4-oxo-indeno[1,2-*b*]pyrroles **63** (Scheme 15A). Further, the authors have extended this methodology for the synthesis of pyrrolo[3,2,*c*]quinolin-4-ones **65** from *N*-(2-haloaryl)propiolamides **64** and isocyanides (Scheme 15B).[14b]



Scheme 15A

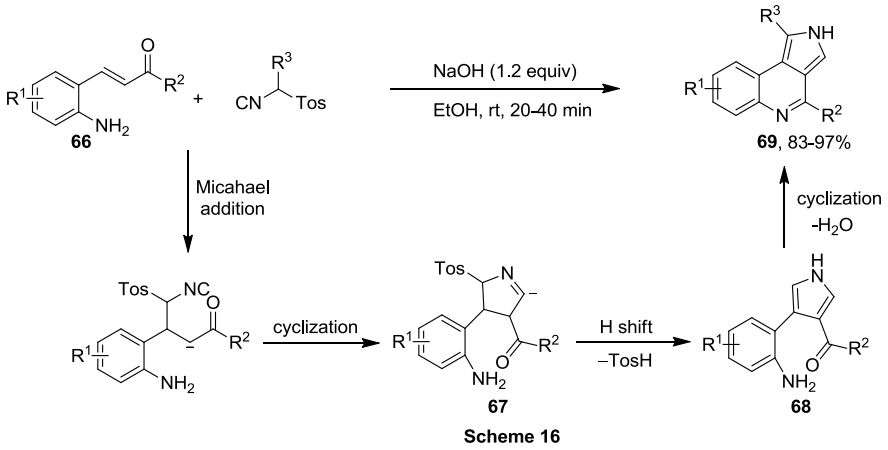


Scheme 15B

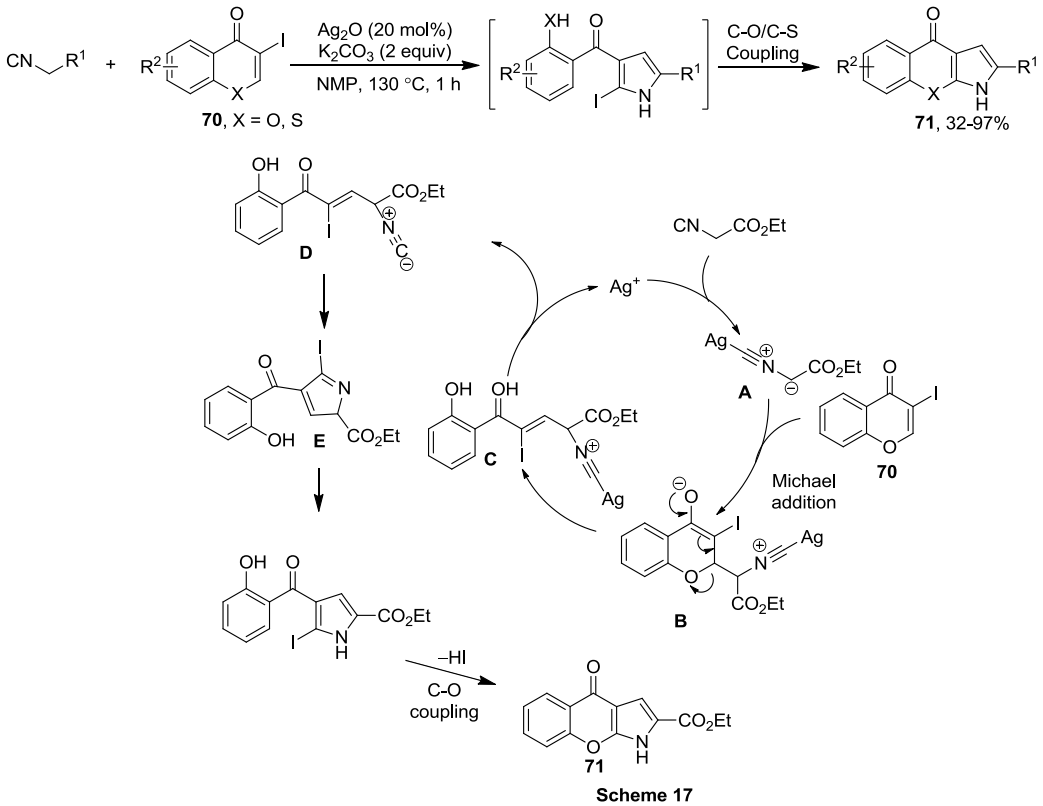
Xu and co-workers have reported a domino formal [3+2] cycloaddition reaction of aminochalcones **66** with tosylmethyl isocyanide derivatives for the synthesis of pyrrolo[3,4-*c*]quinolines **69** in high yields (Scheme 16). The domino process involves, Michael addition of TosMIC to aminochalcones **66**, followed by intramolecular cyclization affording the intermediate **67**. Now, **67** undergoes hydrogen shift and elimination of tosylic acid to give the pyrrole intermediate **68**, which on intramolecular condensation of ketone with amine to furnish pyrrolo[3,4-*c*]quinolines **69** (Scheme 16).[15]

Yang and co-workers have reported a novel and convenient approach to the synthesis of chromeno[2,3-*b*]pyrrolo-4(1*H*)-ones **71** via silver catalyzed cascade reaction of ethyl

isocyanoacetate with 3-iodochromones/thiochromones **70** (Scheme 17). The reaction involves the Michael addition of silver-isocyanide complex **A** to the activated double bond of chromone **70** affording intermediate **C** through the ring opening of complex **B**. The intermediate **D** along with **A** are generated from **C** to end the catalytic cycle. Now, insertion reaction of isocyanide to the C-I bond occurs in **D** to give the complex **E**, which would undergo 1,5 hydrogen shift followed by intramolecular C-O bond formation affords the chromeno[2,3-*b*]pyrrolo-4(1*H*)-ones (Scheme 17).[16]

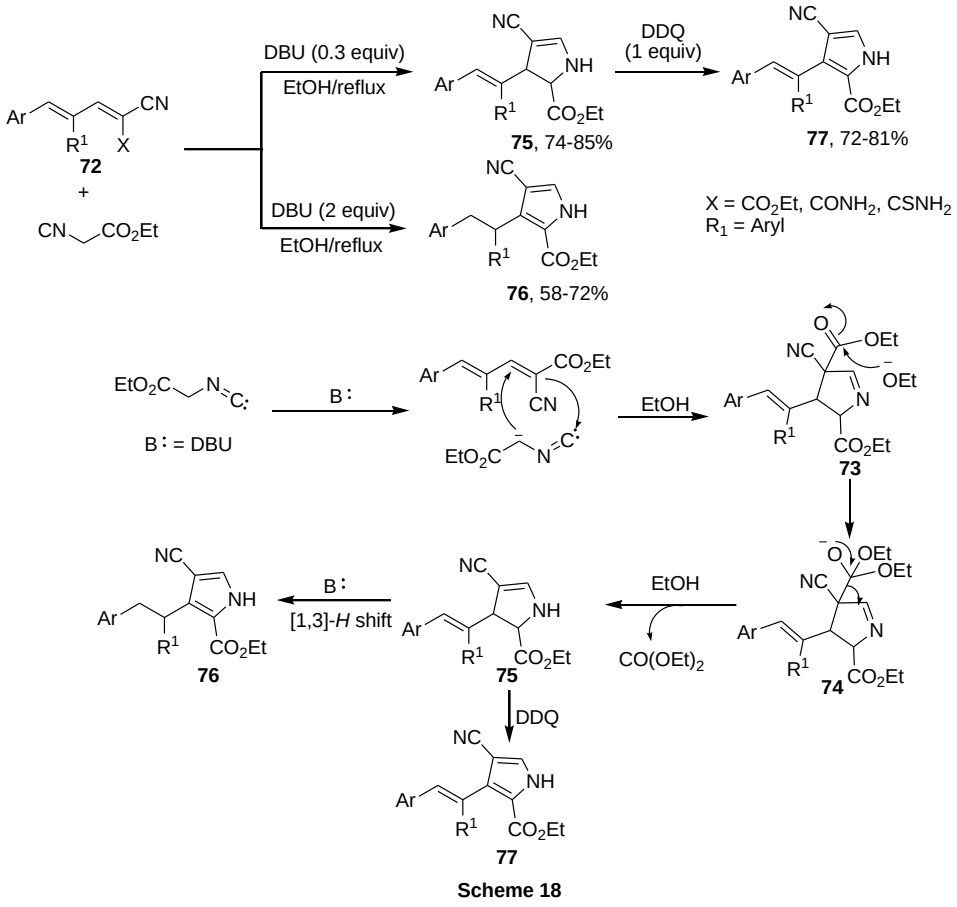


Scheme 16



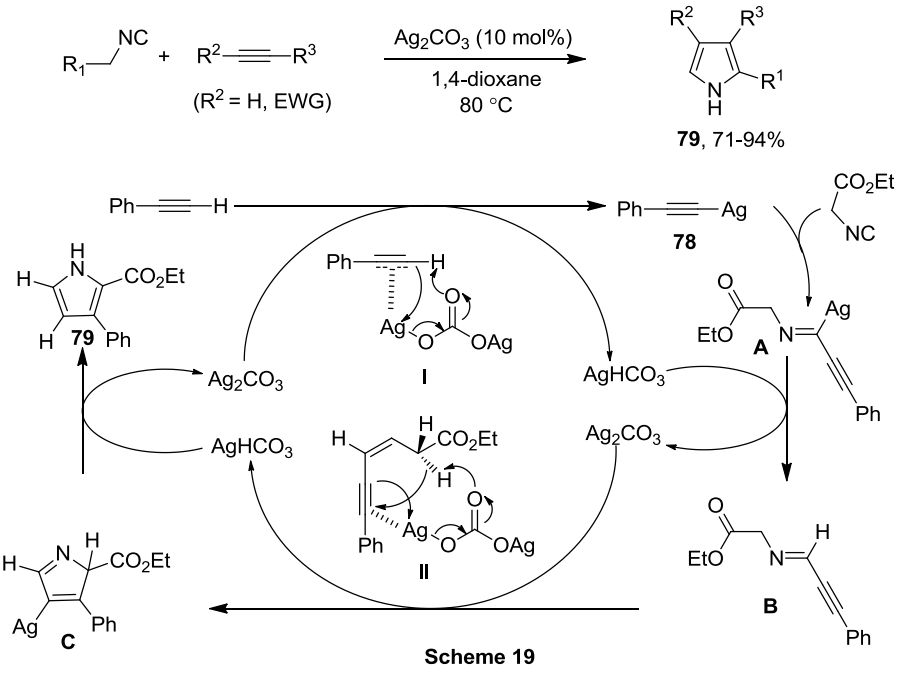
Scheme 17

Dong and co-workers have developed a facile and divergent synthesis of 2,3-dihydro-1*H*-pyrroles **75**, 3-alkyl-1*H*-pyrroles **76** and 3-alkenyl-1*H*-pyrroles **77** via formal [2+3] cycloaddition of 2,4-pentadinitriles **72** and ethyl isocyanoacetate by variation of reaction conditions (Scheme 18). In this reaction 3,4-dihydro-2*H*-pyrrole intermediate **73** is generated by formal [2+3] cycloaddition of 2,4-pentadinitriles **72**, with ethyl isocyanoacetate. Now by the attack of ethoxide ion on **73**, is converted into intermediate **74**, which on elimination of diethyl carbonate provides 2,3-dihydro-1*H*-pyrrole **75**. Finally, in presence of base (DBU) **75** undergoes double [1,3]-*H* shifts to afford 3-alkyl-1*H*-pyrroles **76**. In another way, **75** could be oxidized to 3-alkenyl-1*H*-pyrroles **77** by DDQ (Scheme 18).[17]

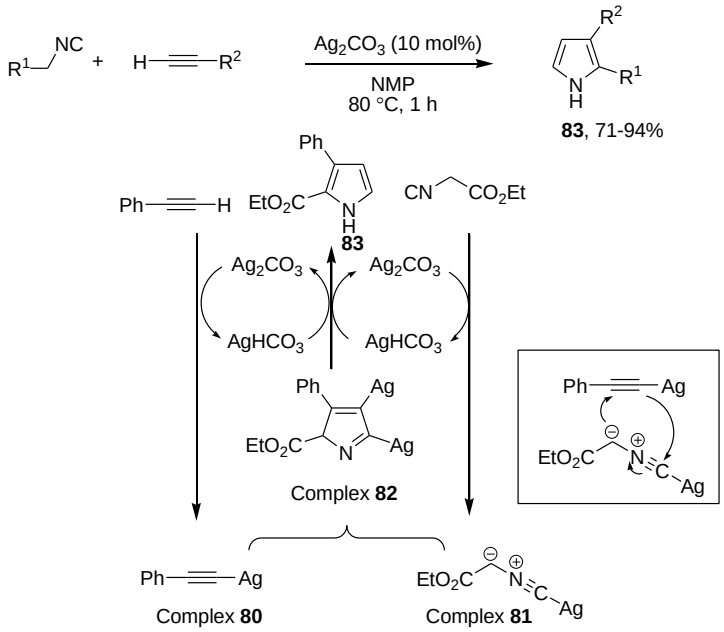


Recently, Bi and co-workers have developed a unique robust method for the synthesis of oligosubstituted pyrroles **79** via silver catalyzed cycloaddition of isocyanides with unactivated terminal alkynes in excellent yields (Scheme 19). The mechanism of reaction involves the formation of silver acetylide intermediate **78** through the agostic interaction (**I**)

between phenylacetylene and Ag_2CO_3. Now 1,1 insertion of the isocyanide into metal-carbon bond takes place, providing the acetylenic imido complex **A**, which readily undergoes protonolysis with $AgHCO_3$ to give the acetylinic imide **B**. Subsequently, a possible interaction (**II**) between intermediate **B** and Ag_2CO_3 occurs, yielding the metallic 2*H*-pyrrolenine species **C** through the intramolecular cyclization of acetylinc imide. Finally intermediate **C** undergoes 1,5-hydrogen shift and protonation by $AgHCO_3$ to give oligosubstituted pyrroles **79** (Scheme 19).[18]



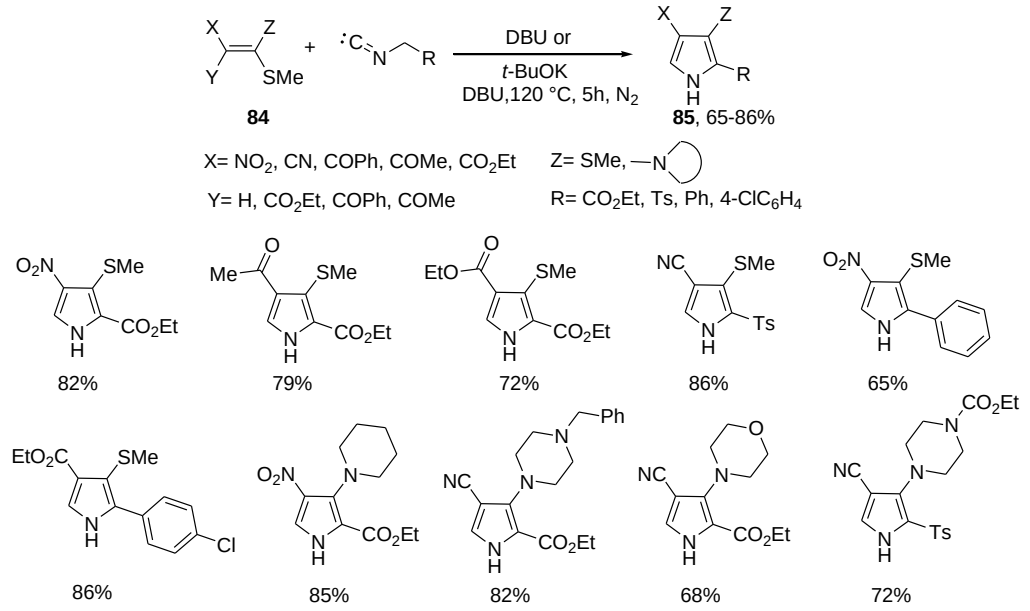
Similarly/Simultaneously, Lei and co-workers have developed silver catalyzed click synthesis of substituted pyrroles **83** via cycloaddition of isocyanides with unactivated terminal alkynes in good yields. In this reaction, both the silver-acetylide complex **80** and silver-isocyanide complex **81** would be generated from alkyne and isocyanide in presence of Ag_2CO_3. Now, cycloaddition between complex **80** and complex **81** would takes place to give complex **82**, and finally protonation and tautomerization of **82**, provides substituted pyrroles **83** (Scheme 20).[19]



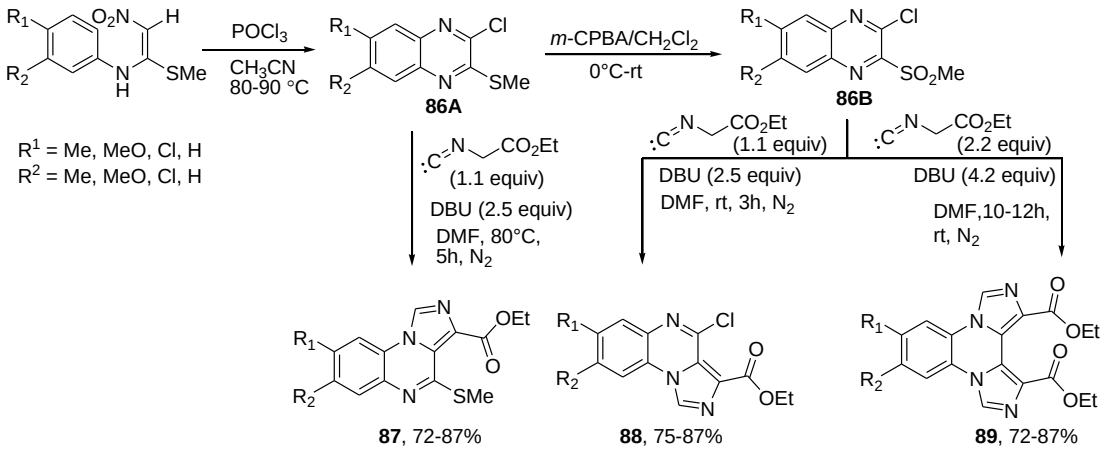
Scheme 20

Our research group has also utilized the activated methylene isocyanides for the synthesis of various five membered and fused heterocycles. Recently, our research group has developed an efficient highly regioselective synthesis of 2,3,4-trisubstituted pyrroles **85** via 1,3-dipolar cycloaddition of readily accessible polarized ketene *S*,*S*- and *N*,*S*-acetals **84** with activated methylene isocyanides in good yields (Scheme 21).[3] This methodology allows precise control over the introduction of a number of substituents and functionalities (tosyl, carbalkoxy, aryl, cyano, nitro, acetyl, benzoyl, cyclic amines) at the three positions of the pyrrole ring and it is the first example of the Barton-Zard reaction in which a nitro group is retained in the 4-position of the pyrrole ring (Scheme 21).[3]

Similarly, our research group has also developed an efficient route for regio- and chemoselective synthesis of substituted imidazo[1,5-*a*]quinoxaline-3-carboxylates **87** or **88**, and novel diimidazo[1,5-*a*:5',1'-*c*]quinoxalines **89** via base-induced cycloaddition of ethyl isocyanoacetate to unsymmetrically substituted 3-chloro-2-(methylthio)/2-(methylsulfonyl)quinoxalines **86A** and **86B** in excellent yields (Scheme 22).[20i]



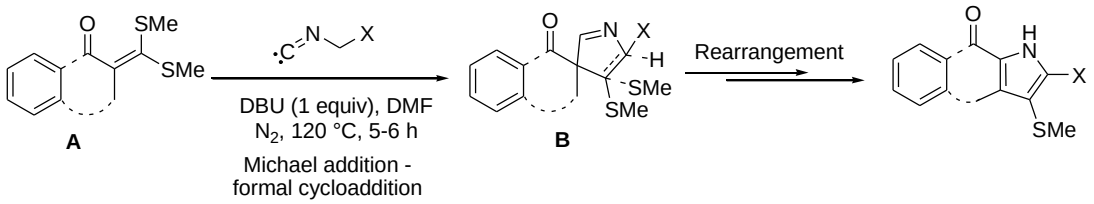
Scheme 21



Scheme 22

In an effort to extend this type of chemistry, we were prompted to examine the reaction of cyclic oxoketene dithioacetals **A** with various activated methylene isocyanides. At the outset, it was anticipated that the reaction of **A** with methylene isocyanide anions might yield first the strained spiroheterocycles such as **B**, which might undergo further reaction/rearrangement including cleavage of cyclic ketones (Scheme 23). Indeed, when few of the selected cyclic α-oxoketene dithioacetals reacted with various activated methylene isocyanides in the presence of DBU as base, the isolated products were found to be annulated pyrroles with diverse structural features, formed through a mechanistically interesting,

multistep domino process involving one carbon ring expansion of cyclic ketones as the key step.



Scheme 23

2.3 Results and Discussion

2.3.1 Introduction of Annulated Pyrroles

Oligo substituted pyrroles represent important class of five membered heterocycles, being basic constituents of numerous natural products,[21] potent pharmaceuticals[21,22] molecular sensors and devices.[22,23] Similarly, condensed pyrroles like indoloquinones and pyrroloquinolines have attracted considerable attention owing to the significant biological activity associated with such kind of compounds. Thus, naturally occurring mitomycin C (MMC) **90** bearing indolequinone pharmacophore represents an archetypal quinone bioreductive anticancer agent, which is in clinical use since 1970 for treatment of various types of tumors (Chart 2). [24,25] Another MMC analogue, E09 (apaziquone) **91** is in phase II clinical trial for bladder cancer,[26] whereas ES 936 **92**[27] and naturally occurring BE-10988 **93**[28] show promising activity against pancreatic cancer and as topoisomerase II inhibitor respectively. Similarly, increasing interest has been devoted in recent years to pyrrolo[3,2-*c*]quinolin-4-ones **94**[29] (Chart 3), since several of its analogue tricyclic systems are found in

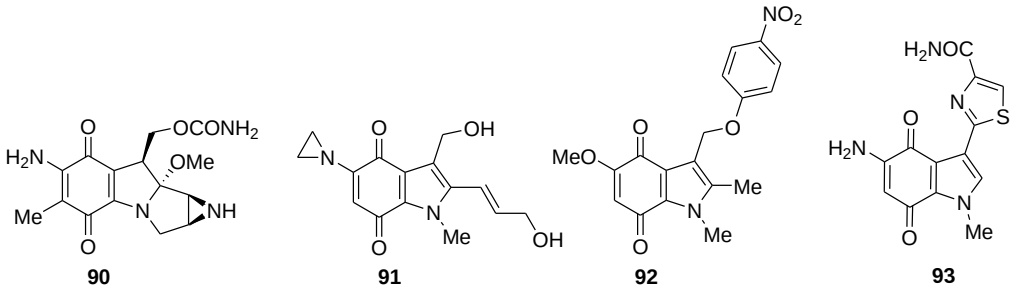


Chart 2. Biologically important indolequinones.

biologically important natural products such as martinelline **94a** and martinellic acid **94b**,[30-32] which are first naturally occurring non-peptide bradykinin B_1 and B_2 receptor antagonist to be identified.[30,32] Besides several derivatives of such a tricyclic angular heterocycle possess a wide spectrum of biological activities, most notably gastric (H^+/K^+) ATPase inhibitor,[33] antitumor,[34] hypotensive[35] and anti inflammatory[36] and others. A few examples of pyrrolo[3,4-*c*]quinolones **95** have also been reported,[37b] which are shown to display caspase inhibitor[37b,38a] and serotonergic[38b] activity. On the other hand, pyrrolo[2,3-*c*]quinolone framework **96** is not much explored,[39] although this structural framework is present in few alkaloids.[40] Among linear pyrroloquinolones, the corresponding pyrrolo[3,2-*b*]quinolone ring system **97** was previously unknown and has been recently synthesized by Witkop-Winterfeldt oxidation of γ-carboline derivatives (Chart 3).[41] A few of the conformationally constrained annulated pyrroles have been synthesized recently as potential HMG-CoA reductase inhibitors.[42] Therefore, in view of the importance and wide range of biological activities displayed by pyrrolo-fused heterocycles, development of new general synthetic strategies for this class of compounds is very much desirable.

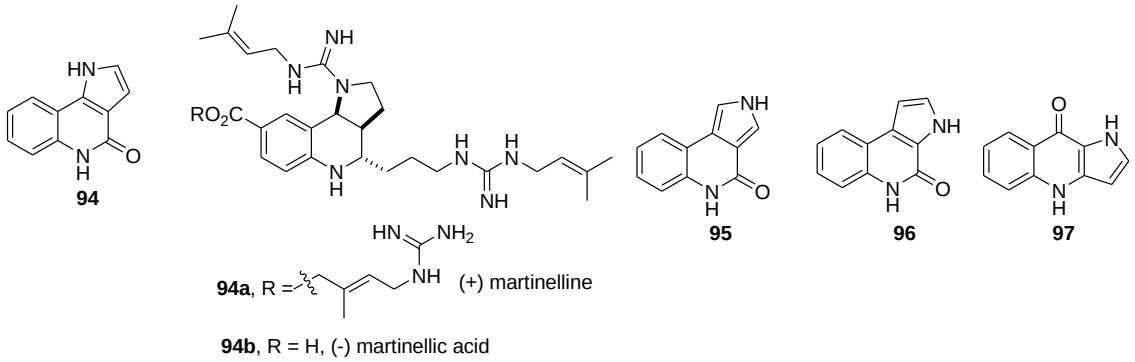


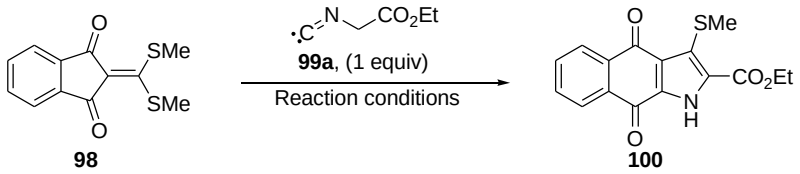
Chart 3. Structures of various pyrroloquinolones.

2.3.2 Optimization of Reaction Conditions for the Formation of 100

The reaction of cyclic ketene dithioacetal **98** derived from 1,3-indanedione with ethyl isocyanoacetate (**99a**) was first examined in the presence of various bases and solvents for optimization of reaction conditions leading to the formation of observed product/s (Table 1). Thus when **98** (1 equiv) was reacted with **99a** (1 equiv) in the presence of either DBU (1 equiv) or potassium *tert*-butoxide (1 equiv) as base in DMF at 120 °C, work-up of the reaction mixture furnished only one product, which was characterized as 2-[carbethoxy-3-

(methylthio)]-pyrrolo[2,3-*b*]napthoquinone **100** on the basis of its spectral and analytical data (Table 1, entries 1-2). With 0.5 equiv of DBU, the reaction was not complete even after 24 h under identical conditions (entry 3), whereas lowering the reaction temperature or use of CH_3CN as solvent, resulted in lower yields of **100** requiring longer time (entries 4-5). Similarly, use of other bases such as NaH, NaOH or Cs_2CO_3 also afforded **100** in lower yields (entries 6-8).

Table 1. Optimization of Reaction Conditions for the Formation of 100[a]

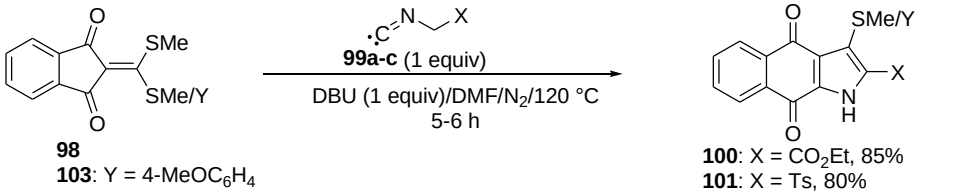


Entry	Base (equiv)	Solvent	T (°C)	t (h)	Yield (%)
1	DBU (1.0)	DMF	120	5	85
2	*t*BuOK (1.0)	DMF	120	6	72
3	DBU (0.5)	DMF	120	24	52 (31)[b]
4	DBU (1.0)	DMF	80	10	70
5	*t*BuOK (1.0)	CH_3CN	80	10	68
6	NaH (1.0)	DMF	120	6	70
7	NaOH (1.0)	DMF	80	12	63
8	CS_2CO_3 (1.0)	DMF	120	6	65

[a]Reaction conditions: **98** (0.5 mmol), **99a** (1 equiv), and base (1 equiv) in 2 mL of solvent under N_2 atmosphere. [b]Yield of recovered **98**.

2.3.3 Reaction of 98 and 103 with Activated Methylene Isocyanides 99a-c

Under identical conditions, the reaction of **98** with tosylmethyl isocyanide (**99b**) also furnished the corresponding tosyl substituted pyrrolonapthoquinone **101** in 80% yield (Scheme 24). The structure of **101** was further confirmed with the help of X-ray crystallographic data (Figure 1). A preliminary study of this work has been reported by Nimesh from our laboratory.[43] After the publication of this work, we have tried to improve the yields of **100** and **101**, we have observed the maximum of 85% and 80% repectively (Scheme 24).



98
103: Y = 4-$MeOC_6H_4$

100: X = CO_2Et, 85%
101: X = Ts, 80%
102: X = 4-ClC_6H_4, 65%
104: X = CO_2Et,
Y = 4-$MeOC_6H_4$, 75%

Scheme 24

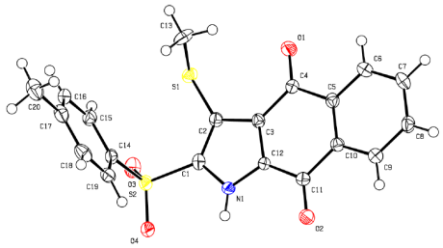


Figure 1. X-Ray crystal structure of **101**

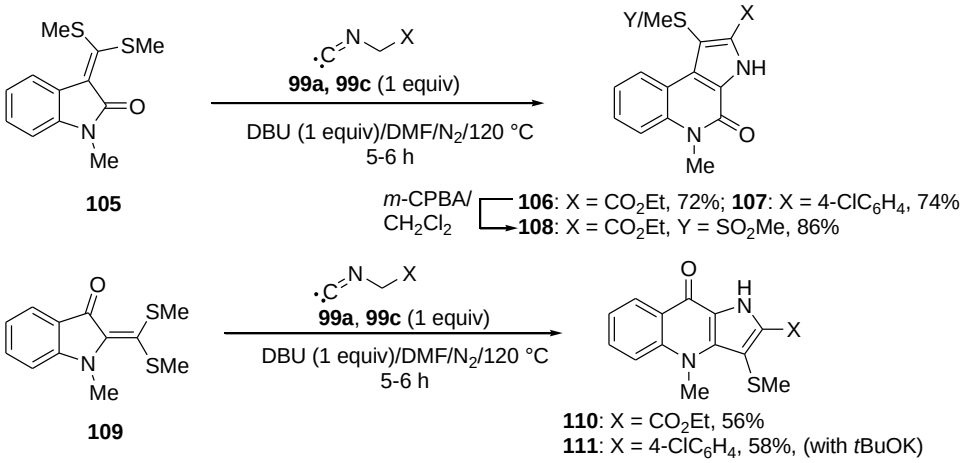
Similarly, further diversity at 2- position of the pyrrolonapthoquinone was introduced by reacting **98** with 4-chlorobenzyl isocyanide **99c** under similar conditions, affording 2-(4-chlorophenyl) substitiuted pyrrolonapthoquinone **102** in 65% yield. Interestingly, the 2-[(methylthio)-(4-methoxyphenyl)methylene]-1,3-indanedione **103** also reacted smoothly with ethyl isocyanoacetate under identical conditions, yielding substituted pyrrolonapthoquinone **104** in 75% yield (Scheme 24).

The generality and scope of this unusual rearrangement was examined by reacting a few selected cyclic ketene dithioacetals with various activated methylene isocyanides as shown in Schemes 25-28.

2.3.4 Synthesis of Substituted Pyrrolo[2,3-*c*]quinolones and Pyrrolo[3,2-*b*]quinolones

Thus, when the cyclic S,S-acetal **105** from 2-oxindole was subjected to reaction with methylene isocyanides **99a** and **99c** under optimized conditions, product analysis revealed that the reaction follows a similar pattern as **98**, furnishing the corresponding substituted pyrrolo[2,3-*c*]quinolones **106** and **107** in good yields (Scheme 25). The structure of **106** was further confirmed by X-ray crystallographic data of the product **108** (Figure 2) obtained by *m*-CPBA oxidation of **106**.

The reaction of ketene dithioacetal **109** from 3-oxindole with **99a** and **99c** similarly provided linearly substituted pyrrolo[3,2-*b*]quinolones **110-111** although in moderate yields because of the poor solubility of products in most of solvents (Scheme 25).



Scheme 25

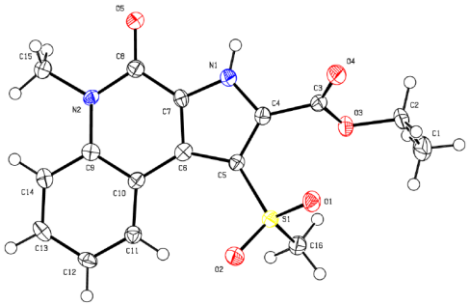
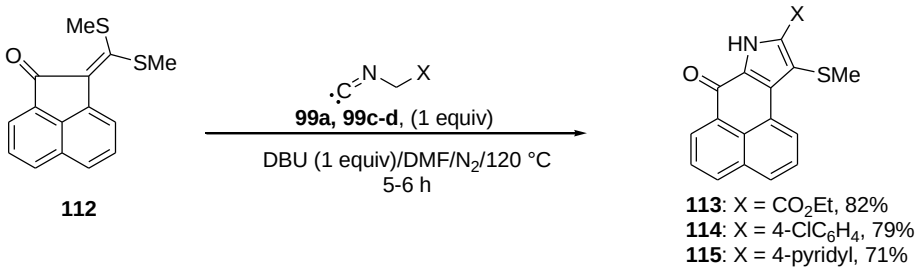


Figure 2. X-Ray crystal structure of **108**

2.3.5 Synthesis of Tetracyclic Indoles 113-115

The reaction was next extended to oxoketene dithioaceteal **112** derived from acenapthenone, which also followed a similar course, involving pyrrole annulation, along with ring expansion of the five membered cyclic ketone, thus providing novel tetracyclic indole derivatives **113-115** in high yields, on treatment with various methylene isocyanides **99a**, **99c** and 4-pyridylmethyl isocyanide **99d**, respectively, under identical conditions (Scheme 26). The structures of products, **113-114** were further confirmed by their X-ray crystallographic data (Figures 3 and 4).



Scheme 26

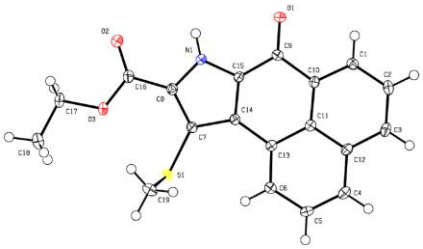


Figure 3. X-Ray crystal structure of **113**

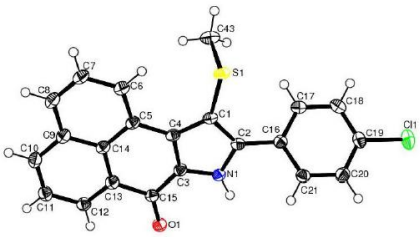
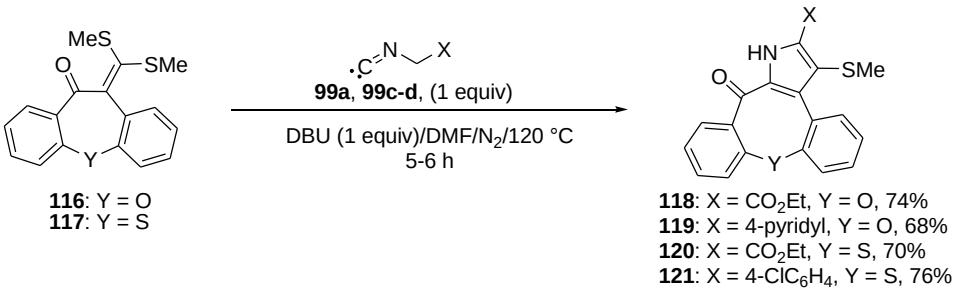


Figure 4. X-Ray crystal structure of **114**

2.3.6 Synthesis of Pyrroloe Annulated Dibenzoxacinone and Dibenzothiocinone

To further evaluate the generality and scope of this unexpected rearrangement for the construction of novel large ring pyrrole annulated heterocycles, the reaction of α-oxoketene dithioacetals **116-117**(from dibenzoxepin-10-one and dibenzothiepin-10-one, respectively), with various methylene isocyanides **99a**, **99c-d** was examined (Scheme 27). Indeed, to our delight, the reaction proceeded as expected, with the formation of tetracyclic pyrrolo-fused dibenzooxocinone and dibenzothiocinone derivatives **118-121** in high yields (Scheme 27). The structures of products, **118** and **121** were further confirmed by their X-ray crystallographic data (Figures 5 and 6).



Scheme 27

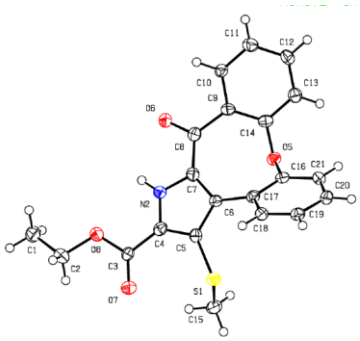


Figure 5. X-Ray crystal structure of **118**

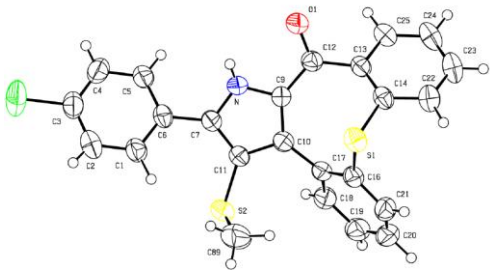
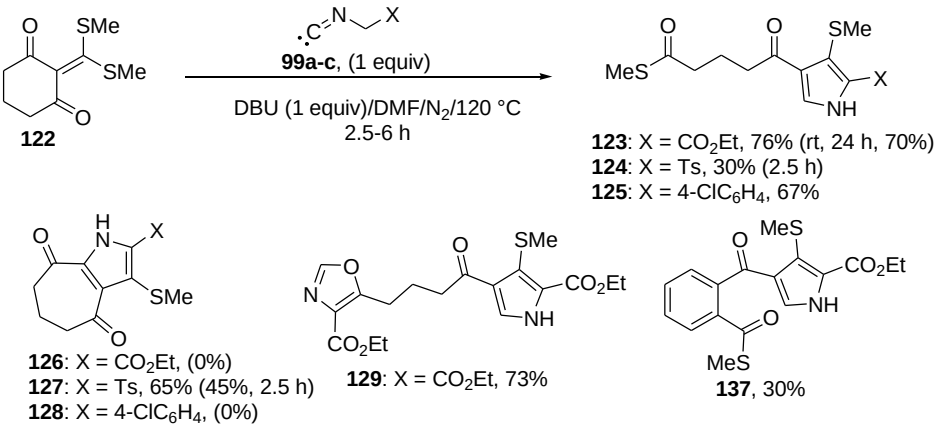


Figure 6. X-Ray crystal structure of **121**

2.3.7 Reaction of 122 with Methylene Isocyanides

Interestingly, the ketene dithioacetal **122** from 1,3-cyclohexanedione behaved differently, when reacted with one equiv of ethyl isocyanoacetate (**99a**) under identical conditions and no trace of ring expanded pyrrolo-fused 1,3-cycloheptanedione **126** was detected in the reaction mixture. The product isolated was characterized as 2-carbethoxy-3-(methylthio)-pyrrole-4-[(5-oxo)-pentane]carbothioate **123** (76%) (Scheme 28). On the other hand, treatment of **122** with tosylmethyl isocyanide **99b** (1 equiv) under identical conditions (DBU, DMF,120 ^{0}C, 6 h) furnished the pyrroloannulated cycloheptanedione **127** in 65% yield[37a], whereas, disrupting the reaction after 2.5 h, afforded the corresponding pyrrolocarbothioate **124** (30%) along with **127 (**45%) (Scheme 28). The reaction of **122** with



Scheme 28

4-chlorobenzyl isocyanide **99c** also yielded the corresponding 2-(4-chlorophenyl)pyrrole carbothioate **125** (67%) under identical conditions, with no trace of the corresponding

pyrroloannulated product **128**. Interestingly, when **122** was reacted with two equiv of ethyl isocyanoacetate **99a** in the presence of DBU (2 equiv) in DMF at 120 ^{0}C for 5 h, the isolated product was characterized as the four carbon tethered pyrrole/oxazole derivative **129** (73%) which is evidently formed by addition-cyclization of **99a** to carbothioate functionality in **123** (Scheme 28).

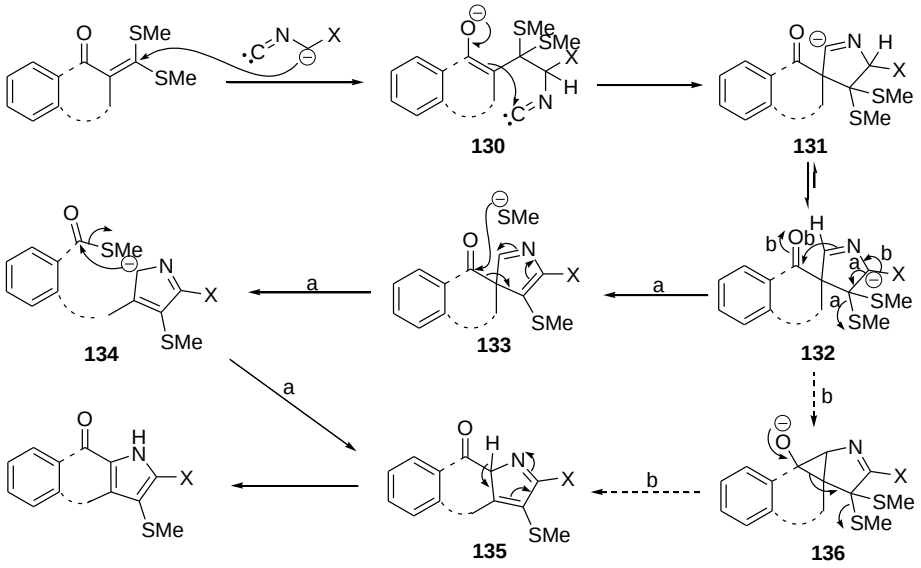
2.3.8 Proposed Mechanism for the Formation of Annulated Pyrroles

The probable mechanism for the formation of various annulated pyrroles from the corresponding cyclic oxoketene dithioacetals i**s** shown in the Scheme 29. Thus initial 1,4-conjugate addition of methylene isocyanide carbanion to oxoketene dithioacetal followed by intramolecular cyclization of the adduct **130**, initially furnishes the unstable spiropyrrolenine anion **131**, which equilibriates to more stable aza-allyl anion **132**. Subsequent elimination of methylthiolate anion in **132** affords the sterically constrained spiroketone intermediate **133** (route a), which appears to undergo facile ring cleavage by nucleophilic attack of methylthiolate anion on carbonyl group of **133** yielding *o*-substituted carbothioate intermediate **134** with a pendant pyrrolyl carbanion. Finally, intramolecular cyclization of the intermediate **134** *via* nucleophilic attack of pyrrolyl anion (at unsubstituted carbon) on carbothioate and elimination of methylthiolate anion affords the rearranged pyrrole annulated products in good yields (route a, Scheme 29).

The above mechanism was indeed confirmed by isolation of *o*-substituted benzocarbothioate intermediate **137** in 30% yield (along with pyrrolonaphthoquinone **100**, 50%), when ketene dithioacetal **98** was reacted with isocyanoacetate **99a** (1 equiv) in the presence of DBU (1 equiv) in DMF at room temperature for 24 h (Scheme 28). The intermediate carbothioate **137** was transformed completely into pyrrolonaphthoquinone **100** (77%), when the above reaction mixture was heated at 120 ^{o}C for 5 h (Scheme 28). Further, the formation of pyrrole-4-[(5-oxo)-pentane]carbothioate **123** in the reaction of ketene dithioacetal **122** (derived from 1,3-cyclohexanedione) with **99a** under identical conditions, supports the suggested mechanism.[37b]

In an alternate mechanism (route b), the spiroaza-allyl anion intermediate **132** can undergo intramolecular nucleophilic attack on the carbonyl group with the formation of

strained tricyclic alkoxide intermediate **136** which, on ring expansion along with elimination of methylthioate anion and isomerization of the resulting intermediate **135**, affords the observed pyrroloannulated products (route b)(Scheme 29).



Scheme 29

2.4 Conclusion

In summary, we have disclosed a novel domino process involving a base induced reaction of cyclic α-oxoketene dithioacetals with activated methylene isocyanides leading to the formation of a diverse range of annulated pyrroles along with a highly regioselective one carbon ring expansion of cyclic ketones as the key step. The method provides facile access to biologically important fused pyrroles with structures ranging from pyrrolonapthoquinones, angular and linear pyrroloquinolones, tetracyclic fused indoles and pyrrole annulated dibenzooxocinone and dibenzothiocinone derivatives. The new strategy further opens the possibility of rational design of direct synthesis of novel annulated pyrroles through the proper choice of substrates. Also, isolation of open chain pyrrole carbothioates such as **123-125** and 4-carbon tethered pyrroles/oxazoles **129** in the reaction of 1,3-cyclohexanone dithioacetal **122** with various methylene isocyanides under identical conditions (Scheme 6), makes this rearrangement more deserving and interesting for further detailed synthetic and mechanistic studies, which are currently underway in our laboratory.

2.5 Experimental Section

2.5.1 General Information. All the chemicals were commercially purchased and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using Merck TLC Silica gel plates and visualized with UV light. Flash chromatography was performed using Merck silica gel (100-200 mesh). Nuclear magnetic resonance spectra were recorded on (400 MHz) Fourier transform NMR spectrometer with $CDCl_3$ and DMSO-d_6 as solvent. Chemical shifts were reported in δ ppm (parts per million) using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-d_6 in ^{1}H-NMR, δ 77.16 for $CDCl_3$ and δ 39.5 for DMSO-d_6 in ^{13}C-NMR). Coupling constants were reported as J values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (double doublet), tt (triple triplet), td (triple doublet) m (multiplet) and br (broad). Infrared spectra were recorded with FTIR instrument and HRMS on Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. X-ray single crystal data of compounds **101**, **108**, **113**, **118** and **121** was collected on a Bruker Smart-CCD diffractometer using MoK_α radiation (λ = 0.71073 Å), at room temperature. For compound **114** crystal data was collected on Agilent Technologies Super NOVA CCD system. The structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares against F^2 using SHELXL-97 software. The crystal structure of **114** shows two independent molecules in an asymmetric unit.

The scanned copies of ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in supporting information of *Org. Lett.* **2013**, *15*, 5250.

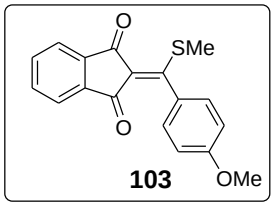
General Procedure and Characterization Data.

The desired methylene isocyanides **99a**,[44] **99c**,[45] and **99d**[46] were prepared according to the reported procedures, whereas the corresponding tosylmethyl isocyanide **99b** was commercially purchased. The corresponding known cyclic α-oxoketene dithioacetals **98**,[47] **105**,[48] **109**,[49] **112**[50] and **116**[51] were prepared according to the reported methods in the literature. The unknown oxoketene dithioacetal **117** and the known **122**[52] were prepared following the general procedure reported for oxoketene dithioacteals **112**,[50] **116**[51] from the corresponding dibenzothiepin-10-one[53] (2.0 g, 8.8 mmol) and 1,3-cyclohexanedione (5.0 g,

44.4 mmol) respectively using sodium hydride (100%) (2 equiv) as base in DMF. The procedure for preparation of unknown **103** and spectral/analytical data for **117**, **122**, **103** is given below.

Synthesis of 2-[(4-Methoxyphenyl)(methylthio)methylene]-2*H*-indene-1,3-dione (103). To a stirred, cooled (-78 °C) solution of **98** (0.50 g, 2.0 mmol) in dry THF (10 mL), 4-methoxyphenylmagnesium bromide (0.50 mL, 2.3 mmol) [freshly prepared from the 4-bromoanisole (0.28 mL, 2.3 mmol) and magnesium metal (82.8 mg, 3.45 mmol) in 10 mL of THF] was added slowly with the help of syringe. The reaction mixture was further stirred for 3 h at -78 °C (monitored by TLC), brought to room temperature and poured into saturated NH_4Cl (50 mL) solution and extracted with EtOAc (3 x 25 mL). The combined extracts were washed with water (2 x 30 mL), brine (30 mL), dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give crude product, which was purified by column chromatography over silica gel using EtOAc/hexane (1:9) as eluent.

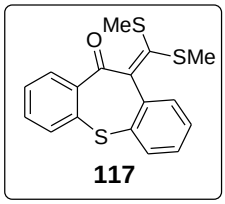
2-[(4-Methoxyphenyl)(methylthio)methylene]-2*H*-indene-1,3-dione (103). Yellow solid



103

(0.49 g, 80%): mp 147-149 °C; R_f 0.2 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2923, 1673, 1602, 1529, 1506, 1253, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.89 (m, 1H), 7.75-7.64 (m, 3H), 7.13 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 186.8, 174.2, 160.7, 140.9, 140.7, 134.52, 134.5, 129.0, 126.6, 124.6, 123.0, 122.6, 114.2, 55.4, 16.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_3S$ $[M + H]^+$ 311.0742, found 311.0736.

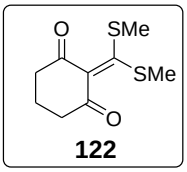
11-[bis(methylthio)methylene]-10,11-dihydrodibenzothiepin-10-one (117). Yellow solid



117

(2.24 g, 77%): mp 150-152 °C; R_f 0.65 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2916, 1646, 1425, 1289, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.20 (m, 1H), 7.64 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.57-7.54 (m, 1H), 7.40 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 7.39-7.31 (m, 3H), 7.23 (td, J = 7.6 Hz, 1.6 Hz, 1H), 2.40 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 148.1, 143.2, 141.6, 140.0, 137.4, 135.1, 132.5, 132.4, 132.0, 131.6, 130.7, 129.4, 128.1, 127.7, 18.2, 17.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}OS_3$ $[M + H]^+$ 331.0285, found 331.0275.

2-[Bis(methylthio)methylene]cyclohexane-1,3-dione (122). Yellow viscous liquid (6.07 g, 63%); R_f 0.25 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2936, 1616, 1375, 1301, 1158, 873; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (t, J = 6.6 Hz, 4H), 2.50 (s, 6H), 1.96 (quin, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 189.8, 125.6, 39.2, 21.9, 18.6; HRMS (ESI) *m/z* calcd for $C_9H_{13}O_2S_2$ $[M + H]^+$ 217.0357, found 217.0353.



122

General procedure for the reaction of cyclic α-oxoketene dithioacetals 98, 105, 109, 112, 116-117, 122 and 103 with activated methylene isocyanides: Synthesis of annulated pyrroles. To a stirred solution of appropriate α-oxoketene dithioacatal (0.5 mmol) and the corresponding activated methylene isocyanide **99** (0.5 mmol) in DMF (2 mL), DBU (0.07 mL, 0.5 mmol) was added dropwise under N_2 atmosphere. The reaction mixture was heated at 120 °C with constant stirring for 5-6 h (monitored by TLC). It was then poured into saturated NH_4Cl (50 mL) solution and extracted with EtOAc (3 x 25 mL), the combined extracts were washed with water (2 x 30 mL), brine (30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the crude products, which were purified by column chromatography over silica gel using EtOAc/hexane as eluent.

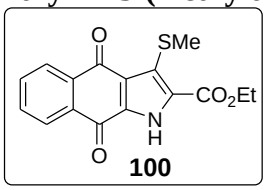
The ketene dithioacetal **109** remained unchanged, when reacted with 4-chlorobenzyl isocyanide **99c** in the presence of DBU under optimized conditions, whereas with potassium *tert*-butoxide (1equiv) as base, quinolone **111** was obtained in 58% yield.

The reaction of cyclic oxoketene dithioacetal **122** with **99a-c** furnished open chain pyrrole carbothioates **123-125** (along with **127** from TOSMIC) under these conditions. The carbothioate **123** was formed in comparable yield (70%), when **122** and **99a** were reacted at room temperature (24 h) under similar conditions.

When **122** was reacted with 2 equiv of **99a** (1.0 mmol) in presence of DBU (1.0 mmol) under above described conditions pyrrole/oxazole derivative **129** was formed exclusively. The same tetherd pyrrole/oxazole **129** was also obtained in parallel yield (78%), when the carbothioate **123** was reacted with one equiv of ethyl isocyanoacetate **99a** either *in situ*, without isolation, or separately, after purification, under identical conditions.

The spectral data of all newly synthesized annulated pyrroles **100-102**, **104**, **106-107**, **110-111**, **113-115**, **118-121**, **127**, carbothioates **123-125** and **129** and the intermediate **137** are given below.

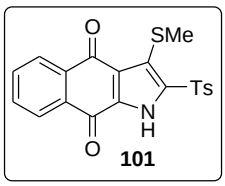
Ethyl 3-(methylthio)-4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indole-2-carboxylate (100).



100

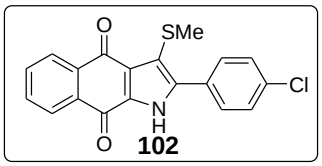
Obtained from **98** and isocyanide **99a**, yellow solid (134.0 mg, 85%): mp 172-174 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3230, 2918, 1690, 1668, 1303, 1265, 966; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (br s, 1H), 8.27 (dd, J =7.6 Hz, 1.2 Hz, 1H), 8.17 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.70 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.72 (td, J = 7.6 Hz, 1.2 Hz, 1H), 4.46 (q, J = 7.2 Hz, 2H), 2.64 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 171.1, 159.5, 135.1, 134.5, 133.9, 133.3, 132.6, 127.9, 127.7, 126.7, 126.6, 126.5, 62.1, 19.2, 14.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}NO_4S$ $[M]^+$ 315.0565, found 315.0559.

3-(Methylthio)-2-tosyl-1H-benzo[*f*]indole-4,9-dione (101). Obtained from **98** and isocyanide **99b**, yellow solid (158.7 mg, 80%): mp 291-293 °C; R_f 0.1 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3196, 1669, 1588, 1334, 1222; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (td, J = 7.0 Hz, 1.9 Hz, 2H), 8.03 (d, J = 8.1 Hz, 2H), 7.77 (dt, J = 7.0 Hz, 1.9 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 2.42 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 178.8, 175.2, 144.7, 137.6, 137.2, 134.6, 133.8, 133.1, 132.3, 129.5, 127.6, 126.5, 126.2, 125.9, 121.1, 100.1, 21.2, 18.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{15}NO_4S_2$ $[M]^+$ 397.0442, found 397.0446.



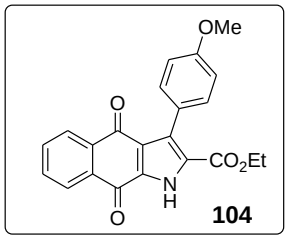
101

2-(4-Chlorophenyl)-3-(methylthio)-1*H*-benzo[*f*]indole-4,9-dione (102). Obtained from **98** and isocyanide **99c**, red solid (114.7 mg, 65%): mp 274-276 °C; R_f 0.55 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3220, 1668, 1639, 1587, 830; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.4 (br s, 1H), 8.12-8.07 (m, 2H), 7.84-7.81 (m, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.6, 174.5, 140.4, 133.9, 133.8, 133.7, 133.5, 133.4, 132.6, 131.2, 128.4, 128.3, 126.8, 126.4, 125.8, 114.7, 18.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{12}ClNO_2SNa$ $[M + Na]^+$ 376.0175, found 376.0180.

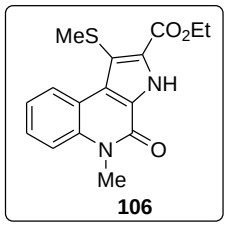


102

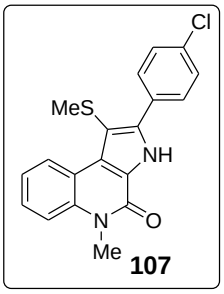
Ethyl 3-(4-methoxyphenyl)-4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indole-2-carboxylate (104). Obtained from **103** and isocyanide **99a**, yellow solid (140.6 mg, 75%): mp 200-202 °C; R_f 0.5 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3234, 2940, 1705, 1653, 1462, 1307, 1271, 977; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (br s, 1H), 8.20-8.15 (m, 2H), 7.75-7.69 (m, 2H), 7.44 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 176.6, 160.2, 159.8, 135.2, 134.4, 133.3, 133.27, 132.8, 131.8, 131.7, 127.5, 126.5, 125.2, 124.3, 123.3, 113.0, 61.7, 55.4, 14.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}NO_5Na$ $[M + Na]^+$ 398.1004, found 398.1004.



Ethyl 5-methyl-1-(methylthio)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-2-carboxylate (106). Obtained from **105** and isocyanide **99a**, white solid (0.67 g, 72%): mp 188-190 °C; R_f 0.3 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3153, 2359, 1697, 1660, 1273; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (br s, 1H), 9.36 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.55-7.50 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.40-7.36 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.49 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 155.3, 137.1, 129.9, 127.9, 126.4, 124.6, 123.8, 123.0, 119.2, 117.6, 115.3, 61.6, 29.7, 20.2, 14.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}N_2O_3S$ $[M]^+$ 316.0882, found 316.0875.

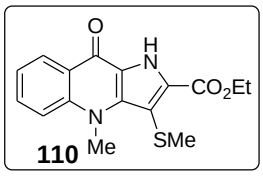


2-(4-Chlorophenyl)-5-methyl-1-(methylthio)-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one (107).[54] Obtained from **105** and isocyanide **99c**, white solid (130.9 mg, 74%): mp 328-330 °C; R_f 0.6 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3175, 2954, 1639, 1565, 1440, 1330, 822, 764; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (br s, 1H), 9.13 (dd, J =8.0 Hz, 1.6 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.61-7.51 (m, 4H), 7.38 (t, J = 7.2 Hz, 1H), 3.74 (s, 3H), 2.24 (s, 3H); HRMS (ESI) *m/z* calcd for $C_{19}H_{16}N_2ClOS$ $[M + H]^+$ 355.0672, found 355.0658.



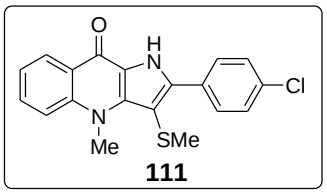
Ethyl 4-methyl-3-(methylthio)-9-oxo-4,9-dihydro-1*H*-pyrrolo[3,2-*b*]quinoline-2-carboxylate (110). Obtained from **109** and isocyanide **99a**, pale yellow solid (88.4 mg, 56%)[55]: mp 225-227 °C; R_f 0.5 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3230, 2942, 1710, 1675,

1460, 1307, 1275, 977; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (br s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.42-7.35 (m, 2H), 7.24-7.19 (m, 1H), 4.46 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 2.71 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 155.4, 144.2, 138.3, 136.1, 125.1, 124.8, 120.6, 118.0, 117.9, 116.6, 110.5, 61.5, 34.5, 15.7, 14.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}N_2O_3S$ $[M]^+$ 316.0882, found 316.0888.



110

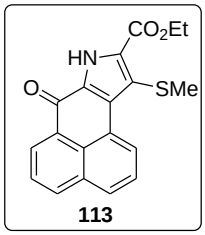
2-(4-Chlorophenyl)-4-methyl-3-(methylthio)-1*H*-pyrrolo[3,2-*b*]quinolin-9(4*H*)-one



111

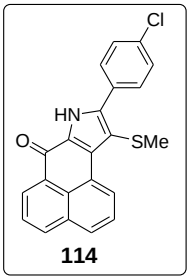
(111). Obtained from **109** and isocyanide **99c**, off-white solid (102.6 mg, 58%)[55]: mp 290-292 °C; R_f 0.25 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3115, 2917, 1628, 1574, 1528, 1271, 746; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (br s, 1H), 8.37 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.82-7.73 (m, 4H), 7.57 (d, J = 8.4 Hz, 2H), 7.32 (td, J = 7.6 Hz, 0.8 Hz, 1H), 4.52 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 143.2, 141.4, 137.1, 133.6, 131.5, 131.4, 129.6, 128.1, 125.5, 123.1, 121.0, 120.5, 115.1, 97.5, 32.3, 22.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{16}ClN_2OS$ $[M + H]^+$ 355.0672, found 355.0663.

Ethyl 10-(methylthio)-7-oxo-7,8-dihydronaphtho[1,8-*ef*]indole-9-carboxylate (113).



113

Obtained from **112** and isocyanide **99a** yellow solid (138.1 mg, 82%): mp 198-200 °C; R_f 0.3 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3174, 1704, 1638, 1290; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (br s, 1H), 9.62 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 8.77 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 8.24 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.99 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 4.49 (q, 7.2 Hz, 2H), 2.53 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 159.6, 136.3, 133.0, 130.2, 130.0, 129.8, 129.5, 129.2, 127.4, 127.1, 126.9, 126.2, 125.9, 119.3, 61.7, 19.9, 14.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{16}NO_3S$ $[M + H]^+$ 338.0851, found 338.0840.

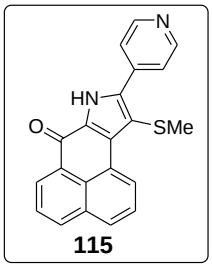


114

9-(4-Chlorophenyl)-10-(methylthio)naphtho[1,8-*ef*]indol-7(8*H*)-one (114). Obtained from **112** and isocyanide **99c**, yellow solid (148.1 mg, 79%): mp 298-300 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3169, 3081, 1632, 1610, 1551, 1442, 1294, 780; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (br s, 1H), 9.43 (d, J = 7.2 Hz, 1H), 8.65 (d, J = 7.2 Hz, 1H), 8.42 (d,

J = 8.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.91- 7.86 (m, 3H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.4Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.9, 142.5, 135.3, 133.4, 132.4, 131.1, 129.5, 129.4, 129.2, 129.1, 129.0, 128.8, 128.2, 126.9, 126.3, 125.8, 125.75, 109.3, 19.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{15}ClNOS$ $[M + H]^+$ 376.0563, found 376.0558.

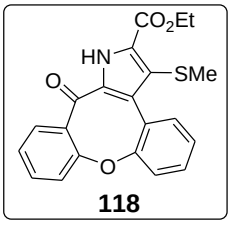
10-(Methylthio)-9-(pyridin-4-yl)naphtho[1,8-*ef*]indol-7(8*H*)-one (115). Obtained from



115

112 and isocyanide **99d**, yellow solid (121.4 mg, 71%): mp 330-332 °C; R_f 0.4 (4:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3182, 2903, 1631, 1602, 1573, 1293, 969, 779; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.23 (br s, 1H), 9.42 (dd, *J* = 6.4 Hz, 1.2 Hz, 1H), 8.73 (dd, *J* = 4.4 Hz, 1.6 Hz, 2H), 8.65 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 8.42 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.91 (dd, *J* = 4.4 Hz, 1.6 Hz, 2H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 149.6, 140.5, 137.6, 135.6, 132.5, 129.6, 129.5, 129.2, 129.1, 127.0, 126.4, 125.9, 125.6, 123.4, 110.7, 19.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}N_2OS$ $[M + H]^+$ 343.0905, found 343.0894.

2-Carbethoxy-3-(methylthio)-pyrrolo-[2,3-*e*]-dibenzo[*b,g*]-oxocin-10-one (118). Obtained

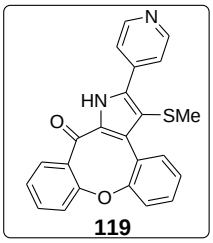


118

from **116** and isocyanide **99a**, white solid (140.2 mg, 74%): mp 146-148 °C; R_f 0.3 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3424, 3284, 2918, 1714, 1688, 1600, 1467, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (br s, 1H), 8.04 (dd, *J*= 8.0 Hz, 1.6 Hz, 1H), 7.80 (dd, *J* = 7.4 Hz, 1.6 Hz, 1H), 7.60 (td, *J* = 7.4 Hz, 1.6 Hz, 1H), 7.52-7.46 (m, 2H), 7.36 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.31-7.20 (m, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.22 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 160.7, 159.2, 157.6, 135.4, 132.7, 132.5, 131.5, 130.4, 129.9, 127.9, 126.7, 125.8, 125.6, 124.9, 123.7, 123.0, 121.7, 61.4, 19.9, 14.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}NO_4S$ $[M + H]^+$ 380.0957, found 380.0954.

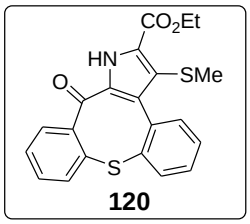
2-(4-Pyridyl)-3-(methylthio)-pyrrolo-[2,3-*e*]-dibenzo[*b,g*]-oxocin-10-one (119). Obtained from **116** and isocyanide **99d**, yellow solid (130.5 mg, 68%): mp 238-240 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 2930, 1595, 1449, 1284, 1087; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (br s, 1H), 8.72 (br s, 2H), 8.07 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.98 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.85 (br d, *J* = 3.6 Hz, 2H), 7.61 (td, *J* = 8.2 Hz, 1.6 Hz, 1H), 7.54 (dd, *J* = 5.6 Hz,

1.2 Hz, 1H) 7.52 (dd, *J* = 5.6 Hz, 1.2 Hz, 1H), 7.41 (td, *J* = 8.2 Hz, 1.6 Hz, 1H), 7.31-7.26 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 160.6, 157.8, 150.4, 138.4, 137.3, 135.3, 132.7, 132.1, 131.7, 130.8, 130.1, 127.9, 126.0, 125.99, 125.1, 123.8, 122.2, 122.0, 116.8, 19.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{17}N_2O_2S$ $[M + H]^+$ 385.1011, found 385.1004.



119

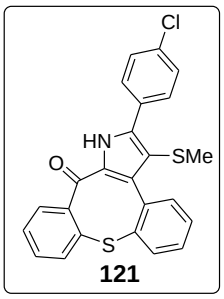
2-Carbethoxy-3-(methylthio)-pyrrolo-[2,3-*e*]-dibenzo[*b,g*]-thiocin-10-one (120).



120

Obtained from **117** and isocyanide **99a**, pale yellow solid (138.2 mg, 70%): mp 148-150 °C; R_f 0.4 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3440, 2918, 1712, 1697, 1616, 1286, 1234, 1205, 1050, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (br s, 1H), 7.86 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.75 (dd, *J* = 2.8 Hz, 2.0 Hz, 1H), 7.73 (dd, *J* = 2.8 Hz, 2.0 Hz, 1H), 7.63 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.43 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.36 (tt, *J* = 7.2 Hz, 1.2 Hz, 2H), 7.32 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 2.11 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 159.4, 141.8, 138.3, 137.9, 136.1, 135.7, 134.6, 133.2, 133.1, 132.6, 132.4, 131.4, 129.4, 129.3, 128.4, 127.2, 123.9, 61.6, 19.8, 14.6; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}NO_3S_2$ $[M + H]^+$ 396.0728, found 396.0726.

2-(4-Chlorophenyl)-3-(methylthio)-pyrrolo-[2,3-*e*]-dibenzo[*b,g*]-thiocin-10-one (121).

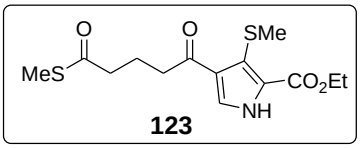


121

Obtained from **117** and isocyanide **99c**, yellow solid (164.5 mg, 76%): mp 235-237 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3286, 2926, 2852, 1734, 1587, 1462, 1396, 1293; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (br s, 1H), 7.88 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.81 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.74 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.68 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.41-7.39 (m, 1H), 7.38-7.34 (m, 2H), 7.32-7.30 (m, 1H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 142.4, 138.8, 138.3, 137.7, 136.7, 135.6, 135.0, 134.6, 132.9, 132.7, 132.67, 132.2, 132.16, 129.7, 129.5, 129.3, 129.1, 129.08, 128.4, 116.0, 19.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{17}ClNOS_2$ $[M + H]^+$ 434.0440, found 434.0423.

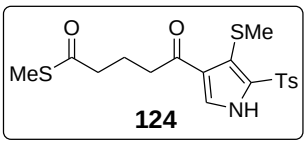
Ethyl 3-(methylthio)-4-(5-(methylthio)-5-oxopentanoyl)-1*H*-pyrrole-2-carboxylate (123). Obtained from **122** and isocyanide **99a**, yellow solid (125.0 mg, 76%): mp 63-65 °C; R_f 0.5 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3278, 2933, 1690, 1535, 1447, 1374, 1256, 1175, 933,

771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (br s, 1H), 7.52 (d, J = 3.6 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 3.00 (t, J = 7.2 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 2.46 (s, 3H), 2.30 (s, 3H), 2.08 (quin, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 195.1, 160.1, 128.2, 126.9, 125.0, 124.0, 61.3, 43.0, 39.9, 20.4, 20.1, 14.5, 11.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}NO_4S_2Na$ $[M + Na]^+$ 352.0653, found 352.0641.



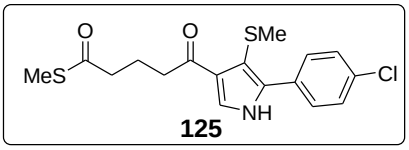
123

S-Methyl 5-(4-(methylthio)-5-tosyl-1*H*-pyrrol-3-yl)-5-oxopentanethioate (124). Obtained from **122** and isocyanide **99b**, semi-solid (61.6 mg, 30%); R_f 0.35 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3269, 2929, 1671, 1336, 1142, 1079; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (br s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 3.6 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 2.19 (s, 3H), 2.04 (quin, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 194.4, 145.0, 137.9, 133.3, 129.8, 128.6, 128.2, 126.6, 120.4, 42.9, 39.4, 21.8, 20.14, 20.12, 11.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NO_4S_3$ $[M + H]^+$ 412.0711, found 412.0707.



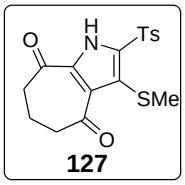
124

S-Methyl 5-(5-(4-chlorophenyl)-4-(methylthio)-1*H*-pyrrol-3-yl)-5-oxopentanethioate (125). Obtained from **122** and isocyanide **99c**, white solid (122.9 mg, 67%)[56]: mp 105-107 °C; R_f 0.4 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3271, 2926, 1660, 1492, 1381, 1094, 1013, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 3.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 2.10 (quin, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 194.9, 135.3, 134.2, 130.0, 129.5, 129.0, 127.4, 125.4, 112.8, 43.2, 39.2, 20.7, 20.3, 11.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}ClNO_2S_2$ $[M + H]^+$ 368.0546, found 368.0543.



125

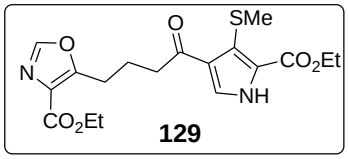
3-(Methylthio)-2-tosyl-6,7-dihydrocyclohepta[*b*]pyrrole-4,8(1*H*,5*H*)-dione (127). Obtained from **122** and isocyanide **99b**, yellow solid (117.9 mg, 65%)[56]: mp 148-150 °C; R_f 0.3 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3290, 2938, 1720, 1660, 1440, 1366,1256, 1175; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (br s,



127

1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.90-2.87 (m, 4H), 2.43 (s, 3H), 2.20 (s, 3H), 2.12-2.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 191.2, 145.7, 137.5, 136.8, 131.8, 129.9, 128.8, 127.8, 122.4, 44.7, 42.2, 21.9, 19.9, 18.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}NO_4S_2$ $[M + H]^+$ 364.0677, found 364.0677.

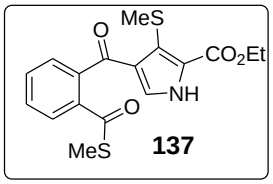
Ethyl 5-(4-(5-(ethoxycarbonyl)-4-(methylthio)-1*H*-pyrrol-3-yl)-4-oxobutyl)oxazole-4-carboxylate (129). Obtained from **122** and isocyanide **99a**, white solid (143.8, mg, 73%): mp



129

95-97 °C; R_f 0.3 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3278, 2918, 2867, 1705, 1653, 1528, 1433, 1367, 1256, 1175; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 7.77 (s, 1H), 7.47 (d, *J* = 3.6 Hz, 1H) 4.40 (q, *J* = 7.2 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.17 (t, *J* = 7.2 Hz, 2H) 3.02 (t, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 2.13 (quin, *J* = 6.0 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 162.2, 160.0, 159.6, 149.3, 128.5, 127.5, 126.4, 125.1, 123.8, 61.3, 61.2, 40.1, 25.4, 22.3, 20.2, 14.5, 14.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{23}N_2O_6S$ $[M + H]^+$ 395.1277, found 395.1275.

Ethyl 4-(2-(carbonyl)benzoyl)-3-(methylthio)-1*H*-pyrrole-2-carboxylate (137). Obtained



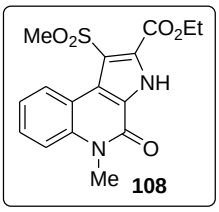
137

from **98** and isocyanide **99a**, semi-solid (54.5 mg, 30%); R_f 0.2 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3293, 2933, 1729, 1660, 1535, 1440, 1367, 1256, 1175,926; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (br s, 1H), 7.89 (dd, *J* =7.6 Hz, 1.2 Hz, 1H), 7.57 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.53 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.43 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.48 (s, 3H), 2.35 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 190.7, 160.2, 140.7, 137.2, 132.0, 129.9, 129.0, 128.4, 128.0, 125.6, 124.6, 61.3, 19.4, 14.5, 12.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}NO_4S_2$ $[M + H]^+$ 364.0677, found 364.0663.

***m*-CPBA oxidation of 106 to 108.** A solution of *m*-CPBA (0.70 g, 4.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of **106** (0.56 g, 1.8 mmol), in CH_2Cl_2 (10 mL) at 0 °C under N_2 atmosphere and stirring was continued for 4 h (monitored by TLC). The reaction mixture was poured into ice cooled water (100 mL), extracted with $CHCl_3$ (3 x 50 mL), washed with water (2 x 50 mL), 5% $NaHCO_3$ (2 x 50 mL), brine (1 x 50 mL), dried

(Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude **108**, which was purified by column chromatography over silica gel using EtOAc/hexane (2:3) as eluent.

Ethyl 5-methyl-1-(methylsulfonyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-2-carboxylate (108). White solid (0.54 g, 86%): mp 224-226 °C; R_f 0.3 (6:4 EtOAc:hexane);



108

IR (KBr, cm^{-1}) 3101, 2987, 1743, 1634, 1299; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 8.81(br s, 1H), 7.42 (dd, J = 6.96 Hz, 1.36 Hz, 2H), 7.36 (d, J = 7.56 Hz, 1H), 7.24 (d, J = 6.9 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 3.69 (s, 3H), 3.26 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 160.1, 154.1, 136.8, 134.4, 127.8, 126.2, 123.2, 122.5, 122.1, 118.1, 115.9, 114.7, 62.0, 44.2, 28.8, 13.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}N_2O_5SNa$ $[M + Na]^+$ 371.0678, found 371.0667.

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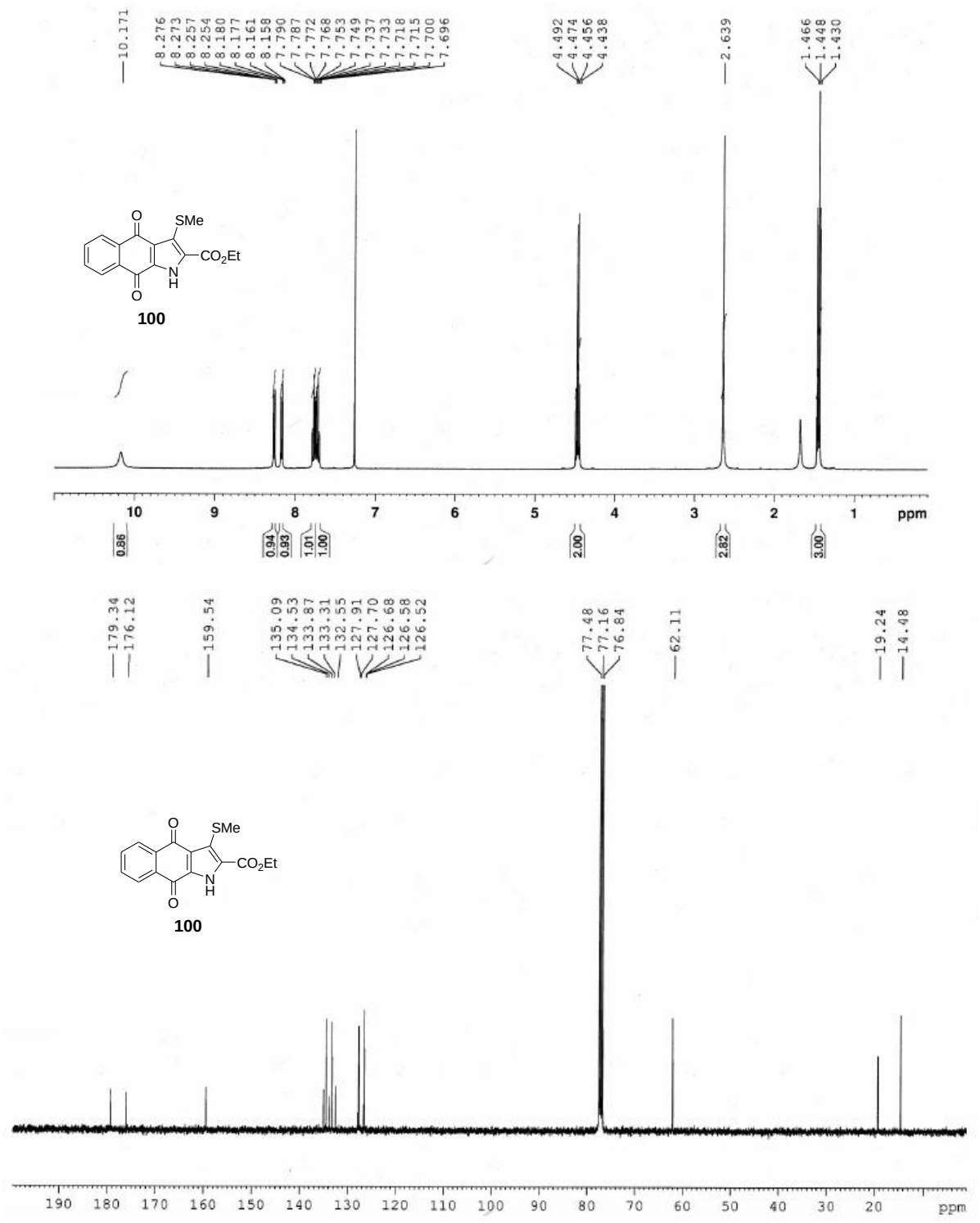
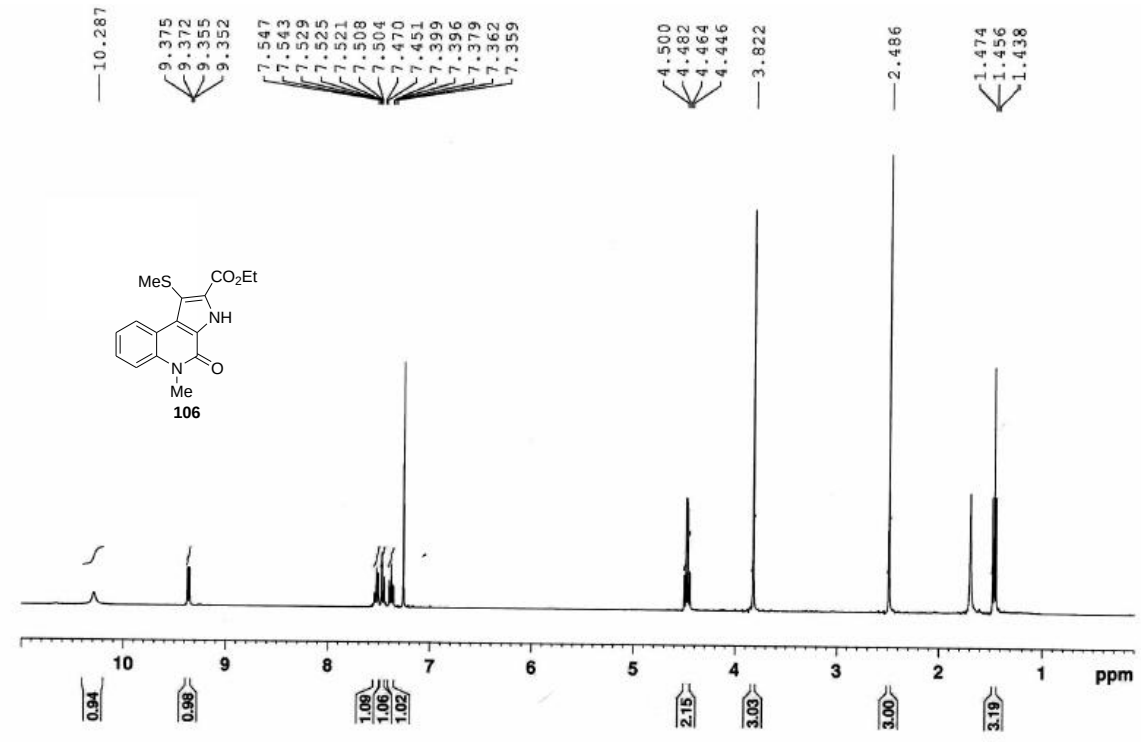
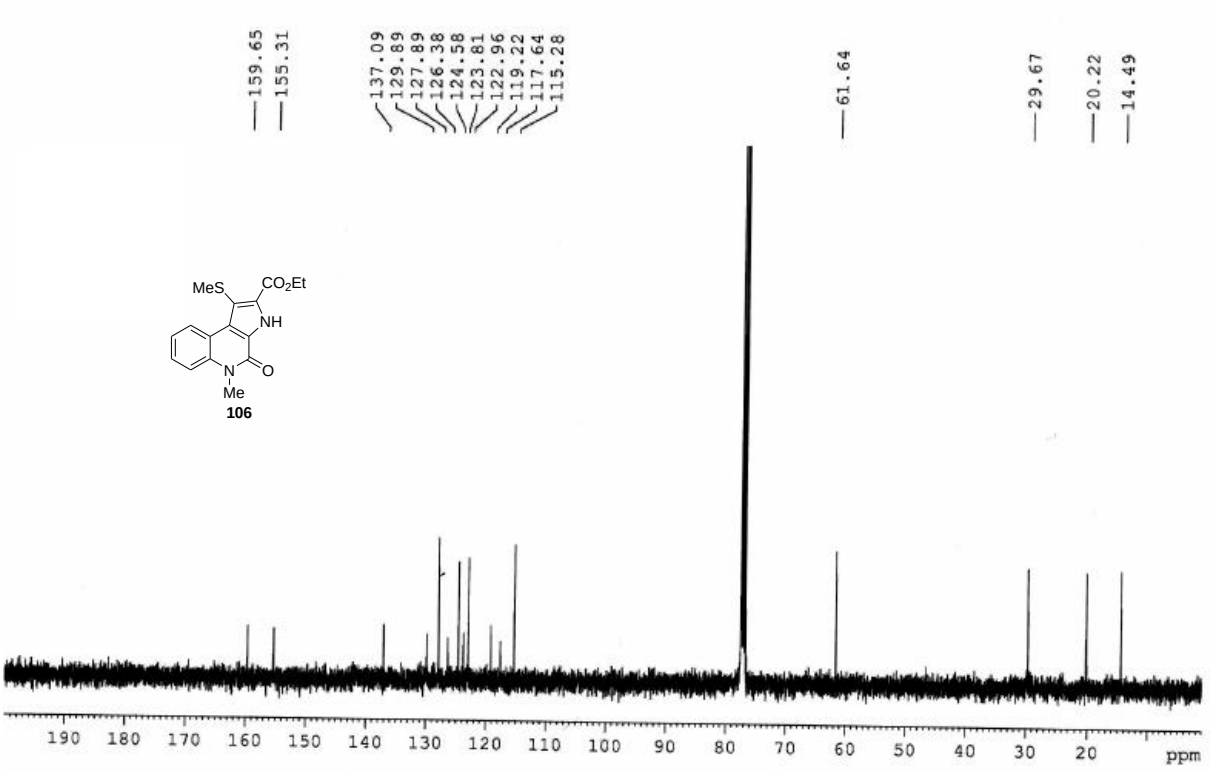
54. Because of poor solubility of **107** in various solvents, its ^{13}C NMR spectrum could not be recorded.
55. Moderate isolated yields of products **110**-**111** are due to their poor solubility in various solvents, although reaction mixture showed complete conversion to products (TLC).
56. Attempts to increase the yields of products **125** or **127** by continuing the reaction for longer time (20 h) resulted in decomposition of products.

2.7 Representative Spectra

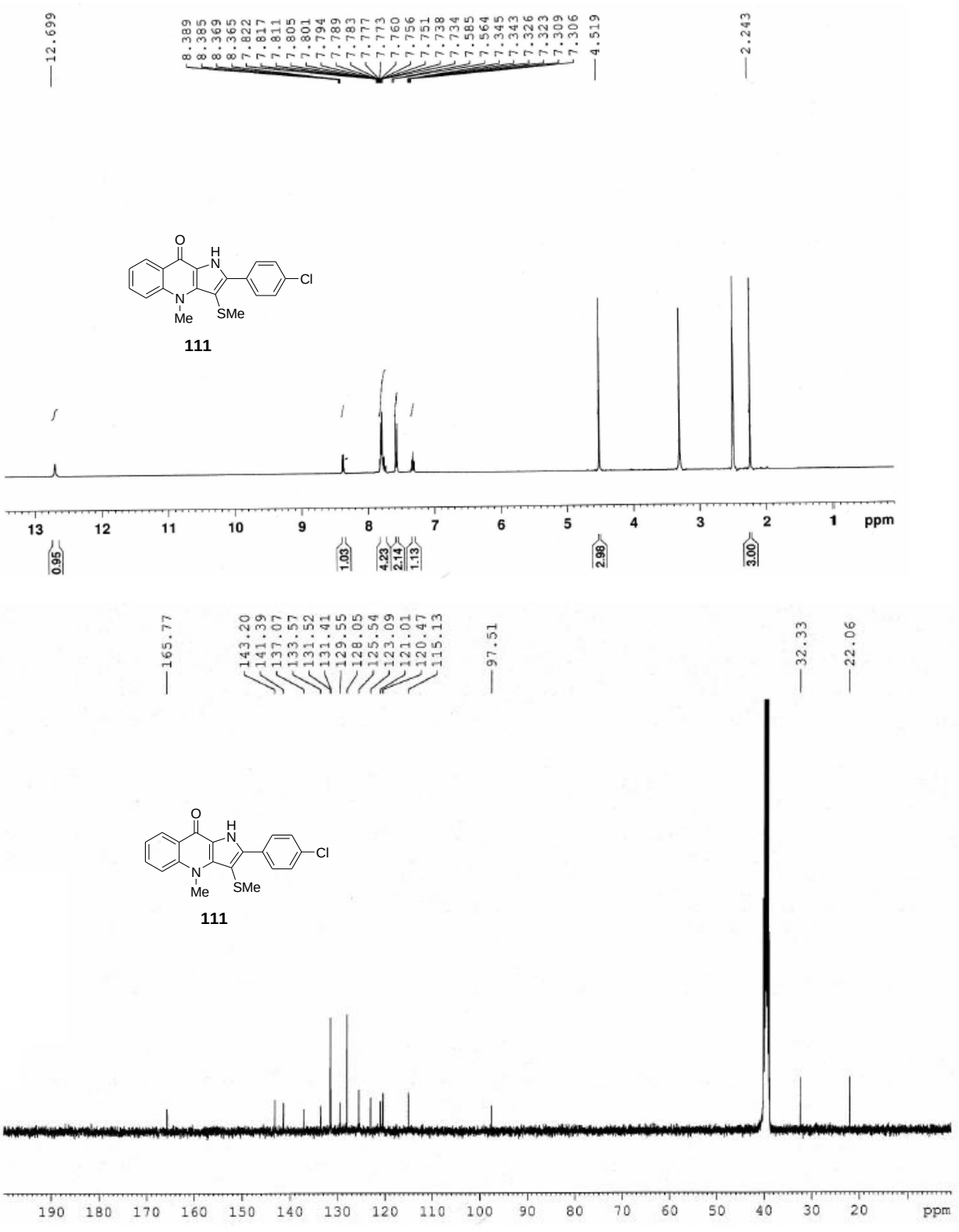


^{1}H and ^{13}C NMR Spectra of compound **100**

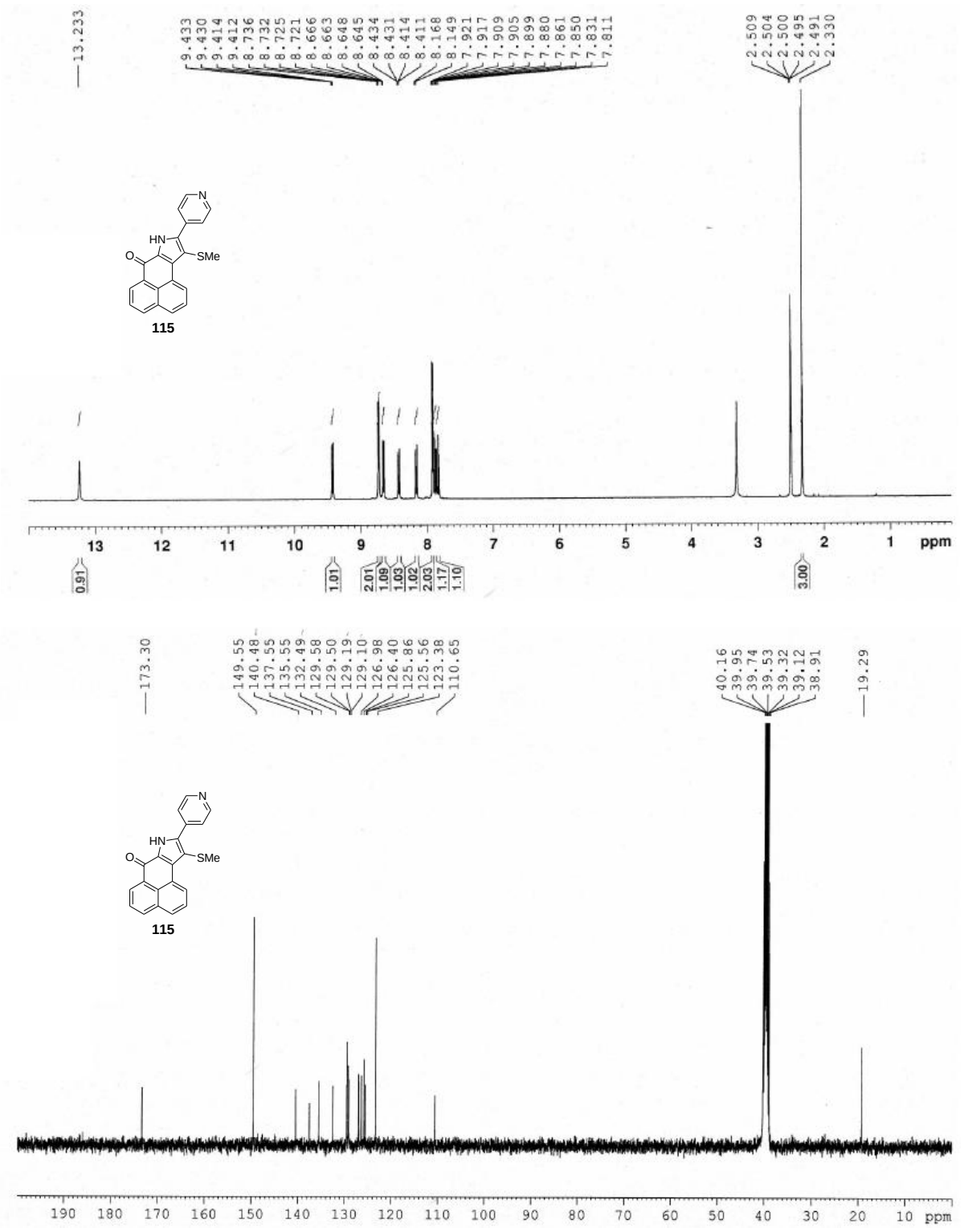




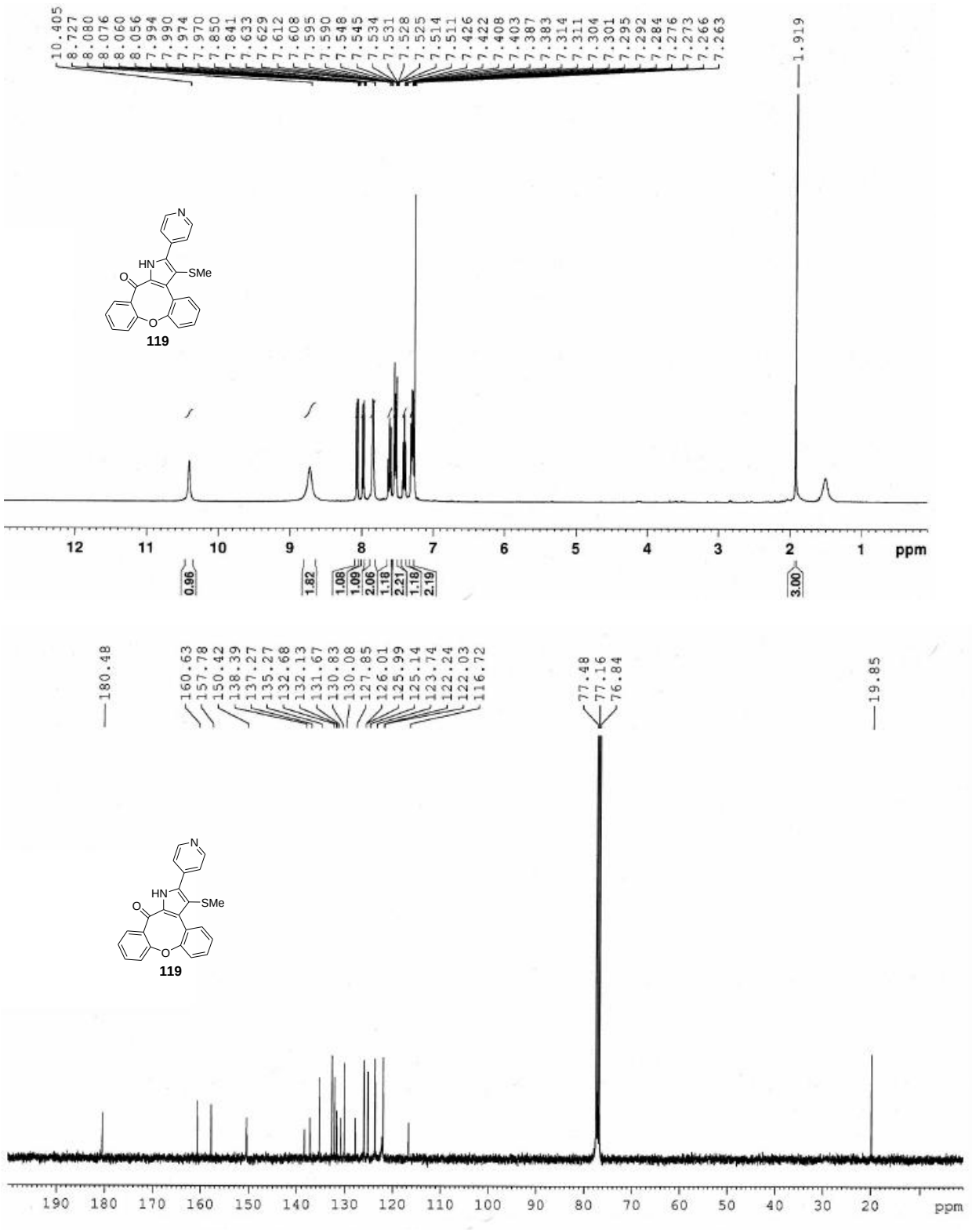
^{1}H and ^{13}C NMR Spectra of compound **106**



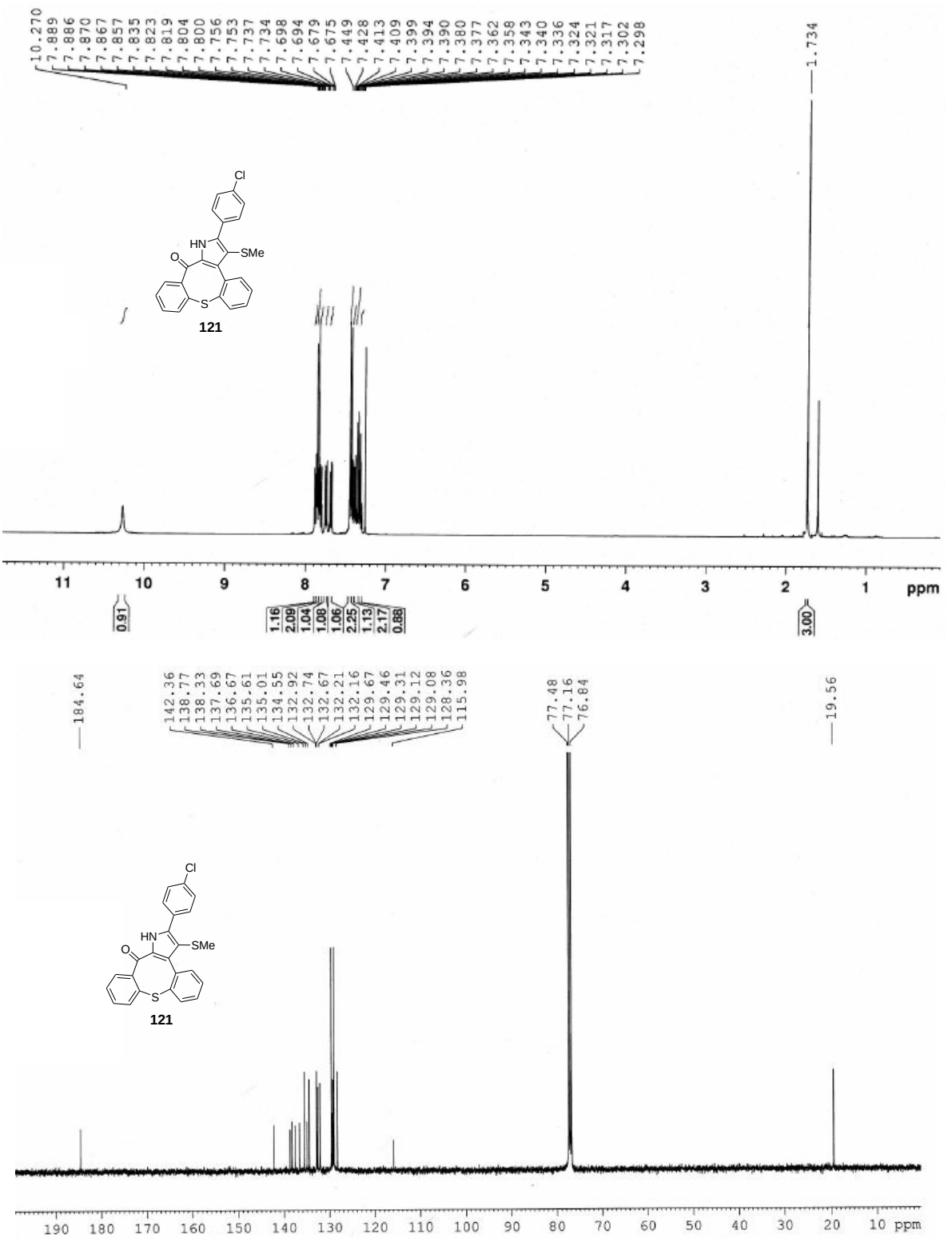
^{1}H and ^{13}C NMR Spectra of compound **111**



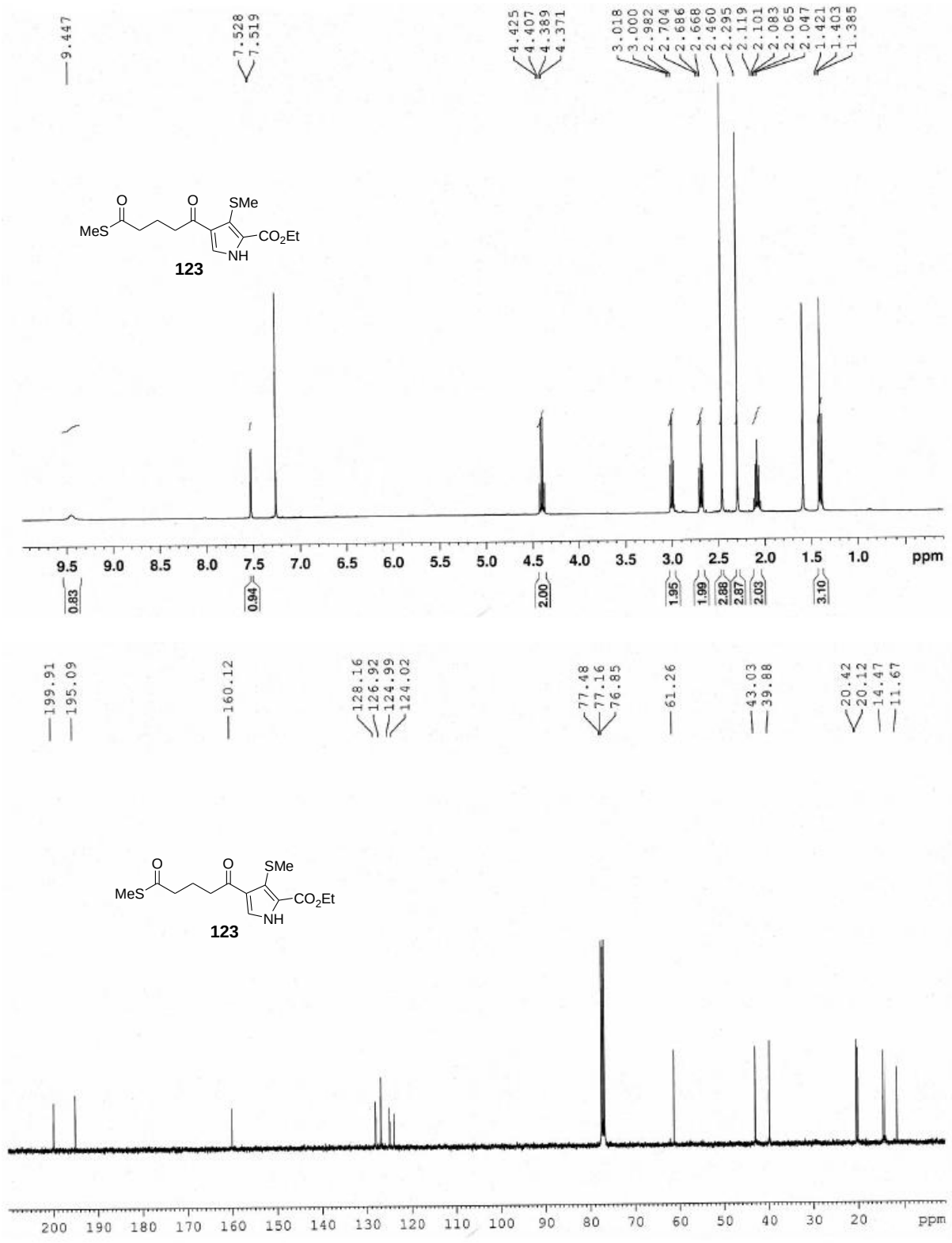
^{1}H and ^{13}C NMR Spectra of compound **115**



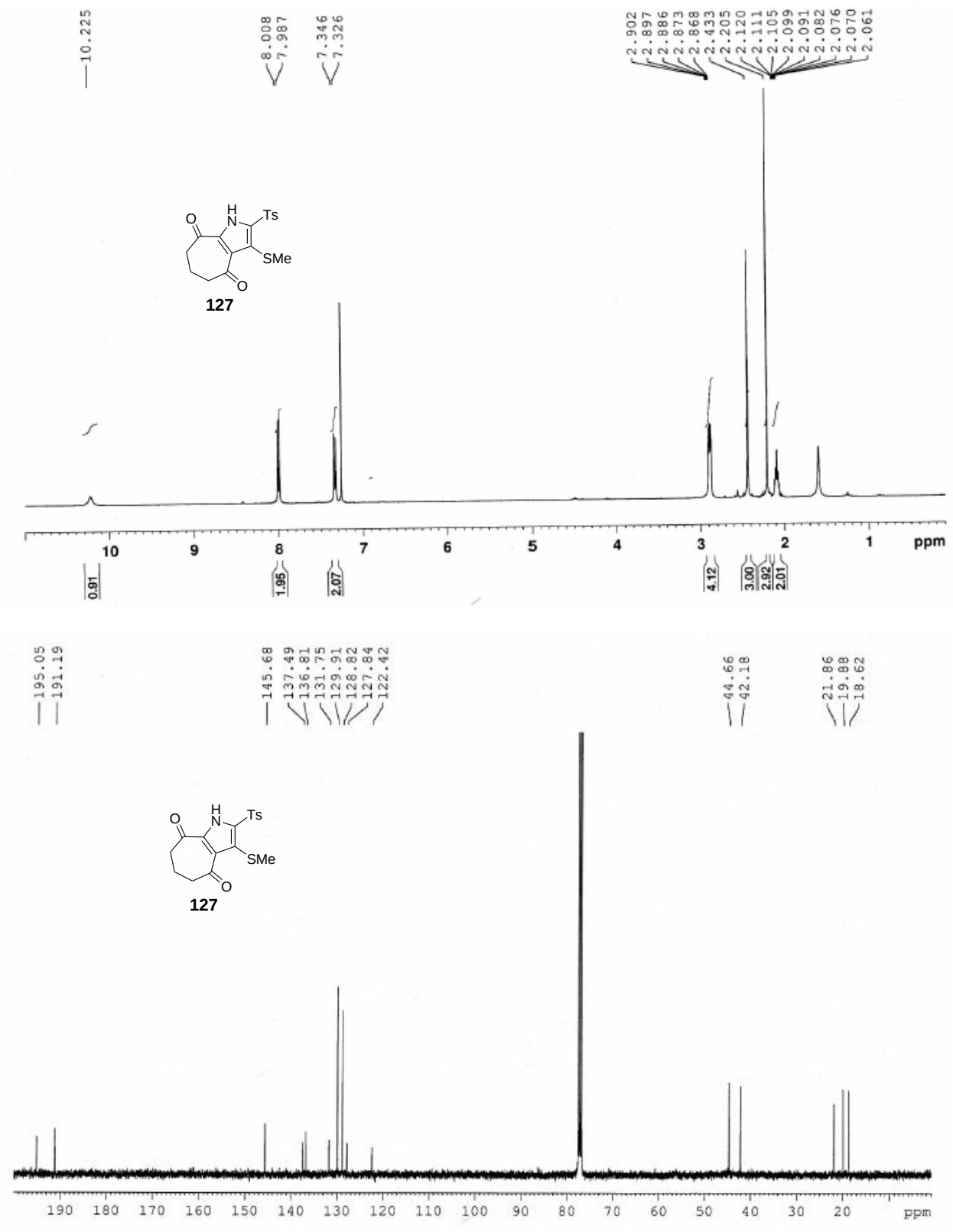
^{1}H and ^{13}C NMR Spectra of compound **119**



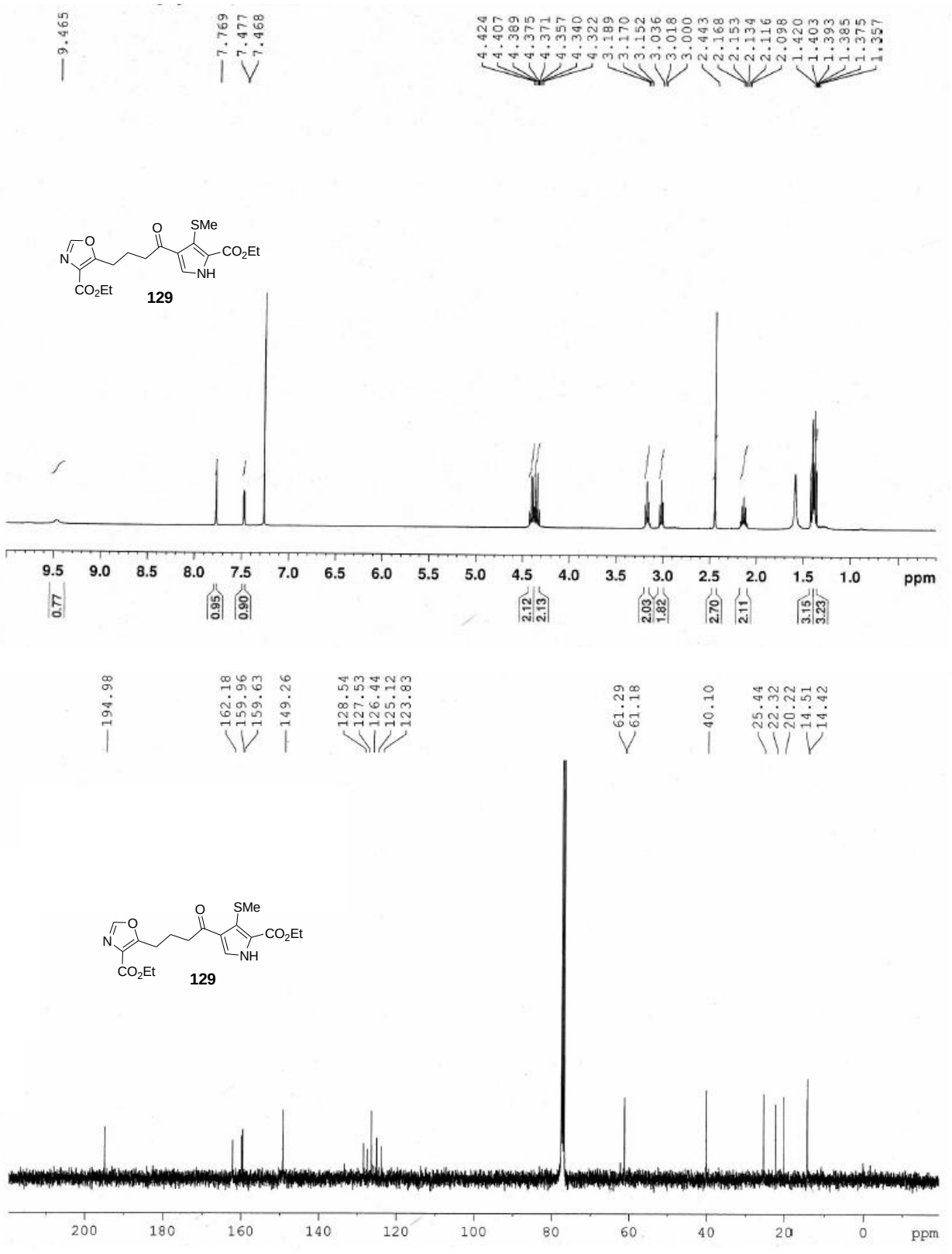
^{1}H and ^{13}C NMR Spectra of compound **121**



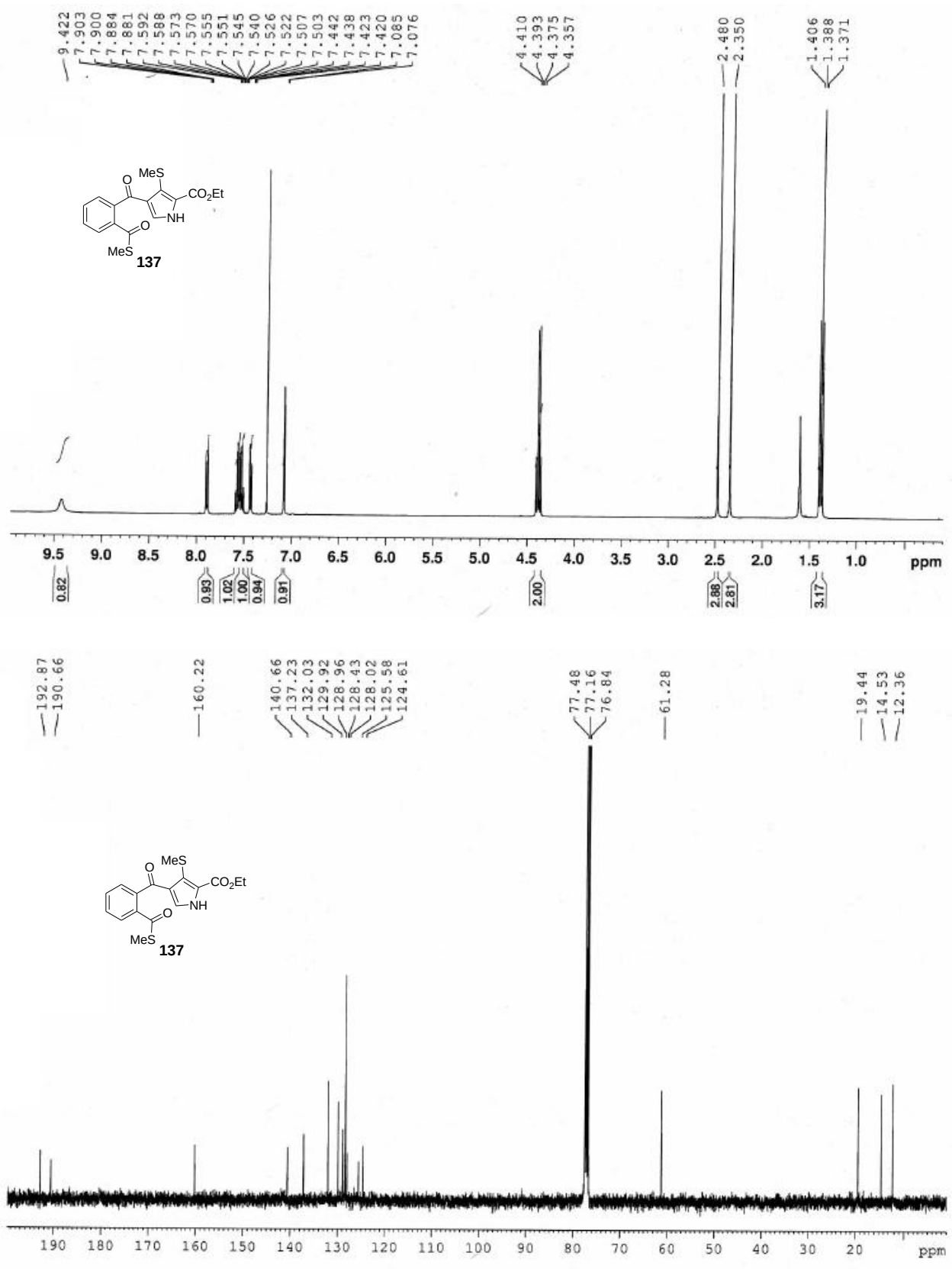
^{1}H and ^{13}C NMR Spectra of compound **123**



^{1}H and ^{13}C NMR Spectra of compound **127**



^{1}H and ^{13}C NMR Spectra of compound **129**



^{1}H and ^{13}C NMR Spectra of compound **137**

Chapter 3

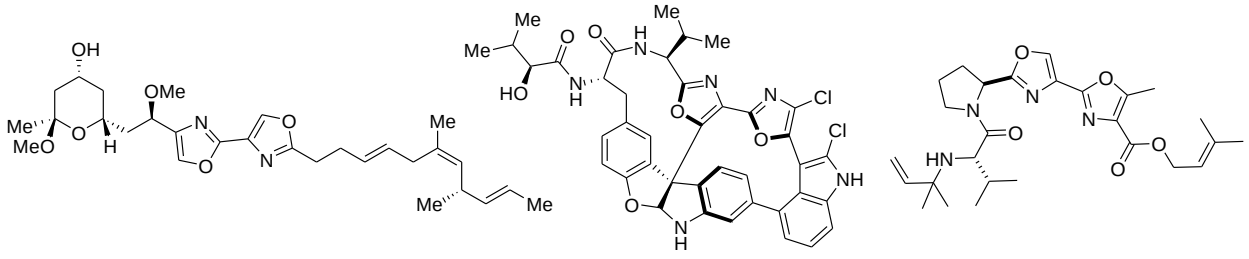
Synthesis of 2,5-Bis(hetero)aryl 4'-Substituted 4,5'-Bisoxazoles via Copper(I)-Catalyzed Domino Reactions of Activated Methylene Isocyanides with 2-(Het)aryl-4-[(het)aryl)(methylthio)methylene]oxazol-5(4H)ones*

3.1 Introduction

The oxazole heterocycle is a fundamental ring system, present in various natural products, pharmaceuticals, agrochemicals, peptidomimetics and polymers.[1] Naturally occuring oxazoles range in structures from relatively simple 2,5-disubstituted derivatives (pimprinine and pimprinethine)[2] to more complex biologically important bis- and tris-oxazoles containing cyclic peptides and macrolides.[1b-e] Examples include hennoxazole A **1**[3] with a 2,4'-bisoxazole moiety displaying strong antiherpes simplex virus activity, diazonamide A **2** (cytotoxic activity),[4] muscoride A **3**[5] and IB 01211 **4**[6] are other examples of natural products, having two contiguous 2,4'-bisoxazole motifs in their cyclic frameworks. Macrolides such as ulapualide A **5**,[7] mycalolide A **6**,[8a-b] kabiramides[8b-c] with potent

*The overall results of study described in this chapter have been published in *J. Org. Chem.* **2013**, *78*, 3948.

antifungal activity and cyclic peptide YM-216391[9] (telomerase inhibitor) contain three contiguous 2,4'-oxazole rings (Charts 1 and 2). On the other hand, telomestatin **7**,[10] a C_2-$C_{4'}$ linked macrocyclic heptaoxazole is shown to be most powerful telomerase inhibitor described till date, which has found application in cancer chemotherapy. A few of the examples of biologically active bis-, tris- and polyoxazoles are shown in the Charts 1 and 2. These naturally occurring polyoxazoles display C_2-$C_{4'}$ linkage as a result of their biosynthesis from amino acids such as serine and threonine.[1d-e,11] To the best of our knowledge, no example of naturally occurring 4,5'-bisoxazole is reported, and only a few examples of synthetic 2,2'-**8**,[12a] 2,5'-**9**,[12b] 4,4'-**10**,[12c] 4,5'-bisoxazoles **11**[13] and 5,5'-bisoxazoles **12**[14] are known in the literature (Chart 3).

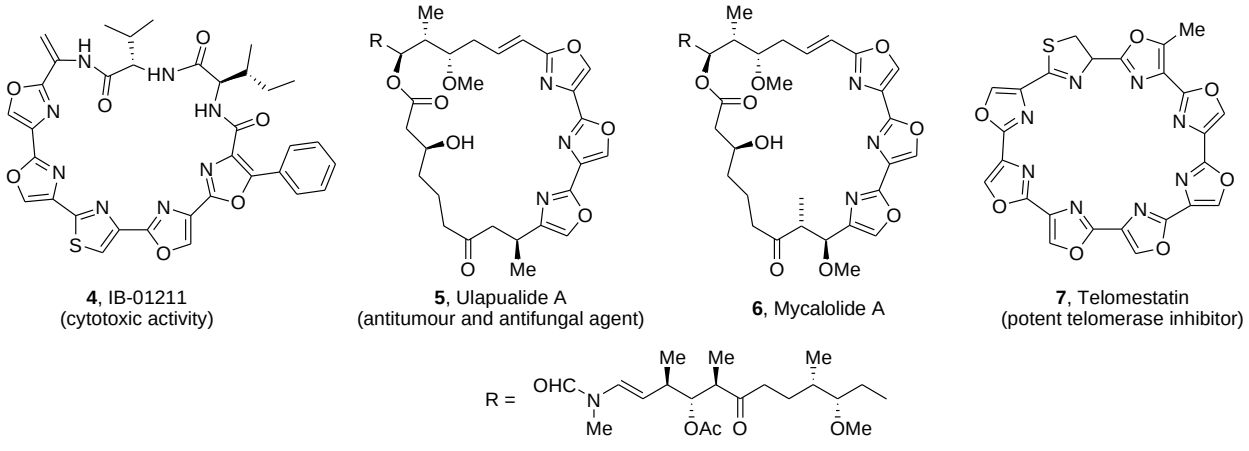


1, (-) Hennaxazole A
(potent antiviral activity)

2, Diazonamide A
(cytotoxic activity)

3, Muscoride A

Chart 1. Biologically active natural products incorporating bisoxazoles



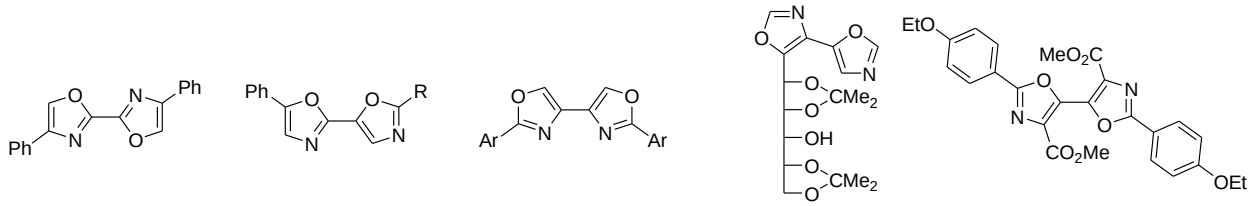
4, IB-01211
(cytotoxic activity)

5, Ulapualide A
(antitumour and antifungal agent)

6, Mycalolide A

7, Telomestatin
(potent telomerase inhibitor)

Chart 2. Biologically active natural products incorporating tris- and polyoxazoles



8, 2,2'-bisoxazole **9**, 2,5'-bisoxazole; R = Ph, Bu, Cy **10**, 4,4'-bisoxazole; Ar = Ph,4-$MeOC_6H_4$, 4-C_6H_4F **11**, 4,5'-bisoxazole **12**, 5,5'-bisoxazole

Chart 3. Examples of bisoxazoles containing 2,2'-, 2,5'-, 4,4'-, 4,5'- and 5,5'-linkage

In the present chapter we have described a novel copper-catalyzed domino reaction involving ring opening of 2-phenyl/(2-thienyl)-4-[(hetero)aryl-(methylthio)methylene]-5-oxazolones **66** with various activated methylene isocyanide pronucleophiles **71** and subsequent in situ intramolecular cyclization of the resulting diversely functionalized open chain adducts **72**, thus providing straightforward direct route to a wide range of 2,5,4'-substituted 4,5'-bisoxazoles **73** in excellent yields (Scheme 17). Before presenting our results, a short literature survey of recent methods for the synthesis of bisoxazole has been described in the following section.

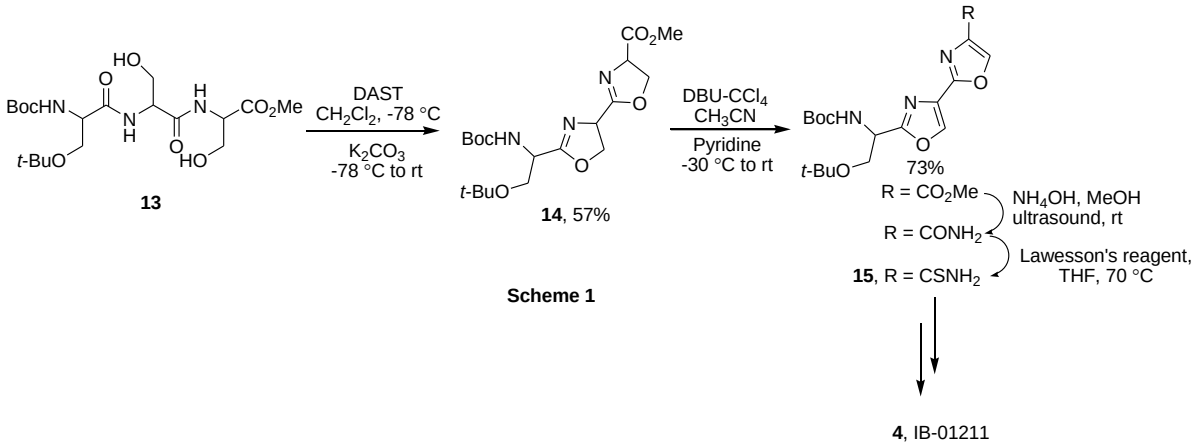
3.2 Synthesis of Substituted Bisoxazoles: A Short Recent Literature Survey

The unique and complex structures of these bis- and tris- oxazole containing natural products, along with their important pharmacological properties, has stimulated considerable interest in the synthesis of compounds containing directly linked 2,4'-bis (or tris-/poly) oxazole cores.

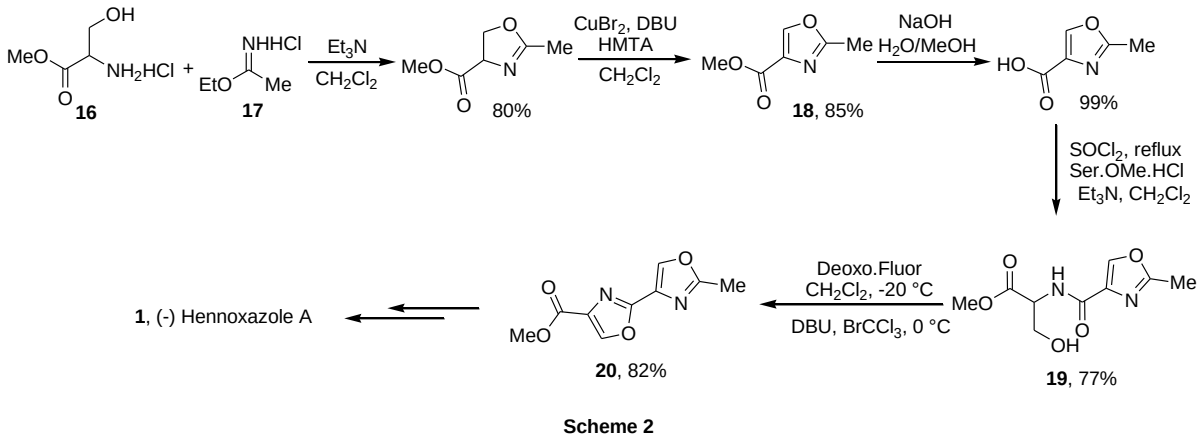
Thus, Alvarez and co-workers have reported the synthesis of 2,4'-bisoxazole **15**, an intermediate in the synthesis of IB-01211 macrolide **4**, starting from tri-Ser peptide **13** (Scheme 1). The overall strategy involves, activation of hydroxyl group using DAST, followed by cyclization in the presence of K_2CO_3 providing bisoxazoline **14**, which on dehydrogenative- oxidation affords bisoxazole **15** in good yield (Scheme 1). This is the first report of the one-pot formation of two concatenated oxazoles by cyclodehydration and oxidation of amino acids (Scheme 1).[15]

Smith and co-workers have reported the synthesis of 2,4'-bisoxazole **20**, an intermediate in the synthesis of hennoxazole A **1**, through sequential formation of two oxazole rings involving synthesis of 2-methyloxazole-4-carboxylate **18** through

cyclocondensation of serine carboxylate **16** with ethyl acetimidate **17** (Scheme 2). Subsequently the second oxazole ring on oxazole **20** is elaborated through serine amide **19** followed by its oxidative cyclodehydration to bisoxazole **20** in the presence of Deoxo-Fluor/DBU-$BrCCl_3$ (Scheme 2).[16]

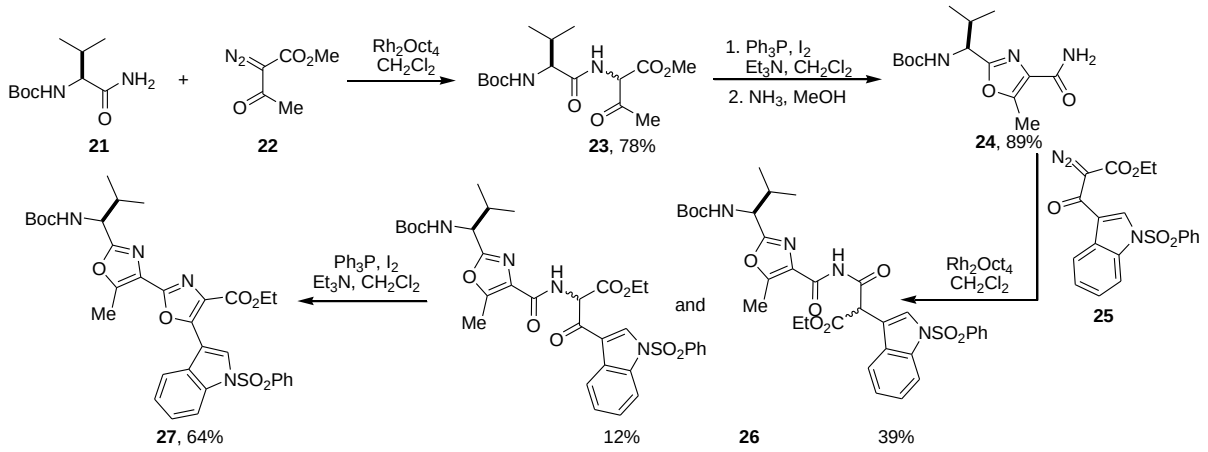


Scheme 1



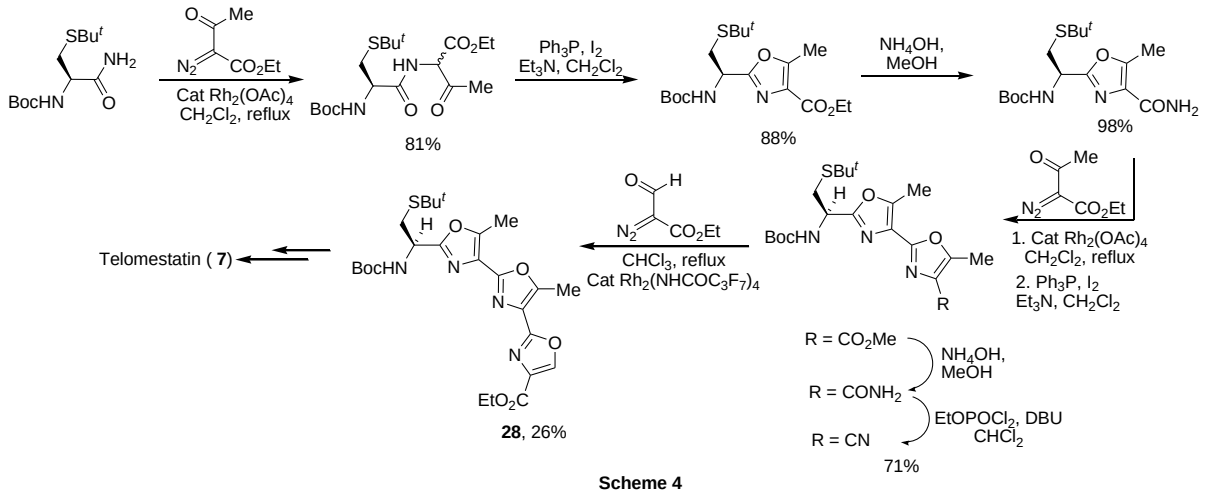
Scheme 2

Moody and co-workers have developed a new approach to 2,4'-bisoxazole through rhodium catalyzed carbene N-H insertion. Thus, an *α*-diazocarbonyl-*β*-ketoester such as **22** is reacted with a primary amide **21** in the presence of rhodium catalyst yielding ketoamide **23**, which on cyclodehydration in the presence of Wipf's reagent ($PPh_3/I_2/Et_3N$) affords 2,5-disubstituted oxazole-4-amide **24** in good yields (Scheme 3). Elaboration of the primary amide group in oxazole **24** to the bisoxazole **27** was achieved following similar sequence of reactions, by reacting it with indole substituted *α*-diazocarbonyl-*β*-ketoester **25** in the presence of rhodium catalyst followed by intramolecular cyclization of the resulting intermediate **26** in presence of Wipf's reagent (Scheme 3).[17a]



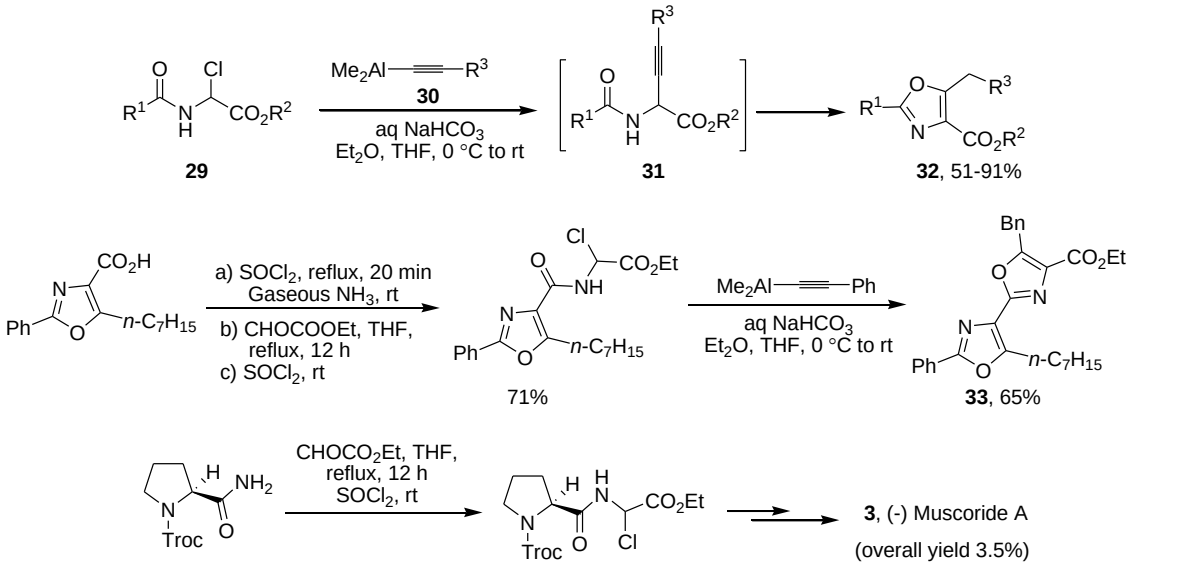
Scheme 3

Moody and co-workers further applied this rhodium carbene chemistry for the synthesis of trisoxazole **28**, an intermediate in the synthesis of anticancer agent telomestatin **7** (Chart 2, Scheme 4).[17b]



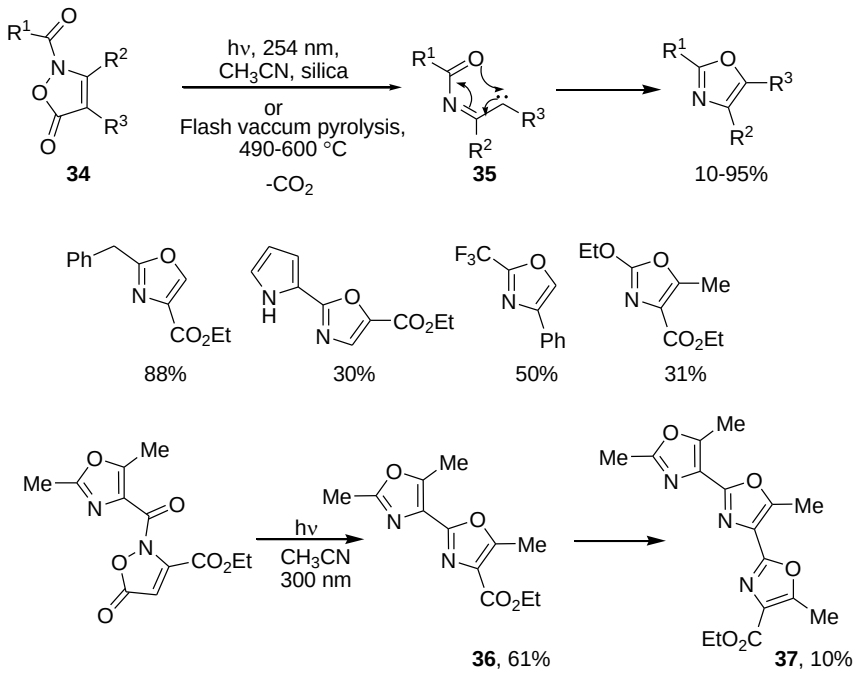
Scheme 4

Ciufolini and co-workers have described a novel one pot synthesis of oxazole such as **32** via cycloisomerization of propargylamide **31** (generated in situ by treatment of *α*-chloroglycinate **29** with alkynyl dimethyl aluminium reagent **30**) (Scheme 5). The aluminium reagent **30** also acts as catalyst for the cycloisomerization of propargylamide **31** to oxazole **32** in good yields. This methodology was further applied in iterative manner, for the construction of second ring of bisoxazole **33** (Scheme 5). Ciufolini and coworkers have further applied this strategy in the total synthesis of bisoxazole containing a secondary metabolite (-) muscoride A **3** (Chart 1 and Scheme 5).[18]



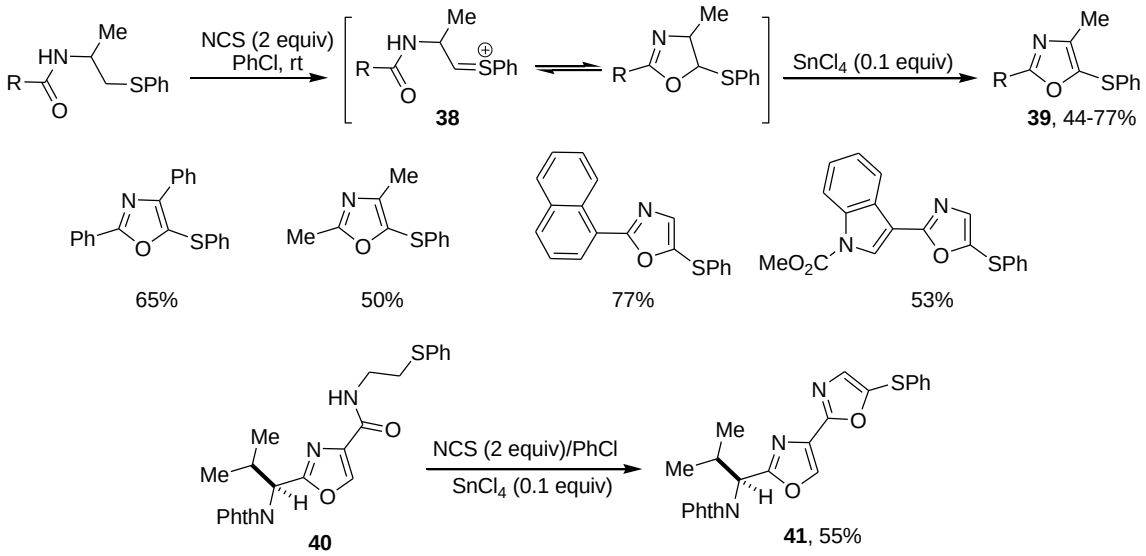
Scheme 5

Prager and co-workers have developed a new route for the synthesis of oxazoles through photolysis/pyrolysis of *N*-acylisoxazolones **34** involving an intramolecular cyclization of an iminocarbene intermediate **35** formed via photolytic elimination of carbon dioxide (Scheme 6). They have further extended this methodology for the synthesis of bis- and trisoxazoles **36** and **37** in iterative fashion (Scheme 6).[19]



Scheme 6

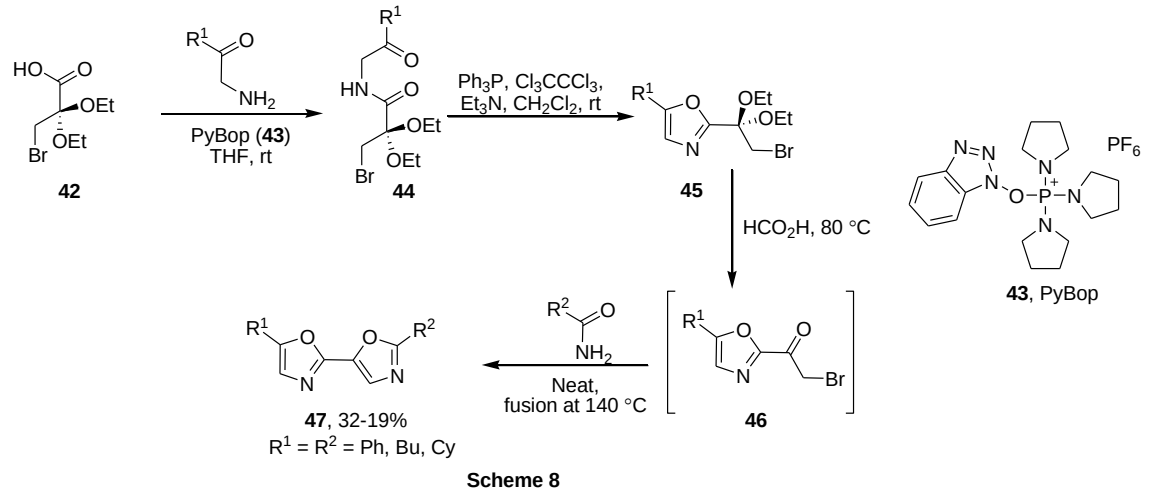
Magnus and co-workers have reported the synthesis of 4-thiophenyloxazoles **39** from readily available *N*-acylamino-2-thiophenyl derivatives via Pummerer reaction methodology (Scheme **7**). The overall process involves treatment of *N*-acylamino-2-sulfides with *N*-chlorosuccinimide followed by addition of $SnCl_4$ to give intermedium sulfenium ion **38** which on intramolecular cyclization affords various substituted oxazoles in moderate to good yields (Scheme **7**). They have further applied this methodology for the synthesis of 2,4'-bisoxazole such as **41** starting from the intermediate **40** (Scheme 7).[20]



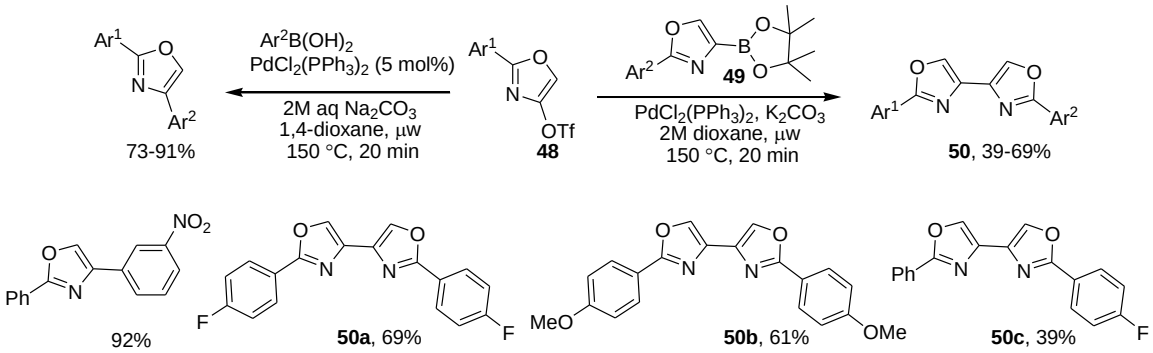
Scheme 7

Laurent and co-workers have reported the synthesis of 2,5'-bisoxazoles **47** from *α*-bromo ketones in moderate yields (Scheme 8). The required masked *α*-bromo ketone **45** was prepared by the coupling of 3-bromo-2,2-diethoxypropionic acid **42** with *α*-amino ketone in presence of PyBop **43**, followed by the cyclodehydration of the resultant amide **44**. This masked *α*-bromo ketone **45** was subjected to hydrolysis to give α-bromo ketone **46**, which was finally condensed with amide to give 2,5'-bisoxazole **47** (Scheme 8).[21]

The substituted bisoxazoles have also been synthesized through transition metal cross-coupling reactions (Schemes 9-14). Thus Greany and co-workers have described a new method for arylation of oxazoles at 2 and 4-positions using Suzuki coupling under microwave irradiation conditions (Scheme 9). They have also applied this method for the synthesis of dimeric 4,4'-bisoxazoles such as **50a-c** via Suzuki coupling of 2-substituted 4-oxazolylboronic acids **49** with oxazole triflates **48** (Scheme 9).[22]

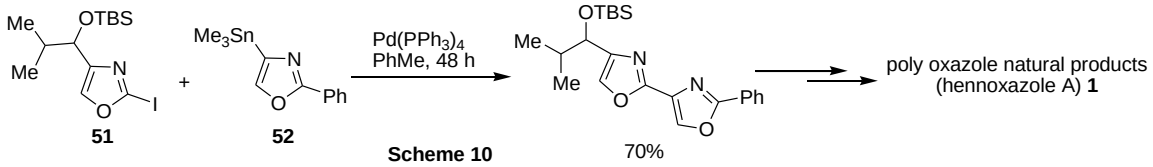


Scheme 8



Scheme 9

Barret and co-workers have reported the synthesis of 2,4'-bisoxazole through Stille coupling of 2-oxazolyl iodide **51** with 4-oxazolyl trimethylstannane **52** (Scheme 10). This method is useful for the synthesis of polyoxazole containing natural products such as hennoxazole A **1**.[23]

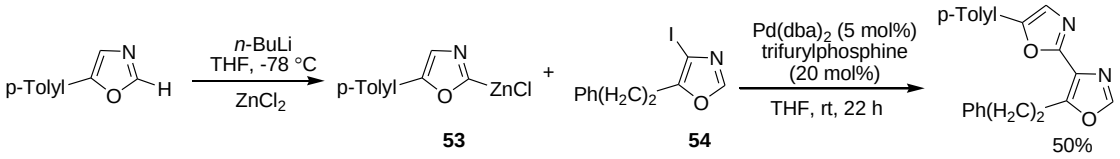


Scheme 10

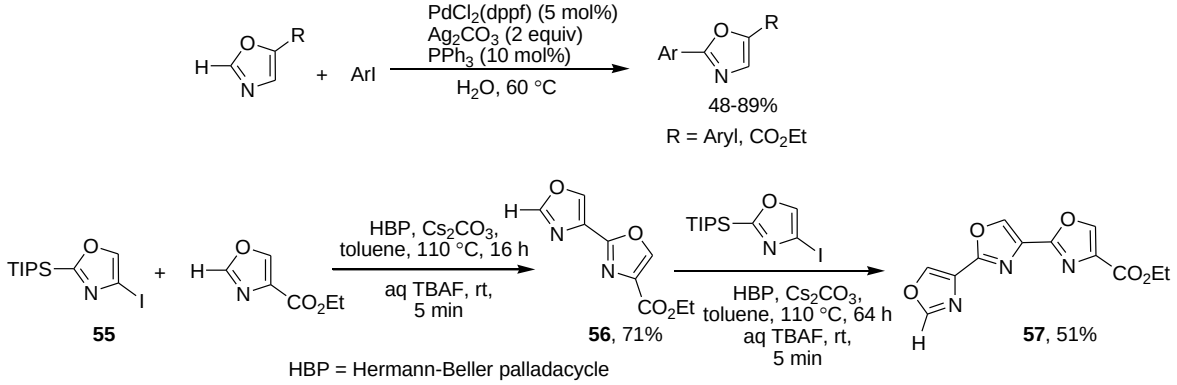
Vedejs and co-workers have developed an alternative route for the synthesis of 2,4'-bis-oxazole through Negishi coupling of 2-halozincated oxazole **53** with 4-iodo-5-alkyloxazole **54** (Scheme 11).[24]

Greaney and co-workers have developed palladium catalyzed direct arylation method for the C-2 position of oxazoles using $PdCl_2/PPh_3$ as catalyst and silver carbonate as

reoxidant (Scheme 12). They have also applied this method for the synthesis of 2,4'-bis- and tris-oxazoles such as **56** and **57** by using 2-triisopropylsilyl-4-iodooxazole **55** as electrophile in the arylation sequence (Scheme 12).[25]

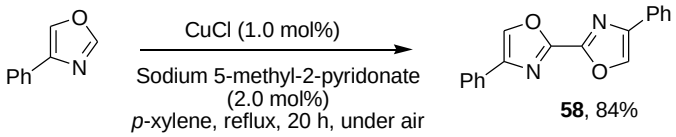


Scheme 11



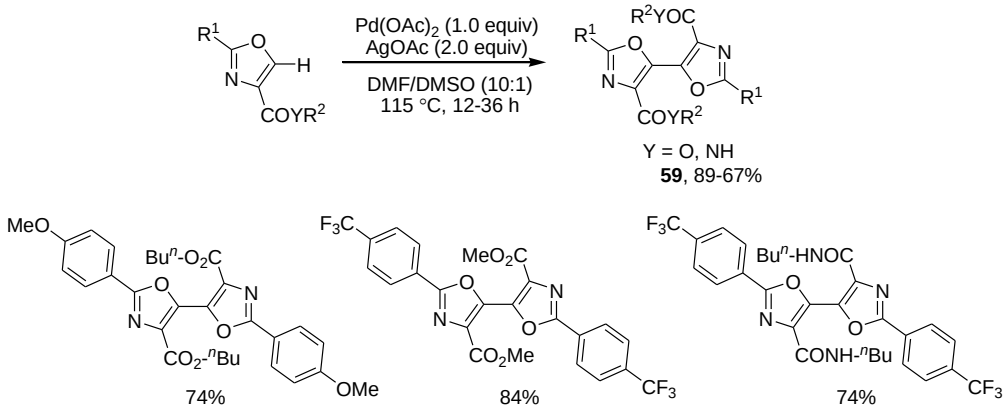
Scheme 12

Yamaguchi and co-workers have described a convenient method for the synthesis of 2,2'-bisoxazole **58** via CuCl/sodium 2-pyridonate catalyzed oxidative homocoupling of azoles using air as an oxidant (Scheme 13).[26]



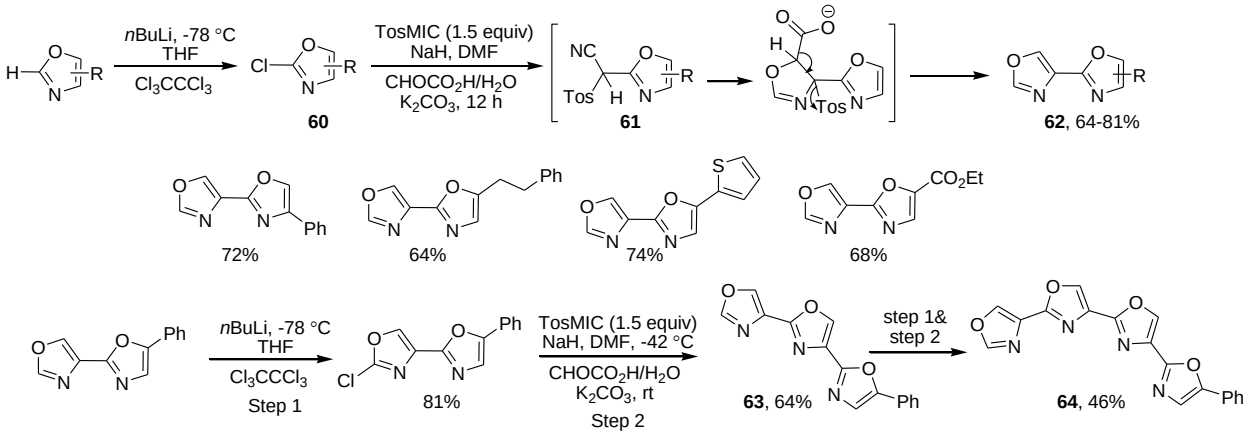
Scheme 13

Yao and co-workers have reported an efficient method for the synthesis of 5,5'-bisoxazoles **59** via $Pd(OAc)_2$ catalyzed homocoupling of oxazole-4-carboxylic derivatives in good to excellent yields (Scheme 14). The reaction tolerates a broad substrate scope on oxazole rings including alkyl, carbonyl, and electron-withdrawing/donating group substituted phenyl groups (Scheme 14).[27]



Scheme 14

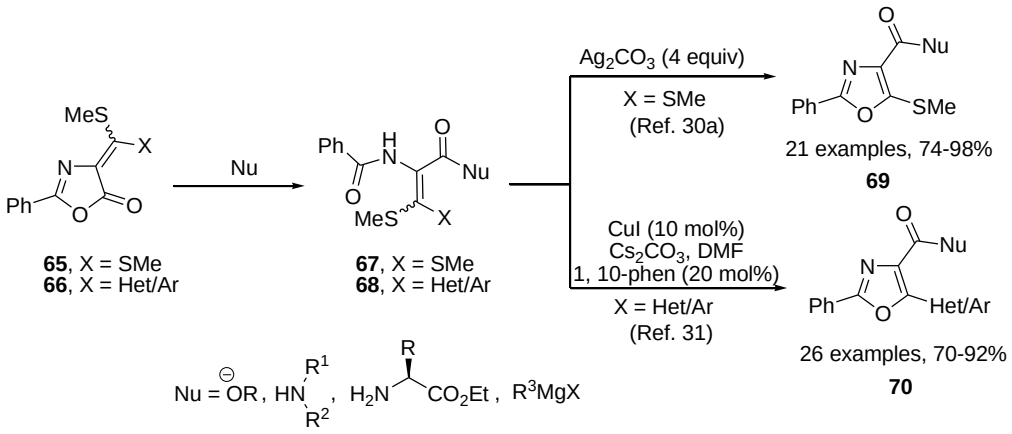
Vedejs and co-workers have also developed an efficient iterative process for the synthesis of polyoxazoles through TosMIC cycloaddition (Scheme 15). The overall strategy involves direct chlorination of 2-lithio oxazoles with hexachloroethane in THF providing a selective general protocol for preparation of 2- chlorooxazoles **60** (Scheme 15). Subsequent S_NAr-type substitution with ToSMIC anion forms an isonitrile intermediate **61** that provides the corresponding 2,4'-bis-oxazole **62** upon reaction with glyoxalic acid monohydrtate in one pot sequence. This two stage process allows the synthesis of bis-, tris- and tetra-substituted oxazoles **62**, **63** and **64** in good yields (Scheme 15).[28]



Scheme 15

As part of the program to develop new synthetic methods for construction of wide range of small molecule heterocyclic libraries with potential biological activity,[29] our research group has recently reported a substrate controlled diversity oriented synthesis of 2-phenyl-5-(methylthio)-4-substituted oxazoles **69** and other heterocycles using a general 2-

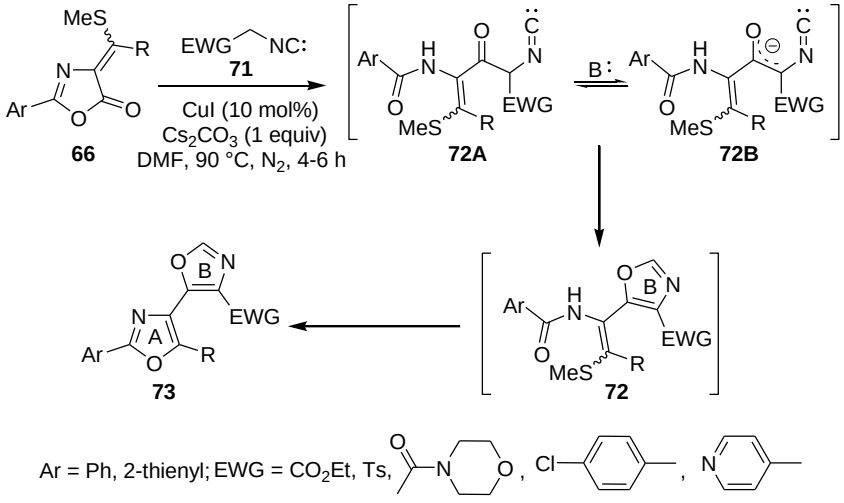
phenyl-4-bis(methylthio)methyleneoxazol-5(4*H*)-one **65** as versatile synthetic template.[30a-b] The overall strategy involves nucleophilic azalactone ring opening of **65** by various oxygen (alkoxide), nitrogen (amines) and carbon (Grignard reagents) nucleophiles followed by further synthetic transformations of the resulting open chain enamide adducts **67** (Scheme 16).[30a-b] In continuation of these studies, as a further extension of this strategy, we have recently described the synthesis of a new class of 5-oxazolone based synthons i.e., 2-phenyl-4-[(aryl/heteroaryl)-(methylthio)methylene]-oxazol-5(4*H*)-ones **66** and utilized them to develop a two step synthesis of a variety of 5-aryl/heteroaryl-4-functionalized oxazoles **70** and related natural products (Scheme 16).[31] The key step in this new protocol involves copper catalyzed intramolecular cyclization of functionalized β-(methylthio)enamides **68**, which were obtained by ring opening of newly synthesized oxazolone precursors **66** by various oxygen, nitrogen and carbon nucleophiles (Scheme 16).[31]



Scheme 16

During the course of these studies, we further anticipated that the use of activated methylene isocyanides as the pronucleophiles instead of common nucleophiles in the ring opening of oxazolone pecursors **66**, which would bring about a different kind of rearrangement-cyclizaton process. Some of the recent novel transformations along with domino reactions of activated methylene pronucleophiles with various substrates have already been discussed in the Chapter 2. Thus, we envisaged that the nucleophilic ring opening of oxazolone **66** by an activated methylene isocyanide **71** pronucleophile would give the acyclic intermediate **72A** having a *β*-ketoisonitrile moiety, which would undergo facile proton abstraction and subsequent intramolecular cyclization of the resulting enolate **72B** to

the oxazole intermediate **72**, as observed earlier by Schollkopf and other workers in the acylation studies of isocyanoacetate anion with various acylating agents.[32-34] It was further speculated that the resulting *α*-(5-oxazolyl)- *α*-benzoylamido intermediate **72** would also undergo cyclization via an intramolecular 5-*endo-trig* process in the presence of a base or metal catalyst with the formation of a second oxazole ring (A),[30-31] thus providing a facile access to novel 2,5,4'-substituted 4,5'-bisoxazoles **73** (Scheme 17). We have successfully achieved this goal and described in this chapter a novel copper catalyzed domino reaction of 2phenyl/thienyl-4-[(hetaryl)-(methylthio)methylene]-5-oxazolones **66** with activated methylene isocyanide pronucleophiles **71** providing a straightforward direct synthesis of of a wide range of 2,5,4'-substituted -4,5'-bisoxazoles **73** in excellent yields (Scheme 17).[30c]



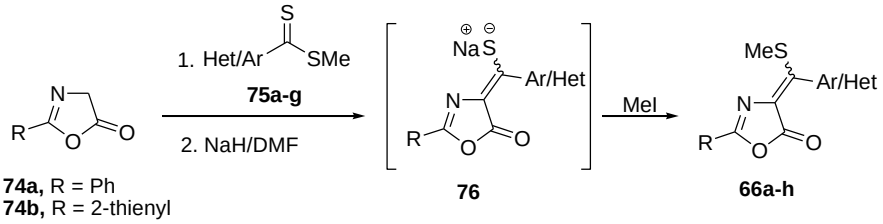
Scheme 17

3.3 Results and Discussion

3.3.1 Synthesis of 2-Phenyl/(2-thienyl)-4-[(aryl/heteroaryl)-(methylthio)methylene]-oxazol-5-ones (66a-h)

The desired 2-phenyl-4-(hetero)arylidene-5-oxazolone precursors **66a-f** were synthesized by condensation of 2-phenyloxazole-5(4*H*)-one **74a** with various aryl/heteroaryl dithioesters **75** in the presence of sodium hydride in DMF followed by alkylation of thiolate salts **76** with methyl iodide as reported earlier.[31] Further diversity in the 5-oxazolone framework was introduced by synthesis of the corresponding 2-[(2-thienyl)]-4-[(hetero)aryl-

(methylthio)]-5-oxazolones **66g-h** from the corresponding 2-(2-thienyl)-5-oxazolone **74b** following the similar procedure (Scheme 18).

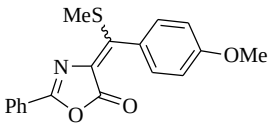


74a, R = Ph
74b, R = 2-thienyl

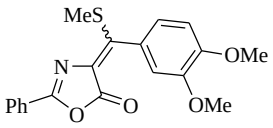
76

66a-h

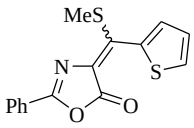
Scheme 18



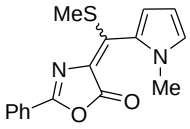
66a, 80%, *E/Z* = 60:40



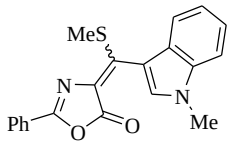
66b, 78%, *E/Z* = 63:37



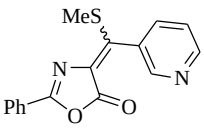
66c, 70%, *E/Z* = 55:45



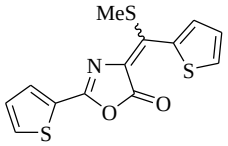
66d, 75%, *E/Z* = 75:25



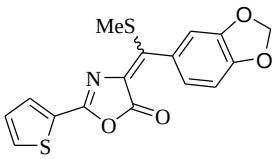
66e, 78%, *E/Z* = 64:36



66f, 60%, *E/Z* = 57:43



66g, 62%, *E/Z* = 78:22



66h, 72%, *E/Z* = 34:66

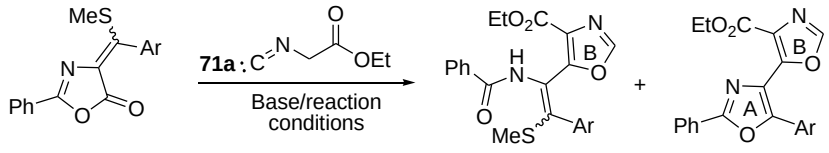
3.3.2 Optimization of Reaction Conditions for the Formation of Bisoxazole 73aa from 66a and 71a in the Presence of Different Bases and Copper-Catalysts

The reaction of oxazolone **66a** with ethyl isocyanoacetate **71a** in the presence of various bases and Cu catalysts was selected as the model reaction for optimizing reaction conditions for the formation of bisoxazole **73aa** (Tables 1 and 2). Thus when **66a** was reacted with **71a** in the presence of DBU as base at 60 °C for 10 h, analysis of the reaction mixture showed formation of only one product (86%), which was characterized as the acyclic adduct **72aa** bearing an oxazole B ring (Table 1, entry 1). Use of other bases like potassium *t*-butoxide, sodium hydride and cesium carbonate which are commonly employed in similar protocols, also yielded only the product **72aa** in 83-88% yields at lower temperature (entries 2-4, Table 1). On the other hand, use of weaker base like triethylamine furnished **72aa** in decreased yield (45%) along with unreacted **66a**, even after prolonged reaction time (entry 5). Formation of oxazole derivative **72aa** from **66a** and **71a** is in line with our predicted course of reaction[33,34] involving nucleophilic ring opening of **66a** by isocyanoacetate anion

followed by base induced spontaneous intramolecular cyclization of the newly formed α-acylisocyanoacetate moiety in the initially formed open chain intermediate **72aa** (Scheme 17). No trace of the desired bisoxazole **73aa** could be detected in the reaction mixture. However when the reaction of **66a** and **71a** in the presence of DBU was continued for longer time (25 h) at higher temperature (90 °C), formation of **73aa** was observed albeit in 10% yield along with **72aa** (70%) (Table 1, entry 6), whereas increasing the reaction temperature to 120 °C resulted in complete disappearance of **72aa**, furnishing the bisoxazole **73aa** in increased yield of 66% along with some polymeric mixture (Table 1, entry 7). Similarly the bisoxazole **73aa** was observed as the exclusive product in 61-67% overall yield with *t*BuOK, NaH or Cs_2CO_3 as bases at higher temperature and longer reaction time (Table 1, entries 8-10).

With the base mediated tandem ring opening-cyclization of **66a** with isocyanoacetate **71a** to bisoxazole **73aa** in hand, we further became interested in its copper-catalyzed variant with a view to enhance the efficiency of the reaction under milder reaction conditions.[31] Recently,

Table 1. Optimization of Reaction Conditions for the Formation of Bisoxazole 73aa from 66a and 71a in the Presence of Different Bases[a]



66a **66a,72aa,73aa,** Ar = 4-MeoC$_6$H$_5$ **72aa** **73aa**

entry	Base	solvent	t (h)	T (°C)	yield (%)	
					72aa	**73aa**
1	DBU	DMF	10	60	86	-
2	*t*BuOK	THF	10	60	88	-
3	NaH	DMF	10	60	84	-
4	Cs_2CO_3	DMF	10	60	83	-
5	Et_3N	THF	25	60	45 (41)[b]	-
6	DBU	DMF	25	90	70	10
7	DBU	DMF	25	120	-	66
8	*t*BuOK	DMF	25	120	-	67
9	NaH	DMF	24	120	-	61
10	Cs_2CO_3	DMF	25	120	-	64

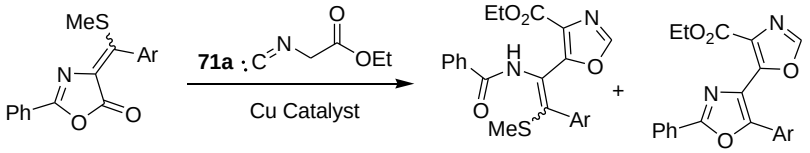
[a]Reaction conditions: **66a** (0.3 mmol), **71a** (1 equiv) and base (1 equiv) in 2 mL of solvent. [b]Yield of recovered **66a**.

great progress has been made in the use of transition metal catalyzed reactions of activated metylene isocyanides with double and triple bonds.[32] Thus de Meijere and coworkers[35a-b] and Yamamoto *et al*[35c-d] have independently reported the copper-catalyzed formal cycloaddition reactions of isocyanoacetates and alkynes furnishing oligosubstitued pyrroles in good yields. Cai and coworkers have recently described novel copper-catalyzed domino reactions of activated methylene isocyanides with 1-(2-haloaryl)-2-yn-1-ones[36a] and N-(2-haloaryl)propiolamides[36b] providing efficient synthesis of 4-oxo-indeno[1,2-*b*]pyrroles and pyrrolo[3,2-*c*]quinolin-4-ones respectively via a formal [3+2] cycloaddition and subsequent intramolecular aryl C-C coupling of the resulting organocopper intermediate.

Encouraged by these findings, we conducted a detailed study of the reaction of oxazolone **66a** with ethyl isocyanoacetate **71a** under various copper catalysts and the results are depicted in the Table 2. A detailed survey of the screening of various combinations of catalysts and ligands revealed that most of the copper catalysts employed in these reactions demonstrated moderate to good activity in the formation of bisoxazole **73aa** under varying conditions, whereas CuI (10 mol%) in the presence of cesium carbonate in DMF turned out to be most efficient and effectively promoted formation of **73aa** within 4 h at 90 ^{0}C in 75% yield (Table 2, entry 12). With copper powder and Cu(I) oxide as catalysts, in the presence or absence of ligand, **73aa** was obtained in lower yields (61-68%) requiring higher temperature and prolonged reaction time (entries 3-6), whereas, formation of only open-chain oxazole adduct **72aa** was observed at reduced temperature and time with copper powder under identical conditions (entries 1-2). On the other hand, in the presence of Cu_2O/phen, the bisoxazole **73aa** was obtained only in 22% yield along with open chain adduct **72aa** as the major product (entry 7). Similarly other copper catalysts like CuCl, CuBr and CuI in the presence of PPh_3 or Cs_2CO_3 also gave inferior results (entries 8-11), whereas a combination of CuI/PPh_3 and Cs_2CO_3 (entry 13) resulted in significant increased yield of **73aa** (entry 13). Use of Ag_2CO_3 (in stoichiometric amount) was found to be less effective and did not show complete conversion of **72aa** to **73aa** even after prolonged time (entry 15). Similarly, decreasing the catalyst loading to 5 mol% of CuI gave **73aa** only in slightly reduced yield (70%) requiring longer time (10 h) for completion of reaction (entry 14). As a control experiment, when **66a** was reacted with **71a** in the absence of CuI, using one equivalent of Cs_2CO_3 under identical conditions as described in entry 14, the bisoxazole **73aa** was formed

in only traces along with **72aa** as the major product (entry 16), thus showing that the presence of CuI as catalyst facilitates the formation of bisoxazole **73aa** from **72aa** (entry 16 vs entry 14). Among solvents, we tested, DMF showed best results, whereas other solvents like 1,4- dioxane, toluene, acetonitrile and ethyl acetate (with CuI/Cs_2CO_3) gave the desired product **73aa** only in moderate yields.

Table 2. Optimization of Reaction Conditions for the Formation of Bisoxazole 73aa from 66a and Isocyanoacetate 71a in the Presence of Copper-Catalysts[a]



66a **66a,72aa,73aa,** Ar = 4-$MeOC_6H_4$ **72aa** **73aa**

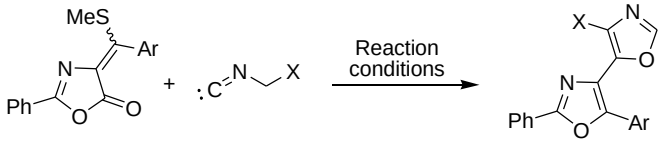
entry	Catalyst	solvent	t (h)	T (°C)	yield (%)	
					72aa	**73aa**
1	Cu powder/ PPh_3	Dioxane	2	90	80	-
2	Cu powder/ phen	Dioxane	2	90	78	-
3	Cu powder/ PPh_3	Dioxane	12	100	-	68
4	Cu powder/ phen	Dioxane	17	100	-	65
5[b]	Cu_2O	DMF	24	100	-	61
6	Cu_2O/PPh_3	DMF	18	90	-	66
7	Cu_2O/phen	Dioxane	20	100	72	22
8	$CuCl/PPh_3$	Dioxane	20	100	trace	-
9	$CuBr/PPh_3$	Dioxane	25	100	70	10
10	CuI/PPh_3	DMF	20	90	25	55
11[c]	$CuCl/Cs_2CO_3$	DMF	10	90	15	70
12[c]	CuI/Cs_2CO_3	DMF	4	90	-	75
13[d]	CuI/PPh_3 / Cs_2CO_3	DMF	10	90	-	70
14[e]	CuI/Cs_2CO_3	DMF	10	90	-	70
15[f]	Ag_2CO_3	CH_3CN	20	80	38	52
16[g]	Cs_2CO_3	DMF	10	90	81	trace

Reaction conditions: All reactions were performed with 0.3 mmol of **66a**, 1 equiv of **71a** in 2 mL of solvent. [a]Catalyst (10 mol%) and ligand (20 mol%). [b]Cu_2O (10 mol%).[c]Catalyst (10 mol %) and Cs_2CO_3 (1 equiv).[d]CuI (10 mol%), PPh_3 (20 mol%) and Cs_2CO_3 (1 equiv). [e]Catalyst (5 mol %) and base (1 equiv).[f]Stoichiometric amount of Ag_2CO_3. [g]Cs_2CO_3 (1 equiv).

The scope and limitations of this novel base induced and copper-catalyzed domino reaction for bisoxazole synthesis was next examined by employing a variety of acceptor substituted methylene isocyanides **71b-e** in the reaction with oxazolone **66a** (Table 3). The results of

these studies reveal that the reaction of **66a** with tosylmethyl isocyanide **71b**, N- morpholino-α- isocyanoacetamide **71c**, 4-chlorobenzyl isocyanide **71d** and 4-pyridylmethyl isocyanide **71e** in the presence of bases like potassium *t*-butoxide and DBU afforded the corresponding 4'- substituted bisoxazoles **73ab-73ae** in moderate to good yields requiring higher temperature and longer reaction time (Table 3, entries 1-8). However, increased yields of bisoxazoles **73ab-73ae** (76-91%) were obtained under copper catalyzed reaction conditions

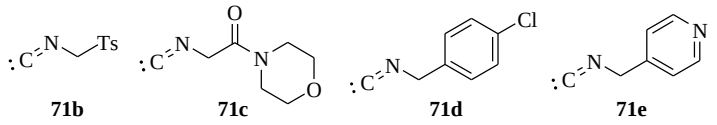
Table 3. Synthesis of Bisoxazoles 73ab-73ae Using 66a and Isocyanides 71b-e[a]



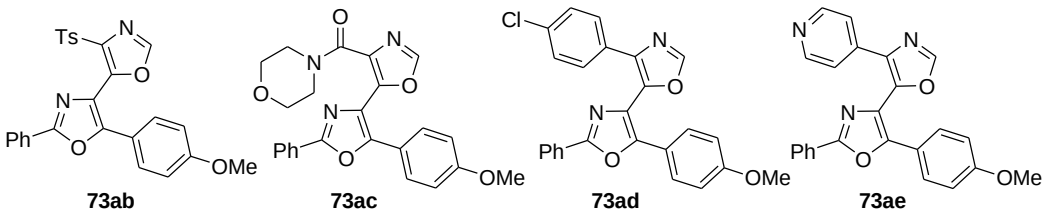
66a **71b-e** **73ab-73ae**

entry	CN X **71**	base/catalyst	t (h)	T (°C)	product **73**	yield (%)
1	**71b**	*t*BuOK	12	140	**73ab**	69
2	**71b**	DBU	15	140	**73ab**	60
3	**71c**	*t*BuOK	24	140	**73ac**	58
4	**71c**	DBU	24	140	**73ac**	60
5	**71d**	*t*BuOK	16	140	**73ad**	60
6	**71d**	DBU	18	140	**73ad**	50
7	**71e**	*t*BuOK	28	140	**73ae**	55
8	**71e**	DBU	28	140	**73ae**	50
9[b]	**71b**	CuI/Cs_2CO_3	4	90	**73ab**	76
10[b]	**71c**	CuI/Cs_2CO_3	5	90	**73ac**	85
11[b]	**71d**	CuI/Cs_2CO_3	4	90	**73ad**	91
12[b]	**71e**	CuI/Cs_2CO_3	6	90	**73ae**	78

Reaction conditions: [a]**66a** (0.3 mmol), **71** (1 equiv) and base (1 equiv) in 2 mL of DMF.
[b]CuI (10 mol%) and Cs_2CO_3 (1 equiv).



71b **71c** **71d** **71e**

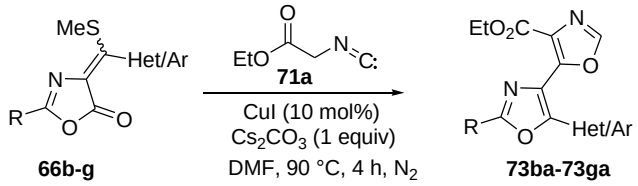


73ab **73ac** **73ad** **73ae**

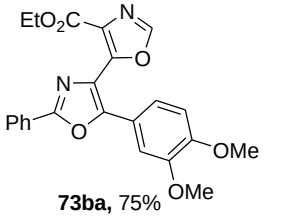
in the presence of CuI/Cs_2CO_3, which efficiently promoted the reaction at lower temperature 90 ^{0}C, within 4-6 h (Table 3, entries 9-12). Therefore these optimized reaction conditions (CuI/Cs_2CO_3) were employed throughout in our subsequent studies.

3.3.3 Synthesis of 2,5-Bis(hetero)aryl-4'-carbethoxy-4,5'-bisoxazoles 73

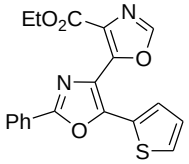
Having established the copper-catalyzed reaction conditions for the formation of bisoxazoles **73aa-73ae** from **66a** and **71a-e** (Table 3), the reaction of a various substituted 2-phenyl/(2-thienyl)-4-[(aryl/heteroaryl)-(methylthio)-methylene]-oxazol-5(4*H*)-ones **66b-h** with activated methylene isocyanides **71a-e** was carried with a view to enhance substrate scope of the reaction for a diversity oriented synthesis of a variety of novel 2,5'-bisoxazoles carrying wide range substituents at 2,5 and 4' positions of two bisoxazole rings. These results are summarized in Schemes 19-23. Thus 2-phenyl-5-(3,4-bismethoxyphenyl)-, 5-(2-thienyl)-, 5-[2-(1-N-methyl)pyrrolyl], 5-[3-(1-N-methyl)indolyl]-4'-carbethoxybisoxazoles (**73ba-73fa**) and the corresponding (2-thienyl) derivative **73ga** were obtained in overall high yields, when ethyl isocyanoacetate **71a** was reacted with oxazolones **66b-g** under standard copper-catalyzed reaction conditions (Scheme 19).



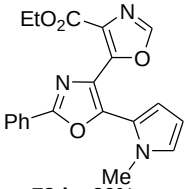
Scheme 19



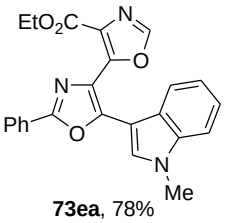
73ba, 75%



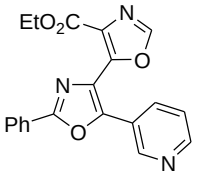
73ca, 79%



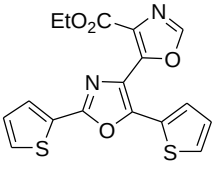
73da, 80%



73ea, 78%



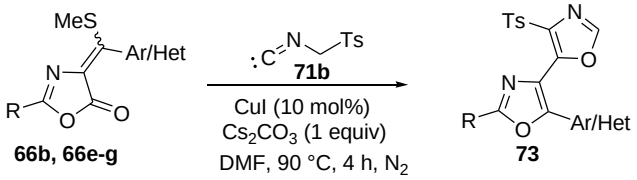
73fa, 72%



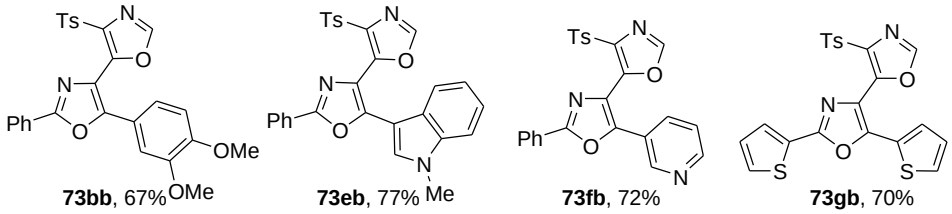
73ga, 71%

3.3.4 Synthesis of 2,5-[Bis(hetero)aryl]-4'-tosyl-4,5'-bisoxazoles 73

The novel domino reaction was found to be equally facile with tosylmethyl isocyanide **71b**, which readily reacts with oxazolones **66b** and **66e-g** under identical reaction conditions furnishing 2,5 bis(hetero)aryl-4'-tosyl-4,5'-bisoxazoles **73bb** and **73eb-73gb** in 67-77% yields (Scheme 20).

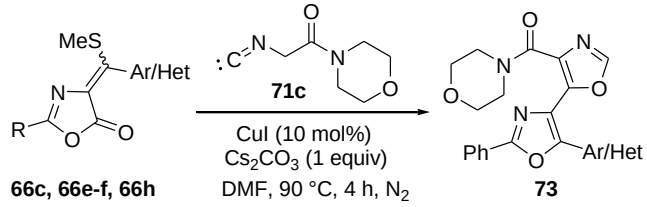


Scheme 20

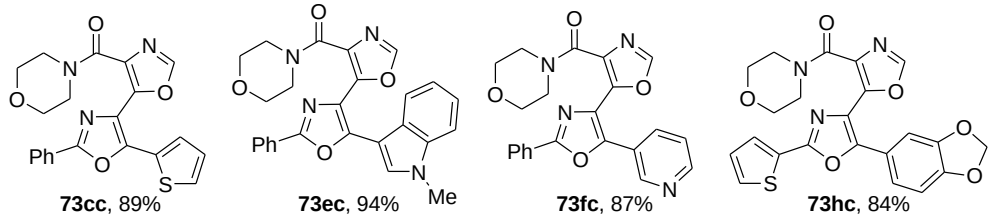


3.3.5 Synthesis of 2,5-Bis[(hetero)aryl]-4'-(N-morpholinocarbonyl)-4,5'-bisoxazoles 73

Similarly the corresponding bisoxazoles **73cc**, **73ec**, **73fc** and **73hc** carrying a 4'-(N-morpholino)amide functionality could also be prepared in excellent yields by employing N-(morpholino)isocyanoacetamide **71c** as reaction partner with oxazolones **66c**, **66e-f** and **66h** respectively (Scheme 21).

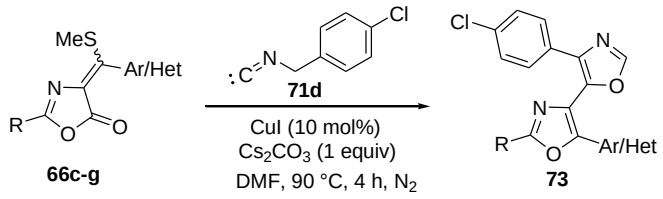


Scheme 21

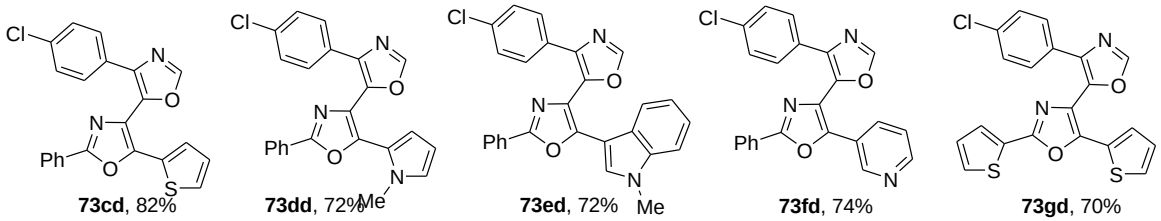


3.3.6 Synthesis of 2,5-Bis[(hetero)aryl]-4'-(4-chlorophenyl)-4,5'-bisoxazoles 73

Versatility of the reaction was further demonstrated by employing less acidic 4-chlorobenzyl isocyanide **71d,** which also reacted smoothly with various 4-(aryl/heteroaryl)methylene oxazolones **66c-g** under similar conditions providing 2,5-bis(hetero)aryl-4'-(4-chlorophenyl)-bisoxazoles **73cd-73gd** in excellent yields (Scheme 22).



Scheme 22

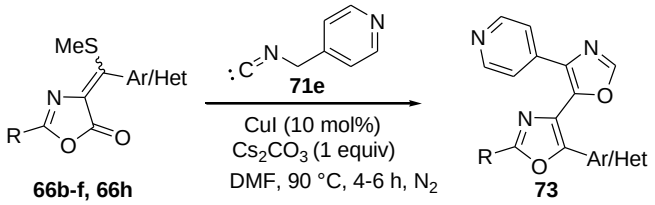


3.3.7 Synthesis of 2,5-Bis[(hetero)aryl]-4'-(4-pyridyl)-4, 5'-bisoxazoles 73

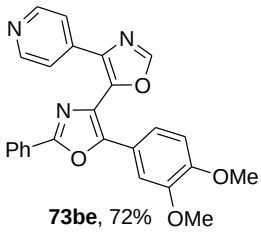
Further substituent diversity was introduced by installation of a 4-pyridyl moiety in the 4' position of bisoxazole framework by reacting 4-pyridylmethyl isocyanide **71e** with various oxazolones (**66b-f, 66h**) under identical conditions, yielding product bisoxazoles **73be-73fe, 73he** in high yields (Scheme 23). The synthesis of these novel pyridyl substituted bisoxazoles, especially the 5,4'-bis(pyridyl) derivative **73fe** is particularly noteworthy, since the pyridyl group is an important pharmacophore in various pharmaceutically important compounds.

3.3.8 Proposed Mechanism for Cu(I) Catalyzed Formation of Bisoxazoles 73 from 66

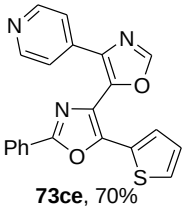
Based on our experimental observations and literature precedent, a plausible mechanism for this novel copper-catalyzed domino process leading to bisoxazoles **73** from oxazolones **66** and isocyanides **71** is depicted in the Schemes 24 and 25. Thus the initiating step appears to be the formation of α-cuprioisocyanide species **A** or its tautomer **A**[1] by reaction of isocyanides with CuI in the presence of base. Subsequent nucleophilic ring



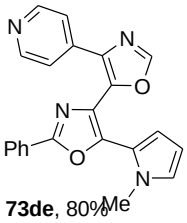
Scheme 23



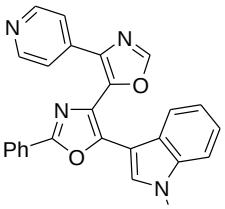
73be, 72%



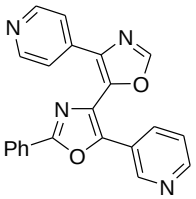
73ce, 70%



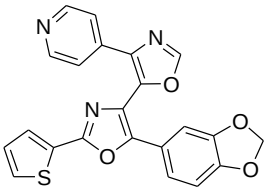
73de, 80%



73ee, 80%



73fe, 78%



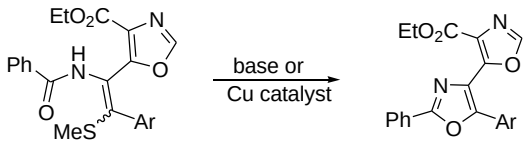
73he, 72%

opening of the lactone ring of oxazolone **66** by intermediate **A** and/or **A**[1], generates the acyclic α-acylisonitrile intermediate **B**, which exists in equilibrium with the copper enolate **C** in the basic medium. The intermediate **C** undergoes facile intramolecular cyclization by attack on isonitrile carbon to furnish the 2-oxazolocopper intermediate **D** (Scheme 24). The C-Cu bond in the intermediate **D** is protonated by isocyanide **71**, furnishing the initially formed oxazole (B ring) containing acyclic product **72** at lower temperature, with the regeneration of the copper intermediate **A** and/or **A**[1], thus completing the catalytic cycle for the formation of initial product **72**.

Regarding possible mechanism for the formation of second oxazole ring (A) of the bisoxazole **73** from the intermediate **D** or **72** at higher temperature, our studies reveal that intramolecular cyclization of **72aa** to **73aa** is much more efficient in the presence of copper catalyst (CuI/Cs_2CO_3) yielding bisoxazole **73aa** in 88% yield within 4 h (Table 4, entry 1), whereas under base induced conditions (Cs_2CO_3/DMF), in the absence of CuI, reaction was not complete even after 36 h, providing **73aa** in maximum yield of 65% along with unreacted starting material (Table 4, entries 2-3). Similarly other bases like potassium *t*-butoxide or DBU also furnished **73aa** in lower yields requiring more drastic reaction

conditions (Table 4, entries 4,5). These observations evidently show that the formation of second oxazole ring (A) of bisoxazole **73** by intramolecular cyclization of the intermediate **72** is facilitated in the presence of Cu(I) catalyst.

Table 4. Intramolecular Cyclization of Open Chain Adduct 72aa to Bisoxazole 73aa



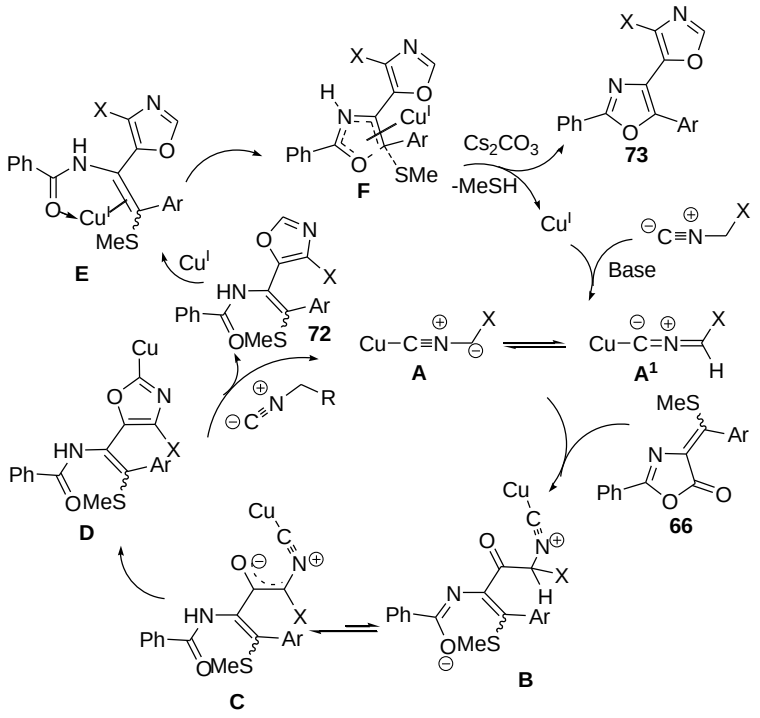
72aa Ar = 4-$MeOC_6H_4$ **73aa**

entry	reagent conditions[a]	solvent	T (°C)	t (h)	yield(%) **73aa**
1	CuI/Cs_2CO_3	DMF	90	4	88
2	Cs_2CO_3	DMF	90	25	60 (24)[b]
3	Cs_2CO_3	DMF	90	36	65 (20)[b]
4	*t*BuOK	DMF	90	30	63
5	DBU	DMF	90	32	59

[a]Reaction Conditions: Catalyst (10 mol %), base (1 equiv).
[b]Yield of recovered **72aa.**

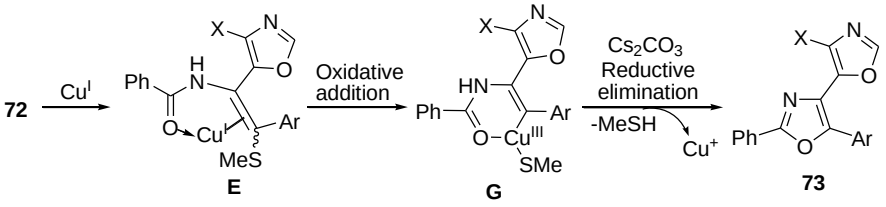
On the basis of known mechanisms of Ullman type condensations[37] along with the related mechanistic studies on the synthesis of benzoazoles by Cu(I) catalyzed intramolecular cyclization of *o*-halobenzanilides,[38] we propose two possible mechanisms for the formation of **A** ring of bisoxazole **73** via copper catalyzed intramolecular cyclization of β-(methylthio)vinylenamide functionality present in the intermediate **72** (Schemes 24 and 25).

Thus the coordination of amide functionality of **72** with cuprous ion, first forms the chelated intermediate **E**,[39] which undergoes intramolecular nucleophilic substitution at the electrophilic double bond through the transition state intermediate **F** (Scheme 24). Subsequent Cs_2CO_3 assisted elimination of MeSH in the intermediate **F** and the decomposition of the resulting bisoxazole-Cu complex furnishes the bisoxazole **73** along with the regenerated Cu(I) catalyst (Scheme 24). The present mechanism is similar to that proposed by Paine[37e] and later by Ma and co-workers in their detailed study of Cu(I) catalyzed coupling reaction of aryl halides with α-amino acids, involving a π-complex intermediate.[40] Alternatively, the initially formed intermediate **E** can undergo oxidative addition, forming the Cu^{III} containing transient intermediate **G** (Scheme 25). Subsequent reductive elimination of G in the presence of Cs_2CO_3 affords the bisoxazole **73** and Cu(I) catalyst.[37a-d,38a-c] In the absence of literature examples of Cu(I) catalyzed coupling reactions



Scheme 24

3.3.9 Proposed Alternate Mechanism for Copper Catalyzed Formation of Bisoxazoles 73 from Acyclic Precursors 72



Scheme 25

of aryl/vinylthioethers with nitrogen or oxygen nucleophiles, we prefer former mechanism involving intramolecular nucleophilic substitution of methylthio group in the intermediate **F** (Scheme 24). However further study is required to investigate the detailed mechanism and role of copper catalyst in this transformation.

3.4 Conclusion

In conclusion, we have demonstrated a novel, mild and efficient Cu(I) catalyzed domino process from readily accessible oxazolones **66** and activated methylene isocyanides **71** providing a straightforward direct route for diversity oriented synthesis of hitherto unreported 2,5,4'-trisubstituted-4,5'-bisoxazoles. The reaction displays broad substrate scope and excellent functional group compatibility by employing wide range of substituted

oxazolones and isocyanides furnishing bisoxazoles with three potential points of diversity. The overall domino process comprising of one C-C and two C-O bonds formations involves initial acylation of cupriomethylene isocyanides (α-cupriomethyleneisocyanides) by nucleophilic ring opening of oxazolones followed by sequential construction of two oxazole rings in the presence of copper catalyst. It should be noted, that although transition metal catalyzed synthesis of oxazolines by reaction of carbonyl compounds with activated methylene isocyanoacetate is a well documented efficient methodology,[41] the analogous catalytic process for oxazole formation via α-acylation of activated methylene isocyanides has not been much explored.[42]

We believe that the synthesis reported herein, can find application in a number of fields including combinatorial and solid phase synthesis as well as in automation, increasing the popularity of these novel bisoxazoles, in view of medicinal importance of natural products containing this versatile scaffold.

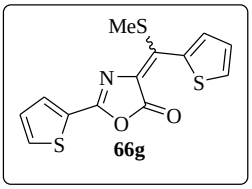
3.5 Experimental Section

3.5.1 General Information. All the chemicals were commercially purchased and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using Merck TLC Silica gel plates and visualized with UV light. Flash chromatography was performed using Merck silica gel (100-200 mesh). Nuclear magnetic resonance spectra were recorded on (400 MHz) Fourier transform NMR spectrometer with $CDCl_3$, DMSO-d_6 (or) Acetone-d_6 as solvent. Chemical shifts were reported in δ ppm (parts per million) using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$,δ 2.50 for DMSO-d_6 and δ 2.05 for Acetone-d_6 in ^{1}H-NMR, δ 77.16 for $CDCl_3$ and δ 39.5 for DMSO-d_6 in ^{13}C-NMR). Coupling constants were reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), ddd (doublet of doublet of doublet), td (triple doublet) m (multiplet) and br (broad). Infrared spectra were recorded with FTIR instrument and HRMS on Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

The scanned copies of ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in supporting information of *J. Org. Chem.* **2013**, *78*, 3948.

The desired activated methylene isocyanides **71a**,[43] **71c**,[44] **71d**[45] and **71e**[46] were prepared according to the reported procedures, whereas the corresponding tosylmethyl isocyanide **71b** was commercially purchased. The dithioesters **75a-c**,[47a] **75g**,[47a] **75d-e**,[29e,47b] and **75f**[47c] required for the synthesis of 5-oxazolone precursors **66a-h** were prepared according to the reported methods in literature.

3.5.2 General Procedure for the Synthesis of 2-Phenyl/(2-thienyl)-4-[(aryl/heteroaryl)-(methylthio)methylene]-oxazole-5-ones (66a-h). The oxazalones **66a-h** were prepared following our earlier reported procedure[31] by reaction of the corresponding 2-phenyl- **(74a)** and 2-(2-thienyl)-oxazol-5-ones **(74b)** (3.0 mmol) with the appropriate (hetero)aryl dithioesters **75** (3.0 mmol) in the presence of sodium hydride (0.31 g, 7.8 mmol) in DMF (10 mL) followed by treatment with methyl iodide (0.28 mL, 4.5 mmol) and work-up as reported.[31] 2-Phenyl-4-[(aryl/heteroaryl)-(methylthio)methylene]-5-oxazolones **66a-f** were characterized by comparison of their spectral and analytical data with that of reported.[31] The spectral and analytical data of unknown oxazolones **66g** and **66h** are given below.

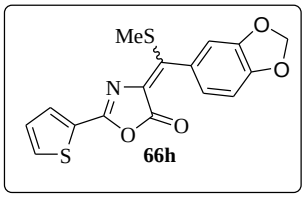


66g

(*E*/*Z*) 4-[(Methylthio)(2-thienyl)methylene]-2-(2-thienyl)oxazol-5(4*H*)-one (66g). Obtained from 2-(2-thienyl)oxazolone **74b** and dithioester **75c** (Ar = 2-thienyl), (*E*:*Z* = 78:22), brown solid (0.571 g, 62%): mp 128-130 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3101, 2926, 1771, 1616, 1396, 852, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 4.0 Hz, 1.2 Hz, 0.78H), 7.82-7.79 (m, 1H), 7.72 (dd, *J* = 4.8 Hz, 1.2 Hz, 0.78H), 7.63-7.60 (m, 1H), 7.59 (dd, *J* = 4.8 Hz, 1.2 Hz, 0.22H), 7.39 (dd, *J* = 3.6 Hz, 1.2 Hz, 0.22H), 7.21 (dd, *J* = 5.2 Hz, 4.0 Hz, 0.78H), 7.19-7.15 (m, 1.22H), 2.58 (s, 2.6H), 2.49 (s, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 156.0, 144.4, 140.3, 134.3, 134.2, 132.4, 132.3, 131.9, 131.3, 130.7, 129.3, 129.0, 128.9, 128.7, 128.6, 128.22, 128.19, 19.9, 18.0; HRMS (ESI) *m/z* calcd for $C_{13}H_9NO_2S_3$ $[M + H]^+$ 307.9874, found 307.9859.

(*E*/*Z*) 4-(Benzo[*d*][1,3]dioxol-5-yl(methylthio)methylene)-2-(2-thienyl)oxazol-5(4*H*)-one (66h). Obtained from oxazolone **74b** and dithioester **75g** (Ar = 3,4-methylenedioxyphenyl), (*E*:*Z* = 34:66), yellow solid (0.745 g, 72%): mp 126-128 °C; R_f 0.4 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3102, 2926, 1772, 1608, 1476, 1425, 1205, 1028, 971, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 4.0 Hz, 1.2 Hz, 0.34H), 7.73 (dd, *J* = 3.6 Hz, 1.2 Hz, 0.66H), 7.60

(dd, *J* = 4.8 Hz, 1.2 Hz, 0.34H), 7.53 (dd, *J* = 4.8 Hz, 1.2Hz, 0.66H), 7.15 (dd, *J* = 4.8 Hz, 3.6 Hz, 0.34H), 7.11 (dd, *J* = 5.0 Hz, 4.0 Hz, 0.66H), 7.01 (dd, *J* = 8.0 Hz, 1.6 Hz, 0.66H), 6.97

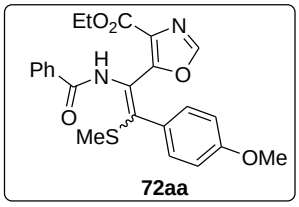


66h

(d, *J* = 1.6 Hz, 0.66H), 6.94 (s, 0.34H), 6.92-6.89 (m, 0.66H), 6.86 (dd, *J* = 8.0 Hz, 1.6 Hz, 0.34H), 6.81 (d, *J* = 1.6 Hz, 0.34H), 6.06 (s, 1.32H), 6.05 (s, 0.68H), 2.26 (s, 1.02H), 2.22 (s, 1.98H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 161.9, 156.3, 156.1, 155.5, 155.4, 149.5, 149.3, 148.3, 148.1, 132.1, 131.7, 131.66, 131.4, 129.3, 129.1, 128.9, 128.5, 128.4, 128.1, 128.0, 126.3, 125.1, 123.7, 110.7, 109.6, 108.8, 108.6, 101.8, 17.3, 16.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}NO_4S_2$ $[M + H]^+$ 346.0208, found 346.0192.

3.5.3 General Procedure for Base Induced Reaction of 4-[(4-Methoxyphenyl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-one (66a) with Ethyl Isocyanoacetate (71a). To a stirred solution of oxazolone **66a** (97.6 mg, 0.3 mmol) and **71a** (33.9 mg, 0.3 mmol) in DMF or THF (2 mL), the appropriate base (DBU, *t*BuOK, NaH, Cs_2CO_3, Et_3N) (0.3 mmol) was added and the reaction mixture was further stirred at room temperature for 10-25 h (Table 1). It was then poured into saturated NH_4Cl solution (50 mL), extracted with EtOAc (3 x 25 mL), washed with water (2 x 30 mL), brine (30 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure to give mixture of acyclic adduct **72aa** and bisoxazole **73aa**, which were purified by column chromatography on silica gel using EtOAc-hexane as eluent. The yields of products **72aa** and **73aa** isolated in various experiments are given in Table 1 (entries 1-10)

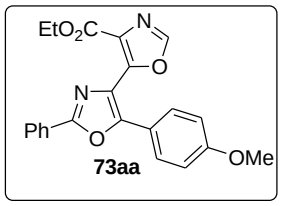
(*E*/*Z*) Ethyl 5-[1-benzamido-2-(4-methoxyphenyl)-2-(methylthio)vinyl]-oxazole-4-carboxylate (72aa). Obtained as a yellow solid (*E:Z* = 22:78): mp 104-106 °C; R_f 0.35 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3262, 3135, 1700, 1662, 1605, 1574, 1511, 1479, 1285, 1246, 1171, 1095, 1045; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 0.38H), 7.96 (s, 0.62H), 7.90 (d, *J* = 6.8 Hz, 0.64H), 7.85 (s, 0.62H), 7.58-7.55 (m, 2.38H), 7.50-7.44 (m, 3H), 7.37-7.33 (m, 1.24H), 7.14 (dd, *J* = 6.4 Hz, 2.0 Hz, 0.76H), 6.96 (dt, *J* = 8.8 Hz, 2.4 Hz, 1.24H), 6.79 (dd, *J* = 7.0 Hz, 1.8 Hz, 0.76H), 4.37-4.27 (m, 2H), 3.83 (s, 1.86H), 3.78 (s, 1.14H), 1.98 (s, 1.14H), 1.92 (s, 1.86H), 1.37-1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 161.7, 161.6, 160.3, 159.8, 152.7, 152.3, 149.6, 149.3, 139.4, 138.9, 133.8, 133.6,



72aa

132.1, 132.0, 131.0, 130.9, 129.1, 128.8, 128.7, 127.6, 127.3, 127.2, 127.1, 119.1, 119.0, 114.6, 114.0, 61.4, 61.3, 55.5, 55.3, 16.0, 15.7, 14.4, 14.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}N_2O_5S$ $[M + Na]^+$ 461.1147, found 461.1144.

2-Phenyl-5-(4-methoxyphenyl)-4'-carbethoxy-4,5'-bisoxazole (73aa). Obtained as a pale yellow solid: mp 128-130 °C; R_f 0.5 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3129, 2977, 2931, 2842, 1712, 1505, 1256, 1174, 1091, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15-8.12 (m, 2H), 8.05 (s, 1H), 7.53(d, J = 8.8 Hz, 2H), 7.51-7.49 (m, 3H), 6.92 (d, J = 8.8 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 160.3, 159.3, 152.8, 150.2, 147.1, 131.2, 129.5, 129.4, 127.4, 126.2, 126.0, 121.8, 119.3, 114.7, 60.7, 55.4, 13.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_2O_5$ $[M + Na]^+$ 413.1113, found 413.1115.



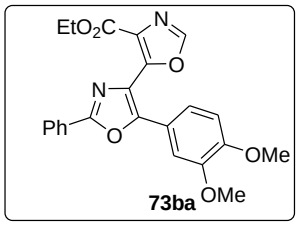
73aa

3.5.4 General Procedure for Copper(I) Catalyzed Domino Reaction of 2-Phenyl/(2-thienyl)-4-[(aryl/heteroaryl)-(methylthio)methylene]-5-oxazolones (66a-h) with Activated Methylene Isocyanides (71a-e): Synthesis of 2,5-Bis(aryl/heteroaryl)-4'-substituted-4,5'-bisoxazoles (73aa-73he). To a stirring solution of the corresponding 5-oxazolone **66** (0.3 mmol) and appropriate activated methylene isocyanides **71** (0.3 mmol) in DMF (2 mL), CuI (5.7 mg, 10 mol%) was added under nitrogen atmosphere, followed by addition of Cs_2CO_3 (97.7 mg, 0.3 mmol). The reaction mixture was then stirred at 90 °C for 4-6 h (monitored by TLC). It was then poured into saturated NH_4Cl (50 mL) solution, extracted with EtOAc (3 x 25 mL), washed with water (2 x 30 mL), brine (30 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude bisoxazoles **73aa-73he**, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

2-Phenyl-5-(4-methoxyphenyl)-4'-carbethoxy-4,5'-bisoxazole (73aa). Obtained from oxazolone **66a** and isocyanide **71a**, as pale yellow solid (89.9 mg, 75%) (under copper catalyzed conditions): spectral and analytical data is given earlier.

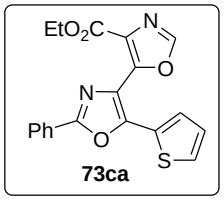
2-Phenyl-5-(3,4-dimethoxyphenyl)-4'-carbethoxy-4,5'-bisoxazole (73ba). Obtained from oxazolone **66b** and isocyanide **71a**, pale yellow solid (88.7 mg, 75%): mp 112-114 °C; R_f

0.52 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3116, 2932, 2837, 1716, 1511, 1256, 1098, 703; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14-8.13 (m, 2H), 8.06 (s, 1H), 7.51-7.50 (m, 3H), 7.19 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.3, 151.0, 150.9, 150.5, 149.3, 131.0, 130.3, 129.0, 127.5, 126.8, 126.7, 122.4, 120.5, 119.3, 111.4, 108.8, 61.5, 56.1, 56.0, 14.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_2O_6$ $[M + Na]^+$ 443.1219, found 443.1225.



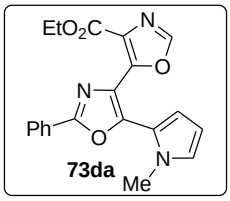
73ba

2-Phenyl-5-(2-thienyl)-4'-carbethoxy-4,5'-bisoxazole (73ca). Obtained from oxazolone **66c** and isocyanide **71a**, grey solid (96.0 mg, 79%): mp 138-140 °C; R_f 0.5 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3111, 2928, 1725, 1297, 1184, 1079, 1026, 705; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14-8.11 (m, 2H), 8.07 (s, 1H), 7.52-7.50 (m, 3H), 7.40 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.36 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.08 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.3, 151.1, 147.2, 146.7, 131.2, 131.0, 129.1, 128.8, 128.0, 127.7, 126.9, 126.8, 126.5, 122.8, 61.5, 14.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}N_2O_4S$ $[M + Na]^+$ 389.0572, found 389.0573.



73ca

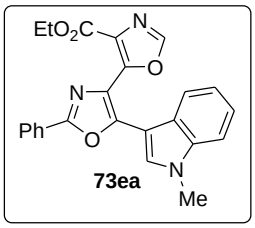
2-Phenyl-5-(1-methyl-2-pyrrolyl)-4'-carbethoxy-4,5'-bisoxazole (73da). Obtained from oxazolone **66d** and isocyanide **71a**, grey solid (97.4 mg, 80%): mp 136-138 °C; R_f 0.52 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3116, 2996, 1727, 1511, 1180, 1085, 728; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.99 (s, 1H), 7.50-7.49 (m, 3H), 6.78 (dd, J = 2.6 Hz, 1.6 Hz, 1H), 6.30 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.13 (dd, J = 3.6 Hz, 2.6 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.6, 150.6, 147.8, 145.0, 131.0, 129.7, 129.1, 126.9, 126.6, 126.3, 124.2, 120.1, 112.8, 109.0, 61.4, 36.0, 14.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}N_3O_4$ $[M + Na]^+$ 386.1117, found 386.1116.



73da

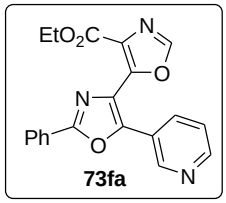
2-Phenyl-5-(1-methyl-3-indolyl)-4'-carbethoxy-4,5'-bisoxazole (73ea). Obtained from oxazolone **66e** and isocyanide **71a**, white solid (92.5 mg, 78%): mp 168-170 °C; R_f 0.35 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3105, 2978, 1706, 1587, 1410, 1278, 1203, 1114, 731; ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.13-8.11 (m, 2H), 7.78 (s, 1H), 7.75 (d, J = 8.0

Hz, 1H), 7.64-7.56 (m, 4H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 159.7, 150.6, 148.9, 148.7, 137.0, 130.7, 130.0, 129.1, 128.5, 127.2, 126.5, 125.5, 123.2, 121.5, 121.0, 120.8, 110.0, 103.5, 61.4, 33.4, 14.1; HRMS (ESI) *m/z* calcd for $C_{24}H_{19}N_3O_4$ $[M + Na]^+$ 436.1273, found 436.1276.



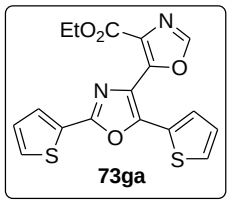
73ea

2-Phenyl-5-(3-pyridyl)-4'-carbethoxy-4,5'-bisoxazole (73fa). Obtained from oxazolone **66f** and isocyanide **71a**, brown solid (87.8 mg, 72%): mp 146-148 °C; R_f 0.5 (6:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3079, 2925, 1719, 1417, 1297, 1095, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 1.6 Hz, 1H), 8.62 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 8.16-8.14 (m, 2H), 8.08 (s, 1H), 7.89-7.86 (ddd, *J* = 8.0 Hz, 2.2 Hz, 0.8 Hz, 1H), 7.53-7.52 (m, 3H), 7.35 (ddd, *J* = 8.0 Hz, 4.8 Hz, 0.8 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 160.6, 151.2, 150.4, 148.1, 147.5, 147.1, 133.0, 131.5, 130.7, 129.2, 126.9, 126.4, 125.1, 124.2, 123.6, 61.6, 14.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{15}N_3O_4$ $[M + Na]^+$ 384.0960, found 384.0964.



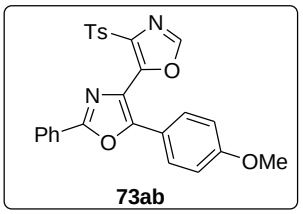
73fa

2,5-Bis(2-thienyl)-4'-carbethoxy-4,5'-bisoxazole (73ga). Obtained from oxazolone **66g** and isocyanide **71a**, brown solid (79.3 mg, 71%): mp 163-165 °C; R_f 0.2 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3101, 2933, 2852, 1727, 1587, 1175, 1050, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.80 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 7.51 (dd, *J* = 4.8 Hz, 0.8 Hz, 1H), 7.39 (dd, *J* = 5.2 Hz, 0.8 Hz, 1H), 7.35 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 7.16 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 7.07 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H) 4.21 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 156.6, 151.2, 146.9, 146.1, 131.1, 129.5, 128.9, 128.7, 128.5, 128.2, 127.9, 127.7, 126.9, 122.6, 61.5, 14.0; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}N_2O_4S_2$ $[M + H]^+$ 373.0317, found 373.0304.



73ga

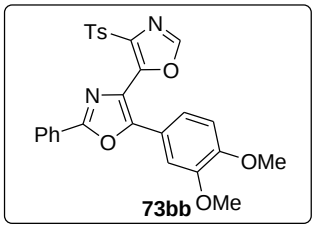
2-Phenyl-5-(4-methoxyphenyl)-4'-(4-tosyl)-4,5'-bisoxazole (73ab). Obtained from oxazolone **66a** and isocyanide **71b**, pale yellow solid (106.0 mg, 73%): mp 183-185 °C; R_f 0.54 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3148, 2929, 2862, 1499, 1334, 1264, 1148, 1091; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.14-8.11 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 2H),



73ab

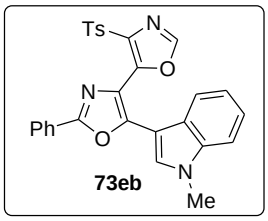
7.65-7.61 (m, 3H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.3, 151.9, 151.0, 146.1, 145.1, 139.3, 136.8, 131.0, 129.8, 129.1, 128.9, 128.2, 126.9, 126.6, 120.7, 119.7, 114.6, 55.5, 21.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{20}N_2O_5S$ $[M + Na]^+$ 495.0991, found 495.0994.

2-Phenyl-5-(3,4-dimethoxyphenyl)-4'-(4-tosyl)-4,5'-bisoxazole (73bb). Obtained from oxazolone **66b** and isocyanide **71b**, pale yellow solid (94.7 mg, 67%): mp 188-190 °C; R_f 0.52 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3015, 2932, 2829, 1511, 1340, 1264, 1142, 1021; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.16-8.13 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.65-7.62 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.08 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 151.9, 151.1, 150.7, 149.4, 146.1, 145.2, 139.5, 136.7, 131.1, 129.8, 129.1, 128.8, 126.8, 126.7, 120.9, 119.81, 119.79, 111.5, 109.3, 56.1, 56.0, 21.8; HRMS (ESI) *m/z* calcd for $C_{27}H_{22}N_2O_6S$ $[M + Na]^+$ 525.1096, found 525.1093.



73bb

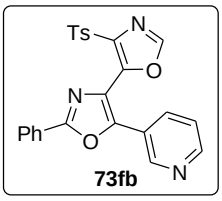
2-Phenyl-5-(1-methyl-3-indolyl)-4'-(4-tosyl)-4,5'-bisoxazole (73eb). Obtained from oxazolone **66e** and isocyanide **71b**, pale yellow solid (109.5 mg, 77%): mp 216-218 °C; R_f 0.45 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3130, 3066, 1649, 1574, 1328, 1152, 913; ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.46 (s, 1H), 8.24-8.21 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.87 (dd, *J* = 6.8 Hz, 1.6 Hz, 2H), 7.66-7.57 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.35-7.30 (m, 3H), 7.25-7.21 (m, 1H), 3.86 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4, 153.0, 149.2, 145.2, 145.0, 137.6, 136.7, 136.4, 131.0, 130.2, 129.8, 129.5, 127.9, 126.3, 125.9, 124.5, 122.7, 121.4, 119.7, 118.4, 110.8, 100.9, 33.0, 21.1; HRMS (ESI) *m/z* calcd for $C_{28}H_{21}N_3O_4S$ $[M + Na]^+$ 518.1150, found 518.1155.



73eb

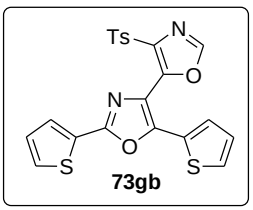
2-Phenyl-5-(3-pyridyl)-4'-(4-tosyl)-4,5'-bisoxazole (73fb). Obtained from oxazolone **66f** and isocyanide **71b**, brown solid (107.8 mg, 72%): mp 190-192 °C; R_f 0.56 (6:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3123, 2928, 1335, 1152, 705, 667, 598; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.86 (d, J = 1.6 Hz, 1H), 8.66 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.16-8.14 (m, 2H), 8.00 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.89 (ddd, J = 9.0 Hz, 2.0 Hz, 0.8 Hz 1H), 7.57-7.53 (m, 3H), 7.38 (ddd, J = 9.0 Hz, 4.8 Hz, 0.4 Hz, 1H), 7.3 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 153.9, 150.6, 148.6, 146.6, 145.5, 143.7, 138.6, 136.0, 133.6, 131.8, 130.0, 129.5, 128.0, 126.6, 125.6, 124.2, 123.0, 122.8, 21.1; HRMS (ESI) *m/z* calcd for $C_{24}H_{17}N_3O_4S$ $[M + Na]^+$ 466.0837, found 466.0838.



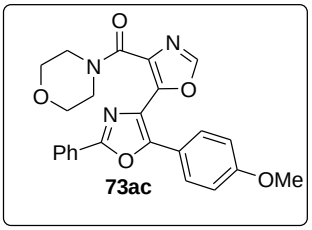
73fb

2,5-Bis(2-thienyl)-4'-(4-tosyl)-4,5'-bisoxazole (73gb). Obtained from oxazolone **66g** and isocyanide **71b**, off-white solid (95.4 mg, 70%): mp 128-130 °C; R_f 0.5 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3109, 2954, 1587, 1330, 1153, 712, 602; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 2H), 7.99 (s, 1H), 7.79 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.53 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.43 (dd, J = 4.8 Hz, 0.8 Hz, 1H), 7.39 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H),7.18 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 7.09 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 150.9, 146.8, 145.2, 144.8, 139.9, 136.8, 129.8, 129.6, 129.1, 129.0, 128.8, 128.34, 128.26, 128.1, 128.0, 127.6, 121.3, 21.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{14}N_2O_4S_3$ $[M + H]^+$ 455.0194, found 455.0174.



73gb

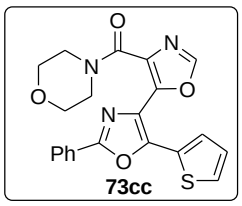
2-Phenyl-5-(4-methoxyphenyl)-4'-(N-morpholinocarbonyl)-4,5'-bisoxazole (73ac). Obtained from oxazolone **66a** and isocyanide **71c**, yellow solid (112.6 mg, 85%): mp 163-165 °C; R_f 0.2 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3142, 2960, 2852, 1630, 1505, 1436, 1253, 1121, 832; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.07 (m, 2H), 7.98 (s, 1H), 7.65 (d, J = 9.0 Hz, 2H), 7.51-7.47 (m, 3H), 6.98 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.70-3.56 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 160.3, 159.4, 151.6, 148.3, 142.0, 131.3, 131.1, 129.3, 128.2, 126.07, 126.0, 122.7, 119.2, 114.4, 66.0, 65.8, 55.4, 46.7, 41.7; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}N_3O_5$ $[M + Na]^+$ 454.1379, found 454.1383.



73ac

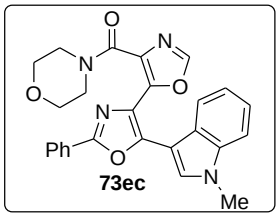
2-Phenyl-5-(2-thienyl)-4'-(N-morpholinocarbonyl)-4,5'-bisoxazole (73cc). Obtained from oxazolone **66c** and isocyanide **71c**, grey solid (120.3 mg, 89%): mp 218-220 °C; R_f 0.25 (8:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3105, 2902, 2859, 1625, 1498, 1114, 919, 699; ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 8.02 (s, 1H), 7.66 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.50-7.49 (m, 3H), 7.46 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.14 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 3.76 (br s, 4H), 3.66 (br s, 2H), 3.59 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 159.5, 151.8, 143.4, 141.0, 131.8, 131.5, 129.4, 129.1, 128.3, 127.9, 127.6, 126.2, 125.6, 123.2, 66.1, 65.8, 46.7, 41.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}N_3O_4S$ $[M + Na]^+$ 430.0837, found 430.0833.



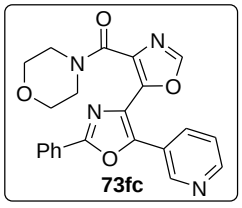
73cc

2-Phenyl-5-(1-methyl-3-indolyl)-4'-(N-morpholinocarbonyl)-4,5'-bisoxazole (73ec). Obtained from oxazolone **66e** and isocyanide **71c**, yellow solid (122.6 mg, 94%): mp 220-222 °C; R_f 0.2 (9:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3135, 2902, 2852, 1625, 1568, 1114, 737; ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.32 (s, 1H), 8.19-8.16 (m, 2H), 8.04 (s, 1H), 8.00 (dt, J = 7.2 Hz, 1.2 Hz, 1H), 7.63-7.54 (m, 4H), 7.34-7.30 (m, 1H), 7.26-7.22 (m, 1H), 3.97 (s, 3H), 3.58 (br s, 4H), 3.48 (br s, 2H), 3.41 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5, 158.7, 151.3, 146.0, 141.9, 136.7, 130.9, 130.4, 130.3, 129.4, 126.3, 125.8, 125.0, 122.6, 121.4, 121.1, 120.0, 110.7, 101.3, 66.0, 65.8, 46.7, 41.8, 33.1; HRMS (ESI) *m/z* calcd for $C_{26}H_{22}N_4O_4$ $[M + Na]^+$ 477.1539, found 477.1535.



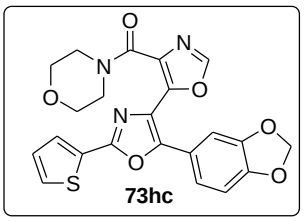
73ec

2-Phenyl-5-(3-pyridyl)-4'-(N-morpholinocarbonyl)-4,5'-bisoxazole (73fc). Obtained from oxazolone **66f** and isocyanide **71c**, pale yellow solid (118.1 mg, 87%): mp 210-212 °C; R_f 0.40 (1:1 DCM:acetone); IR (KBr, cm^{-1}) 3092, 2978, 2865, 1625, 1505, 1108, 957; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 8.66 (br s, 1H), 8.12-8.09 (m, 2H), 8.04 (br d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 7.54-7.49 (m, 3H), 7.44-7.41 (m, 1H), 3.76-3.67 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 161.6, 150.3, 150.1, 147.7, 146.1, 143.5, 134.0, 132.7, 131.5, 129.1, 126.9, 126.4, 125.9, 123.7, 66.9, 66.7, 47.5, 42.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_4O_4$ $[M + Na]^+$ 425.1226, found 425.1228.



73fc

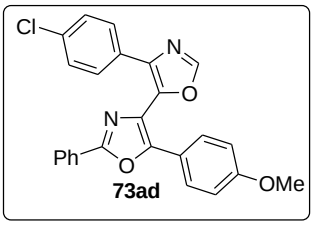
2-(2-Thienyl)-5-(benzo[*d*][1,3]dioxol-5-yl)-4'-(N-morpholinocarbonyl)-4,5'-bisoxazole (73hc). Obtained from oxazolone **66h** and isocyanide **71c**, pale yellow solid (113.7 mg, 84%): mp 188-190 °C; R_f 0.30 (8:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3096, 2926, 2844, 1640, 1501, 1457, 1243, 1104, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.73 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 7.48 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.23 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.15-



73hc

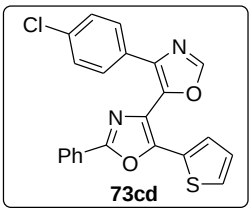
7.13 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.04 (s, 2H), 3.75-3.60 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 156.8, 150.0, 148.9, 148.4, 148.1, 143.4, 132.2, 129.2, 129.1, 128.6, 128.2, 123.2, 121.5, 121.2, 108.9, 107.1, 101.7, 66.8, 66.7, 47.4, 42.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}N_3O_6S$ $[M + H]^+$ 452.0916, found 452.0903.

2-Phenyl-5-(4-methoxyphenyl)-4'-(4-chlorophenyl)-4,5'-bisoxazole (73ad). Obtained from oxazolone **66a** and isocyanide **71d**, white solid (120.0 mg, 91%): mp 158-160 °C; R_f 0.53 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3129, 2829, 1607, 1511, 1256, 1180, 1091, 931, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.13 (m, 2H), 8.05 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 2H), 7.52-7.49 (m, 3H), 7.45 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 160.3, 150.8, 149.4, 138.6, 136.9, 134.1, 130.8, 129.4, 128.9, 128.5, 128.4, 127.5, 126.8, 126.5, 123.4, 119.8, 114.2, 55.4; HRMS (ESI) *m/z* calcd for $C_{25}H_{17}ClN_2O_3$ $[M + Na]^+$ 451.0825, found 451.0821.



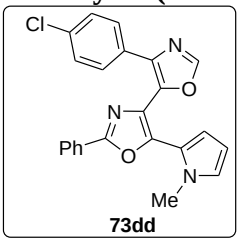
73ad

2-Phenyl-5-(2-thienyl)-4'-(4-chlorophenyl)-4,5'-bisoxazole (73cd). Obtained from oxazolone **66c** and isocyanide **71d**, white solid (110.1 mg, 82%): mp 150-152 °C; R_f 0.65 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3085, 2991, 1561, 1518, 1479, 1089, 837, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.12 (m, 2H), 8.08 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.53-7.51 (m, 3H), 7.35 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.30-7.28 (m, 3H), 7.01 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 151.0, 145.3, 137.81, 137.76, 134.4, 131.2, 129.6, 129.1, 128.7, 128.6, 128.0, 127.7, 126.84, 126.79, 126.6, 124.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{13}ClN_2O_2S$ $[M + Na]^+$ 427.0284, found 427.0286.



73cd

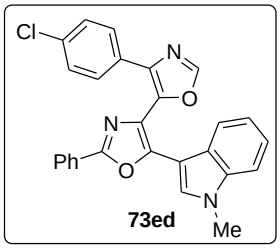
2-Phenyl-5-(1-methyl-2-pyrrolyl)-4'-(4-chlorophenyl)-4,5'-bisoxazole (73dd). Obtained from oxazolone **66d** and isocyanide **71d**, off-white solid (96.9 mg, 72%): mp 116-118 °C; R_f 0.6 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3117, 2928, 2852, 1518, 1486, 1089, 932, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.07 (m, 2H), 7.99 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.51-7.50 (m, 3H),



73dd

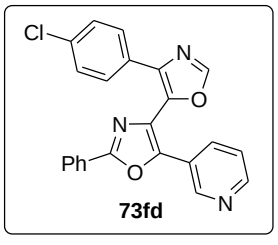
7.29 (d, *J* = 8.6 Hz, 2H), 6.71 (dd, *J* = 2.4 Hz, 1.6 Hz, 1H), 6.28 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H), 6.087 (dd, *J* = 3.6 Hz, 2.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 150.5, 143.0, 138.5, 136.8, 134.0, 130.9, 129.6, 129.0, 128.7, 128.3, 126.8, 126.4, 126.0, 125.5, 119.7, 113.2, 108.8, 35.7; HRMS (ESI) *m/z* calcd for $C_{23}H_{16}ClN_3O_2$ $[M + Na]^+$ 424.0829, found 424.0829.

2-Phenyl-5-(1-methyl-3-indolyl)-4'-(4-chlorophenyl)-4,5'-bisoxazole (73ed). Obtained from oxazolone **66e** and isocyanide **71d**, reddish brown solid (93.4 mg, 72%): mp 165-167 °C; R_f 0.5 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3130, 3054, 2928, 1574, 1479, 1102, 907, 731; ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.37 (s, 1H), 8.21-8.18 (m, 2H), 7.96-7.90 (m, 3H), 7.64-7.57 (m, 4H), 7.48 (dt, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.33-7.27 (m, 3H), 7.24-7.19 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 150.7, 147.0, 139.3, 136.9, 136.2, 133.9, 130.7, 129.8, 129.1, 128.8, 128.6, 128.4, 127.3, 126.5, 125.5, 123.1, 122.4, 121.3, 120.8, 109.9, 103.0, 33.2; HRMS (ESI) *m/z* calcd for $C_{27}H_{18}ClN_3O_2$ $[M + Na]^+$ 474.0985, found 474.0982.



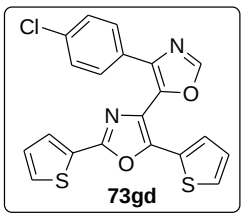
73ed

2-Phenyl-5-(3-pyridyl)-4'-(4-chlorophenyl)-4,5'-bisoxazole (73fd). Obtained from oxazolone **66f** and isocyanide **71d**, pale yellow solid (99.8 mg, 74%): mp 148-150 °C; R_f 0.42 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3142, 3035, 1662, 1555, 1518, 1089, 938, 699; ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.88 (d, *J* = 2.1 Hz, 1H), 8.56 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 8.44 (s, 1H), 8.23-8.20 (m, 2H), 8.04-8.01 (ddd, *J* = 8.0 Hz, 2.1 Hz, 1.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.63-7.60 (m, 3H), 7.42 (ddd, *J* = 8.0 Hz, 4.8 Hz, 1.2 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 151.1, 150.1, 147.2, 146.2, 137.8, 137.7, 134.6, 133.1, 131.5, 129.3, 129.2, 128.8, 128.7, 126.9, 126.8, 126.5, 123.9, 123.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{14}ClN_3O_2$ $[M + H]^+$ 400.0853, found 400.0857.



73fd

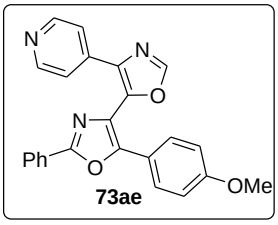
2,5-Bis(2-thienyl)-4'-(4-chlorophenyl)-4,5'-bisoxazole (73gd). Obtained from oxazolone **66g** and isocyanide **71d**, pale yellow solid (87.5 mg, 71%): mp 158-160 °C; R_f 0.5 (2:8 EtOAc:hexane); IR (KBr, cm^{-1}) 3101, 2926, 2859, 1720, 1602, 1521, 1234, 1094, 837, 712; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.91 (dd, *J* = 5.1 Hz, 1.2 Hz, 1H), 7.89 (dd, *J* =



73gd

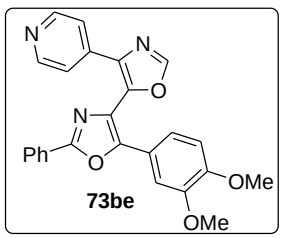
4.8 Hz, 1.2 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.71 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.41 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 7.30 (dd, *J* = 5.1 Hz, 4.0 Hz, 1H), 7.13 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 151.1, 144.8, 137.9, 137.5, 130.4, 129.54, 129.49, 128.97, 128.93, 128.7, 128.6, 128.3, 128.2, 127.9, 127.7, 126.8, 124.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{11}ClN_2O_2S_2$ $[M + H]^+$ 411.0029, found 411.0015.

2-Phenyl-5-(4-methoxyphenyl)-4'-(4-pyridyl)-4,5'-bisoxazole (73ae). Obtained from oxazolone **66a** and isocyanide **71e**, off-white solid (92.5 mg, 78%): mp 158-160 °C; R_f 0.2 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 2947, 2933, 2845, 1734, 1602, 1433, 1271, 1168, 845; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.9 Hz, 2H), 8.13-8.16 (m, 2H), 8.08 (s, 1H), 7.73 (dd, *J* = 4.9 Hz, 1.6 Hz, 2H), 7.50-7.54 (m 3H), 7.49 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.6, 151.1, 150.0, 146.1, 141.0, 138.5, 135.6, 131.1, 129.1, 127.7, 126.8, 126.7, 123.1, 121.4, 119.8, 114.5, 55.2; HRMS (ESI) *m/z* calcd for $C_{24}H_{17}N_3O_3$ $[M + H]^+$ 396.1348, found 396.1337.



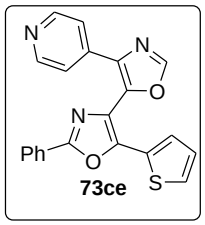
73ae

2-Phenyl-5-(3,4-dimethoxyphenyl)-4'-(4-pyridyl)-4,5'-bisoxazole (73be). Obtained from oxazolone **66b** and isocyanide **71e**, yellow solid (86.1 mg, 72%): mp 159-161 °C; R_f 0.4 (7:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3060, 2934, 2840, 1599, 1511, 1259, 1026, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.8 Hz, 1.6 Hz, 2H), 8.16-8.14 (m, 2H), 8.09 (s, 1H), 7.74 (dd, *J* = 4.8 Hz, 1.6 Hz, 2H), 7.54-7.52 (m, 3H), 7.16 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.1, 150.5, 150.1, 150.0, 149.3, 141.1, 138.5, 135.8, 131.2, 139.1, 126.8, 126.7, 123.2, 121.3, 119.8, 119.6, 111.5, 109.1, 56.1, 56.0; HRMS (ESI) *m/z* calcd for $C_{25}H_{19}N_3O_4$ $[M + H]^+$ 426.1454, found 426.1454.



73be

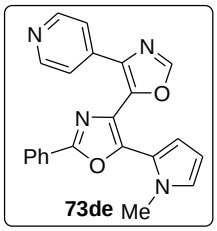
2-Phenyl-5-(2-thienyl)-4'-(4-pyridyl)-4,5'-bisoxazole (73ce). Obtained from oxazolone **66c** and isocyanide **71e**, grey solid (86.2 mg, 70%): mp 128-130 °C; R_f 0.55 (7:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3085, 3060, 2928, 1662, 1599, 1410, 906, 705, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 6.0 Hz, 2H), 8.15-8.12 (m, 2H), 8.12 (s, 1H), 7.78 (dd, *J* = 4.8 Hz, 1.6 Hz, 2H), 7.55-7.51 (m, 3H), 7.38 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.34 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 7.032 (dd,



73ce

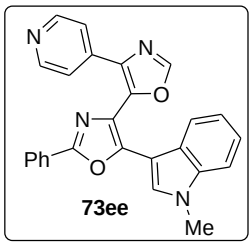
J =5.2 Hz, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.1, 150.0, 145.7, 140.2, 138.6, 136.3, 131.4, 129.2, 128.4, 128.04, 128.01, 127.1, 126.8, 126.5, 123.7, 121.6; HRMS (ESI) *m/z* calcd for $C_{21}H_{13}N_3O_2S$ $[M + H]^+$ 372.0807, found 372.0809.

2-Phenyl-5-(1-methyl-2-pyrrolyl)-4'-(4-pyridyl)-4,5'-bisoxazole (73de). Obtained from oxazolone **66d** and isocyanide **71e**, brown solid (98.8 mg, 80%): mp 148-150 °C; R_f 0.53 (7:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3092, 3061, 3006,1611, 1572, 1486, 1094, 937; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 4.8 Hz, 1.4 Hz, 2H), 8.10-8.08 (m, 2H), 8.02 (s, 1H), 7.78 (dd, *J* = 4.8 Hz, 1.4 Hz, 2H), 7.53-7.50 (m, 3H), 6.73 (dd, *J* = 2.8 Hz, 1.6 Hz, 1H), 6.32 (dd, *J* = 4.0 Hz, 1.6 Hz, 1H), 6.09 (dd, *J* = 4.0 Hz, 2.8 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 150.7, 149.7, 143.4, 140.7, 138.6, 135.3, 131.0, 129.0, 126.6, 126.4, 126.2, 125.0, 121.6, 119.5, 113.4, 108.9, 35.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}N_4O_2$ $[M + H]^+$ 369.1352, found 369.1354.



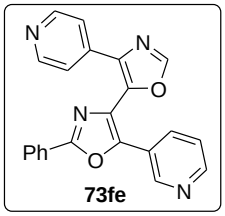
73de

2-Phenyl-5-(1-methyl-3-indolyl)-4'-(4-pyridyl)-4,5'-bisoxazole (73ee). Obtained from oxazolone **66e** and isocyanide **71e**, yellow solid (96.0 mg, 80%): mp 188-190 °C; R_f 0.33 (7:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3061, 2810, 1619, 1580, 1486, 1376, 1110, 898; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.51 (dd, *J* = 4.6 Hz, 1.6 Hz, 2H), 8.12 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.77 (dd, *J* = 4.6 Hz, 1.6 Hz, 2H), 7.72 (s, 1H), 7.65-7.59 (m, 3H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.29 (td, *J* = 7.7 Hz, 1.2 Hz, 1H), 7.22 (td, *J* = 7.7 Hz, 1.2 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 150.8, 149.7, 147.5, 141.7, 138.8, 137.0, 134.8, 130.8, 129.1, 128.8,127.2, 126.5, 125.4, 123.2, 122.0, 121.49, 121.46, 120.8, 110.1, 103.0, 33.4; HRMS (ESI) *m/z* calcd for $C_{26}H_{18}N_4O_2$ $[M + H]^+$ 419.1508, found 419.1511.



73ee

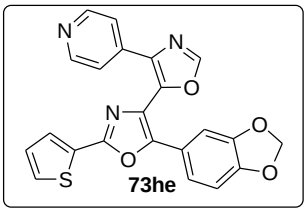
2-Phenyl-5-(3-pyridyl)-4'-(4-pyridyl)-4,5'-bisoxazole (73fe). Obtained from oxazolone **66f** and isocyanide **71e**, pale yellow solid (96.4 mg, 78%): mp 138-140 °C; R_f 0.40 (0.5:9.5 MeOH:DCM); IR (KBr, cm^{-1}) 3091, 3040, 1607, 1550, 1480, 1402, 1091, 938, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (br d, *J* = 2.0 Hz, 1H), 8.59-8.57 (m, 3H), 8.17-8.15 (m, 2H), 8.09 (s, 1H), 7.86 (ddd, *J* = 8.0 Hz, 2.2 Hz, 1.6 Hz, 1H), 7.79 (dd, *J* = 4.4 Hz, 1.6 Hz, 2H), 7.57-7.52 (m, 3H),



73fe

7.31 (ddd, *J* = 8.0 Hz, 5.0 Hz, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 151.2 ,150.3, 150.1, 147.4, 146.7, 140.,0 138.3, 136.4, 133.3, 131.7, 129.3, 126.9, 126.4 126.3, 123.8, 123.6, 121.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{14}N_4O_2$ $[M + H]^+$ 367.1195, found 367.1193.

2-(2-Thienyl)-(5-(benzo[*d*][1,3]dioxol-5-yl)-4'-(4-pyridyl)-4,5'-bisoxazole (73he).



Obtained from oxazolone **66h** and isocyanide **71e**, off-white solid (89.7 mg, 72%): mp 167-169 °C; R_f 0.40 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3388, 3094, 2903, 1609, 1506, 1477, 1249, 1035, 720; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.54 (br s, 2H), 7.93 (dd, *J* = 3.6 Hz, 1.0 Hz, 1H), 7.85 (dd, *J* = 5.2 Hz, 1.0 Hz, 1H), 7.67 (d, *J* = 3.6 Hz, 2H), 7.29 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 7.06-7.04 (m, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 151.3, 149.2, 149.1, 149.0, 148.2, 140.8, 139.1, 135.5, 129.5, 128.9, 128.8, 128.3, 123.1, 120.9, 120.7, 108.9, 106.3, 101.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{13}N_3O_4S$ $[M + H]^+$ 416.0705, found 416.0705.

3.6 References

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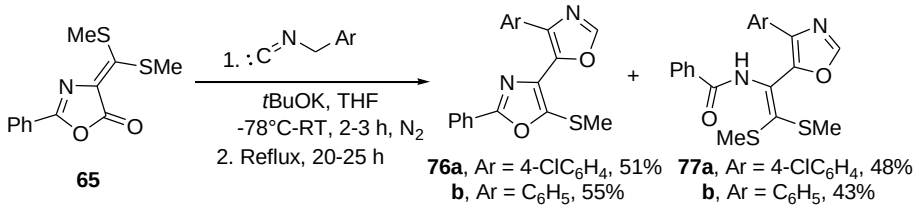
precursors **77a-b** (43-48%) under THF/reflux for 20-25 h. These reaction conditions (THF/reflux) were somehow omitted in the Scheme and experimental section of earlier paper.[29f]



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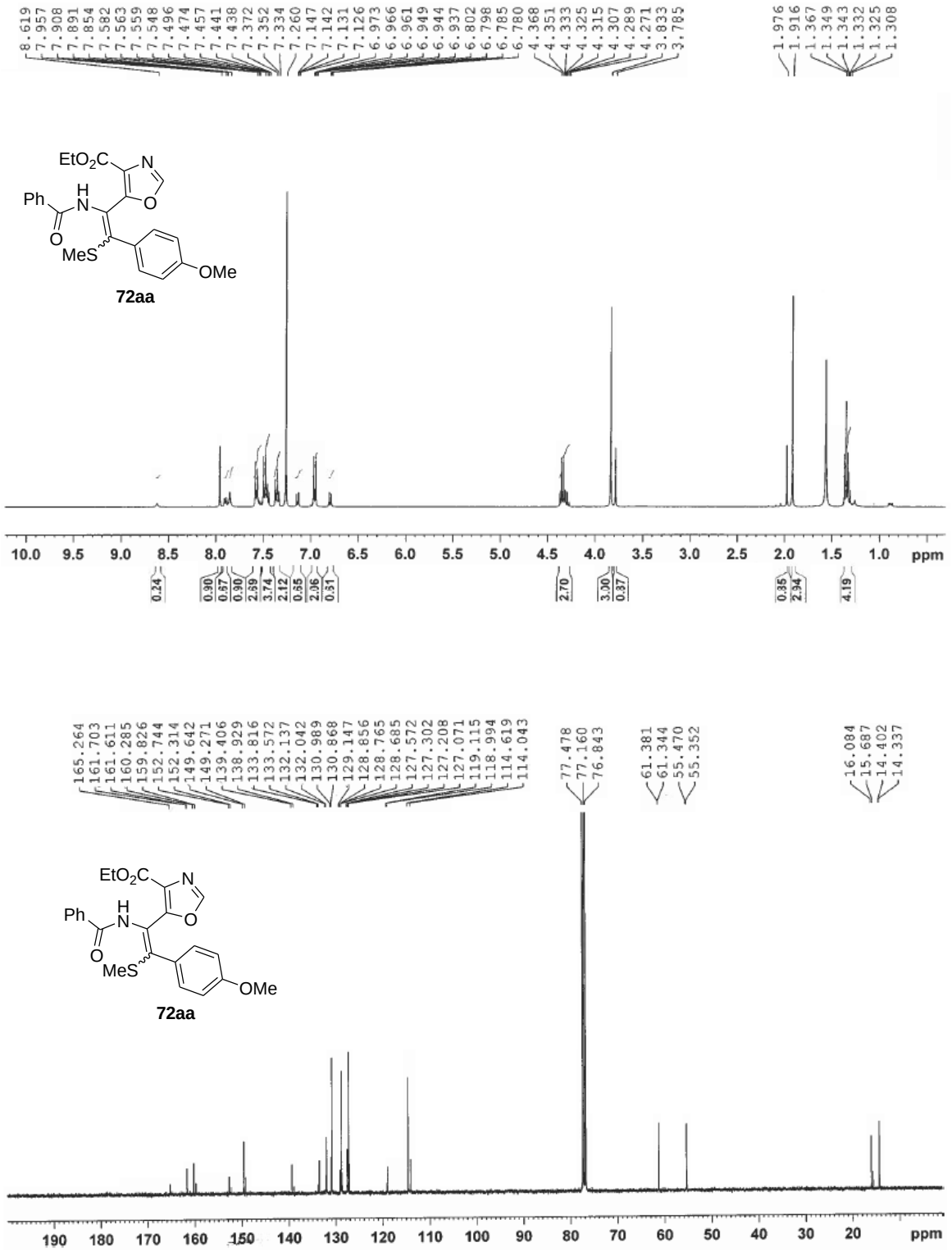
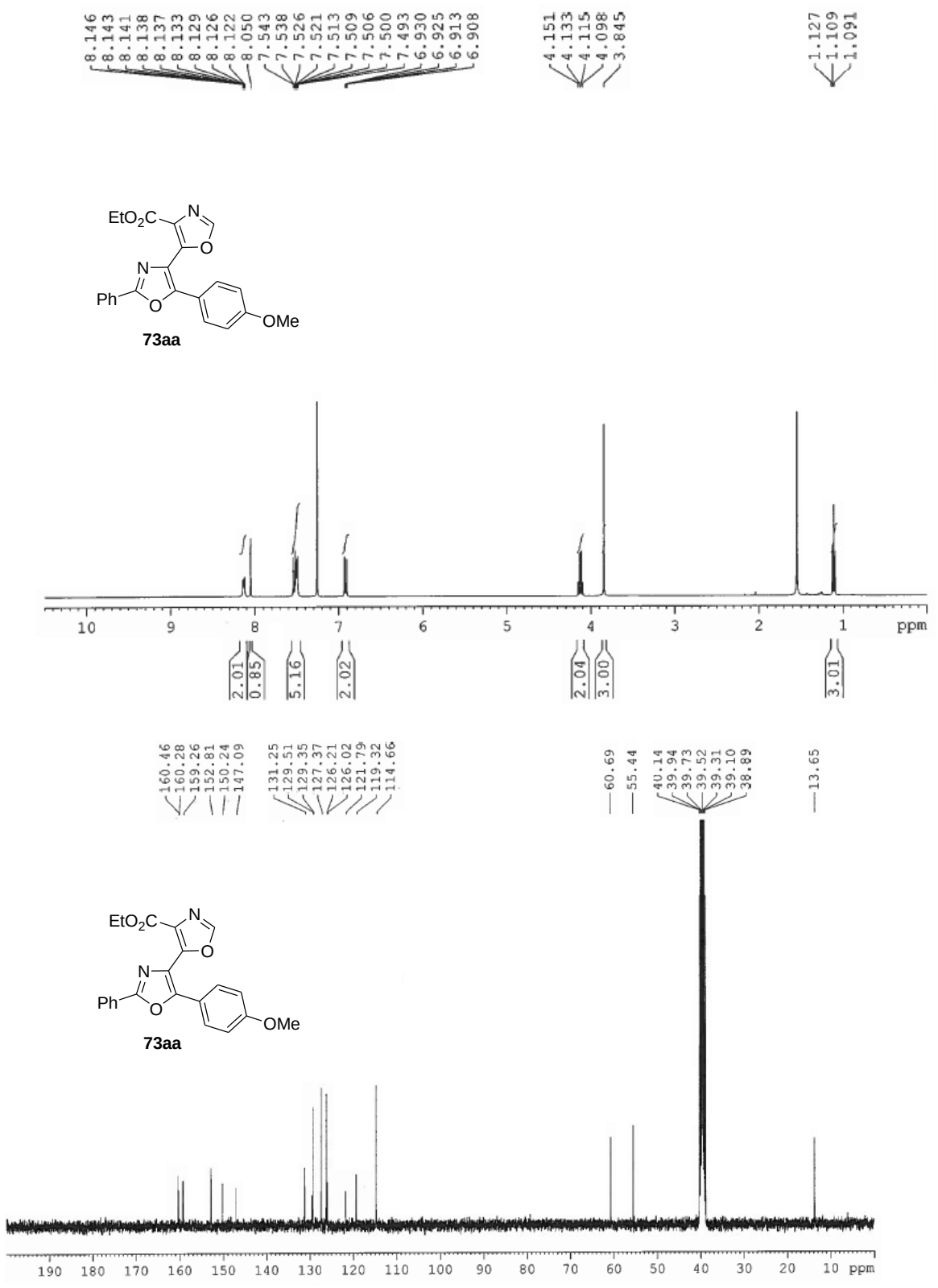
3.7 Representative spectra



^{1}H and ^{13}C NMR Spectra of compound **72aa**



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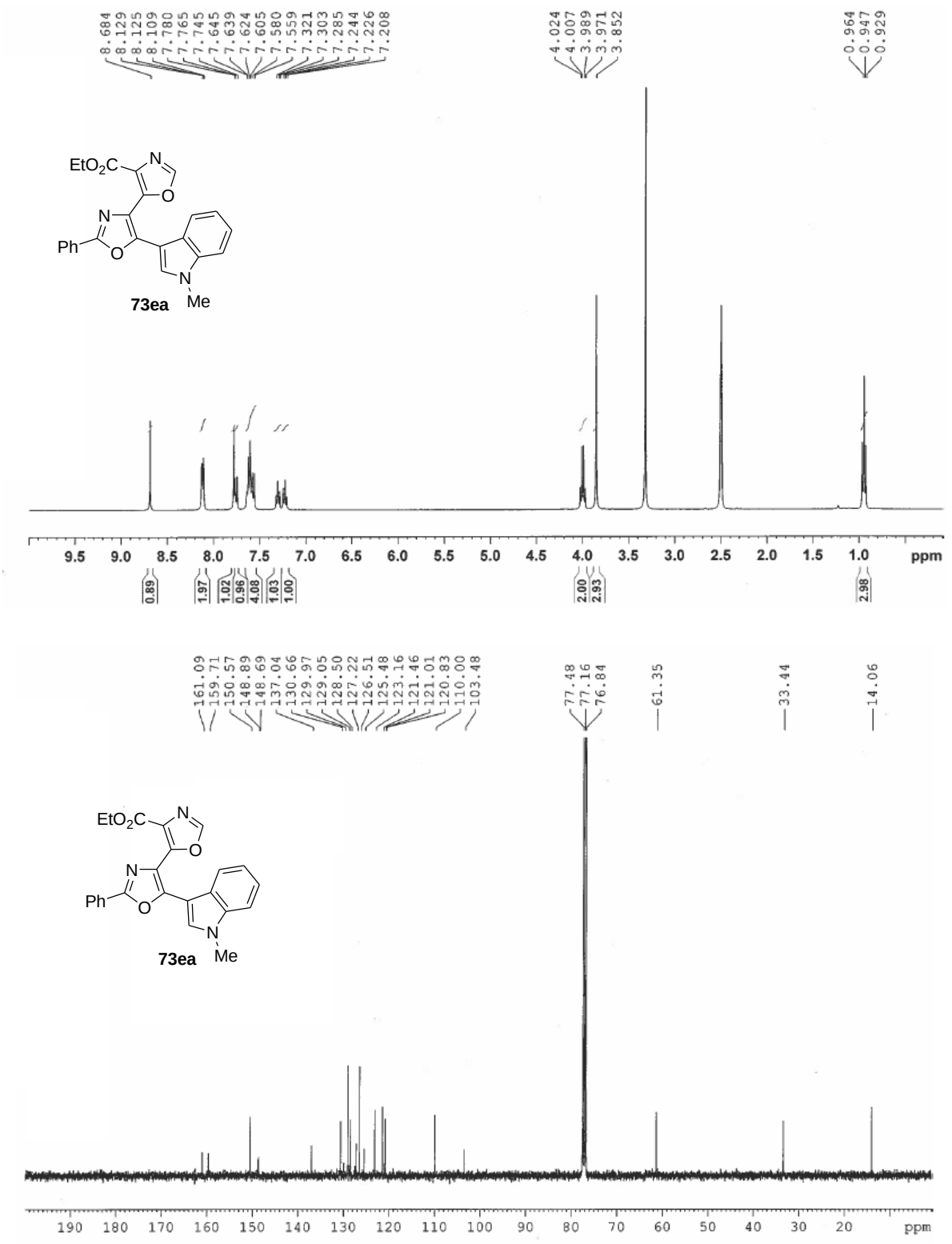

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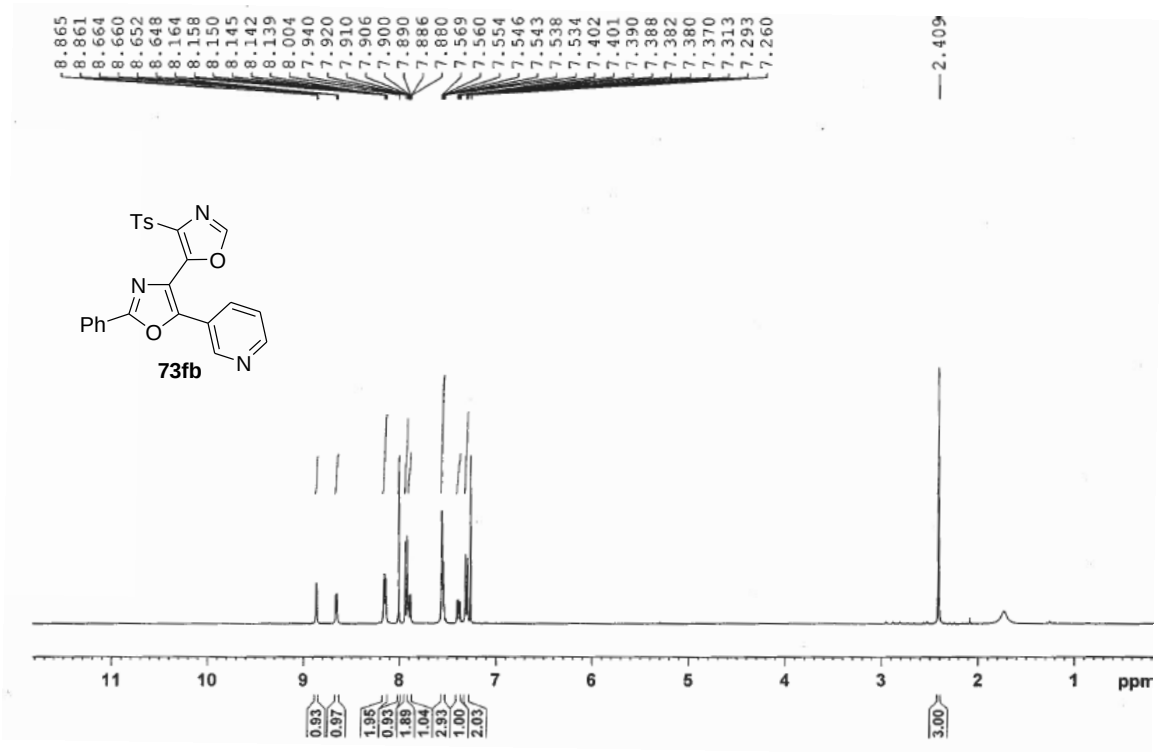

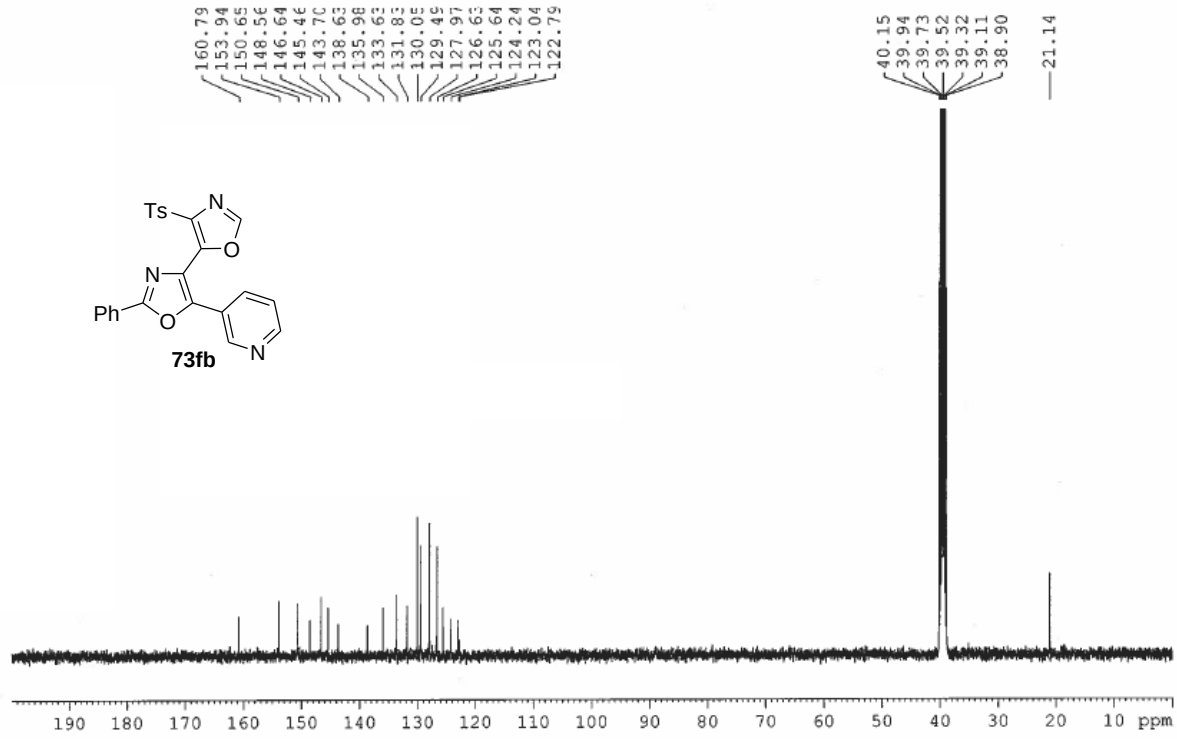

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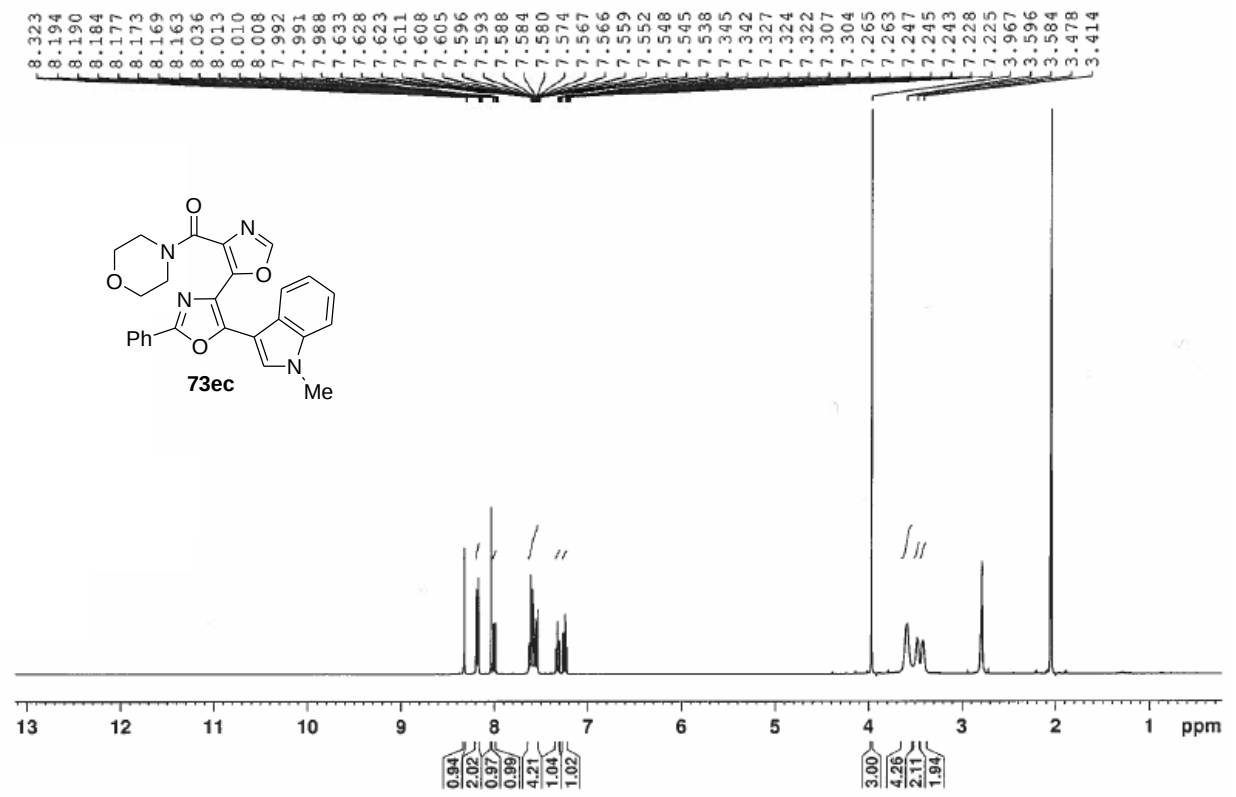

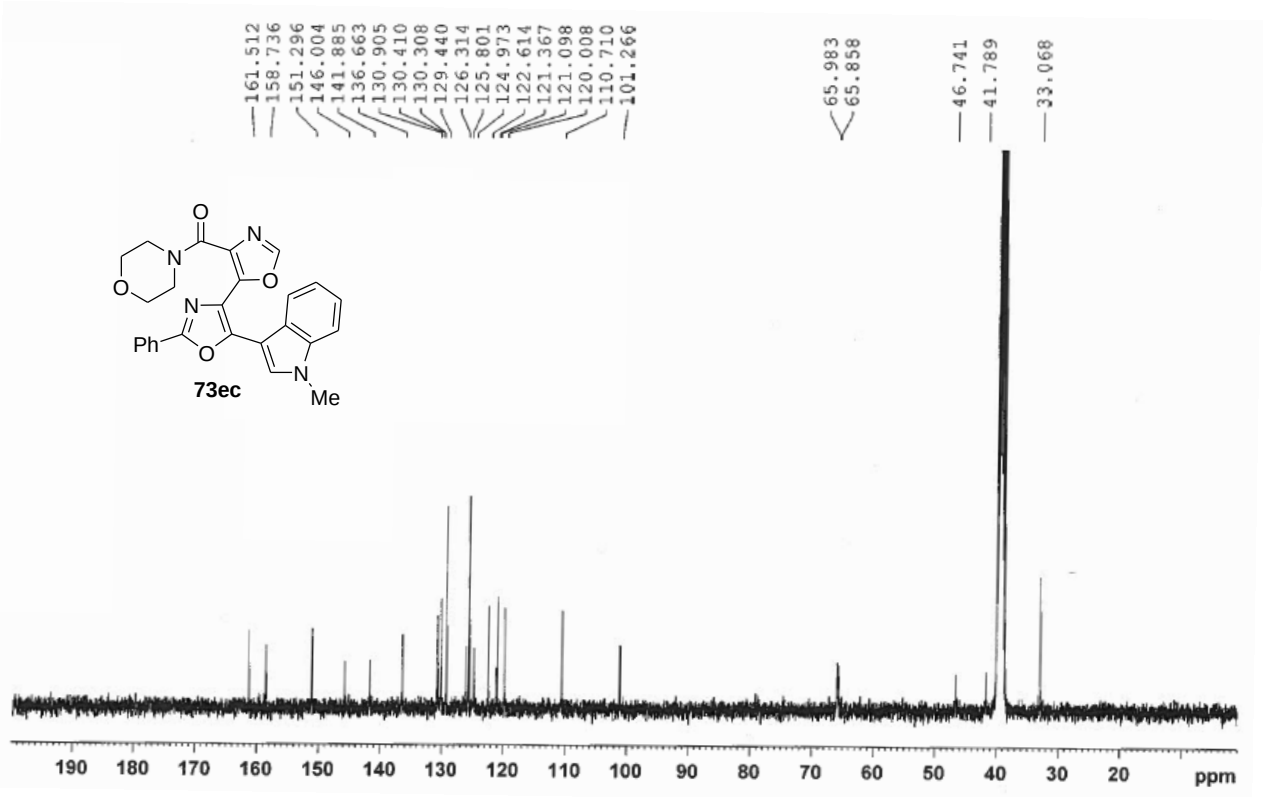

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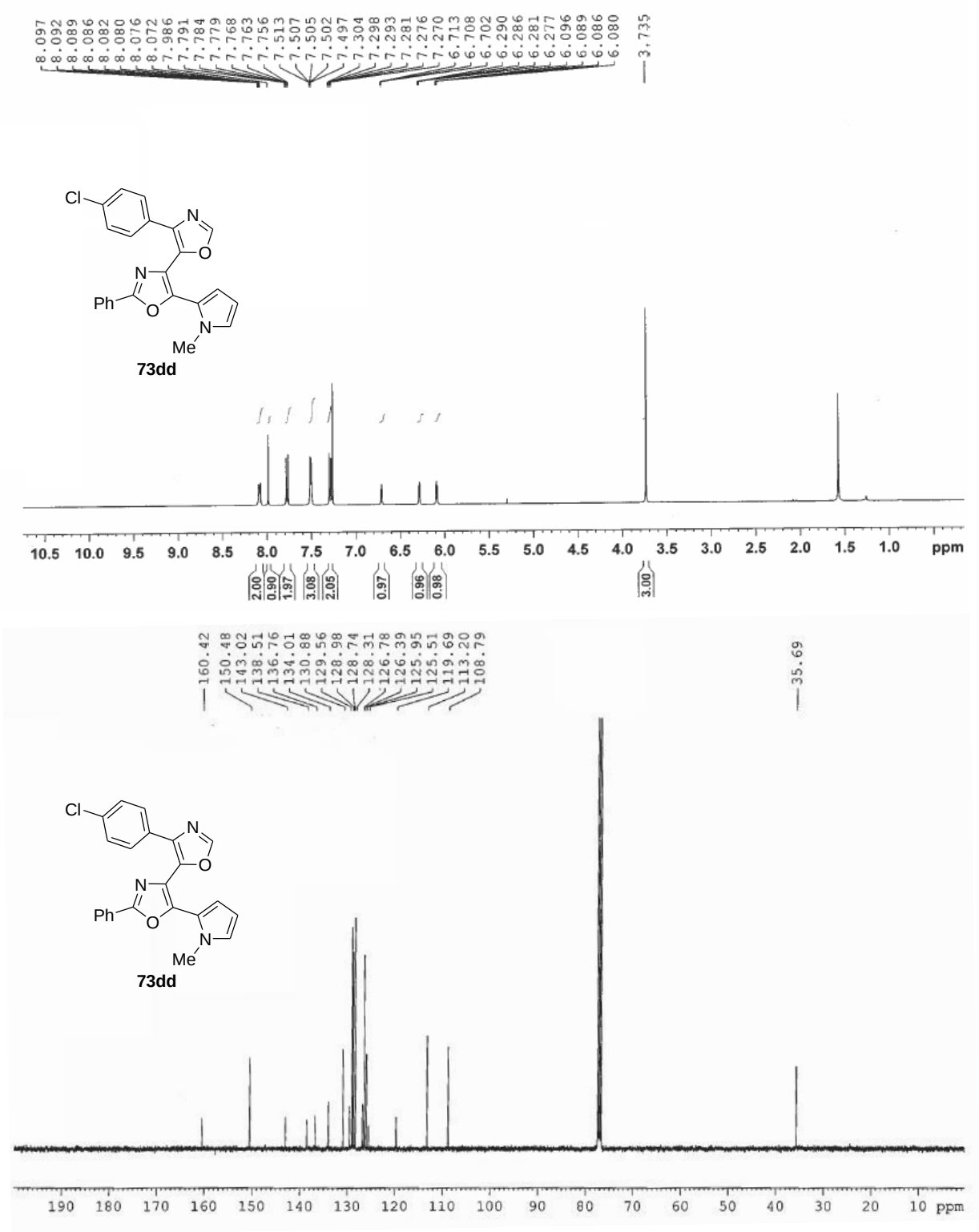

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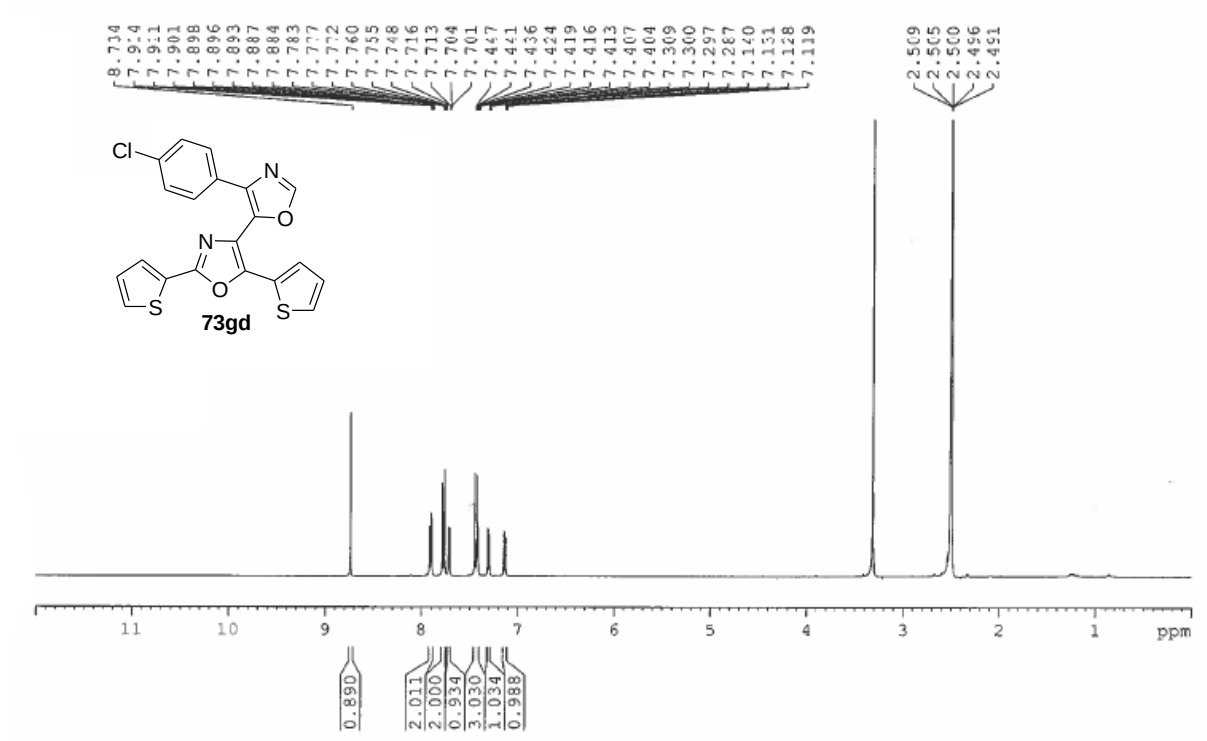

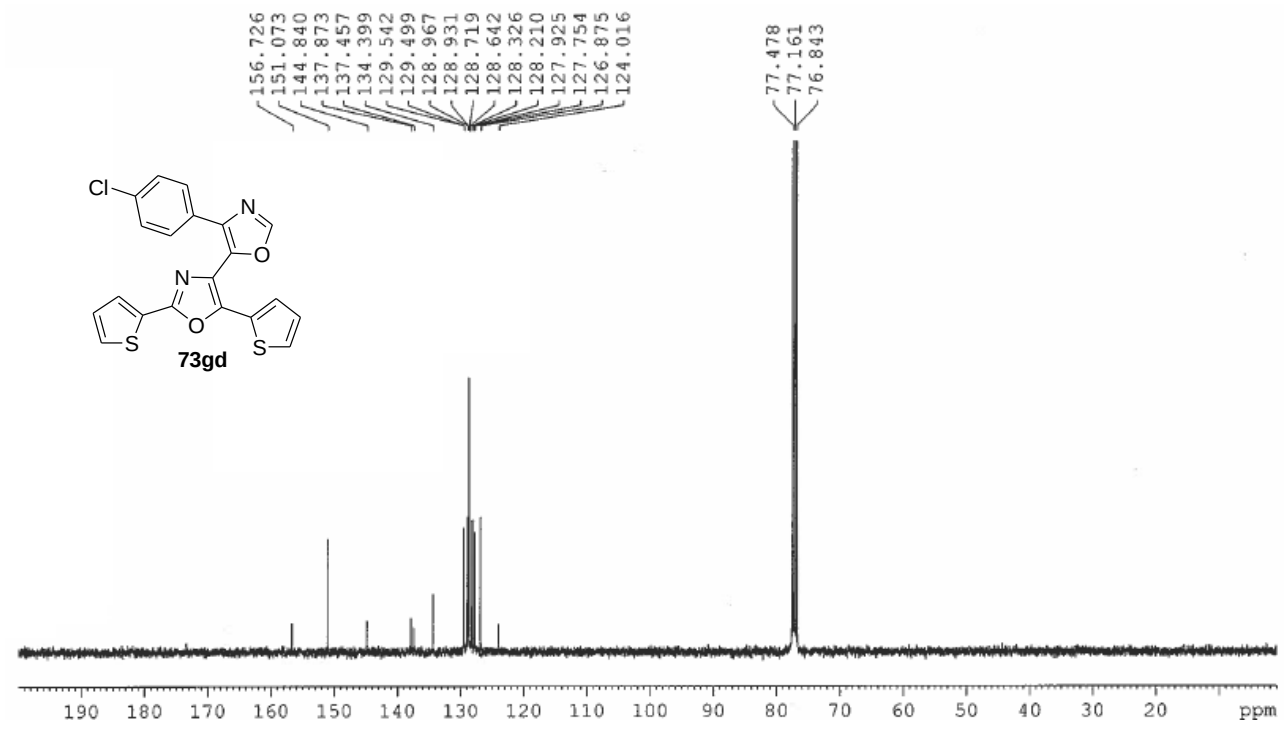

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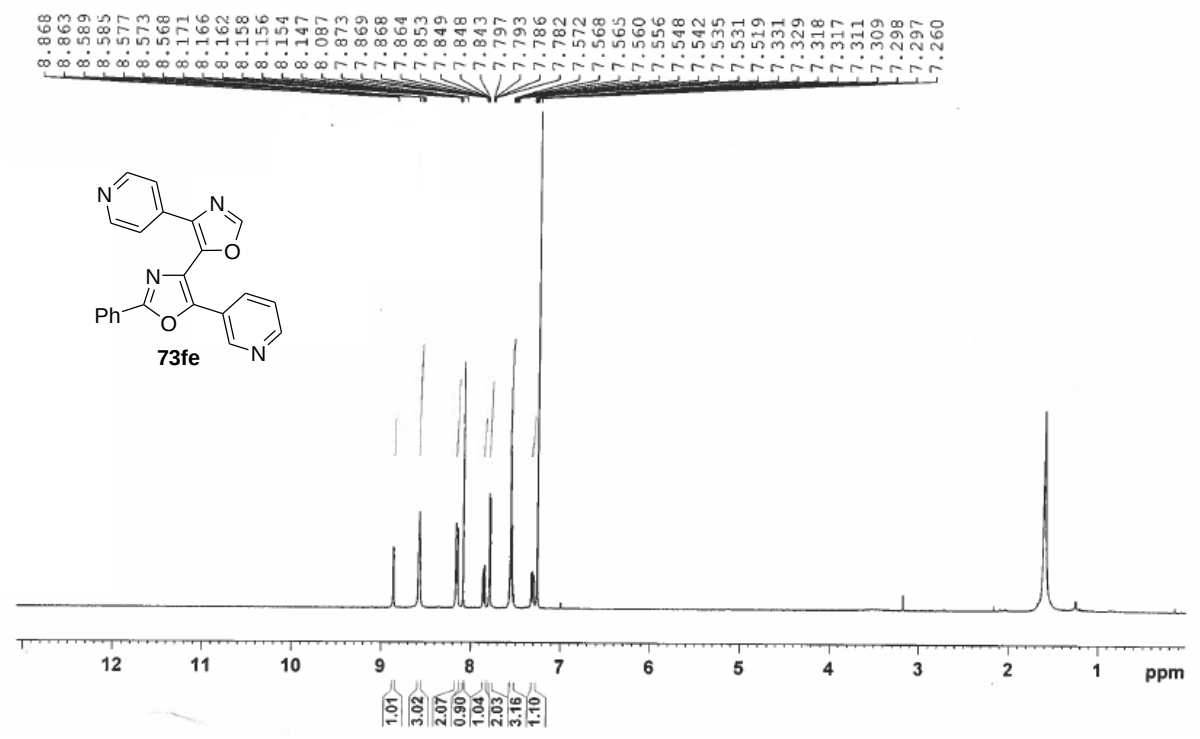

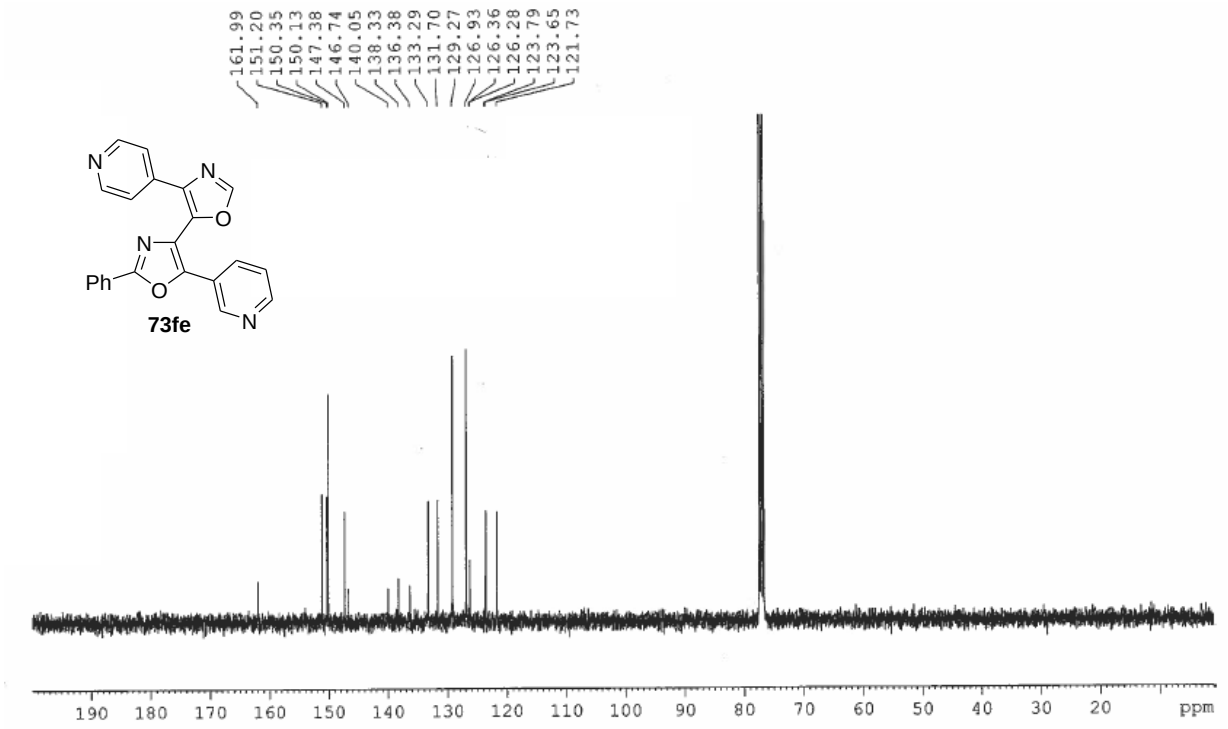

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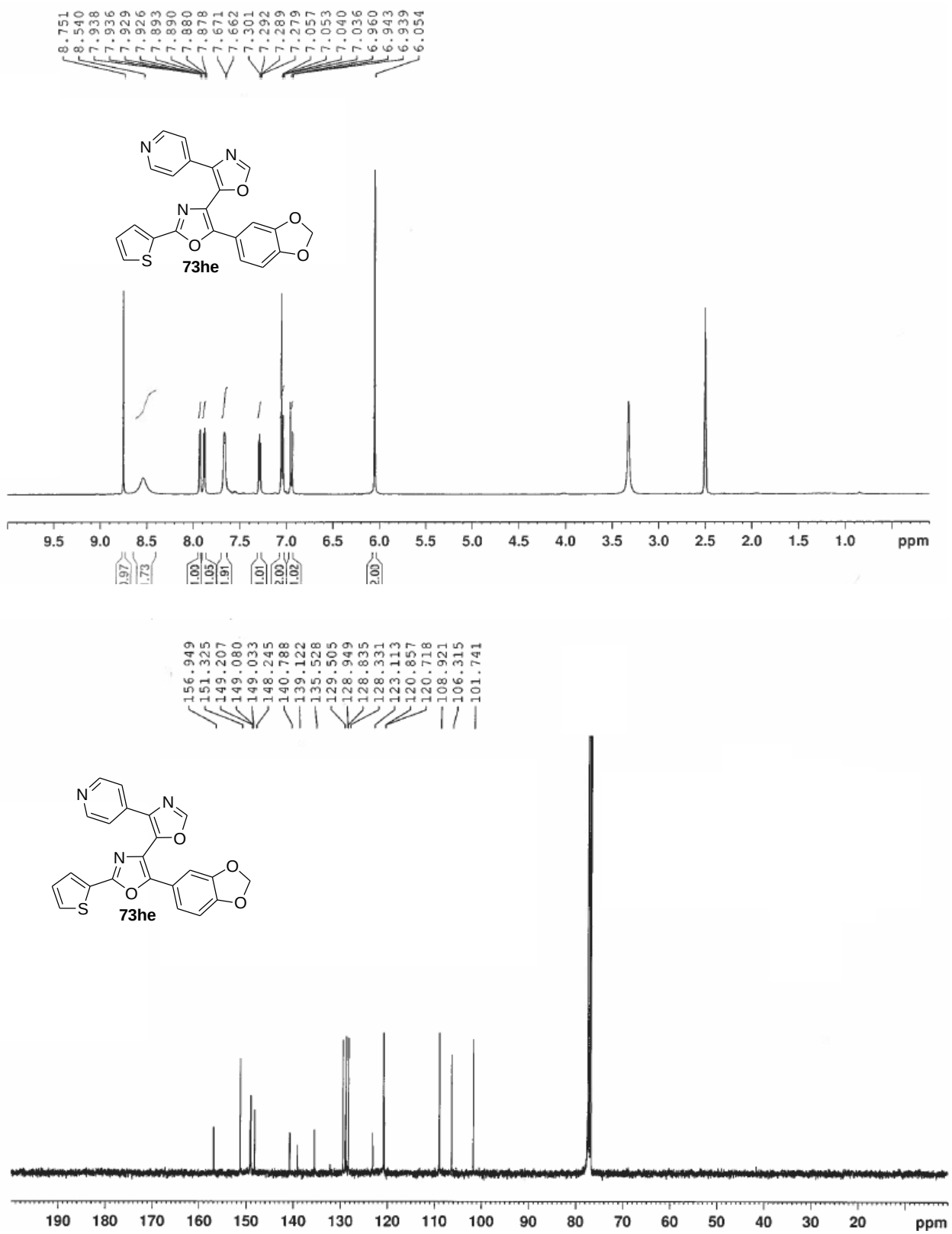


^{1}H and ^{13}C NMR Spectra of compound **73he**

Chapter 4

Amine Directed Pd(II) Catalyzed C-H Activation-Intramolecular Amination of N-Het(aryl)/Acyl Enaminonitriles and Enaminones: An Approach towards Multisubstituted Indoles and Hetero-Fused Pyrroles*

4.1 Introduction

Indole ring system represents a key heterocyclic motif[1] that occurs ubiquitously in biologically active natural products[2] as well as in numerous therapeutic agents[3] and in optoelectronic functional materials.[4] Substituted indoles are generally known as 'privileged structures' in medicinal chemistry, as they are capable of binding to many receptors with high affinity.[3] The synthesis of indole has been an important area of research for over 100 years, since the first report of Fischer indole synthesis in 1883[5] and a variety of well established powerful methods are now available.[5] However, lack of availability of starting materials along with functional group tolerance often limits the scope and generality of a particular indole synthesis. Consequently, development of efficient, selective and atom

*The overall results of study described in this chapter have been published in *J. Org. Chem.* **2016**, *81*, 2035.

economical methods for the synthesis of indoles from readily available starting materials is highly desirable. Among the reportaire of recent methods, transition metal catalyzed inter- and intramolecular C-C and/or C-N bond forming reactions are the most powerful and attractive routes for the synthesis of indoles.[5-6] Among the various transition metal based sources, the palladium compounds have been one of the most widely used catalysts and arguably, the palladium catalyzed intramolecular cyclization of 2-alkynylanilines[6-8] as well as intermolecular coupling of 2-haloanilines with terminal/internal alkynes[9] are among the most frequently used recent methods for the synthesis of 2,3-substituted indoles as shown in the Figure 1.[10] Indoles can also be prepared by precursors containing nitrogen nucleophiles and alkenes (carbon-carbon double bonds) (Figure 2).[6d] Recently, palladium and copper catalyzed intra- and intermolecular amination and C-C bond formation reactions of substituted aryl halides or pseudohalides have also been employed for the synthesis of substituted indoles as depicted in Figure 3.[11]

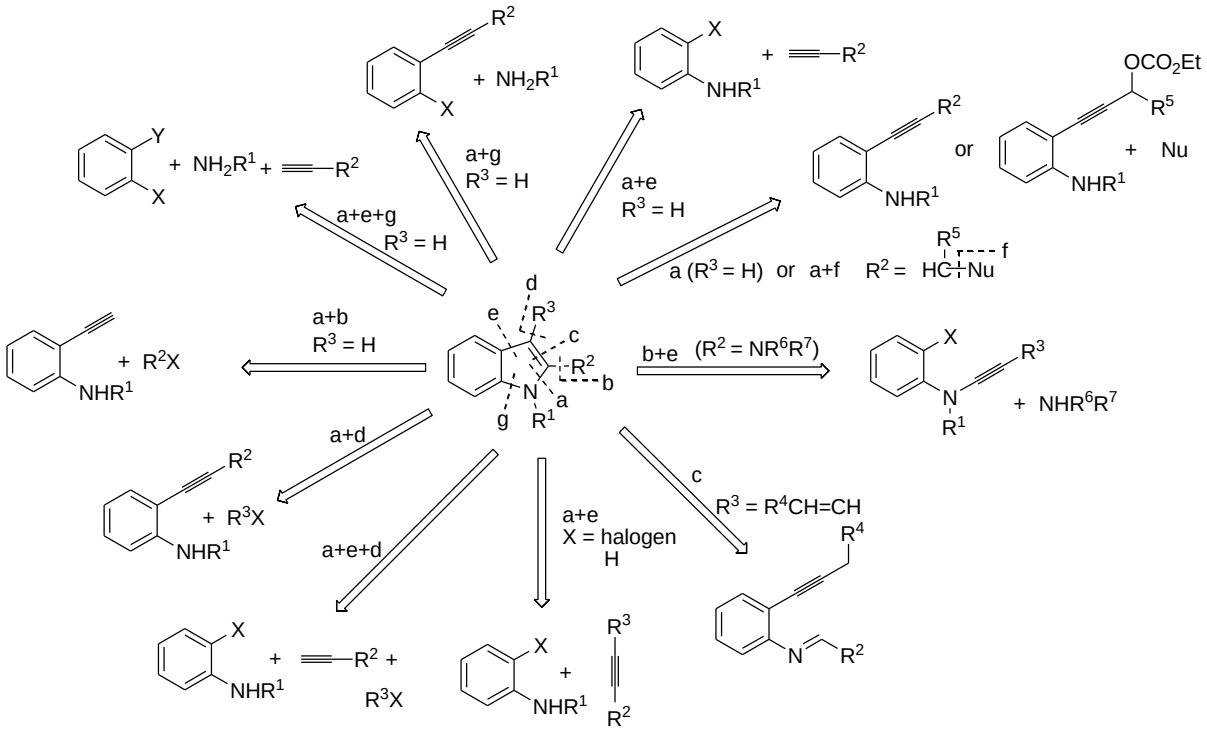


Figure 1. Retrosynthetic representation of the main alkyne-based palladium-catalyzed assemblies of the pyrrole ring

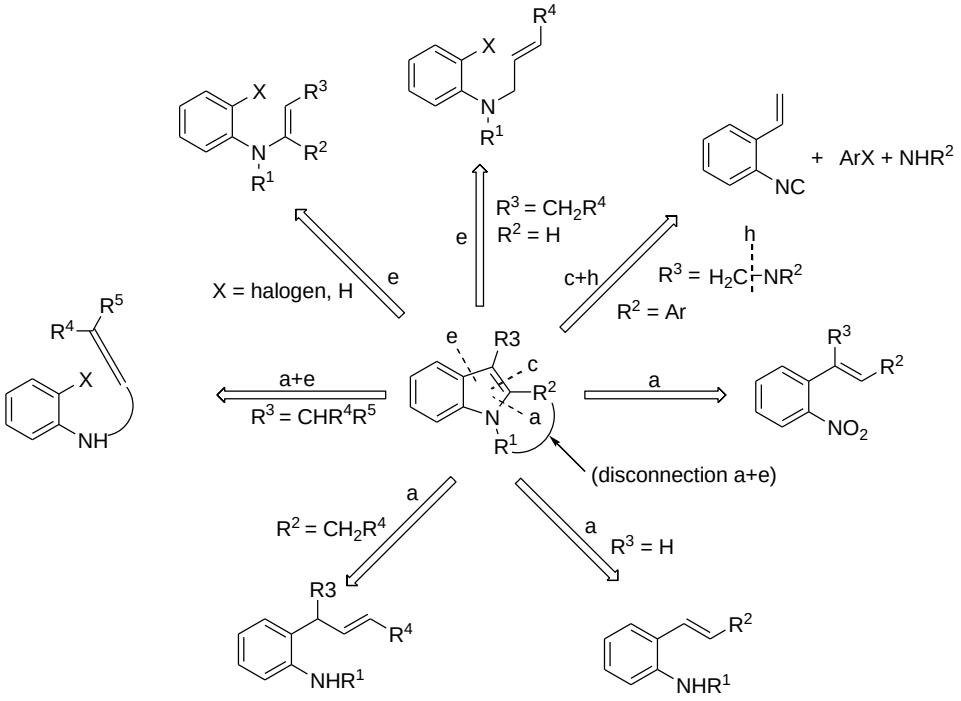


Figure 2. Retrosynthetic representation of the main alkene-based palladium-catalyzed assemblies of the pyrrole ring

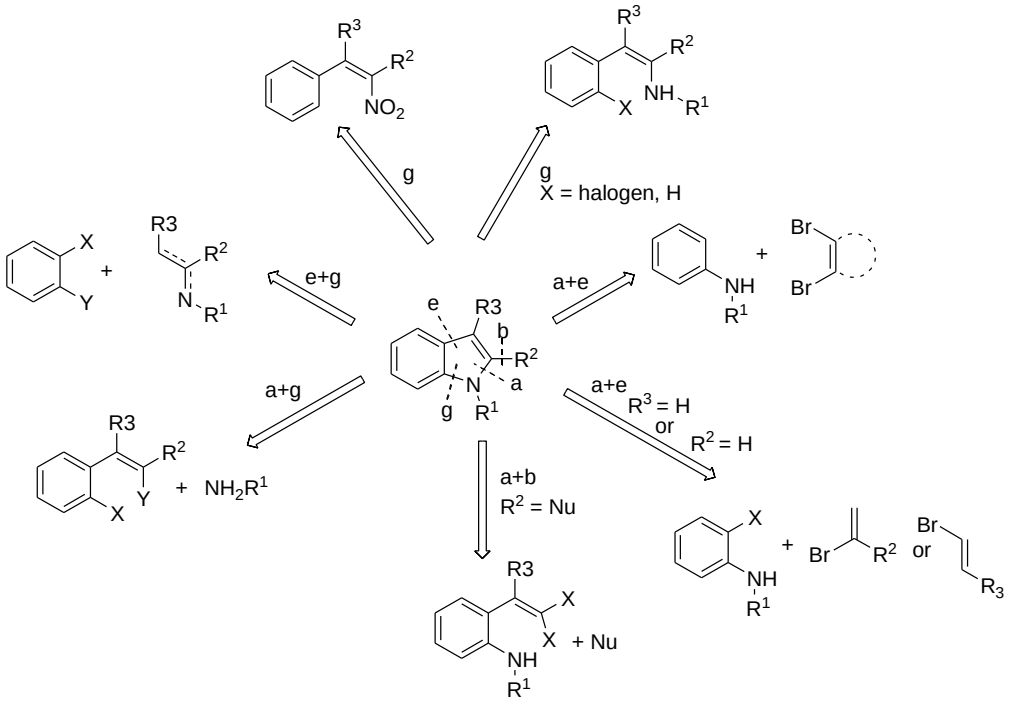


Figure 3. Retrosynthetic representation of the main palladium and copper catalyzed construction of the pyrrole ring via *N*-vinylation and *N*-arylation reactions

More recently, an increasing number of examples have appeared in the literature involving transition metal catalyzed oxidative C-H functionalization as a fundamental step for the construction of various heterocycles.[12] This mode of reactivity is particularly attractive since the necessity to install an activating group functionality such as halide in the starting material is eliminated, thus opening up much wider range of more readily accessible precursors.[12] Various catalytic systems based on rhodium, ruthenium and palladium including copper and iron[12d,12f,13] have been developed to effect oxidative C-C and C-heteroatom bond formation.[12] While most of the earlier reported examples involve intermolecular C-H functionalization,[14] only recently, following Buchwald's pioneering report of carbazole synthesis via Pd(II) catalyzed intramolecular C-H activation/C-N bond formation,[15] has attention been turned to use of these C-H functionalization reactions for the construction of various heterocyclic ring systems through intramolecular C-heteroatom bond formation (Scheme 1).[12c-d,16]

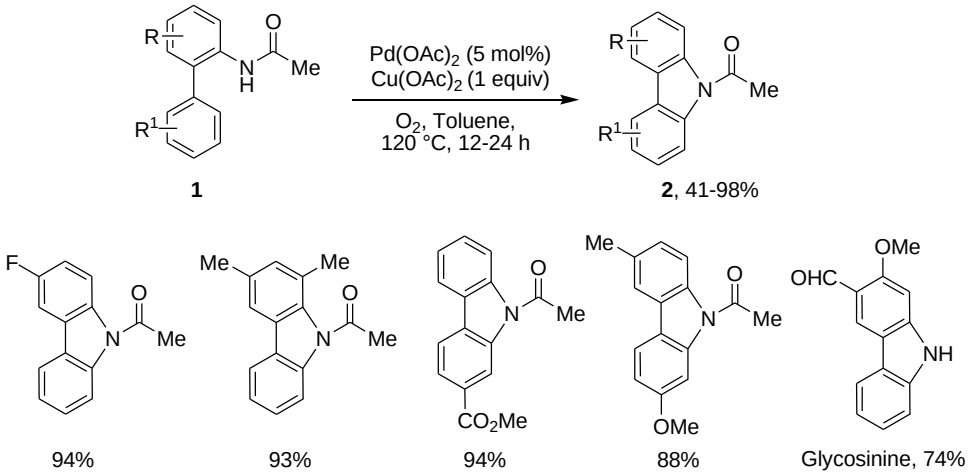
In the present chapter, we have reported an efficient route to multisubstituted indoles via palladium catalyzed intramolecular oxidative C-H activation-amination of readily available 2-(het)aryl-3-(het)aryl/alkyl-3-(het)aryl/acylaminoacrylontrile/enaminone precursors (Scheme 42). Before describing our results, a short recent literature survey of synthesis of benzoheterocycles including those of indoles, through transition metal catalyzed intramolecular C-H functinalization-C-heterocyclization has been highlighted in the following section.

4.2. Synthesis of Benzoheterocycles via Transition Metal Catalyzed Intramolecular C-H Functionalization/C-Heterocyclization

4.2.1 Synthesis of Nitrogen Containing Benzoheterocycles via Transition Metal Catalyzed Intramolecular C-H Activation/C-N Bond formation

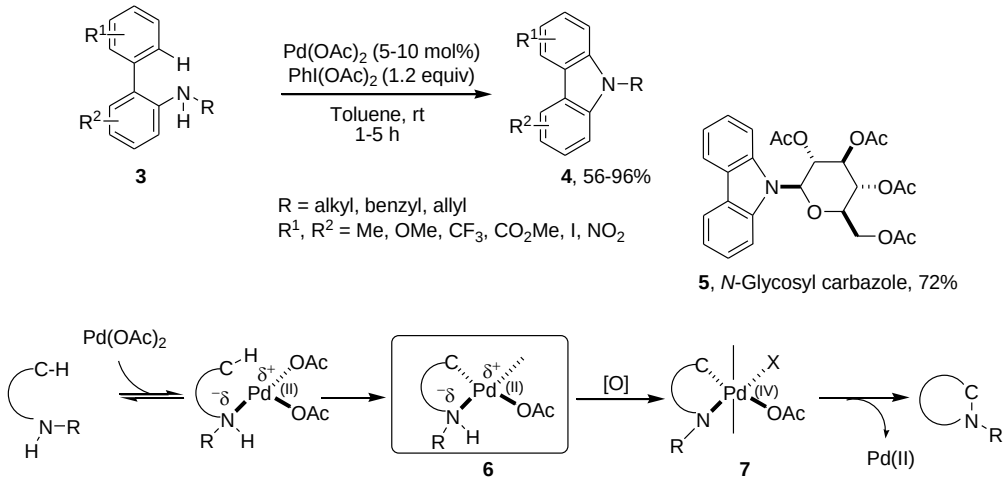
Buchwald and co-workers had reported in their pioneer study, synthesis of substituted carbazoles **2** via palladium-catalyzed oxidative intramolecular C-H functionalization heterocyclization of 2-arylacetanildes **1** (Scheme 1). It should be noted that this cyclization does not require any directing group for CH activation as reported in previous examples, on the other hand the directing group (in the present case the acylamino group) acts as reaction

partner. The reaction allows assembly of carbazoles with a variety of substitution patterns and functional groups under relatively mild conditions. They had further applied this method for the synthesis of three naturally occurring carbazoles (mukonine, mukonidine and glycosinine) (Scheme 1).[15]



Scheme 1

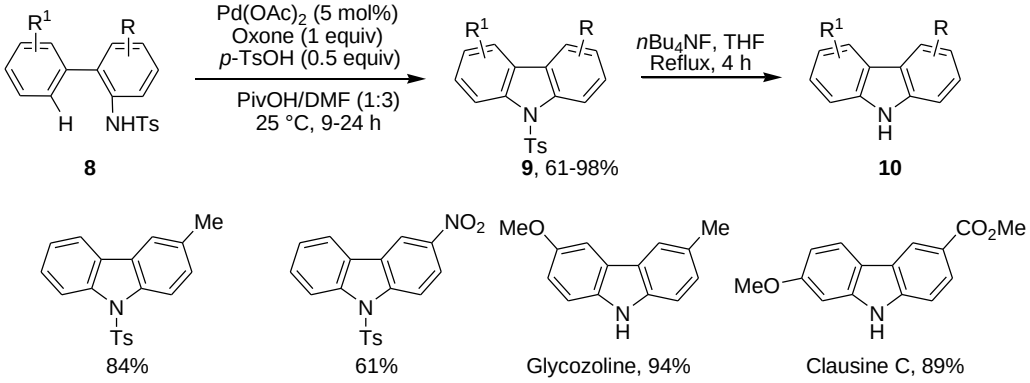
In a subsequent work, Gaunt and co-workers have reported synthesis of *N*-alkyl carbazoles **4** via Pd(II)-catalyzed intramolecular oxidative C-H amination of 2-aryl-*N*-alkylanilines **3**, using phenyliodine(III)diacetate (PIDA) as an oxidant (Scheme 2). The reaction proceeds at room temperature under very mild conditions with broad substrate scope and could be applied for the synthesis of *N*-glycosyl carbazoles such as **5** (Scheme 2). The



Scheme 2

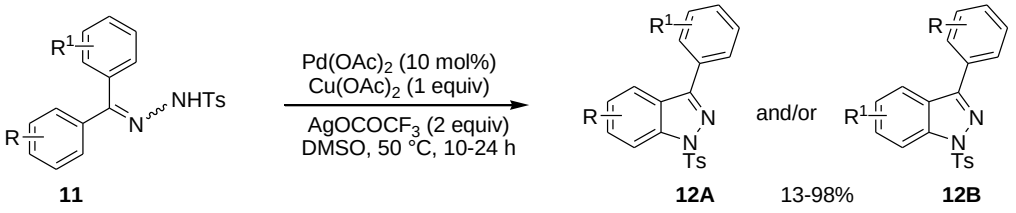
authors have suggested a mechanism involving a Pd(IV) species **7** (through oxidation of *N*-coordinated Pd(II) intermediate **6**), which undergoes reductive elimination leading to intramolecular C-N bond formation (Scheme 2).[17]

Youn and co-workers have recently developed a versatile approach for the synthesis of *N*-tosylcarbazoles **9** through Pd-catalyzed intramolecular oxidative C-H amination of *N*-tosyl-2-arylanilines **8** under ambient temperature using oxone as an oxidant and pivalic acid as additive. The *N*-tosylcarbazoles could be cleaved to *NH*-carbazoles **10** by treatment with tetrabutyl ammonium fluoride (Scheme 3).[18]



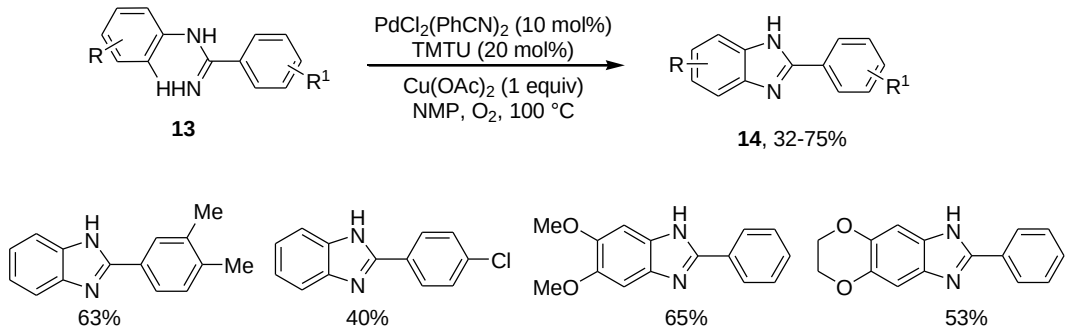
Scheme 3

Inamoto and co-workers have described an oxidative intramolecular palladium-catalyzed C-H activation-cyclization of benzophenone *N*-tosylhydrazones **11** affording substituted indazoles **12** in moderate to good yields (Scheme 4). However, the method suffers from regioselectivity problem and affords mixture of regioisomeric indazoles **12A** and **12B** and the yields of indoles is usually moderate and good only in few cases (Scheme 4).[19]

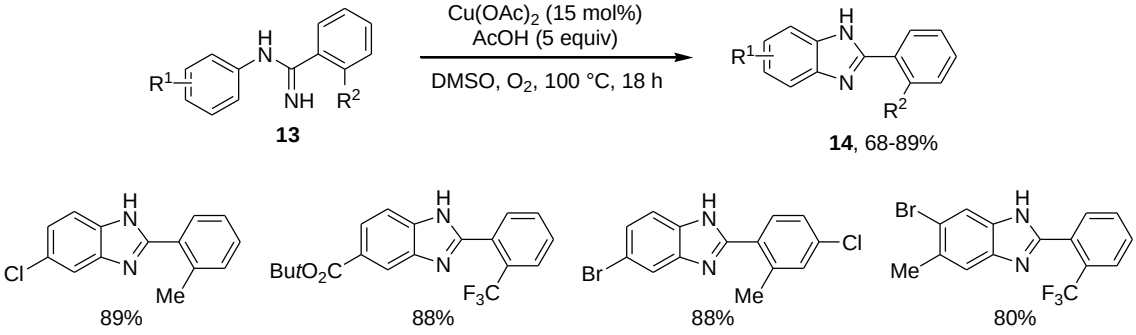


Scheme 4

Shi and co-workers have developed a novel and straightforward method for the synthesis of 1*H*-benzo[*d*]imidazoles **14** through Pd(II)-catalyzed intramolecular C-H activation/C-N bond formation starting from readily available *N*-phenylbenzimidamides **13** under mild reaction conditions using $Cu(OAc)_2$ under O_2 atmosphere as oxidant and tetramethylthiourea (TMTU) as an additive (Scheme 5).[20] This transformation has a broad substrate scope and different functionalities survived well. In a parallel study, Buchwald's group has also simultaneously reported $Cu(OAc)_2$ catalyzed synthesis of benzimidazoles from amidines **13** (derived from *ortho*-substituted arylnitriles) through C-H functionalization/C-N bond formation (Scheme 6).[13a] On the other hand, functionalized amidines derived from arylnitriles without any *ortho*-substituents showed little conversion to benzimidazoles.

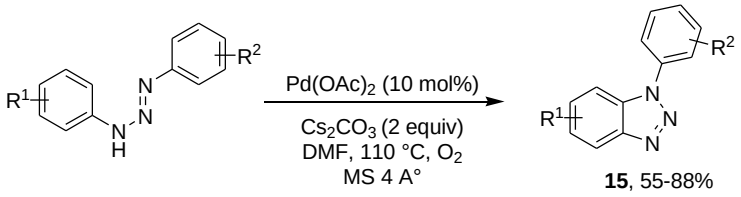


Scheme 5



Scheme 6

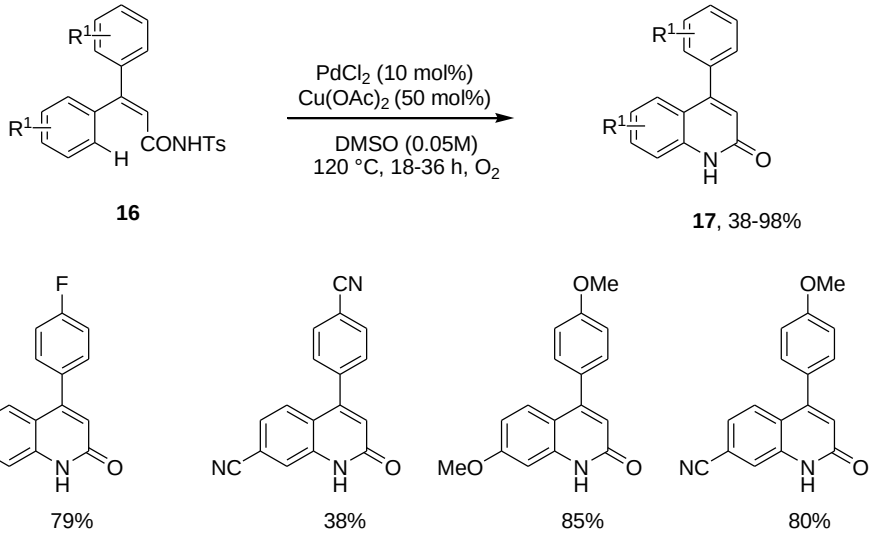
Punniyamurthy and co-workers have recently developed a novel protocol for the synthesis of 1-aryl-1*H*-benzotriazoles **15** via Pd-catalyzed C-H activation of aryltriazines followed by intramolecular amination under relatively milder conditions using oxygen as an oxidant (Scheme 7).[21]



R^1, R^2 = H, COMe, CO_2Et, Br, Cl, Et, OMe, Me, NO_2

Scheme 7

Inamoto and co-workers have developed a catalytic synthetic approach to pharmaceutically important, substituted 2-quinolinones **17** through palladium catalyzed oxidative intramolecular C-H functionalization/amidation of *N*-tosyl 3,3-diarylacrylamides **16** in the presence of an O_2 atmosphere and semicatalytic amount of $Cu(OAc)_2$ as a reoxidation which proved to be crucial for this process (Scheme 8).[16d]

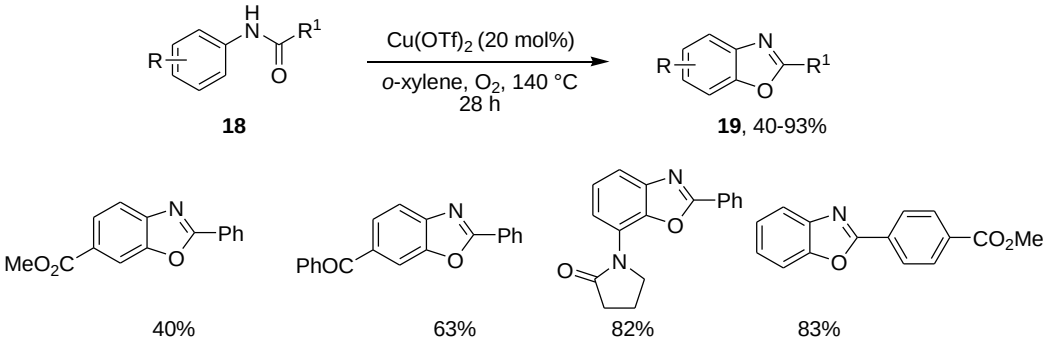


Scheme 8

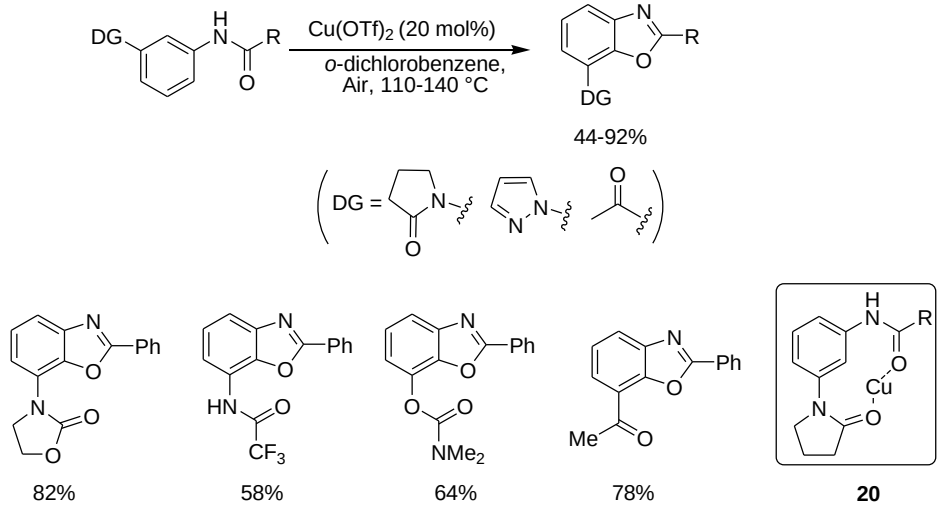
4.2.2 Synthesis of Oxygen Containing Benzoheterocycles via Transition Metal Catalyzed Intramolecular C-H Activation/C-O Bond Formation

Unlike synthesis of benzoheterocycles by intramolecular C-H functionalization/C-N bond formation, there are only limited examples of the synthesis of oxygen containing benzoheterocycles by transition metal catalyzed intramolecular C-H activation/C-O bond formation.[22.] Thus, Nagasawa and co-workers have reported an efficient method for the synthesis of functionalized 2-arylbenzoxazoles **19** through $Cu(OTf)_2$ catalyzed

intramolecular oxidative C-O coupling of benzanilides **18** under oxygen atmosphere (Scheme 9). Advantages of this method include simplicity of operation, high regioselectivity, and use of readily available, inexpensive, and harmless starting materials (Scheme 9).[22a] In a detailed study,[22b] they have further demonstrated that the regioselectivity of the reaction can be controlled by the presence of a directing group *meta* to the anilide moiety, affording selectively only 7-substituted oxazoles (Scheme 10). The *meta* substituent in these substrates seemingly act as additional directing group to promote formation of a doubly coordinated intermediate such as **20** (Scheme 10).[22b]

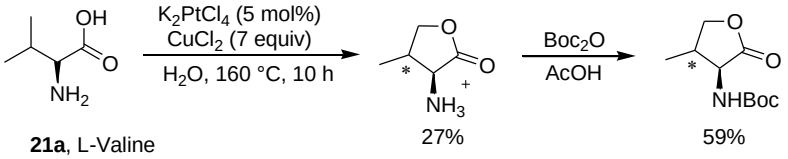


Scheme 9

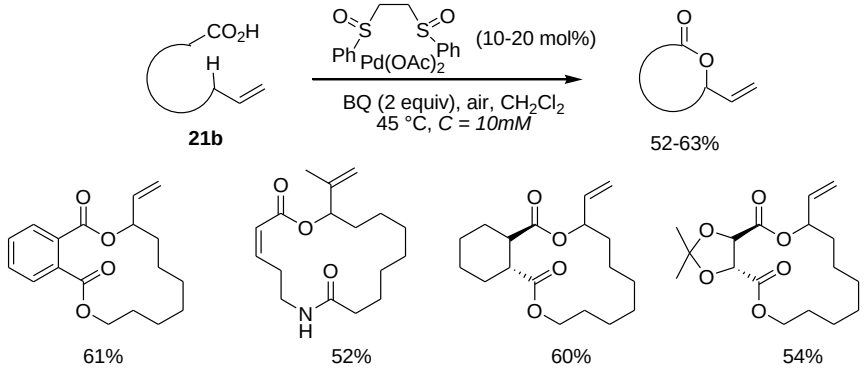


Scheme 10

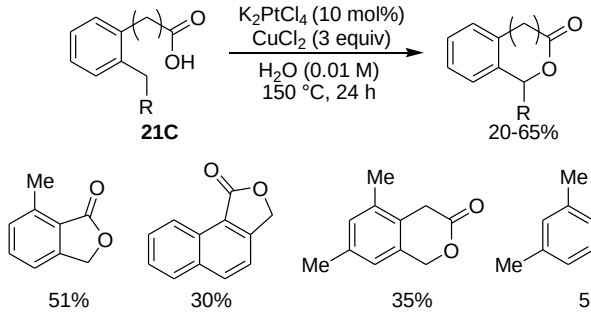
Recent studies have revealed that hydroxyl group in carboxylic acids **21a**, **21b**, **21c** and **21d** can be used as nucleophile in oxidative lactonization via Pt or Pd catalyzed C(sp^3)-H activation (Schemes 11, 12, 13A and 13B).[23a-d]



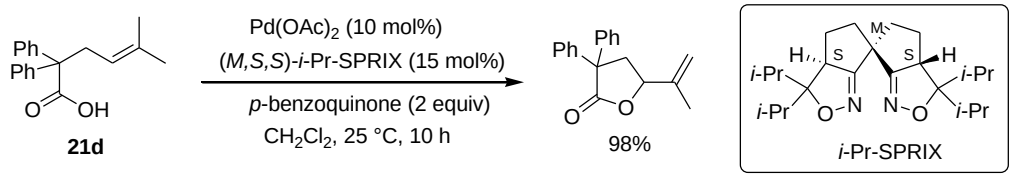
Scheme 11



Scheme 12

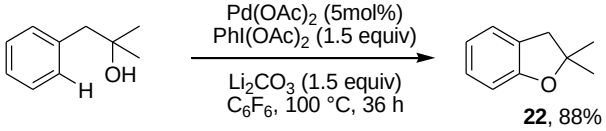


Scheme 13A



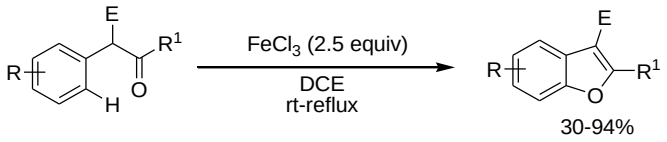
Scheme 13B

In 2010, Yu and coworkers described first example of a dihydrobenzofuran **22** synthesis that involves tertiary alcohol directed cycloetherification process that is catalyzed by $Pd(OAc)_2$ and $PhI(OAc)_2$ as oxidant (Scheme 14).[24]



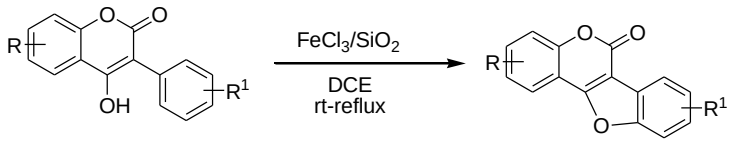
Scheme 14

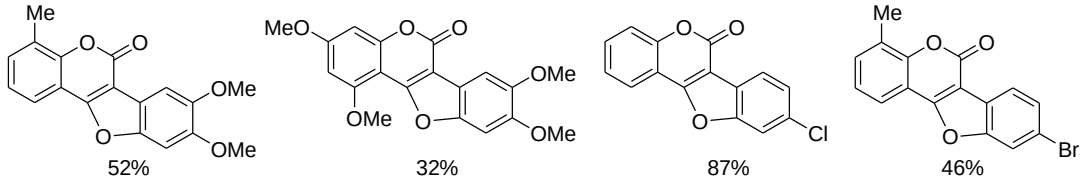
Despite success of these earlier studies and other oxidative C-O bond forming cyclization, C-H cycloetherification reactions that employ phenols as nucleophiles remain underdeveloped. There are few examples of intramolecular cycloetherification mediated by stoichiometric amount of $FeCl_3$ (Schemes 15A and 15B).[25a-b]



R = alkoxy groups
R^1 = alkyl, aryl
E = CN, CO_2Et, COR^1

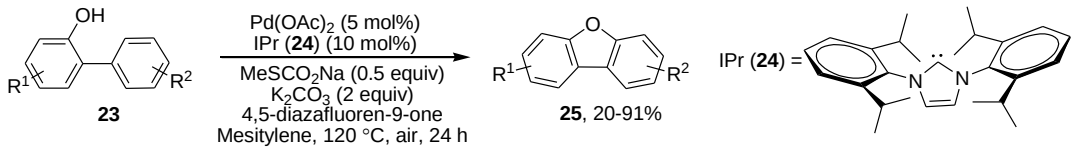
Scheme 15A

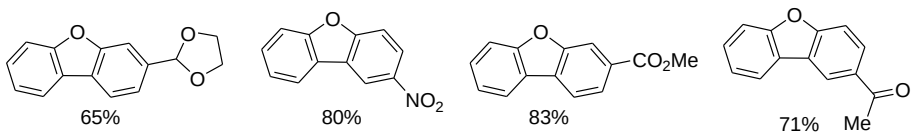




Scheme 15B

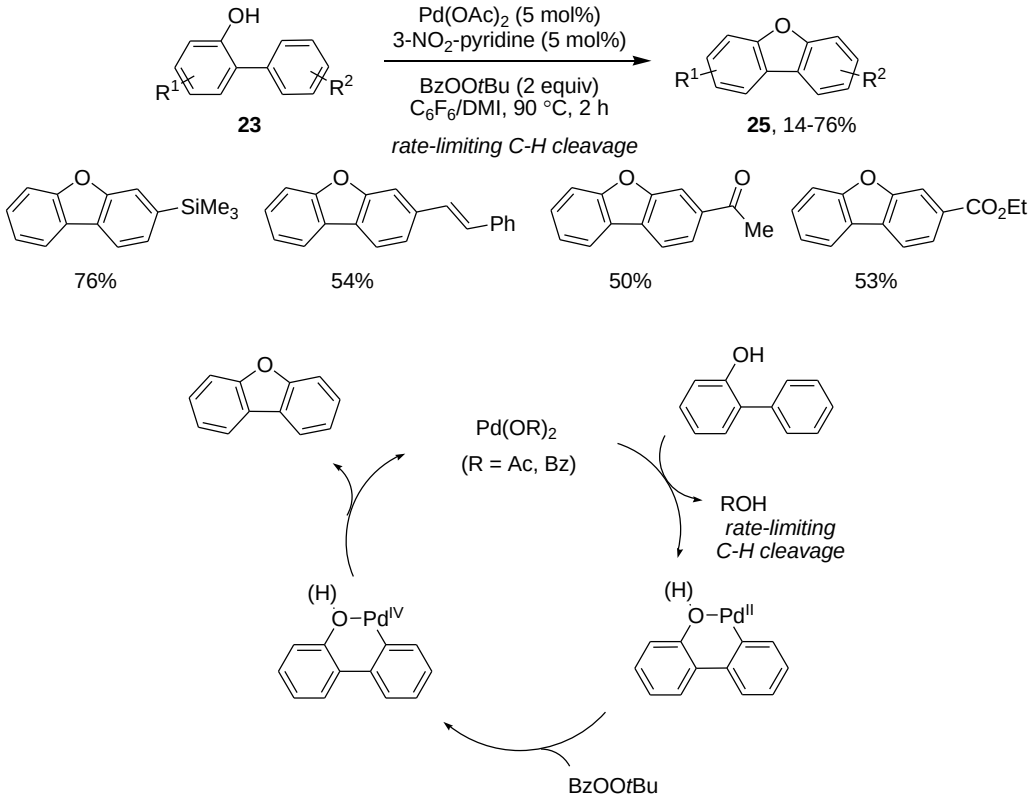
Recently Liu and coworkers described a novel and elegant approach for the synthesis of dibenzofurans **25** via palladium catalyzed cyclization of 2-arylphenols **23** using air as an oxidant in presence of IPr **24** and 4,5-diazafluoren-9-one ligand combination and additives such as $MesCO_2Na$, K_2CO_3 and molecular sieves. They have further demonstrated that C-O bond formation is rate limiting step in this reaction (Scheme 16).[26]





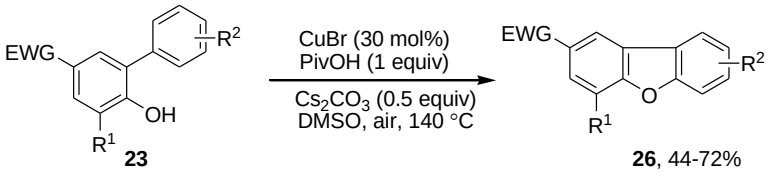
Scheme 16

Yoshikai and co-workers have developed a new method for the synthesis of dibenzofurans **25** from 2-arylphenols **23** via Pd(II)-catalyzed intramolecular C-H bond activation followed by C-O bond formation using 3-nitropyridine as a ligand, and *tert*-butyl peroxybenzoate (BzOO*t*Bu) as an oxidant (Scheme 17).[27] Mechanistic experiments suggest that the reaction involves Pd(II)-mediated C-H bond cleavage as the rate-limiting step, which is followed by oxidation to a high oxidation state palladium species and subsequent C-O bond-forming reductive elimination.[27]



Scheme 17

Recently Zhu and coworkers have described a direct method for preparation of multisubstituted dibenzofurans **26** involving copper catalyzed aerobic C-H activation/cycloetherification of o-arylphenols **23** in the presence of Cs_2CO_3 and pivalic acid as additives. The presence of a strong *para* electron withdrawing group (i.e. NO_2, CN, CHO) on the phenol is essential for the success of reaction. They have proposed a mechanistic pathway involving an irreversible rate limiting CMD step for C-H activation (Scheme 18).[28]

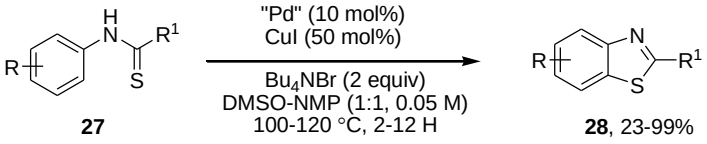


EWG = NO2, CN, CHO;
R^1 = H, F, Cl, Ph; R^2 = H, Me, OMe, F, Cl, Br, Ph

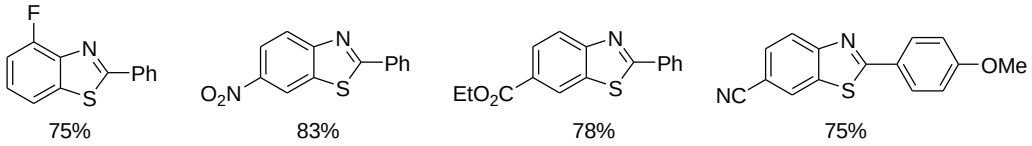
Scheme 18

4.2.3 Synthesis of Sulfur Containing Benzoheterocycles via Transition Metal Catalyzed Intramolecular C-H Activation/C-S Bond Formation

Examples of catalytic intramolecular C-H functionalization/C-S bond formation leading to sulfur containing benzoheterocycles such as benzothiazoles and benzo[*b*]thiophenes are only very few in the literature, presumably due to catalytic poisoning by sulfur. Thus, Inamoto and co-workers have reported a versatile method for the synthesis of 2-substituted benzothiazoles **28** from readily available substituted thiobenzanilides **27** via oxidative palladium-catalyzed C-H activation followed by intramolecular C-S bond formation (Scheme 19).[29a] The novel catalytic system consists of 10 mol% of Pd(II) salt, 50 mol% of CuI and 2 equiv of Bu_4NBr which greatly enhances this transformation, by enabling the process to be performed more efficiently and quickly in terms of higher yields (Scheme 19).[29a]

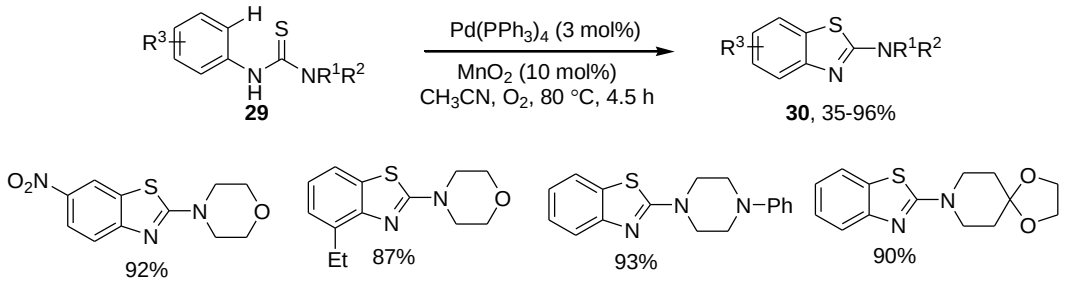


"Pd" = $PdCl_2$, $PdCl_2$(cod), $PdBr_2$



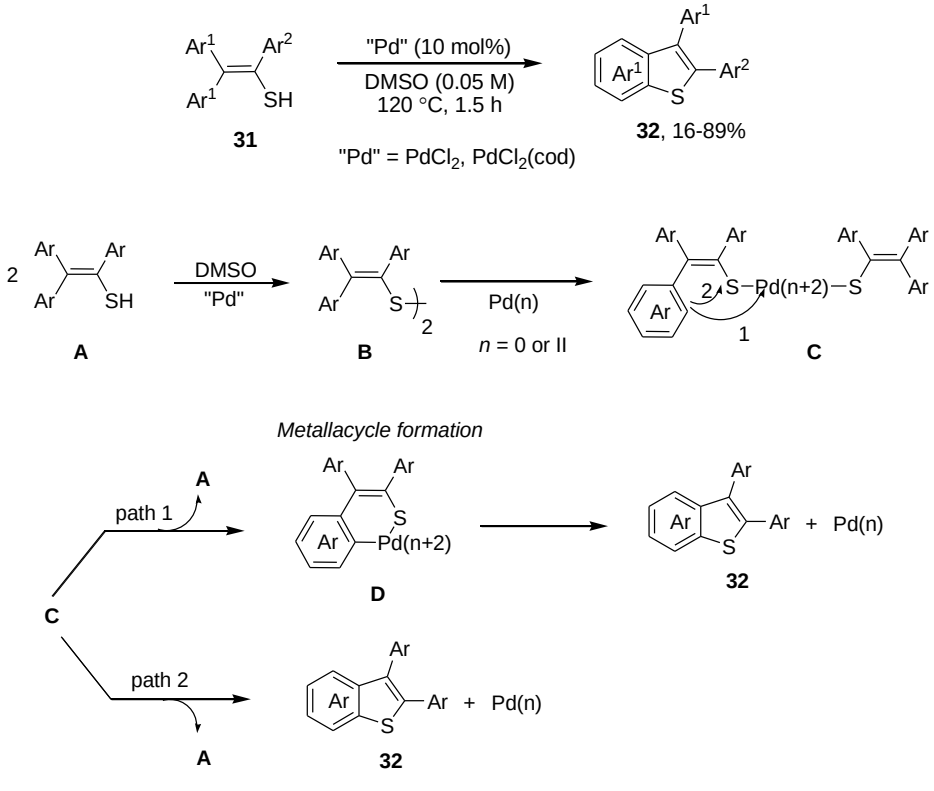
Scheme 19

Another example of the synthesis of 2-aminobenzothiazoles **30** via Palladium-catalyzed intramolecular C-H functionalization/C-S bond formation of *N*-arylthioureas **29** has been recently reported by Batey and coworkers (Scheme 20).[29b] This reaction employs $Pd(PPh_3)_4$ as catalyst along with MnO_2 as reoxidant under oxygen atmosphere at 80 °C.[29b]



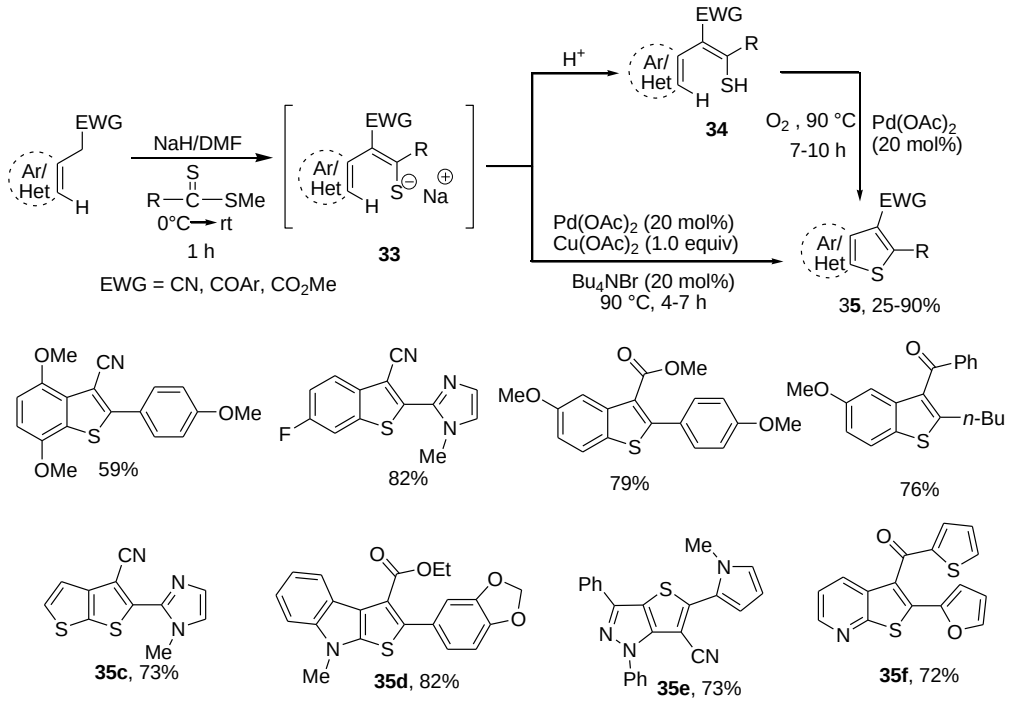
Scheme 20

Inamoto and coworkers have recently reported one-pot conversions of thioenols such as **31** to multisubstituted benzo[*b*]thiophenes **32** in the presence of palladium catalyst such as $PdCl_2$ or $PdCl_2$(COD) without any redox active reagents in the presence of DMSO as solvent (Scheme 21). They have further demonstrated that the reaction proceeds through intermediacy of disulfide **B** (formed by oxidation of thioenol by DMSO), which after oxidative addition to palladium followed by electrophilic attack of aryl ring either at palladium centre or at sulfur atom affords benzothiophenes in moderate to good yields (Scheme 21).[30]



Scheme 21

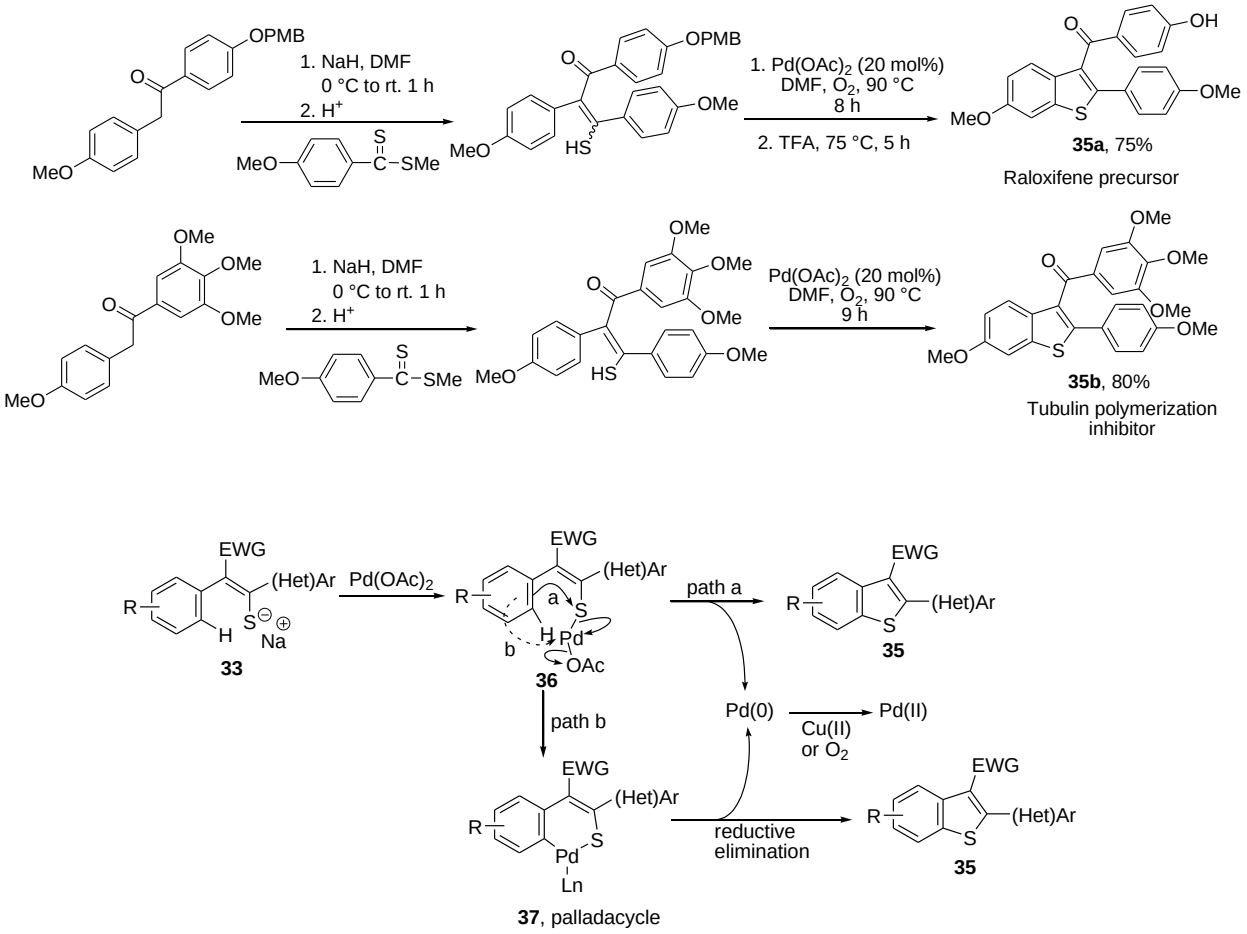
Our research group has recently described an efficient one-pot or two- step high yielding route to multisubstituted benzo[*b*]thiophenes **35** through palladium catalyzed intramolecular C-H functionalization-arylthiolation of enethiolate salts **33** (generated in situ through base mediated condensation of substituted arylacetonitriles, deoxybenzoins or arylacetates with het(aryl) dithioacetates) under the influence of palladium acetate (or palladium chloride)/cupric acetate catalytic system and Bu_4NBr as additive (Scheme 22).[31] In



Scheme 22

few cases, the yields of benzo[*b*]thiophenes were better in two step process by employing enethiols **34** as substrates and oxygen as reoxidant (instead of cupric acetate). The protocol could also be extended to the synthesis of raloxifene precursor **35a** and tubulin polymerization inhibitor **35b** in good yields (Scheme 22). The versatility of this newly developed method was further demonstrated by elaborating it for the synthesis of thieno-fused heterocycles (Scheme 22) such as thieno[2,3-*b*]thiophenes **35c**, thieno[2,3-*b*]indoles **35d**, thieno[2,3-*c*]pyrazoles **35e** and thieno[2,3-*b*]pyridines **35f**. The mechanism involves the reaction of thioenol (or thioenolate) with $Pd(OAc)_2$ or $PdCl_2$ leads to formation of Pd-S adduct **36**. Subsequent attack of aryl ring on sulfur atom in **36**, similar to electrophilic substitution, furnishes benzo[*b*]thiophene **35** with concurrent release of reduced palladium

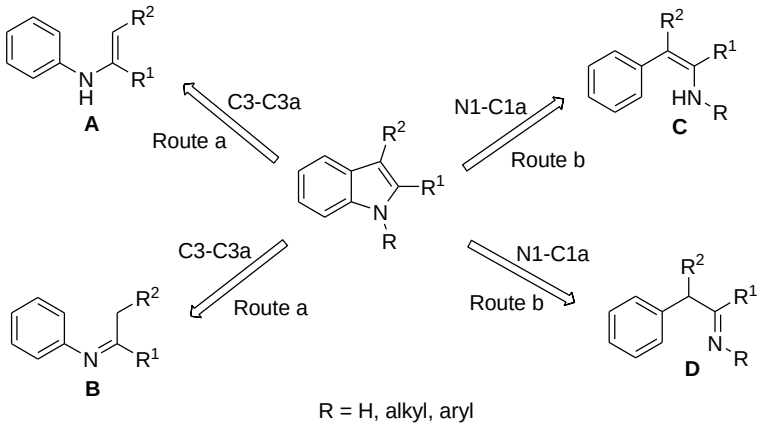
species followed by rearomatization (pathway a). Alternatively, aromatic ring attacks the palladium center in **36** to afford palladacycle intermediate **37** followed by reductive elimination leading to benzothiophene **35** and reduced Pd(0) species, which is reoxidized to Pd(II) in the presence of oxidants like oxygen or cupric acetate (pathway b) (Scheme 22).[31]



Scheme 22

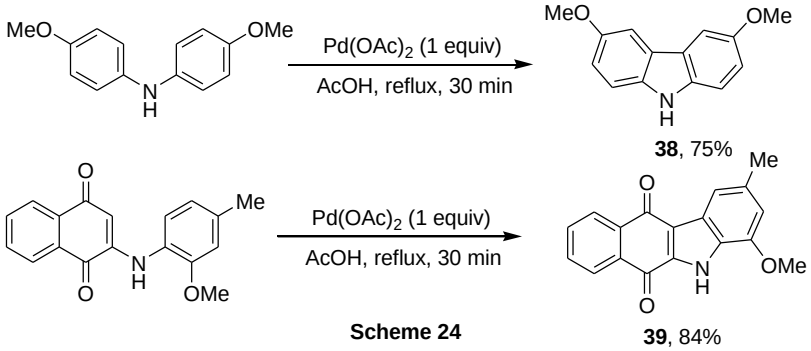
4.2.4 Synthesis of Substituted Indoles via Intramolecular C-H Activation/C-C or C-N Bond Formation

The C-H activation/intramolecular cyclization protocols through either C3-C3a or N1-C1a bond formation, routes a and b have also been applied for synthesis of indoles in recent years and intramolecular cross dehydrogenative coupling (CDC) (route a)[32] has become a promising protocol for the synthesis of indoles from enamines and imines involving C3-C3a bond formation as shown in Scheme 23.[32]



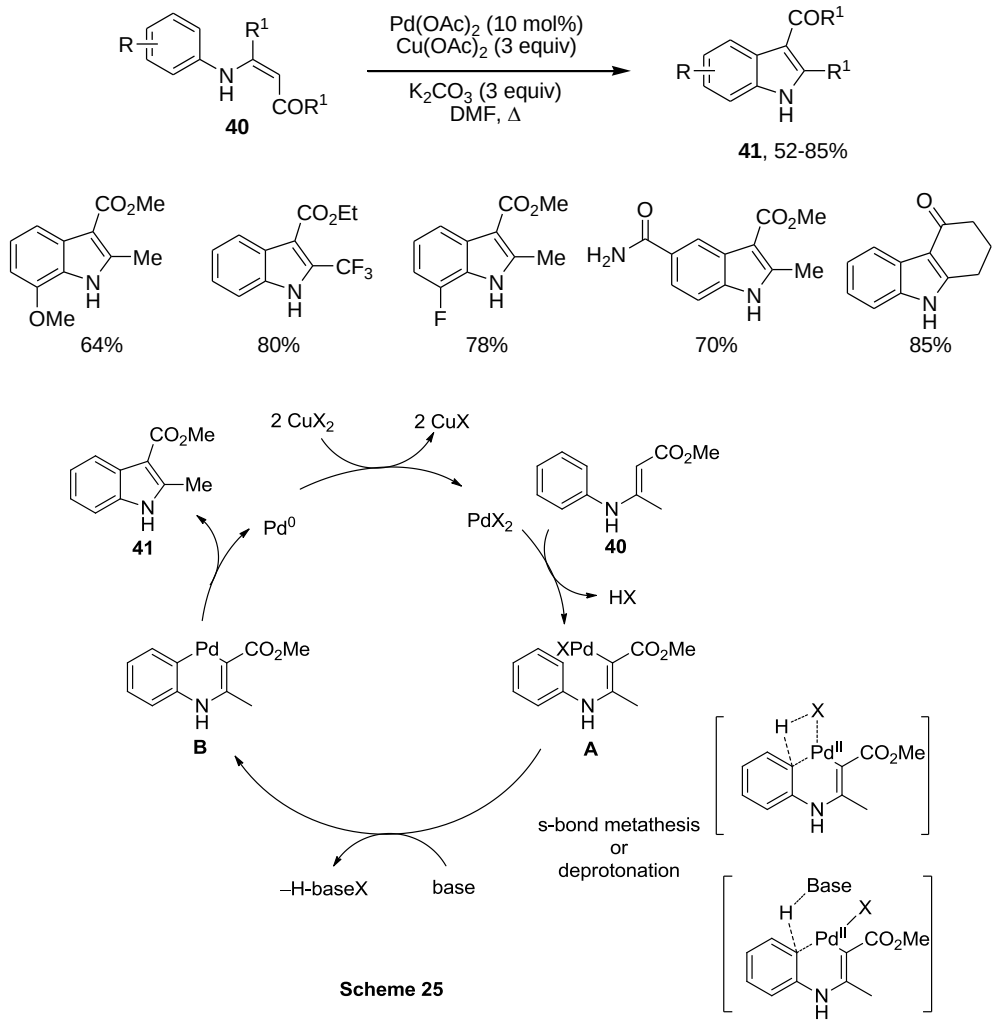
Scheme 23: The Development of the CDC Approach to Indoles

Akermark et al[33a] and Knolker[33b-c] et al have first reported in their independent studies, formation of carbazole **38** and carbazoloquinone derivatives **39** by an exciting Pd catalyzed and mediated intramolecular oxidative Heck type coupling (Scheme 24). Best results were obtained by employing electron rich aniline substrates since these reactions proceed by electrophilic aromatic palladation mechanism. However the need for acidic reaction conditions and limited scope restricts the applicability of these methods.



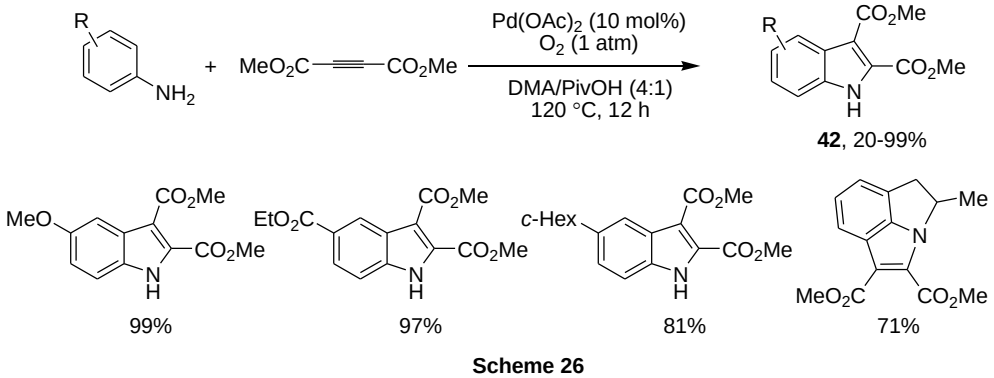
Scheme 24

In a detailed pioneering study in two papers, Glorius and co-workers have recently reported, an efficient synthesis of functionalized indoles **41** via Pd(II) catalyzed oxidative cyclization of *N*-arylenaminones/esters **40** ($Pd(OAc)_2/Cu(OAc)_2$) generated in situ by condensation of simple anilines with 1,3-dicarbonyl compounds (Scheme 25). This method is an attractive alternative to Heck coupling reactions, which requires the use of *ortho*-halogen substituted anilines. In a detailed mechanistic study, the authors have ruled out the electrophilic palladation of aniline and suggested a sigma bond metathesis or deprotonation pathway (Scheme 25).[34]



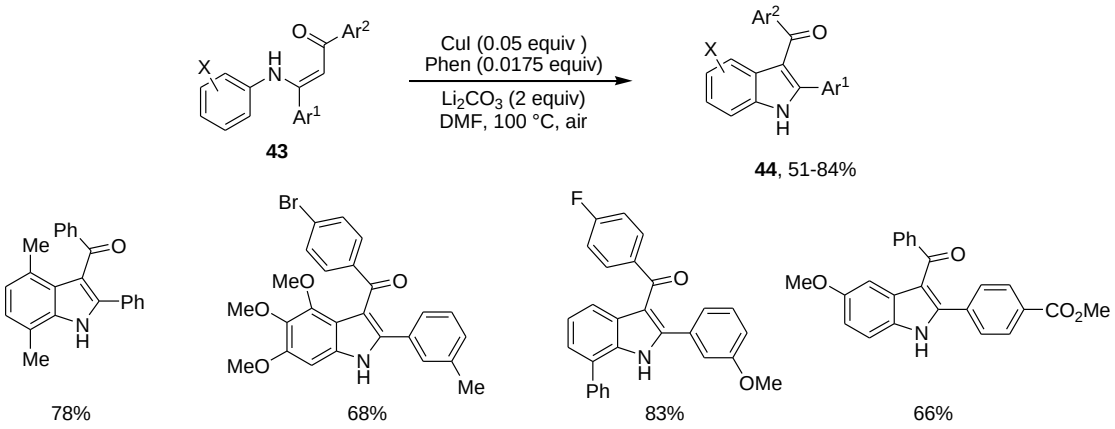
Scheme 25

Jiao and co-workers have described an efficient and direct C-H activation approach to indoles **42** from simple and readily available anilines and electron deficient alkynes by palladium catalyzed C-H activation using dioxygen (O_2) as the oxidant (Scheme 26).[35]



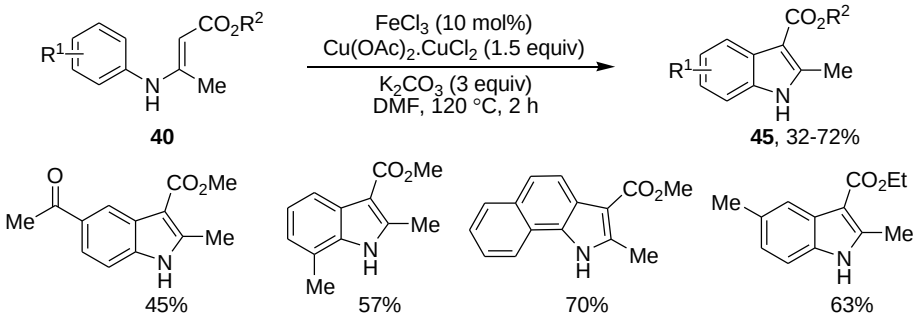
Scheme 26

Cacchi and co-workers have developed an efficient approach to construction of multisubstituted indole skeleton **44** from *N*-aryl enaminones **43**, that involves an intramolecular copper-catalyzed aryl C-H functionalization, through C_3-C_{3a} bond formation, in the presence of phenanthroline ligand (Scheme 27).[13b]



Scheme 27

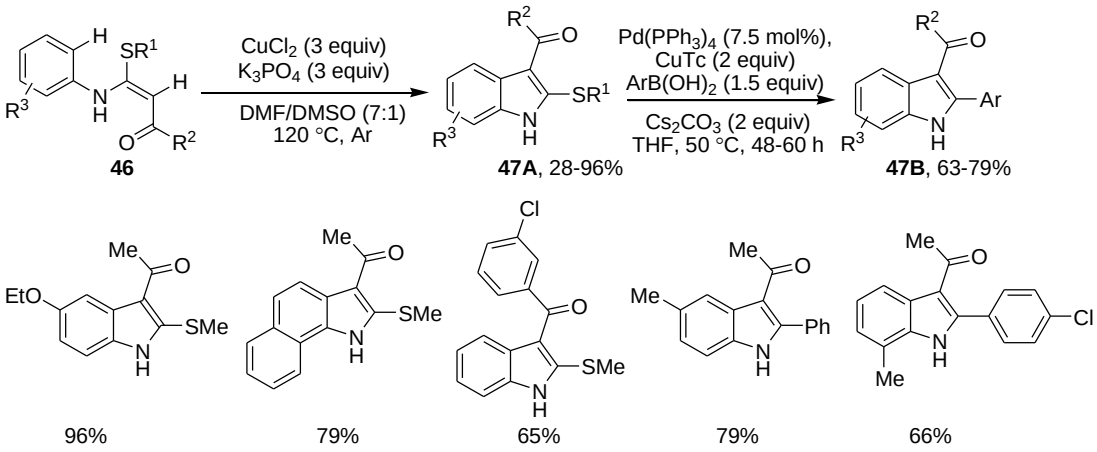
Liang and co-workers have reported an efficient method for the synthesis of substituted indoles **45** via iron catalyzed intramolecular oxidative coupling of aryl and vinylic C-H bonds of *N*-aryl enaminoesters **40**, with high functional group tolerance (Scheme 28). The use of cheap and environmentally benign iron catalyst combined with the highly active $Cu(OAc)_2.CuCl_2$ as oxidant, makes this C-H activation reaction more practical and attractive for indole synthesis (Scheme 28).[13c]



Scheme 28

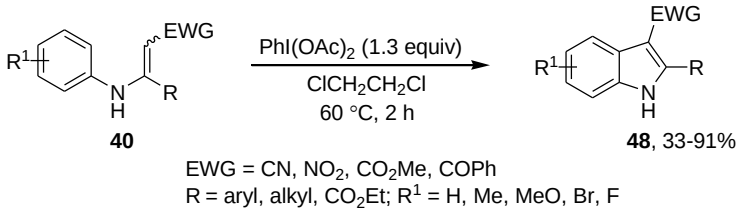
Yu and co-workers have recently reported an efficient method for the synthesis of 2-thioalkyl-3-acylindoles **47A** through $CuCl_2$-mediated intramolecular C-H/C-H cross-dehydrogenative coupling (CDC) of *α*-aroylketene-*N*,*S*-acetals **46** (Scheme 29). The readily

tunable C-S bond transformations of these 2-(methylthio)indoles **47** through Liebskind-Strogl cross-coupling or nucleophilic condensation to give functionalized indoles render this method a promising alternative route to access highly functionalized indole derivatives **47B** (Scheme 29).[36]



Scheme 29

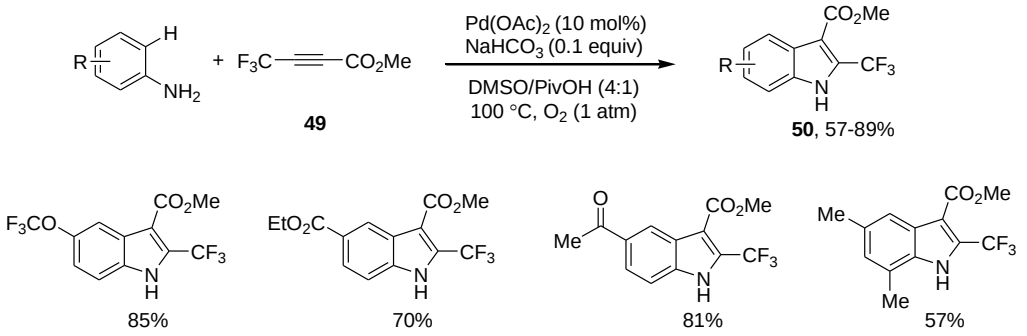
Zhao and co-workers have developed a new transition metal free method for functionalized indoles **48** from *N*-arylenaminonitriles such as **40** via PIDA-mediated oxidative C-C bond formation (Scheme 30). The advantages of this reaction are facilitative preparation of *N*-aryl enaminonitriles, good functional group tolerance, and mild reaction conditions (Scheme 30).[37]



Scheme 30

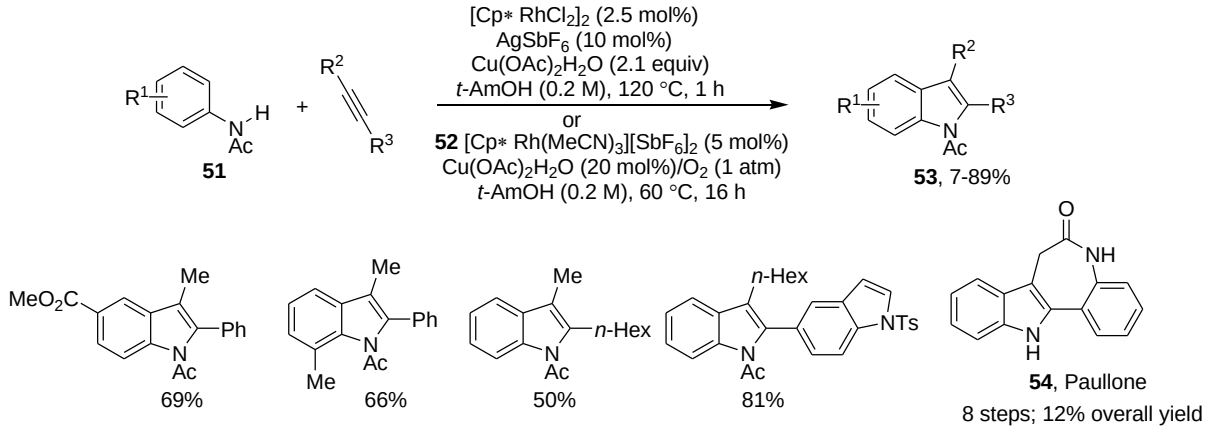
Recently Cao and co-workers have reported a mild and efficient one-pot synthesis of 2-perfluoroalkylated indoles **50** via Michael-type addition/palladium-catalyzed intramolecular cross-dehydrogenative coupling (CDC) of anilines with activated alkynes in presence of molecular oxygen as the sole oxidant at 100 °C in DMSO (Scheme 31). This

reaction is highly regioselective when unsymmetrical internal alkynes such as perfluoroalk-2-ynoates **49** are employed (Scheme 31).[32f]

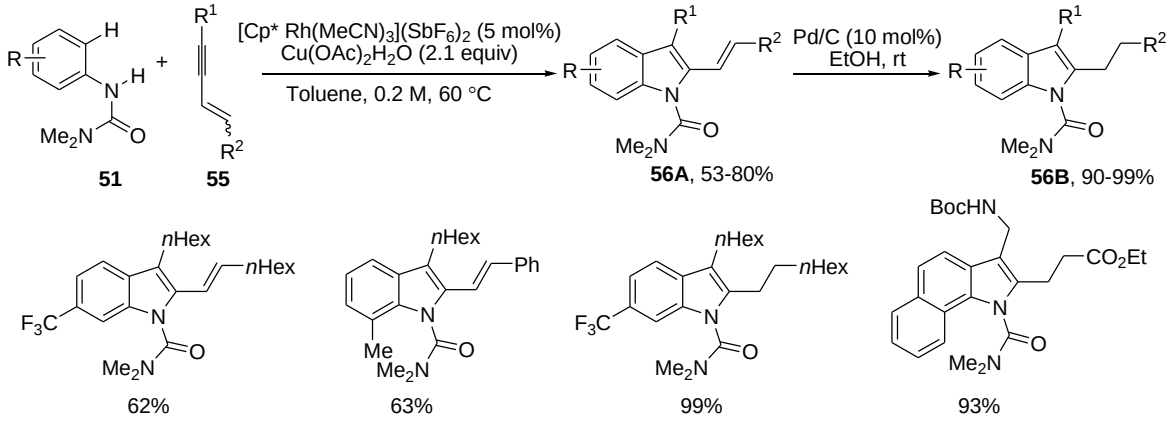


Scheme 31

Fagnou and co-workers have described a different approach to indoles **53** namely via rhodium(III) catalyzed oxidative coupling of in situ generated adducts of *N*-acetylanilines **51** and alkynes in the presence of $AgSb_6$ catalyst and $Cu(OAc)_2.H_2O$ as oxidant (Scheme 32A).[38a-b] This reaction is also achieved with second generation of rhodium catalysts such as **52**, using molecular oxygen as the terminal oxidant under mild temperature (60 °C) conditions. The applicability of the method is exemplified by an efficient synthesis of paullone **54**, a tetracyclic indole derivative which is known to inhibit cyclin-dependent kinases (CDKs) and glycogen synthase kinases (GSKs) (Scheme 32A).[38a-b] In continuation of these studies they have further developed a new method for the synthesis of unsymmetrical 2,3-aliphatic substituted indoles **56B**, via rhodium catalyzed union of enynes **55** and *N*-acetylanilines **51** and subsequent facile hydrogenation of **56 A** (Scheme 32B).[38c]

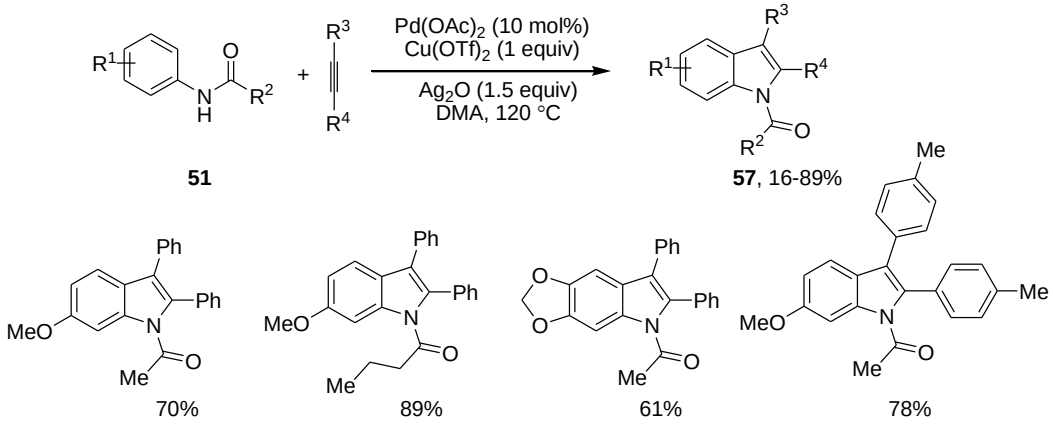


Scheme 32A



Scheme 32B

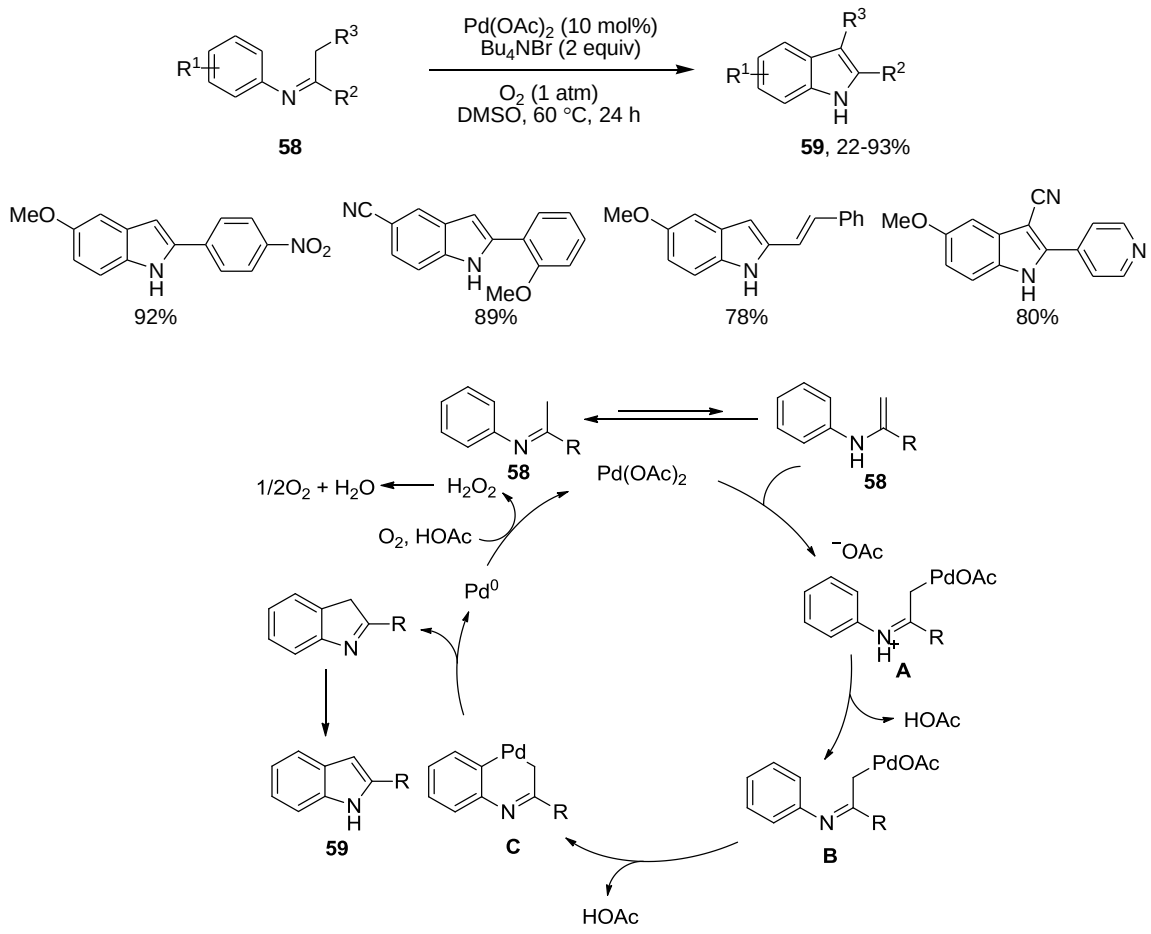
Lu and coworkers have developed an efficient method for the construction of 1,2-bisarylindoles **57** skeleton via palladium catalyzed intramolecular oxidative C-H activation of adducts from *N*-arylamides **51** and substituted diarylacetylenes, using cupric triflate and Ag_2O as oxidants (Scheme 33). The acetamido group in this transformation functions as directing group as well as provides a nitrogen atom for the indole ring. Both stoichiometric and catalytic versions of this reaction have been successfully developed.[39]



Scheme 33

Yoshikai and co-workers have made a significant breakthrough for indole **59** synthesis through palladium-catalyzed aerobic oxidative cyclization of *N*-arylimines **58** prepared from simple ketones and anilines (Scheme 34).[40] The reaction likely involves palladation of *N*-arylenamines **A** formed via imine-enamine tautomerization (Scheme 34). The process allows quick and atom-economical assembly of indole rings from inexpensive and readily available anilines and ketones and tolerates a broad range of functional groups

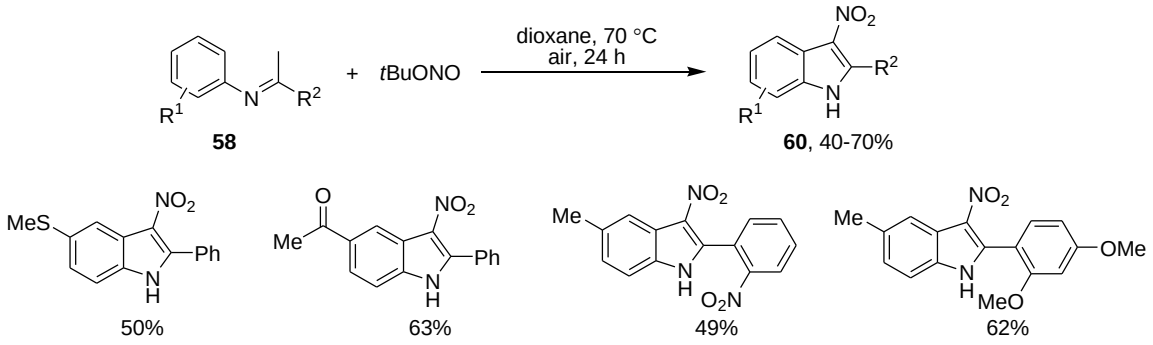
(Scheme 34). Besides, this indole synthesis could readily be scaled up to gram quantity without difficulty. The mechanistic studies have revealed a Pd(II)/Pd(0) redox process with initial electrophilic palladation of nucleophilic enamine, generated in situ by tautomerization of imine followed by deprotonation and formation of palladium complex **B,** which undergoes electrophilic aromatic palladation by a concerted metalation-deprotonation mechanism followed by subsequent reductive elimination to generate the 3H-indoles, which can tautomerize quickly affording the indole products and Pd(0) complex, which can be reoxidize to Pd(II) complex by oxygen.[40]



Scheme 34

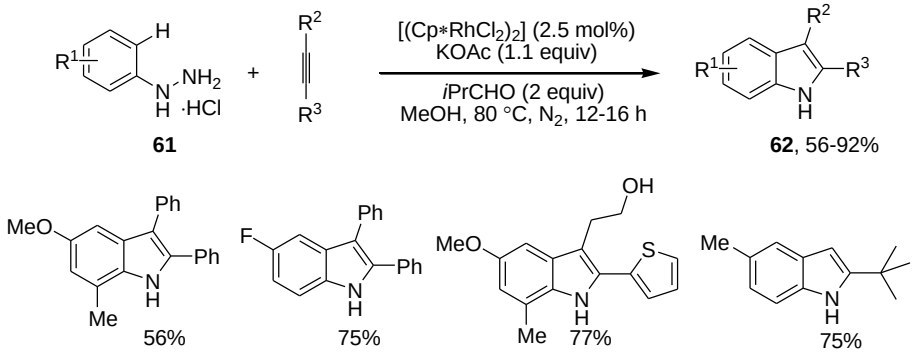
In a related work, Li and co-workers have reported a new metal-free route for the synthesis of 3-nitroindoles **60** by the nitrative cyclization of *N*-arylimines **58** with *tert*-butyl nitrite. This radical transformation involves oxidative dehydrogenation, nitration, cyclization and isomerization sequence and provides an operationally simple and atom economical

access to indoles with high functional group compability and excellent selectivity control (Scheme 35).[32g]



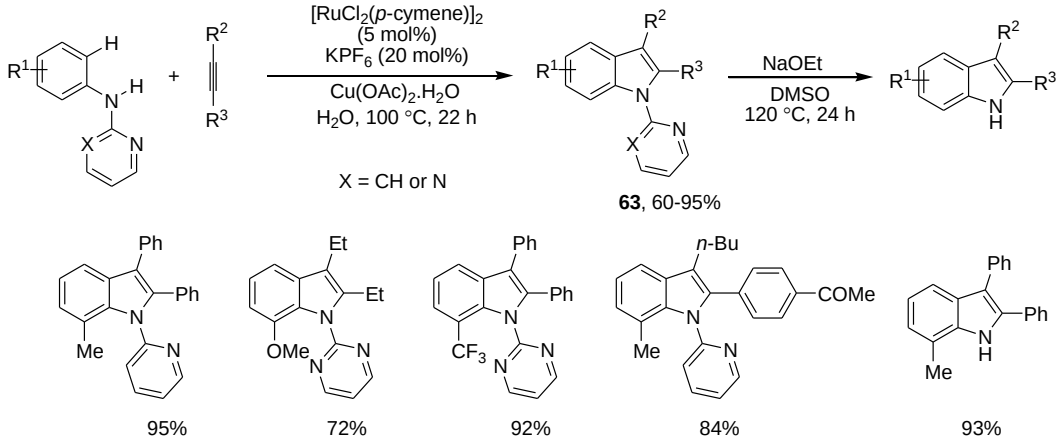
Scheme 35

Hua and co-workers have reported an efficient, practical, and external oxidant-free indoles **62** synthesis through rhodium catalyzed C-H activation of hydrazones **61** (generated by in situ condensation of hydrazines and C=O source) and alkynes. In this novel C-H activation strategy, hydrazone acts as an auto-formed and auto-cleavable directing group and its N-N bond acts as internal oxidant, which enables efficient and external oxidant free synthesis of unprotected indoles such as **62** from readily available hydrazines and alkynes (Scheme 36).[32e]



Scheme 36

Ackermann and co-workers have recently reported first ruthenium catalyzed oxidative annulations of alkynes through oxidative C-H functionalization with anilines bearing removable directing groups (Scheme 37). The most efficient catalysis is accomplished with a cationic ruthenium (II) complex in water as a sustainable solvent, providing general access to various bioactive indoles **63** (Scheme 37).[41]

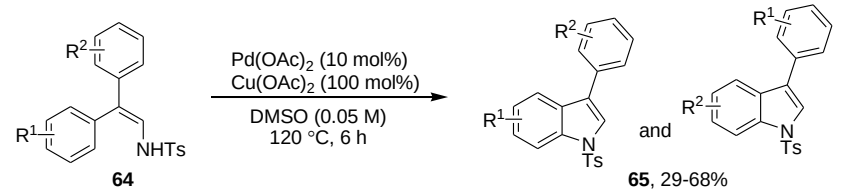


Scheme 37

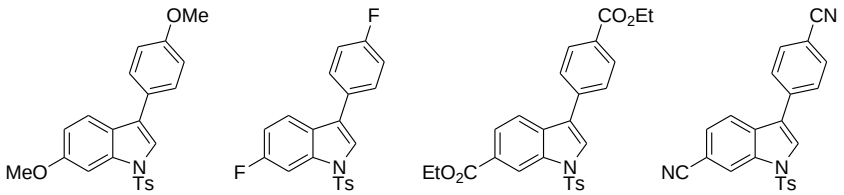
Despite significant progress in indole synthesis through cross-dehydrative coupling (CDC) involving C3-C3a bond formation as described with various examples, a practical synthetic method for substituted indoles via catalytic intramolecular C-H-activation/C-N bond formation involving construction of N1-C1a bond, parallel to carbazole synthesis, is yet to be realized (Scheme 23, route b).[12c,15,17,18] There are few reports in the literature describing indole synthesis via intramolecular C-H functionalization/C-N bond formation (Scheme 23), which are described in the following section.

Thus, Inamoto and co-workers have developed a new approach to 3-substituted indoles **65** through palladium-catalyzed C-H activation followed by intramolecular amination of enamines **64** (Scheme 38). However this method suffers from lack of generality, moderate to low yields as well as regioselective problems, when two aryl groups are unsymmetrically substituted.[42]

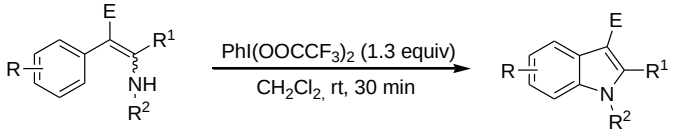
Zhao and co-workers have reported synthesis of *N*-aryl/alkyl -2-alkyl-3-cyanoindoles **67** via phenyliodine bis(trifluoroacetate) (PIFA) mediated intramolecular oxidative cyclization of *N*-aryl-2-aryl-enaminonitriles **66** (Scheme 39). However, use of stoichiometric amount of expensive PIFA and rather a narrow functional group scope (synthesis of only 2-methylindole and one with (2-*n*-propyl) group has been reported) are main disadvantages. Besides the method suffers from lack of regioselectivity with *m*-substituted (2-aryl)enaminonitriles yielding mixture of 5-and 7-substituted indoles (Scheme 39).[43]



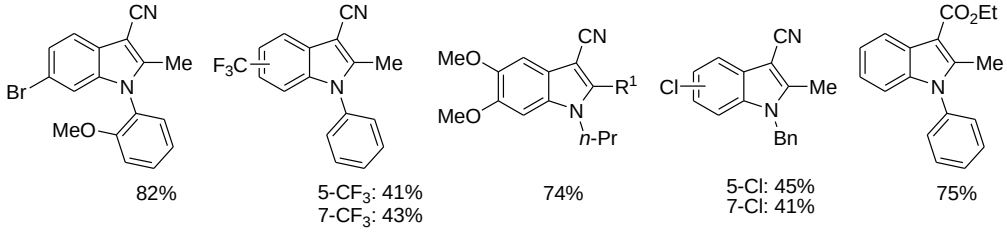
64 **65**, 29-68%



Scheme 38

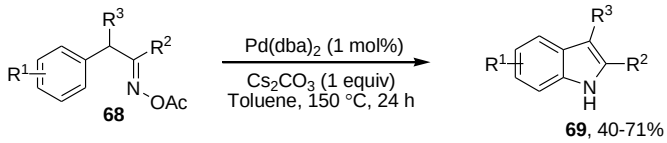


66 **67**, 70-92%

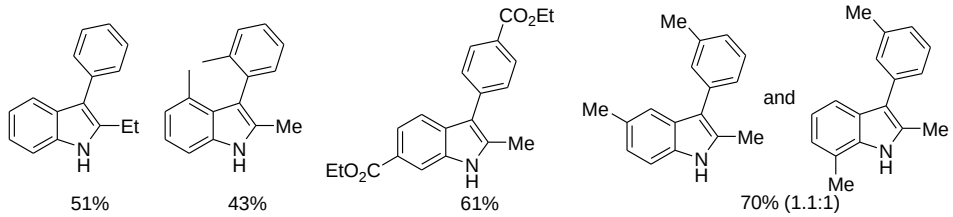


Scheme 39

Hartwig and co-workers have recently reported a complementary strategy for the synthesis of indoles **69** via intramolecular C-H amination of oxime esters **68** involving oxidative addition of Pd(0) species in N-O bond, which eliminates the need for external oxidant (Scheme 40). However, the generality and scope of the reaction is limited only to few



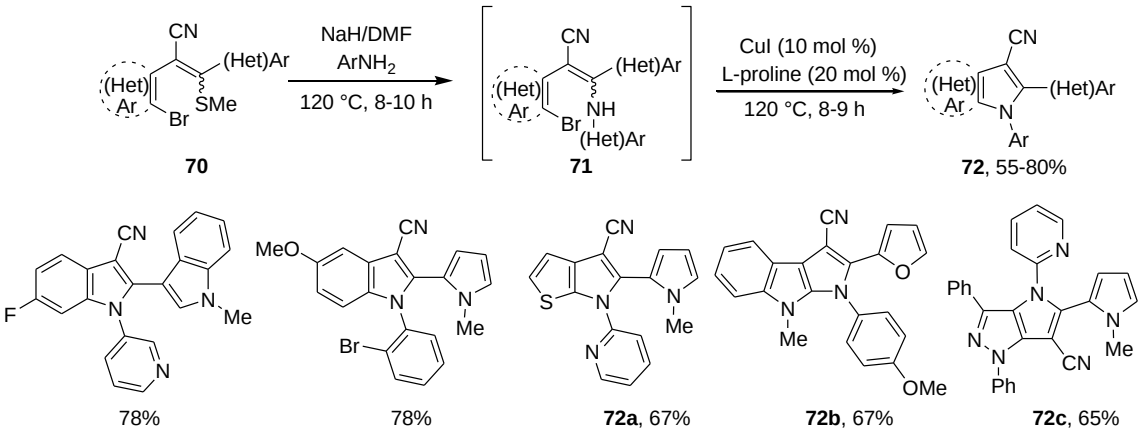
68 **69**, 40-71%



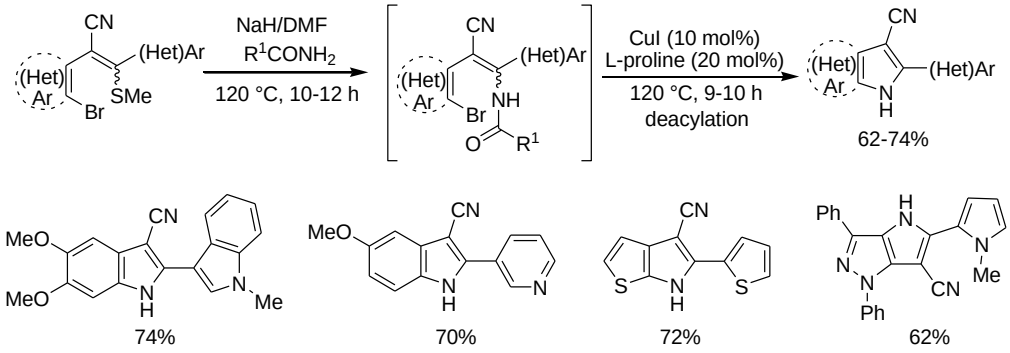
Scheme 40

3-aryl-2-methylindoles in moderate to good yields along with regioselectivity problem in some *m*-substituted aryl derivatives (Scheme 40).[44]

Our research group has recently reported a novel high yielding route to substituted 1-*N*-(het)aryl/NH-2-(het)aryl/alkyl-3-cyanoindoles **72** and the related pyrrolo fused heterocycles such as thienopyrroles **72a**, pyrroloindoles **72b**, and pyrazolopyrroles **72c** involving sequential one pot base mediated and copper catalyzed inter and intramolecular amination of 2-[2-bromo(het)aryl]-3-(het)-aryl-3-(methylthio)acrylonitrile **70** precursors with primary amines or amides via in situ generated enamio nitrile **71** precursors (Schemes 41A and 41B).[1] The overall protocol involves formation of N(1)-C(2) and N(1)-C(7a) bond formation respectively, in a two-step one-pot procedure (Scheme 41A).[1]



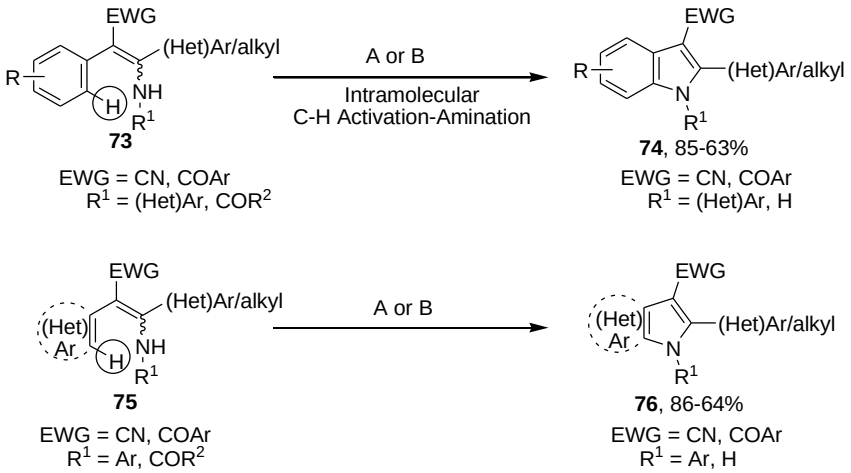
Scheme 41A



Scheme 41B

In continuation of these studies, we now developed an efficient route to 1- *N*-aryl/NH-2-(het)aryl/alkyl-3-cyano/aroylindoles and their heterofused analogs **74** and **76** by

palladium catalyzed intramolecular oxidative C-H functionalization-amination of readily available 2,3-(het)aryl-3-*N*-aryl/acylenaminonitriles and enaminones **73** or **75** (Scheme 42). The results of these studies are described in the following section of this chapter. The key feature of this protocol is that it utilizes an aminoaryl group as directing group as well as nucleophilic coupling partner in this intramolecular C-H heterofunctionalization process. Besides, the reaction displays high regioselectivity and good functional group tolerance at various positions of indole skeleton along with high yields in this cyclization reaction (Scheme 42).

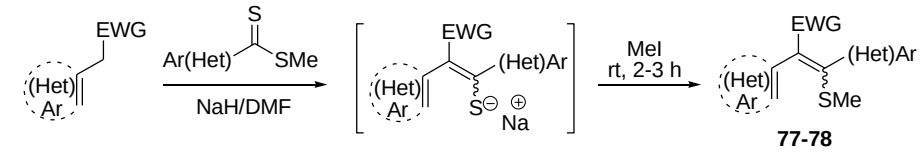


Scheme 42

4.3 Results and Discussion

4.3.1 Synthesis of 3-(Methylthio)-2-het(aryl)-3-het(aryl)/alkylacrylonitrile/enone Precursors 77-78

The desired acrylonitrile and enone precursors **77a-j**, **77m-n** (Table 2), **77p-r** (Table 4), **78a-b**, **78d-h** (Tables 3-4) were prepared following the similar procedure reported for the corresponding 2-(2-bromohet(aryl-3-(methylthio)acrylonitrile precursors **70**[49] by base induced condensation of the corresponding 2-bromoarylacetonitriles with (het)aryl dithioesters, followed by in situ S-methylation of the resulting enethiolate intermediates (Scheme 43)



Scheme 43

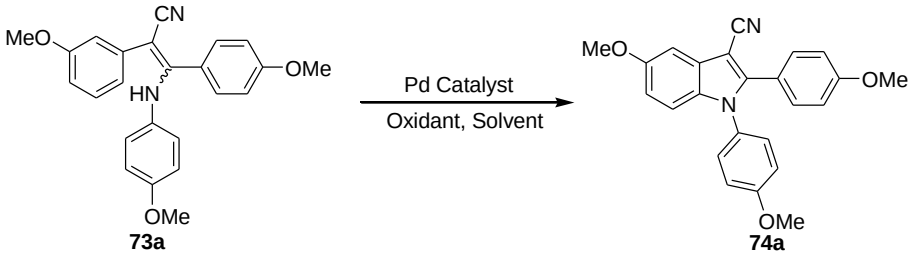
4.3.2 Synthesis of 1-*N*-(Het)aryl-2,3-Substituted Indoles 74 from Enaminonitriles/ Enaminones 73

The desired *N*-arylenaminonitriles **73a-j** and enaminones **73m-n** were prepared in good yields by nucleophilic displacement on the corresponding β-(methylthio)acrylonitriles **77a-j**[1a] or the corresponding enones **77m-n** by the appropriate arylamines in presence of sodium hydride or butyl lithium, as the base respectively (Table 2, see experimental). The corresponding 3-alkyl- and N-benzylenaminonitriles **73k-l** and **73o** on the other hand, were obtained by direct condensation of the respective α-(thioacyl) (or acyl)arylacetonitriles **77k-l** and **77o** with appropriate amines in the presence of acetic acid in ethanol (Table 2, see experimental).

4.3.2.1 Optimization of Reaction Conditions for the Synthesis of Indole 74a from 73a

We began our investigation on the proposed palladium catalyzed intramolecular C-H functionalization-amination, using enaminonitrile **73a** as the test substrate for optimizing the reaction conditions, leading to the indole **74a** (Table 1). Our studies revealed that the reaction of **73a** with 20 mol% of $Pd(OAc)_2$, $Cu(OAc)_2$ (1 equiv), in DMSO in air afforded the indole **74a** in 61% yield (Table 1, entry 1). On the other hand, **74a** was obtained in 75% yield, when the same reaction was conducted under the atmosphere of oxygen (entry 2). Among all the palladium complexes examined, $Pd(OAc)_2$ was found to be most effective catalyst for this transformation (entries 3-5) and in the absence of $Pd(OAc)_2$, formation of indole **74a** was not observed (entry 6), thus demonstrating that the role of $Cu(OAc)_2$ was mainly to reoxidize the reduced palladium species. Similarly, the other reoxidants such as $PhI(OAc)_2$, $KHSO_5$, AgOAc, oxone and benzoquinone used for similar palladium catalyzed oxidative C-H activation – heterofunctionalization reactions were found to be either less efficient (entries 7-9) or unsuccessful (entries 10 and 11) in this reaction. Similarly, performing the reaction in other solvents like DMF or toluene gave decreased yield of **74a** (entries 12 and13). Also, a

Table 1. Optimization of Reaction Conditions for the Synthesis of Indole 74a from 73a[a]



73a **74a**

entry	Pd catalyst (mol%)	oxidant (equiv)	gas atm	time, h/temp, °C	solvent	%yield **74a**
1	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$ (1.0)	Air	20 h, 120 °C	DMSO	61
2	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$ (1.0)	O_2	8 h, 120 °C	DMSO	75
3	$PdCl_2$ (20 mol%)	$Cu(OAc)_2$ (1.0)	O_2	12 h, 120 °C	DMSO	60
4	$PdCl_2(PPh_3)_2$(20 mol%)	$Cu(OAc)_2$ (1.0)	O_2	12 h, 120 °C	DMSO	66
5	$PdCl_2(CH_3CN)_2$(20 mol%)	$Cu(OAc)_2$ (1.0)	O_2	10 h, 120 °C	DMSO	55
6	—	$Cu(OAc)_2$ (1.0)	O_2	20 h, 120 °C	DMSO	NR
7	$Pd(OAc)_2$ (20 mol%)	$PhI(OAc)_2$(1.0)	O_2	15 h, 120 °C	DMSO	48
8	$Pd(OAc)_2$ (20 mol%)	$KHSO_5$(1.0)	O_2	10 h, 120 °C	DMSO	69
9	$Pd(OAc)_2$ (20 mol%)	AgOAc(1.0)	O_2	24 h, 120 °C	DMSO	62
10	$Pd(OAc)_2$ (20 mol%)	Oxone (1.0)	O_2	24 h, 120 °C	DMSO	Trace
11	$Pd(OAc)_2$ (20 mol%)	benzoquinone	O_2	24 h, 120 °C	DMSO	Trace
12	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$ (1.0)	O_2	8 h, 120 °C	DMF	64
13	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$ (1.0)	O_2	26 h, 110 °C	Toluene	51
14	$Pd(OAc)_2$ (10 mol%)	$Cu(OAc)_2$ (1.0)	O_2	14 h, 120 °C	DMSO	65
15	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$:H_2O(1.0)	O_2	8 h, 120 °C	DMSO	65
16	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$:H_2O(1.0)	O_2	8 h, 120 °C	DMF	63

17	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$ (0.5)	O_2	15 h, 120 °C	DMSO	68
18	$Pd(OAc)_2$ (20 mol%)	—	O_2	12 h, 120 °C	DMSO	65
19	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$ (1.0) Bu_4NBr (1.0)	O_2	6 h, 120 °C	DMSO	70
20	$Pd(OAc)_2$ (20 mol%)	$Cu(OAc)_2$ (1.0) Na_2CO_3 (2.0) PivOH (1.0)	O_2	15 h, 110 °C	DMSO	58
21	$Pd(OAc)_2$ (20 mol%)	Ag_2CO_3 (1.0) PivOH (1.0)	O_2	10 h, 120 °C	DMSO	81
22	$Pd(OAc)_2$ (20 mol%)	Ag_2CO_3 (0.5) PivOH (0.5)	O_2	17 h, 120 °C	DMSO	67

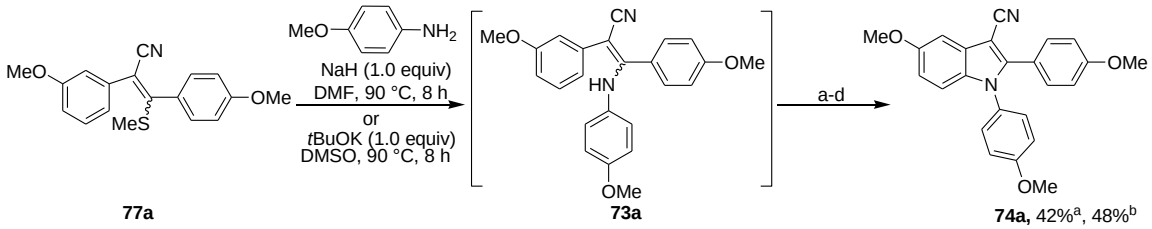
[a]Reactions were performed with **73a** (0.3 mmol) in 2 mL of solvent.

reduced amount of catalytic loading resulted in a significant drop in the conversion (entry 14). Use of $Cu(OAc)_2.H_2O$ (1 equiv) as oxidant (15 and 16), or decreasing the amount of $Cu(OAc)_2$ (entry 17) or conducting the reaction in the absence of $Cu(OAc)_2$ under oxygen atmosphere (entry 18) afforded reduced yields of the indole **74a**. Use of Bu_4NBr as additive, although facilitated the reaction within 6 h, however without any improvement in the yield of indole **74a** (entry 19). We also conducted few optimization experiments in the presence of pivalic acid as additive, which has been reported to exhibit unprecedented reactivity in few C-H activation- functionalization reactions.[45] Thus, performing the reaction in the presence of sodium carbonate (2 equiv) and pivalic acid (1 equiv) did not yield any encouraging results affording the indole **74a** only in 58% yield (entry 20), however, replacement of sodium carbonate by silver carbonate (1 equiv) under similar conditions resulted in considerable increase in the yield of indole **74a** (entry 21). On the other hand, decreasing the amount of silver carbonate (0.5 equiv) afforded reduced yield of indole **74a** (entry 22). We therefore identified these two optimal conditions (entries 2 and 21) for subsequent studies and conducted most of the experiments under both conditions.

4.3.2.2 One-Pot Synthesis of *N*-substituted Indole 74a from 2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-3-(methylthio)acrylonitrile 77a

With optimized reaction conditions in hand for the two step synthesis of indole **74a** from 3-(methylthio)acrylonitrile **77a**, we next attempted one-pot sequence by generating enaminonitrile **73a** in situ from **77a** and 4-methoxyaniline in presence of either sodium hydride or potasium *t*-butoxide as base and subjecting it to intramolecular C-H amination

under optimized reaction conditions (Scheme 44). However, indole **74a** could be obtained in maximum yield of only 64% under $Pd(OAc)_2$ catalyzed oxidative cyclization conditions in the presence of silver carbonate and pivalic acid. We therefore performed all subsequent reactions under two step conditions starting from pure enaminonitriles/enaminones **73** or **75** obtained from **77** and **78** respectively (Tables 2 and 3).



[a]$Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv), DMF, O_2, 120 °C, 15 h, 42% (with NaH)

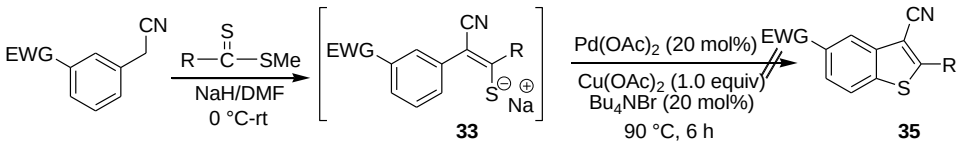
[b]$Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv), DMSO, O_2, 120 °C, 15 h, 48% (with *t*BuOK)

[c]$Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv), DMSO, O_2, Bu_4NBr (1.0 equiv), 120 °C, 8 h, 58% (with *t*BuOK)

[d]$Pd(OAc)_2$ (20 mol%), Ag_2CO_3 (1.0 equiv), PivOH(1.0 equiv), DMSO, O_2, 120 °C, 12 h, 64% (with *t*BuOK)

Scheme 44

With the realization of optimized reaction conditions for the synthesis of indole **74a** from enaminonitrile **73a**, we next evaluated the generality and scope of this new protocol for introduction of different substituents at various positions of indole nucleus. These results are summarized in the Table 2. Thus the reaction was found to be amenable with both electron donating and electron withdrawing substituents on the 2- aryl ring of enaminonitriles **73a-d**, furnishing the substituted indoles **74a-d** in high yields (Table 2, entries 1-4). Also, it is pertinent to note, that enaminonitriles **73e** and **73f** bearing an electron withdrawing substituents (F and CN) *para* to the cyclization position also underwent facile intramolecular C-H arylamination, furnishing the indoles **74e-f** in high yields (Table 2, entries 5 and 6). These results are contrary to our earlier observations during palladium catalyzed intramolecular C-H functionalization-arylthiolation of the corresponding enethiolates (**33a-b**) bearing an electron withdrawing groups at 3-position, which failed to furnish the corresponding benzo[*b*]thiophenes **35a-b** under optimized conditions (Scheme 45).[31a] The

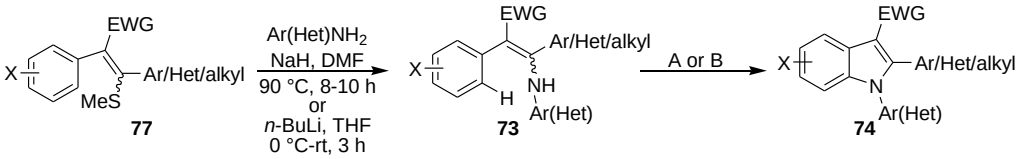


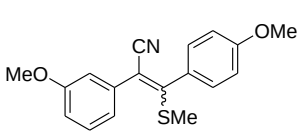
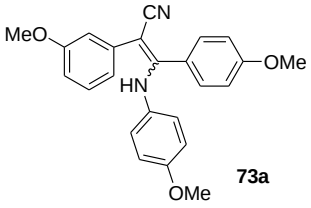
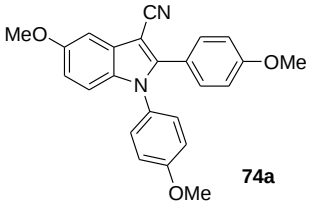
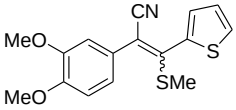
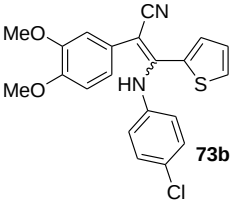
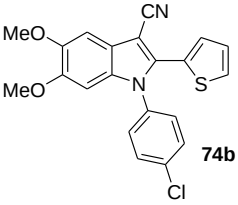
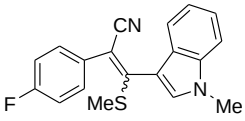
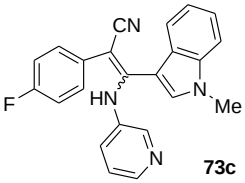
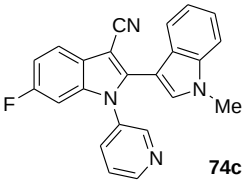
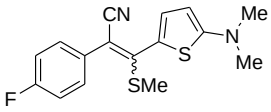
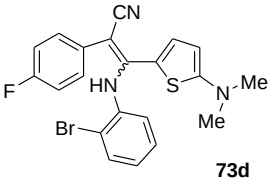
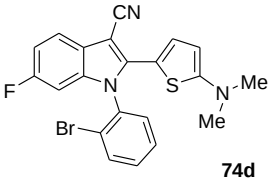
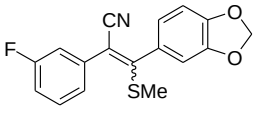
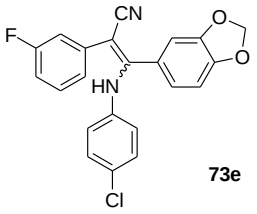
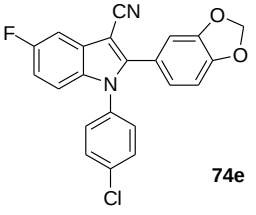
EWG = F, CN

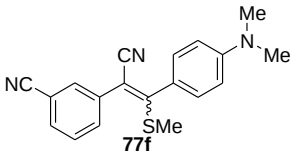
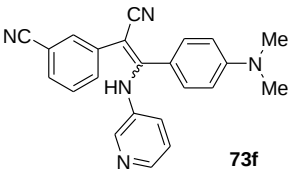
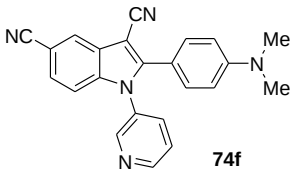
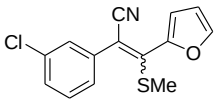
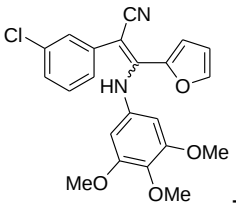
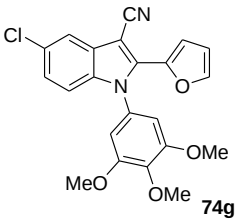
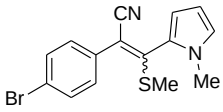
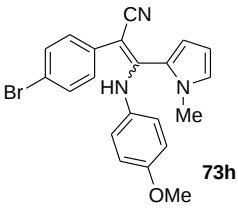
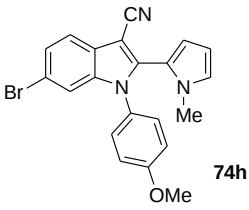
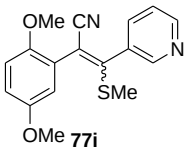
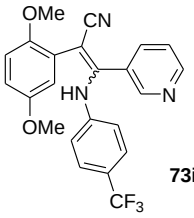
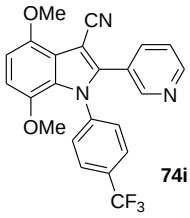
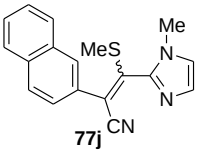
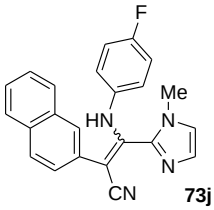
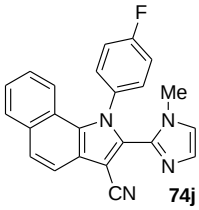
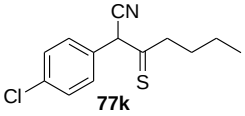
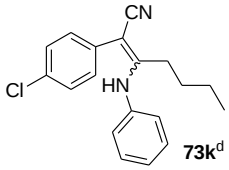
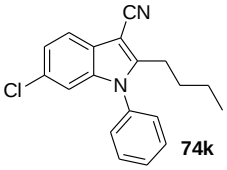
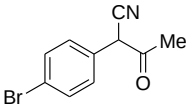
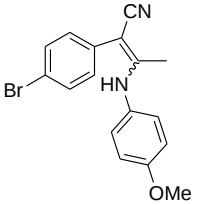
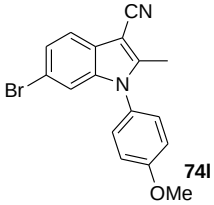
33, **35a**, EWG = F; R = 2-thienyl
b, EWG = CN; R = 2-furyl

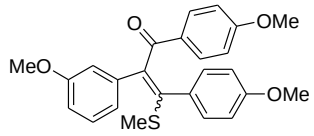
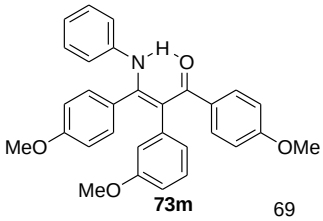
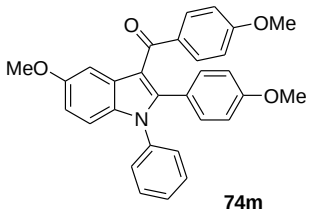
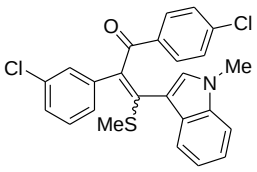
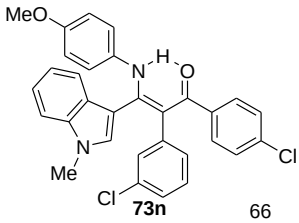
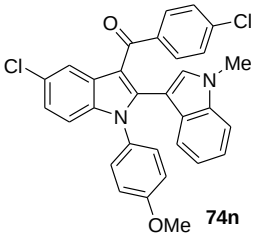
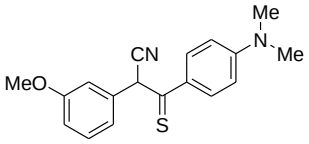
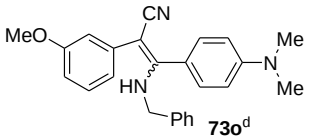
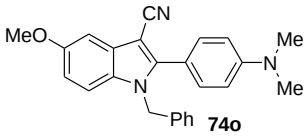
Scheme 45

Table 2: Synthesis of 1-*N*-(Het)aryl-2,3-Substituted Indoles 74 from Enaminonitriles/ Enaminones 73



entry	substrate **77**	substrate	yield (%) **73**	product	yield (%) **74**
1	 **77a**	 **73a**	80	 **74a**	75[a], 81[b], 73[c]
2	 **77b**	 **73b**	87	 **74b**	70[a], 73[b]
3	 **77c**	 **73c**	71	 **74c**	74[a], 76[b]
4	 **77d**	 **73d**	74	 **74d**	84[a], 85[b]
5	 **77e**	 **73e**	65	 **74e**	72[a], 75[b]

entry	substrate **77**	substrate	yield (%) **73**	product	yield (%) **74**
6	 **77f**	 **73f**	82	 **74f**	70[a], 74[b]
7	 **77g**	 **73g**	67	 **74g**	81[a], 83[b]
8	 **77h**	 **73h**	73	 **74h**	76[a], 78[b]
9	 **77i**	 **73i**	64	 **74i**	71[a], 76[b]
10	 **77j**	 **73j**	68	 **74j**	79[a], 80[b]
11	 **77k**	 **73k**[d]	70	 **74k**	72[a], 75[b]
12	 **77l**	 **73l**[d]	72	 **74l**	76[a], 70[b]

entry	substrate **77**	substrate	yield (%) **73**	product	yield (%) **74**
13	 **77m**	 **73m**	69	 **74m**	63[a], 60[b]
14	 **77n**	 **73n**	66	 **74n**	73[a], 65[b]
15	 **77o**	 **73o**[d]	62	 **74o**	0[a,b]

Reaction conditions: Method A: **73** (0.3 mmol), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv) in DMSO (2 mL) heated under O_2 atm at 120 °C for 8-10 h. Method B: **73** (0.3 mmol), $Pd(OAc)_2$ (20 mol), Ag_2CO_3 (1.0 equiv), PivOH (1.0 equiv) in DMSO (2 mL) heated under O_2 atm at 120 °C for 10-12 h. [a]Yields of indoles **74**by method A.[b]Yields of indoles **74** by method B.[c]Yield obtained on 3.0 mmol scale. [d]Prepared from α–(thioacyl or acyl)arylacetonitriles.

intramolecular C-H arylamination of 3-chloro- and 4-bromo-2-arylenaminonitriles **73g** and **73h** also proceeded smoothly under these conditions, affording the 5-chloro and 6-bromo substituted indoles **74g-h** in excellent yields (Table 2, entries 7-8). Further, we have found that the reaction displays high regioselectivity in the intramolecular cyclization of 3-substituted 2-arylenaminonitriles (**73a**, **73e-g**) affording only 5-substituted indoles **74a**, **74e-g** and no trace of the corresponding 7-substituted indoles were detected in the reaction mixture (Table 2, entries 1, 5-7). It should be noted that the previous workers have reported the formation of regioisomeric mixtures of 5- and 7-substituted indoles in the oxidative intramolecular cyclization (C-H amination) of 3-substituted enamine/enaminonitriles.[42,43] The versatility of this intramolecular C-H amination was further demonstrated by the synthesis of sterically crowded 1,2,3,4,7-pentasubstituted indole **74i** in high yield, when the corresponding **2-**[2,5-bis(methoxy)phenyl] substituted enaminonitrile **73i** was subjected to catalytic oxidative cyclization under similar conditions (Table 2, entry 9). Similarly the benzo-fused indole **74j** could also be obtained in good yield from the (*β*-naphthyl) substituted enaminonitrile **73j** (entry 10). The synthetic potential of this protocol was further evident

from efficient introduction of diverse range of substituted aryl and het(aryl) groups such as (2-thienyl-) (entries 2 and 4), (3-indolyl-) (entry 3), (2-furyl-) (entry 7), (2-*N*-methylpyrrolyl-) (entry 8), (2-imadozolyl-) (entry 10) and (3-pyridyl-) (entry 9) groups at 2-position of indole ring by intramolecular cycloamination of readily available 3-(het)aryl substituted enaminonitriles **73a-j**. It should be noted that despite broad application of palladium (or copper) catalyzed synthesis of 2-substituted indoles from relevant acetylene precursors,[7-10] the related methods for synthesis of biologically important 2-(het)aryl indoles are scarce in the literature.

The methodology could also be extended for the synthesis of 2-alkylindoles **74k-l** in good yields, from the respective 3-alkylenaminonitriles **73k-l** (entries 11 and 12). Further, a range of commercially available anilines bearing electron donating, electron withdrawing and sterically constrained substituents could be installed in *N*-arylindoles **74** (Table 2) as N-coupling partners. Entries 3 and 6 display the synthesis of 1-*N*-(3-pyridyl)indoles **74c** and **74f** by intramolecular cyclization of the enaminonitriles **73c** and **73f** respectively. The scope and utility of this method was further examined by installing other electron withdrawing groups at 3-position of indole rings. Thus, intramolecular oxidative cyclization of enaminones[46] **73m-n** also proceeded efficiently under optimized conditions affording the substituted 3-aroylindoles **74m-n** in good yields (Table 2, entries 13 and14).

However, our attempts to synthesize *N*-benzylindole **74o** from the corresponding *N*-benzylenaminonitrile **73o** under optimized reaction conditions, including those of Gaunt[17] were not successful and only starting material was recovered unchanged (Table 2, entry 15).

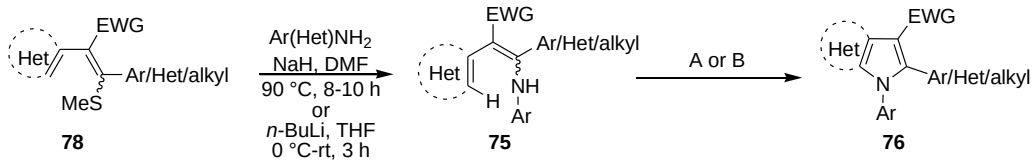
4.3.3 Synthesis of Substituted Hetero- Fused Pyrroles 76

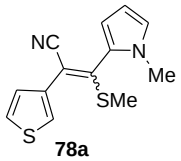
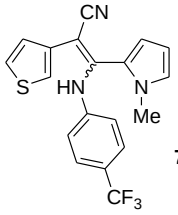
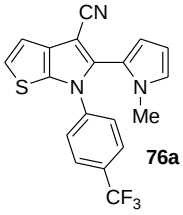
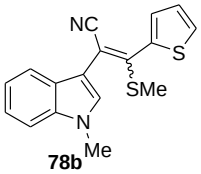
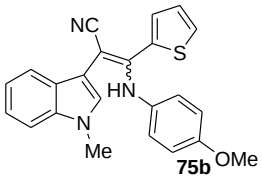
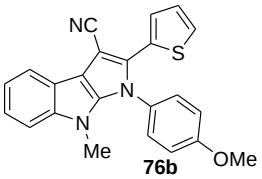
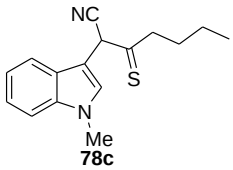
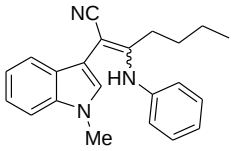
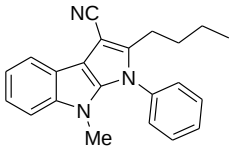
With the successful implementation of this intramolecular C-H amination methodology for the synthesis of multisubstituted indoles, we next elaborated this protocol for the construction of heterofused pyrroles as depicted in Table 3. It is pertinent to note that despite several examples of transition metal catalyzed intramolecular C-H activation-heterofunctionalization reactions leading to 5- and 6-membered benzofused heterocycles reported in the literature, examples of a parallel protocol involving intramolecular C-H – heterocyclization on five or six membered heterocycles furnishing fused heterocycles are only scarce. We therefore synthesized the desired 2-(het)arylenaminonitrile **75a-d** and the

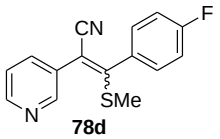
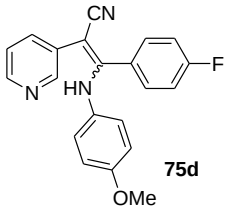
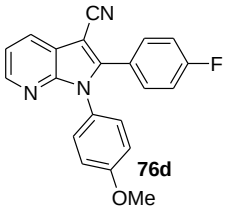
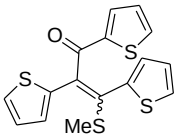
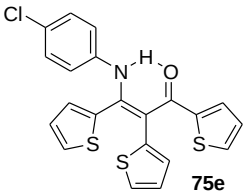
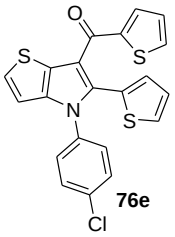
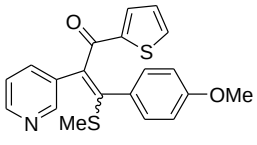
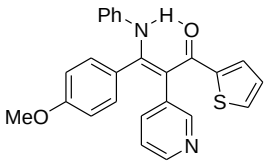
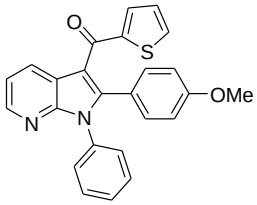
enaminone **75e-f** precursors by reacting the corresponding 3-(methylthio)enaminonitriles **78a-b, 78d**, enones **78e-f** and α-(thioacyl)arylacetonitrile **78c** with the relevant amines following the similar procedure as described for enaminonitriles and enones **73** (Table 3, see experimental).

To our delight, these substrates underwent smooth intramolecular C-H activation-cycloamination under previously described optimal conditions,[47] furnishing the various substituted heterofused pyrroles such as thieno[2,3-*b*]pyrrole (**76a)** (entry 1), thieno[3,2-*b*]pyrrole **76e** (entry 5), pyrrolo[2,3-*b*]indole **76b-c** (Table 3, entries 2 and 3), and 7-azaindoles **76d, 76f** (entries 4 and 6) in good yields (Table 3).

Table 3: Synthesis of Substituted Hetero- Fused Pyrroles 76



entry	substrate **78**	substrate	yield (%) **75**	product	yield (%) **76**
1	 **78a**	 **75a**	72	 **76a**	81[a], 83[b]
2	 **78b**	 **75b**	67	 **76b**	75[a], 74[b]
3	 **78c**	 **75c**[c]	61	 **76c**	70[a]

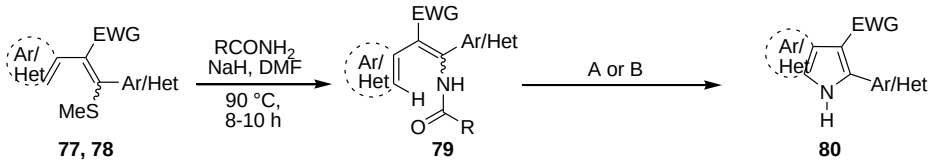
4	 **78d**	 **75d**	74	 **76d**	86[a], 82[b]
5	 **78e**	 **75e**	60	 **76e**	68[a]
6	 **78f**	 **75f**	68	 **76f**	77[a]

Reaction conditions:Method A: **75** (0.3 mmol), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv) in DMSO (2 mL) heated under O_2 atm at 120 °C for 8-10 h Method B: **75** (0.3 mmol), $Pd(OAc)_2$ (20 mol), Ag_2CO_3 (1.0 equiv), PivOH (1.0 equiv) in DMSO (2 mL) heated under O_2 atm at 120 °C for 10-12 h.[a]Yields of 76 by method A. [b]Yields of **76** by method B.[c]prepared from α-(thioacyl)arylacetonitriles.

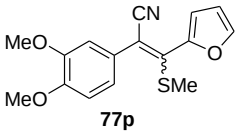
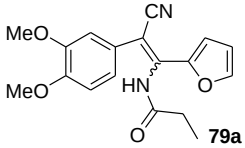
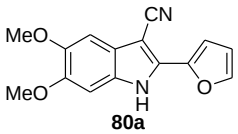
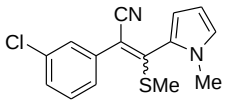
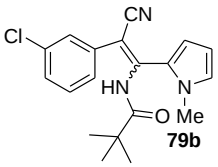
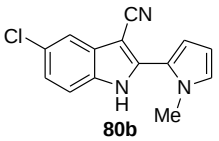
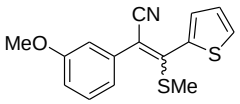
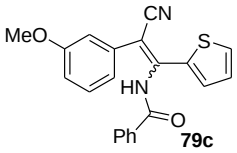
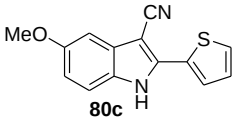
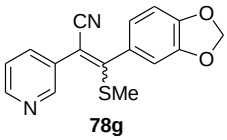
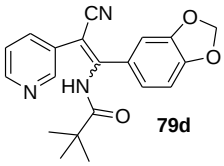
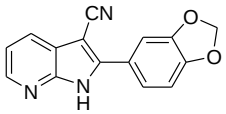
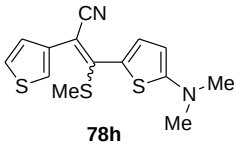
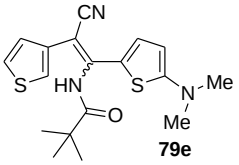
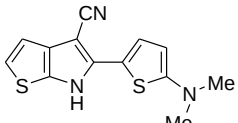
4.3.4 Synthesis of 1-unsubstituted NH-Indoles 80 from N-acylenaminonitriles 79

Encouraged by the above studies, we next undertook the synthesis of few 1-N-unsubstituted (NH) indoles **80** via palladium catalyzed intramolecular C-H amination of the corresponding N-acylenaminonitriles **79** as shown in the Table 4. The requisite N-acylenaminonitrile precursors **79a-e** were synthesized via conjugate displacement on 2-het(aryl)-3-(methylthio)acrylonitriles **77** or **78** by the respective primary amides in presence of sodium hydride as base (see experimental). Thus, catalytic intramolecular C-H cycloamination of these N-acylenamides **79a-e** under previously described conditions proceeded efficiently to afford the corresponding 1-N unsubstituted indoles **80a-c** and hetero fused pyrroles **80d-e** in good yields via in situ hydrolysis of the resulting N-acylindoles as observed in our previous studies[1a] (Table 4, entries 1-5).[47]

Table 4: Synthesis of 1-unsubstituted NH-Indoles 80 from N-acylenaminonitriles 79



77, 78 **79** **80**

entry	substrate **77**, **78**	substrate	yield (%) **79**	product	yield (%) **80**
1	 **77p**	 **79a**	68	 **80a**	77[a]
2	 **77q**	 **79b**	71	 **80b**	68[a], 71[b]
3	 **77r**	 **79c**	64	 **80c**	70[a], 74[b]
4	 **78g**	 **79d**	60	 **80d**	73[a], 69[b]
5	 **78h**	 **79e**	67	 **80e**	64[a]

Reaction conditions: Method A: **79** (0.3 mmol), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 equiv) in DMSO (2 mL) heated under O_2 atm at 120 °C for 8-10 h. Method B: **79** (0.3 mmol), $Pd(OAc)_2$ (20 mol), Ag_2CO_3 (1.0 equiv), PivOH (1.0 equiv) in DMSO (2 mL) heated under O_2 atm at 120 °C for 10-12 h.[a]Yields of **80** by method A.[b]Yields of **80** by method B.

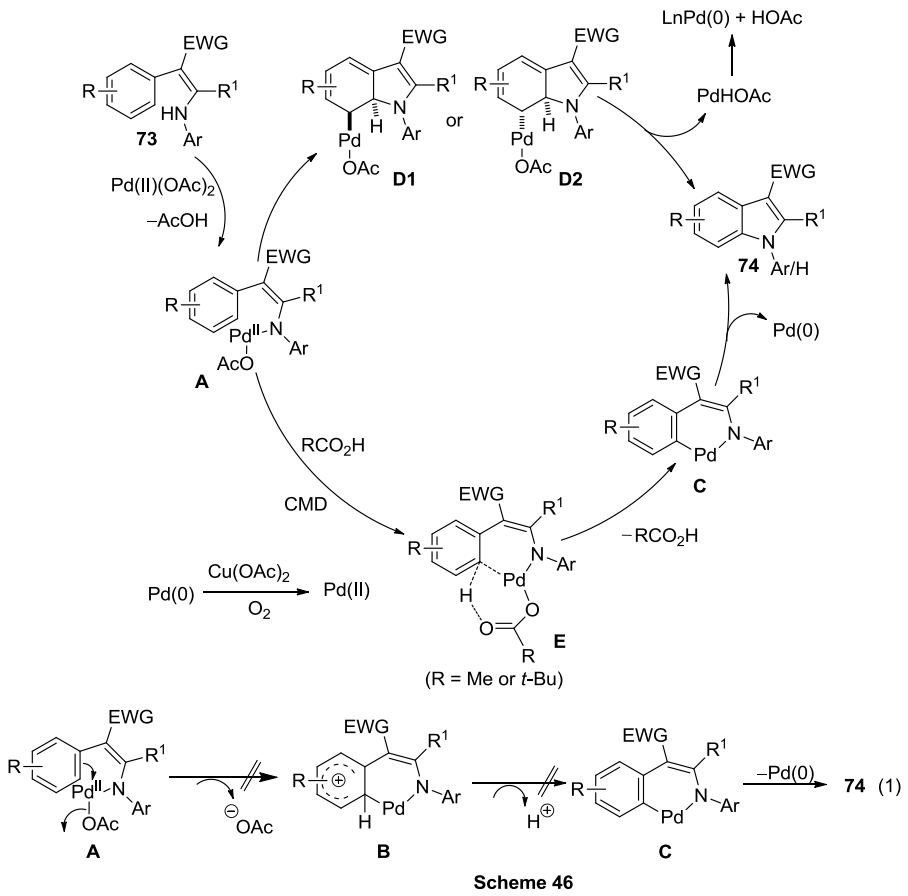
4.3.5 Plausible Mechanistic Pathways for Formation of Indole 74 from 73

Although, a full mechanistic understanding of the reaction has yet to be established, however on the basis of previous mechanisms, analogous to those proposed to similar palladium catalyzed process along with our observations, we suggest a plausible mechanistic pathways as shown in the Scheme 3. Thus arylamino moiety in the substrates **73** can readily coordinate with Pd(II) catalyst to form palladium(II) aminoaryl/amide complex **A** with concomitant release of acetic acid. Once the palladium is in close proximity to the C-H bond

of aryl ring, the initially formed coordinated Pd complex **A** could facilitate *ortho*-palladation process and evolve into product indole **74** by different mechanisms (Scheme 46). Thus the intermediate **A** could be converted to the palladacycle **C** via an intramolecular electrophilic palladation (SE_{Ar}) mechanism[15,22] through intermediate **B** (Scheme 46, eq. 1). However this reaction mechanism appears to be inconsistent with the observation that substrates bearing both electron withdrawing as well as electron donating substituents at 3- position display comparable reactivity, yielding product indoles in good yields regardless of the electronic character of the substituents (Table 2, entries 5-7 vs entries 1-2). These studies suggest that an electrophilic palladation mechanism does not operate. We therefore propose two alternative pathways for this cycloamination reaction as displayed in the Scheme 46. Thus the coordinated Pd(II) complex **A** can undergo intramolecular cyclization through insertion into arene to give intermediate **D1** (Heck like) or **D2** (Wacker like), which would undergo β-hydrogen elimination to give indole **74**.[15b] The third possible pathway may involve σ bond metathesis through irreversible ligand assisted 'concerted metallation-deprotonation' (CMD) mechanism[48] involving intermediate **E**. Subsequent reductive elimination gives the product indole **74** through palladacycle intermediate **C,** with concurrent formation of Pd(0), which is then oxidized by cupric actate (or oxygen) to regenerate Pd(II) species. In view of the observation that reaction proceeds efficiently in the presence of pivalic acid as additive, wherein an anionic pivalate (or acetate)-Pd bond ligand aids in proton abstraction, a σ bond metathesis pathway through CMD mechanism, is more likely preferred in this process. However a possible pathway involving $Cu(OAc)_2$ promoted oxidation of palladacycle intermediate C to more highly oxidized species facilitating reductive elimination of palladium(II) and C-N bond formation cannot be ruled out at the current time.[17]

The excellent regioselectivity observed in these reactions with the formation of only 5-substituted indoles, in cases where two regioisomeric products could be obtained (Table 2, entries 1, 2, 5, 6, 7, 13, 14, and 15, Table 4, entries 1-3), suggests that this ring forming reaction may be controlled by steric factors. On the other hand, the observed regioselectivie cyclization of 2-(3-thienyl)enaminonitriles **75a** (Table 3, entry 1) and **79e** (Table 4, entry 5) at 2- position of the thiophene ring, can be rationalized in terms of the stability of the product thieno[2,3-b]pyrrloles **76a** and **80e** in comparison to the products formed by cyclization at 4-position. Similarly, in the case of the corresponding 3-(3-pyridyl)enaminonitriles **75d**, **79d**

and enaminone **75f** (Table 3, entries 4 and 6, Table 4, entry 4), the observed regioselectivity yielding only 7-azaindoles **76d**, **76f** and **80d** respectively, appears to be governed by the proximity of pyridyl nitrogen,which might complex with palladium acetate in the palladacycle **C** (Scheme 46), thus directing the cyclization at 2- position of the pyridine ring instead of at 4- position.



Scheme 46

4.4 Conclusion

In summary, we have developed an efficient palladium catalyzed intramolecular oxidative C-H functionalization-C-N bond forming approach for substituted N-aryl/NH indoles from readily available N-aryl/acylenaminonitriles and enaminones. This C-H functionalization strategy allows the assembly of indoles with a variety of substitution pattern and functional groups under relatively mild conditions and both electron donating and electron withdrawing groups are tolerated in the benzene ring. The reaction displays high regioselectivity and broad substrate scope with functional group diversity in comparison to

earlier described similar reactions. Furthermore, this methodology can be extended to other novel pyrrolo fused heteroaromatics, a feature that is noteworthy, since most of the previously reported intramolecular C-H activation-C-heteroatom bond forming reactions employ substituted benzene precursors, leading to benzoheterocycles, while extension of this strategey for the synthesis of fused heteroaromatics is scarce in the literature. Although a detailed mechanistic study is yet to be undertaken, the reaction represents one of the few examples, in which an aryl C-H bond is activated by an aminoaryl directing group, that subsequently acts as the reaction partner in the same process.[16c] Such kind of intramolecular C-H heterofunctionalization reactions, in which heteroatoms act as directing group as well as internal nucleophiles, are useful and atom economical processes for the construction of heterocyclic scaffolds, since they obviate the necessity of a directing ligand in the substrate, which lessens the advantageous impact of C-H functionalization process over the other methods that employ prefunctionalized C-(pseudo) halogen bond containing substrates. The widespread use of indole skeleton in natural products and designed compounds, combined with its pharmaceutical importance should render the method broadly useful. Further study to understand precise mechanism as well as to expand the range of substrates is currently underway in our laboratory.

4.5 Experimental Section

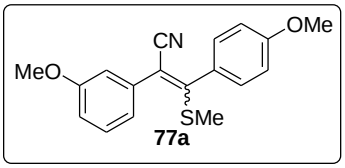
4.5.1 General Information. All reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using standard TLC silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100–200 mesh). Nuclear magnetic resonance spectra were recorded on (400 MHz) FT–NMR spectrometer with $CDCl_3$ or DMSO–d_6 as solvent. Chemical shifts were reported in δ ppm using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO–d_6 in ^{1}H–NMR, δ 77.16 for $CDCl_3$ and δ 39.52 for DMSO–d_6 in ^{13}C–NMR). Coupling constants were reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet) and br (broad). Infrared spectra of neat samples were recorded in ATR (attenuated

total reflectance) mode using FT–IR instrument and HRMS on Q–TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

The scanned copies of ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in supporting information of *J. Org. Chem.* **2016**, *81*, 2035.

4.5.2 General Procedure for the synthesis of 3-(methylthio)-2-het(aryl)-3-het(aryl)/alkylacrylonitriles/enones 77-78. The desired acrylonitrile and enone precursors **77a-j**, **77m-n** (Table 2), **77p-r** (Table 4), **78a-b**, **78d-h** (Tables 3-4) were prepared following the similar procedure reported for the corresponding 2-(2-bromohet(aryl-3-(methylthio)acrylonitrile precursors **70**.[49] A solution of the appropriate (het)arylacetonitrile/deoxybenzoin (3.0 mmol) in dry DMF (10 mL) was added to a stirred solution of NaH (144.0 mg, 6.0 mmol, 60% suspension in mineral oil) in DMF at 0 °C. After stirring the reaction mixture for 30 min, the reaction mixture was cooled to 0 °C, and a solution of the corresponding het(aryl)dithioester (3.0 mmol) in DMF (3 mL) was added and the reaction mixture was further stirred for 1 h at room temperature followed by alkylation with methyl iodide (0.22 mL, 3.6 mmol) at 0 °C. After stirring for 0.5 h at room temperature (monitored by TLC), the reaction mixture was diluted with saturated NH_4Cl solution (25 mL), extracted with EtOAc (2 x 25 mL), the combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude products were purified by column chromatography using EtOAc/hexane as eluent. The spectral and analytical data of all the unknown precursors **77** and **78** is given below.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-3-(methylthio)acrylonitrile (77a). Obtained

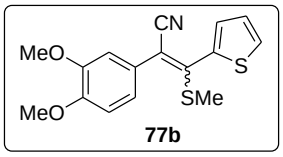


77a

as a 55: 45 inseparable mixture of geometrical isomers, yellow semi solid (727.7 mg, 78%): R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2923, 2195, 1519, 1446, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.8 Hz, 1.1H), 7.35 (t, J = 8.4 Hz, 0.55H), 7.19-7.17 (m, 0.55H), 7.15-7.12 (m, 1.35H), 7.05 (t, J = 8.0 Hz, 0.55H), 7.00 (d, J = 8.8 Hz, 1.1H), 6.92 (dd, J = 8.4 Hz, 2.4 Hz, 0.55H), 6.82 (d, J = 8.8 Hz, 0.9H), 6.72-6.67 (m, 0.9H), 6.63-6.62 (m, 0.45H), 3.86 (s, 1.65H), 3.85 (s, 1.65H), 3.79 (s, 1.35H), 3.59 (s, 1.35H), 2.08 (s, 1.35H), 1.90 (s, 1.65H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.9, 160.7, 160.0, 159.8, 159.4, 158.3, 135.7, 135.3,

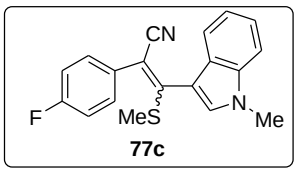
131.4, 130.6, 129.7, 129.4, 128.4, 126.8, 122.0, 121.7, 119.1, 119.0, 114.72, 114.68, 114.5, 114.4, 114.3, 108.9, 108.5, 55.51, 55.48, 55.44, 55.2, 16.9, 16.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}NO_2S$ $[M + H]^+$ 312.1058, found 312.1065.

2-(3,4-Dimethoxyphenyl)-3-(methylthio)-3-(thiophen-2-yl)acrylonitrile (77b). Obtained as a 60:40 inseparable mixture of geometrical isomers, yellow solid (789.3 mg, 83%): mp 81-83 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2927, 2195, 1519, 1416, 1136; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 5.2 Hz, 1.2 Hz, 0.4H), 7.44 (dd, J = 3.6 Hz, 0.8 Hz, 0.4H), 7.42 (dd, J = 4.8 Hz, 0.8 Hz, 0.6H), 7.18 (dd, J = 8.4 Hz, 2.0 Hz, 0.4H), 7.14-7.12 (m, 0.8H), 6.99-6.95 (m, 1.2H), 6.93-6.90 (m, 1.0H), 6.74 (d, J = 8.4 Hz, 0.6H), 6.63 (d, J = 2.0 Hz, 0.6H), 3.92 (s, 2.4H), 3.84 (s, 1.8H), 3.61 (s, 1.8H), 2.27 (s, 1.8H), 2.04 (s, 1.2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.7, 149.6, 149.5, 149.0, 148.8, 147.4, 138.6, 137.7, 130.9, 130.1, 130.0, 129.5, 127.9, 127.8, 126.8, 126.5, 122.6, 122.3, 119.1, 118.8, 112.3, 112.1, 111.5, 111.1, 111.0, 110.1, 56.2, 56.1, 56.0, 55.8, 17.6, 17.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}NO_2S_2$ $[M + H]^+$ 318.0622, found 318.0617.



77b

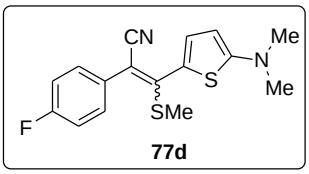
2-(4-Fluorophenyl)-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)acrylonitrile (77c). Obtained as a 65:35 inseparable mixture of geometrical isomers, yellow solid (656.8 mg, 68%): mp 75-77 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2933, 2190, 1500, 1210, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 0.65H), 7.63-7.60 (m, 1.3H), 7.50 (s,0.65H), 7.44-7.37 (m, 1H), 7.34-7.27 (m, 1.35H), 7.27-7.17 (m, 1.35H), 7.16-7.12 (m, 1.35H), 7.09-7.05 (m, 0.35H), 7.01 (s, 0.35H), 6.80-6.76 (m, 0.65H), 3.88 (s, 1.95H), 3.75 (s, 1.05H), 2.20 (s, 1.05H), 1.98 (s, 1.95H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5 (d, $^1J_{C\text{-}F}$ = 248.0 Hz), 161.9 (d, $^1J_{C\text{-}F}$ = 247.0 Hz), 153.9, 151.7, 137.5, 137.4, 131.9, 131.79, 131.75, 131.6, 131.5, 131.0, 130.8, 130.73, 130.66, 130.6, 126.4, 125.8, 123.03, 122.99, 121.29, 121.26, 120.7, 120.5, 120.2, 119.8, 115.61, 115.60, 115.4, 110.9, 110.1, 109.89, 109.85, 105.8, 105.5, 33.5, 33.4, 17.14, 17.05; HRMS (ESI) *m/z* calcd for $C_{19}H_{16}FN_2S$ $[M + H]^+$ 323.1018, found 323.1019.



77c

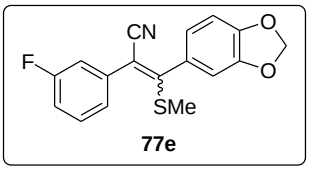
3-(5-(Dimethylamino)thiophen-2-yl)-2-(4-fluorophenyl)-3-(methylthio)acrylonitrile (77d). Obtained as a single geometrical isomer, brown solid (849.0 mg, 89%): mp 85-87 °C;

R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2920, 2190, 1485, 1221, 840; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.00-6.95 (m, 2H), 6.91 (d, J = 4.2 Hz, 1H), 5.69 (d, J = 4.2 Hz, 1H), 2.92 (s, 6H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.5, 162.3 (d, $^1J_{C\text{-}F}$ = 247.0 Hz), 149.2, 135.3, 131.8, 131.7, 131.6, 131.5, 120.6, 120.5, 116.0, 115.8, 103.6, 102.6, 42.1, 18.8; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}FN_2S_2$ $[M + H]^+$ 319.0739, found 319.0729.



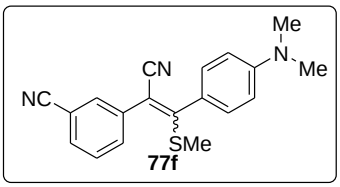
77d

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-(3-fluorophenyl)-3-(methylthio)acrylonitrile (77e). Obtained as a 70:30 inseparable mixture of geometrical isomers, yellow semi solid (741.8 mg, 79%): R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2935, 2210, 1510, 1262, 869; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 0.7H), 7.35-7.32 (m, 0.3H), 7.17-7.12 (m, 0.7H), 7.10-7.04 (m, 0.3H), 6.98-6.91 (, 1.7H), 6.88-6.83 (m, 0.6H), 6.82-6.80 (m, 0.6H), 6.79-6.74 (m, 0.6H), 6.67-6.65 (m, 1.5H), 6.05 (s, 0.6H), 6.00 (s, 1.4H), 2.11 (s, 2.1H), 1.96 (s, 0.9); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{C\text{-}F}$ = 246.0 Hz), 162.6 (d, $^1J_{C\text{-}F}$ = 245.0 Hz), 160.7, 159.4, 149.2, 149.1, 148.5, 148.4, 136.5, 136.4, 135.9, 135.8, 130.4, 130.3, 130.1, 130.0, 129.7, 127.8, 125.2, 125.12, 125.09, 124.3, 123.3, 118.6, 118.5, 116.6, 116.4, 116.3, 116.1, 116.0, 115.8, 115.2, 115.0, 109.8, 109.2, 109.0, 108.9, 108.0, 107.95, 107.8, 101.87, 101.85, 16.8, 16.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}FNO_2S$ $[M + H]^+$ 314.0651, found 314.0645.



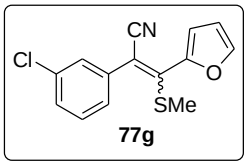
77e

3-(1-Cyano-2-(4-(dimethylamino)phenyl)-2-(methylthio)vinyl)benzonitrile (77f). Obtained as a 75:25 inseparable mixture of geometrical isomers, yellow solid (679.4 mg, 71%): mp 104-106 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2907, 2230, 2199, 1600, 1515, 1170, 814; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.93 (m, 0.75H), 7.83 (dt, J = 8.0 Hz, 1.2 Hz, 0.75H), 7.62 (dt, J = 8.0 Hz, 1.2 Hz, 0.75H), 7.53 (t, J = 8.0 Hz, 0.75H), 7.43-7.37 (m, 2.25H), 7.29 (d, J = 7.6Hz, 0.25H), 7.02 (d, J = 8.8 Hz, 0.5H), 6.76 (d, J = 8.8 Hz, 1.5H), 6.55 (d, J = 8.8 Hz, 0.5H), 3.05 (s, 4.5H), 2.99 (s, 1.5H), 2.15 (s, 0.75H), 1.98 (s, 2.25H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.5, 162.7, 151.8, 151.6, 136.9, 136.3, 133.9, 133.6, 133.2, 132.9, 131.7, 131.6, 130.7, 130.6, 129.6, 129.3, 122.4, 119.9, 119.3, 119.1, 118.5, 118.4, 113.0, 112.7, 111.9, 111.8, 104.5, 103.9, 40.2, 40.1, 17.3, 16.9; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_3S$ $[M + H]^+$ 320.1221, found 320.1217.



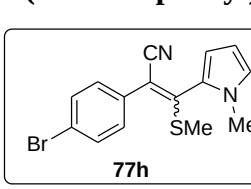
77f

2-(3-Chlorophenyl)-3-(furan-2-yl)-3-(methylthio)acrylonitrile (77g). Obtained as a 80:20 inseparable mixture of geometrical isomers, brown semi solid (602.2 mg, 73%): R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2960, 2208, 1498, 1255, 842; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 2.0 Hz, 0.8 Hz, 0.8H), 7.59-7.58 (m, 0.8H), 7.48-7.45 (m, 0.8H), 7.39-7.34 (m, 1.8H), 7.24-7.18 (m, 0.4H), 7.15-7.14 (m, 0.2H), 7.07-7.04 (m, 1H), 6.61 (dd, J = 3.6 Hz, 0.8 Hz, 0.2H), 6.58 (dd, J = 3.2 Hz, 1.6 Hz, 0.8H), 6.46 (dd, J = 3.6 Hz, 1.6 Hz, 0.2H), 2.39 (s, 0.6H), 2.09 (s, 2.4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.5, 147.7, 147.3, 145.33, 145.27, 145.2, 136.5, 135.9, 134.7, 134.5, 130.0, 129.8, 129.5, 129.2, 128.8, 128.7, 127.7, 127.0, 118.7, 118.5, 117.0, 116.1, 112.6, 112.3, 109.0, 106.8, 17.5, 17.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}ClNOS$ $[M + H]^+$ 276.0250 and 278.0220, found 276.0246 and 278.0212.



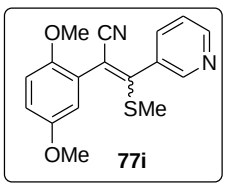
77g

2-(4-Bromophenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)-3-(methylthio)acrylonitrile (77h). Obtained as a 60:40 inseparable mixture of geometrical isomers, yellow solid (784.4 mg, 79%): mp 103-105 °C; R_f 0.6 (1:2 EtOAc/hexane); IR (neat, cm^{-1}) 2920, 2202, 1482, 1049, 861; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 0.8H), 7.51 (d, J = 8.8 Hz, 0.8H), 7.32 (d, J = 8.8 Hz, 1.2H), 6.87 (d, J = 8.8 Hz, 1.2H), 6.80 (t, J = 2.0 Hz, 0.4H), 6.65 (t, J = 2.0 Hz, 0.6H), 6.41 (dd, J = 4.0 Hz, 2.0 Hz, 0.4H), 6.30 (dd, J = 4.0 Hz, 2.0 Hz, 0.6H), 6.22 (dd, J = 3.6 Hz, 2.8 Hz, 0.4H), 6.20 (dd, J = 3.6 Hz, 2.4 Hz, 0.6H), 3.7 (s, 1.2H), 3.13 (s, 1.8H), 2.21 (s, 1.8H), 1.89 (s, 1.2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 149.8, 133.8, 132.7, 132.0, 131.9, 130.8, 129.6, 126.9, 126.5, 125.8, 125.6, 123.1, 122.0, 118.6, 118.5, 114.4, 113.5, 109.9, 109.5, 108.9, 107.1, 34.4, 16.8, 16.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}BrN_2S$ $[M + H]^+$ 333.0061 and 335.0041, found 333.0058 and 335.0037.



77h

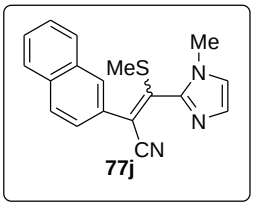
2-(2,5-Dimethoxyphenyl)-3-(methylthio)-3-(pyridin-3-yl)acrylonitrile (77i). Obtained as a 65:35 inseparable mixture of geometrical isomers, yellow semi solid (627.1 mg, 67%): R_f 0.3 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2962, 2210, 1513, 1276, 842; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 1.6 Hz, 0.35H), 8.70 (dd, J = 4.8 Hz, 1.6 Hz, 0.35H), 8.46 (dd, J = 4.8 Hz, 1.6 Hz, 0.65H), 8.39 (d, J = 2.0 Hz, 0.65H), 7.87 (dt, J = 8.0 Hz, 2.0 Hz, 0.35H), 7.49 (dt, J = 8.0 Hz, 2.0 Hz, 0.65H), 7.45 (ddd, J = 8.0 Hz, 4.8 Hz, 0.8 Hz, 0.35H), 7.18 (ddd, J = 8.0 Hz, 4.8 Hz,



77i

0.8 Hz, 0.65H), 6.96-6.91 (m, 1.05H), 6.73 (dd, *J* = 9.2 Hz, 3.2 Hz, 0.65H), 6.65 (d, *J* = 9.2 Hz, 0.65H), 6.49 (d, *J* = 3.2 Hz, 0.65H), 3.87 (s, 1.05H), 3.80 (s, 1.05H), 3.64 (s, 1.95H), 3.58 (s, 1.95H), 2.11 (s, 1.95H), 1.87 (s, 1.05H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.2, 155.3, 153.6, 153.5, 151.3, 151.2, 150.9, 150.1, 150.0, 149.8, 136.84, 136.79, 132.2, 131.7, 123.7, 123.1, 122.7, 117.8, 117.6, 116.7, 116.5, 116.3, 116.1, 113.0, 112.6, 108.3, 107.5, 56.5, 56.1, 56.0, 55.9, 16.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}N_2O_2S$ $[M + H]^+$ 313.1011, found 313.1009.

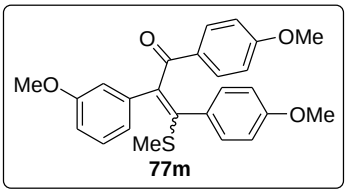
3-(1-Methyl-1*H*-imidazol-2-yl)-3-(methylthio)-2-(naphthalen-2-yl)acrylonitrile (77j).



77j

Obtained as a 55:45 inseparable mixture of geometrical isomers, off white solid (750.2 mg, 82%): mp 70-72 °C; R_f 0.3 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2925, 2208, 1470, 1276, 859; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.6 Hz, 0.45H), 7.93-7.85 (m, 1.55H), 7.78-7.69 (m, 1.55H), 7.67 (d, *J* = 1.6 Hz, 0.55H), 7.63 (d, *J* = 8.4 Hz, 0.55H), 7.56-7.53 (m, 1.0H), 7.48-7.44 (m, 1.35H), 7.25 (d, *J* = 1.2 Hz, 0.45H), 7.06 (d, *J* = 0.8 Hz, 0.45H), 6.96 (dd, *J* = 8.8 Hz, 2.0 Hz, 0.55H), 6.78 (d, *J* = 1.2 Hz, 0.55H), 3.82 (s, 1.35H), 3.07 (s, 1.65H), 2.20 (s, 1.65H), 1.96 (s, 1.35H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 147.6, 146.5, 141.4, 140.1, 133.3, 133.0, 132.9, 132.8, 130.9, 130.4, 129.9, 129.6, 129.0, 128.6, 128.5, 128.43, 128.41, 128.0, 127.8, 127.6, 127.4, 127.2, 126.9, 126.8, 125.5, 124.4, 122.3, 122.2, 117.51, 117.47, 113.4, 112.3, 33.4, 33.1, 15.6; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}N_3S$ $[M + H]^+$ 306.1065, found 306.1061.

2-(3-Methoxyphenyl)-1,3-bis(4-methoxyphenyl)-3-(methylthio)prop-2-en-1-one (77m).

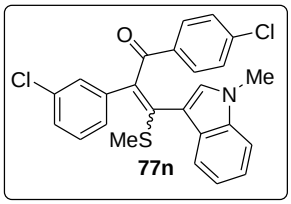


77m

Obtained as a 65:35 inseparable mixture of geometrical isomers, yellow semi solid (1.02 gm, 81%): R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2835, 1649, 1459, 1243, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.8 Hz, 1.3H), 7.76 (d, *J* = 8.8 Hz, 0.7H), 7.30 (d, *J* = 8.8 Hz, 1.3H), 7.29-7.25 (m, 1.05H), 7.16-7.14 (m, 0.7H), 7.02-6.95 (m, 2H), 6.85-680 (m, 1.65H), 6.74-6.67 (m, 2H), 6.66-6.61 (m, 1.3H), 3.86 (s, 1.95H), 3.81 (s, 1.05H), 3.79 (s, 1.95H), 3.77 (s, 1.05H), 3.71 (s, 1.05H), 3.55 (s, 1.95H), 1.844 (s, 1.05H), 1.840 (s, 1.95H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.6, 195.3, 163.8, 163.3, 159.62, 159.60, 159.5, 159.4, 141.3, 139.9, 138.8, 138.6, 138.4, 137.8, 132.1, 132.0, 131.9, 131.4,

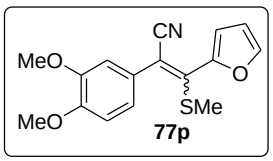
130.3, 130.1, 129.6, 129.41, 129.35, 128.7, 122.1, 121.8, 114.8, 114.6, 114.2, 114.0, 113.71, 113.67, 113.60, 113.56, 55.6, 55.5, 55.42, 55.40, 55.3, 55.2, 16.3, 16.1; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}O_4S$ $[M + H]^+$ 421.1474, found 421.1468.

2-(3-Chlorophenyl)-1-(4-chlorophenyl)-3-(1-methyl-1H-indol-3-yl)-3-(methylthio)prop-2-en-1-one (77n). Obtained as a 65:35 inseparable mixture of geometrical isomers, yellow solid (933.5 mg, 69%): mp 116-118 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2922, 1658, 1585, 1250, 780; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 0.65H), 7.89-7.87 (m, 0.65H), 7.59 (t, J = 2.0 Hz, 0.65H), 7.54 (d, J = 8.0 Hz, 0.35H), 7.45-7.44 (m, 2.45H), 7.34 (t, J = 7.6 Hz, 0.65H), 7.31-7.29 (m, 1.0H), 7.25-7.19 (m, 1.0H), 7.18 (d, J = 2.0 Hz, 0.65H), 7.16-7.14 (m, 0.35H), 7.10-7.04 (m, 1.65H), 7.01-6.96 (m, 0.65H), 6.95-6.91 (m, 2.3H), 3.78 (s, 1.05H), 3.58 (s, 1.95H), 1.95 (s, 1.95H), 1.84 (s, 1.05H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.1, 195.7, 142.0, 140.1 139.9, 139.5, 137.8, 137.5, 137.1, 136.5, 136.4, 135.7, 135.5, 134.8, 134.3, 134.2, 132.1, 131.5, 130.9, 129.9, 129.8, 129.7, 129.6, 129.3, 128.9, 128.1, 127.9, 127.8, 127.5, 127.3, 126.7, 126.5, 123.0, 122.6, 120.9, 120.7, 120.6, 120.5, 112.4, 110.4, 109.7, 109.6, 33.3, 33.0, 16.5, 16.4; HRMS (ESI) *m/z* calcd for $C_{25}H_{20}Cl_2NOS$ $[M + H]^+$ 452.0643 and 454.0613, found 452.0639 and 454.0616.



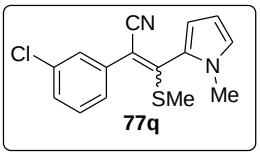
77n

2-(3,4-Dimethoxyphenyl)-3-(furan-2-yl)-3-(methylthio)acrylonitrile (77p). Obtained as a 75:25 inseparable mixture of geometrical isomers, brown semi solid (693.5 mg, 77%): R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2925, 2204, 1457, 1241, 807; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.62 (m, 0.25H), 7.40 (d, J = 0.8 Hz, 0.75H), 7.18-7.13 (m, 0.75H), 7.01 (d, J = 3.6 Hz, 0.25H), 6.91 (d, J = 8.0 Hz, 0.25H), 6.87 (dd, J = 8.4 Hz, 2.0 Hz, 0.75H), 6.77 (d, J = 8.4 Hz, 0.75H), 6.58 (d, J = 2.0 Hz, 0.75H), 6.55 (d, J = 3.6 Hz, 0.75H), 6.45 (dd, J = 3.6 Hz, 2.0 Hz, 0.75H), 3.92 (s, 0.75H), 3.91 (s, 0.75H), 3.87 (s, 2.25H), 3.69 (s, 2.25H), 2.34 (s, 2.25H), 2.06 (s, 0.75H), ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.6, 149.4, 148.9, 148.8, 148.7, 148.1, 144.7, 144.6, 144.5, 141.8, 127.1, 126.4, 122.5, 121.7, 119.0, 118.7, 115.8, 115.2, 112.2, 111.9, 111.5, 111.1, 110.91, 110.88, 108.4, 56.1, 56.0, 55.9, 55.7, 17.1, 17.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}NO_3S$ $[M + H]^+$ 302.0851, found 302.0845.



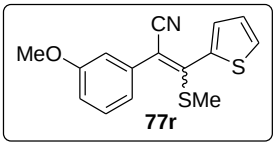
77p

2-(3-Chlorophenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)-3-(methylthio)acrylonitrile (77q).



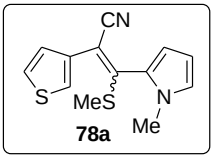
Obtained as a 50:50 inseparable mixture of geometrical isomers, yellow semi solid (682.5 mg, 79%): R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2931, 2202, 1483, 1248, 824; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 3.2 Hz, 2.0 Hz, 0.5H), 7.5 (dt, *J* = 7.2 Hz, 1.6 Hz, 0.5H), 7.40-7.33 (m, 1H), 7.15-7.10 (m, 1H), 6.96 (dd, *J* = 2.4 Hz, 2.0 Hz, 0.5H), 6.88 (dt, *J* = 6.4 Hz, 2.0 Hz, 0.5H), 6.80 (dd, *J* = 2.4 Hz, 2.0 Hz, 0.5H), 6.67 (dd, *J* = 3.2 Hz, 2.0 Hz, 0.5H), 6.42 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.5H), 6.32 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.5H), 6.23-6.21 (m, 1H), 3.71 (s, 1.5H), 3.14 (s, 1.5H), 2.22 (s, 1.5H), 1.90 (s, 1.5H),; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.2, 150.7, 136.6, 135.4, 134.7, 130.0, 129.8, 129.3, 129.1, 128.1, 128.0, 127.4, 126.8, 126.6, 126.2, 125.9, 125.5, 118.52, 118.45, 114.6, 113.6, 109.9, 109.1, 108.9, 106.6, 34.42, 34.38, 16.8, 16.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}ClN_2S$ $[M + H]^+$ 289.0566 and 291.0537, found 289.0561 and 291.0532.

2-(3-Methoxyphenyl)-3-(methylthio)-3-(thiophen-2-yl)acrylonitrile (77r). Obtained as a



60:40 inseparable mixture of geometrical isomers, yellow semi solid (860.9 mg, 83%): R_f 0.6 (1:2 EtOAc/hexane); IR (neat, cm^{-1}) 2930, 2210, 1470, 1276, 824; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 5.2 Hz, 1.2 Hz, 0.6H), 7.47 (dd, *J* = 3.6 Hz, 1.2 Hz, 0.6H), 7.42 (dd, *J* = 4.8 Hz, 1.2 Hz, 0.4H), 7.35 (t, *J* = 8.0 Hz, 0.6H), 7.19-7.12 (m, 2.2H), 6.98-6.91 (m, 1.4H), 6.85 (ddd, *J* = 7.6 Hz, 1.6 Hz, 0.8 Hz, 0.4H), 6.78 (ddd, *J* = 8.4 Hz, 2.8 Hz, 0.8 Hz, 0.4H), 6.74-6.73 (m, 0.4H), 3.84 (s, 1.8H), 3.65 (s, 1.2H), 2.30 (s, 1.2H), 2.04 (s, 1.8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 159.7, 151.2, 149.6, 138.4, 137.3, 135.6, 135.3, 131.2, 130.3, 129.8, 129.74, 129.68, 127.90, 127.86, 121.80, 121.78, 119.0, 118.7, 115.03, 114.99, 114.7, 114.2, 111.2, 110.0, 55.5, 55.3, 17.7, 17.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}NOS_2$ $[M + H]^+$ 288.0517, found 288.0511.

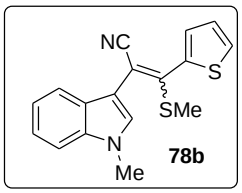
3-(1-Methyl-1*H*-pyrrol-2-yl)-3-(methylthio)-2-(thiophen-3-yl)acrylonitrile (78a).



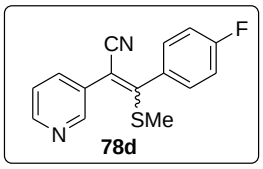
Obtained as a 55:45 inseparable mixture of geometrical isomers, brown semi solid (623.9 mg, 80%): R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2989, 2209, 1483, 1278, 838; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 2.8 Hz, 1.6 Hz, 0.45H), 7.55 (dd, *J* = 5.2 Hz, 1.6 Hz, 0.45H), 7.38 (dd, *J* = 5.2 Hz, 2.8 Hz,

0.45H), 7.11 (dd, *J* = 5.2 Hz, 2.8 Hz, 0.55H), 6.97 (dd, *J* = 2.8 Hz, 1.2 Hz, 0.55H), 6.78 (t, *J* = 2.0 Hz, 0.45H), 6.72 (t, *J* = 2.0 Hz, 0.55H), 6.37-6.34 (m, 1H), 6.29-6.24 (m, 1.1H), 6.21 (dd, *J* = 3.2 Hz, 2.4 Hz, 0.45H), 3.66 (s, 1.35H), 3.21 (s, 1.65H), 2.16 (s, 1.65H), 1.94 (s, 1.35H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 148.5, 146.8, 135.4, 134.0, 128.3, 127.1, 126.4, 126.3, 126.0, 125.72, 125.67, 125.1, 124.5, 118.7, 118.4, 112.92, 112.87, 109.7, 108.7, 106.6, 105.2, 34.3, 34.2, 16.4, 16.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}N_2S_2$ $[M + H]^+$ 261.0520, found 261.0513.

2-(1-Methyl-1*H*-indol-3-yl)-3-(methylthio)-3-(thiophen-2-yl)acrylonitrile (78b). Obtained as a 60:40 inseparable mixture of geometrical isomers, brown solid (669.5 mg, 72%): mp 85-87 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2919, 2201, 1473, 1222, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 0.4H), 7.53 (dd, *J* = 5.2 Hz, 1.2 Hz, 0.4H), 7.46-7.45 (m, 0.8H), 7.38-7.29 (m, 1.6H), 7.27-7.17 (m, 2.0H), 7.15 (dd, *J* = 5.2 Hz, 3.6 Hz, 0.4H), 7.10 (s, 0.6H), 7.09 (dd, *J* = 4.0 Hz, 1.2 Hz, 0.6H), 7.01-6.97 (m, 0.6H), 6.88 (dd, *J* = 4.8 Hz, 3.2 Hz, 0.6H), 3.86 (s, 1.2H), 3.74 (s, 1.8H), 2.35 (s, 1.8H), 2.05 (s, 1.2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 146.7, 143.3, 139.0, 138.8, 136.9, 136.7, 131.1, 131.0, 130.8, 130.0, 129.6, 129.1, 127.7, 127.6, 126.0, 125.3, 122.8, 122.5, 120.64, 120.58, 120.3, 119.5, 119.2, 109.8, 109.7, 109.6, 108.5, 106.2, 104.0, 33.4, 33.2, 17.9, 17.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}N_2S_2$ $[M + H]^+$ 311.0677, found 311.0676.

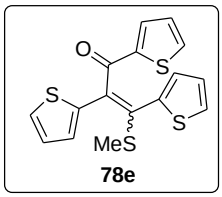


3-(4-Fluorophenyl)-3-(methylthio)-2-(pyridin-3-yl)acrylonitrile (78d). Obtained as a single geometrical isomer, off-white solid (502.1 mg, 62%): mp 80-82 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2932, 2206, 1498, 1418,1229, 810;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 8.26 (d, *J* = 1.6 Hz, 1H), 7.43 (dt, *J* = 8.0 Hz, 2.4 Hz, 1H), 7.19-7.16 (m, 2H), 7.14-7.11 (m, 1H), 7.05-7.01 (m, 2H), 2.09 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.5 (d, $^{1}J_{C\text{-}F}$ = 251.0 Hz), 159.9, 150.2, 148.9, 136.4, 131.8, 131.7, 130.5, 129.94, 129.91, 123.3, 117.8, 116.9, 116.6, 106.3, 16.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}FN_2S$ $[M + H]^+$ 271.0705, found 271.0701.



3-(Methylthio)-1,2,3-tri(thiophen-2-yl)prop-2-en-1-one (78e). Obtained as a 55:45 inseparable mixture of geometrical isomers, brown semi solid (676.6 mg, 65%): R_f 0.5 (1:9

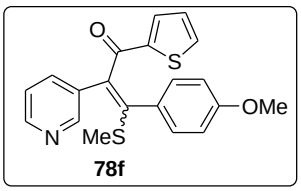
EtOAc/hexane); IR (neat, cm^{-1}) 2839, 1652, 1592, 1258, 831; ^1H NMR (400 MHz, $CDCl_3$) δ



78e

7.76 (d, *J* = 3.6 Hz, 0.45H), 7.70 (d, *J* = 4.8 Hz, 0.45H), 7.54-7.48 (m, 1.45H), 7.40 (d, *J* = 5.2 Hz, 0.55H), 7.264-7.265 (m, 0.55H), 7.17-7.13 (m, 1.45H), 7.07-7.04 (m, 1.1H), 7.01 (dd, *J* = 4.8 Hz, 3.6 Hz, 0.55H), 6.97-6.93 (m, 0.9H), 6.87-6.80 (m, 1.55H), 2.17 (s, 1.65H), 1.97 (s, 1.35H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 188.8, 187.3, 143.9, 143.6, 141.0, 138.1, 137.8, 135.9, 135.04, 135.0, 134.88, 134.86, 134.7, 134.3, 131.0, 130.6, 130.17, 130.15, 129.8, 129.1, 128.9, 128.8, 128.5, 128.0, 127.7, 127.6, 127.5, 127.2, 126.8, 126.7, 17.3, 16.7; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}OS_4$ $[M + H]^+$ 348.9849, found 348.9849.

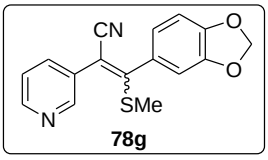
3-(4-Methoxyphenyl)-3-(methylthio)-2-(pyridin-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one (78f). Obtained as a 55:45 inseparable mixture of geometrical isomers, yellow solid (1.1 gm,



78f

66%): mp 85-87 °C; R_f 0.6 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2917, 1629, 1602, 1504, 1406, 828; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 0.45H), 8.54 (d, *J* = 4.8 Hz, 0.45H), 8.31-8.30 (m, 1.1H), 7.87 (dt, *J* = 7.6 Hz, 2.0 Hz, 0.45H), 7.72 (dd, *J* = 3.6 Hz, 1.2 Hz, 0.55H), 7.69 (dd, *J* = 4.8 Hz, 1.2 Hz, 0.55H), 7.47-7.46 (m, 0.55H), 7.43 (dt, *J* = 8.0 Hz, 1.6 Hz, 0.9H), 7.34-7.32 (m, 1.1H), 7.27-7.24 (m, 1.1H), 7.14 (dd, *J* = 4.8 Hz, 4.0 Hz, 0.45H), 7.06 (dd, *J* = 7.6 Hz, 4.8 Hz, 0.9H), 6.90 (t, *J* = 4.8 Hz, 0.45H), 6.81 (d, *J* = 8.8 Hz, 1.1H), 6.76 (d, *J* = 8.8 Hz, 0.9H), 3.79 (s, 1.65H), 3.74 (s, 1.35H), 1.88 (s, 1.35H), 1.87 (s, 1.65H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 188.7, 188.2, 160.0, 150.6, 150.5, 148.9, 148.0, 145.9, 144.6, 144.2, 143.5, 136.7, 136.6, 135.4, 134.9, 134.7, 134.6, 134.4, 134.0, 133.8, 133.4, 131.7, 131.4, 129.0, 128.6, 128.4, 127.9, 127.5, 123.3, 123.2, 114.4, 114.0, 55.4, 55.3, 16.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{18}NO_2S_2$ $[M + H]^+$ 368.0779, found 368.0773.

3-(Benzo[*d*][1,3]dioxol-5-yl)-3-(methylthio)-2-(pyridin-3-yl)acrylonitrile (78g). Obtained

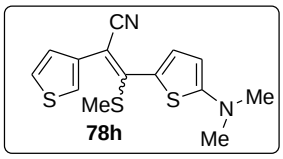


78g

as a 70:30 inseparable mixture of geometrical isomers, off-white solid (973.7 mg, 69%): mp 94-96 °C; R_f 0.3 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2924, 2199, 1483, 1249, 876; ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 0.7H), 8.60 (d, *J* = 4.4 Hz, 0.7H), 8.38 (d, *J* = 4.0 Hz, 0.3H), 8.28 (d, *J* = 1.6 Hz, 0.3H), 7.89 (dt, *J* = 8.0 Hz, 2.0 Hz, 0.7H), 7.51 (dt, *J* = 8.0 Hz, 2.0 Hz, 0.3H), 7.38 (dd, *J* = 8.0 Hz, 4.8 Hz, 0.7H), 7.16 (dd, *J* = 8.0 Hz, 4.8 Hz, 0.3H), 7.0 (dd, *J* = 8.0 Hz, 2.0 Hz, 0.7H),

6.94-6.92 (m, 1.3H), 6.72 (d, *J* = 8.0 Hz, 0.3H), 6.68-6.63 (m, 0.7H), 6.06 (s, 1.4H), 5.99 (s, 0.6H), 2.13 (s, 0.9H), 1.97 (s, 2.1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0, 160.8, 150.2, 150.1, 149.6, 149.4, 149.3, 148.7, 148.6, 148.5, 136.6, 136.2, 130.8, 130.3, 129.3, 127.4, 124.2, 123.4, 123.3, 118.3, 118.1, 109.7, 109.1, 108.9, 105.6, 105.5, 101.9, 16.8, 16.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}N_2O_2S$ $[M + H]^+$ 297.0698, found 297.0698.

3-(5-(Dimethylamino)thiophen-2-yl)-3-(methylthio)-2-(thiophen-3-yl)acrylonitrile (78h).



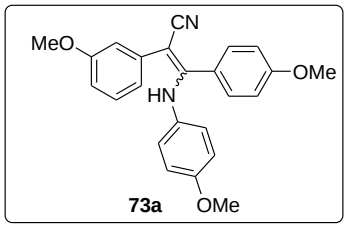
78h

Obtained as a 58:42 inseparable mixture of geometrical isomers, red solid (755.2 mg, 82%): mp 62-64 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2927, 2187, 1485, 1323, 913; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 3.2 Hz, 1.2 Hz, 0.48H), 7.51-7.48 (m, 1H), 7.34 (dd, *J* = 2.8 Hz, 1.2 Hz, 0.52H), 7.32 (dd, *J* = 4.8 Hz, 2.8 Hz, 0.52H), 7.16 (dd, *J* = 5.2 Hz, 2.8 Hz, 0.48H), 6.94 (d, *J* = 4.0 Hz, 0.48H), 6.90 (dd, *J* = 5.2 Hz, 1.2 Hz, 0.52H), 5.92 (d, *J* = 4.0 Hz, 0.48H), 5.74 (d, *J* = 4.0 Hz, 0.52H), 3.03 (s, 2.88H), 2.95 (s, 3.12H), 2.43 (s, 1.56H), 2.15 (s, 1.44H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 164.4, 164.1, 149.3, 148.2, 135.94, 135.91, 134.5, 133.3, 128.4, 127.9, 125.6, 125.4, 125.3, 122.9, 121.1, 120.8, 120.2, 103.3, 102.7, 100.6, 97.9, 42.3, 42.2, 18.7, 18.6; HRMS (ESI) *m/z* calcd for $C_{14}H_{15}N_2S_3$ $[M + H]^+$ 307.0397, found 307.0400.

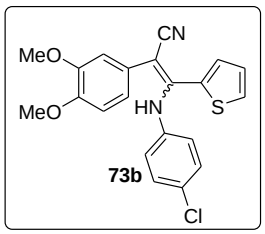
4.5.3 General Procedure for the synthesis of *N*-aryl/acylenaminonitrile/enaminones 73a-j, **75a-b**, **75d-f**, **79a-e.** A solution of 3-(methylthio)acrylonitrile **77** or **78** (1.0 mmol) in dry DMF (3 mL) was added to a stirred suspension of het(aryl)amine or the corresponding aryl/alky amide (1.1 mmol) and NaH (28.8 mg, 1.2 mmol, 60% suspension in mineral oil) in DMF (5 mL) at room temperature, followed by heating at 90 °C for 8-10 h (monitored by TLC). It was then poured into saturated NH_4Cl (25 mL) solution, extracted with EtOAc (2 x 25 mL), washed with water (2 x 25 mL), brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude products, which were purified by column chromatography using EtOAc/hexane as eluent.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-3-(4-methoxyphenylamino)acrylonitrile (73a). Obtained as a 75:25 inseparable mixture of geometrical isomers, pale yellow solid (308.8 mg, 80%): mp 83-85 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3310, 2928, 2196, 1491, 1249, 855; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (br s, 0.25H), 8.84 (br s, 0.75H), 7.50, (d, *J* = 8.8 Hz, 1.5H), 7.21 (t, *J* = 8.0 Hz, 0.75H), 7.15 (d, *J* = 8.8 Hz, 0.75H),

7.05 (t, *J* = 8.0 Hz, 0.25H), 6.99-6.94 (m, 2.25H), 6.87-6.79 (m, 1.75H), 6.75-6.72 (m, 1.25H), 6.69 (d, *J* = 9.2 Hz, 1.5H), 6.62 (d, *J* = 9.2 Hz, 1.5H), 6.56 (d, *J* = 8.0 Hz, 0.25H), 6.44 (t, *J* = 2.0 Hz, 0.25H), 3.79 (s, 2.25H), 3.70 (s, 0.75H), 3.67 (s, 2.25H), 3.66 (s, 0.75H), 3.60 (s, 2.25H), 3.52 (s, 0.75H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3, 160.9, 160.5, 159.4, 156.5, 156.2, 156.0, 155.4, 135.7, 135.5, 133.7, 133.2, 132.4, 131.9, 131.6, 130.5, 129.2, 125.6, 124.3, 124.2, 123.3, 122.3, 122.1, 120.8, 114.6, 114.4, 114.3, 114.2, 114.1, 114.0, 113.5, 112.4, 87.4, 85.3, 55.53, 55.49, 55.46, 55.41, 55.4, 55.1; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_2O_3$ $[M + H]^+$ 387.1709, found 387.1704.

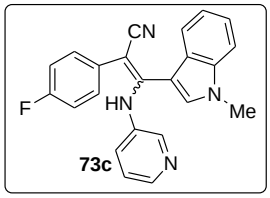


3-(4-Chlorophenylamino)-2-(3,4-dimethoxyphenyl)-3-(thiophen-2-yl)acrylonitrile (73b).



Obtained as a 75:25 inseparable mixture of geometrical isomers, yellow solid (344.5 mg, 87%): mp 201-201 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3307, 2919, 2196, 1518, 1249, 855; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 3.2 Hz, 0.75H), 7.47 (dd, *J* = 4.8 Hz, 0.4 Hz, 0.75H), 7.36 (d, *J* = 4.0 Hz, 0.25H), 7.13-7.08 (m, 3H), 7.04, (dd, *J* = 8.4 Hz, 2.0 Hz, 0.75H), 6.95 (d, *J* = 2.0 Hz, 0.75H), 6.87-6.81 (m, 1.5H), 6.75-6.70 (m, 0.75H), 6.62 (d, *J* = 8.8 Hz, 1.5H), 6.58 (d, *J* = 2.0 Hz, 0.25H), 6.32 (br s, 0.75H), 3.88 (s, 2.25H), 3.85 (s, 0.75H), 3.78 (s, 2.25H), 3.63 (s, 0.75H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 149.7, 149.3, 148.8, 148.6, 146.7, 145.6, 140.0, 139.3, 135.9, 134.4, 132.4, 132.0, 130.3, 130.0, 129.3, 129.2, 128.8, 128.4, 128.0, 127.7, 125.9, 125.6, 122.3, 122.2, 121.19, 121.15, 121.10, 120.1, 112.7, 111.9, 111.5, 111.2, 92.6, 90.9, 56.14, 56.07, 55.98, 55.78; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}ClN_2O_2S$ $[M + H]^+$ 397.0778 and 399.0748, found 397.0772 and 399.0753.

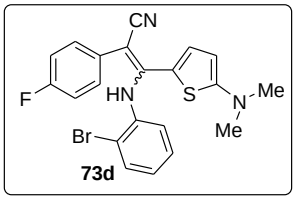
2-(4-Fluorophenyl)-3-(1-methyl-1*H*-indol-3-yl)-3-(pyridin-3-ylamino)acrylonitrile (73c).



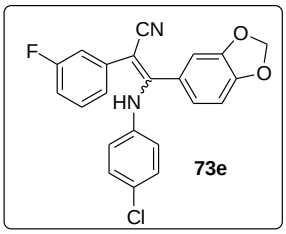
Obtained as a 85:15 inseparable mixture of geometrical isomers, yellow solid (261.2 mg, 71%): mp 176-178 °C; R_f 0.6 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3280, 2953, 2190, 1599, 1463, 1120; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.8 Hz, 1H), 8.06 (dd, *J* = 4.4 Hz, 1.2 Hz, 1H), 7.77 (s, 0.85H), 7.63 (s, 0.15H), 7.49-7.41 (m, 3H), 7.34-7.31 (m, 1H), 7.23-7.19 (m, 1.15H), 7.09-7.04 (m, 2.85H), 7.01-6.98 (m, 1H), 6.92 (d, *J* = 4.8 Hz, 0.85H),

6.90 (d, *J* = 4.4 Hz, 0.15H), 6.48 (br s, 0.15H), 6.42 (br s, 0.85H), 3.87 (s, 2.55H), 3.86 (s, 0.45H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.1 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 148.6, 147.6, 147.3, 143.9, 142.5 (d, $^{1}J_{C\text{-}F}$ = 237.0 Hz), 142.2, 141.4, 138.6, 138.2, 138.1, 138.0, 137.5, 137.3, 133.3, 133.0, 130.7, 130.6, 130.5, 130.0, 129.9, 128.9, 127.2, 126.1, 126.0, 125.6, 125.4, 123.4, 123.03, 122.98, 122.4, 121.4, 120.8, 120.7, 116.7, 116.4, 115.6, 115.4, 110.21, 110.16, 1.09.9, 108.0, 106.3, 89.1, 88.2, 33.7, 33.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}FN_4$ $[M + H]^+$ 369.1515, found 369.1513.

3-(2-Bromophenylamino)-3-(5-(dimethylamino)thiophen-2-yl)-2-(4-fluorophenyl)acrylonitrile (73d). Obtained as a 75:25 inseparable mixture of geometrical isomers, orange solid (326.3 mg, 74%): mp 52-54 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3305, 2928, 2186, 1461, 1273, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 4.4 Hz, 0.75H), 7.52 (dd, *J* = 8.0 Hz, 1.6 Hz, 0.25H), 7.41 (dd, *J* = 8.0 Hz, 1.6 Hz, 0.75H), 7.34-7.30 (m, 1.75H), 7.11-7.06 (m, 0.25H), 7.0-6.92 (m, 1.5H), 6.91-6.87 (m, 1.5H), 6.82-6.78 (m, 0.25H), 6.76-6.70 (m, 2H), 6.57 (br s, 0.25H), 6.14 (br s, 0.75H), 5.89 (d, *J* = 4.0 Hz, 0.75H), 5.59 (d, *J* = 4.4 Hz, 0.25H) 3.00 (s, 4.5H), 2.88 (s, 1.5H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 164.2, 163.8, 161.9 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 161.7 (d, $^{1}J_{C\text{-}F}$ = 246.0 Hz), 147.1, 145.7, 140.1, 139.3, 135.2, 134.5, 132.9, 132.6, 131.6, 131.5, 130.6, 130.5, 130.0, 129.8, 129.7, 128.2, 128.0, 126.9, 123.3, 123.2, 122.6, 120.8, 120.7, 120.0, 118.7, 116.9, 116.0, 115.8, 115.7, 115.6, 114.3, 113.8, 103.0, 102.2, 88.1, 87.2, 42.3, 42.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}BrFN_3S$ $[M + H]^+$ 442.0389 and 444.0368, found 442.0387 and 444.0369.

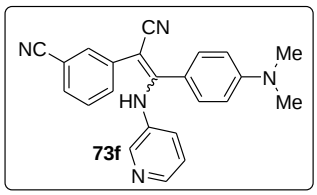


3-(Benzo[*d*][1,3]dioxol-5-yl)-3-(4-chlorophenylamino)-2-(3-fluorophenyl)acrylonitrile (73e). Obtained as a single geometrical isomer, yellow solid (254.8 mg, 65%): mp 85-87 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3265, 2191, 1487, 1245, 819; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.33 (m, 1H), 7.9 (s, 1H), 7.21-7.16 (m, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.01-6.96 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.50 (br s, 1H), 6.02 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.4 (d, $^{1}J_{C\text{-}F}$ = 246.0 Hz), 154.1, 150.2, 148.3, 138.9, 135.9, 135.8, 131.2, 131.1, 129.3, 128.9, 126.7, 125.0, 124.17, 124.15, 123.0, 122.0, 115.7, 115.4, 115.2, 115.0, 109.8, 109.0, 101.9, 89.5; HRMS



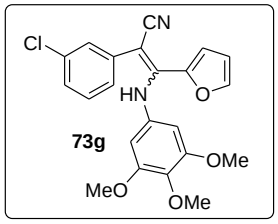
(ESI) *m/z* calcd for $C_{22}H_{15}ClFN_2O_2$ $[M + H]^+$ 393.0806 and 395.0777, found 393.0800 and 395.0780.

3-(1-Cyano-2-(4-(dimethylamino)phenyl)-2-(pyridin-3-ylamino)vinyl)benzonitrile (73f).



Obtained as a single geometrical isomer, pale yellow solid (299.3 mg, 82%): mp 175-177 °C; R_f 0.3 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3243, 2985, 2232, 2192, 1606, 1366, 1193, 817; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 4.4 Hz, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.73 (s, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.46-7.40 (m, 2H), 7.03-6.99 (m, 1H), 6.92-6.90 (m, 1H), 6.66 (d, J = 8.8 Hz, 2H), 6.42 (br s, 1H), 3.03 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.1, 154.7, 150.7, 149.8, 138.7, 136.3, 135.6, 135.1, 131.3, 131.0, 130.3, 128.8, 126.4, 125.7, 118.7, 113.8, 113.7, 111.5, 111.4, 40.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_5$ $[M + H]^+$ 366.1719, found 366.1710.

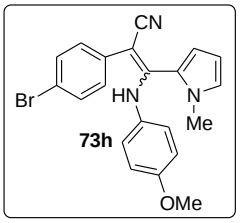
2-(3-Chlorophenyl)-3-(furan-2-yl)-3-(3,4,5-trimethoxyphenylamino)acrylonitrile (73g).



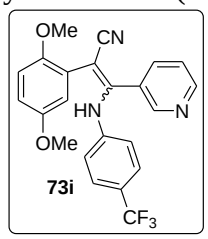
Obtained as a 75:25 inseparable mixture of geometrical isomers, yellow solid (274.7 mg, 67%): mp 105-107 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3282, 2946, 2188, 1463, 1120, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 0.75H), 7.36 (s, 0.5H), 7.28-7.26 (m, 2H), 7.20-7.08 (m, 2.25H), 6.99 (s, 0.25H), 6.89 (br s, 0.25H), 6.59 (d, J = 1.2 Hz, 0.75H), 6.44 (br s, 0.75H), 6.37 (d, J = 3.2 Hz, 0.5H), 5.98 (s, 0.5H), 5.92 (s, 1.5H), 3.77 (s, 0.75H), 3.71 (s, 2.25H), 3.68 (s, 1.5H), 3.66 (s, 4.5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.6, 153.5, 147.1, 145.3, 144.7, 144.6, 144.1, 142.4, 136.3, 135.8, 135.5, 135.4, 134.7, 134.6, 134.4, 130.0, 129.7, 128.7, 128.5, 127.6, 127.2, 126.9, 126.2, 121.4, 119.7, 116.8, 112.7, 112.4, 98.5, 98.4, 87.7, 84.9, 61.1, 56.11, 56.08; HRMS (ESI) *m/z* calcd for $C_{22}H_{20}ClN_2O_4$ $[M + H]^+$ 411.1112 and 413.1082, found 411.1108 and 413.1081.

2-(4-Bromophenyl)-3-(4-methoxyphenylamino)-3-(1-methyl-*1H*-pyrrol-2-yl)acrylonitrile (73h). Obtained as a 90:10 inseparable mixture of geometrical isomers, yellow solid (297.1 mg, 73%): mp 155-157 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3293, 2939, 2192, 1508, 1240, 823; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 0.2H), 7.37 (d, J = 8.8 Hz, 0.2H), 7.27 (d, J = 8.4 Hz, 1.8H), 6.98 (br s, 0.9H), 6.77 (d, J =

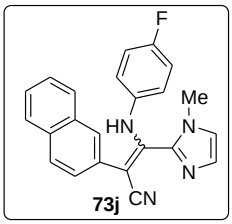
8.8 Hz, 1.8H), 6.73-6.71 (m, 2H), 6.65-6.63 (m, 2H), 6.58 (t, *J* = 2.0 Hz, 0.9H), 6.48 (d, *J* = 8.0 Hz, 0.2H), 6.44 (br s, 0.1H), 6.23-6.19 (m, 0.1H), 6.10-6.05 (m, 1.8H), 3.73 (s, 2.7H), 3.72 (s, 0.3H), 3.43 (s, 0.3H), 3.19 (s, 2.7H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 156.4, 156.0, 147.4, 145.7, 133.8, 133.5, 133.3, 133.0, 132.6, 131.6, 130.0, 129.4, 127.1, 126.2, 123.8, 122.8, 121.8, 121.2, 120.9, 120.6, 119.6, 116.6, 116.4, 115.0, 114.7, 114.5, 109.7, 109.4, 86.8, 84.2, 55.6, 55.5, 35.0, 34.6; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}BrN_3O$ $[M + H]^+$ 408.0711 and 410.0691, found 408.0707 and 410.0688.



2-(2,5-Dimethoxyphenyl)-3-(pyridin-3-yl)-3-(4-(trifluoromethyl)phenylamino)acrylonitrile (73i). Obtained as a single geometrical isomer, yellow solid (272.0 mg, 64%): mp 77- 79 °C; R_f 0.5 (3:2 EtOAc/hexane); IR (neat, cm^{-1}) 3253, 2925, 2179, 1604, 1245, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.8 (s, 1H), 8.68 (d, *J* = 4.0 Hz, 1H), 8.05 (dt, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.02 (dd, *J* = 2.0 Hz, 1.2 Hz, 1H), 6.93-6.92 (m, 2H), 6.83 (br s, 1H), 6.60 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 154.5, 151.6, 151.0, 150.7, 150.6, 143.4, 137.7, 129.5, 126.4 (q, $J_{C\text{-}F}$ = 4.0 Hz), 125.2, 124.8, 123.7, 121.8, 120.5, 120.4, 116.34, 116.25, 113.8, 90.4, 56.8, 56.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}F_3N_3O_2$ $[M + H]^+$ 426.1429, found 426.1426.

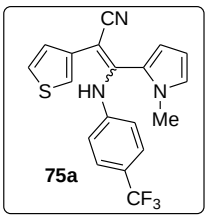


3-(4-Fluorophenylamino)-3-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-yl)acrylonitrile (73j). Obtained as a 50:50 inseparable mixture of geometrical isomers, yellow solid (250.2 mg, 68%): mp 153-155 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3123, 2197, 1505, 1228, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (s, 0.5H), 7.84-7.79 (m, 1.5H), 7.72 (dd, *J* = 5.6 Hz, 3.2 Hz, 0.5H), 7.65 (dd, *J* = 6.4 Hz, 2.8 Hz, 0.5H), 7.59 (t, *J* = 8.4 Hz, 1H), 7.51-7.50 (m, 1.5H), 7.42 (dd, *J* = 6.0 Hz, 3.2 Hz, 1H), 7.37 (br s, 0.5H), 7.21 (s, 0.5H), 7.10 (s, 0.5H), 6.95-6.87 (m, 3H), 6.82-6.75 (m, 1H), 6.74-6.70 (m, 1H), 6.58 (dd, *J* = 8.4 Hz, 4.4 Hz, 1H), 3.63 (s, 1.5H), 3.15 (s, 1.5H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7 (d, $^{1}J_{C\text{-}F}$ = 243.0 Hz), 159.5 (d, $^{1}J_{C\text{-}F}$ = 243.0 Hz), 143.9, 142.7, 140.2, 139.4, 135.8, 135.76, 135.73, 135.69, 133.7, 133.5, 132.9, 132.1, 130.7, 130.6, 130.3, 129.9, 129.4, 128.4, 128.2,

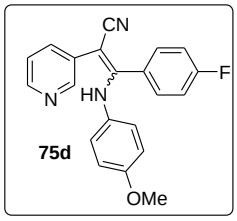


128.1, 128.0, 127.9, 127.6, 127.1, 127.0, 126.7, 126.5, 125.5, 125.3, 123.6, 123.0, 122.84, 122.76, 121.63, 121.55, 120.1, 119.5, 116.31, 116.28, 116.09, 116.05, 92.5, 89.9, 33.9, 33.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}FN_4$ $[M + H]^+$ 369.1515, found 369.1522.

3-(1-Methyl-1*H*-pyrrol-2-yl)-2-(thiophen-3-yl)-3-(4-(trifluoromethyl)phenylamino)acrylonitrile (75a). Obtained as a single geometrical isomer, yellow solid (268.5 mg, 72%): mp 130-132 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3399, 2981, 2202, 1518, 1112, 838; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 7.41-7.37 (m, 3H), 7.23 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 6.76 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.74-6.73 (m, 1H), 6.71 (br s, 1H), 6.50 (d, J = 8.4 Hz, 2H), 6.26 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 3.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.8, 142.7, 133.7, 127.6, 127.5, 126.8 (q, $J_{C\text{-}F}$ = 4.0 Hz), 124.7, 124.5, 124.2, 123.8, 122.9, 120.9, 117.4, 116.7, 109.8, 88.0, 35.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}F_3N_3S$ $[M + H]^+$ 374.0939, found 374.0936.



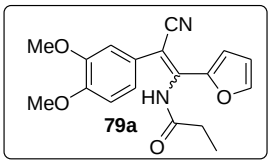
3-(4-Methoxyphenylamino)-2-(1-methyl-1*H*-indol-3-yl)-3-(thiophen-2-yl)acrylonitrile (75b). Obtained as a 90:10 inseparable mixture of geometrical isomers, yellow solid (257.9 mg, 67%): mp 72-74 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3307, 2924, 2196, 1491, 1249, 855; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 3.6 Hz, 1.2 Hz, 0.9H), 7.53 (d, J = 8.0 Hz, 0.9H), 7.40 (dd, J = 5.2 Hz, 1.2 Hz, 0.9H), 7.35 (d, J = 8.4 Hz, 1H), 7.29 (s, 0.9H), 7.27-7.23 (m, 0.9H), 7.19-7.16 (m, 0.2H), 7.09-7.04 (m, 1.8H), 7.02-6.98 (m, 0.1H), 6.96-6.95 (m, 0.1H), 6.91 (s, 0.1H), 6.82-6.80 (m, 0.2H), 6.77 (s, 0.1H), 6.73-6.70 (m, 0.3H), 6.66 (s, 3.7H), 6.38 (s, 0.9H), 3.81 (s, 2.7H), 3.73 (s, 0.3H), 3.71 (s, 0.3H), 3.70 (s, 2.7H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.0, 146.6, 137.3, 135.4, 134.0, 131.6, 129.5, 129.2, 127.3, 125.5, 123.0, 122.6, 122.1, 120.5, 120.2, 114.4, 110.0, 107.4, 81.9, 55.5, 33.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_3OS$ $[M + H]^+$ 386.1327, found 386.1315.



3-(4-Fluorophenyl)-3-(4-methoxyphenylamino)-2-(pyridin-3-yl)acrylonitrile (75d). Obtained as a single geometrical isomer, off-white solid (255.3 mg, 74%): mp 85-87 °C; R_f 0.3 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3310, 2922, 2199, 1490, 1142, 855; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 8.45-8.43 (m, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.60-7.56 (m, 2H),

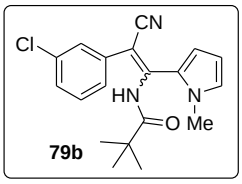
7.31-7.29 (m, 1H), 7.08 (t, *J* = 8.8 Hz, 2H), 6.71 (br s, 1H), 6.63-6.62 (m, 4H), 3.69 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 164.2 (d, $^{1}J_{C\text{-}F}$ = 251.0 Hz), 156.7, 155.6, 149.6, 148.5, 136.2, 132.9, 132.8, 132.5, 132.3, 132.2, 129.6, 125.1, 123.9, 121.3, 116.3, 116.1, 114.5, 84.1, 55.6; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}FN_3O$ $[M + H]^+$ 346.1356, found 346.1349.

***N*-(2-Cyano-2-(3,4-dimethoxyphenyl)-1-(furan-2-yl)vinyl)propionamide (79a)**. Obtained



as a 85:15 inseparable mixture of geometrical isomers, brown solid (221.6 mg, 68%): mp 165-167 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3238, 2216, 1668, 1488, 1276; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.0 Hz, 0.85H), 7.37 (d, *J* = 1.6 Hz, 0.15H), 7.34 (br s, 0.15H), 7.16 (d, *J* = 3.6 Hz, 0.85H), 7.04 (dd, *J* = 8.4 Hz, 2.0 Hz, 0.85H), 6.98 (br s, 0.85H), 6.95 (d, *J* = 2.0 Hz, 0.85H), 6.93-6.88 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 0.15H), 6.73 (d, *J* = 2.0 Hz, 0.15H), 6.56 (dd, *J* = 3.6 Hz, 2.0 Hz, 0.85H), 6.36 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.15H), 6.27 (d, *J* = 3.6 Hz, 0.15H), 3.90 (s, 2.55H), 3.88 (s, 0.45H), 3.85 (s, 2.55H), 3.74 (s, 0.45H), 2.45 (q, *J* = 7.6 Hz, 0.3H), 2.24 (q, *J* = 7.6 Hz, 1.7H), 1.25 (t, *J* = 7.6 Hz, 0.45H), 1.10 (t, *J* = 7.6 Hz, 2.55H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 172.2, 149.9, 149.8, 149.6, 149.1, 148.3, 147.3, 144.5, 144.4, 136.7, 135.6, 124.9, 124.8, 122.1, 121.6, 119.3, 118.3, 115.6, 112.9, 112.6, 112.5, 112.0, 111.7, 111.5, 111.4, 99.9, 56.2, 56.1, 56.03, 56.0, 30.2, 29.8, 9.4, 9.3; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}N_2O_4$ $[M + H]^+$ 327.1345, found 327.1340.

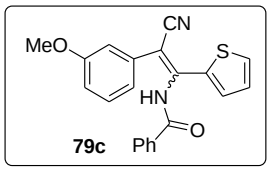
***N*-(2-(3-Chlorophenyl)-2-cyano-1-(1-methyl-1*H*-pyrrol-2-yl)vinyl)pivalamide (79b)**.



Obtained as a single geometrical isomer, yellow solid (242.1 mg, 71%): mp 140-142 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3238, 2972, 2210, 1670, 1582, 1206; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 1.2 Hz, 1H), 7.39-7.37 (m, 2H), 7.34-7.30 (m, 1H), 7.28 (br s, 1H), 6.82 (t, *J* = 2.0 Hz, 1H), 6.61 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H), 6.23 (dd, *J* = 4.0 Hz, 2.8 Hz, 1H), 3.66 (s, 3H), 1.14 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.4, 141.0, 135.2, 134.9, 130.8, 128.9, 128.3, 128.1, 126.8, 126.7, 119.5, 115.4, 109.4, 99.1, 40.1, 35.1, 27.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}ClN_3O$ $[M + H]^+$ 342.1373 and 344.1344, found 342.1370 and 344.1349.

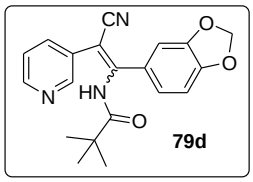
***N*-(2-Cyano-2-(3-methoxyphenyl)-1-(thiophen-2-yl)vinyl)benzamide (79c)**. Obtained as a 60:40 inseparable mixture of geometrical isomers, yellow semi solid (230.4 mg, 64%): R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3242, 2980, 2212, 1673, 1477, 1089, 708; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.06 (br s, 0.4H), 7.92 (d, J = 7.6 Hz, 0.6H), 7.84-7.83 (m, 1H), 7.77 (br s, 0.6H), 7.68 (d, J = 7.2 Hz, 1.2H), 7.62-7.57 (m, 0.8H), 7.55-7.49 (m, 1.8H), 7.44-7.38 (m, 1.2H), 7.30-7.21 (m, 0.8H), 7.15 (dd, J = 4.8 Hz, 4.0 Hz, 0.8H), 7.09-7.01 (m, 1.8H), 6.95-6.90 (m, 0.8H), 6.87-6.86 (m, 1.2H), 3.71 (s, 1.2H), 3.70 (s, 1.8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 165.6, 160.3, 159.9, 142.3, 141.7, 137.1, 136.2, 133.8, 133.4, 133.2, 133.1, 132.9, 132.8, 132.7, 131.4, 131.1, 130.5, 130.0, 129.7, 129.0, 128.9, 128.1, 127.6, 127.5, 122.0, 120.7, 119.5, 119.3, 118.1, 115.6, 115.3, 114.6, 113.4, 104.3, 102.0, 55.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}N_2O_2S$ $[M + H]^+$ 361.1011, found 361.0999.



79c

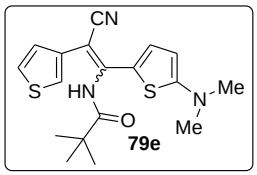
_N_-(1-(Benzo[*d*][1,3]dioxol-5-yl)-2-cyano-2-(pyridin-3-yl)vinyl)pivalamide (79d).



79d

Obtained as a 90:10 inseparable mixture of geometrical isomers, pale yellow solid (209.4 mg, 60%): mp 153-155 °C; R_f 0.3 (3:2 EtOAc/hexane); IR (neat, cm^{-1}) 3242, 2942, 2219, 1665, 1519, 1276; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1.8H), 8.39 (s, 0.1H), 8.28 (s, 0.1H), 7.82-7.77 (m, 1H), 7.54-7.50 (m, 1H), 7.37 (br s, 0.9H), 7.18 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 6.99 (s, 0.9H), 6.88 (d, J = 8.0 Hz, 0.9H), 6.67 (s, 0.2H), 6.58 (s, 0.1H), 6.03 (s, 1.8H), 5.95 (s, 0.2H), 1.20 (s, 0.9H), 1.12 (s, 8.1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.6, 175.7, 150.7, 150.6, 150.5, 150.2, 149.9, 149.5, 149.1, 148.7, 148.3, 136.5, 136.3, 130.3, 128.1, 126.3, 124.3, 124.1, 123.7, 119.0, 117.8, 109.1, 108.9, 108.8, 108.4, 102.0, 101.9, 98.3, 97.4, 40.1, 40.0, 27.3, 27.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{20}N_3O_3$ $[M + H]^+$ 350.1505, found 350.1516.

_N_-(2-Cyano-1-(5-(dimethylamino)thiophen-2-yl)-2-(thiophen-3-yl)vinyl)pivalamide



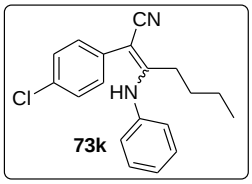
79e

(79e). Obtained as a 60:40 inseparable mixture of geometrical isomers, yellow semi solid (240.5 mg, 67%): R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3239, 2216, 1668, 1488, 1208, 809; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 4.4 Hz, 0.6H), 7.38-7.34 (m, 1H), 7.32-7.29 (m, 1H), 7.26-7.24 (m, 0.4H), 7.12 (dd, J = 5.2 Hz, 1.2 Hz, 0.6H), 7.07 (br s, 0.6H), 7.02 (dd, J = 4.8 Hz, 0.8 Hz, 0.4H), 6.85 (d, J = 4.4 Hz, 0.4H), 5.87 (d, J = 5.4 Hz, 0.6H), 5.68 (d, J = 4.0 Hz, 0.4H), 3.00 (s, 3.6H), 2.91 (s, 2.4H), 1.35 (s, 3.6H), 1.20 (s, 5.4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.1, 176.5, 164.2, 163.4, 141.7, 141.5, 134.5, 133.9, 133.5, 133.3, 128.3,

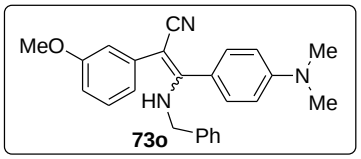
127.2, 126.3, 126.1, 125.9, 124.1, 120.9, 119.9, 119.4, 119.1, 103.1, 102.4, 93.5, 91.4, 42.3, 42.1, 39.94, 39.9, 27.5, 27.4; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_3OS_2$ $[M + H]^+$ 360.1204, found 360.1208.

4.5.4 General Procedure for the synthesis of *N*-aryl/benzylenaminonitriles 73k, 73o and 75c. A solution of of *α*-(thioacylaryl)acetonitriles **77k**, **77o**, **78c** (1.0 mmol) (prepared by condensation of respective (het)arylacetonitriles and dithioesters in presence of sodium hydride in DMF[1a] and used as such without purification), corresponding amines (1.2 mmol) in acetic acid (0.068 mL, 1.2 mmol) and ethanol (20 mL) was heated at 70 °C with stirring for 6-8 h (monitored by TLC). The reaction mixture was evaporated under reduced pressure, poured into saturated $NaHCO_3$ solution (20 mL), extracted with EtOAc (2 x 25 mL). The combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), concentrated under reduced pressure. And the crude products were purified by column chromatography using EtOAc/hexane as eluent.

2-(4-Chlorophenyl)-3-(phenylamino)hept-2-enenitrile (73k). Obtained as a 90:10 inseparable mixture of geometrical isomers, yellow solid (217.0 mg, 70%): mp 45-47 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3305, 2928, 2186, 1569, 834; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 6H), 7.18-7.11 (m, 1.2H), 6.96 (d, *J* = 7.6 Hz, 1.8H), 6.78 (br s, 0.1H), 6.43 (br s, 0.9H), 2.69 (t, *J* = 8.0 Hz, 1.8H), 2.39 (t, *J* = 8.0 Hz, 0.2H), 1.55-1.52 (m, 1.8H), 1.35-1.30 (m, 2H), 1.09-1.01 (m, 0.2H), 0.83 (t, *J* = 7.2 Hz, 2.7H), 0.62 (t, *J* = 7.2 Hz, 0.3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9, 158.7, 138.9, 133.3, 132.8, 132.0, 131.3, 130.4, 129.6, 129.5, 129.4, 129.0, 126.2, 125.8, 125.4, 124.5, 121.4, 84.1, 31.5, 30.5, 29.8, 27.7, 22.4, 22.2, 13.7, 13.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}ClN_2$ $[M + H]^+$ 311.1315 and 313.1286, found 311.1310 and 313.1285.

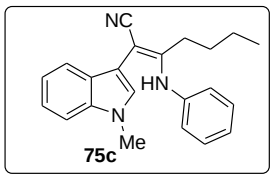


3-(Benzylamino)-3-(4-(dimethylamino)phenyl)-2-(3-methoxyphenyl)acrylonitrile (73o). Obtained as a single geometrical isomer, yellow solid (712.3 mg, 62%): mp 85-87 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3282, 2946, 2188, 1504, 1229; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.86 (t, *J* = 2.0 Hz, 1H), 6.57 (d, *J* = 8.8 Hz, 2H), 4.67 (br s, 3H), 3.76 (s,

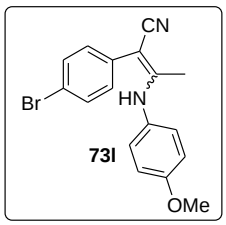


3H), 2.96 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.4, 161.8, 160.4, 150.7, 139.8, 135.5, 130.5, 129.1, 128.7, 127.8, 127.3, 122.7, 120.6, 119.2, 115.5, 113.8, 112.0, 55.4, 47.3, 40.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{26}N_3O$ $[M + H]^+$ 384.2076, found 384.2080.

2-(1-Methyl-1*H*-indol-3-yl)-3-(phenylamino)hept-2-enenitrile (75c). Obtained as a single geometrical isomer, off-white solid (200.6 mg, 61%): mp 85-87 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3250, 2917, 2182, 1603, 1245, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.31-7.25 (m, 3H), 7.18 (s, 1H), 7.17-7.12 (m, 2H), 6.98 (d, J = 7.6 Hz, 2H), 6.45 (br s, 1H), 3.81 (s, 3H), 2.80 (t, J = 7.6 Hz, 2H), 1.56-151 (m, 2H), 1.36 (sextet, J = 7.2 Hz, 2H), 0.85 (t, J = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 139.5, 137.2, 129.3, 129.1, 126.2, 125.3, 124.6, 122.5, 122.2, 120.2, 119.9, 109.9, 106.3, 33.1, 30.7, 30.3, 22.4, 13.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}N_3$ $[M + H]^+$ 330.1970, found 330.1966.



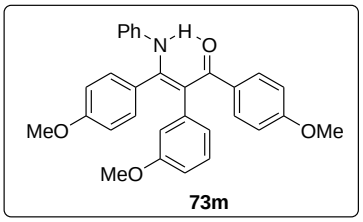
2-(4-Bromophenyl)-3-(4-methoxyphenylamino)but-2-enenitrile (73l). Enaminonitrile **73l** was prepared following the reported procedure[43] by condensation of α-acetyl-(4-bromophenyl)acetonitrile (237.0 mg, 1.0 mmol) with 4-methoxyaniline (135.3 mg, 1.1 mmol) in presence of acetic acid (0.068 mL, 1.2 mmol) in refluxing ethanol (20 mL) . Obtained as a 90:10 inseparable mixture of geometrical isomers, off-white solid (246.2 mg, 72%): mp 158-160 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3256, 2926, 2179, 1510, 1245, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 1.8H), 7.46 (d, J = 8.4 Hz, 0.2H), 7.32 (d, J = 8.4 Hz, 1.8H), 7.17 (d, J = 8.4 Hz, 0.2H), 7.07 (d, J = 8.8 Hz, 0.2H), 6.95 (d, J = 8.8 Hz, 1.8H), 6.90-6.88 (m, 0.3H), 6.85 (d, J = 8.8 Hz, 1.8H), 6.57 (br s, 0.9H), 3.82 (s, 0.3H), 3.80 (s, 2.7H), 2.19 (s, 2.7H), 1.91 (s, 0.3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.3, 155.6, 132.8, 132.5, 131.8, 131.3, 130.8, 127.4, 121.4, 114.7, 81.8, 55.7, 18.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}BrN_2O$ $[M + H]^+$ 343.0446 and 345.0426, found 343.0440 and 345.0422.



4.5.5 General Procedure for the synthesis of *N*-arylenaminones 73m-n and 75e-f. A solution of 3-(methylthio)enones **77m-n** and **78e-f** (1.0 mmol) in dry THF (5 mL) was added to a stirred solution of arylamine (1.1 mmol) and *n*-BuLi (0.75 mL, 1.6 M solution in hexane, 1.2 mmol) in THF (10 mL) at 0 °C and the reaction mixture was further stirred for 2-3 h at

room temperature (monitored by TLC). It was then poured into saturated NH_4Cl (25 mL) solution, extracted with EtOAc (2 x 25 mL), washed with water (2 x 25 mL), brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude products, which were purified by column chromatography using EtOAc/hexane as eluent.

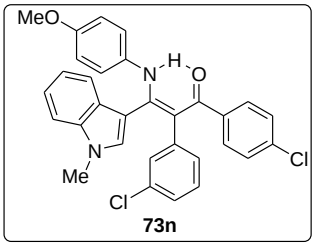
2-(3-Methoxyphenyl)-1,3-bis(4-methoxyphenyl)-3-(phenylamino)prop-2-en-1-one (73m).



73m

Obtained as yellow solid (320.8 mg, 69%): mp 45-47 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3264, 2993, 1639, 1424, 1244, 832; ^1H NMR (400 MHz, $CDCl_3$) δ 13.89 (s, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.09 (t, J = 8.0 Hz, 2H), 6.95 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 2H), 6.66-6.59 (m, 4H), 6.50 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.43 (d, J = 7.6 Hz, 1H), 6.37 (s, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.49 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.5, 161.4, 160.4, 159.5, 158.8, 141.0, 140.0, 135.3, 131.3, 130.4, 128.7, 128.3, 126.8, 126.5, 124.1, 123.8, 118.9, 113.5, 112.7, 111.8, 55.28, 55.24, 55.21; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}NO_4$ $[M + H]^+$ 466.2018, found 466.2020.

2-(3-Chlorophenyl)-1-(4-chlorophenyl)-3-(4-methoxyphenylamino)-3-(1-methyl-*1H*-indol-3-yl)prop-2-en-1-one (73n). Obtained as a single geometrical isomer, yellow solid

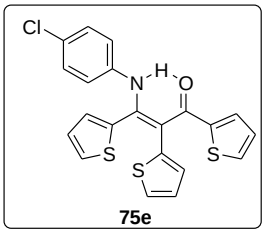


73n

(347.1 mg, 66%): mp 138-140 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3372, 2918, 1656, 1455, 1246, 927; ^1H NMR (400 MHz, $CDCl_3$) δ 14.19 (s, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.12-7.08 (m, 5H), 6.93-6.90 (m, 1H), 6.87-6.85 (m, 1H), 6.84-6.79 (m, 3H), 6.77 (t, J = 8.0 Hz, 1H), 6.68-6.66 (m, 1H), 6.55 (d, J = 8.8 Hz, 2H), 6.42 (s, 1H), 3.66 (s, 3H), 3.57 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.3, 158.8, 156.7, 142.2, 141.4, 136.3, 134.6, 133.2, 133.1, 132.9, 131.5, 131.3, 129.6, 128.4, 127.8, 126.0, 125.5, 124.5, 122.3, 120.7, 120.5, 114.0, 110.7, 109.3, 108.4, 55.4, 33.0; HRMS (ESI) *m/z* calcd for $C_{31}H_{25}Cl_2N_2O_2$ $[M + H]^+$ 527.1293 and 529.1264, found 527.1287 and 529.1262.

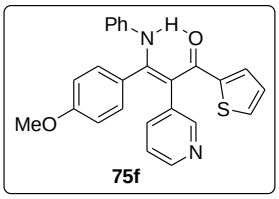
3-(4-Chlorophenylamino)-1,2,3-tri(thiophen-2-yl)prop-2-en-1-one (75e). Obtained as a single geometrical isomer, pale green solid (255.6 mg, 60%): mp 143-145 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3391, 1606, 1485, 1262, 844; ^1H NMR (400 MHz, $CDCl_3$) δ

14.04 (s, 1H), 7.41 (dd, *J* = 4.8 Hz, 0.8 Hz, 1H), 7.28-7.25 (m, 2H), 7.11 (d, *J* = 8.8 Hz, 0.8 Hz, 2H), 6.92-6.88 (m, 2H), 6.84 (dd, *J* = 4.8 Hz, 4.0 Hz, 1H), 6.79-6.77 (m, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.66 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 183.8, 156.8, 146.1, 139.9, 138.3, 134.0, 132.5, 132.2, 131.6, 131.0, 130.4, 129.0, 128.9, 127.9, 127.5, 126.9, 126.6, 124.7, 102.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClNOS_3$ $[M + H]^+$ 428.0004 and 429.9975, found 427.9997 and 429.9968.



75e

3-(4-Methoxyphenyl)-3-(phenylamino)-2-(pyridin-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one (75f). Obtained as a single geometrical isomer, yellow solid (280.1 mg, 68%): mp 48-50 °C; R_f 0.5 (3:2 EtOAc/hexane); IR (neat, cm^{-1}) 3265, 1630, 1571, 1495, 1244, 912; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.11 (s, 1H), 8.37-8.35 (m, 2H), 7.35 (d, *J* = 5.2 Hz, 2H), 7.122-7.06 (m, 3H), 7.00-6.96 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.77-6.73 (m, 3H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.40 (d, *J* = 3.6 Hz, 1H), 3.68 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 183.0, 163.3, 159.7, 154.3, 147.7, 146.9, 141.2, 139.3, 135.1, 131.2, 131.0, 128.9, 127.3, 125.9, 124.7, 123.9, 123.0, 114.4, 113.8, 106.9, 55.2; HRMS (ESI) *m/z* calcd for $C_{25}H_{21}N_2O_2S$ $[M + H]^+$ 413.1324, found 413.1318.



75f

4.5.6 General procedure for palladium catalyzed intramolecular C-H functionalization-amination of enaminonitriles/enaminones 73, 75 and 79: Synthesis of substituted N-het(aryl)/NH- 3-cyano/aroyl indoles 74a-n, 76a-e and the corresponding hetero-fused pyrroles 80a-f

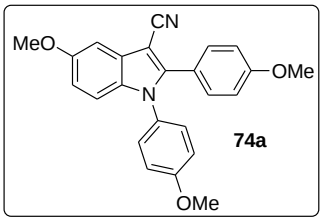
Method A: A suspension of enaminonitrile/enaminone **73**, **75** or **79** (0.3 mmol), $Pd(OAc)_2$ (13.4 mg, 20 mol%), and $Cu(OAc)_2$ (54.3 mg, 0.3 mmol) in dry DMSO (2 mL) was evacuated and backfilled with oxygen (3 cycles) and then stirred at 120 °C for 8-10 h (monitored by TLC). The reaction mixture was cooled to room temperature, diluted with distilled water (20 mL) and extracted with EtOAc (2 x 30 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude products, which were purified by column chromatography using EtOAc/hexane as eluent.

Method B: A suspension of enaminonitrile/enaminone **73, 75,** or **79** (0.3 mmol), $Pd(OAc)_2$ (13.4 mg, 20 mol%), Ag_2CO_3 (82.7 mg, 0.3 mmol), and PivOH (30.6 mg, 0.3 mmol) in dry DMSO (2 mL) was evacuated and backfilled with oxygen (3 cycles) and then stirred at 120 °C for 10-12 h (monitored by TLC). The reaction mixture was worked-up as described for method A and the crude indoles thus obtained, were purified by column chromatography using EtOAc/hexane as eluent.

4.5.7 One-Pot Synthesis of *N*-substituted Indole 74a from 2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-3-(methylthio)acrylonitrile 77a.

A solution of 2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-3-(methylthio)acrylonitrile **77a** (311.0 mg, 1.0 mmol) in dry DMF or DMSO (3 mL) was added to a stirred suspension of 4-methoxy aniline (123.0 mg, 1.0 mmol) and NaH (24.0 mg, 1.0 mmol, 60% suspension in mineral oil) or *t*BuOK (112.2 mg, 1.0 mmol) in DMF or DMSO (5 mL) at room temperature, followed by heating at 90 °C for 8 h (monitored by TLC). After cooling to room temperature, $Pd(OAc)_2$ (44.9 mg, 20 mol%), oxidant (1.0 equiv), and additive (1.0 equiv) were added to the reaction mixture, evacuated and backfilled with oxygen (3 cycles) and then stirred at 120 °C for 8-15 h (monitored by TLC). The reaction mixture was cooled to room temperature, diluted with distilled water (20 mL) and extracted with EtOAc (2 x 30 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude products, which were purified by column chromatography using EtOAc/hexane as eluent.

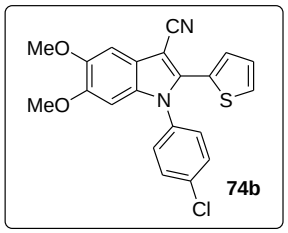
5-Methoxy-1,2-bis(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (74a).[1a] Obtained from



74a

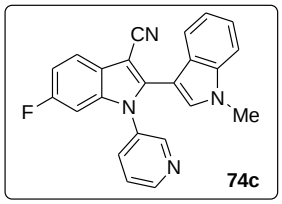
enaminonitrile **73a**,white solid (85.8 mg, 75%): mp 140-142 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2936, 2208, 1514, 1479, 803; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 9.2 Hz, 2H), 7.08 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 9.2 Hz, 2H), 6.89 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.85 (d = J = 8.8 Hz, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 159.5, 156.5, 147.4, 132.9, 131.3, 129.7, 129.2, 128.5, 121.4, 117.3, 114.9, 114.6, 114.3, 112.5, 100.6, 85.9, 56.0, 55.7, 55.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}N_2O_3$ $[M + H]^+$ 385.1552, found 385.1547.

1-(4-Chlorophenyl)-5,6-dimethoxy-2-(thiophen-2-yl)-1*H*-indole-3-carbonitrile (74b).[1a]



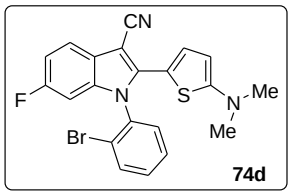
Obtained from enaminonitrile **73b**,white solid (87.30 mg, 73%): mp 194-196 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2988, 2209, 1483, 1278, 874; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.8 Hz, 2H), 7.35- 7.34 (m, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 7.03 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 6.50 (s, 1H), 3.99 (s, 3H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.2, 147.9, 138.8, 135.7, 135.1, 132.4, 130.4, 130.2, 129.9, 129.6, 128.5, 127.6, 120.8, 116.8, 100.6, 94.2, 86.9, 56.6, 56.5; HRMS (ESI) *m/z* calcd for $C_{21}H_{16}ClN_2O_2S$ $[M + H]^+$ 395.0621 and 397.0592, found 395.0597 and 397.0560.

6-Fluoro-2-(1-methyl-1*H*-indol-3-yl)-1-(pyridin-3-yl)-1*H*-indole-3-carbonitrile (74c).[1a]

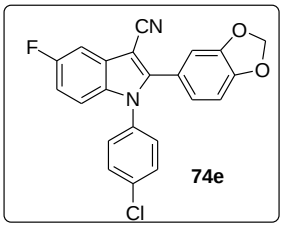


Obtained from enaminonitrile **73c**, pale yellow solid (83.10 mg, 76%): mp 190-192 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 2956, 2189, 1465, 1225, 845; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69-8.67 (m, 1H), 8.30 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 7.95 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.45-7.36 (m, 6H), 7.33 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 7.07-7.02 (m, 2H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0 (d, $^1J_{C\text{-}F}$ = 240.0 Hz), 149.0 (d, $^2J_{C\text{-}F}$ = 110.0 Hz), 137.5, 137.4, 137.1, 134.6, 134.0, 130.8, 125.6, 124.4, 124.2, 122.9, 120.6, 120.51, 120.50 (d, $^2J_{C\text{-}F}$ = 100.0 Hz), 120.0, 116.3, 112.0, 111.8, 110.0, 102.9, 98.0, 97.8, 88.0, 33.4; HRMS (ESI) *m/z* calcd for $C_{23}H_{16}FN_4$ $[M + H]^+$ 367.1359, found 367.1348.

1-(2-Bromophenyl)-2-(5-(dimethylamino)thiophen-2-yl)-6-fluoro-1*H*-indole-3-carbonitrile (74d). Obtained from enaminonitrile **73d**, yellow solid (117.6 mg, 85%): mp 175-177 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2956, 2215, 1615, 1322, 727; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd = J = 8.0 Hz, 1.2 Hz, 1H), 7.36-7.32 (m, 2H), 7.14-7.11 (m, 2H), 7.05-7.01 (m, 2H), 6.93 (t, J = 8.0 Hz, 1H), 5.77 (d, J = 4.8 Hz, 1H), 3.07 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 160.7 (d, $^1J_{C\text{-}F}$ = 240.0 Hz), 143.4, 143.3, 137.5, 137.3, 136.1, 134.4, 131.70, 131.66, 131.2, 129.2, 124.7, 124.4, 119.74, 119.65, 117.4, 112.3, 111.5, 111.2, 102.4, 98.0, 97.7, 82.8, 42.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{16}BrFN_3S$ $[M + H]^+$ 440.0232 and 442. 0212, found 440.0229 and 442.0211.

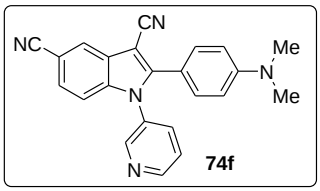


2-(Benzo[*d*][1,3]dioxol-5-yl)-1-(4-chlorophenyl)-5-fluoro-1*H*-indole-3-carbonitrile (74e).



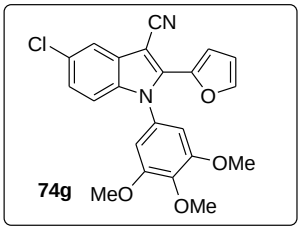
Obtained from enaminonitrile **73e**, white solid (87.3 mg, 75%): mp 175-177 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2922, 2183, 1486, 1218, 917; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.44 (m, 3H), 7.17 (d, J = 8.8 Hz, 2H), 7.14 (t, J = 4.0 Hz, 1H), 7.03 (td, J = 8.2 Hz, 2.4 Hz, 1H), 6.88 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.00 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8 (d, $^1J_{C\text{-}F}$ = 239.0 Hz), 148.7 (d, $^2J_{C\text{-}F}$ = 82.0 Hz), 148.2, 135.1 (d, $^3J_{C\text{-}F}$ = 21.0 Hz), 134.0, 130.3, 129.7, 129.2, 128.4 (d, $^4J_{C\text{-}F}$ = 11.0 Hz), 124.7, 121.8, 115.9, 113.3, 113.0, 112.5, 112.4, 109.4 (d, $^2J_{C\text{-}F}$ = 90.0 Hz), 105.1 (d, $^3J_{C\text{-}F}$ = 25.0 Hz), 101.8, 87.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{13}ClFN_2O_2$ $[M + H]^+$ 391.0650 and 393.0620, found 391.0645 and 393.0614.

2-(4-(Dimethylamino)phenyl)-1-(pyridin-3-yl)-1*H*-indole-3,5-dicarbonitrile (74f).



Obtained from enaminonitrile **73f**, pale yellow solid (80.5 mg, 74%): mp 245-247 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2907, 2222, 2210, 1482, 1233, 827; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 4.0 Hz, 1H), 8.60 (br s, 1H), 8.11 (s, 1H), 7.58 (dt, J = 3.6 Hz, 1.6 Hz, 1H), 7.50 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.46 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 7.24 (s, 1H), 7.19 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 2.99 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 151.0, 150.2, 149.0, 139.1, 135.5, 133.5, 131.1, 128.2, 127.3, 124.5, 124.4, 119.4, 115.5, 113.5, 111.9, 111.8, 106.8, 86.9, 40.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_5$ $[M + H]^+$ 364.1562, found 364.1562.

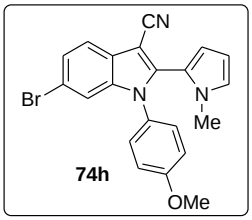
5-Chloro-2-(furan-2-yl)-1-(3,4,5-trimethoxyphenyl)-1*H*-indole-3-carbonitrile (74g).



Obtained from enaminonitrile **73g**, off-white solid (101.5 mg, 83%): mp 245-247 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2969, 2207, 1479, 1253, 825; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.22 (dd, J = 8.6 Hz, 1.6 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.55 (s, 2H), 6.42 (dd, J = 3.6 Hz, 1.8 Hz, 1H), 6.19 (d, J = 3.6 Hz, 1H), 3.97 (s, 3H), 3.82 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.3, 144.6, 143.5, 139.3, 137.76, 136.83, 132.0, 129.1, 128.7, 125.3, 119.1, 115.6, 112.8, 112.6, 112.0, 105.6,

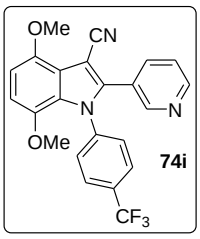
84.2, 61.3, 56.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}ClN_2O_4$ $[M + H]^+$ 409.0955 and 411.0926, found 409.0951 and 411.0924.

6-Bromo-1-(4-methoxyphenyl)-2-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-indole-3-carbonitrile



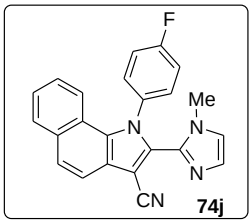
(74h). Obtained from enaminonitrile **73h**, pale yellow solid (101.5 mg, 78%): mp 165-167 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2831, 2206, 1479, 1253, 803; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 6.93 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.81 (t, J = 2.0 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 4.4 Hz, 1.2 Hz, 1H), 6.06 (dd, J = 4.4 Hz, 2.4 Hz, 1H), 4.11 (s, 3H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.0, 158.9, 149.1, 140.0, 134.9, 132.9, 130.2, 127.4, 124.1, 122.8, 121.6, 118.1, 117.8, 115.7, 109.2, 56.0, 38.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}BrN_3O$ $[M + H]^+$ 406.0555 and 408.0535, found 406.0547 and 408.0529.

4,7-Dimethoxy-2-(pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-indole-3-carbonitrile



(74i). Obtained from enaminonitrile **73i**, off-white solid (95.3 mg, 76%): mp 98-100 °C; R_f 0.6 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2950, 2218, 1466, 1245, 840; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.46 (br s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.34-7.28 (m, 3H), 6.67 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 4.0 (s, 3H), 3.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.5, 150.4, 147.7, 143.9, 141.9, 141.2, 137.5, 131.0, 130.7, 129.6, 128.0, 125.5 (q, $J_{C\text{-}F}$ = 4.0 Hz), 125.1, 123.7, 119.3, 116.2, 106.9, 102.7, 88.3, 56.3, 56.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{17}F_3N_3O_2$ $[M + H]^+$ 424.1273, found 424.1267.

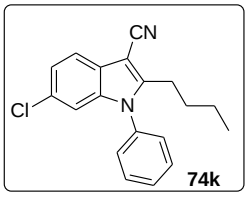
1-(4-Fluorophenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-1*H*-benzo[*g*]indole-3-carbonitrile



(74j). Obtained from enaminonitrile **73j**, off-white solid (87.6 mg, 80%): mp 174-176 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 2985, 2209, 1483, 1278, 838; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.48-7.40 (m, 3H), 7.28-7.24 (m, 1H), 7.19 (t, J = 8.4 Hz, 2H), 7.09 (d, J = 8.8 Hz, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{C\text{-}F}$ = 249.0 Hz), 135.2, 134.60, 134.57, 132.7, 131.8, 130.9 (d, $^4J_{C\text{-}F}$ = 9.0 Hz), 130.1, 129.7, 126.0 (d,

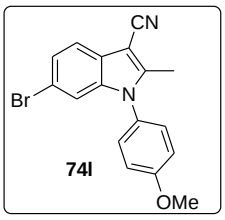
$^{2}J_{C\text{-}F}$ = 92.0 Hz), 125.2, 124.6, 122.7, 122.3, 120.9, 118.3, 116.8 (d, $^{3}J_{C\text{-}F}$ = 23.0 Hz), 115.1, 92.0, 34.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{16}FN_4$ $[M + H]^+$ 367.1359, found 367.1353.

2-Butyl-6-chloro-1-phenyl-1*H*-indole-3-carbonitrile (74k). Obtained from enaminonitrile



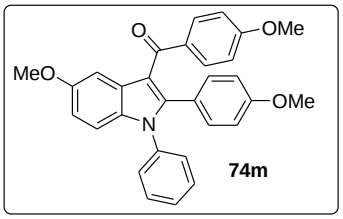
73k, yellow semisolid (69.4 mg, 75%): R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2832, 2209, 1479, 1253, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.58 (m, 4H), 7.33-7.31 (m, 2H), 7.24 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.0 (d, *J* = 1.6 Hz, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 1.55-1.47 (m, 2H), 1.34-1.22 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 151.3, 138.0, 135.7, 130.3, 129.8, 129.7, 128.1, 125.6, 123.3, 120.0, 115.9, 111.3, 86.4, 31.1, 26.2, 22.3, 13.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}ClN_2$ $[M + H]^+$ 309.1159 and 311.1129, found 309.1158 and 311.1129.

6-Bromo-1-(4-methoxyphenyl)-2-methyl-1*H*-indole-3-carbonitrile (74l). Obtained from



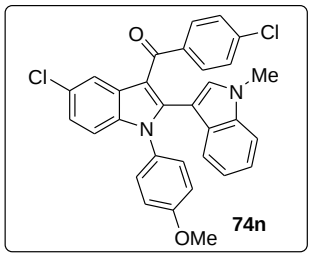
enaminonitrile **73l**, white solid (87.6 mg, 76%): mp 128-130 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 2989, 2219, 1515, 1245, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4 Hz, 1.4 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 1.4 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 2.41 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 147.2, 138.5, 129.0, 128.1, 125.8, 120.3, 117.1, 115.9, 115.5, 114.3, 86.5, 55.8, 12.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}BrN_2O$ $[M + H]^+$ 341.0290 and 343.0269, found 341.0283 and 343.0263.

(5-Methoxy-2-(4-methoxyphenyl)-1-phenyl-1*H*-indol-3-yl)(4-methoxyphenyl)methanone (74m). Obtained from enaminone **73m**, off-white solid (87.3 mg, 63%): mp 128-130 °C; R_f

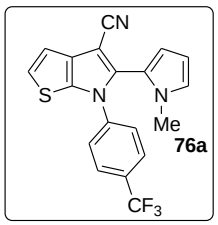


0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2921, 1732, 1488, 1261, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.40-7.34 (m, 3H), 7.19-7.18 (m, 2H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.88 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 192.4, 163.0, 162.4, 159.5, 156.3, 144.9, 137.7, 133.4, 132.7, 132.0, 131.9, 129.6, 129.5, 128.6, 128.5, 128.0, 127.8, 114.0, 113.9, 113.4, 113.1, 56.0, 55.5, 55.3; HRMS (ESI) *m/z* calcd for $C_{30}H_{26}NO_4$ $[M + H]^+$ 464.1862, found 464.1856.

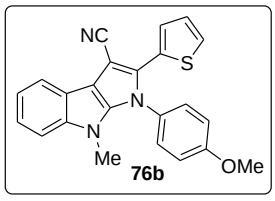
(5-Chloro-1-(4-methoxyphenyl)-2-(1-methyl-1*H*-indol-3-yl)-1*H*-indol-3-yl)(4-chlorophenyl)methanone (74n). Obtained from enaminone **73n**, yellow solid (115.0 mg, 73%): mp 152-154 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2917, 1762, 1585, 1250, 902; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81-8.79 (m, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.42-.41 (m, 1H), 7.39-7.29 (m, 4H), 7.23-7.16 (m, 5H), 7.08 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.5, 169.5, 157.6, 150.0, 142.8, 141.4, 138.6, 136.8, 134.9, 133.6, 133.5, 129.1, 129.0, 128.4, 128.1, 127.1, 126.2, 123.0, 122.9, 121.6, 121.0, 113.1, 109.63, 109.59, 109.0, 55.2, 32.9; HRMS (ESI) *m/z* calcd for $C_{31}H_{23}Cl_2N_2O_2$ $[M + H]^+$ 525.1137 and 527.1107, found 525.1131 and 527.1106.



5-(1-Methyl-1*H*-pyrrol-2-yl)-6-(4-(trifluoromethyl)phenyl)-6*H*-thieno[2,3-*b*]pyrrole-4-carbonitrile (76a). Obtained from enaminonitrile **75a**, off-white solid (91.7 mg, 83%): mp 95-97 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2932, 2217, 1416, 1322, 847; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 5.2 Hz, 1H), 7.07 (d, J = 5.2 Hz, 1H), 6.71 (dd, J = 2.4 Hz, 1.6 Hz, 1H), 6.31(dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.19 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 3.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.5, 137.6, 136.9, 130.8, 130.1, 129.8, 127.1 (q, $J_{C\text{-}F}$ = 4.0 Hz), 125.2, 124.0, 120.9, 120.6, 117.3, 115.7, 114.4, 109.2, 90.8, 34.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{13}F_3N_3S$ $[M + H]^+$ 372.0782, found 372.0770.

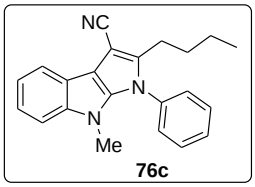


1-(4-Methoxyphenyl)-8-methyl-2-(thiophen-2-yl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (76b). Obtained from enaminonitrile **75b**, pale yellow solid (91.7 mg, 75%): mp 118-120 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2930, 2186, 1508, 1236, 824; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.92 (m, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.30 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.28-7.25 (m, 2H), 7.24-7.21 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.98 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 3.91 (s, 3H), 3.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0, 140.9, 140.4, 134.6, 131.1, 130.8, 128.3, 128.1, 127.2, 127.0, 122.2, 120.4, 119.4, 117.7, 114.9,



114.3, 109.4, 107.4, 84.2, 55.8, 30.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_3OS$ $[M + H]^+$ 384.1171, found 384.1166.

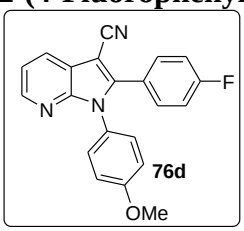
2-Butyl-8-methyl-1-phenyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (76c).



76c

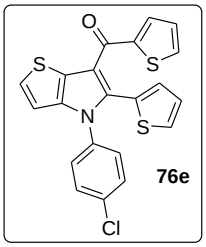
Obtained from enaminonitrile **75c**, pink solid (68.6 mg, 70%): mp 145-147 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2956, 2220, 1464, 1245, 840; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 1H), 7.60-7.59 (m, 3H), 7.45-7.43 (m, 2H), 7.25-7.18 (m, 3H), 3.25 (s, 3H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.45 (quintet, *J* = 7.6 Hz, 2H), 1.26 (sextet, *J* = 7.6 Hz, 2H), 0.80 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.4, 140.3, 139.0, 136.0, 130.0, 129.9, 128.7, 121.5, 120.0, 119.6, 119.0, 117.6, 109.3, 105.8, 83.7, 32.0, 30.2, 26.1, 22.2, 13.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_3$ $[M + H]^+$ 328.1814, found 328.1809.

2-(4-Fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (76d). Obtained from enaminonitrile **75d**, white solid (68.6 mg, 86%): mp 122-124 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 2982, 2209, 1483, 1278, 874; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 8.13 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.44-7.40 (m, 2H), 7.31 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.08 (t, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{C\text{-}F}$ = 250.0 Hz), 159.6, 148.5, 146.9, 132.0, 131.9, 129.4, 127.9, 127.7, 124.53, 124.50, 120.3, 119.0, 116.2, 116.0, 115.6, 114.8, 85.0, 55.5; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}FN_3O$ $[M + H]^+$ 344.1199, found 344.1199.



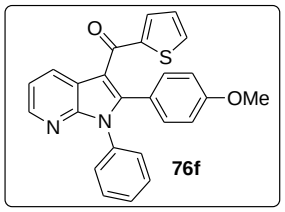
76d

(4-(4-Chlorophenyl)-5-(thiophen-2-yl)-4*H*-thieno[3,2-*b*]pyrrol-6-yl)(thiophen-2-yl)methanone (76e). Obtained from enaminone **75e**, pale yellow solid (86.4 mg, 68%): mp 166-168 °C; R_f 0.5 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2922, 1728, 1488, 1261, 883; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.54 (m, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.271-7.269 (m, 1H), 7.24-7.21 (m, 3H), 6.94-6.91 (m, 2H), 6.84 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 6.82 (d, *J* = 5.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.4, 144.5, 144.3, 136.8, 134.2, 133.9, 133.03, 133.0, 131.5, 131.4, 129.7, 128.7, 128.3, 127.5, 127.0, 126.7, 125.5, 110.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{13}ClNOS_3$ $[M + H]^+$ 425.9848 and 427.9818, found 425.9844 and 427.9816.



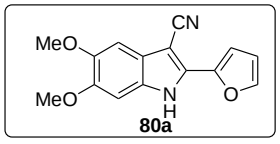
76e

(2-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)(thiophen-2-yl)methanone (76f). Obtained from enaminone **75f**, pale yellow solid (94.7 mg, 77%): mp 126-128 °C; R_f 0.5 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2835, 1650, 1504, 1243, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.35 (d, J = 5.2 Hz, 2H), 7.122-7.05 (m, 3H), 6.99 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.77-6.73 (m, 3H), 6.60 (d, J = 8.8 Hz, 2H), 6.40 (d, J = 3.6 Hz, 1H), 3.68 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.0, 162.3, 158.7, 153.3, 146.7, 145.9, 140.2, 138.3, 134.1, 130.2, 130.0, 127.9, 126.3, 124.9, 123.7, 122.9, 122.0, 113.4, 112.8, 105.9, 54.2 HRMS (ESI) *m/z* calcd for $C_{25}H_{19}N_2O_2S$ $[M + H]^+$ 411.1167, found 411.1160.



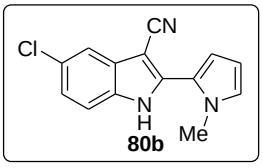
76f

2-(Furan-2-yl)-5,6-dimethoxy-1*H*-indole-3-carbonitrile (80a). Obtained from N-acylenaminonitrile **79a**, brown solid (62.0 mg, 77%): mp 145-147 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3201, 2832, 2219, 1486, 1211, 992; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.51 (s, 1H), 7.17 (d, J = 3.2 Hz, 1H), 7.11 (s, 1H), 6.90 (s, 1H), 6.60 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.9, 147.4, 144.7, 142.8, 134.1, 129.0, 121.4, 116.6, 112.8, 109.7, 100.6, 94.8, 81.7, 56.42, 56.40; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}N_2O_3$ $[M + H]^+$ 269.0926, found 269.0925.



80a

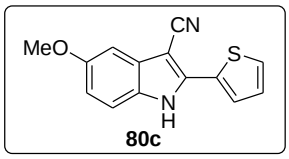
5-Chloro-2-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-indole-3-carbonitrile (80b). Obtained from N-acylenaminonitrile **79b**, off-white solid (54.1 mg, 71%): mp 200-202 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3292, 2209, 1427, 1278, 798; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 6.88 (t, J = 2.0 Hz, 1H), 6.58 (dd, J = 4.0 Hz, 1.6 Hz, 1H), 6.28 (dd, J = 4.0 Hz, 2.8 Hz, 1H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.2, 133.2, 129.7, 128.6, 127.2, 124.9, 122.6, 119.1, 116.2, 113.0, 112.7, 109.6, 85.0, 35.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}ClN_3$ $[M + H]^+$ 256.0642 and 258.0612, found 256.0633 and 258.0604.



80b

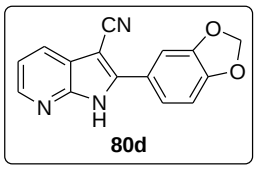
5-Methoxy-2-(thiophen-2-yl)-1*H*-indole-3-carbonitrile (80c).[1a] Obtained from N-acylenaminonitrile **79c**, off-white solid (56.3 mg, 74%): mp 191-193 °C; R_f 0.4 (2:3

EtOAc/hexane); IR (neat, cm^{-1}) 3233, 2981, 2214, 1464, 1219, 819; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.74 (d, J = 3.2 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.18 (t, J = 4.4 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 6.93 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.4, 139.3, 131.5, 129.8, 129.6, 128.7, 127.4, 127.3, 116.8, 115.4, 112.6, 100.8, 83.7, 56.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}N_2OS$ $[M + H]^+$ 255.0592, found 255.0589.



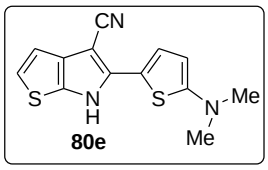
80c

2-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (80d). Obtained from N-acylenaminonitrile **79d**, off-white solid (57.7 mg, 73%): mp 280-282 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3237, 2989, 2218, 1464, 1254, 819; ^1H NMR (400 MHz, DMSO-d_6) δ 13.07 (br s, 1H), 8.39 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.06 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.58 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.16 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 149.1, 148.0, 147.7, 145.6, 145.1, 126.8, 122.6, 122.2, 120.8, 118.2, 116.4, 109.1, 107.2, 101.9, 79.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{10}N_3O_2$ $[M + H]^+$ 264.0773, found 264.0766.



80d

5-(5-(Dimethylamino)thiophen-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-4-carbonitrile (80e). Obtained from N-acylenaminonitrile **79e**, pale yellow solid (52.5 mg, 64%): mp 165-167 °C; R_f 0.6 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3204, 2829, 2216, 1486, 1211, 811; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (br s, 1H), 7.39 (d, J = 5.2 Hz, 1H), 7.36 (d, J = 4.2 Hz, 1H), 7.23 (d, J = 5.2 Hz, 1H), 5.83 (d, J = 4.2 Hz, 1H), 3.01 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.7, 152.4, 146.0, 131.6, 129.3, 129.1, 119.0, 117.1, 116.4, 102.6, 93.7, 42.5; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}N_3S_2$ $[M + H]^+$ 274.0473, found 274.0479.



80e

4.6 References

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47. Since both procedures A ($Pd(OAc)_2$/$Cu(OAc)_2$/DMSO/O_2) and B ($Pd(OAc)_2$/Ag_2CO_3/Pivalic acid/DMSO/O_2) gave nearly comparable yields of indoles **74a-n** (Table 2), only selected examples of hetero fused pyrroles **76** (Table 3) and NH indoles **80** (Table 4) were synthesized by method B.

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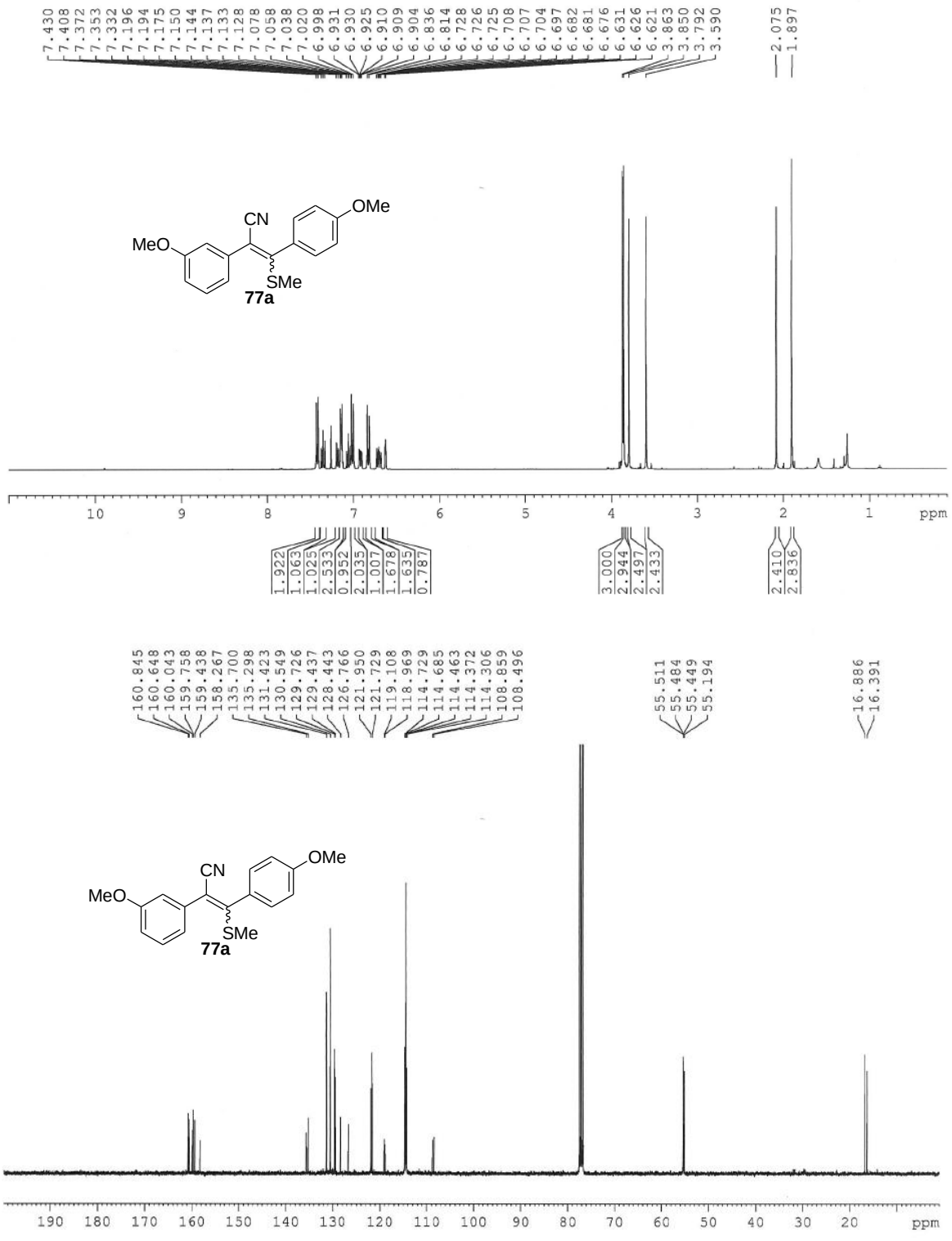
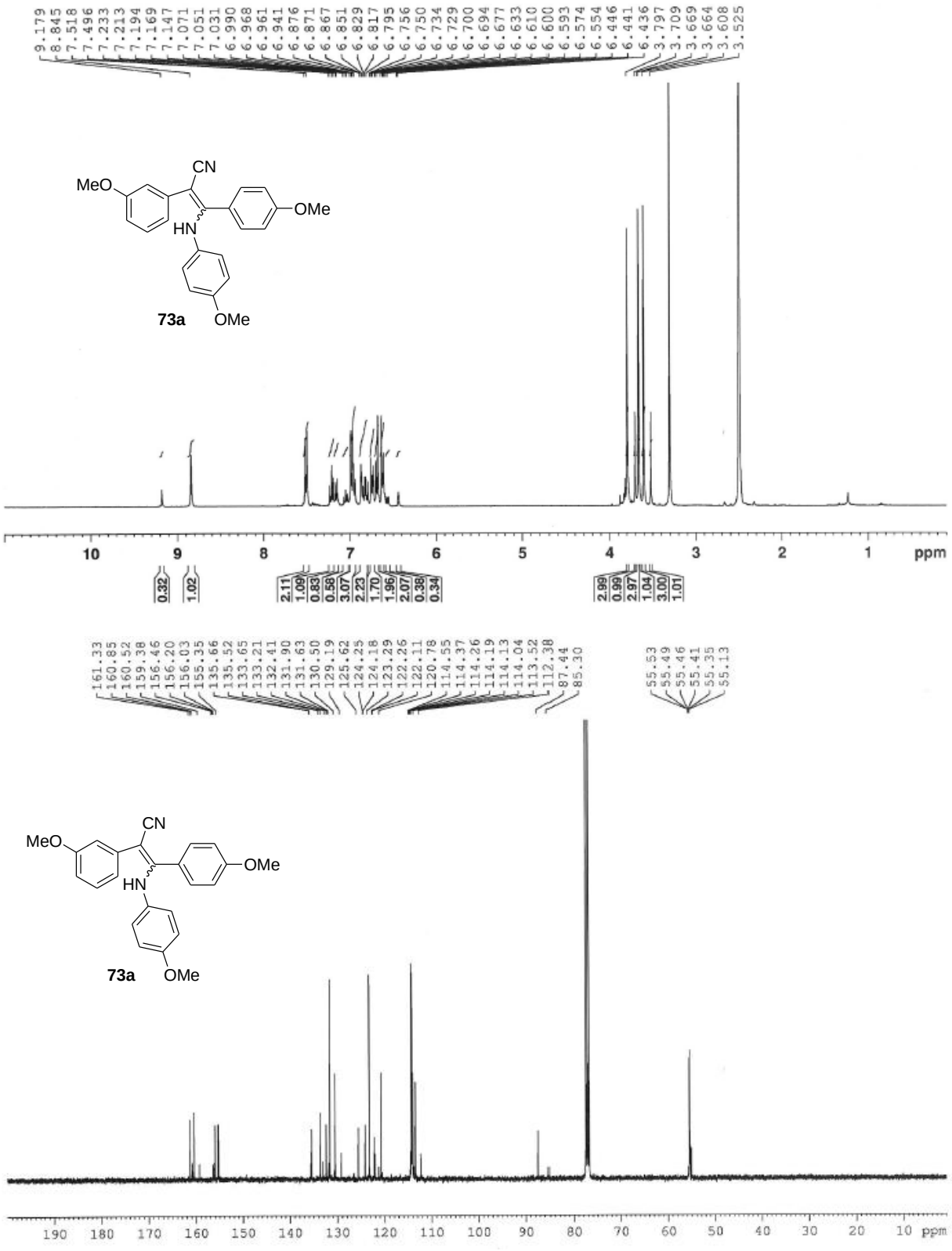
4.7 Representative spectra



^{1}H and ^{13}C NMR Spectra of compound **77a**



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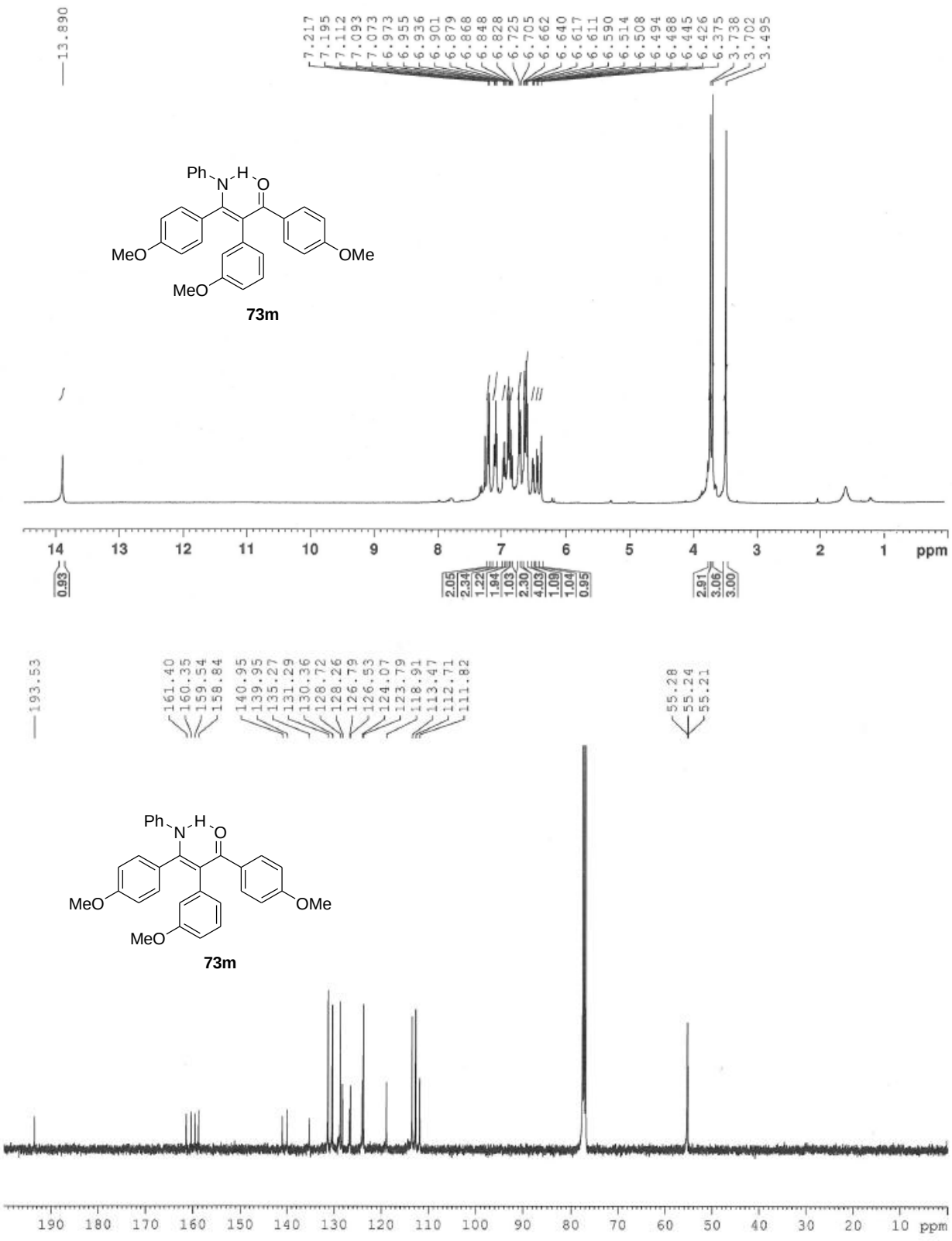

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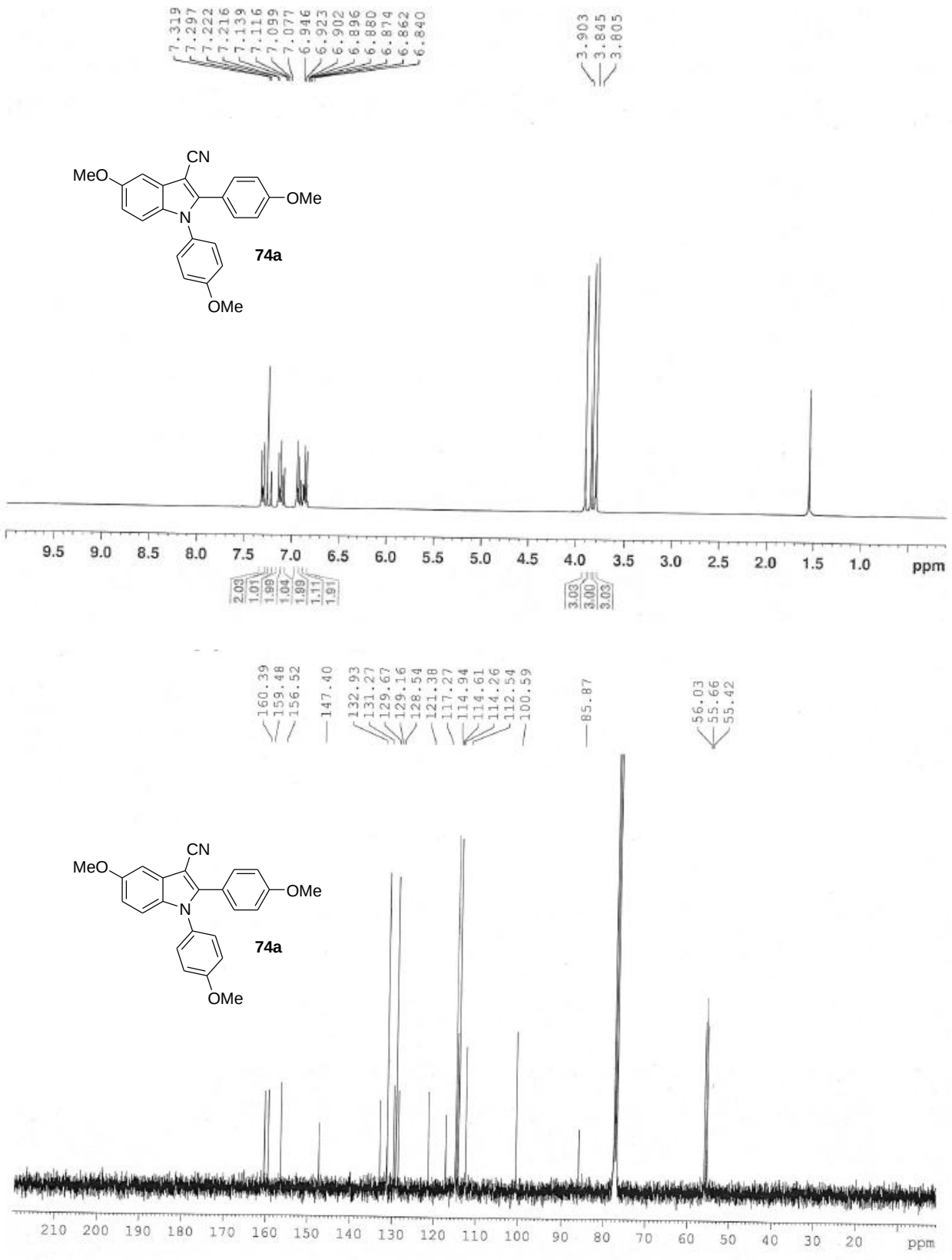

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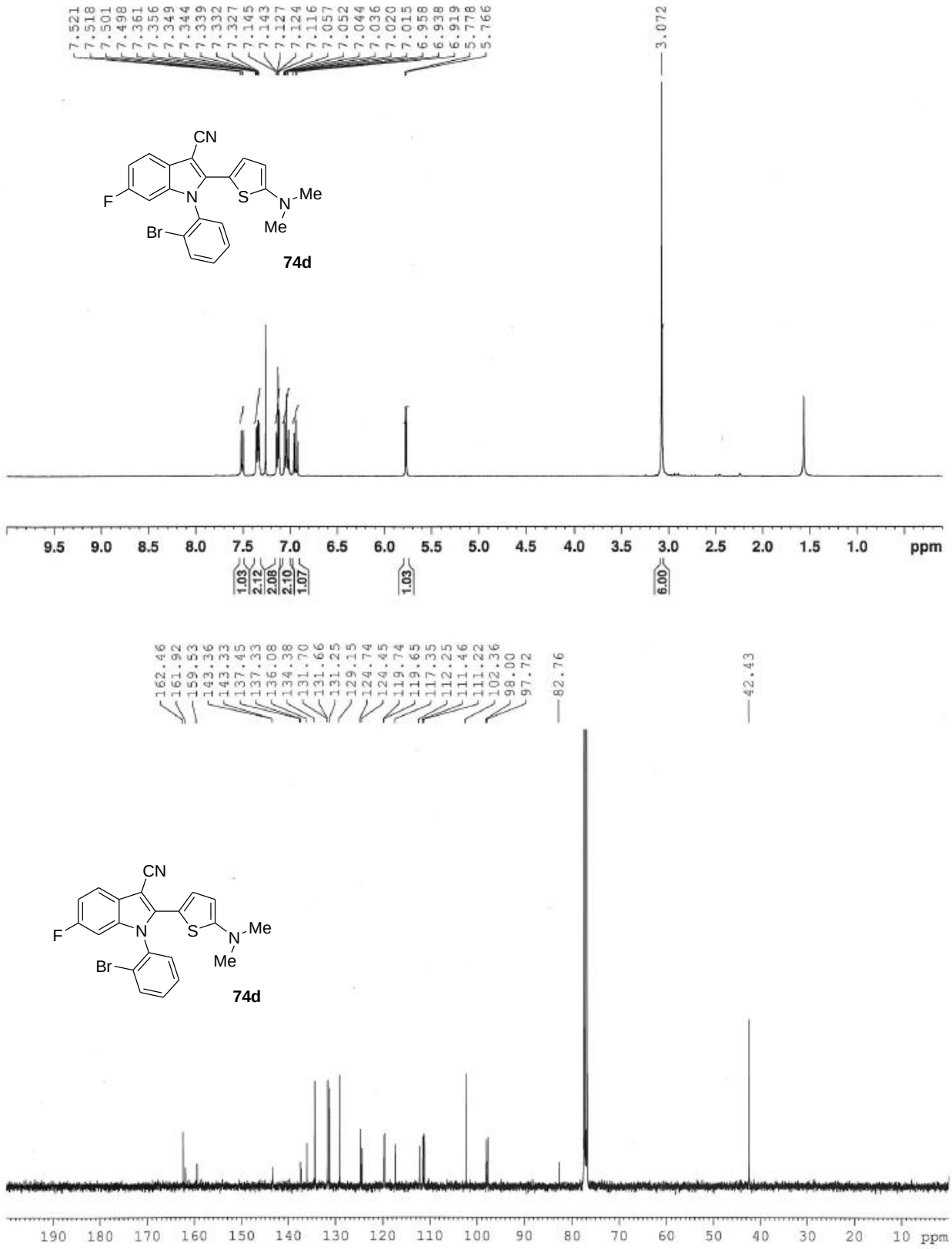
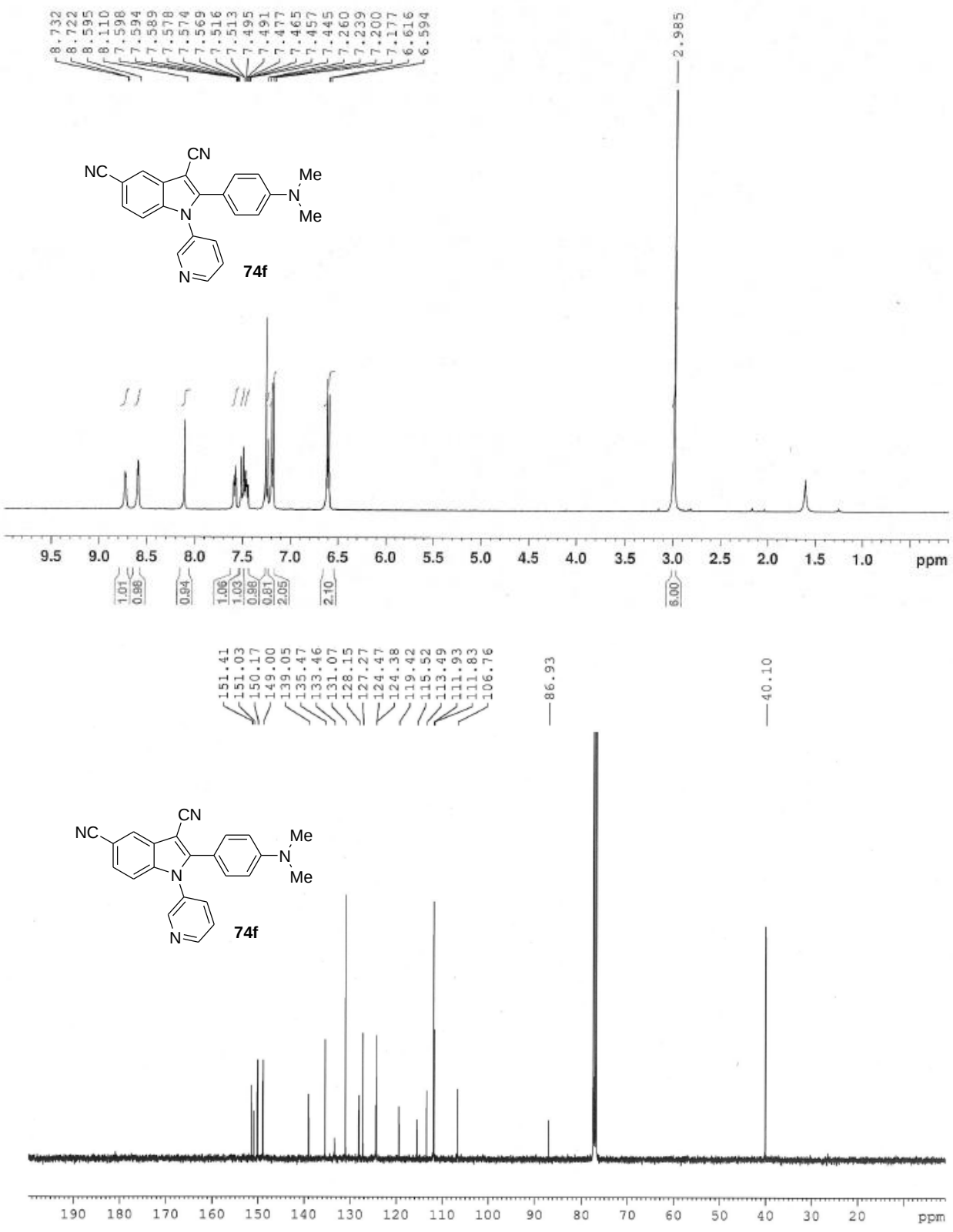


^{1}H and ^{13}C NMR Spectra of compound **74d**



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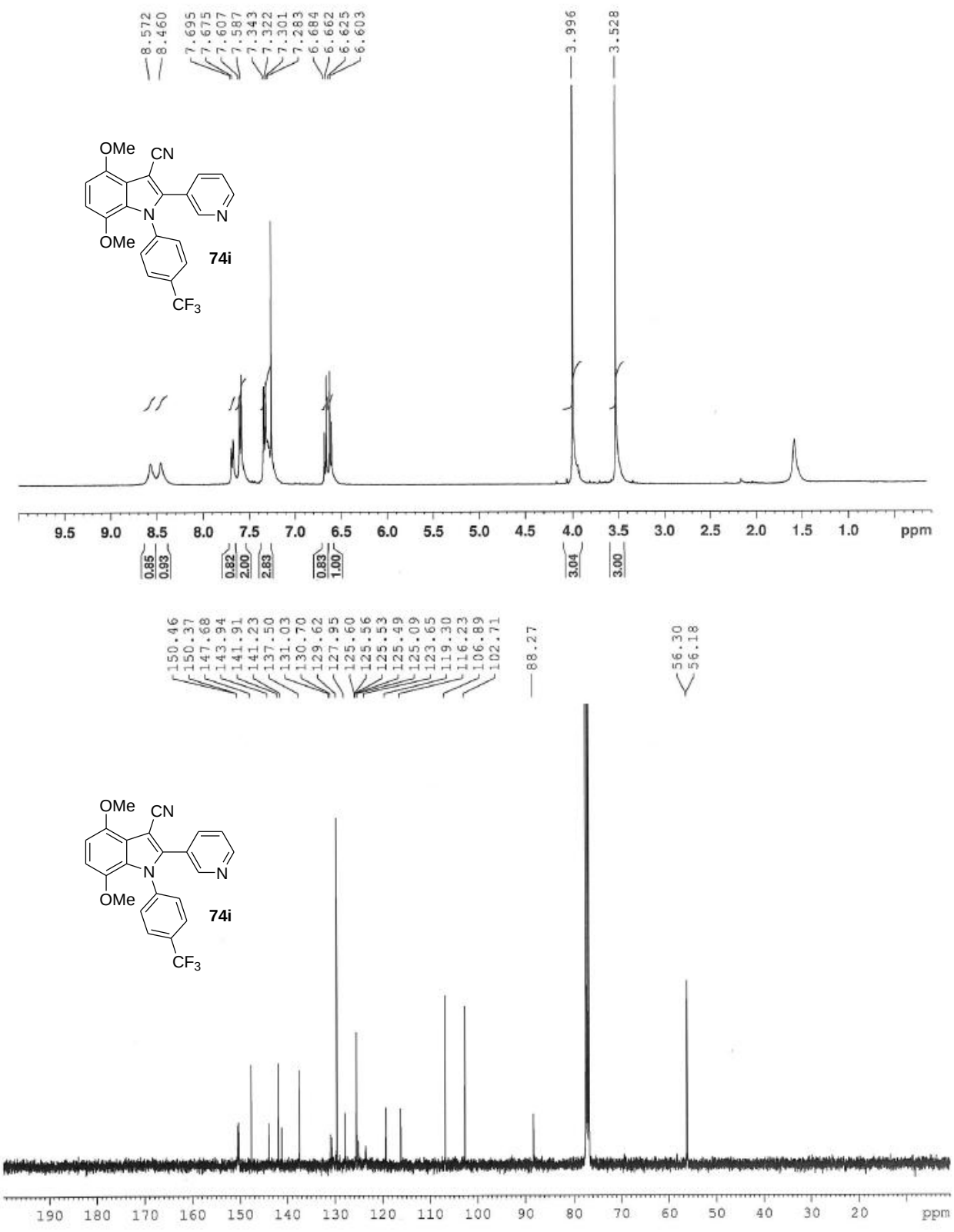

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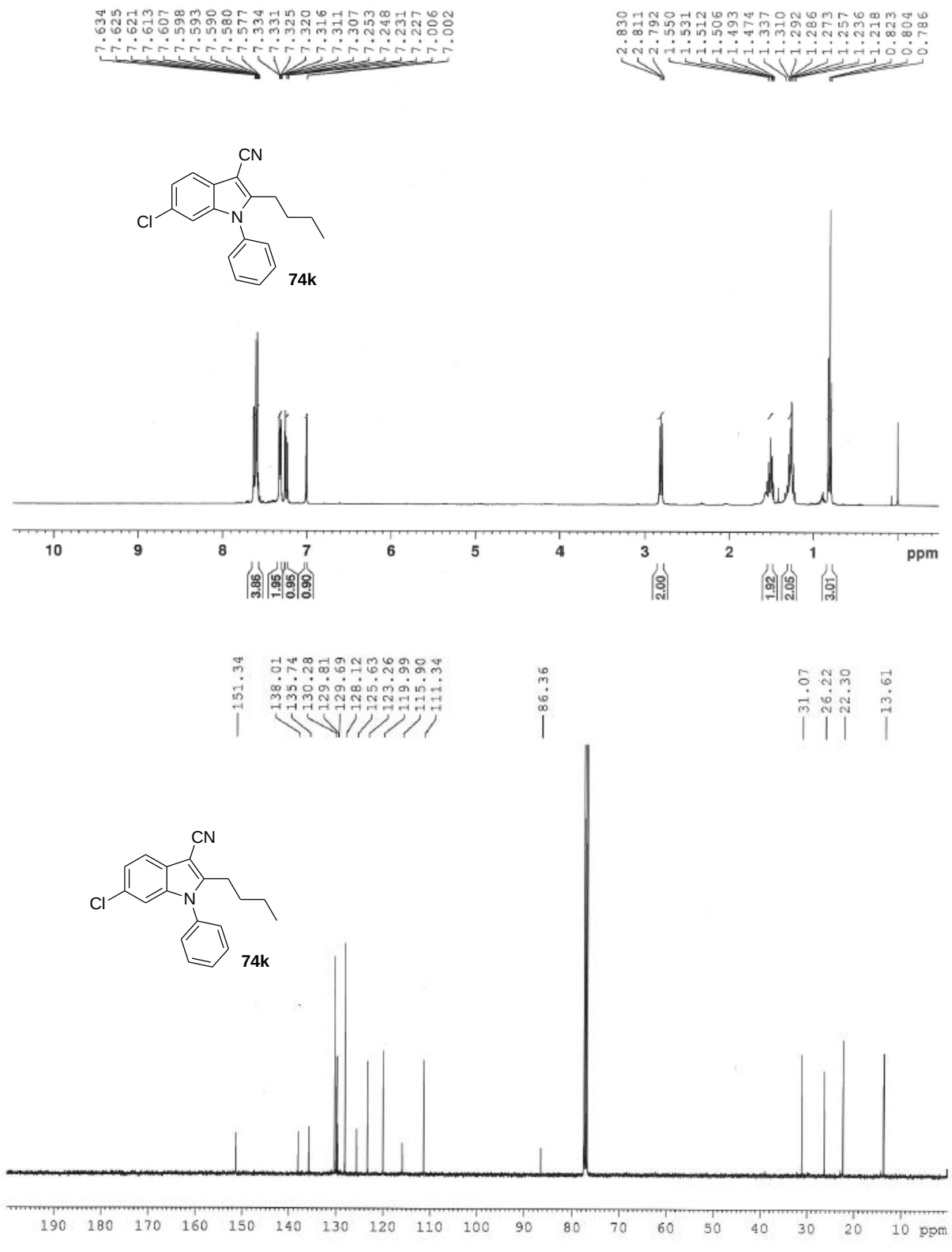

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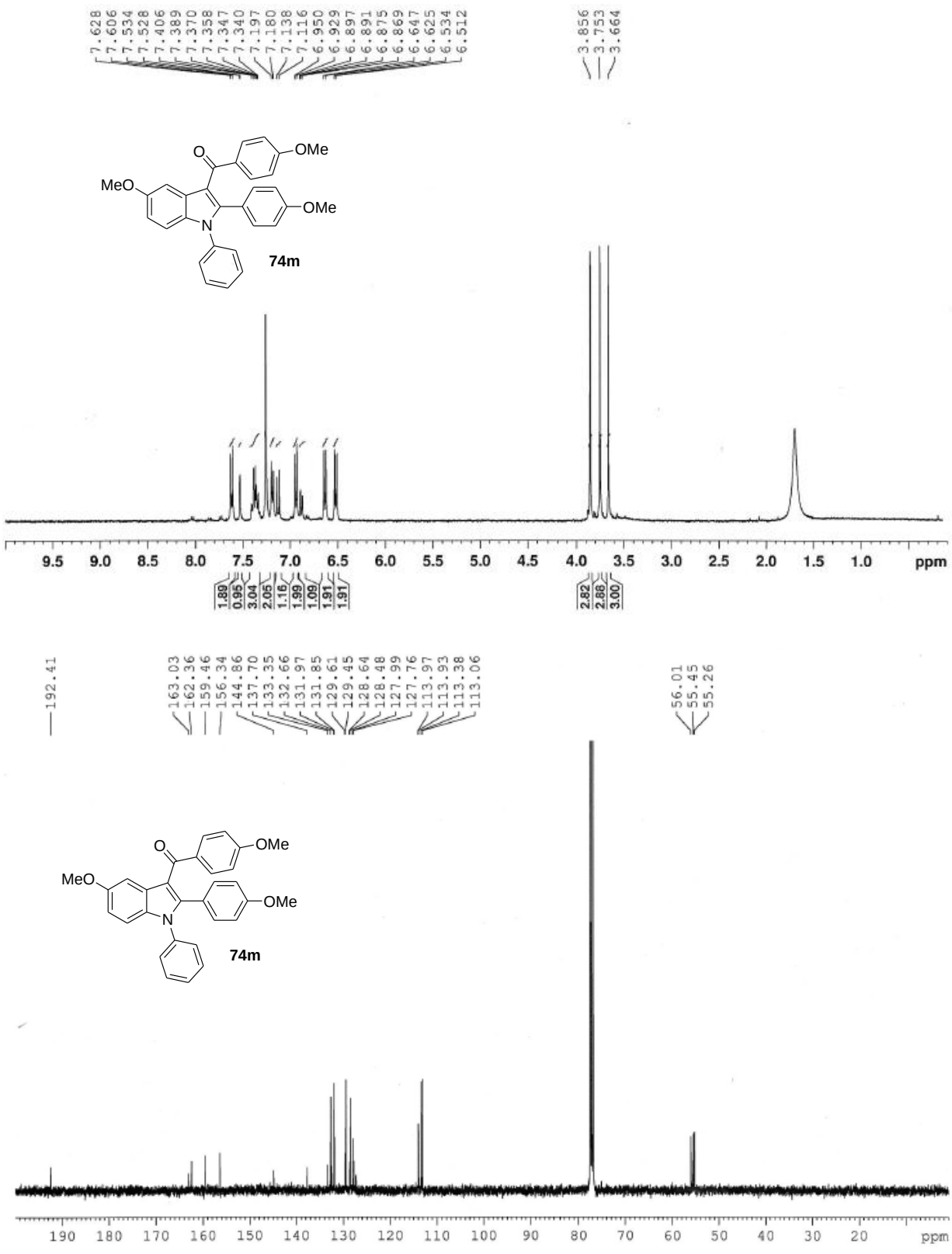
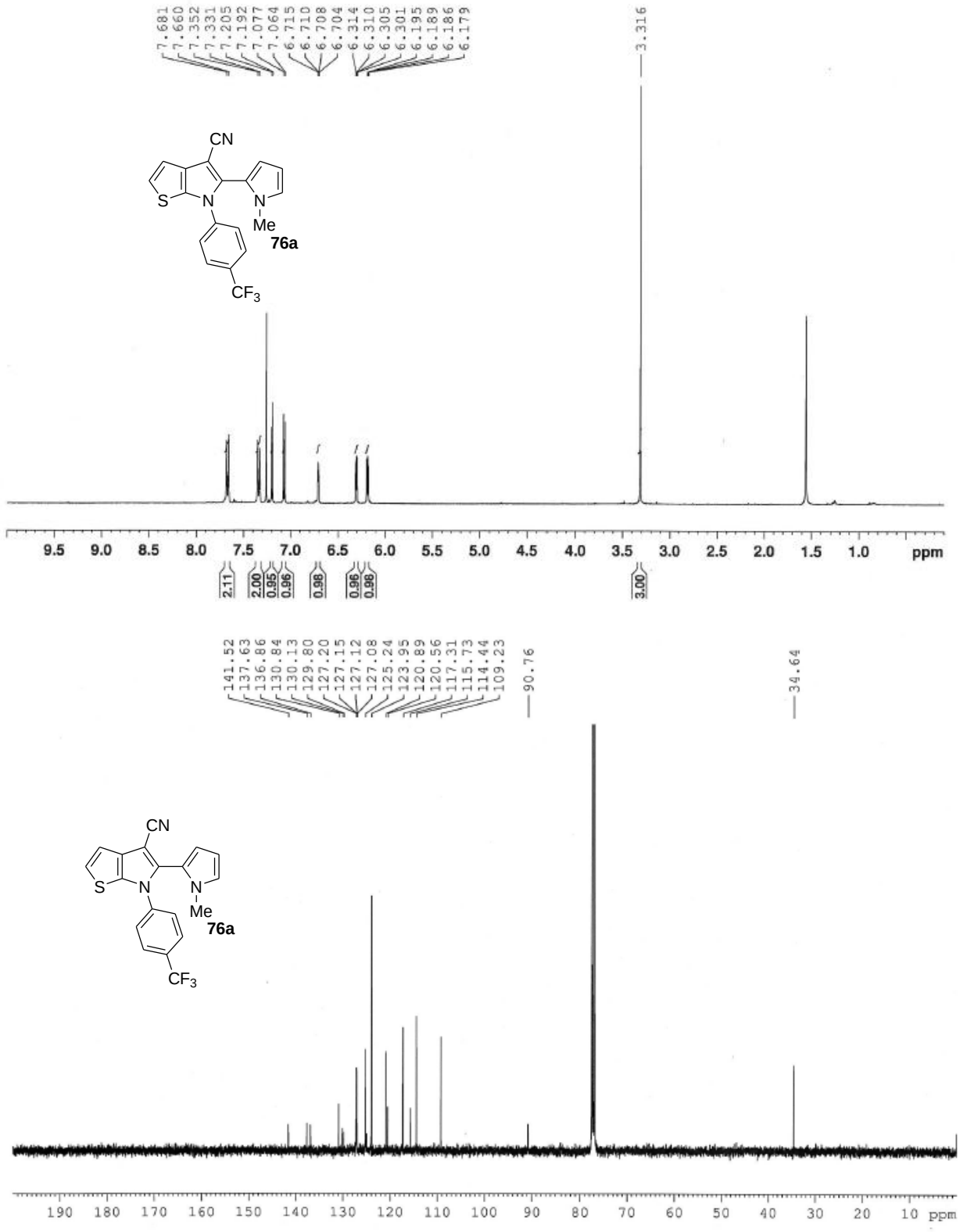
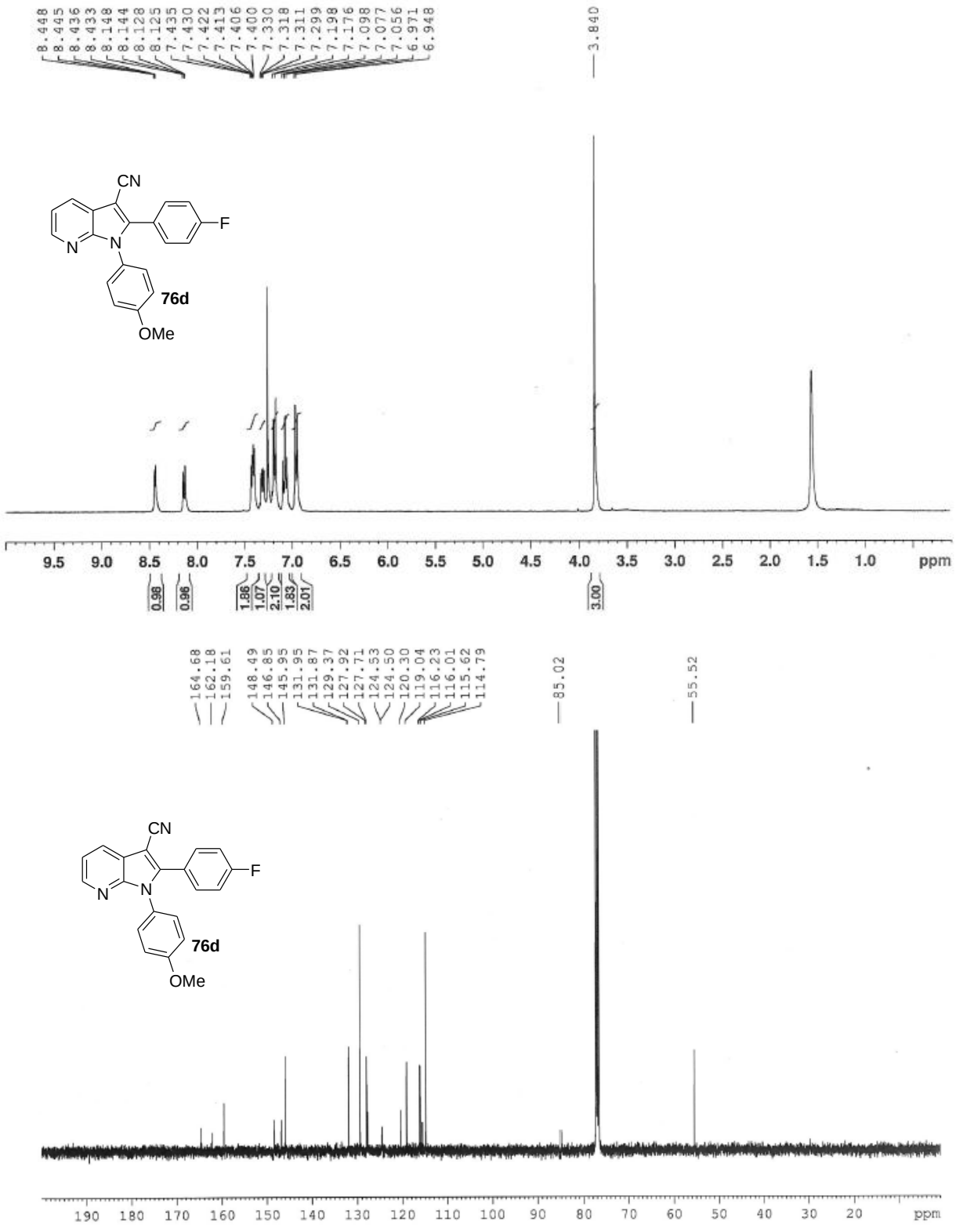


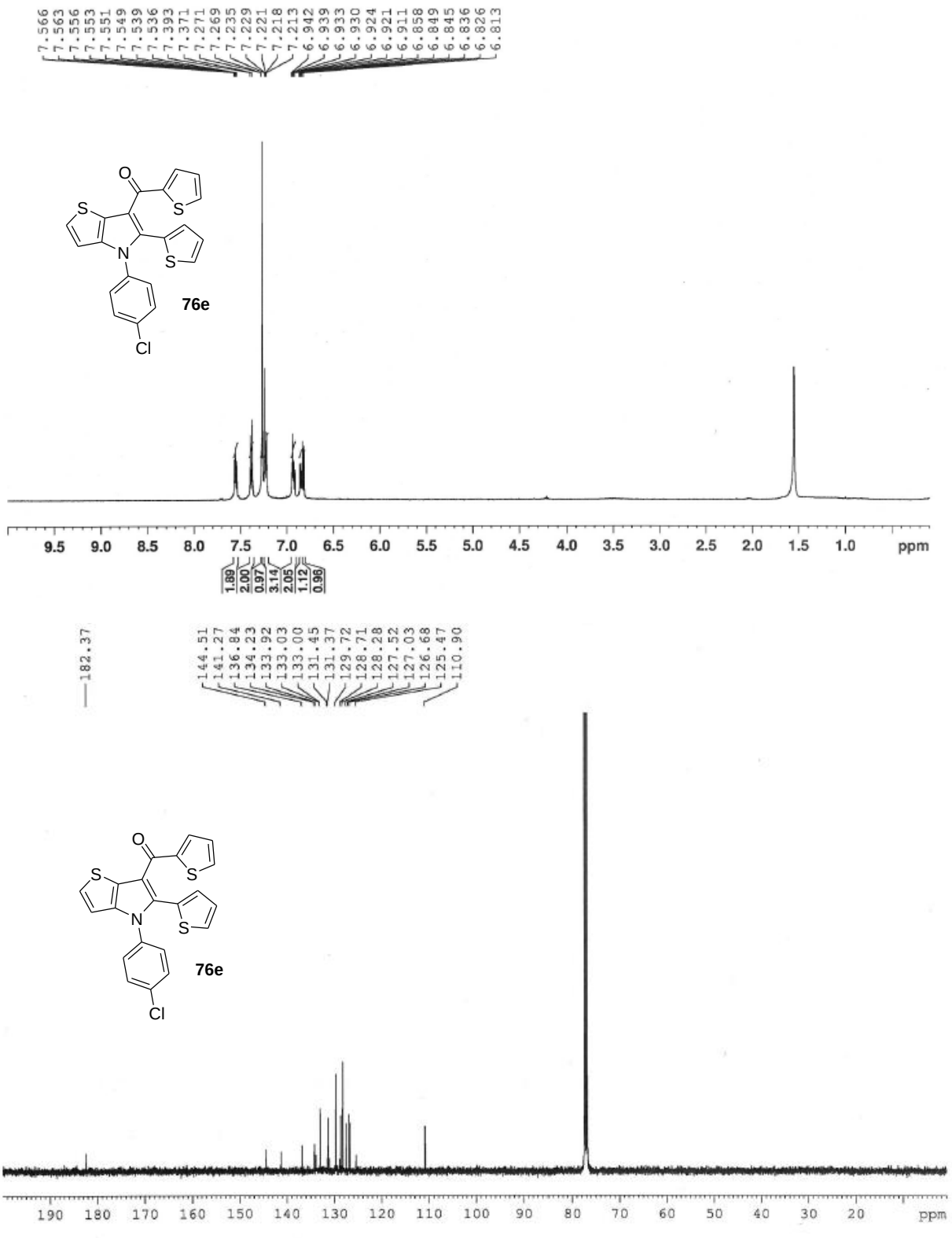
^{1}H and ^{13}C NMR Spectra of compound **74m**



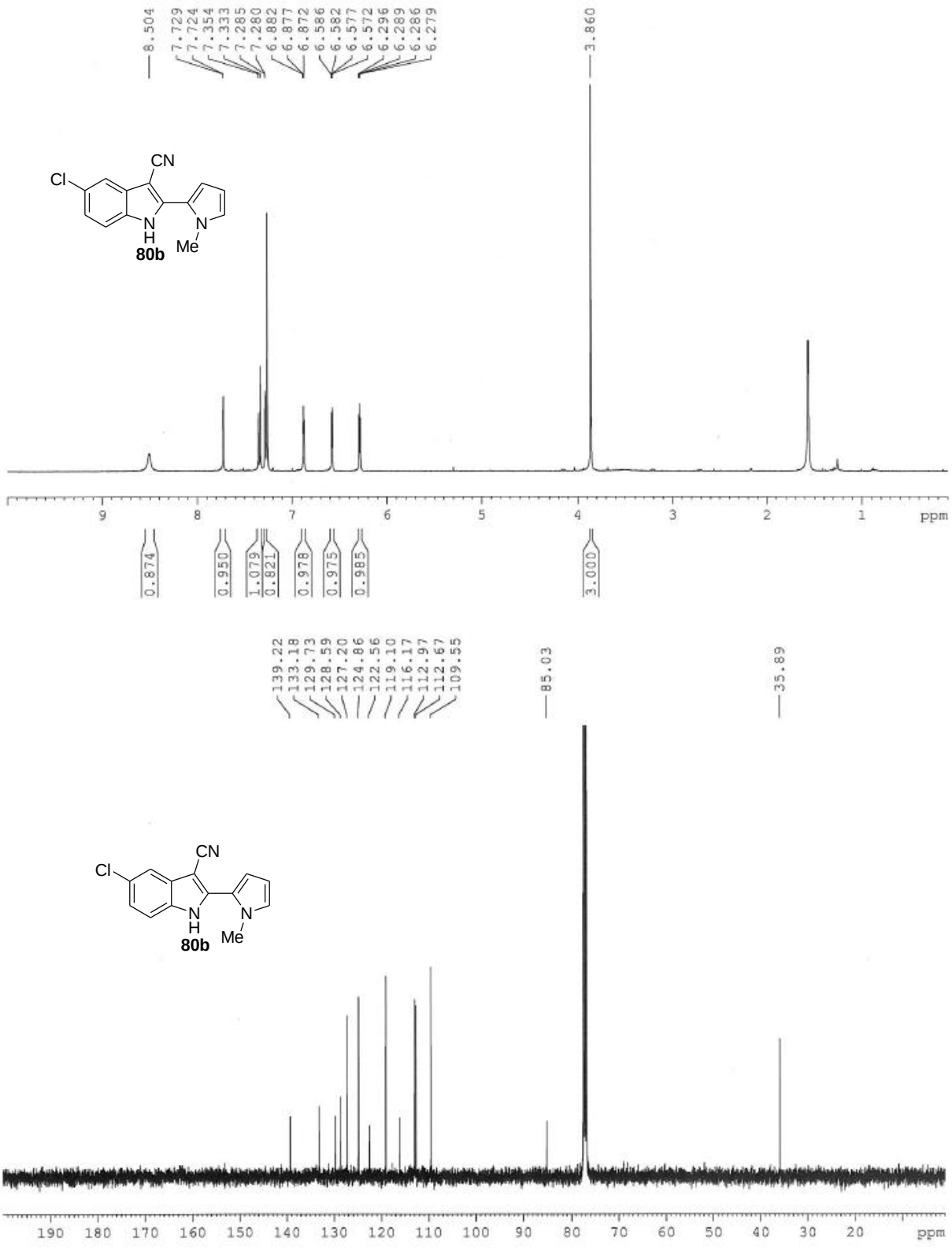
^{1}H and ^{13}C NMR Spectra of compound **76a**



^{1}H and ^{13}C NMR Spectra of compound **76d**



^{1}H and ^{13}C NMR Spectra of compound **76e**



^{1}H and ^{13}C NMR Spectra of compound **80b**

Chapter 5

*One-Pot Three Component Synthesis of 2,4,5-Trisubstituted Imidazoles via [2+2+1] Cycloannulation of 1,3-Bishet(aryl)-monothio-1,3-diketones, α-Substituted Methylamines and Sodium Nitrite through α-Nitrosation of Enaminones**

5.1 Introduction

Imidazole heterocycles are regarded as privileged structural motifs,[1] which are prevalent in several highly significant biomolecules, including essential amino acids, histidine, histamine **1**,[2a] biotin and bioactive natural products such as pilocarpine alkaloids.[1b,2] They also constitute core structure of many therapeutic agents[3a] and marketed drugs such as dacarbazine **2**, cimetidine **3**, metronidazole **4**, losartan **5**,[3]eprosartan **6** (Chart 1).[3] Several of the imidazole derivatives display broad range of biological activities, acting as antibacterial agents,[4a] angiotensin II inhibitors,[4b] antifungal,[4c] anti-inflammatory,[4d] anticancer agents[4e-f] and inhibitors of p[38] MAP kinase (**7**, **8**, **9**) (Chart 1),[4g-h] apart from behaving as plant growth regulators.[4i] Similarly, apoptozole **10**,[4j] a tetra substituted imidazole derivative

*The overall results of study described in this chapter have been published in *J. Org. Chem.* **2016**, *81*, 5606.

has been shown to exhibit high cellular potency for promoting membrane trafficking of mutant CFTR and its chloride channel activity in cystic fibrosis cells (Chart 1).

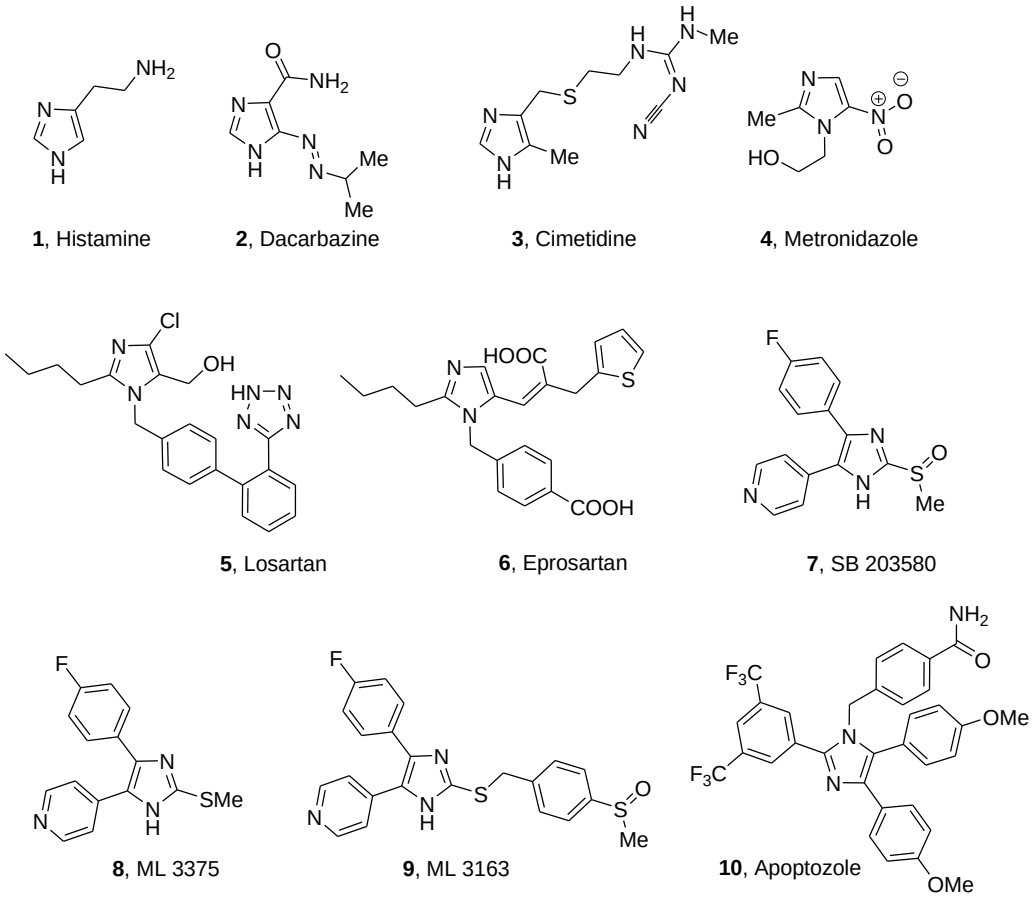
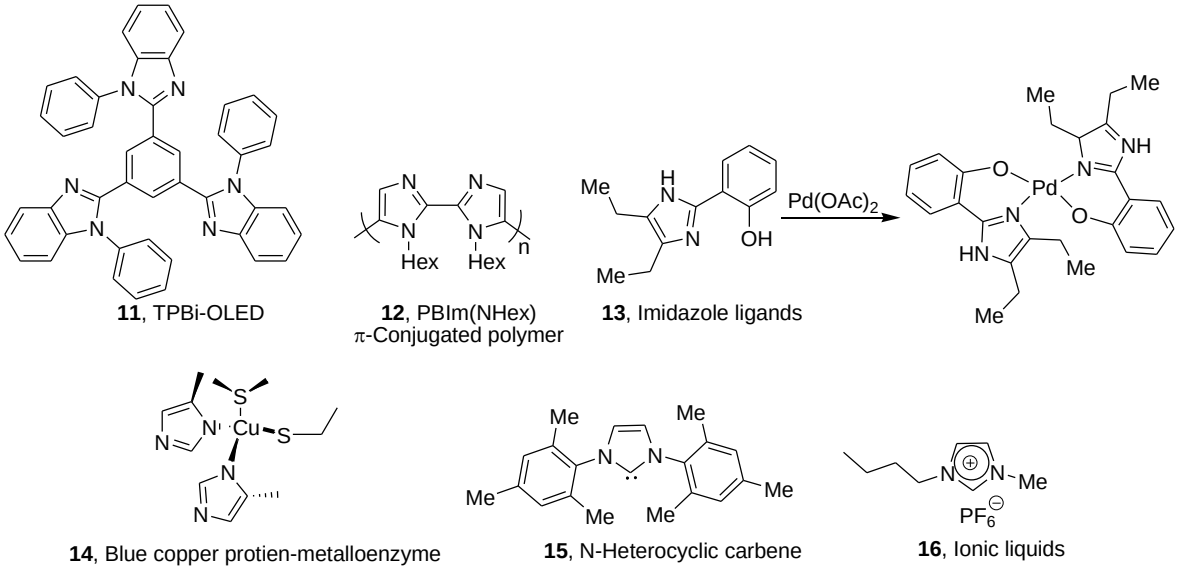


Chart 1: Biologically active imidazole ring containing compounds

Substituted imidazoles have also found applications as functional materials in organic electroluminescent devices (OLED) **11**,[5a-c] conjugated and functional polymers such as **12**,[5d] in coordination chemistry as important ligands like **13**,[6a] metalloenzymes **14**,[6b,c] and non natural metal complexes (**14**)[6d] precursors of stable carbene ligands[7a] and as NHCS (**15**)[7b] and ionic liquids (**16**) (Chart 2).[8] Therefore, a good deal of interest exists in developing new, efficient, atom economical complimentary methods for the synthesis of functionalized tri- and tetrasubstituted imidazoles with absolute regiocontrol.[9-1]

In the present chapter we have reported a one-pot, three step synthesis of 2,4,5-trisubstituted imidazoles via [2+2+1] cycloannulation of 1,3-bishet(aryl)-monothio-1,3-



11, TPBi-OLED

12, PBIm(NHex) π-Conjugated polymer

13, Imidazole ligands

14, Blue copper protien-metalloenzyme

15, N-Heterocyclic carbene

16, Ionic liquids

Chart 2: Some of the important imidazole compounds in various fields of chemistry

diketones, α-substituted methylamines and sodium nitrite through α-nitrosation of enaminones under very mild conditions (Scheme 20).

5.2 Synthesis of Substituted Imidazoles: A Short Literature Survey

Before presenting our work, a short survey of recent methods for imidazole synthesis has been described in the following section. Multicomponent reactions play important role in organic synthesis and are powerful tool for generating molecular complexity and diversity with greater efficiency in a one-pot process from readily available precursors.[11] These reactions also form basis for the synthesis of substituted imidazoles. Thus 2,4,5-tri- and 1,2,4,5-tetrasubstituted imidazoles such as **20** are generally synthesized by three or four component cyclocondensation of either 1,2-diketones **17**,[12,13] α-ketomonooximes **18,** α-hydroxy,[13] acetoxy,[13] or silyloxyketones **19** or nitriles[13e] with aldehydes and ammonium acetate and/or primary amines usually under classical heating or in refluxing acetic acid or lewis acid catalysts (Chart 3). However, these reactions, although effective for certain substrates, sometimes give poor yields of imidazoles, requiring longer reaction time,[13] besides, in four component condensation reactions, imidazoles were obtained in varying level of purity after laborious work-up and purification. Therefore many efforts have been made in recent years to improve the reaction conditions[14] by performing these reactions under microwave,[15a-d] ultrasonic,[15e] or under superheating conditions using continuous flow

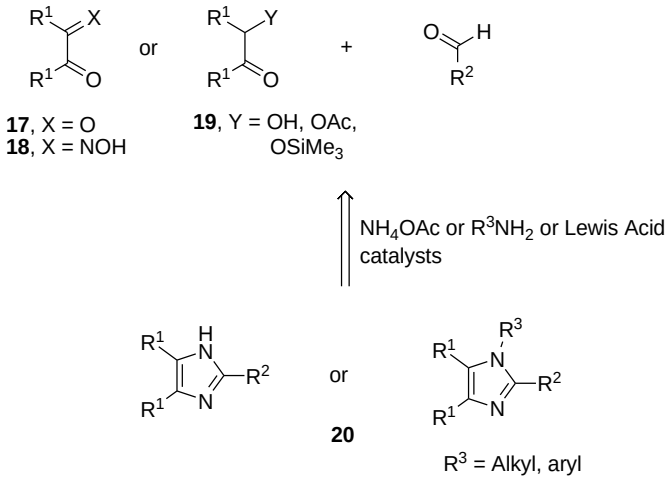


Chart 3: Multicomponent approach to substituted imidazoles

microreactor,[15f] and also in the presence of various Lewis acid catalysts. Thus a large variety of catalysts such as silica gel/zeolite HY, silica gel /$NaHSO_4$ or $HClO_4$-SiO_2, silica supported sulphuric acid, $BF_3.SiO_2$ heteropolyacids, $InCl_3.3H_2O$, $NiCl_2.6H_2O$, Al_2O_3, ceric ammonium nitrate, ionic liquids, molecular iodine or proline have been employed to improve the yields of substituted imidazoles in these reactions.[15g] However, these multicomponent approaches towards substituted imidazoles are usually restricted to fixed pattern of substitution, mostly 4,5- bis(het)arylimidazoles, and do not address the regiochemical problem, as most of the precursors are usually symmetrically substituted diary/(het)arylketones or their analogs furnishing only symmetrically substituted 4,5-diaryl/(het)arylimidazoles.[15-16] Some of the earlier classical methods for imidazole synthesis[15a] include reaction of α-haloketones (**21**, **23**)

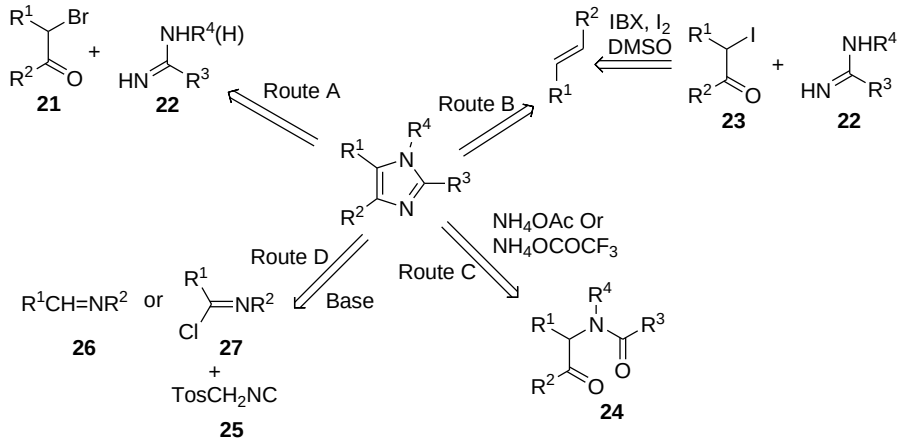
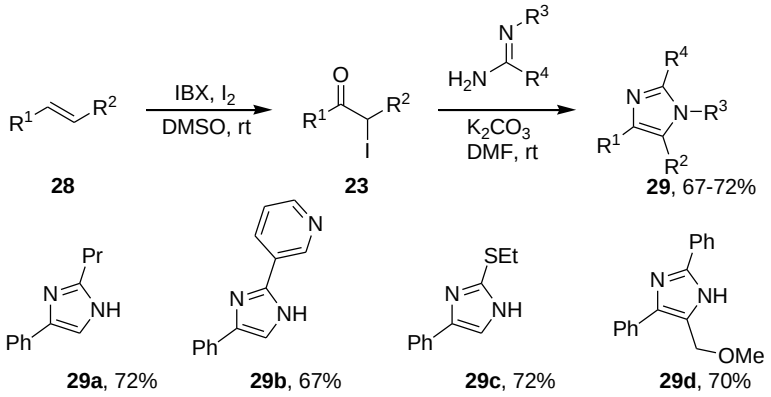


Chart 4: Classical approaches for substituted imidazole synthesis

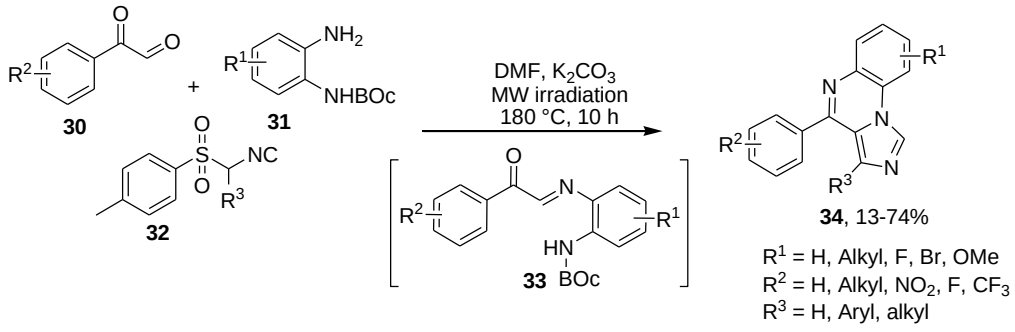
with amidines (**22**) (Route A and B),[16-17] cyclocondensation of *α*-acylaminoketones such as **24** with ammonium acetate (Route C)[18] and base promoted reaction of *p*-tosylmethyl isocyanide **25** with aldimines/imidoyl chloride (**26**, **27**) (Route D) (van Leusen reaction)[19] as shown in the Chart 4.

Thus, Smith and co-workers have reported the synthesis of 2,4,5-trisubstituted imidazoles **29** in a two-step protocol from *α*-iodoketones **23**, which are prepared from alkenes **28** via ketoiodination with IBX, followed by heterocyclization with amidines in the presence of potassium carbonate (Scheme 1).[20]



Scheme 1

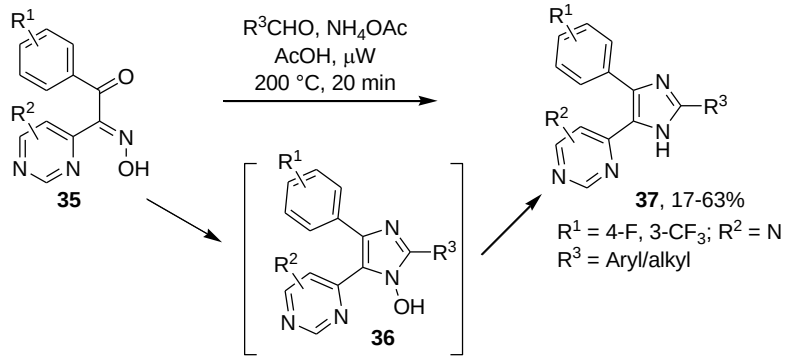
Recently, Hulme and co-workers have reported a one-pot two step multicomponent strategy for the synthesis of imidazo-[1,5-*a*]-quinoxalines **34** from arylglyoxaldehydes **30**, *N*-protected *O*-phenylenediamines **31** and *p*-tosylmethyl isocyanide **32** under base mediated microwave conditions via intermediates of a Schiff base **33** (Scheme 2).[21]



Scheme 2

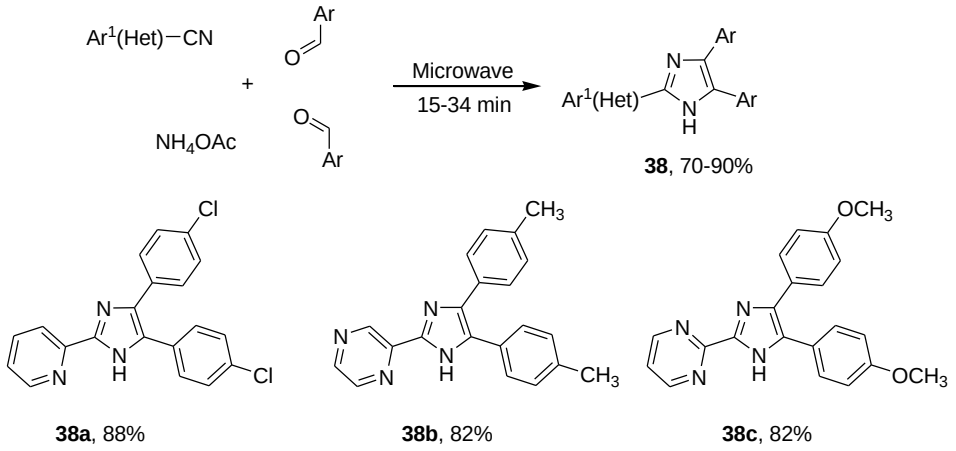
Combs and co-workers have developed an efficient microwave-assisted multicomponent two-step synthesis of 2,4,5-triaryl-imidazoles **37** directly from *α*-ketooximes

35, aldehyde and ammonium acetate. The reaction involves an unprecedented in situ thermal reduction of the N-O bond in the intermediate **36** upon microwave irradiation at 200 °C for 20 min (Scheme 3).[22]



Scheme 3

Li and co-workers have developed a microwave-assisted synthesis of substituted imidazoles such as **38** via four component domino process from heteroaryl nitriles, aromatic aldehydes and ammonium acetate under solvent free microwave-irradiation conditions in very good yields (Scheme 4).[23]

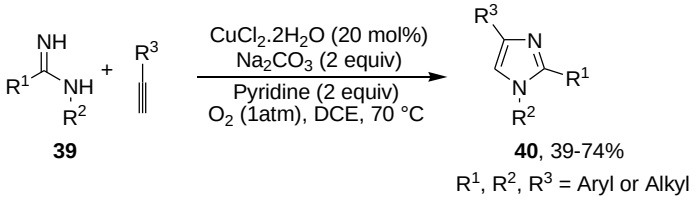


Scheme 4

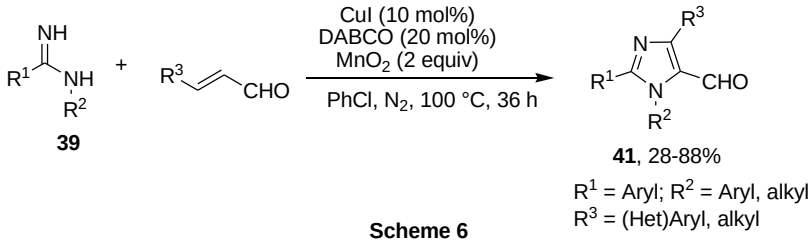
In recent years, transition metal catalyzed reactions have attracted considerable attention for the synthesis of substituted imidazoles. Thus, Neuville and co-workers have recently reported a range of 1,2,4-trisubstitited imidazoles such as **40** via regioselective $CuCl_2.2H_2O$ catalyzed oxidative diamination of terminal alkynes with amidines **39** (Scheme 5).[24]

Recently, Chen and co-workers have developed a practical, atom economical and highly functional group compatible synthesis of 1,2,4,5-tetrasubstitited imidazoles such as **41**, via

copper-catalyzed oxidative coupling of amidine **39** and *α,β*-unsaturated aldehyde using manganese dioxide as oxidant. Preservation of aldehyde functionality in this transformation is note worthy (Scheme 6).[25]

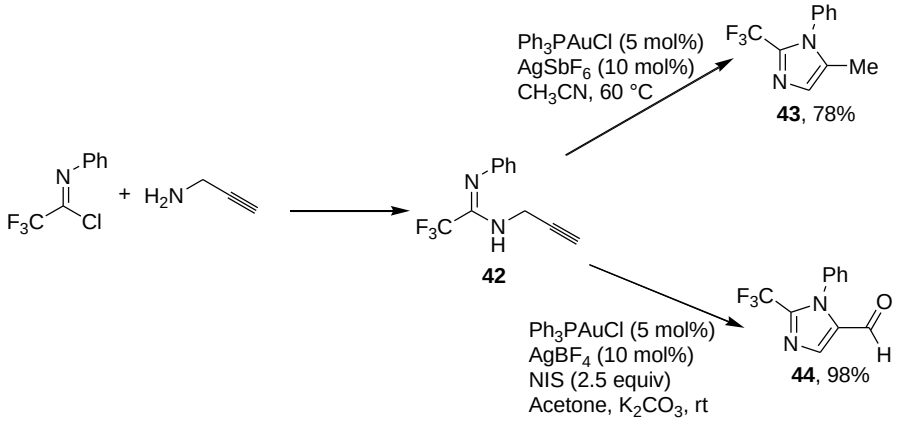


Scheme 5



Scheme 6

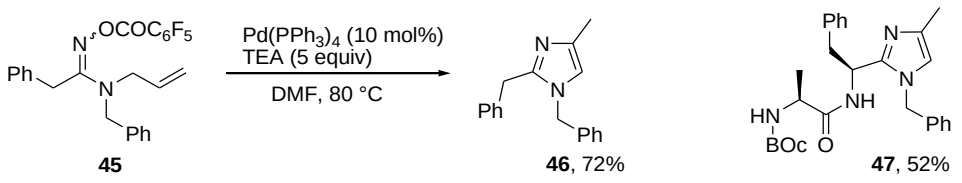
Wu and co-workers have developed the synthesis of *N*-aryl-imidazole derivatives such as **43** and **44** via gold catalysis (Scheme 7). Thus, propargylamidine **42** (prepared from imidoyl chloride and propargyl amine) in presence of gold(I) catalyst undergoes 5-*exo-dig* cyclization to afford imidazole **43**, whereas imidazole-5-carbaldehyde **44** was formed in the presence of gold(I) catalyst and NIS (Scheme 7).[26]



Scheme 7

Abell and co-workers have described a versatile method for the synthesis of 1-benzyl-4-methylimidazoles such as **46** with a range of substituents at 2-position based upon a palladium catalyzed amino Heck reaction of an *O*-pentafluorobenzoylamidoximes **45** on treatment with $Pd(PPh_3)_4$ catalyst and triethylamine (Scheme 8). This sequence has also been

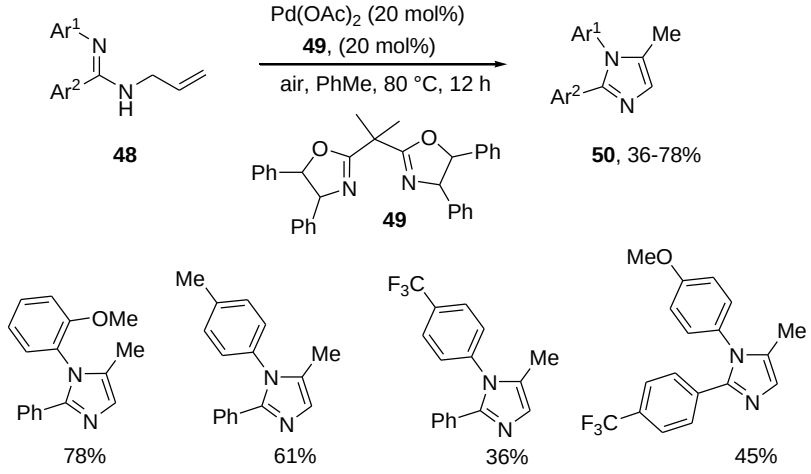
used to prepare optically active amino acid mimitics such as **47** containing C-terminal imidazole (Scheme 8).[27]



45 **46**, 72% **47**, 52%

Scheme 8

Recently, Wang and co-workers have developed a palladium catalyzed Wacker-type intramolecular annulation process for the synthesis of multisubstituted imidazoles such as **50**, from *N*-allylamidine **48** using $Pd(OAc)_2$ catalyst, O_2 as oxidant and **49** as ligand (Scheme 9).[28]



48 **49** **50**, 36-78%

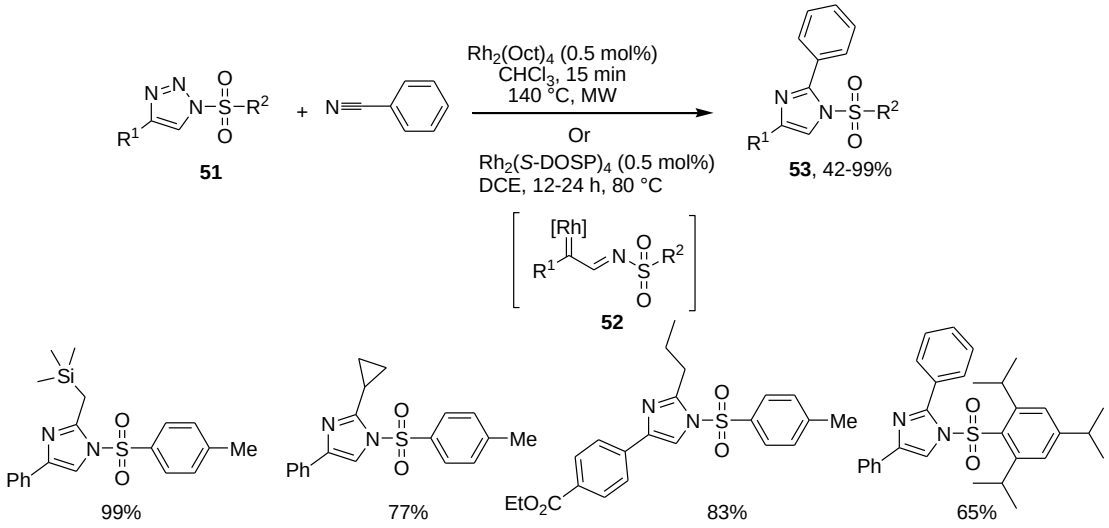
78% 61% 36% 45%

Scheme 9

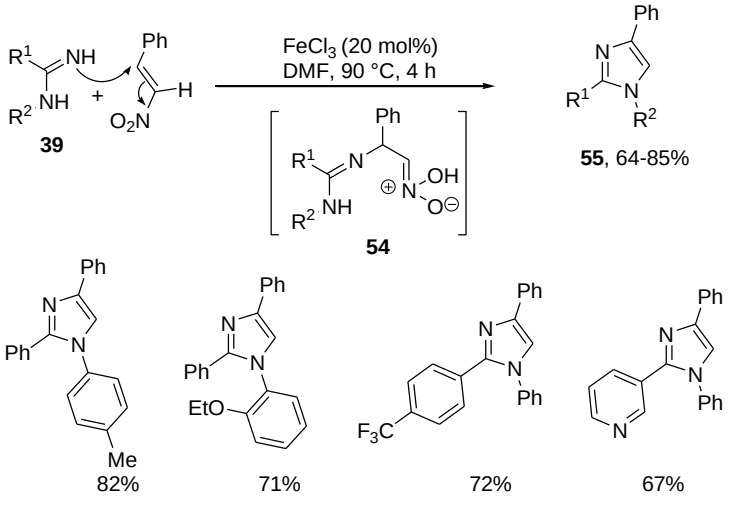
A new highly modular two-step synthesis of substituted imidazoles **53** involving Rh(II) complex catalyzed ring opening of *N*-sulfonyl-1,2,3-triazole **51** has been reported recently by Fokin and co-workers (Scheme 10). The overall reaction involves formation of a Rh-iminocarbenoid **52**, from **51** and its subsequent cycloaddition with various nitriles to afford imidazoles such as **53** (Scheme 10).[29]

Chen and co-workers have recently reported a novel and efficient iron(III)-catalyzed synthesis of substituted imidazoles such as **55**, via [3+2] cycloaddition of nitroolefins and *N*-aryl benzamidines **39** under air atmosphere (Scheme 11). The method is atom-economical, eco-friendly and is shown to be highly regioselectively proceeding through intramolecular

$FeCl_3$ catalyzed Michael addition of amidine **39** to nitroolefin through adduct **54** (Scheme 11).[30]



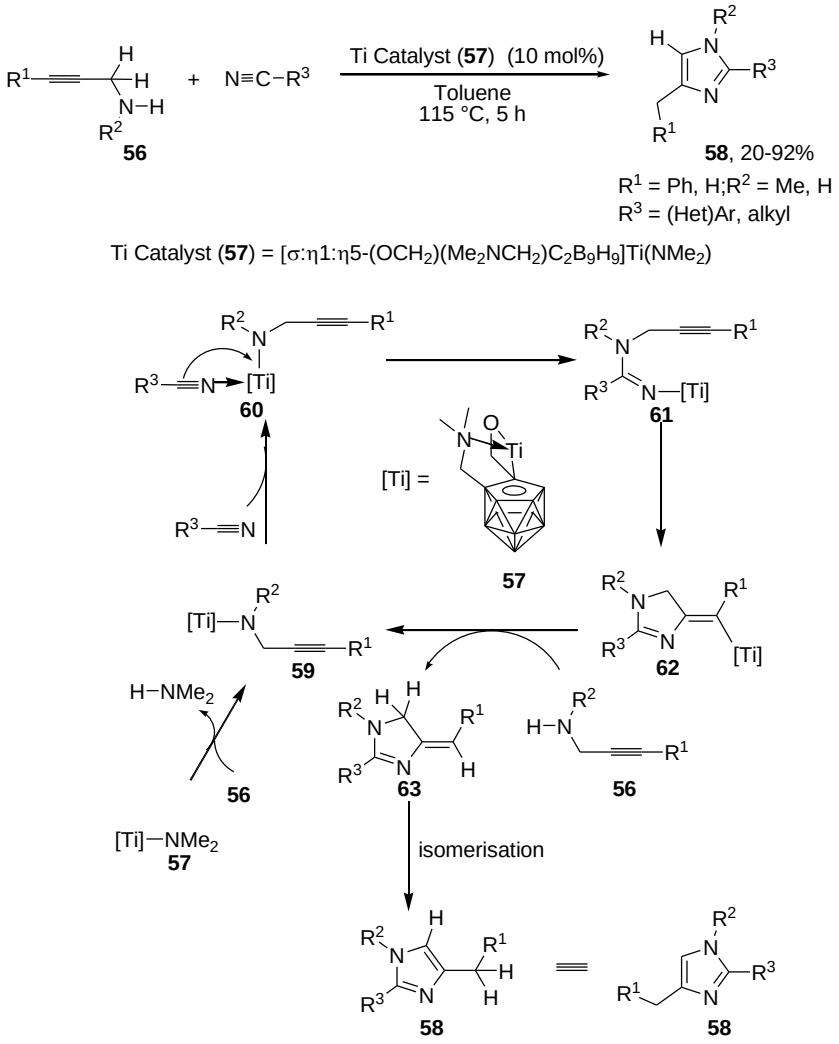
Scheme 10



Scheme 11

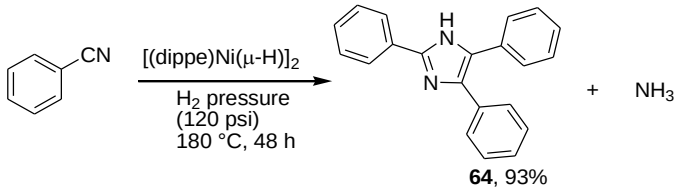
Xie and co-workers have developed thermodynamically and kinetically very stable titanacarborane monoamide based robust catalyst and utilized it for the synthesis of a series of trisubstituted imidazoles (Scheme 12). Thus treatment of *N*-substituted propargyl amine **56** with nitriles in presence of 10 mol% of **57** provides imidazoles such as **58** in high yield. The authors have proposed a possible reaction pathway involving generation of titanacarborane amide intermediate **59** (from **56** and **57**), which coordinates with nitrile to give **60** (Scheme

12). Now **60** undergoes migratory insertion to intermediate **61,** which on intramolecular insertion of C≡C bond providing the newly formed Ti-N bond complex **62**. Finally, catalytic cycle is completed by acid-base reaction of **62** with propargyl amine **56** to regenerate **59** and release dihydroimidazole **63**, which undergoes isomerization to produce substituted imidazole **58** (Scheme 12).[31]



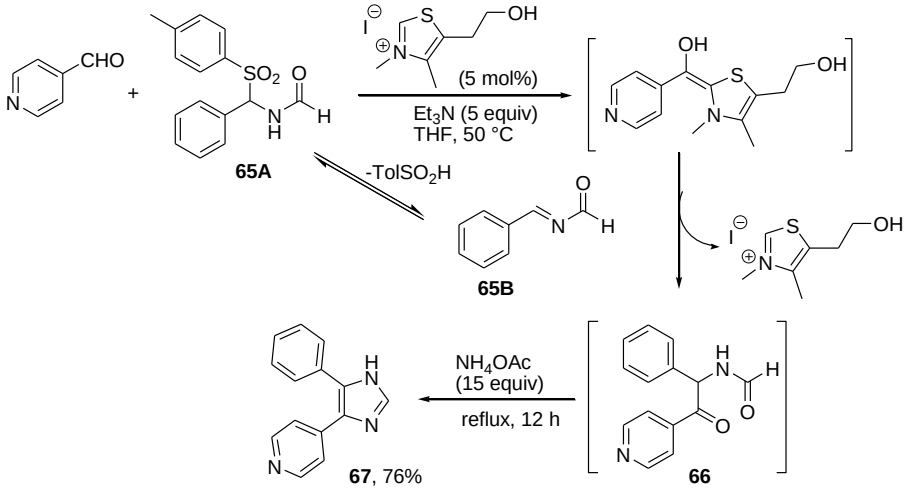
Scheme 12

Barrios-Francisco and co-workers have described Ni(0) catalyzed one-pot synthesis of substituted imidazoles such as **64** from benzonitrile**,** under low H_2 pressure conditions (Scheme 13).[32]



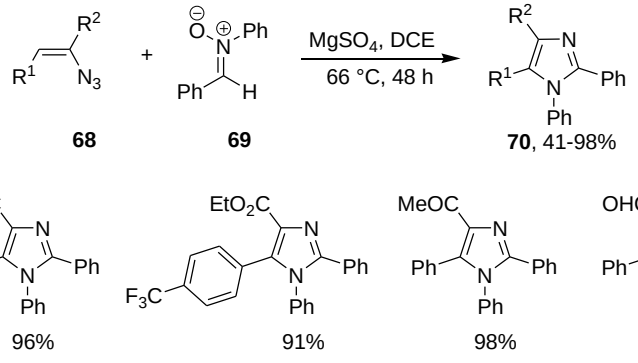
Scheme 13

Tillyer and co-workers have reported an organocatalytic one-pot synthesis of substituted imidazoles such as **67** by thiazolium salt catalyzed addition of an aldehyde to an acyl imine **65B** (generated in situ from the corresponding α-amidosulfones **65A**) (Scheme 14). The α-ketoamide **66**, undergoes in situ ring closure in the presence of ammonium acetate in a one-pot process to give imidazole **67** (Scheme 14).[33]



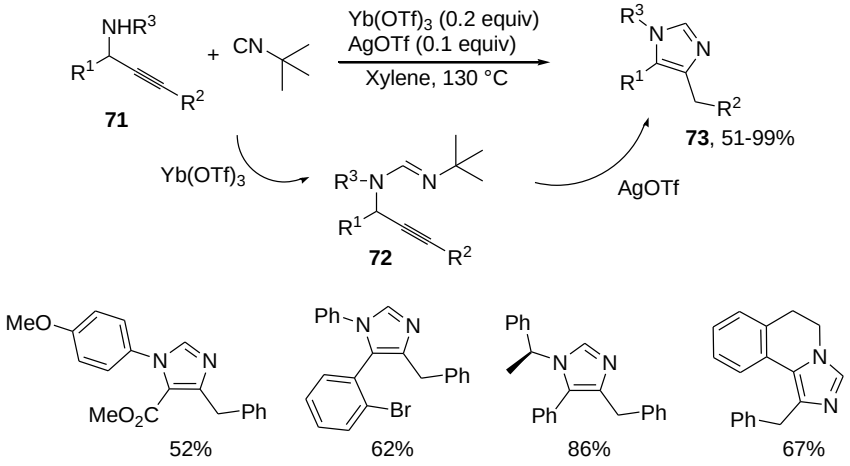
Scheme 14

Wang and co-workers have recently demonstrated the formation of 1,2,4,5-tetrasubstituted imidazoles such as **70** in high yields, from 2-azido acrylate **68** and nitrone **69** under mild reaction conditions without using any metal, acid or base (Scheme 15).[34]



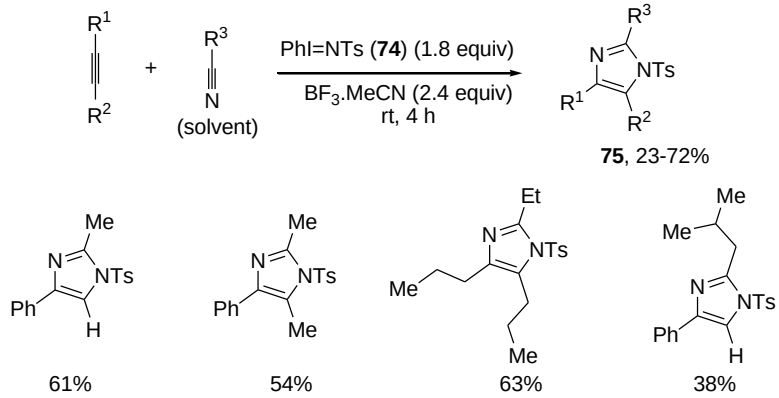
Scheme 15

Recently, Zhu and co-workers have reported the synthesis of 1,4,5-trisubstituted imidazoles **73** by the reaction of propargyl amine **71** with *tert*-butyl-isonitrile in presence of $Yb(OTf)_3$ and AgOTf. In this multiple catalytic system, $Yb(OTf)_3$ catalyzes the insertion of isonitrile to the N-H bond of amines **71** to give amidine **72**, which undergoes AgOTf catalyzed the 5-*exo*-*dig* cyclization to give imidazole **73** (Scheme 16).[35]



Scheme 16

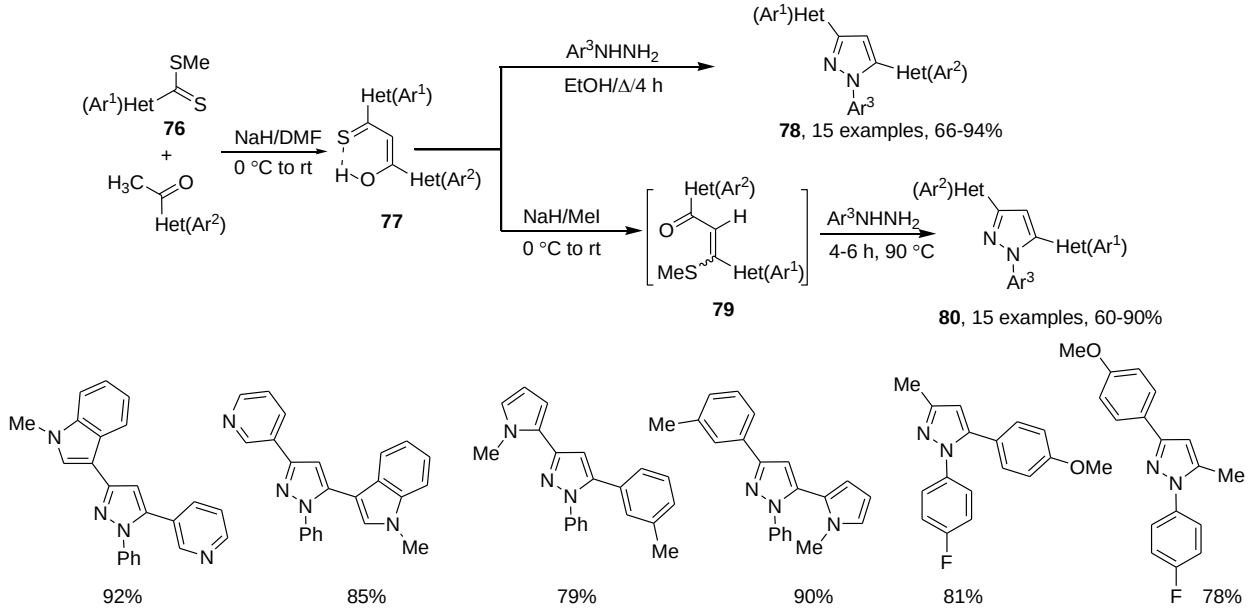
Saito and co-workers have reported a boron trifluoride nitrile complexes promoted oxidative [2+2+1] annulations of alkynes, nitriles and iminoiodanes **74** to give the corresponding 2,4-disubstituted or 2,4,5-trisubstituted *N*-tosylimidazoles **75** in moderate to good yields with high regioselctivites (Scheme 17).[36]



Scheme 17

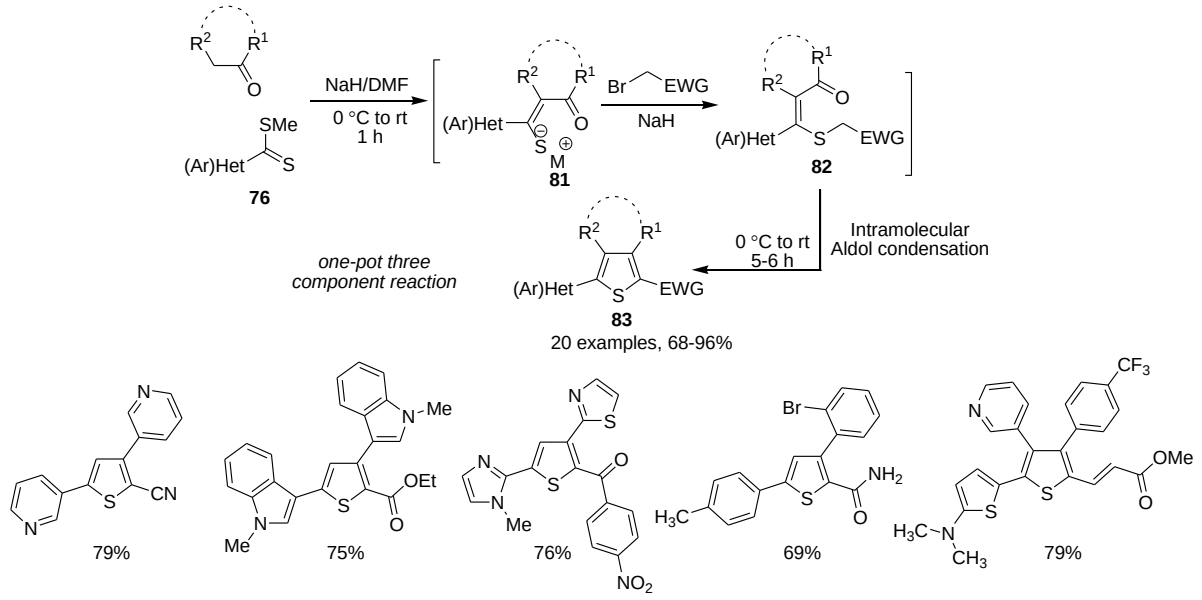
Recently our research group has developed two efficient and highly regioselective routes for the synthesis of 1-aryl-3,5-bis(het)arylpyrazoles with complementary regioselectivity starting from active methylene ketones. In the first protocol, 1,3-bis(het)aryl-monothio-1,3-diketones **77** (prepared by condensation of active methylene ketones with

het(aryl) dithioesters **76** in the presence of sodium hydride) reacts with arylhydrazines under neutral conditions furnishing 1-aryl-3,5-bis(het)arylpyrazoles **78** (Scheme 18). In the second protocol the corresponding 3-(methylthio)-1,3-bis(het)aryl-2-propenones **79** (prepared in situ by base-induced alkylation of 1,3-monothiodiketones **77**) reacts with arylhydrazines in the presence of sodium hydride yielding 1-aryl-3,5-bis(het)arylpyrazoles **80** in a one-pot three component fashion (Scheme 18).[37]



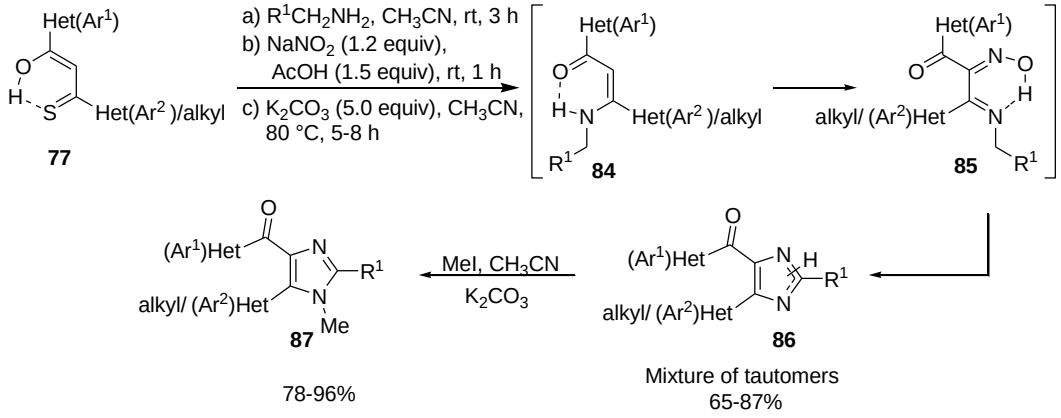
Scheme 18

Similarly, our research group has also developed an efficient sequential one-pot three component method for the synthesis of highly functionalized tri– and tetrasubstituted thiophenes **83** from readily available (het)aryl active methylene ketones and (het)aryl dithioesters **76** as thiocarbonyl precursors (Scheme19). The reaction involves sequential base mediated condensation of (het)aryl active methylene ketones with (het)aryl dithioesters **76** followed by *S*–alkylation of the resulting enethiolate salts **81** with activated halomethylene compounds and concurrent intramolecular aldol type condensation of *S*–alkylated compounds **82** affording substituted thiophenes **83** in excellent yields. The methodology has also been extended for the synthesis of highly fluorescent push–pull substituted thiophene–5–acrylates by using bromocrotonate as activated methylene alkylating agent (Scheme 19).[38]



Scheme 19

In continuation of these studies, directed towards exploring synthetic applications of these 1,3-bishet(aryl)-monothio-1,3-diketones **77**, we now report a regiocontrolled sequential one-pot synthesis of 2-substituted-4(5)-(acyl)-5(4)-het(aryl)/alkylimidazoles **86** and their subsequent alkylation to the corresponding *N*-methyl analogues **87** (Scheme 20). The overall strategy involves formation of three C-N bonds in contiguous fashion via (1) regioselective condensation of 1,3-monothioketones with substituted α-methylamines generating enaminones **84**, (2) in situ α-nitrosation of enaminones **84** with sodium nitrite and acetic acid to give the corresponding α-hydroxyiminoimine intermediates **85**, (3) base mediated in situ cyclodehydration of hydroxyiminoimines **85** to imidazoles **86** (Scheme 20).



Scheme 20

5.3 Results and Discussion

5.3.1 Proposed Synthesis of 2,4,5-Substituted Imidazoles from Enaminones

Despite several elegant syntheses of substituted imidazoles, reported in the literature, a direct general approach involving cycloannulation of *N*-alkylenaminones/enaminoesters with an electrophilic nitrogen is still lacking (Figure 1).[39] Enaminones and enaminoesters are shown to be versatile intermediates for heterocycle synthesis.[40]

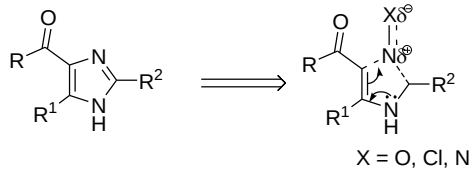
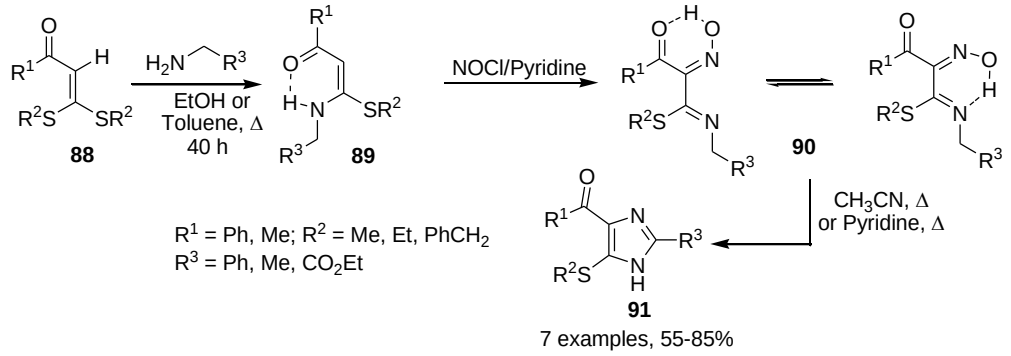


Figure 1

5.3.2 Synthesis of 2,4-Substituted-5-(alkylthio)imidazoles from *α*-Oxoketene-N,S-acetal

Several years ago, during the course of our investigation on synthetic applications of *α*-oxoketene N,S-acetals, a class of versatile functionalized enaminones,[41] we had described in a preliminary communication, a novel route to few 4-acyl-5-(alkylthio)-2-phenylimidazoles **91** through nitrosation of *α*-oxoketene-S-(alkylthio)-*N*-(benzyl)acetals **89** with nitrosyl chloride in pyridine to the corresponding *α*-hydroxyiminoimines **90** and their subsequent cyclodehydration in refluxing acetonitrile/pyridine (Scheme 21).[42a] This reaction, however, employs toxic nitrosyl chloride gas, as nitrosating agent, along with difficult work-up, involving a three step process, starting from displacement reaction on *α*-oxoketene dithioacetals **88**[41a] with benzylamine under prolonged heating in ethanol or toluene[41a-b,43] to furnish the corresponding N,S-acetals **89** in only moderate to good yields.



88 **89** **90** **91**

Scheme 21

Besides, the scope and generality of this reaction was not further examined, which was limited only to few 2-phenyl(one example of 2-carboethoxy)-4-aroyl-5-(alkylthio)-

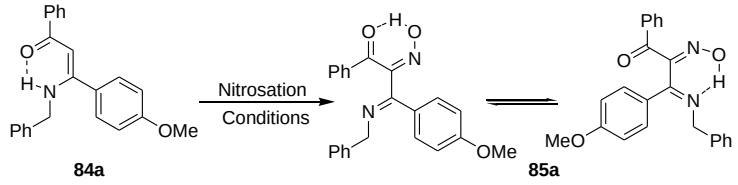
imidazoles **91** (Scheme 21). We therefore conceived of developing a milder, more efficient, one-pot version of this protocol with broader substituent scope for the synthesis of 2,4,5-trisubstituted imidazoles such as **86**, by employing unsymmetrically substituted 1,3-bishet(aryl)/alkyl monothioketones **77** as precursors for enaminones **84** and sodium nitrite as nitrosating agent as depicted in the Schemes 20 and 22.

5.3.3 Synthesis of Imidazole 86a from 1,3-Bis(aryl)monthio1,3-diketone 77a

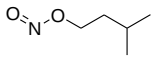
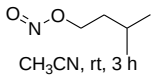
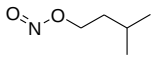
We first examined the stepwise conversion of 1,3-monothioketones **77** to imidazoles **86** (via enaminone **84** and hydroxyiminoimines **85**) and selected monothio-1,3-diketone **77a** and benzylamine as model substrates for optimization of reaction conditions (Scheme 22). Thus **77a** reacted with benzylamine efficiently at room temperature in various solvents like acetonitrile, ethanol or DMF, in highly regiocontrolled fashion, affording the corresponding *N*-benzylenaminone **84a** in excellent yields within 3 h (Scheme 22).

Nitrosation of enaminone **84a** was next examined with milder nitrosating agents such

Table 1. Optimization of Reaction Conditions for Nitrosation of Enaminone 84a to 85a



84a **85a**

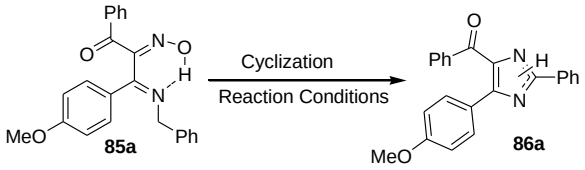
entry	Reaction Conditions	% yield
1[a]	 DMSO, rt, 3 h	75
2[a]	 CH_3CN, rt, 3 h	73
3[a]	 DMF, rt, 3 h	70
4[b]	$NaNO_2$/AcOH rt, 1 h	78
5[b]	$NaNO_2$/AcOH CH_3CN, rt, 1 h	85
6[b]	$NaNO_2$/AcOH DMSO, rt, 3 h	62

Reaction Conditions: [a]**84a** (0.3 mmol), Isoamyl nitrite (1.0 equiv). [b]**84a** (0.3 mmol), $NaNO_2$ (1.2 equiv), AcOH (1.5 equiv) in 3 mL of solvent.

as sodium nitrite/acetic acid or isoamyl nitrite in the presence of various solvents (Table 1), with a view to synthesize α-hydroxyiminoimine intermediate **85a**. Thus, best results were obtained, when enaminone **84a** was reacted with sodium nitrite and acetic acid (1.5 equiv) in acetonitrile as solvent at room temperature, furnishing the hydroxyiminoimine **85a** in 85% yield within one hour (Table 1, entry 5 or Scheme 22).

The nitrosoenaminone **85a**, thus obtained, was subjected to intramolecular cyclodehydration to imidazole **86a** by heating in various solvents like pyridine, toluene, DMSO, DMF and acetonitrile under neutral conditions, as well as, in the presence of mild base like potassium carbonate (Table 2).

Table 2. Optimization of Reaction Conditions for Intramolecular Cyclodehydration of 85a to Imidazole 86a



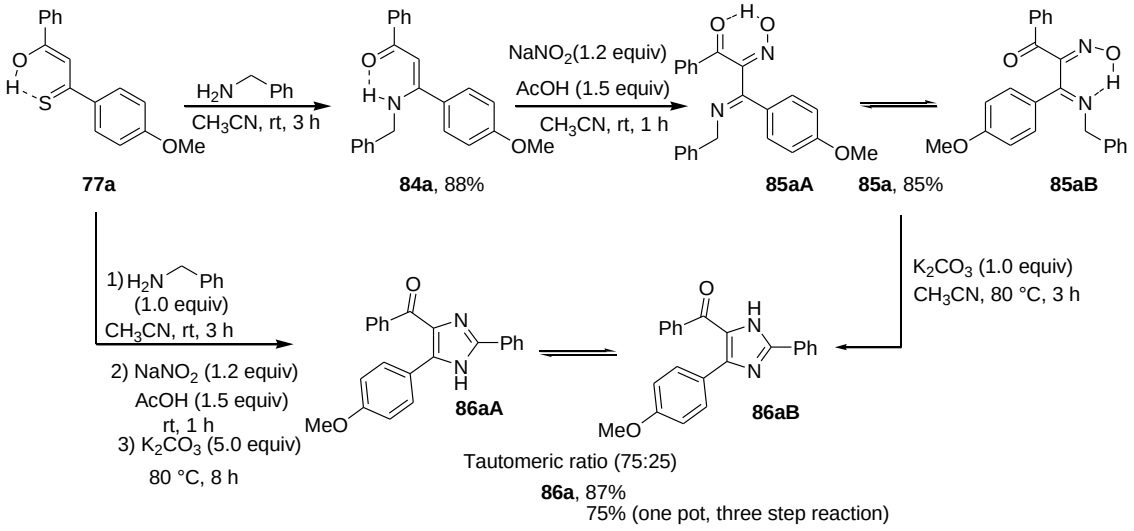
85a **86a**

entry	Reaction Conditions	% yield
1	Pyridine 80 °C, 10 h	69
2	Toluene 100 °C, 15 h	73
3	EtOH, reflux 20 h	52
4	DMSO 80 °C, 10 h	75
5	DMF 80 °C, 10 h	77
6	CH_3CN 80 °C, 12 h	70
7[a]	$DMSO,K_2CO_3$ 80 °C, 7 h	79
8[a]	CH_3CN,K_2CO_3 80 °C, 3 h	87
9[a]	DMF,K_2CO_3 80 °C, 8 h	80

[a] K_2CO_3 (1.0 equiv).

The imidazole **86a** was formed in all these conditions in good yields, whereas best yield (87%) of **86a** was obtained by cyclization of **85a** in refluxing acetonitrile in the presence of potassium carbonate as base (Table 2, entry 8 or Scheme 22). The imidazole **86a** was found to exist in two tautomeric form **86aA** and **86aB** at room temperature, however methylation of **86a** with methyl iodide in the presence of potassium carbonate yielded only

single regioisomer, which was characterized as 1-*N*-methyl-2-phenyl-4-benzoyl-5-(4-methoxyphenyl)imidazole **87a** (Table 4, entry1) on the basis of its spectral and analytical data as well as by single crystal X-ray analysis (Figure 2).



Scheme 22

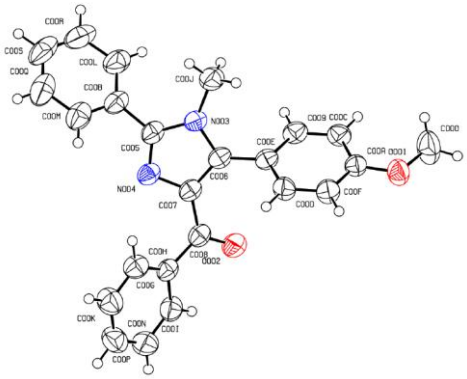
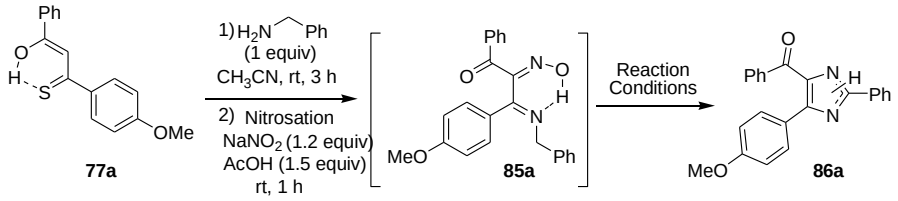


Figure 2. X-Ray crystal structure of **87a**

Having established the optimized reaction conditions for three step transformation of 1,3-monothioketone **77a** to imidazole **86a (**Scheme 22), we next considered to develop a sequential one-pot synthesis of imidazole **86a** from **77a** and benzylamine. Optimization of the reaction conditions revealed that the imidazole **86a** was obtained in lower yields (61-68%) when isoamylnitrite was employed as nitrosating agent in various solvents under one-pot conditions. However, after considerable experimentation, **86a** could be obtained in optimal yield of 75% in a one-pot operation, by generating the enaminone **84a** from **77a** in acetonitrile as solvent, and by employing sodium nitrite/acetic acid as nitrosating agent (in

acetonitrile), followed by heating the reaction mixture in the presence of excess (5 equiv) of potassium carbonate (Table 3, entry 7).

Table 3. Optimization of Reaction Conditions for One-Pot Synthesis of Imidazole 86a from 77a



entry	Reaction Conditions	temp/time	% yield
1	Cs_2CO_3 (3.0 equiv)	80 °C, 12 h	66
2	DBU (3.0 equiv)	80 °C, 24 h	64
3	Pyridine (3.0 equiv)	80 °C, 20 h	60
4	NH_4OAc (3.0 equiv)	80 °C, 30 h	62
5	NaOAc (5.0 equiv)	80 °C, 26 h	57
6	K_2CO_3 (3.0 equiv)	80 °C, 15 h	68
7	K_2CO_3 (5.0 equiv)	80 °C, 8 h	75

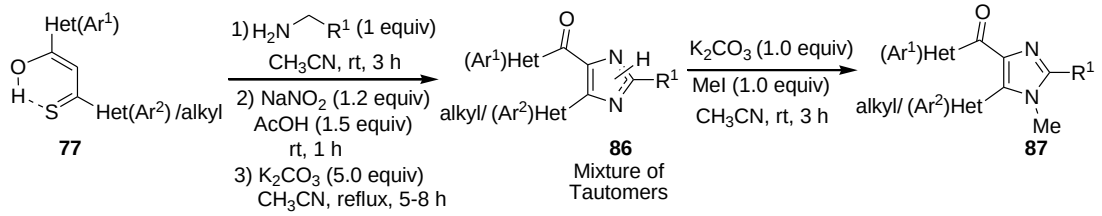
Despite lower yield (75%) of imidazole **86a** compared to stepwise process, these optimized one-pot conditions were used throughout our studies for the synthesis of various 2,4,5-trisubstituted imidazoles **86** (Table 4, entries 2-12), (Table 5, entries 1-3), (Scheme 23).

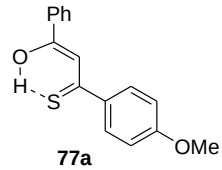
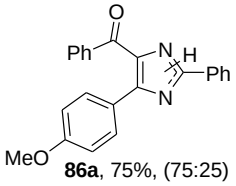
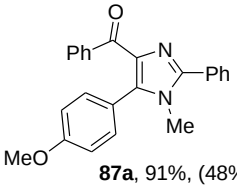
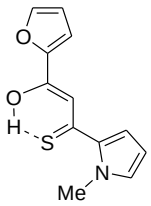
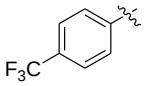
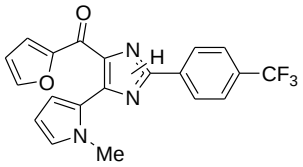
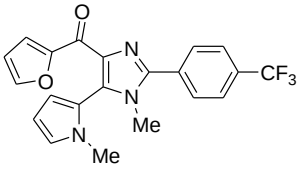
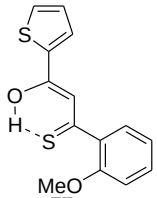
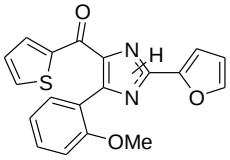
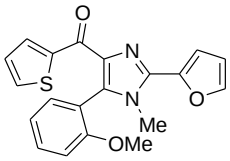
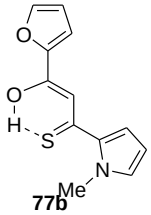
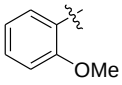
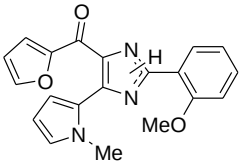
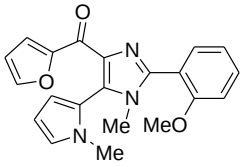
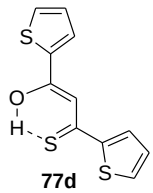
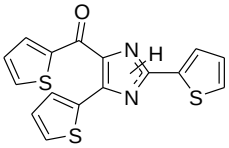
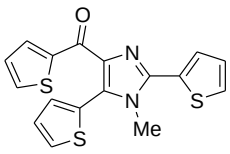
5.3.3.1 Synthesis of 2,4,5-Tri- and 1,2,4,5-Tetrasubstituted Imidazoles 86 and 87

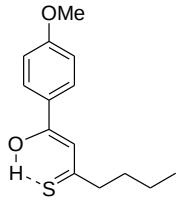
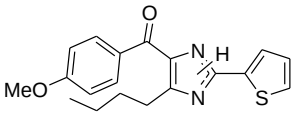
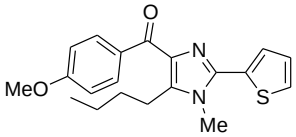
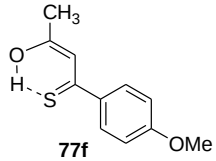
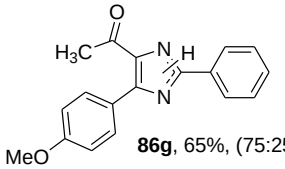
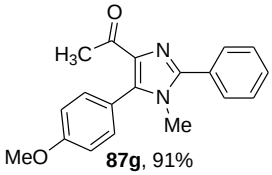
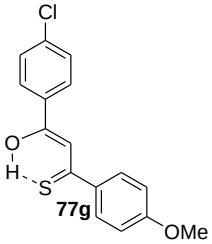
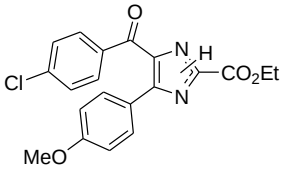
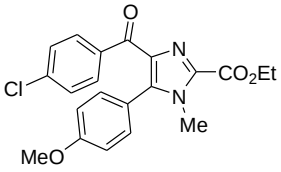
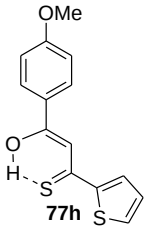
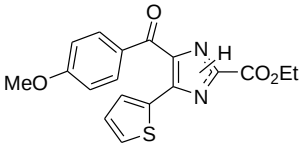
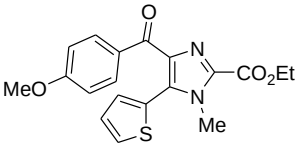
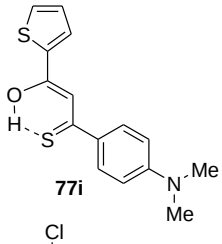
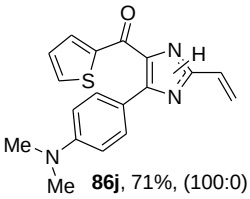
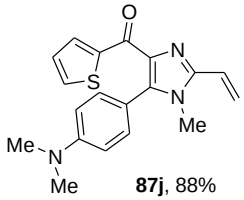
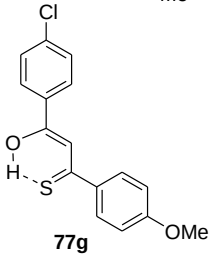
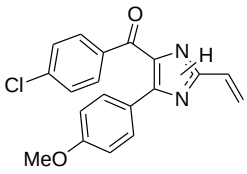
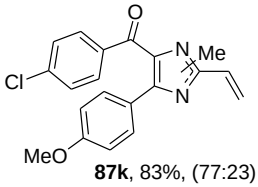
With the optimized reaction conditions in hand for one-pot synthesis of imidazole **86a** from 1,3-monothiodiketone **77a** (Scheme 22, Table 4, entry 1), we next evaluated the generality and scope of this reaction with respect to various substituents at 2-, and 4(5)-positions of imidazole framework. These results are displayed in Table 4. Thus by employing a range of unsymmetrically substituted het(aryl)-1,3-monothioketones **77** and various α-het(aryl)methylamines, it was possible to install a variety of substituted aryl- and het(aryl)-(2-thienyl-, 2-furyl-, 2-(*N*-methyl)pyrrolyl-) groups at 2- and 4(5)- positions of imidazoles **86** (entries 2-5). Entries 3-4 also represent examples of introduction of sterically congested (2-methoxyphenyl) group at either 2- or 4(5) position of imidazole ring. Similary, the

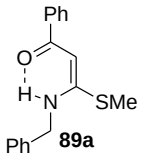
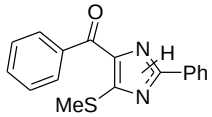
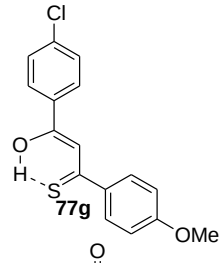
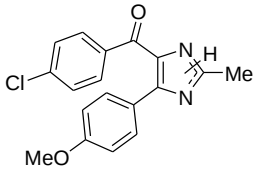
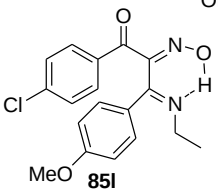
imidazoles **86f** and **86g** carrying an alkyl (*n*-butyl-) or acetyl group respectively at 4(5) positions could also be obtained in good yields from the corresponding 1-(*n*-butyl)-3-aryl

Table 4. Synthesis of 2,4,5-Tri- and 1,2,4,5-Tetrasubstituted Imidazoles 86 and 87



entry	**77**	H_2N R^1	**86** % yield, (tautomeric ratio)	**87** % yield
1	 **77a**		 **86a**, 75%, (75:25)	 **87a**, 91%, (48%)[a]
2	 **77b**		 **86b**, 87%, (50:50)	 **87b**, 93%
3	 **77c**		 **86c**, 82%, (100:0)	 **87c**, 90%
4	 **77b**		 **86d**, 81%, (55:45)	 **87d**, 96%
5	 **77d**		 **86e**, 71%, (100:0)	 **87e**, 89%

entry	**77**	H_2N R^1 R^1	**86** % yield, (tautomeric ratio)	**87** % yield
6	 **77e**		 **86f**, 67%, (90:10)	 **87f**, 84%
7	 **77f**		 **86g**, 65%, (75:25)	 **87g**, 91%
8	 **77g**		 **86h**, 68%, (75:25)	 **87h**, 88%
9	 **77h**		 **86i**, 71%, (100:0)	 **87i**, 89%
10	 **77i**		 **86j**, 71%, (100:0)	 **87j**, 88%
11	 **77g**		 **86k**, 81%, (80:20)	 **87k**, 83%, (77:23)

entry	**77**	H_2N R^1 R^1	**86** % yield, (tautomeric ratio)	**87** % yield
12	 **89a**		 **91a**, 72% (100:0)[b]	–
13	 **77g**		 **86l**, 0%	–
14[c]	 **85l**		**86l**, 0%	–

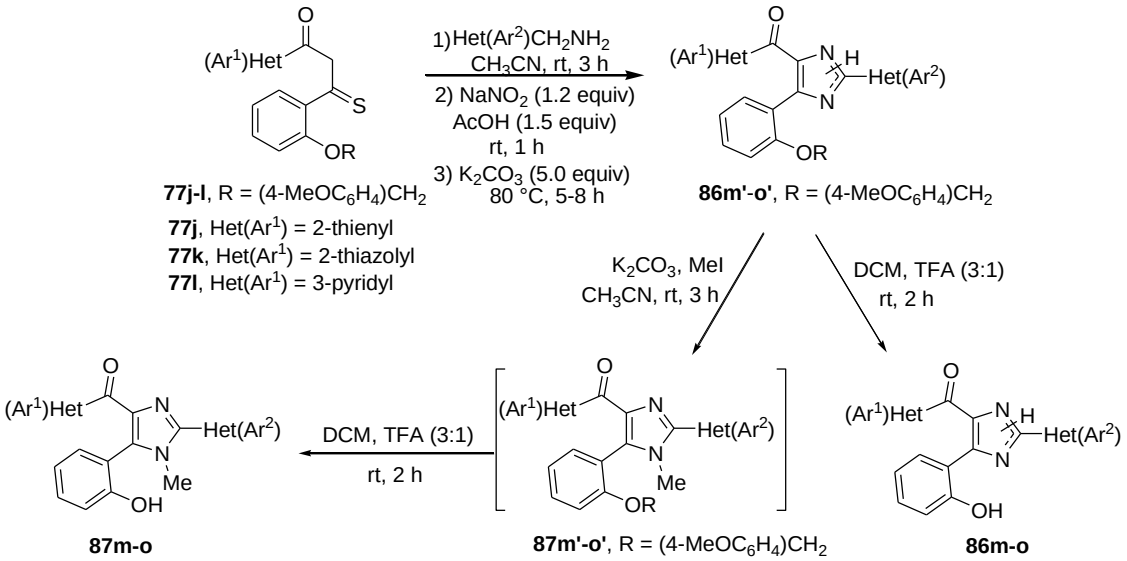
[a]Yield obtained under one-pot condition.[b]Obtained by one-pot nitrosation of N,S-acetal and intramolecular cyclization in presence of K_2CO_3 (5.0 equiv) and CH_3CN.[c]K_2CO_3 (1.0 equiv), CH_3CN, 80 °C, 5-12 h.

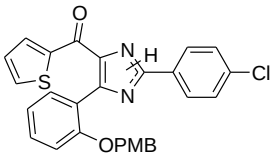
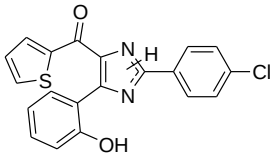
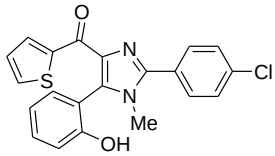
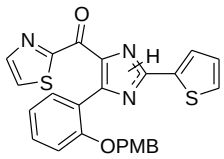
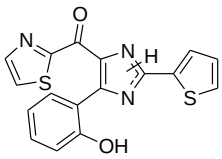
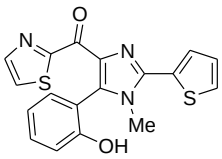
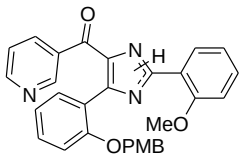
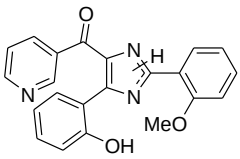
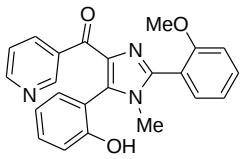
1,3-monothiodiketone **77e** or *α*-(thioaroyl)acetone **77f** under identical conditions (Table 4, entries 6 and 7). This new one-pot protocol was found to be equally efficient for the introduction of functionalities such alkoxycarbonyl or a vinyl group at 2- position of imidazoles by utilizing either ethyl glycinate or allylamine as annulating partners, thus affording the corresponding 4(5)-substituted imidazole- 2-carboxylates **86h-i** (entries 8-9) and 2-vinylimidazoles **86j-k** (entries 10-11) respectively in good yields. The corresponding *α*-oxoketene-N,S-acetal **89a** also underwent one-pot nitrosation and intramolecular cyclization in the presence of potassium carbonate in refluxing acetonitrile or pyridine (61%) to afford the corresponding 4(5)-(methylthio)imidazole **91a** in good yields as single tautomer (Table 4, entry 12).[42a] However, the attempted synthesis of the corresponding 2-methylimidazole **86l** from either 1,3-monothioketone **77g** and ethylamine (under one-pot condition) or from *N*-ethylhydroxyiminoimine **85l** by treatment with potassium carbonate under previous conditions, did not meet with any success, yielding only intractable reaction mixture (Table 4, entries 13-14).

5.3.3.2 Synthesis of 2-Het(aryl)-4(5)-het(aroyl)-5(4)-(2-hydroxyphenyl)imidazoles

The present methodology was also extended for the synthesis of 4(5)-(2-hydroxyphenyl) substituted imidazoles such as **86m-o**, which are known to act as good coordinating ligands for various metal ions (Table 5).[44] Thus the 1,3-monothioketones **77j-l** bearing a [2-(4-methoxybenzyloxy)phenyl] group at thiocarbonyl moiety were subjected to sequential amination with various het(aryl)amines followed by nitrosation and intramolecular cyclocondensation under earlier described one-pot conditions, to afford the corresponding 4(5)-[2-(4-methoxybenzyloxy)phenyl] substituted imidazoles **86m'-o'** in good yields (Table 5, entries 1-3). Subsequent deprotection of (4-methoxybenzyloxy) group in **86m'-o'** with TFA, furnished the corresponding 4(5)-(2-hydroxyphenyl)-5(4)-het(aroyl)imidazoles **86m-o** in high yields (Table 5, entries 1-3). Alternatively, alkylation of imidazoles **86m'-o'** with methyl iodide under previously described conditions, followed by TFA mediated deprotection of (4-methoxybenzyloxy) group in crude *N*-methylimidazoles **87m'-o'**(without isolation), afforded the corresponding 1-(*N*-methyl)-5-(2-hydroxyphenyl)-2-het(aryl)-4-het(aroyl)imidazoles **87m-o** in good yields (Table 5, entries 1-3).

Table 5: Synthesis of 2-Het(aryl)-4(5)-het(aroyl)-5(4)-(2-hydroxyphenyl)imidazoles

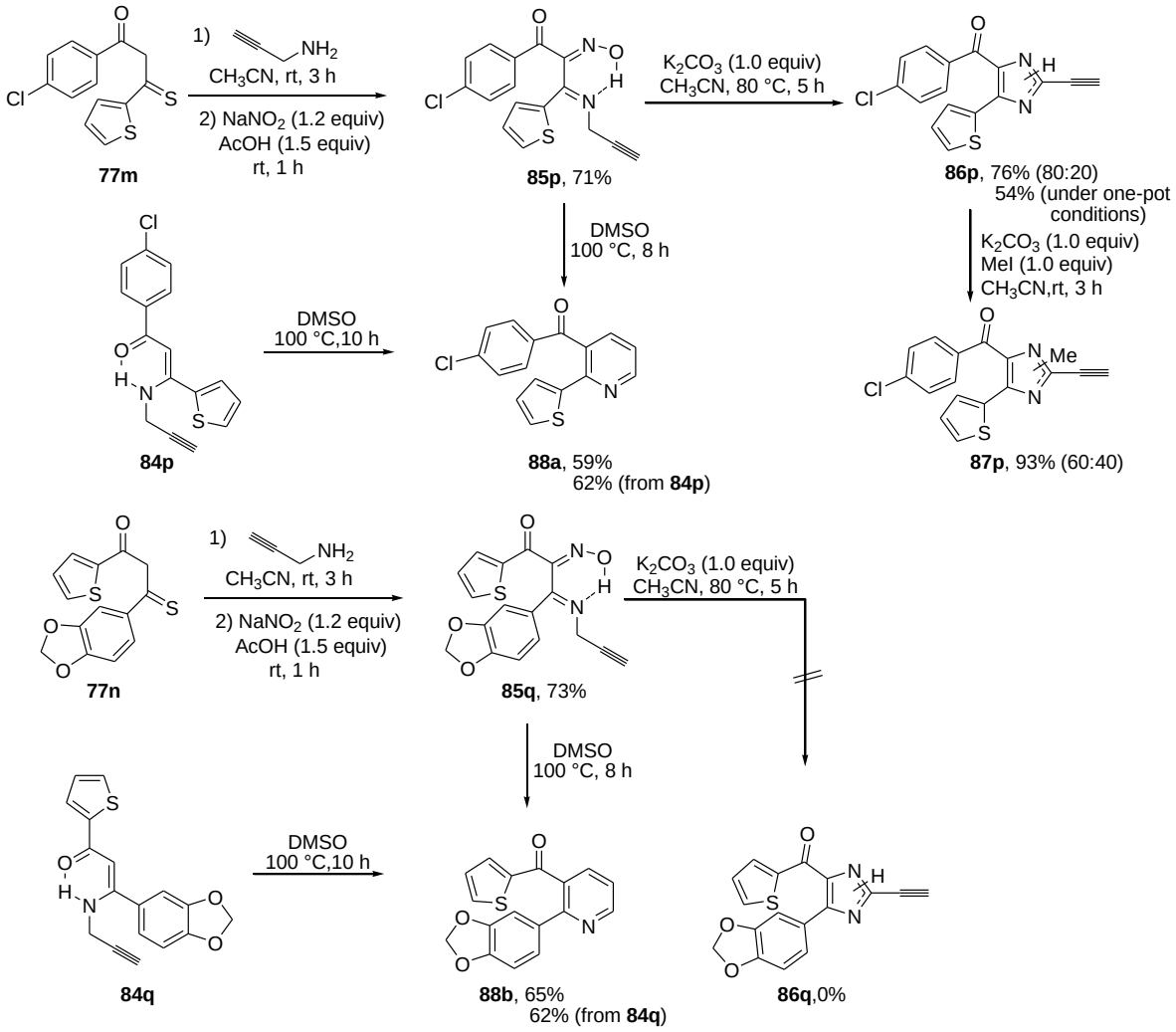


entry	**86'** % yield, (tautomeric ratio)	**86** % yield, (tautomeric ratio)	**87** % yield
1	 **86m'**, 82% (100:0)	 **86m**, 85% (50:50)	 **87m**, 78%
2	 **86n'**, 85% (75:25)	 **86n**, 80% (75:25)	 **87n**, 89%
3	 **86o'**, 77% (90:10)	 **86o**, 80% (100:0)	 **87o**, 82%

5.3.3.3 Synthesis of 2-Ethynyl-4,5-substituted Imidazole and 2,3-Disubstituted Pyridines

We also elaborated this method for the synthesis of 2-ethynylimidazoles such as **86p**, by reacting 1,3-monothioketone **77m**, sequentially with propargylamine, sodium nitrite and potassium carbonate under previously described one-pot conditions, providing **86p** in moderate yield (54%), which could be improved to 76%, when pure *N*-propargylhydroxyiminoimine **85p** was subjected to cyclodehydration in the presence of potassium carbonate (Scheme 23). However, the generality of this reaction for the synthesis of 2-ethynylimidazoles could not be established, and attempted intramolecular cyclization of *N*-propargylhydroxyiminoimine **85q** in the presence of K_2CO_3 did not give the expected imidazole **86q**, but a different product, which could not be characterized. Interestingly, attempted intramolecular thermal cyclodehydration of hydroxyiminoimine **85p** to imidazole **86p** in DMSO at 100 °C gave a new product (59%), which was characterized as the 2,3-substituted pyridine **88a** on the basis of its spectral and analytical data (Scheme 23). Similarly the hydroxyiminoimine **85q** also furnished the 2,3-disubstituted pyridine **88b** in 65% yield under identical conditions. Our search of literature revealed that such kind of substituted pyridines have been reported to be formed by intramolecular cyclization of *N*-

propargylenaminones in the presence of copper(I) salt.[40h] We therefore subjected the enaminones **84p-q** to thermal intramolecular cyclization in DMSO, which also afforded the pyridines **88a-b** in comparable yields (Scheme 23).



Scheme 23

5.3.3.4 Prototopic Tautomerism of *NH* Imidazoles 86

Most of the newly synthesized 4(5)- unsymmetrically substituted *NH* imidazoles **86a-k** and **86m-p** (Table 4, 5 and Scheme 23) display prototropic annular tautomerism[45] as evident from their ^{1}H NMR spectra. Depending on the nature of substituent on either 4- or 5- positions, one tautomer may predominate over the other (Table 4).[46] However alkylation of these imidazoles with methyl iodide in the presence of potassium carbonate, afforded only single regioisomers i.e., 1-*N*-methyl-2,5-bis het(aryl)-4-het(aroyl)imidazoles **87a-j** and **87m-o** in

highly regiocontrolled fashion (Table 4, entries 1-10 and Table 5, entries 1-3), with only few exceptions, wherein a mixture of regioisomeric 1/3-*N*-methylimidazoles were obtained (Table 4, entry 11 and Scheme 23). The regiochemistry of these *N*-methylimidazoles **87** was further confirmed by single crystal X-ray analysis of imidazole **87a** as well as that of sterically crowded derivative **87d** (Table 4, entries 1 and 4), (Figures 2 and 3).

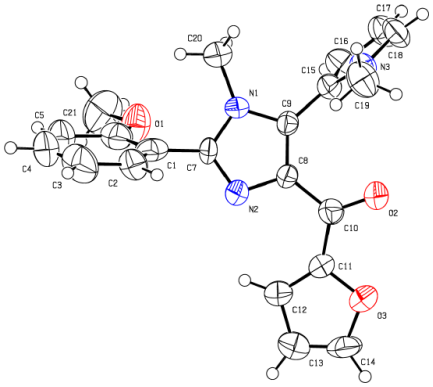
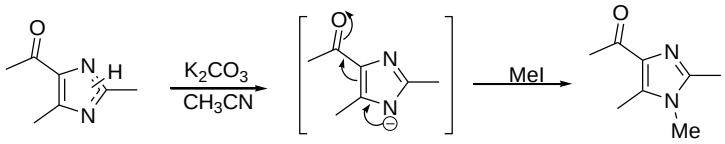


Figure 3. X-Ray crystal structure of **87d**

5.3.3.5 Regioselective *N*-Methylation of Imidazoles 86 to 1-*N*-Methyl-4-het(aroyl)-2,5-substituted Imidazoles 87

The regioselective formation of only *N*-methylimidazole **87** from **86** could be rationalized in terms of formation of a more stabilized anion on nitrogen (**86A**) due to its delocalization over carbonyl group (Scheme 24).



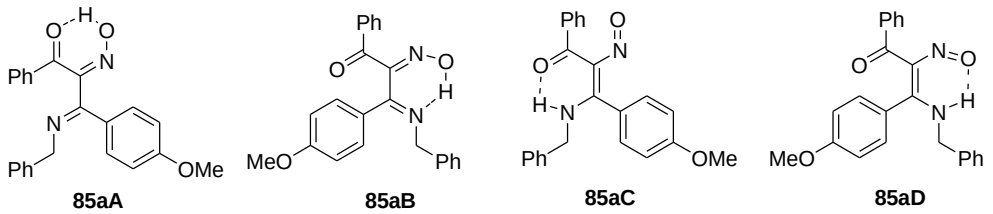
86 **86A** **87**

Scheme 24

5.3.3.6 Prototropic Tautomers of 85a

Although we have not carried out a detailed study of prototopic tautomerism of nitrosoenaminone **85a**, however a comparison of ^{1}H NMR spectra of both enaminone **84a** and **85a** ruled out nitrosoenaminone structure **85aC** or **85aD** (Scheme 25). Thus signal due to *NH* proton in the enaminone **84a**, both in $CDCl_3$ and DMSO-d_6, appears around δ11.6-11.7 as broad triplet (J = 6.0 Hz), whereas benzylic methylene protons are present as sharp doublet (J = 6.0 Hz) at δ 4.4 due to the vicinal coupling between –N*H*CH_2- protons, thus supporting the intramolecular H- bonded enaminone structure **84a** (Scheme 22). On the other

hand, in the ^{1}H NMR spectrum of nitrosoenaminone **85a** in DMSO-d_6, the lower field labile proton appears as a sharp singlet at δ 13.1, whereas the benzylic methylene protons are present as AB quartet displaying geminal coupling of the order of 16.0 Hz. The absence of coupling between benzylic CH_2 and low field labile proton rules out the nitrosoenaminone structures **85aC** or **85aD**, and points to the intramolecularly H-bonded hydroxyiminoimine tautomeric structures such as **85aA-85aB** (Scheme 25). The appearance of methylene protons as AB quartet in the ^{1}H NMR spectrum of **85a**, is probably due to restricted rotation around CH_2-N bond in the hydrogen bonded structure **85aB** (Scheme 25). However further study is required to confirm these structures. The ^{1}H NMR spectra of both *N*-propargyl enaminone **84p** and the corresponding nitroso analog **85p** also displayed similar features.

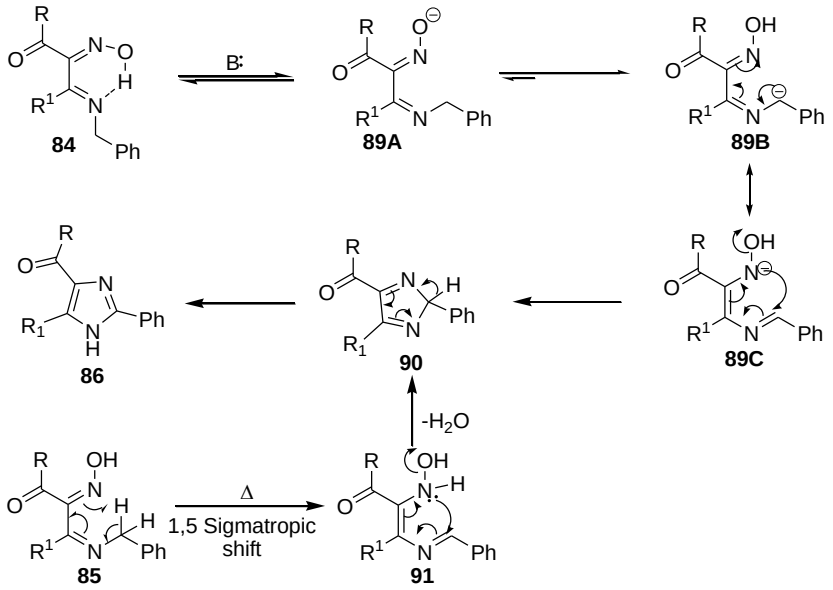


Scheme 25

5.3.3.7 Probable Mechanism of the Formation of Imidazoles 86 from Hydroxyiminoimines 85

As we have observed earlier (Table 2), the hydroxyiminoimine intermediate **85a** undergoes intramolecular thermal cyclodehydration to imidazole **86a** in varying yields in solvents like DMSO, toluene, DMF or acetonitrile under prolonged heating. On the other hand, in the presence of weaker base like K_2CO_3, in refluxing acetonitrile, the reaction proceeds smoothly within 3 h, yielding imidazole **86a** in 87% yield (Table 2). We therefore propose two possible mechanisms for the formation of imidazoles **86** from α-hydroxyiminoimines **85** as shown in the Scheme 26. Thus under basic conditions, the hydroxyiminoimine **85** undergoes proton abstraction to oximate anion **89A**, which exists in equilibrium with carbanionic species **89B**. The intermediate **89B** undergoes facile electrocyclization and elimination of OH group, through delocalized anion **89C** affording imidazole **86** through tautomeric intermediate **90**. Faliure to obtain 2-methylimidazole **86l** from hydroxyiminoimine **85l** (Table 4, entries 13-14) is probably due to lower acidity of aminomethylene protons in **85l**, thus resisting the abstraction of proton by weaker base like

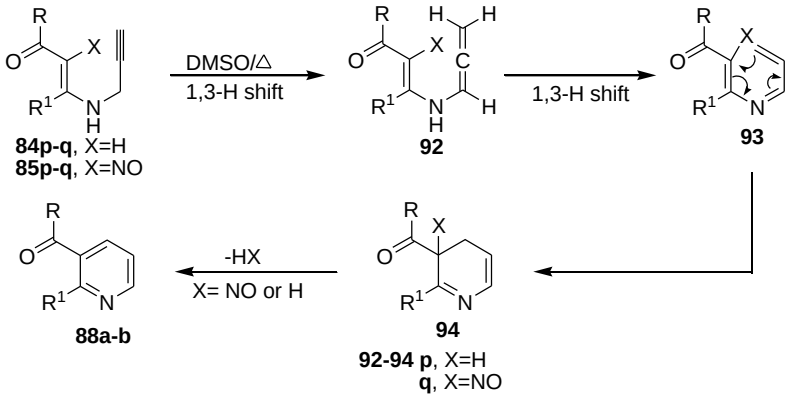
potassium carbonate and formation of the corresponding carbanion for electrocyclization to imidazole **86l**. On the other hand, under neutral thermal conditions, the intermediate **90** appears to be formed via a 1,5-prototopic shift in the hydroxyiminoimine **85** and subsequent intramolecular dehydrative cyclization of the resulting imine intermediate **91** (Scheme 26).



Scheme 26

5.3.3.8 Mechanism of the Formation of Pyridines 88a-b from Enaminones 84p-q and Hydroxyiminoimines 85p-q

Cacchi and coworkers have reported synthesis of substituted pyridines via CuBr (0.4 equiv) catalyzed intramolecular cyclization of *N*-propargylenaminones such as **84** in DMSO.[40h] They have proposed a mechanism involving complexation of Cu^{+} species to triple bond, which facilitates 6-*endo*-cyclization to pyridines **88** by intramolecular nucleophilic attack of enaminone (α- to the carbonyl group) on acetylenic terminal carbon atom. On the other hand, we have observed the formation of pyridines **88a-b** in comparable yields, from either enaminones **84p-q** or the corresponding hydroxyiminoimine analogs **85p-q** on heating in DMSO in the absence of copper catalyst (Scheme 23). We therefore propose a different mechanism for the formation of pyridines **88a-b** as shown in the Scheme 27. Thus the enaminones **84** or **85** undergo two consecutive thermal 1,3- prototopic shifts to afford the



Scheme 27

azatriene intermediate **93** (through allene intermediate **92**). Subsequent electrocyclization of azatriene **93** to dihydropyridine **94** followed by its dehydrogenation (X = H) or dehydrogenative elimination of nitric oxide (X = NO) furnishes the pyridines **88a-b** in good yields (Scheme 27).

5.4 Conclusion

In summary, we have developed an efficient, highly regiocontrolled, one-pot [2+2+1] annulation approach for the synthesis of a series of diversely functionalized trisubstituted 4(5)-het(aroyl)-2,5(4)-het(aryl)/alkylimidazoles, from readily available precursors i.e., 1,3-bishet(aryl)monothio-1,3-diketones, *α*-substituted methylamines and sodium nitrite (as precursor for ring nitrogen) and their subsequent alkylation to the corresponding *N*-methyl derivatives. This novel sequential one-pot protocol, wherein three new carbon nitrogen bonds are formed in contiguous fashion, involves in situ generation of enaminones from monothio-1,3-diketones, followed by their *α*-nitrosation to *α*-hydroxyiminoimines and subsequent base mediated intramolecular heterocyclization of *α*-hydroxyiminoimines to imidazoles in high yields under mild conditions. Also, by appropriate choice of the 1,3-monothiodiketones and substituted aminomethylene partners, it is possible to modulate a large variety of substituents at 2,4,5- positions of final imidazole products. The method provides rapid access, especially to imidazoles with sterically demanding (het)aromatic groups on 2 and (4)5- positions, as well as to 4(5)- (2-hydroxyphenyl) imidazoles, which are known to be good coordinating ligands. It should be noted that, several synthesis of substituted imidazoles with het(aryl) substituents at 2,4,5 positions have been reported in the literature, whereas the direct general convergent methods for the synthesis of 4(5)-acyl substituted imidazoles are only few in the

literature.[26,47] Also noteworthy is the ease with which 1,3-monothiodiketones react with α-substituted methylamines to give enaminoketones under very mild conditions in highly regiocontrolled fashion, since the reported synthesis of enaminoketones[40a-b] from unsymmetrically substituted 1,3-diketones[40a-b] require drastic conditions and is not regioselective.[48] Although, the present methodology is limited only to the synthesis of 4(5)-het(aroyl)-substituted imidazoles, further work to extend the scope of the reaction, for the introduction of other functionalities in the imidazole ring, such as carboalkoxy /cyano groups via *N*-benzylenaminoesters and *N*-benzylenaminonitriles respectively, or by further transformations of het(aroyl) group (i.e., cleavage of ketone by Baeyer- Villiger reaction) are in progress.

5.5 Experimental Section

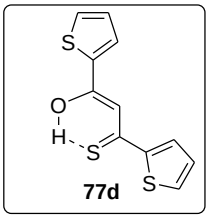
5.5.1 General Information. All reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using standard TLC silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100–200 mesh). Nuclear magnetic resonance spectra were recorded on (400 MHz) FT–NMR spectrometer with $CDCl_3$ or DMSO–d_6 as solvent. Chemical shifts were reported in δ ppm using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO–d_6 in ^{1}H–NMR, δ 77.16 for $CDCl_3$ and δ 39.52 for DMSO–d_6 in ^{13}C–NMR). Coupling constants were reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet) and br (broad). Infrared spectra of neat samples were recorded in ATR (attenuated total reflectance) mode using FT–IR instrument and HRMS on Q–TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

The scanned copies of ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in supporting information of *J. Org. Chem.* **2016**, *81*, 5606.

5.5.2 General Procedure for the Synthesis of 1,3-Bishet(aryl)-monothio-1,3-diketones 77a-n. The desired 1,3-bishet(aryl)-monothio-1,3-diketones were prepared following our earlier reported procedure.[37] To a stirred suspension of NaH (240.0 mg, 10.0 mmol, 60% suspension in mineral oil) in dry DMF (10 mL) under N_2 atmosphere, a solution of het(aryl) methyl ketone (5.0 mmol) and het(aryl) dithioester (5.0 mmol) in DMF (10 mL) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 1h (monitored by TLC). It was then poured into ice-cold water (100 mL), acidified with acetic acid (1 mL), extracted with EtOAc (3 x 50 mL), the combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude products, which were purified by column chromatography using EtOAc/hexane as eluent.

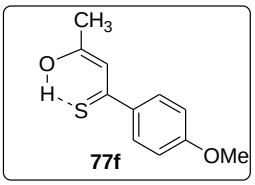
The known 1,3-bishet(aryl)-monothio-1,3-diketones **77a-b**,[37b] were characterized by comparison of their spectral and analytical data with literature data. The spectral and analytical data of unknown 1,3-bishet(aryl)-monothio-1,3-diketones **77d**, **77f-i** and **77j-n** are given below. The monothio-1,3-diketones **77c** and **77e** were found to be unstable during purification by column chromatography and used as such for the preparation of imidazoles **86c** and **86f** without purification.

(*Z*)-3-Hydroxy-1,3-di(thiophen-2-yl)prop-2-ene-1-thione (77d). Obtained as a red solid



(970.2 mg, 77%): mp 65-67 °C; R_f 0.3 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2998, 1569, 1402, 1242, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 15.66 (s, 1H), 7.86 (d, J = 3.6 Hz, 1H), 7.75 (d, J = 4.0 Hz, 1H), 7.65 (d, J = 5.2 Hz, 1H), 7.62 (d, J = 5.2 Hz, 1H), 7.34 (s, 1H), 7.18 (t, J = 4.0 Hz, 1H), 7.15 (t, J = 4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.6, 171.7, 151.6, 140.1, 133.7, 132.3, 130.3, 128.81, 128.79, 127.6, 106.7; HRMS (ESI) *m/z* calcd for $C_{11}H_9OS_3$ $[M + H]^+$ 252.9816, found 252.9808.

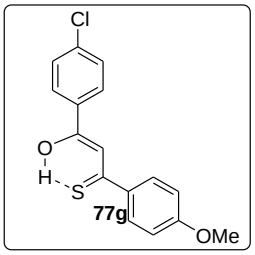
(*Z*)-3-Hydroxy-1-(4-methoxyphenyl)but-2-ene-1-thione (77f). Obtained as a red solid



(676.0 mg, 68%): mp 55-57 °C; R_f 0.5 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2925, 1583, 1553, 1446, 1239, 784; ^1H NMR (400 MHz, $CDCl_3$) δ 14.93 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.74

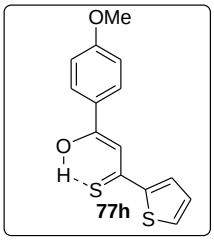
(s, 1H), 3.86 (s, 3H), 2.23 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 200.7, 186.0, 162.7, 137.1, 128.9, 113.8, 112.1, 55.6, 26.1; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}O_2S$ $[M + H]^+$ 209.0636, found 209.0626.

(*Z*)-3-(4-Chlorophenyl)-3-hydroxy-1-(4-methoxyphenyl)prop-2-ene-1-thione (77g).



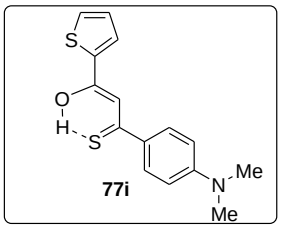
Obtained as a red solid (1.15 g, 76%): mp 95-97 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2834,1585, 1435, 1261, 791; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.77 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.38 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 206.0, 176.9, 162.9, 138.7, 138.3, 134.3, 129.3, 129.0, 128.5, 114.0, 108.6, 55.7; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}ClO_2S$ $[M + H]^+$ 305.0403 and 307.0374, found 305.0401 and 307.0372.

(*Z*)-3-Hydroxy-3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-ene-1-thione (77h).



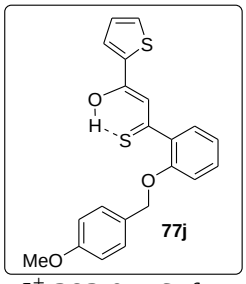
Obtained as a red solid (993.6 mg, 72%): mp 78-80 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2892, 1557, 1397, 1214, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.24 (s, 1H), 7.96 (d, *J* = 9.2 Hz, 2H), 7.76 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 7.60 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.42 (s, 1H), 7.13 (dd, *J* = 5.2 Hz, 4.0 Hz, 1H), 6.98 (d, *J* = 9.2 Hz, 2H), 3.89 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 198.5, 176.5, 163.6, 152.5, 133.7, 129.2, 128.7, 127.4, 127.0, 114.5, 106.3, 55.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{13}O_2S_2$ $[M + H]^+$ 277.0357, found 277.0350.

(*Z*)-1-(4-(Dimethylamino)phenyl)-3-hydroxy-3-(thiophen-2-yl)prop-2-ene-1-thione (77i).

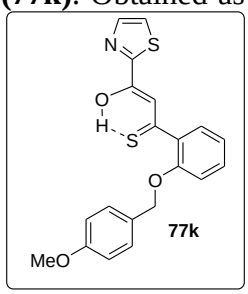


Obtained as a brown solid (1.28 g, 89%): mp 115-117 °C; R_f 0.3 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2921, 1557, 1456, 1249, 790; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.70 (s, 1H), 7.93 (d, *J* = 9.2 Hz, 2H), 7.82 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 7.58 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.31 (s, 1H), 7.15 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H), 6.67 (d, *J* = 9.2 Hz, 2H), 3.07 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 201.2, 171.5, 153.2, 141.6, 132.5, 131.3, 129.4, 129.2, 128.5, 111.1, 106.4, 40.3; HRMS (ESI) *m/z* calcd for $C_{15}H_{16}NOS_2$ $[M + H]^+$ 290.0673, found 290.0669.

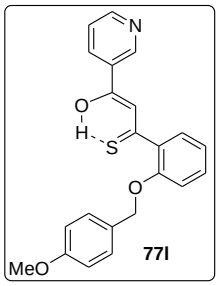
(*Z*)-1-(2-(4-Methoxybenzyloxy)phenyl)-3-hydroxy-3-(thiophen-2-yl)prop-2-ene-1-thione (77j). Obtained as a red solid (1.52 g, 80%): mp 55-57 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3070, 1607, 1512, 1233, 761; ^1H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 1H), 7.59-7.56 (m, 2H), 7.49 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 7.41-7.33 (m, 4H), 7.06-7.02 (m, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.07 (s, 2H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.2, 177.6, 159.6, 154.7, 143.6, 133.8, 132.8, 131.3, 130.60, 130.57, 129.2, 128.7, 128.4, 121.3, 115.9, 114.1, 113.6, 70.7, 55.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}O_3S_2$ $[M + H]^+$ 383.0776, found 383.0773.



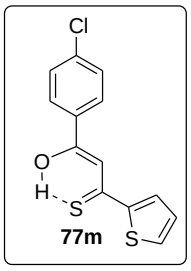
(*Z*)-1-(2-(4-Methoxybenzyloxy)phenyl)-3-hydroxy-3-(thiazol-2-yl)prop-2-ene-1-thione (77k). Obtained as a brown semi-solid (1.58 g, 83%): R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2832, 1583, 1485, 1261, 791; ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.98 (d, *J* = 3.2 Hz, 1H), 7.84 (s, 1H), 7.65 (d, *J* = 3.2 Hz, 1H), 7.47 (dd, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.38-7.33 (m, 3H), 7.03-7.00 (m, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 2H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.1, 176.8, 168.1, 159.4, 154.7, 144.8, 133.4, 131.4, 130.1, 129.1, 128.7, 125.5, 121.1, 115.8, 114.0, 113.5, 70.6, 55.4; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}NO_3S_2Na$ $[M + Na]^+$ 406.0548, found 406.0542.



(*Z*)-1-(2-(4-Methoxybenzyloxy)phenyl)-3-hydroxy-3-(pyridin-3-yl)prop-2-ene-1-thione (77l). Obtained as a red solid (1.60 g, 85%): mp 76-78 °C; R_f 0.3 (3:2 EtOAc/hexane); IR (neat, cm^{-1}) 2921, 1583, 1488, 1239, 784; ^1H NMR (400 MHz, $CDCl_3$) δ 13.29 (s, 1H), 9.01 (d, *J* = 1.6 Hz, 1H), 8.70 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 7.93 (dt, *J* = 4.0 Hz, 2.0 Hz, 1H), 7.62 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.46 (s, 1H), 7.40 (td, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.33-7.28 (m, 3H), 7.06-7.03 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.06 (s, 2H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 196.1, 178.1, 159.7, 154.2, 152.5, 148.7, 135.2, 134.6, 132.3, 131.9, 131.0, 129.4, 128.4, 123.5, 121.4, 115.0, 114.2, 113.3, 70.8, 55.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{20}NO_3S$ $[M + H]^+$ 378.1164, found 378.1154.

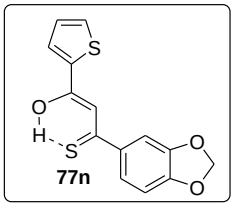


(*Z*)-3-(4-Chlorophenyl)-3-hydroxy-1-(thiophen-2-yl)prop-2-ene-1-thione (77m). Obtained as a red solid (1.21 g, 80%): mp 110-112 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat,



cm^{-1}) 3076, 1581, 1404, 1233, 1053, 704; ^1H NMR (400 MHz, $CDCl_3$) δ 16.02 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 4.4 Hz, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 7.16 (t, J = 4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.8, 174.8, 152.5, 138.8, 134.5, 133.6, 129.4, 128.9, 128.3, 127.9, 106.6; HRMS (ESI) *m/z* calcd for $C_{13}H_{10}ClOS_2$ $[M + H]^+$ 280.9862 and 282.9832, found 280.9852 and 282.9820.

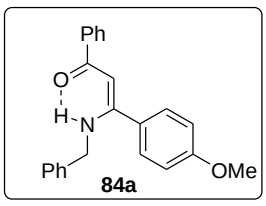
(*Z*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-3-hydroxy-3-(thiophen-2-yl)prop-2-ene-1-thione (77n).



Obtained as a red solid (1.14 g, 79%): mp 65-67 °C; R_f 0.3 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2903, 1557, 1446, 1242, 794; ^1H NMR (400 MHz, $CDCl_3$) δ 14.48 (s, 1H), 7.85 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 7.65 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.40 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.25 (s, 1H), 7.17 (dd, J = 5.2 Hz, 4.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.8, 174.9, 150.6, 148.2, 141.9, 139.0, 132.7, 130.5, 128.7, 122.0, 109.7, 108.2, 107.7, 102.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}O_3S_2$ $[M + H]^+$ 291.015, found 291.0148.

5.5.3 General Procedure for the Synthesis of *N*-Benzyl/propargylenaminones 84a, 84p and 84q. To a stirred solution of 1,3-monothiodiketone (**77a**,**77m**,**77n**) (2.0 mmol) in dry acetonitrile (5 mL), the appropriate α-methyleneamine (2.0 mmol) was added in one slot and the reaction mixture was stirred at room temperature for 3 h (monitored by TLC). It was then diluted with saturated NH_4Cl solution (25 mL), extracted with EtOAc (2 x 25 mL), the combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude products, which were purified by column chromatography using EtOAc/hexane as eluent.

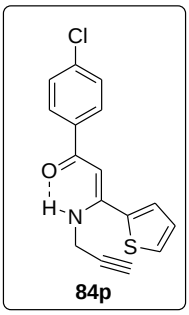
3-(Benzylamino)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (84a). Obtained as a



single tautomer, pale yellow solid (603.6 mg, 88%)(82% in ethanol; 78% in DMF): mp 116-118 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3238, 2920, 1609, 1449, 1271, 734; ^1H NMR (400 MHz, DMSO-d_6) δ 11.67 (t, J = 6.0 Hz, 1H), 7.90-7.87 (m, 2H), 7.50-7.46 (m, 3H), 7.44-7.41 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.28 (m, 1H), 7.26-7.24 (m, 2H), 7.05 (d, J = 8.8 Hz, 2H), 5.84 (s, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100

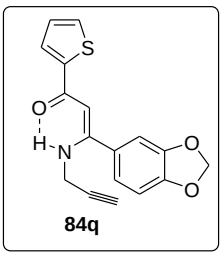
MHz, DMSO-d_6) δ 186.7, 166.2, 160.4, 139.7, 138.7, 130.8, 129.4, 128.7, 128.3, 127.3, 127.0, 126.9, 126.8, 114.1, 92.9, 55.3, 47.7; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}NO_2$ $[M + H]^+$ 344.1651, found 344.1648.

3-(Benzylamino)-3-(methylthio)-1-phenylprop-2-en-1-one (84p). Obtained as a single tautomer, brown solid (487.6 mg, 81%): mp 88-90 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3227, 2114, 1574, 1294, 768; ^1H NMR (400 MHz, $CDCl_3$) δ 11.4 (br s, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.49 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.47 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.15 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 6.00 (s, 1H), 4.17 (dd, J = 6.4 Hz, 2.4 Hz, 2H), 2.36 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.7, 158.7, 138.4, 137.4, 135.4, 129.4, 128.74, 128.67, 128.5, 127.9, 95.0, 79.9, 73.0, 34.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}ClNOS$ $[M + H]^+$ 302.0406, found 302.0403.



84p

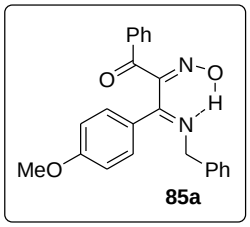
3-(Benzo[*d*][1,3]dioxol-5-yl)-3-(prop-2-ynylamino)-1-(thiophen-2-yl)prop-2-en-1-one (84q). Obtained as a single tautomer, brown solid (528.7 mg, 85%): mp 83-85 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3287, 2898, 2120, 1574, 1231, 773; ^1H NMR (400 MHz, $CDCl_3$) δ 10.91 (br s, 1H), 7.57 (d, J = 3.6 Hz, 1H), 7.48 (d, J = 3.2 Hz, 1H), 7.06 (t, J = 4.0 Hz, 1H), 7.00-6.96 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H), 5.70 (s, 1H), 3.95 (dd, J = 7.2 Hz, 3.6 Hz, 2H), 2.30 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.1, 165.4, 149.2, 148.0, 147.0, 130.7, 128.5, 128.3, 127.9, 122.3, 108.7, 108.5, 101.8, 94.6, 79.9, 72.6, 34.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}NO_3S$ $[M + H]^+$ 312.0694, found 312.0690.



84q

5.5.4 Synthesis of *α*-Hydroxyiminoimine 85a from *N*-Benzylenaminone 84a. To a stirred solution of enaminone **84a** (343.1 mg, 1.0 mmol) in dry acetonitrile (3 mL), 82.8 mg (1.2 mmol) of sodium nitrite and 0.08 mL (1.5 mmol) of acetic acid were added and the reaction mixture was stirred at room temperature for 1 h (monitored by TLC). It was then neutralized with saturated $NaHCO_3$ solution (25 mL), extracted with EtOAc (2 x 25 mL) and the combined extracts were washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford crude **85a**, which was purified by column chromatography using EtOAc/hexane (2:3) as eluent.

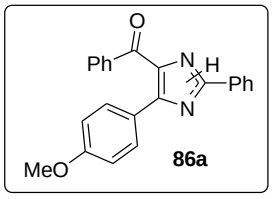
(2*E*,3*E*)-3-(Benzylimino)-2-(hydroxyimino)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (85a). Obtained as a single tautomer, pale yellow solid (632.4 mg, 85%): mp 53-55 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3251, 2923, 1641, 1594, 1325, 687; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.69-7.65 (m, 3H), 7.59-7.56 (m, 2H), 7.39-7.35 (m, 2H), 7.34-7.32 (m, 2H), 7.26-7.25 (m, 1H), 6.99 (d, J = 8.4 Hz, 2H), 4.53 (q, J = 16.0 Hz, 2H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 189.0, 161.1, 159.1, 153.0, 139.7, 135.9, 133.1, 130.1, 128.4, 128.3, 128.2, 128.1, 127.8, 126.5, 114.0, 57.2, 55.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_2O_3$ $[M + H]^+$ 373.1552, found 373.1548.



85a

5.5.5 Base Mediated Intramolecular Cyclization of *α*-Hydroxyiminoimine 85a: Synthesis of Imidazole 86a. To a stirred solution of *α*-hydroxyiminoimine **85a** (186.0 mg, 0.5mmol) in dry acetonitrile (3 mL), 69.1 mg (0.5 mmol) of K_2CO_3 was added at room temperature, and the reaction mixture was heated with stirring at 80 °C for 3 h (monitored by TLC). It was then treated with saturated NH_4Cl solution (25 mL), extracted with EtOAc (2 x 25 mL), the combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude imidazole **86a** thus obtained, was purified by column chromatography using EtOAc/hexane (3:7) as eluent.

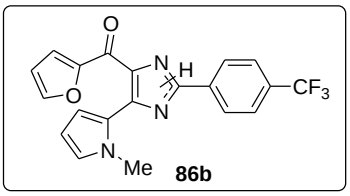
5-(4-Methoxyphenyl)-2-phenyl-1*H*-imidazol-4-yl)(phenyl)methanone and (4-(4-Methoxyphenyl)-2-phenyl-1*H*-imidazol-5-yl)(phenyl)methanone (86a). Obtained as a 75:25 inseparable mixture of tautomers, pale yellow solid (153.9 mg, 87%): mp 150-152 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3264, 1592, 1571, 1423, 1244, 781; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (br s, 0.25H), 13.11, (br s, 0.75H), 8.22-8.20 (m, 0.5H), 8.13-8.11 (m, 1.5H), 8.08-8.05 (m, 1.5H), 7.70 (d, J = 8.8 Hz, 1.5H), 7.61-7.56 (m, 1.5 H), 7.52-7.47 (m, 4H), 7.43-7.40 (m, 0.75H), 7.34-7.27 (m, 0.75H), 7.03 (d, J = 8.8 Hz, 1.5H), 6.71 (d, J = 8.8 Hz, 0.5H), 3.82 (s, 2.25H), 3.69 (s, 0.75H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 188.3, 186.2, 159.6, 158.8, 148.2, 147.6, 146.4, 144.9, 138.8, 138.6, 137.7, 135.4, 132.2, 131.9, 130.7, 130.4, 130.2, 129.7, 129.5, 129.3, 129.2, 128.9, 128.7, 128.1, 127.9, 126.4, 125.7, 121.8, 113.5, 113.1, 55.3, 55.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}N_2O_2$ $[M + H]^+$ 355.1447, found 355.1442.



86a

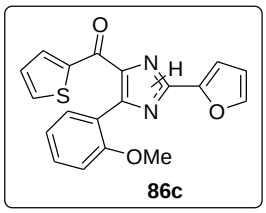
5.5.6 General Procedure for Sequential One-Pot Synthesis of 2,4,5-Trisubstituted Imidazoles 86a-k from Monothio-1,3-diketones 77a-h. To a stirred solution of monothio-1,3-diketone **77** (1.0 mmol) in dry acetonitrile (5 mL), appropriate *α*-methyleneamine (1.0 mmol) was added in one slot and the reaction mixture was further stirred at room temperature for 3 h. After complete consumption of starting materials (monitored by TLC), sodium nitrite (82.8 mg, 1.2 mmol) and acetic acid (0.08 mL, 1.5 mmol) were added to the reaction mixture, followed by further stirring for 1 hr at room temperature. After completion of the reaction (monitored by TLC), 691.0 mg (5.0 mmol) of K_2CO_3 was added and the reaction mixture was heated at 80 °C for 5-8 h (monitored by TLC). After cooling to room temperature, it was then treated with saturated NH_4Cl solution (2 x 25 mL), extracted with EtOAc (3 x 25 mL), the combined organic extract was washed with water (3 x 25 mL), brine (25 mL), dried (Na_2SO_4), and evaporated to give crude residues, which on purification by column chromatography (EtOAc/hexane as eluent) afforded the pure imidazoles **86**.The spectral and analytical data for all newly synthesized imidazoles **86b-k** is given below.

Furan-2-yl(5-(1-methyl-1*H*-pyrrol-2-yl)-2-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-4-yl)methanone and Furan-2-yl(4-(1-methyl-1*H*-pyrrol-2-yl)-2-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)methanone (86b). Obtained as a 50:50 inseparable mixture of tautomers, yellow solid (334.9 mg, 87%): mp 85-87 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3143, 1615, 1465, 1324, 1115, 847; ^1H NMR (400 MHz, $CDCl_3$) δ 11.20 (br s, 0.5H), 10.05 (br s, 0.5H), 8.24-8.20 (m, 1.5H), 8.05 (d, J = 8.0 Hz, 1H), 7.75-7.72 (m, 2H), 7.65 (d, J = 0.8 Hz, 0.5H), 7.52 (d, J = 0.8 Hz, 0.5H), 6.79 (t, J = 2.4 Hz, 0.5 H), 6.69 (t, J = 2.4 Hz, 0.5H), 6.61-6.60 (m, 1H), 6.44 (dd, J = 3.6 Hz, 1.6 Hz, 0.5H), 6.40 (dd, J = 3.6 Hz, 1.6 Hz, 0.5H), 6.33 (dd, J = 3.6 Hz, 1.6 Hz, 0.5H), 6.18 (t, J = 2.8 Hz, 0.5H), 6.14 (t, J = 2.8 Hz, 0.5H), 3.63 (s, 1.5H), 3.57 (s, 1.5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.7, 171.7, 152.1, 151.4, 147.9, 147.0, 144.5, 141.4, 137.6, 132.8, 132.2, 131.7, 131.2, 131.0, 128.5, 126.9, 126.1, 126.04, 126.0, 125.9, 125.42, 125.38, 125.1, 124.6, 122.72, 122.67, 122.5, 121.7, 119.9, 112.7, 112.6, 112.3, 111.4, 108.5, 108.2, 35.0, 34.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{15}F_3N_3O_2$ $[M + H]^+$ 386.1116, found 386.1107.



86b

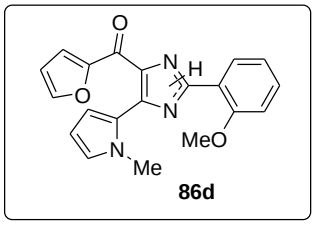
(2-(Furan-2-yl)-5-(2-methoxyphenyl)-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone and (2-(Furan-2-yl)-4-(2-methoxyphenyl)-1*H*-imidazol-5-yl)(thiophen-2-yl)methanone (86c).



86c

Obtained as a single tautomer, pale yellow solid (287.0 mg, 82%): mp 110-112 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3270, 1634, 1427, 1247, 837; ^1H NMR (400 MHz, DMSO-d_6) δ 13.28 (s, 1H), 8.45 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 7.94 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.86 (t, J = 0.8 Hz, 1H), 7.46-741 (m, 2H), 7.24 (dd, J = 4.8 Hz, 4.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.06-7.01 (m, 2H), 6.68 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.4, 156.9, 144.9, 143.7, 143.5, 137.8, 136.1, 134,8, 134.4, 134.2, 131.4, 130.3, 127.9, 119.8, 118.7, 111.8, 111.2, 108.5, 55.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}N_2O_3S$ $[M + H]^+$ 351.0803, found 351.0787.

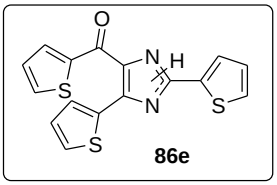
Furan-2-yl(2-(2-methoxyphenyl)-5-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazol-4-yl)methanone and Furan-2-yl(2-(2-methoxyphenyl)-4-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazol-5-yl)methanone (86d). Obtained as a 55:45 inseparable mixture of tautomers,



86d

yellow solid (281.0 mg, 81%): mp 90-92 °C; R_f 0.3 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3388, 1606, 1485, 1205, 1015; ^1H NMR (400 MHz, $CDCl_3$) δ 11.61 (br s, 0.45H), 10.52 (br s, 0.55H), 8.49-8.45 (m, 1H), 8.27 (d, J = 3.6 Hz, 0.55H), 7.66 (s, 0.55H), 7.55 (s, 0.45H), 7.44-7.38 (m, 1H), 7.18-7.11 (m, 1H), 7.08-7.04 (m, 1H), 6.87-6.86 (m, 1H), 6.70 (s, 0.45H), 6.67 (dd, J = 3.6 Hz, 1.6 Hz, 0.45H), 6.60 (dd, J = 3.2 Hz, 1.6 Hz, 0.55H), 6.50 (dd, J = 3.2 Hz, 1.6 Hz, 0.45H), 6.40 (dd, J = 3.6 Hz, 1.6 Hz, 0.55H), 6.26 (t, J = 3.2 Hz, 0.55H), 6.17 (t, J = 3.2 Hz, 0.45H), 4.11 (s, 1.35H), 4.01 (s, 1.65H), 3.72 (s, 1.35H), 3.62 (s, 1.65H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.7, 169.9, 156.7, 156.3, 152.9, 152.4, 146.7, 146.6, 145.5, 144.0, 141.5, 136.7, 131.2, 130.6, 129.8, 128.9, 128.8, 126.5, 126.0, 124.8, 124.7, 122.7, 122.0, 121.9, 121.8, 118.3, 117.6, 117.2, 112.9, 112.6, 112.1, 111.5, 111.4, 110.9, 108.1, 108.0, 56.2, 56.0, 35.6, 35.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_3O_3$ $[M + H]^+$ 348.1348, found 348.1336.

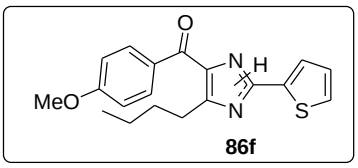
(2,5-Di(thiophen-2-yl)-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone and (2,4-Di(thiophen-2-yl)-1*H*-imidazol-5-yl)(thiophen-2-yl)methanone (86e). Obtained as a single tautomer, yellow solid (242.1 mg, 71%): mp 76-78 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat,



86e

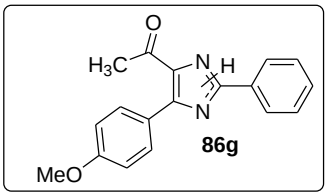
cm^{-1}) 3096, 1601, 1408, 1227, 700; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.3, (br s, 1H), 8.44 (d, J = 3.2 Hz, 1H), 8.02 (d, J = 4.8 Hz, 1H), 7.92 (d, J = 3.2 Hz, 1H), 7.88 (d, J = 3.2 Hz, 1H), 7.73 (d, J = 4.8 Hz, 1H), 7.69 (d, J = 4.8 Hz, 1H), 7.28 (t, J = 4.0 Hz, 1H), 7.25-7.20 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 178.0, 142.8, 141.6, 135.5, 135.1, 134.2, 132.6, 132.5, 129.8, 129.0, 128.9, 128.2, 127.9, 127.0, 126.3; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}N_2OS_3$ [M + H]$^+$ 343.0034, found 343.0028.

(5-Butyl-2-(thiophen-2-yl)-1*H*-imidazol-4-yl)(4-methoxyphenyl)methanone and (4-Butyl-2-(thiophen-2-yl)-1*H*-imidazol-5-yl)(4-methoxyphenyl)methanone (86f). Obtained as a 90:10 inseparable mixture of tautomers, yellow solid (227.8 mg, 67%): mp 81-83 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3244, 1594, 1380, 1252, 701; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03, (br s, 0.1H), 12.95 (br s, 0.9H), 8.32 (d, J = 8.8 Hz, 1.8H), 7.88 (d, J = 2.4 Hz, 0.1H), 7.69 (d, J = 8.8 Hz, 0.2H), 7.61 (d, J = 3.6 Hz, 1H), 7.57 (d, J = 4.8 Hz, 0.9H), 7.15 (dd, J = 4.8 Hz, 4.0 Hz, 1H);, 7.09-7.03 (m, 2H), 3.85 (s, 3H), 2.98 (t, J = 7.6 Hz, 2H), 1.65 (quin, J = 7.6 Hz, 1.8H), 1.51-1.46 (m, 0.2H), 1.40-1.30 (m, 2H), 0.91 (t, J = 7.2 Hz, 2.7H), 0.85 (t, J = 7.2 Hz, 0.3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 185.9, 162.2, 142.0, 139.6, 135.8, 133.5, 132.5, 131.2, 128.0, 126.7, 124.7, 113.2, 55.4, 31.1, 25.1, 22.0, 13.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N_2O_2S$ [M + H]$^+$ 341.1324, found 341.1319.



86f

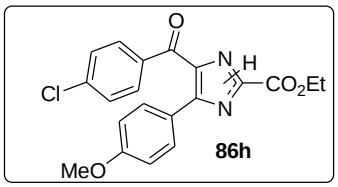
1-(5-(4-Methoxyphenyl)-2-phenyl-1*H*-imidazol-4-yl)ethanone and 1-(4-(4-Methoxyphenyl)-2-phenyl-1*H*-imidazol-5-yl)ethanone (86g). Obtained as a 75:25 inseparable mixture of tautomers, yellow solid (189.8 mg, 65%): mp 195-197 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3273, 1634, 1497, 1247, 1030, 837; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97, (br s, 0.25H), 12.95 (br s, 0.75H), 8.19-8.17 (m, 0.5H), 8.09-8.07 (m, 1.5H), 7.74 (d, J = 8.8 Hz, 1.5H), 7.67 (d, J = 8.8 Hz, 0.5H), 7.51-7.46 (m, 2H), 7.44-7.40 (m, 1H), 7.05-7.00 (m, 2H), 3.83 (s, 2.25H), 3.82 (s, 0.75H), 2.53 (s, 2.25H), 2.28 (s, 0.75H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.0, 187.7, 159.7, 159.4, 147.7, 147.6, 144.7, 136.4, 135.8, 130.9, 130.8, 129.7, 129.5, 129.2, 128.8, 128.7, 128.4, 126.9,



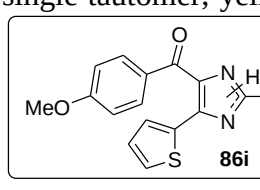
86g

126.5, 125.6, 121.6, 113.3, 55.2, 55.1, 28.4, 28.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_2$ [M + H]$^+$ 293.1290, found 293.1287.

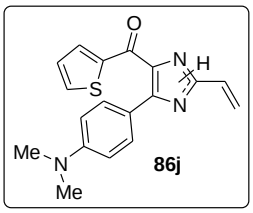
Ethyl 4-(4-chlorobenzoyl)-5-(4-methoxyphenyl)-1*H*-imidazole-2-carboxylate and Ethyl 5-(4-chlorobenzoyl)-4-(4-methoxyphenyl)-1*H*-imidazole-2-carboxylate (86h). Obtained as a 75:25 inseparable mixture of tautomers, yellow solid (261.1 mg, 68%): mp 175-177 °C; R_f 0.3 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3398, 2958, 1680, 1601, 1426, 1259; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (br s, 0.25H), 10.98 (br s, 0.75H), 8.10 (d, *J* = 8.4 Hz, 1.5H), 7.63 (d, *J* = 8.8 Hz, 1.5H), 7.50 (d, *J* = 8.0 Hz, 0.5H), 7.39 (d, *J* = 8.4 Hz, 1.5H), 7.25 (d, *J* = 8.4 Hz, 0.5H), 7.16 (d, *J* = 8.0 Hz, 0.5H), 6.93 (d, *J* = 8.4 Hz, 1.5H), 6.67 (d, *J* = 8.4 Hz, 0.5H), 4.51-4.40 (m, 2H), 3.83 (s, 2.25H), 3.75 (s, 0.75H), 1.44-1.37 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 181.9, 169.5, 162.9, 139.9, 135.2, 133.4, 131.3, 130.3, 129.1, 127.1, 126.1, 122.1, 114.3, 62.6, 55.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{18}ClN_2O_4$ [M + H]$^+$ 385.0955 and 387.0926, found 385.0945 and 387.0917.



Ethyl 4-(4-methoxybenzoyl)-5-(thiophen-2-yl)-1H-imidazole-2-carboxylate and Ethyl 5-(4-methoxybenzoyl)-4-(thiophen-2-yl)-1*H*-imidazole-2-carboxylate (86i). Obtained as a single tautomer, yellow solid (252.7 mg, 71%): mp 150-152 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3358, 1788, 1694, 1254, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (br s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.46 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 7.35 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.04 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 183.7, 164.0, 150.9, 148.7, 131.1, 130.7, 129.5, 129.0, 128.7, 127.8, 123.5, 116.2, 114.2, 64.4, 55.7, 13.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_4S$ [M + H]$^+$ 357.0909, found 357.0918.

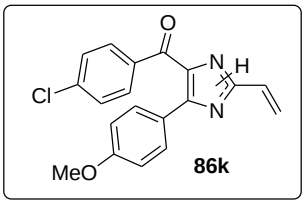


(5-(4-(Dimethylamino)phenyl)-2-vinyl-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone and (4-(4-(Dimethylamino)phenyl)-2-vinyl-1*H*-imidazol-5-yl)(thiophen-2-yl)methanone (86j). Obtained as a single tautomer, pale yellow solid (229.3 mg, 71%): mp 112-114 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3210, 2981, 1608, 1494, 1409, 1150; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 8.37 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 7.92 (dd, *J* = 5.2 Hz, 1.2 Hz,



1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.21 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.66 (dd, *J* = 18.0 Hz, 11.6 Hz, 1H), 6.19 (dd, *J* = 17.6 Hz, 0.8 Hz, 1H), 5.51 (dd, *J* = 11.2 Hz, 0.8 Hz, 1H), 2.97 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 178.4, 150.5, 144.1, 143.7, 139.3, 134.6, 134.5, 133.7, 130.0, 127.6, 125.7, 117.9, 116.2, 111.1, 39.8; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}N_3OS$ $[M + H]^+$ 324.1171, found 324.1166.

(4-Chlorophenyl)(5-(4-methoxyphenyl)-2-vinyl-1*H*-imidazol-4-yl)methanone and (4-Chlorophenyl)(4-(4-methoxyphenyl)-2-vinyl-1*H*-imidazol-5-yl)methanone (86k).

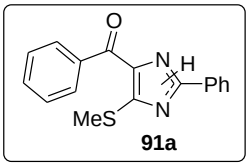


86k

Obtained as a 80:20 inseparable mixture of tautomers, yellow solid (273.7 mg, 81%): mp 60-62 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3224, 2834, 1607, 1586, 1484, 1250; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (br s, 0.2H), 12.97 (br s, 0.8H), 8.28 (d, *J* = 8.8 Hz, 0.2H), 8.08 (d, *J* = 8.0 Hz, 1.6H), 7.91-7.89 (m, 0.4H), 7.66 (d, *J* = 8.4 Hz, 1.6H), 7.54 (d, *J* = 8.0 Hz, 1.6H), 7.33-7.30 (m, 0.8H), 7.02 (d, *J* = 8.4 Hz, 1.6H), 6.72 (d, *J* = 5.6 Hz, 0.4H), 6.63 (dd, *J* = 17.6 Hz, 11.6 Hz, 0.8H), 6.30 (d, *J* = 17.6 Hz, 0.2H), 6.14 (d, *J* = 17.6 Hz, 0.8H), 5.58 (d, *J* = 11.2 Hz, 0.2H), 5.50 (d, *J* = 11.2 Hz, 0.8H), 3.86 (s, 0.6H), 3.81 (s, 2.44H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 186.9, 159.7, 144.5, 138.6, 137.3, 136.7, 134.8, 132.0, 130.5, 127.9, 125.9, 121.6, 118.2, 113.5, 55.3; HRMS (ESI) *m/z* calcd for $C_{19}H_{16}ClN_2O_2$ $[M + H]^+$ 339.0900 and 341.0871, found 339.0900 and 341.0862.

5.5.7 One-Pot Synthesis of Imidazole 91a from N,S-Acetal 89a. To a stirred solution of N,S-acetal **89a**[43] (283.1 mg, 1.0 mmol) in dry acetonitrile (5 mL), 82.8 mg (1.2 mmol) of sodium nitrite and acetic acid (0.08 mL, 1.5 mmol) were added and the reaction mixture was stirred at room temperature for 1 h (monitored by TLC), followed by addition of 691.0 mg (5.0 mmol) of K_2CO_3. It was then heated at 80 °C for 3 h (monitored by TLC) and followed by subsequent work-up and purification as described for imidazoles **86**.

(5-(Methylthio)-2-phenyl-1*H*-imidazol-4-yl)(phenyl)methanone and (4-(Methylthio)-2-phenyl-1*H*-imidazol-5-yl)(phenyl)methanone (91a).[42a]



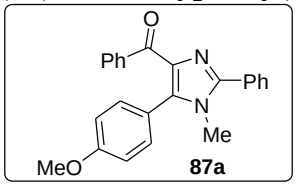
91a

Obtained as a single tautomer, pale yellow solid (211.6 mg, 72%): mp 213-215 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 3247, 1594, 1455, 1284, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (br s, 1H), 8.07-8.05 (m, 2H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.55-7.51 (m, 2H), 7.44-7.43 (m, 3H), 2.59 (s, 3H); $^{13}C\{^{1}H\}$ NMR

(100 MHz, $CDCl_3$) δ 185.3, 150.2, 149.2, 138.6, 132.4, 130.4, 129.1, 128.71, 128.70, 128.1, 126.6, 15.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}N_2OS$ $[M + H]^+$ 295.0905, found 295.0899.

5.5.8 General Procedure for *N*-Methylation of *NH*- Imidazoles 86: Synthesis of 1-*N*-Methy-2,5-bishet(aryl)/alkyl-4-het(aroyl) imidazoles 87a-k, 87p. To a stirred solution of 1(3)-*NH*- imidazoles **86** (0.3mmol) in dry acetonitrile (3 mL) , 41.4 mg (0.3 mmol) of K_2CO_3 was added and the reaction mixture was stirred at room temperature for 1 h, followed by addition of MeI (0.018 mL, 0.3 mmol) and further stirring for 2 h at room temperature (monitored by TLC). The reaction mixture was treated with saturated NH_4Cl solution (25 mL), extracted with EtOAc (2 x 25 mL), the combined organic extracts were washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and evaporated to give crude *N*-methylimidazoles **87**, which were purified by column chromatography using EtOAc/hexane as eluent.

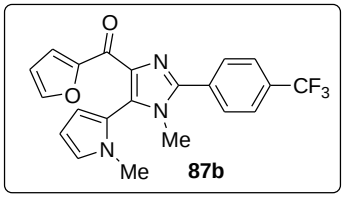
(5-(4-Methoxyphenyl)-1-methyl-2-phenyl-1*H*-imidazol-4-yl)(phenyl)methanone (87a).



87a

Obtained from **86a**, pale yellow solid (100.5 mg, 91%): mp 99-101 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2864, 1635, 1248, 1172, 714; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22-8.20 (m, 2H), 7.76-7.73 (m, 2H), 7.53-7.45 (m, 4H), 7.40-7.37 (m, 4H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.57 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 188.9, 160.3, 147.7, 140.8, 138.5, 137.1, 132.0, 131.9, 130.8, 130.5, 129.4, 129.3, 128.8, 128.0, 121.9, 114.2, 55.5, 33.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}N_2O_2$ $[M + H]^+$ 369.1603, found 369.1590.

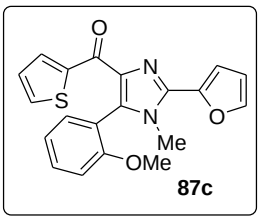
Furan-2-yl(1-methyl-5-(1-methyl-1*H*-pyrrol-2-yl)-2-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-4-yl)methanone (87b). Obtained from **86b**, yellow solid (111.3 mg, 93%): mp



87b

112-114 °C; R_f 0.6 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 2936, 1643, 1475, 1328, 1129, 865; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.64 (dd, *J* = 1.6 Hz, 0.8 Hz, 1H), 6.87 (t, *J* = 2.4 Hz, 1H), 6.55 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H), 6.284-6.280 (m, 2H), 3.62 (s, 3H), 3.55 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.3, 152.0, 146.7, 146.5, 138.6, 133.8, 132.7, 131.4, 131.1, 129.2, 125.7 (q, $J_{C\text{-}F}$ = 4.0 Hz), 124.6, 121.8, 120.1, 112.0, 111.9, 108.2, 34.6, 33.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}F_3N_3O_2$ $[M + H]^+$ 400.1273, found 400.1261.

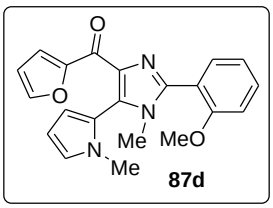
(2-(Furan-2-yl)-5-(2-methoxyphenyl)-1-methyl-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone (87c). Obtained from **86c**, pale yellow solid (98.2 mg, 90%): mp 148-150 °C;



87c

R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2995, 1670, 1499, 1250, 937; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 2.8 Hz, 1H), 7.53-7.50 (m, 2H), 738 (td, J = 8.8 Hz, 1.6 Hz, 1H), 7.31 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.05 (t, J = 4.4 Hz, 1H), 7.00 (t, 7.6 Hz, 1H), 6.96-6.93 (m, 2H), 6.51 (dd, J = 3.2 Hz, 2.0 Hz, 1H), 3.71 (s, 3H), 3.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.2, 157.6, 145.8, 143.9, 143.2, 139.1, 137.5, 136.9, 135.2, 133.8, 133.1, 131.3, 127.7, 120.9, 118.2, 111.8, 111.3, 110.7, 55.7, 32.6; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}N_2O_3S$ $[M + H]^+$ 365.0960, found 365.0954.

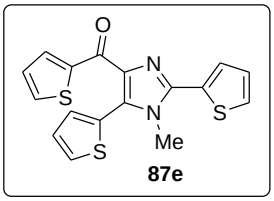
Furan-2-yl(2-(2-methoxyphenyl)-1-methyl-5-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-imidazol-4-yl)methanone (87d). Obtained from **86d**, pale yellow solid (98.2 mg, 96%): mp 155-157 °C;



87d

R_f 0.5 (4:6 EtOAc/hexane); IR (neat, cm^{-1}) 2965, 1630, 1475, 1254, 1019; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.61-7.58 (m, 2H), 7.49 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.12 (td, J = 7.6 Hz, 0.8 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.86 (t, J = 2.0 Hz, 1H), 6.50 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.29-6.25 (m, 2H), 3.86 (s, 3H), 3.56 (s, 3H), 3.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.8, 157.8, 152.4, 146.5, 146.4, 138.4, 132.6, 131.6, 124.3, 121.8, 121.2, 120.9, 119.9, 112.0, 111.6, 111.2, 108.0, 55.7, 34.7, 32.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N_3O_3$ $[M + H]^+$ 362.1505, found 362.1494.

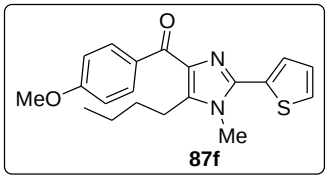
(1-Methyl-2,5-di(thiophen-2-yl)-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone (87e).



87e

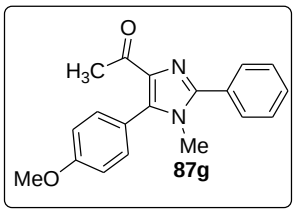
Obtained from **86e**, pale yellow solid (95.0 mg, 89%): mp 90-92 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2928, 1629, 1511, 1416, 1232, 828; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.64 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.56 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.50-7.48 (m, 2H), 7.30 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.20-7.14 (m, 3H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.9, 143.6, 142.7, 138.0, 135.5, 134.3, 132.8, 132.5, 130.9, 128.84, 128.80, 127.82, 127.81, 127.80, 127.4, 127.1, 33.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}N_2OS_3$ $[M + H]^+$ 357.0190, found 357.0173.

(5-Butyl-1-methyl-2-(thiophen-2-yl)-1*H*-imidazol-4-yl)(4-methoxyphenyl)methanone (87f). Obtained from **86f**, pale yellow semi-solid (89.2 mg, 84%): R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2827, 1635, 1497, 1248, 896; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 9.2 Hz, 2H), 7.42 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.37 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.13 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 6.95 (d, J = 9.2 Hz, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.09 (t, J = 8.0 Hz, 2H), 1.69-1.63 (m, 2H), 1.54-1.44 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.6, 162.9, 142.8, 140.7, 136.7, 133.2, 132.7, 131.7, 127.6, 127.2, 127.0, 113.3, 55.6, 31.8, 31.3, 24.8, 22.9, 14.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}N_2O_2S$ $[M + H]^+$ 355.1480, found 355.1474.



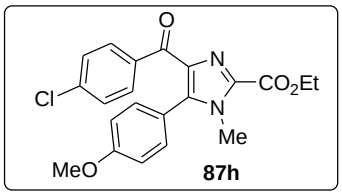
87f

1-(5-(4-Methoxyphenyl)-1-methyl-2-phenyl-1*H*-imidazol-4-yl)ethanone (87g). Obtained from **86g**, off white solid (83.5 mg, 91%): mp 102-104 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2928, 1629, 1511, 1416, 1232, 828; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.68 (m, 2H), 7.52-7.44 (m, 3H), 7.37 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.47 (s, 3H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.7, 160.4, 147.7, 138.4, 137.4, 131.9, 130.4, 129.5, 129.3, 128.9, 121.7, 114.2, 55.5, 33.4, 28.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_2O_2$ $[M + H]^+$ 307.1447, found 307.1440.



87g

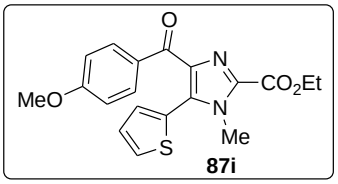
Ethyl 4-(4-chlorobenzoyl)-5-(4-methoxyphenyl)-1-methyl-1*H*-imidazole-2-carboxylate (87h). Obtained from **86h**, off white solid (105.0 mg, 88%): mp 90-92 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2928, 1716, 1650, 1482, 1254, 902; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.0 (d, J = 8.8 Hz, 2H), 4.47 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.9, 160.8, 159.6, 143.1, 138.9, 137.3, 136.14, 136.05, 132.3, 131.9, 128.5, 120.1, 114.3, 62.1, 55.5, 34.1, 14.5; HRMS (ESI) *m/z* calcd for $C_{21}H_{20}ClN_2O_4$ $[M + H]^+$ 399.1112 and 401.1082, found 399.1108 and 401.1074.



87h

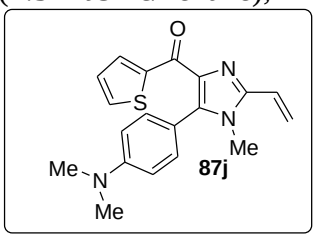
Ethyl 4-(4-methoxybenzoyl)-1-methyl-5-(thiophen-2-yl)-1*H*-imidazole-2-carboxylate (87i). Obtained from **86i**, off white solid (98.7 mg, 89%): mp 108-110 °C; R_f 0.5 (2:3

EtOAc/hexane); IR (neat, cm^{-1}) 2874, 1736, 1588, 1496, 1293, 839; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 2H), 7.38 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.14 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 6.96 (dd, J = 5.2 Hz, 4.0 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.28 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 183.5, 163.8, 150.2, 148.9, 131.7, 131.3, 130.4, 129.3, 127.5, 126.0, 124.5, 118.7, 113.9, 64.4, 55.6, 29.2, 13.9; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_2O_4S$ $[M + H]^+$ 371.1066, found 371.1072.



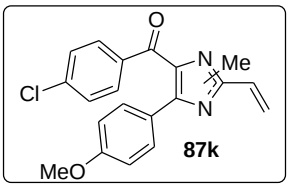
87i

(5-(4-(Dimethylamino)phenyl)-1-methyl-2-vinyl-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone (87j). Obtained from **86j**, yellow solid (88.9 mg, 88%): mp 88-90 °C; R_f 0.6 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 2926, 1621, 1406, 1218, 855; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.60 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.29 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 4.8 Hz, 4.0 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.70 (dd, J = 17.2 Hz, 11.2 Hz, 1H), 6.40 (dd, J = 17.2 Hz, 1.6 Hz, 1H), 5.57 (dd, J = 10.8 Hz, 1.6 Hz, 1H), 3.52 (s, 3H), 3.01 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.9, 167.5, 151.4, 147.6, 134.8, 129.6, 129.1, 127.6, 127.3, 122.3, 116.3, 111.5, 110.0, 40.2, 33.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_3OS$ $[M + H]^+$ 338.1327, found 338.1320.



87j

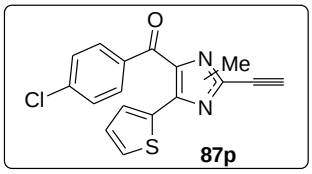
(4-Chlorophenyl)(5-(4-methoxyphenyl)-1-methyl-2-vinyl-1*H*-imidazol-4-yl)methanone and (4-Chlorophenyl)(4-(4-methoxyphenyl)-1-methyl-2-vinyl-1*H*-imidazol-5-yl)methanone (87k). Obtained from **86k**, as a 77:23 inseparable mixture of tautomers, yellow semi-solid (87.6 mg, 83%): mp 88-90 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2922, 1643, 1586, 1455, 1246, 903; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 1.54H), 7.54 (d, J = 8.4 Hz, 0.46H), 7.35 (d, J = 8.4 Hz, 1.54H), 7.29 (d, J = 8.4 Hz, 1.54H), 7.16 (d, J = 8.4 Hz, 0.46H), 7.11 (d, J = 8.4 Hz, 0.46H), 6.97 (d, J = 8.8 Hz, 1.54H), 6.76-6.65 (m, 1H), 6.62 (d, J = 8.8 Hz, 0.46H), 6.49 (dd, J = 17.2 Hz, 1.6 Hz, 0.23H), 6.32 (dd, J = 17.2 Hz, 1.6 Hz, 0.77H), 5.69 (dd, J = 11.2 Hz, 1.6 Hz, 0.23H), 5.58 (dd, J = 11.2 Hz, 1.6 Hz, 0.77H), 3.86 (s, 0.69H), 3.85 (s, 2.31H), 3.72 (s, 0.69H), 3.51 (s, 2.31H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.1, 186.6, 160.3, 159.6, 149.3, 149.1, 145.0, 140.4, 138.8, 138.3, 136.8, 136.7, 136.6, 132.3, 131.9, 131.4, 130.8, 128.3, 128.2, 126.8, 126.3, 123.1, 123.0, 122.2, 121.3, 120.8,



87k

114.1, 113.6, 55.5, 55.4, 32.3, 31.4; HRMS (ESI) *m/z* calcd for $C_{20}H_{18}ClN_2O_2$ $[M + H]^+$ 353.1057 and 355.1027, found 353.1061 and 355.1034.

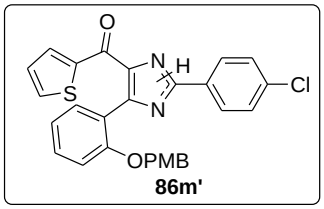
(4-Chlorophenyl)(2-ethynyl-1-methyl-5-(thiophen-2-yl)-1*H*-imidazol-4-yl)methanone and (4-Chlorophenyl)(2-ethynyl-1-methyl-4-(thiophen-2-yl)-1*H*-imidazol-5-yl)methanone (87p). Obtained from **86p**, as a 60:40 inseparable mixture of tautomers, yellow solid (90.9 mg, 93%): mp 85-87 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2925, 2119, 1644, 1586, 1475, 1087; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.8 Hz, 1.2H), 7.68 (d, J = 8.8 Hz, 0.8H), 7.54 (dd, J = 5.2 Hz, 1.2 Hz, 0.6H), 7.39 (d, J = 8.8 Hz, 1.2H), 7.28-7.27 (m, 1.4H), 7.19 (dd, J = 5.2 Hz, 1.2 Hz, 0.4H), 7.16 (dd, J = 5.2 Hz, 3.6 Hz, 0.6H), 6.72 (dd, J = 5.2 Hz, 3.6 Hz, 0.4H), 6.66 (dd, J = 3.6 Hz, 1.2 Hz, 0.4H), 3.88 (s, 1.2H), 3.70 (s, 1.8H), 3.49 (s, 0.4H), 3.42 (s, 0.6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.4, 186.0, 141.5, 140.0, 139.0, 138.6, 136.1, 135.8, 135.3, 134.7, 132.7, 132.2, 131.4, 131.3, 131.0, 129.0, 128.9, 128.5, 128.3, 128.0, 127.5, 127.3, 127.1, 126.4, 84.1, 82.6, 72.8, 72.4, 33.9, 32.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}ClN_2OS$ $[M + H]^+$ 327.0359 and 329.0329, found 327.0352 and 329.0318.



87p

5.5.9 General Procedure for the Synthesis of 4(5)-[2-(4-Methoxybenzyloxy)phenyl]-2,5(4) substituted imidazoles 86m'-o'. The imidazoles **86m'-7o'** were prepared from the respective monothioketones **77j-l** (1.0 mmole) and the appropriate α-methyleneamine (1.0 mmole) and sodium nitrite (82.2 mg, 1.2 mmol) following the general one-pot procedure as described above.

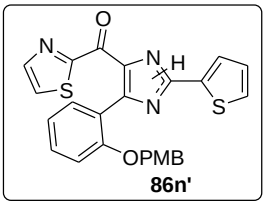
(5-(2-(4-Methoxybenzyloxy)phenyl)-2-(4-chlorophenyl)-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone and (4-(2-(4-Methoxybenzyloxy)phenyl)-2-(4-chlorophenyl)-1*H*-imidazol-5-yl)(thiophen-2-yl)methanone (86m'). Obtained as a single tautomer, yellow solid (410.0 mg, 82%): mp 140-142 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3373, 1608, 1515, 1351, 1235, 749; ^1H NMR (400 MHz, DMSO-d_6) δ 13.30 (br s, 1H), 8.44 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.98 (dd, J = 4.8 Hz, 0.8 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.52-7.44 (m, 2H), 7.27-7.22 (m, 4H), 7.08 (t, J = 7.2 Hz, 1H), 6.67 (d, J = 8.4 Hz, 2H), 5.00 (s, 2H), 3.65 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.2,



86m'

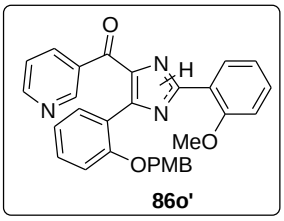
158.7, 156.2, 143.8, 143.3, 136.4, 135.1, 134.8, 134.6, 133.4, 131.5, 130.4, 129.2, 129.0, 128.5, 127.8, 127.0, 120.0, 119.2, 113.3, 112.5, 69.4, 54.9; HRMS (ESI) *m/z* calcd for $C_{28}H_{22}ClN_2O_3S$ $[M + H]^+$ 501.1040 and 503.1010, found 501.1026 and 503.0994.

(5-(2-(4-Methoxybenzyloxy)phenyl)-2-(thiophen-2-yl)-1*H*-imidazol-4-yl)(thiazol-2-yl)methanone and (4-(2-(4-Methoxybenzyloxy)phenyl)-2-(thiophen-2-yl)-1*H*-imidazol-5-yl)(thiazol-2-yl)methanone (86n'). Obtained as a 75:25 inseparable mixture of tautomers, yellow solid (402.0 mg, 85%): mp 72-74 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3279, 1633, 1514, 1481, 1240, 835; ^1H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 0.75H), 13.28 (s, 0.25H), 8.12-8.08 (m, 1.5H), 7.96-7.84 (m, 0.5H), 7.71-7.64 (m, 1.5H), 7.52-7.44 (m, 2H), 7.28-7.20 (m, 3H), 7.13-.7.07 (m, 1.5H), 7.02-6.93 (m, 1H), 6.71 (d, *J* = 8.0 Hz, 0.5H), 6.66 (d, *J* = 8.0 Hz, 1.5H), 4.94 (s, 1.5H), 4.72 (s, 0.5H), 3.68 (s, 0.75H), 3.65 (s, 2.25H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 176.2, 162.9, 158.7, 156.0, 143.8, 141.3, 135.7, 135.5, 132.7, 131.1, 130.7, 129.4, 128.3, 128.2, 127.5, 127.3, 125.6, 120.2, 118.7, 113.4, 112.6, 69.5, 54.9; HRMS (ESI) *m/z* calcd for $C_{25}H_{20}N_3O_3S_2$ $[M + H]^+$ 474.0946, found 474.0943.



86n'

(5-(2-(4-Methoxybenzyloxy)phenyl)-2-(2-methoxyphenyl)-1*H*-imidazol-4-yl)(pyridin-3-yl)methanone and (4-(2-(4-Methoxybenzyloxy)phenyl)-2-(2-methoxyphenyl)-1*H*-imidazol-5-yl)(pyridin-3-yl)methanone (86o'). Obtained as a 90:10 inseparable mixture of tautomers, yellow solid (378.0 mg, 77%): mp 80-82 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3413, 2924, 1643, 1414, 1239, 748; ^1H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 0.9H), 12.08 (s, 0.1H), 9.18 (d, *J* = 1.6 Hz, 0.9H), 8.71 (dd, *J* = 4.4 Hz, 0.8 Hz, 0.9H), 8.51-8.48 (m, 0.2H), 8.35 (dt, *J* = 8.0 Hz, 2.0 Hz, 0.9H), 8.10 (dd, *J* = 7.6 Hz, 1.6 Hz, 0.1H), 7.98 (dd, *J* = 7.6 Hz, 1.6 Hz, 0.9H), 7.70 (d, *J* = 7.6 Hz, 0.1H), 7.51-7.47 (m, 1.8H), 7.44-7.39 (m, 1.8H), 7.24-7.16 (m, 3.8H), 7.13-7.02 (m, 2.2H), 6.97-6.93 (m, 0.2H), 6.83 (d, *J* = 8.8 Hz, 0.2H), 6.72 (d, *J* = 8.4 Hz, 0.2H), 6.68 (d, *J* = 8.8 Hz, 1.8H), 4.97 (s, 1.8H), 4.57 (s, 0.2H), 3.98 (s, 0.3H), 3.87 (s, 2.7H), 3.72 (s, 0.3H), 3.66 (s, 2.7H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 186.3, 158.7, 156.3, 156.1, 151.8, 150.8, 142.9, 137.3, 135.9, 134.9, 133.9, 131.5, 130.5, 130.2, 129.1, 128.9, 128.5, 123.1, 120.7, 120.1, 119.2, 118.0, 113.4, 112.5,

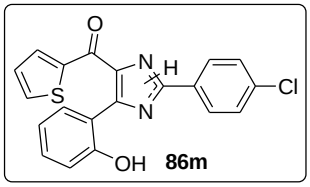


86o'

111.7, 69.5, 55.5, 54.9; HRMS (ESI) *m/z* calcd for $C_{30}H_{26}N_3O_4$ $[M + H]^+$ 492.1923, found 492.1923.

5.5.10 General Procedure for deprotection of 4(5)-[2-(4-Methoxybenzyloxy)phenyl] imidzoles 86m'-o' to (2-(hydroxyphenyl) -2,5(4)-substituted imidazoles 86m-o. To a stirred solution of 4(5)-[4-methoxybenzyloxy)phenyl]imidazoles **86m'-o'** (0.3 mmol) in dichloromethane (3 mL), TFA (1mL) was added and the reaction mixture was further stirred at room temperature for 2 h. It was then neutralized with saturated $NaHCO_3$ solution (25 mL), extracted with DCM (2 x 25 mL), the combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude products, which were purified by column chromatography using EtOAc/hexane as eluent.

(2-(4-Chlorophenyl)-5-(2-hydroxyphenyl)-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone and (2-(4-Chlorophenyl)-4-(2-hydroxyphenyl)-1*H*-imidazol-5-yl)(thiophen-2-yl)methanone (86m). Obtained as a 50:50 inseparable mixture of tautomers, yellow solid

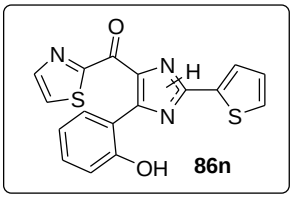


86m

(96.9 mg, 85%): mp 161-163 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3302, 2919, 1589, 1479, 1321, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 11.50 (br s, 0.5H), 11.21 (br s, 0.5H), 10.37 (br s, 0.5H), 9.58 (br s, 0.5H), 8.45 (d, *J* = 3.2 Hz, 0.5H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 4.4 Hz, 0.5H), 7.65 (d, *J* = 4.8 Hz, 0.5H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 3.6 Hz, 0.5H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.24-7.13 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 0.5H), 7.02 (d, *J* = 8.4 Hz, 0.5H), 6.97 (d, *J* = 8.0 Hz, 0.5H), 6.94-6.88 (m, 1H), 6.52 (t, *J* = 7.6 Hz, 0.5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.7, 179.0, 156.7, 155.1, 146.7, 145.8, 141.72, 141.69, 137.36, 137.35, 136.9, 136.8, 136.7, 136.4, 135.8, 135.7, 134.9, 131.6, 131.0, 129.7, 129.5, 129.2, 128.3, 127.8, 127.7, 127.2, 126.9, 126.4, 126.3, 121.8, 121.3, 119.7, 118.8, 117.5, 116.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{14}ClN_2O_2S$ $[M + H]^+$ 381.0465 and 383.0435, found 381.0447 and 383.0423.

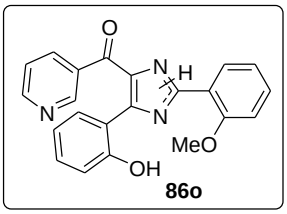
(5-(2-Hydroxyphenyl)-2-(thiophen-2-yl)-1*H*-imidazol-4-yl)(thiazol-2-yl)methanone and (4-(2-Hydroxyphenyl)-2-(thiophen-2-yl)-1*H*-imidazol-5-yl)(thiazol-2-yl)methanone (86n). Obtained as a 75:25 inseparable mixture of tautomers, yellow solid (84.7 mg, 80%): mp 200-202 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 3305, 2923, 1589, 1479, 1263,

821; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 0.25H), 13.36 (s, 0.75H), 9.95 (s, 0.25H), 9.80 (s, 0.75H), 8.12 (d, J = 2.4Hz, 0.75H), 8.03 (s, 0.75H), 7.96-7.92 (m, 0.5H), 7.75 (s, 1H), 7.65 (s, 1H), 7.41 (d, J = 6.8 Hz, 0.75H), 7.26-7.18 (m, 2.25H), 6.90-6.71 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 176.4, 163.1, 155.1, 143.8, 141.2, 136.3, 135.3, 133.0, 131.3, 130.3, 128.1, 127.4, 127.3, 125.5, 118.6, 116.8, 115.6, 54.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}N_3O_2S_2$ $[M + H]^+$ 354.0371, found 354.0366.



86n

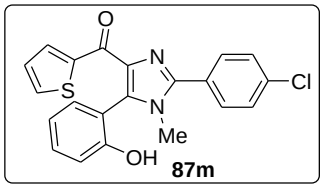
(5-(2-Hydroxyphenyl)-2-(2-methoxyphenyl)-1*H*-imidazol-4-yl)(pyridin-3-yl)methanone and (4-(2-Hydroxyphenyl)-2-(2-methoxyphenyl)-1*H*-imidazol-5-yl)(pyridin-3-yl)methanone (86o). Obtained as a single tautomer, yellow solid (89.0 mg, 80%): mp 110-112 °C; R_f 0.3 (3:2 EtOAc/hexane); IR (neat, cm^{-1}) 3103, 1622, 1581, 1462, 1258, 750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19, (br s, 1H), 9.13 (s, 1H), 8.71 (d, J = 3.6 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.99 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.57 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.53-7.46 (m, 2H), 7.25-7.19 (m, 2H), 7.12 (t, J = 7.2 Hz, 1H), 6.87-6.83 (m, 2H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 185.7, 156.5, 154.7, 151.4, 149.9, 143.2, 137.8, 134.0, 131.2, 131.0, 130.3, 129.1, 123.4, 120.8, 118.7, 116.8, 116.6, 115.7, 112.0, 55.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_3O_3$ $[M + H]^+$ 372.1348, found 372.1337.



86o

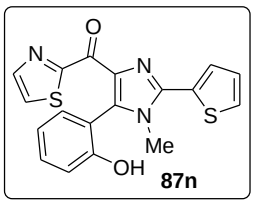
5.5.11 General Procedure for Methylation and Deprotection of 86m'-o': Synthesis of 1-(*N*-Methyl)-5-(2-hydroxyphenyl)-4-het(aroyl)imidazoles 87m-o. To a stirred solution of imidazoles **86m'-o'** (0.3 mmol) in dry acetonitrile (3 mL), K_2CO_3 (41.4 mg, 0.3 mmol) was added and the reaction mixture was stirred at room temperature (1 h), followed by addition of MeI (0.018 mL, 0.3 mmol) and further stirring for 2h (monitored by TLC).Work-up of the reaction mixture as described earlier for methylation of imidazoles **86a-k** afforded crude *N*-methylated imidazoles **87m'-o'** which were subjected to deprotection with TFA without further purification, following the similar procedure and work-up as described for deprotection of **86m'-86o'**. Purification of the crude products thus obtained by column chromatography (EtOAc and hexane as eluent) afforded pure 1-*N*-methylated 4(5)-2-hydroxyphenylimidazoles **87m-o**.

(2-(4-Chlorophenyl)-5-(2-hydroxyphenyl)-1-methyl-1*H*-imidazol-4-yl)(thiophen-2-yl)methanone (87m). Obtained from **86m'**, yellow solid (92.1 mg, 78%): mp 128-130 °C; R_f 0.3 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3242, 1583, 1411, 1227, 835; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 2.8 Hz, 1H), 8.33 (br s, 1H), 7.72-7.70 (m, 3H), 7.52 (d, J = 8.4 Hz, 2H), 7.41 (dt, J = 8.0 Hz, 1.2 Hz, 1H), 7.24-7.15 (m, 3H), 7.06 (t, J = 7.2 Hz, 1H), 3.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.9, 156.8, 148.1, 142.6, 137.9, 137.6, 137.2, 136.0, 131.6, 131.3, 130.6, 129.3, 128.6, 128.2, 121.1, 121.0, 118.6, 34.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{16}ClN_2O_2S$ $[M + H]^+$ 395.0621 and 397.0592, found 395.0615 and 397.0573.



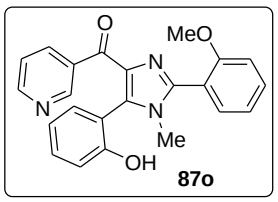
87m

(5-(2-Hydroxyphenyl)-1-methyl-2-(thiophen-2-yl)-1*H*-imidazol-4-yl)(thiazol-2-yl)methanone (87n). Obtained from **86n'**, yellow solid (97.9 mg, 89%): mp 142-144 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3244, 1612, 1463, 1277, 835; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 3.2 Hz, 1H), 7.77 (br s, 1H), 7.71 (d, J = 2.8 Hz, 1H), 7.51-7.48 (m, 2H), 7.36 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.18-7.14 (m, 3H), 7.02 (td, J = 7.6 Hz, 1.2 Hz, 1H), 3.64 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.5, 163.6, 156.3, 144.8, 143.9, 139.2, 136.7, 131.9, 131.8, 131.6, 128.2, 127.9, 127.8, 127.3, 121.1, 120.2, 117.6, 34.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{14}N_3O_2S_2$ $[M + H]^+$ 368.0527, found 368.0515.



87n

(5-(2-Hydroxyphenyl)-2-(2-methoxyphenyl)-1-methyl-1*H*-imidazol-4-yl)(pyridin-3-yl)methanone (87o). Obtained from **86o'**, yellow solid (94.7 mg, 82%): mp 65-67 °C; R_f 0.4 (7:3 EtOAc/hexane); IR (neat, cm^{-1}) 3112, 1660, 1445, 1293, 896; ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (br s, 1H), 8.68 (br s, 1H), 8.57 (d, J = 8.0 Hz, 1H), 7.54-7.48 (m, 2H), 7.41-7.35 (m, 2H), 7.23-7.19 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 7.04-7.01 (m, 3H), 3.88 (s, 3H), 3.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.0, 157.8, 156.6, 152.7, 152.5, 147.6, 138.8, 137.9, 137.7, 132.7, 131.9, 131.60, 131.56, 123.2, 121.3, 120.9, 120.2, 119.3, 118.4, 111.2, 55.8, 33.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_3O_3$ $[M + H]^+$ 386.1505, found 386.1496.

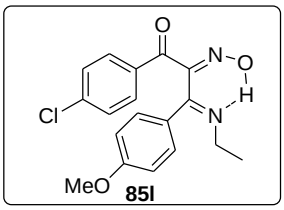


87o

5.5.12 One–pot Synthesis of *N*-propargyl/ethylhydroxyiminoimines 85l, 85p-85q from Monothioketones 77. To a stirred solution of monothio-1,3-diketone (**77g**, **77m-n**) (2.0

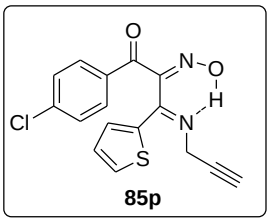
mmol) in dry acetonitrile (5 mL) was added appropriate α-methyleneamine (2.0 mmol) in one slot and reaction mixture was stirred at room temperature for 3 h (monitored by TLC), after complete consumption of starting materials (monitored by TLC), sodium nitrite (165.6 mg, 2.4 mmol) and acetic acid (0.17 mL, 3.0 mmol) were added and reaction mixture was further stirred at room temperature for 1 h (monitored by TLC). It was then neutralized with saturated $NaHCO_3$ solution (25 mL), extracted with EtOAc (3 x 25 mL), the combined organic layer was washed with water (3 x 25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give crude residue which were purified by column chromatography using EtOAc/hexane as eluent.

1-(4-Chlorophenyl)-3-(ethylimino)-2-(hydroxyimino)-3-(4-methoxyphenyl)propan-1-one (85l). Obtained as a single tautomer, pale yellow solid (564.1 mg, 82%): mp 54-56 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3251, 2854, 1641, 1449, 1302, 960; ^1H NMR (400 MHz, DMSO-d_6) δ 13.09 (br s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 3.36-3.26 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 187.9, 161.0, 157.8, 153.3, 138.2, 134.6, 132.0, 128.5, 128.1, 114.0, 55.3, 48.2, 15.8; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}ClN_2O_3$ $[M + H]^+$ 345.1006 and 347.0976, found 345.1003 and 347.0967.



85l

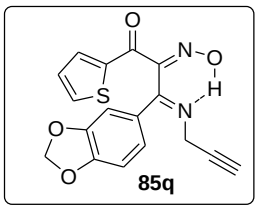
1-(4-Chlorophenyl)-2-(hydroxyimino)-3-(prop-2-ynylimino)-3-(thiophen-2-yl)propan-1-one (85p). Obtained as a single tautomer, yellow solid (468.6 mg, 71%): mp 102-104 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3298, 2172, 1652, 1586, 1274, 718; ^1H NMR (400 MHz, DMSO-d_6) δ 13.45 (br s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 4.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 3.2 Hz, 1H), 7.07 (dd, J = 4.8 Hz, 4.0 Hz, 1H), 4.08 (qd, J = 18.4 Hz, 2.4 Hz, 2H), 3.15 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 187.4, 156.8, 151.2, 141.5, 138.2, 134.4, 132.1, 130.6, 129.7, 128.4, 127.9, 81.0, 74.2, 42.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}ClN_2O_2S$ $[M + H]^+$ 331.0308 and 333.0279, found 331.0298 and 333.0263.



85p

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-(hydroxyimino)-3-(prop-2-ynylimino)-1-(thiophen-2-yl)propan-1-one (85q). Obtained as a single tautomer, yellow solid (496.4 mg, 73%): mp

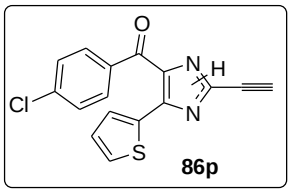
116-118 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3298, 2160, 1652, 1422, 718; ^1H NMR (400 MHz, DMSO-d_6) δ 13.32 (br s, 1H), 8.17 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 8.15 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.31 (dd, J = 5.2 Hz, 4.0 Hz, 1H), 7.24 (d, J = 1.2 Hz, 1H), 6.96 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.08 (d, J = 1.6 Hz, 2H), 4.05 (qd, J = 18.4 Hz, 2.8 Hz, 2H), 3.13 (t, J = 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 179.0, 160.8, 151.9, 149.7, 148.0, 138.9, 137.3, 136.1, 129.7, 128.5, 122.2, 108.2, 105.5, 101.7, 81.3, 73.9, 42.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}N_2O_4S$ $[M + H]^+$ 341.0596, found 341.0594.



85q

5.5.13 Procedure for Synthesis of 2-Ethynyl-4,5-Substituted imidazole 86p from Hydroxyiminoimine 85p. To a stirred solution of *N*-propargylhydroxyiminoimines **85p** (165.0 mg, 0.5 mmol) in dry acetonitrile (3 mL) was added K_2CO_3 (69.1 mg, 0.5 mmol) at room temperature, followed by heating at 80 °C for 3 h (monitored by TLC), the reaction mixture was treated with saturated NH_4Cl solution (25 mL), extracted with EtOAc (2 x 25 mL), the combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/hexane (3:7) as eluent.

(4-Chlorophenyl)(2-ethynyl-5-(thiophen-2-yl)-1*H*-imidazol-4-yl)methanone and (4-Chlorophenyl)(2-ethynyl-4-(thiophen-2-yl)-1*H*-imidazol-5-yl)methanone (86p). Obtained as a 80:20 inseparable mixture of tautomers, yellow solid (71.3 mg, 76%): mp 162-164 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3217, 2981, 2120, 1679, 1645, 1479, 1261, 891; ^1H NMR (400 MHz, DMSO-d_6) δ 13.89 (br s, 0.8H), 13.75 (br s, 0.2H), 8.10 (d, J = 8.4 Hz, 1.6 H), 7.94 (d, J = 8.4 Hz, 0.4 H), 7.83 (d, J = 2.8 Hz, 0.8 H), 7.73-7.70 (m, 1.2H), 7.60-7.54 (m, 2H), 7.21-7.19 (m, 0.8H), 7.01-6.99 (m, 0.2H), 4.62 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 186.1, 166.4, 137.2, 136.5, 134.6, 132.8, 132.0, 129.3, 129.0, 128.5, 128.1, 127.3, 82.7, 74.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{10}ClN_2OS$ $[M + H]^+$ 313.0202 and 315.0173, found 313.0199 and 315.0159.



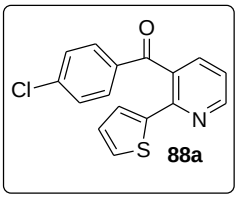
86p

5.5.14 Base Mediated Intramolecular Cyclization of *α*-Hydroxyiminoimine 85q. Attempted cyclization of hydroxyiminoimine **85q** in presence of K_2CO_3 as described for **85p**,

did not give the expected imidazole **86q**, but a different product, which could not be characterized (in the absence of single crystal X-ray data): yellow solid (58.3 mg, 60%): mp 101-103 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 3273, 2127, 1658, 1598, 1449, 1235, 1065; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 4.0 Hz, 0.8 Hz, 1H), 7.61 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.00 (dd, J = 5.2 Hz, 4.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 5.97 (s, 2H), 2.74 (d, J = 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.4, 168.5, 151.1, 148.3, 139.8, 135.4, 135.0, 128.4, 125.0, 123.4, 108.8, 108.4, 101.8, 98.9, 91.9, 78.2, 76.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{11}N_2O_3S$ $[M + H]^+$ 323.0490 and found 324.0276.

5.5.15 Intramolecular Thermal Cyclization of *N*-propargyl- *α*-Hydroxyiminoimines 85p-q and *N*-Propargyl-Enaminones 84p-q: Synthesis of 2,3-Substituted Pyridine 88a and 88b. A solution of either hydroxyiminoimine **85p-q** (0.3 mmol) or *N*-propargylenaminone **84p-q** (0.3 mmol) in dry DMSO (5 mL) was heated at 100 °C for 8-10 h (monitored by TLC). The reaction mixture was treated with saturated NH_4Cl solution (25 mL), extracted with EtOAc (2 x 25 mL), the combined organic layer was washed with water (2 x 25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford crude residue which were purified by column chromatography using EtOAc/hexane as eluent.

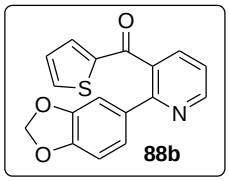
(4-Chlorophenyl)(2-(thiophen-2-yl)pyridin-3-yl)methanone (88a). Obtained from **85p**,



88a

brown semi solid (53.2 mg, 59%): R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2921, 1664, 1578, 1437, 1274, 706; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, J = 5.2 Hz, 2.0 Hz, 1H), 7.71-7.68 (m, 3H), 7.35-7.26 (m, 4H), 7.04 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 6.84 (dd, J = 5.2 Hz, 4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.0, 150.8, 149.8, 142.6, 140.5, 136.6, 134.7, 132.4, 131.3, 129.2, 129.0, 128.8, 128.1, 121.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}ClNOS$ $[M + H]^+$ 300.0250 and 302.0220, found 300.0245 and 302.0212.

(2-(Benzo[*d*][1,3]dioxol-5-yl)pyridin-3-yl)(thiophen-2-yl)methanone (88b). Obtained from **85q**, pale yellow solid (60.2 mg, 65%): mp 85-87 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2896, 1644, 1501, 1405, 1230, 1046, 735; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 7.84 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.63 (dd, J = 8.0 Hz, 0.8 Hz, 1H),

7.34 (dd, *J* = 7.6 Hz, 4.8 Hz, 1H), 7.24 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 7.16 (d, *J* = 1.6 Hz, 1H), 

88b
7.03 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 6.97 (dd, *J* = 4.8 Hz, 4.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.93 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 189.4, 156.4, 150.9, 148.5, 148.1, 144.1, 136.9, 135.4, 135.3, 134.2, 133.6, 128.3, 123.8, 121.3, 109.5, 108.4, 101.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}NO_3S$ $[M + H]^+$ 310.0538, found 310.0525.

5.6 References:

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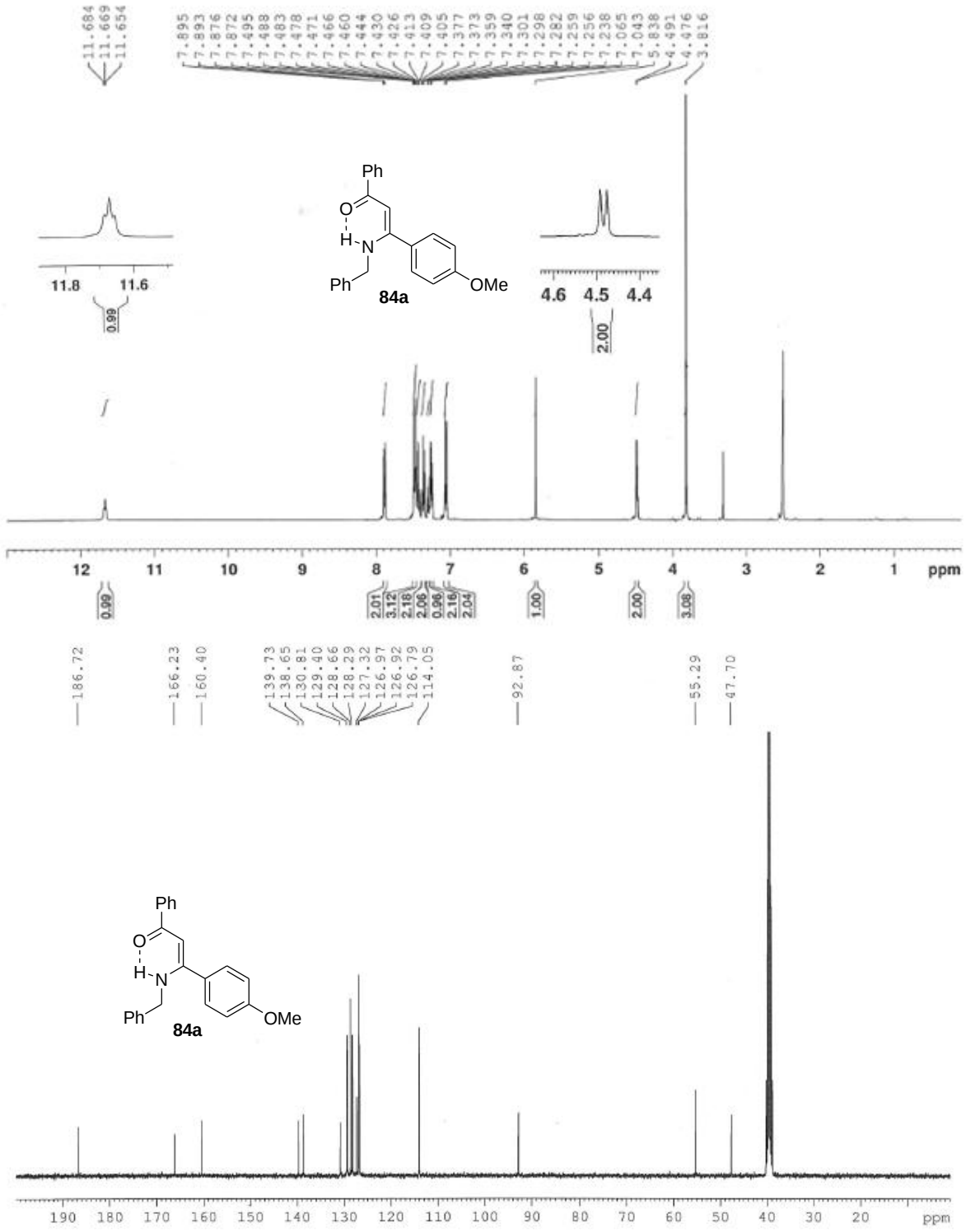
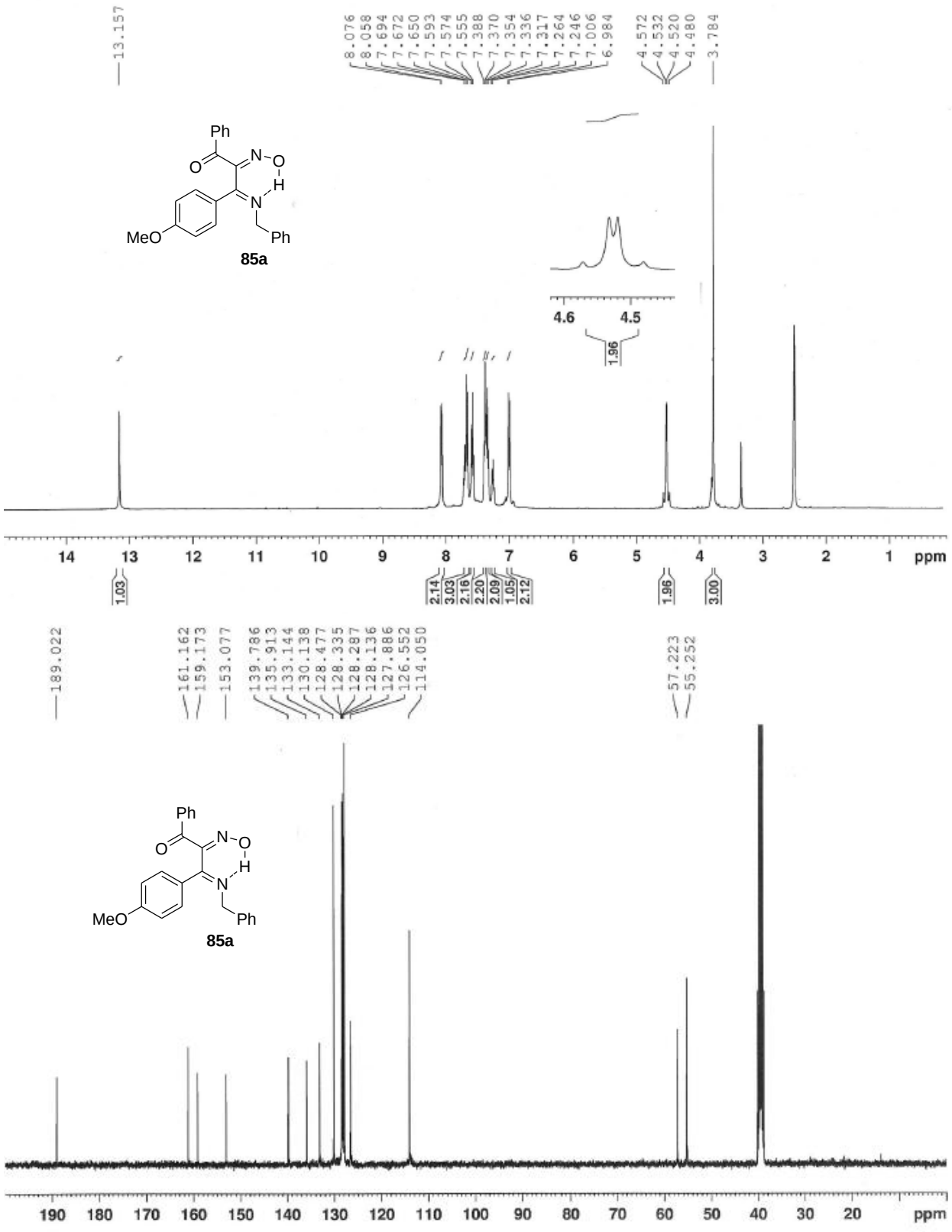
5.7 Representative Spectra



^{1}H and ^{13}C NMR Spectra of compound **84a** in DMSO-d_6



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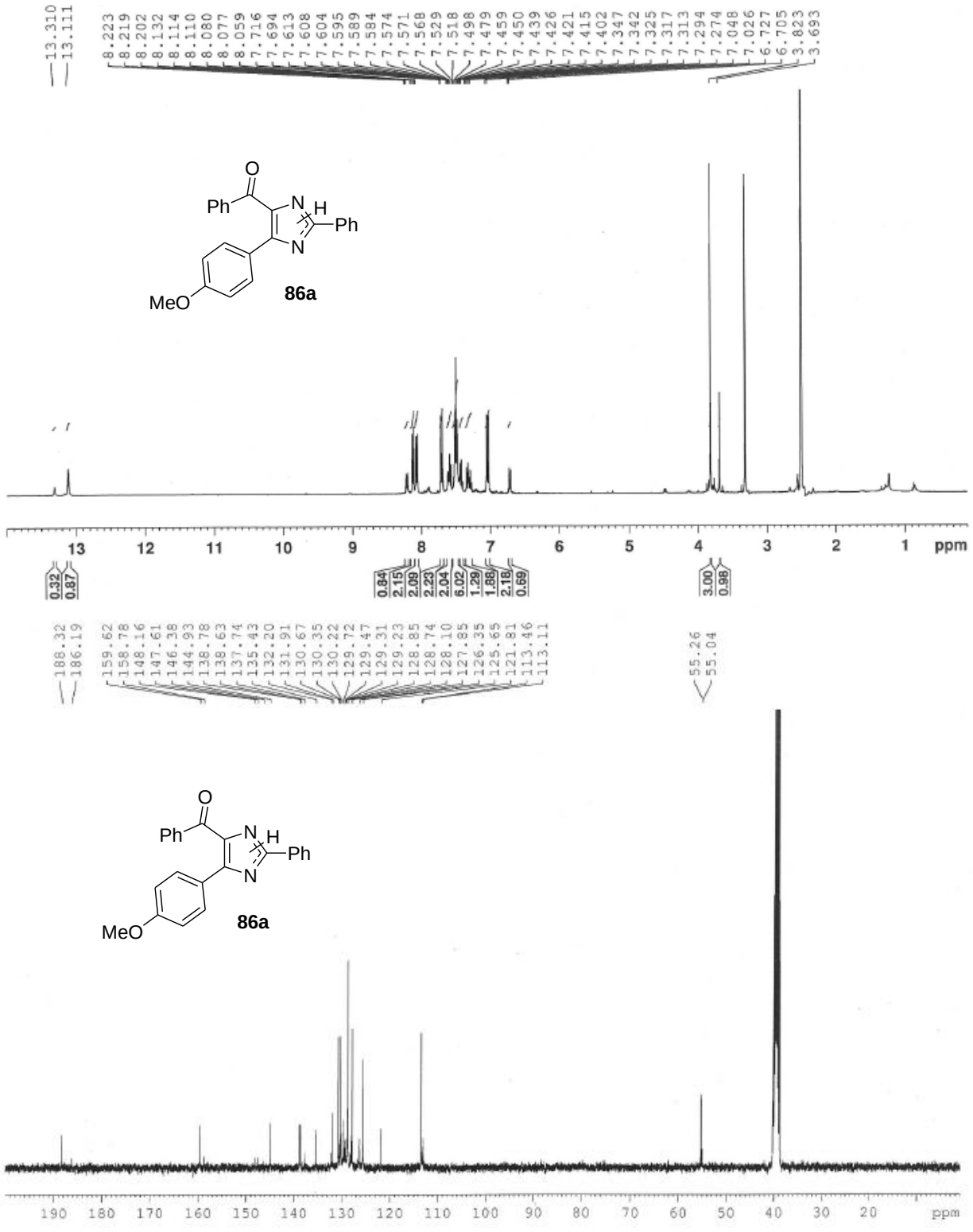
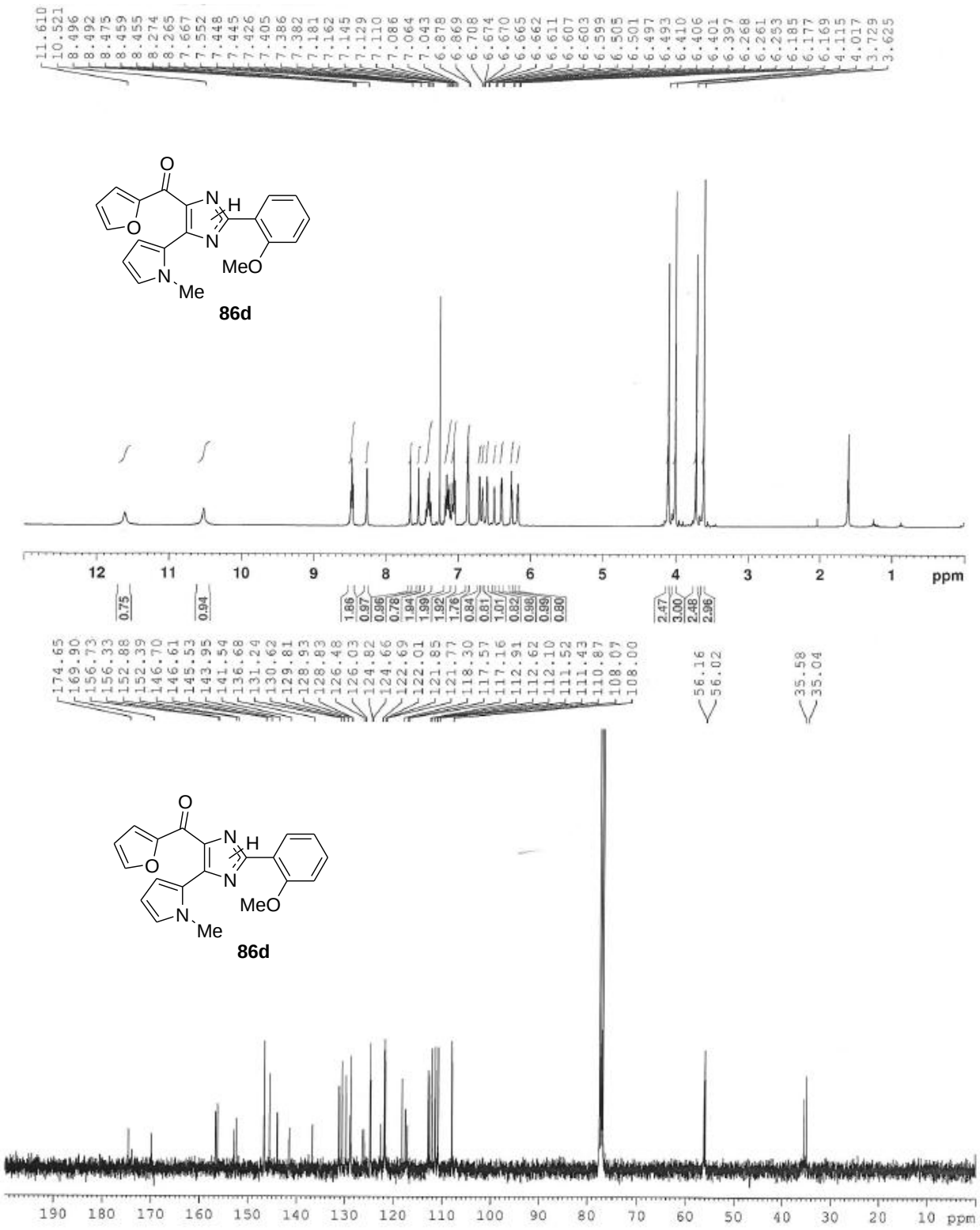
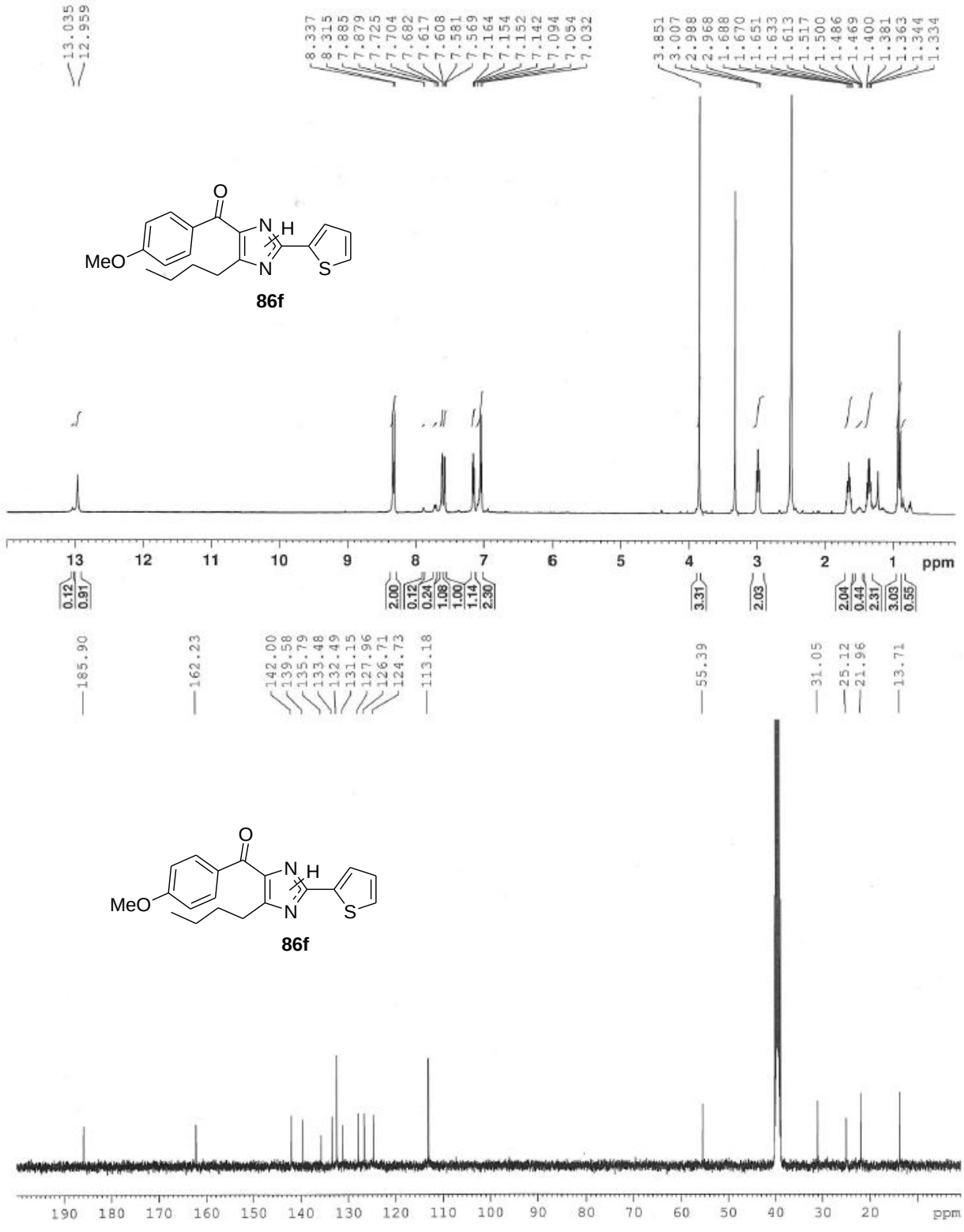


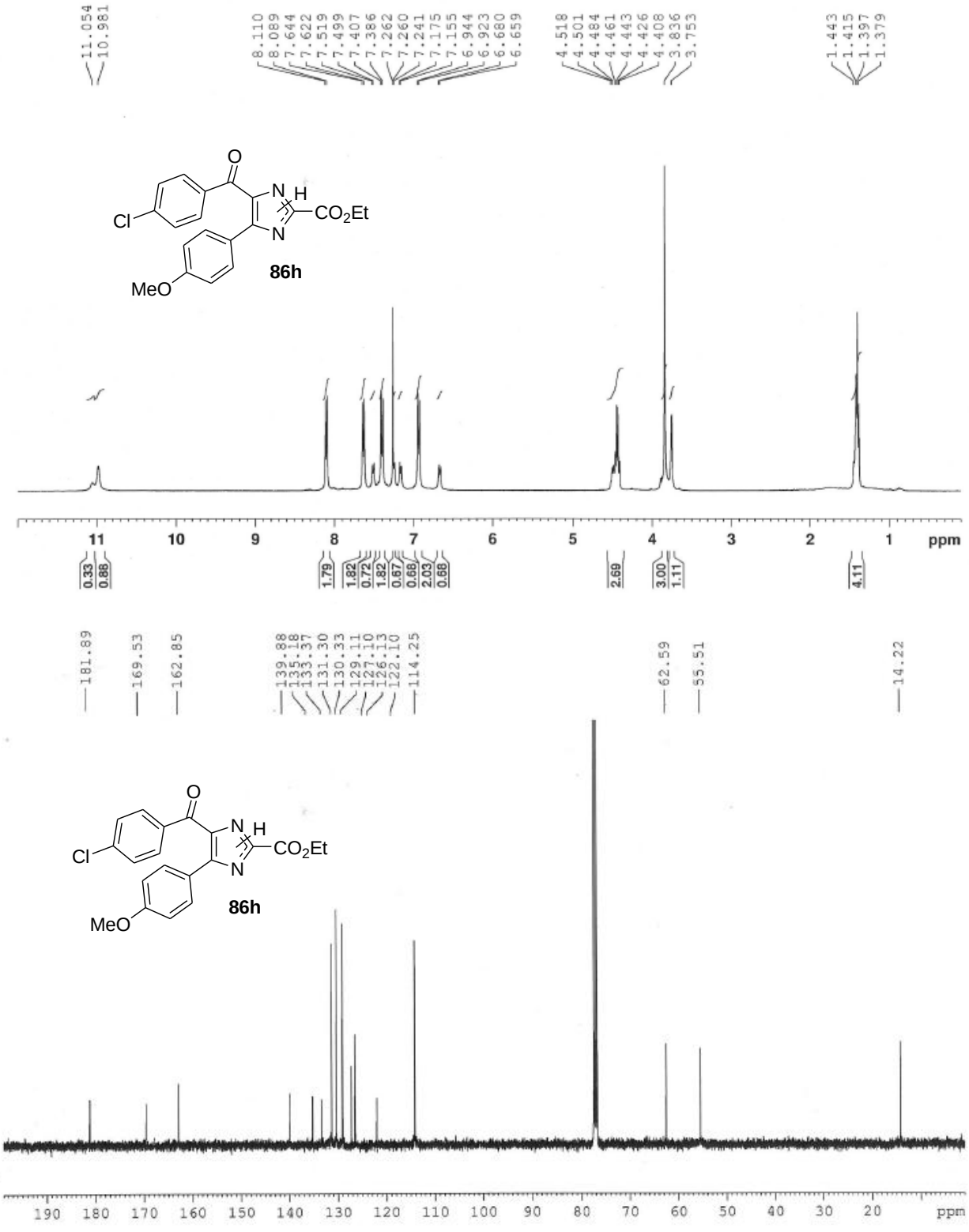
^{1}H and ^{13}C NMR Spectra of compound **86a** in DMSO-d_6



^{1}H and ^{13}C NMR Spectra of compound **86d** in $CDCl_3$



^{1}H and ^{13}C NMR Spectra of compound **86f** in DMSO-d_6



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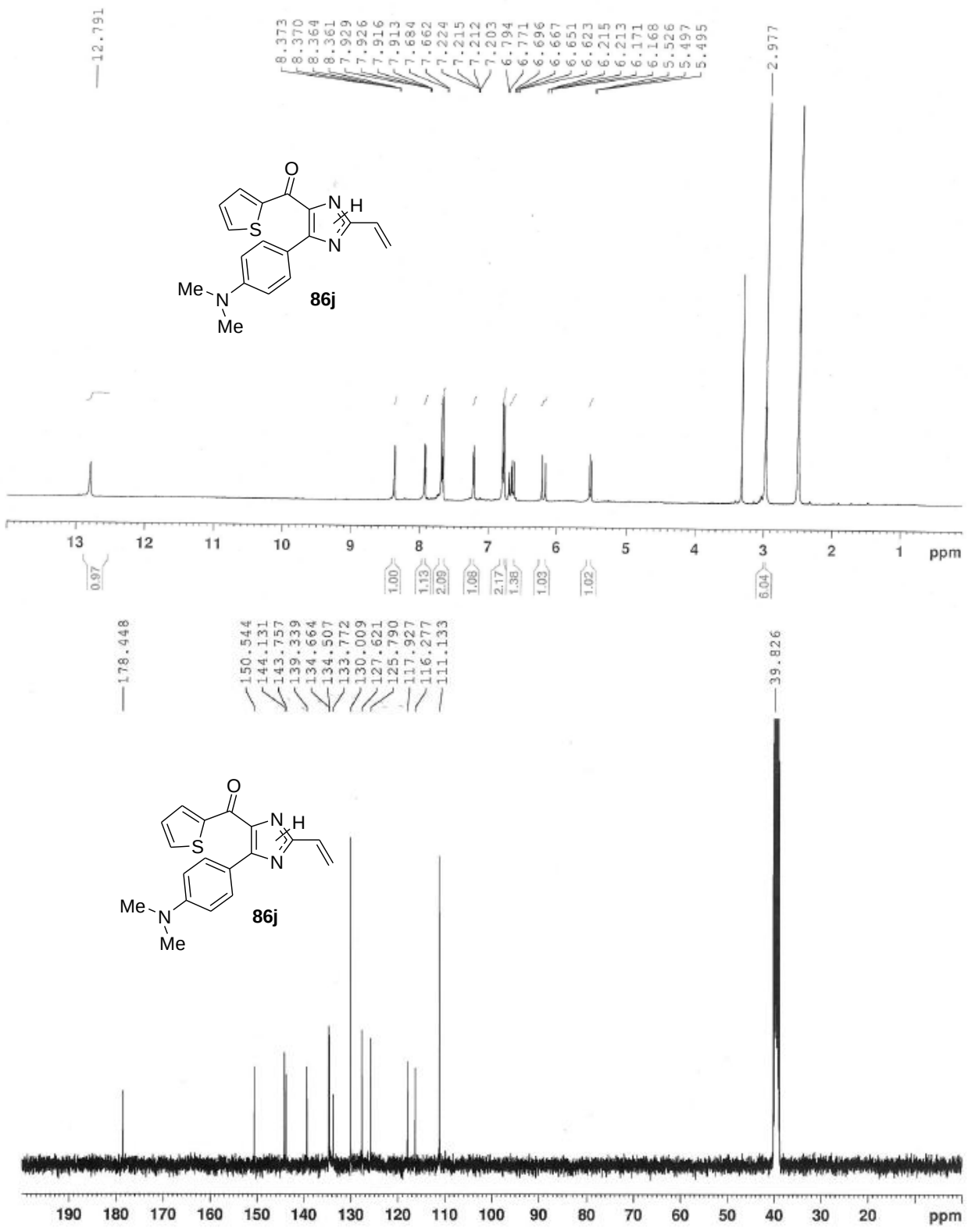

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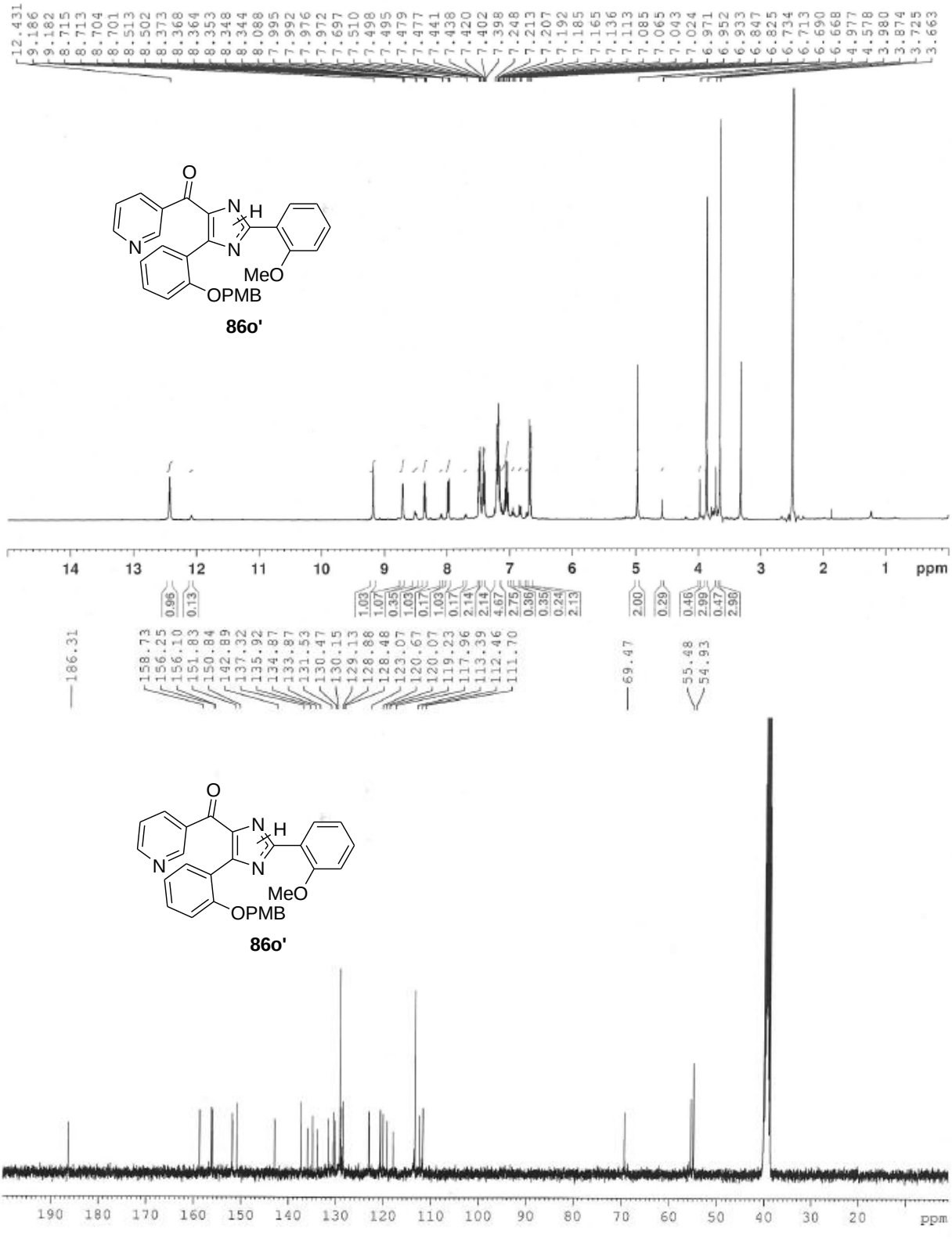

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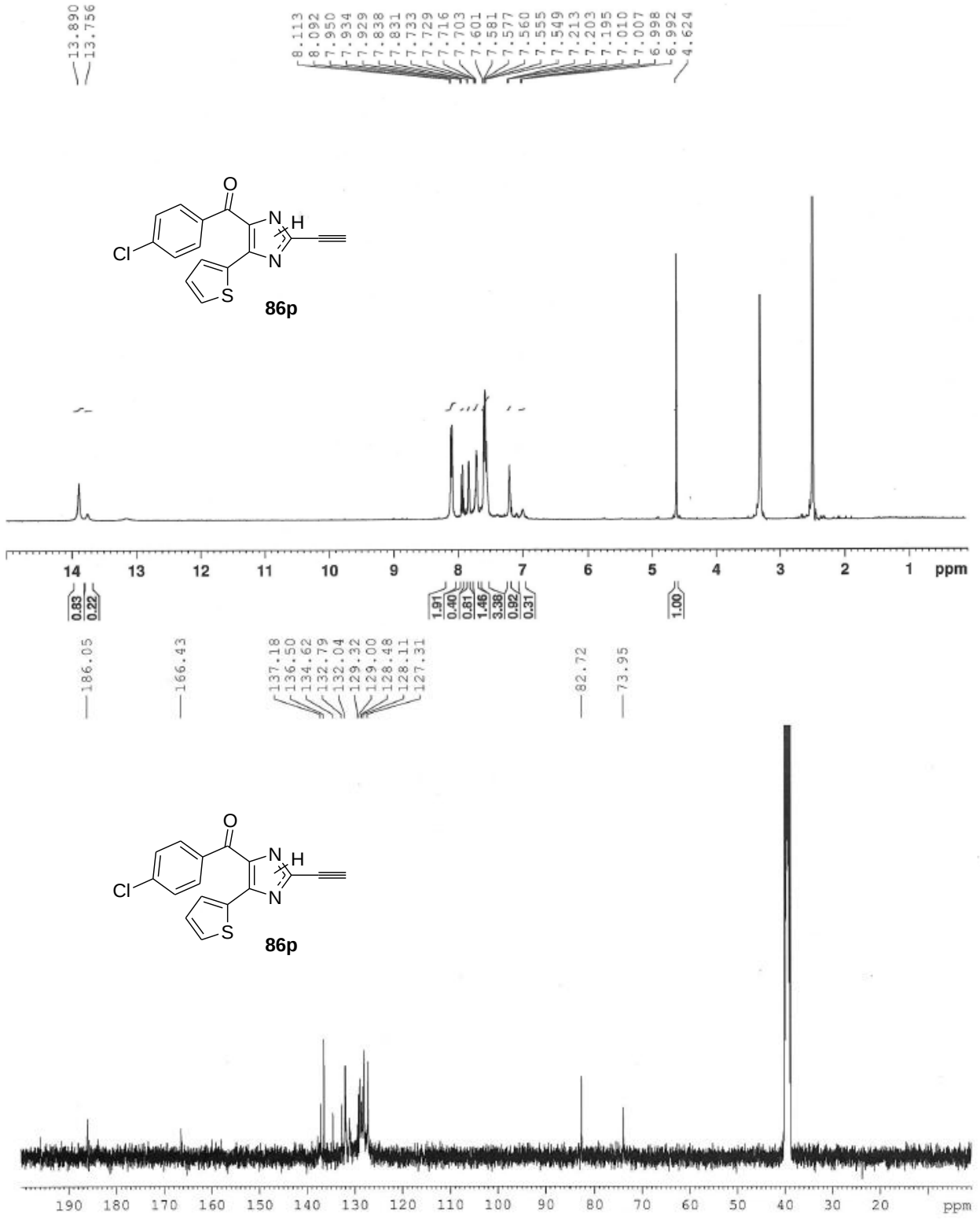
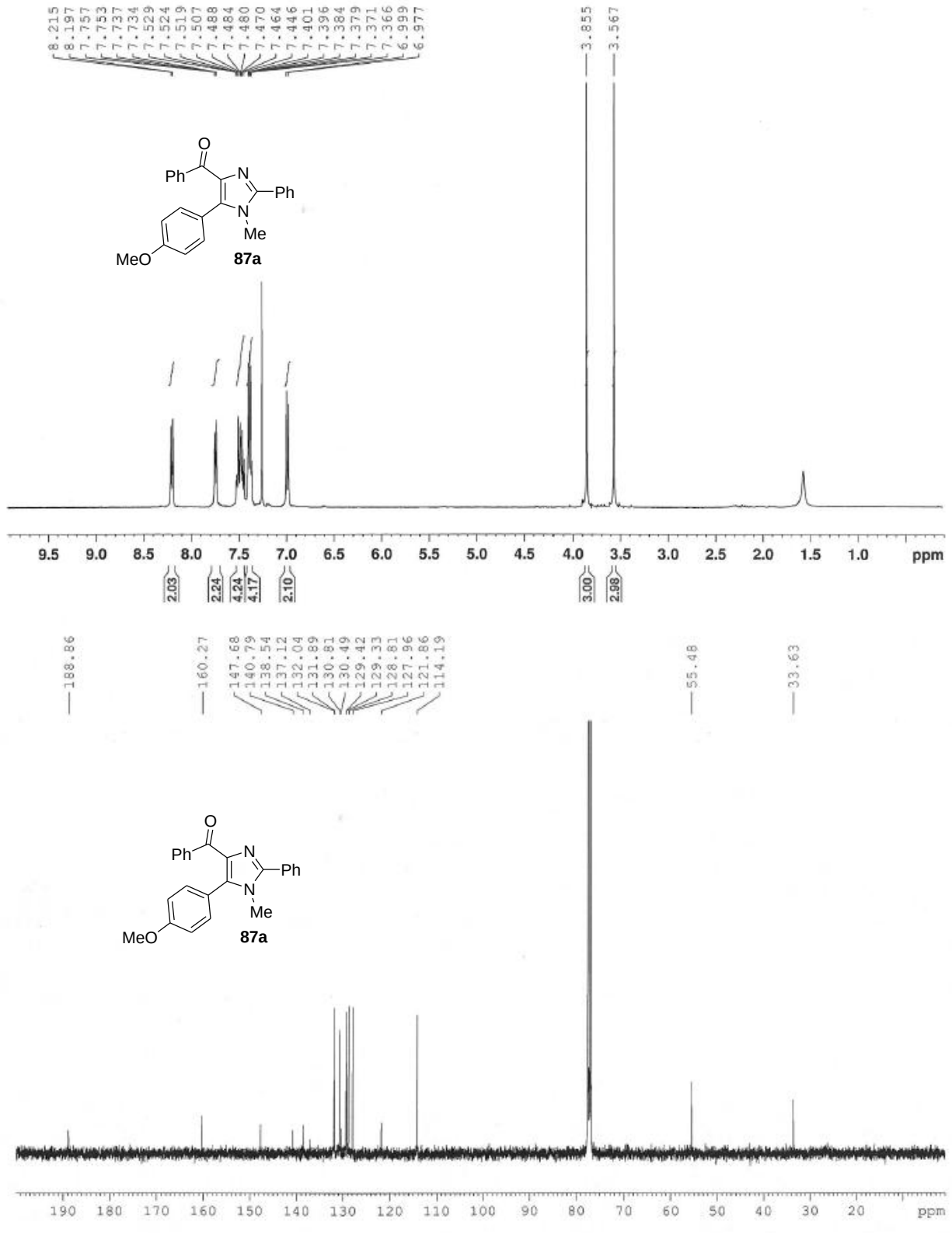
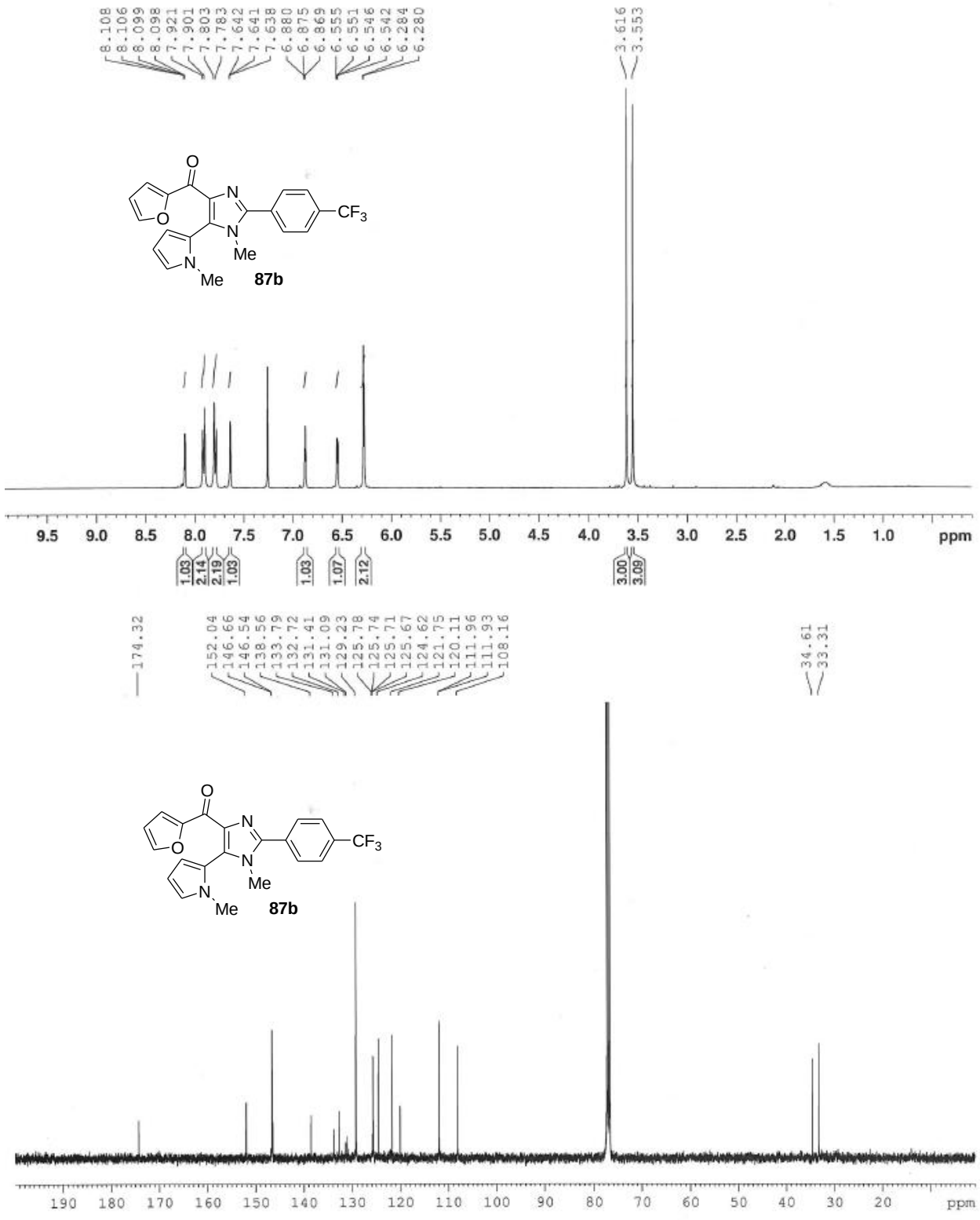


^{1}H and ^{13}C NMR Spectra of compound **86p** in DMSO-d_6



^{1}H and ^{13}C NMR Spectra of compound **87a** in $CDCl_3$



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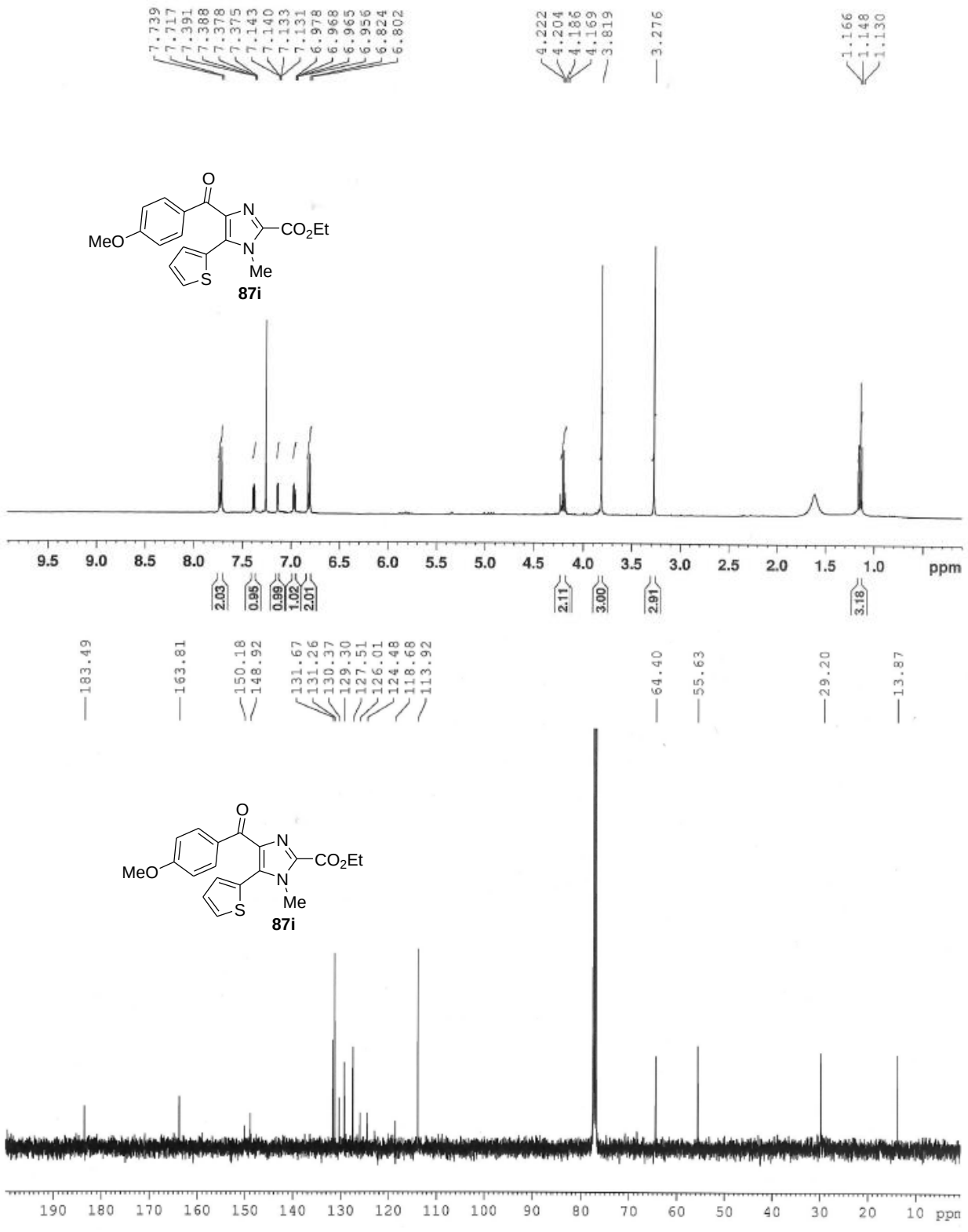
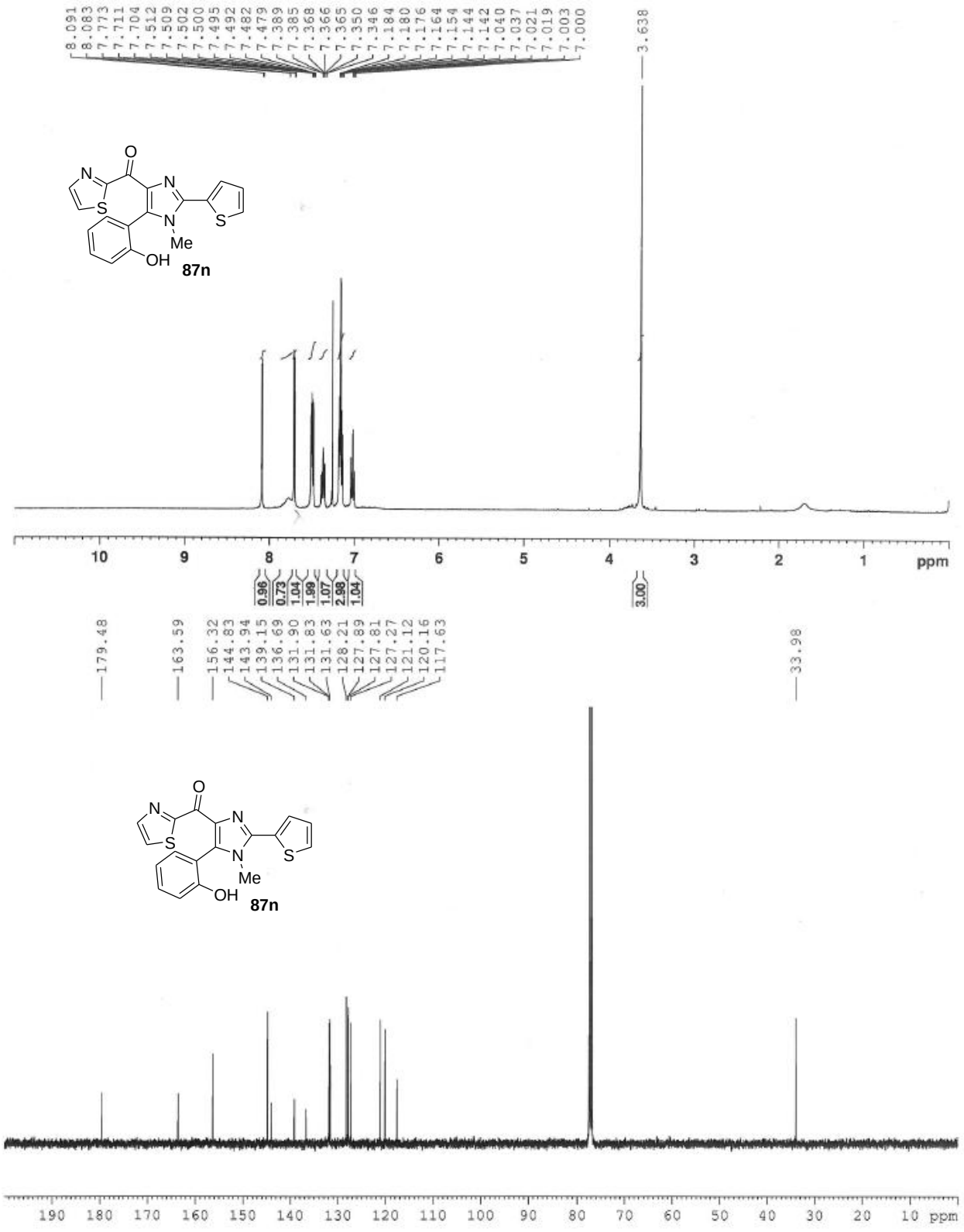
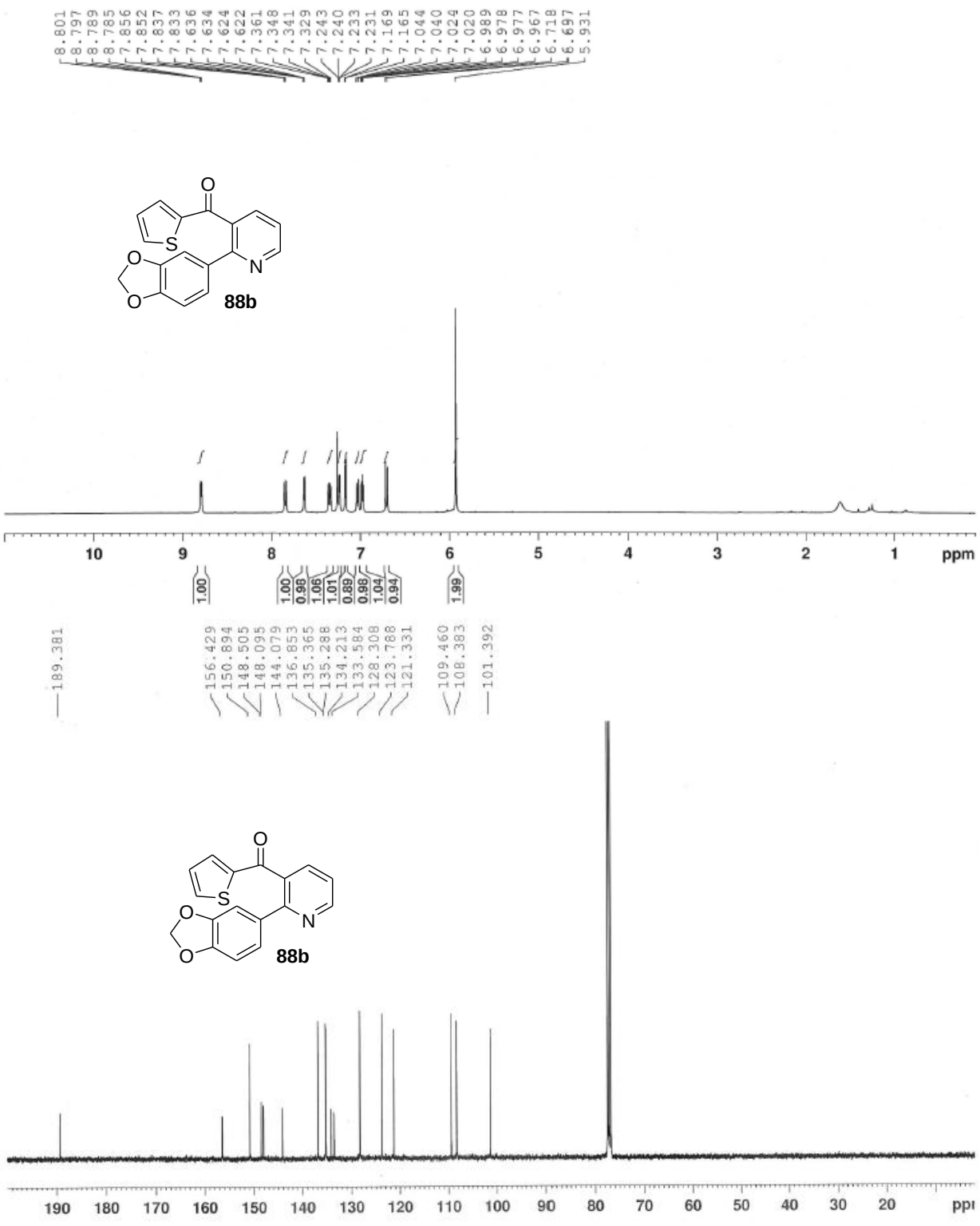


^{1}H and ^{13}C NMR Spectra of compound **87i** in $CDCl_3$



^{1}H and ^{13}C NMR Spectra of compound **87n** in $CDCl_3$



^{1}H and ^{13}C NMR Spectra of compound **88b** in $CDCl_3$

Chapter 6

*A Novel One-Pot, Two Step Synthesis of Multisubstituted Benzo[b]thiophenes via Sequential Copper Catalyzed C-S Bond Formation and Palladium Catalyzed Arene-Alkene Coupling via Intramolecular Heck Reaction**

6.1 Introduction

Benzo[*b*]thiophenes and its derivatives represent an important class of heterocyclic compounds because of their frequent occurrence in nature and wide range of biological activity displayed by this class of compounds.[1,2] Several marketed drugs contain the benzothiophene core, such as zileuton **1**,[2] a potent and selective inhibitor of 5-lipoxygenase, besides, a number of 2-arylbenzo[*b*]thiophenes derivatives have been recognized as selective estrogen receptor modulators (SERMs) for the treatment of postmenopausal disorders. Thus, Raloxifene **2** (Chart 1),[3] a commercial drug (Evista, Lilly) has been used for prevention and treatment of osteoporosis in postmenopausal women, whereas some of its derivatives such as Arzoxifene **3**,[1,4] are also under investigation for breast cancer therapy as well as for control and treatment of uterine cancer and Alzhiemer's disease.[5] Recently, a few of 2-arylbenzo[*b*]thiophene derivatives

*Unpublished Result.

such as **4a-b** have been recognized as tubulin polymerization inhibitors[1,6] as rigid analogues of Combrestatin A4 (Chart 1).[6] Also, benzo[*b*]thiophene and its condensed analogs are important structural components in the development of optoelectronic materials, including organic photovoltaics and field effect transistors.[1a] Consequently, research directed towards concise new syntheses of multisubstituted benzo[*b*]thiophenes and its condensed analogs has been actively pursued in recent years[1] and many efficient methods have been developed.

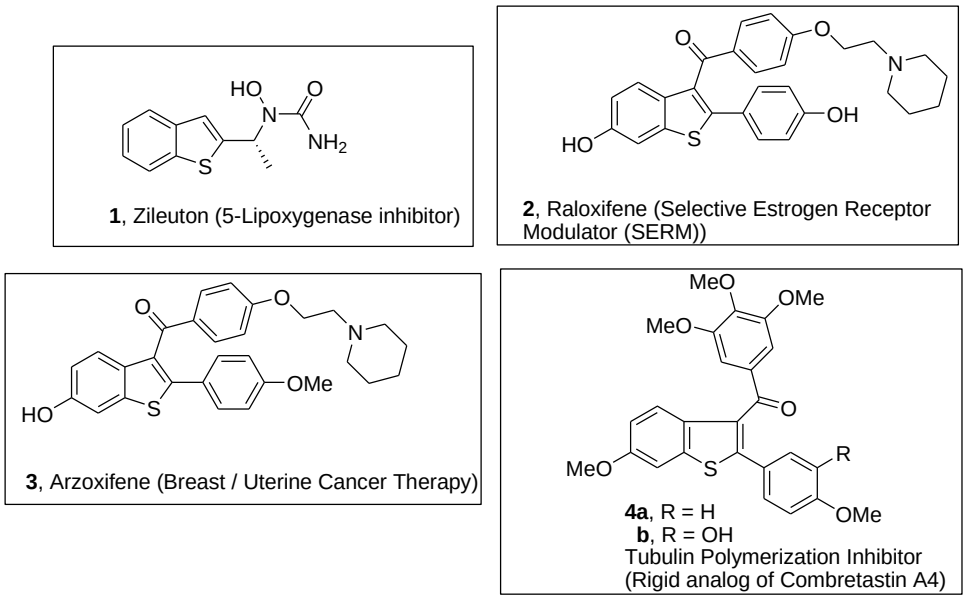
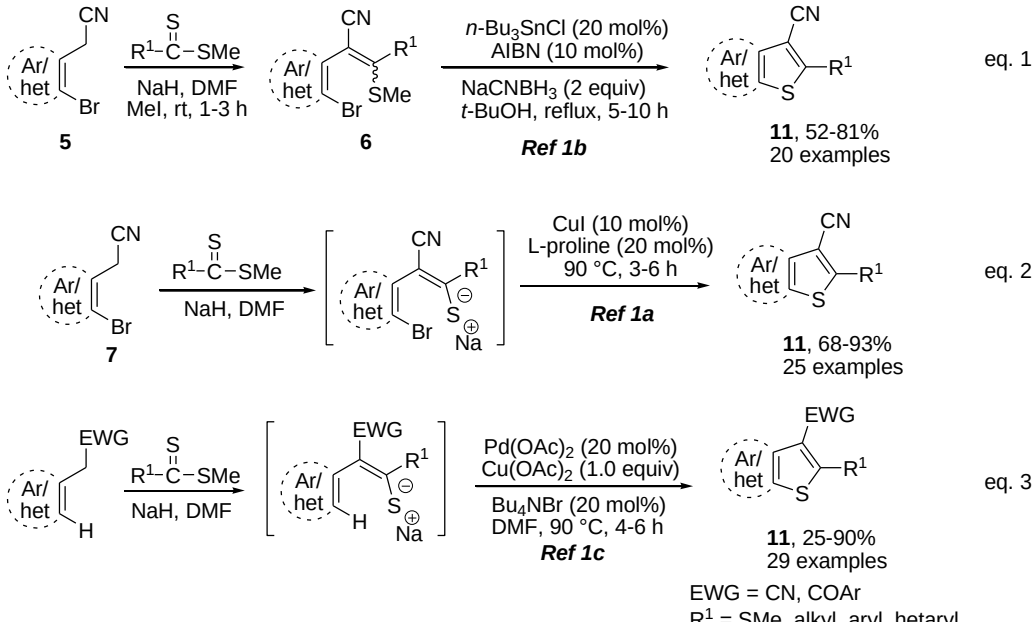


Chart 1. Biologically important benzo[*b*]thiophenes

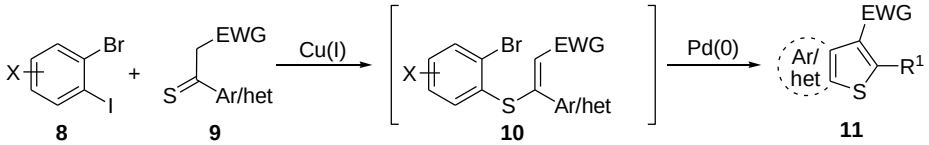
During the course of continued studies directed towards development of new and efficient methods for five and six-membered heterocycles, employing novel organosulfur synthons, our research group has previously reported new synthetic approaches for substituted benzo[*b*]thiophenes **11** as shown in the Scheme 1. Thus, the first approach involves intramolecular radical cyclization of 3-(methylthio)-3-(het)aryl/alkyl-1-[2-bromo(het)aryl]acrylonitriles by in situ trapping and S-methylation of the resulting carbon centered radical (eq. 1).[1b,1d] These precursors **6** are prepared by base induced condensation of the corresponding 2-bromohetarylacetonitriles **5** with (het)aryldithioesters followed by in situ S-methylation of the resulting enethiolate intermediates.[7] In an improved version (eq. 2), we have recently reported an efficient one-pot synthesis of substituted benzo[*b*]thiophenes and their hetero fused analogs, involving sequential base mediated condensation of substituted 2-bromo(het)arylacetonitriles **7** with a range of dithioesters and other thiocarbonyl variants, followed by CuI catalyzed

intramolecular C-S arylation of the resulting thioenolate intermediates.[1a] In a further improved version (eq. 3), our research group has recently disclosed a novel one-pot, two-step synthesis of highly functionalized benzo[*b*]thiophenes and their hetero-fused analogs by palladium catalyzed oxidative intramolecular C-H functionalization-arylthiolation of in situ generated thioenolates.[1c] This latter approach eliminates the requirement of a *o*-halo substituent thus opening up a much wider range of more readily accessible precursors (for details, see Chapter 4, Scheme 22 and related discussion). In continuation of these studies, we now report in this chapter, a new convergent one-pot approach to benzo[*b*]thiophenes, from 1-iodo-2-bromoarenes **8** and 1,3 substituted -1,3-monothiodiketones **9**, involving sequential copper catalyzed C-S bond formation, followed by Pd catalyzed arene-alkene coupling via intramolecular Heck reaction of the resulting thiovinyl intermediates **10** (Scheme 1). Before presenting our results, a short literature survey of recent syntheses of benzo[*b*]thiophenes and other related benzoheterocycles initiated by intermolecular cross-coupling of aryl halides and active methylene compounds have been presented.

Earlier Work



This Work

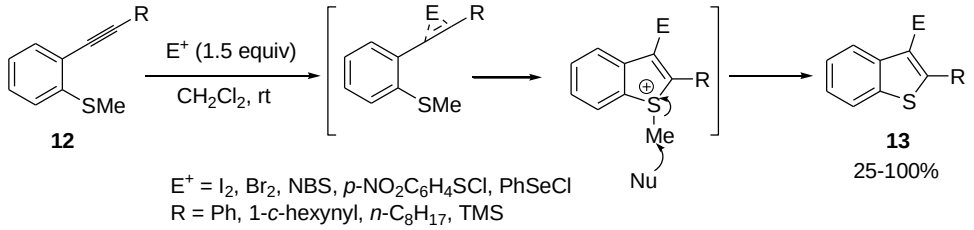


Scheme 1. Synthetic approaches for the synthesis of benzo[*b*]thiophenes from our research group

6.2 Recent Synthesis of Benzo[*b*]thiophenes and Related Benzoheterocycles: A Brief Literature Survey

6.2.1 Synthesis of Substituted Benzo[*b*]thiophenes

Among recent syntheses, the most common approach for benzo[*b*]thiophenes **13** involves intramolecular 5-*endo*-*dig* cyclization of *o*-alkynyl arylthioethers **12** or their surrogates, employing electrophilic reagents such as iodine, bromine, NBS, PhSCl or PhSeCl (Scheme 2).[1a-c,8]

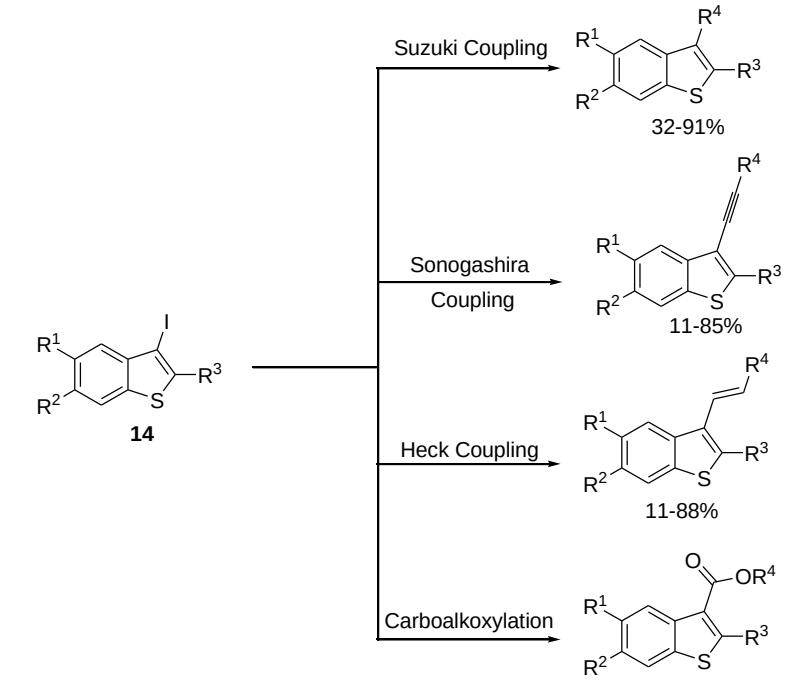


Scheme 2

Thus, an interesting study, regarding electrophilic cyclization of *o*-(1-alkynyl)thioanisole **12** leading to benzo[*b*]thiophenes using I_2, Br_2, NBS, 4-$NO_2C_6H_4SCl$ and PhSeCL as electrophiles, has been reported by Larock and coworkers.[9] They have shown that the nature of electrophile plays important role in this reaction, thus while I_2 and NBS cyclization gave high yield of 3-iodo or 3-bromo benzothiophenes, whereas use of bromine as electrophile gave poor yield of 3-bromobenzo[*b*]thiophens. The carbon-halogen bond of 3-iodobenzo[*b*]thiophenes **14** was efficiently used to generate library of 2,3-substituted benzo[*b*]thiophenes by palladium catalyzed Suzuki-, Miyaura, Sonogashira and Heck coupling (Scheme 3).[9c]

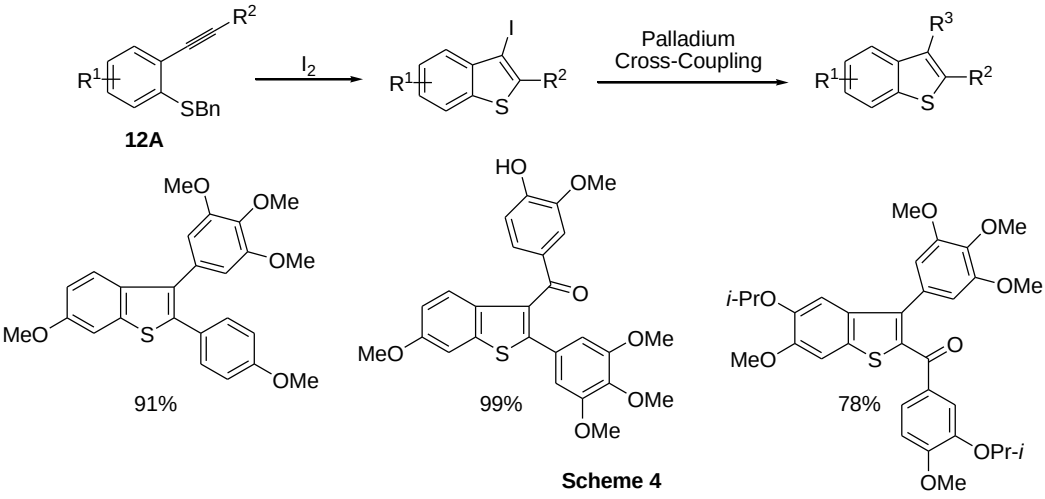
Flynn and coworkers have similarly reported synthesis of benzo[*b*]thiophenes via electrophilic cyclization of *o*-alkynylbenzyl sulfides **12A** in the presence of iodine (Scheme 4).[10a] Subsequently these authors extended the methodology and applied it for the synthesis of few tubulin binding agents (Scheme 4).[10b-c]

This methodology has also been extended to transition metal catalyzed cyclization of these analogs such as palladium,[11a] Cu,[11b] or gold [11c-d] catalyzed annulations (Scheme 5 and 6).

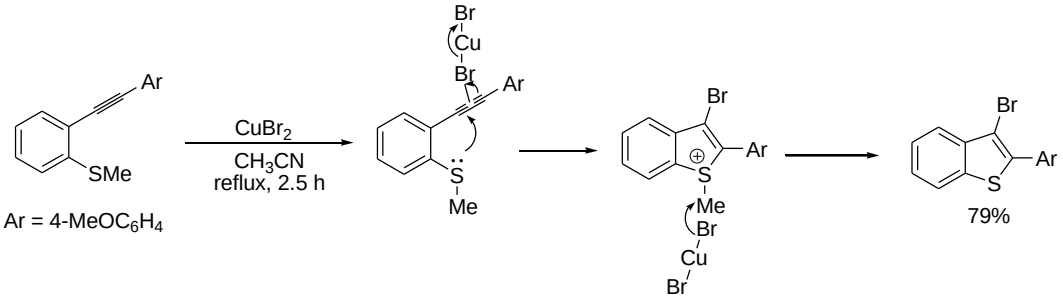


R1, R^2 = H, MeO; R^3 = *p*-MeO-C_6H_4, *p*-NH_2-C_6H_4, 3-thienyl;
R^4 = aryl, (Het)Ar, alcoxyl

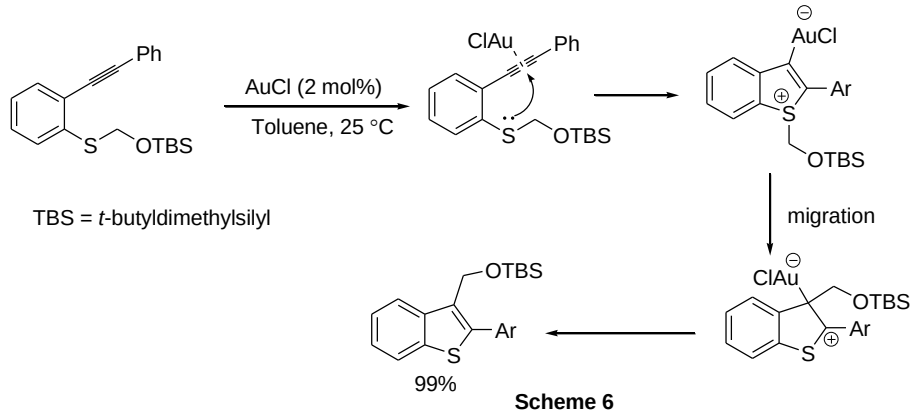
Scheme 3



Scheme 4

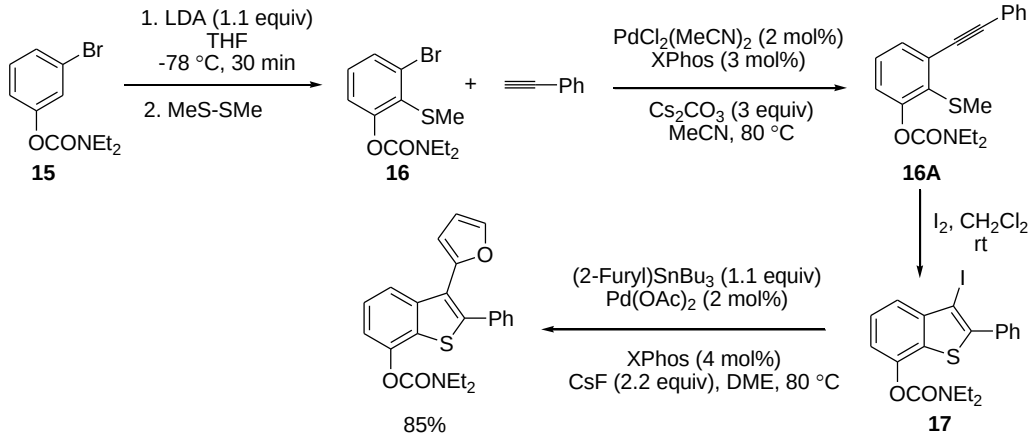


Scheme 5



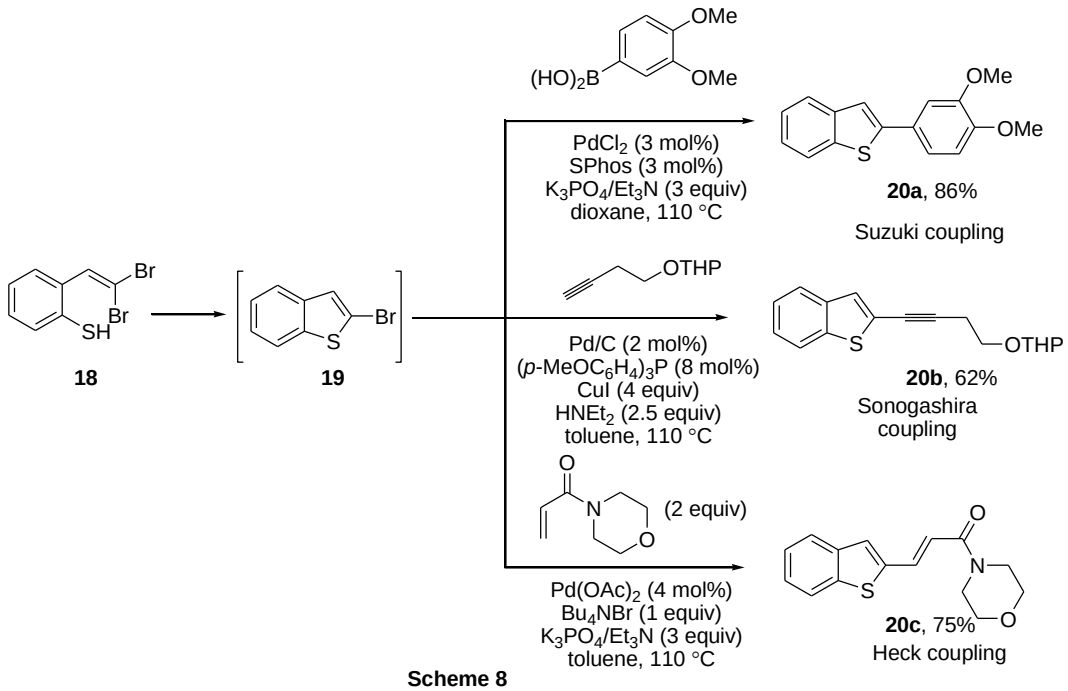
Scheme 6

Sanz and coworkers have described an efficient synthesis of 3-halo-7-oxygen functionalized benzo[*b*]thiophenes **17** bearing different substituents at C2 position, starting from *N*,*N*-dimethyl-*O*-3-halophenylcarbamates **15** (Scheme 7).[12] The key step is *o*-lithiation of **15**, giving rise to 3-halo-2-sulfanylphenol derivatives **16**, followed by Sonogashira coupling of **16**, and subsequent electrophilic cyclization of the resulting acetylenic derivative **16A** in the presence of iodine. The subsequent functionalizaition of these halobenzo[*b*]thiophenes products **17** allows access to a variety of 2,3,7-regioselectively functionalized benzo[*b*]thiophenes (Scheme 7).



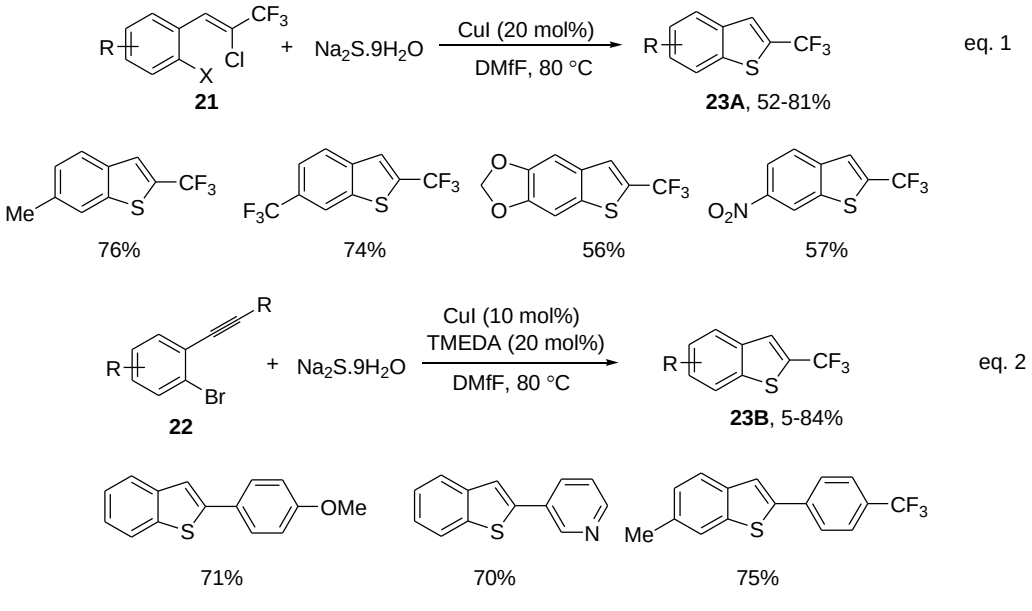
Scheme 7

Lauten and co-workers have reported synthesis of 2-substituted benzo[*b*]thiophenes **19** via palladium or copper catalyzed tandem intramolecular S-vinylation and intermolecular cross-coupling reactions of *o*-(*gem*-dibromovinyl)-thiophenols **18** (Scheme 8).[13a-b] The 2-bromo functionality in these thiophenes is further elaborated to various 2-substituted thiophenes **20a-c** via Suzuki, Sonogashira and Heck coupling respectively (Scheme 8).

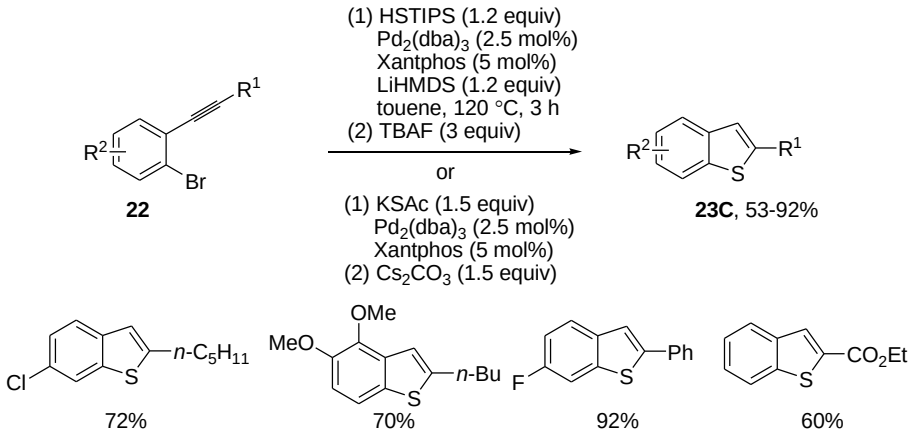


Scheme 8

The crucial bond forming event in the above described reactions is intramolecular attack of nucleophilic sulfur atom on activated C-C multiple bond, leading to formation of the S(1)-C(2) bond of benzothiophenes. These reactions although selective and efficient, however require prior synthesis of difficult to access prefunctionalized thiophenol precursors. Recently, copper catalyzed (or Pd catalyzed) double thiolation of *o*-(2-halovinyl)halobenzenes **21**,[14a] or 2-bromoalkynylbenzenes **22**,[14b] with metal sulfides or its surrogates,[14c] leading to 2-substituted benzo[*b*]thiophenes **23A-C** have also been reported by Zhang and Sanz's research groups (Schemes 9 and 10).[14d]

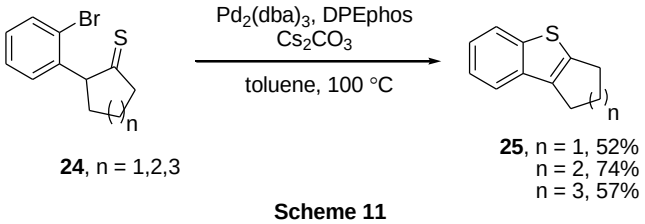


Scheme 9



Scheme 10

These methods involve concomitant formation of S(1)-C(7a) and S(1)-C(2) bonds of benzo[*b*]thiophenes. On the other hand, synthetic approaches to benzo[*b*]thiophenes involving S(1)-C(7a) bond formation via intramolecular C-S coupling/cyclization of *α*-arylthioenol/enolate precursor are scarce in literature.[15] Recently, Willis and co-workers described the synthesis of 2,3-annulated benzo[*b*]thiophenes **25** in moderate to good yields via palladium catalyzed intramolecular cyclization of *o*-(halo)arylsubstituted cyclic thioketones **24** (Scheme 11).[16a,1a-c] The benzo[*b*]thiophene syntheses reported earlier by our research group are also based on this strategy involving intramolecular construction of C-7a bond (Scheme 1, eqs. 1-3).



Scheme 11

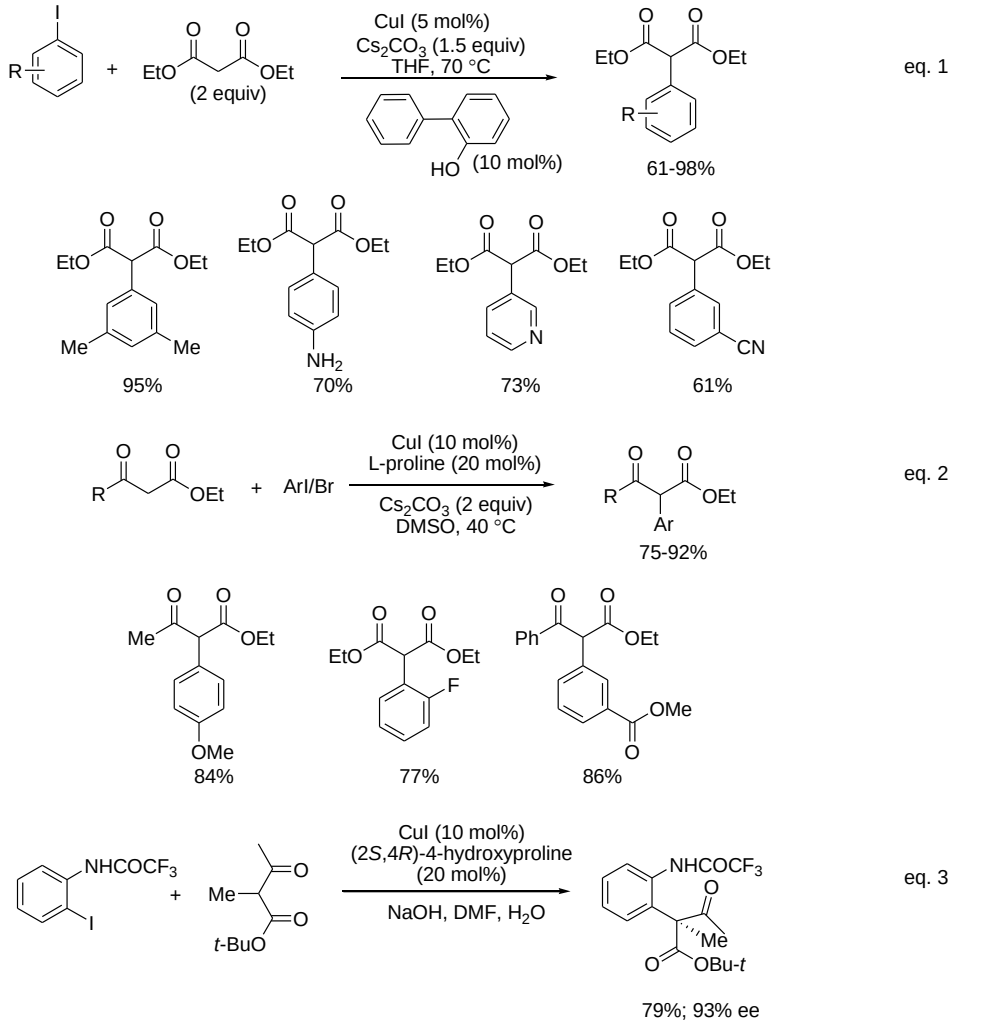
6.2.2 Synthesis of Substituted Benzoheterocycles Initiated by Transition Metal Catalyzed Intermolecular Cross-Coupling of Aryl Halides with Active Methylene Carbonyl Compounds

In recent years, a number of papers have appeared on convergent approaches for the synthesis of benzoheterocycles involving an initial transition metal catalyzed intermolecular cross-coupling of aryl halides with active methylene carbonyl compounds, followed by subsequent intramolecular cyclization of adduct through catalytic-heteroatom bond formation. Since the present work described in this chapter involves a similar

convergent approach for the synthesis of benzo[*b*]thiophenes, a short recent literature survey on these syntheses has been included.

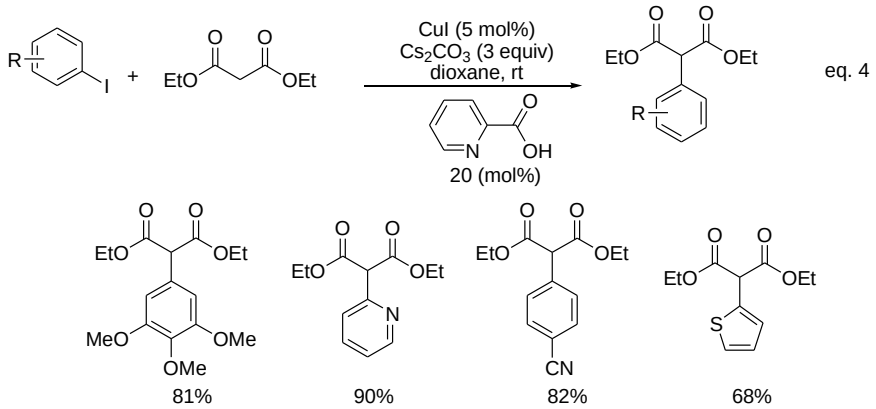
The arylation of active methylene compounds in the presence of copper or copper salts, namely, the Hurtley reaction,[17] is an old transformation with a long history.The scope of this reaction is very narrow, as only *o*-bromobenzoic acid and its closely related bromides are reactive.[17] To overcome this drawback, numerous efforts have been devoted to develop new reaction conditions during the past decades.[17] However, initial success for arylation starting from aryl halides relies on using stoichiometic or even excess amounts of copper salts.[17] The first breakthrough for this arylation to use catalytic amounts of CuI was made by Miura and co-workers in 1993, in which the coupling reaction was carried out at 120 °C in DMSO. Under these conditions the products decomposed readily and therefore good yields were not obtained in some cases. In addition, only aryl iodides were suitable for this process and aryl bromide was found to afford poor conversion under the described conditions. A milder protocol was developed by Buchwald and Hennessy in 2002 to employ CuI/2-phenylphenol as a catalytic system to perform the arylation of diethyl malonate (Scheme 12, eq. 1).[18] Unfortunately, their substrates are still limited to aryl iodides. Furthermore, in the above two processes, two equivalent of activated methylene compounds were required to ensure good yields, which would become problematic when some expensive activated methylene compounds were employed. Ma and coworkers[17] have recently demonstrated that by using CuI/L-proline as catalyst a variety of active methylene coumpounds could be coupled with various aryl halides with great diversity (Scheme 12, eq. 2). In contrast with the previous processes[17] excellent conversions were obtained when aryl bromides were employed. Both aryl iodides and aryl bromides are compatible with these reaction conditions.

In a subsequent paper, Ma and coworkers[19] observed that CuI-catalyzed coupling between aryl iodides and *β*-keto esters can be performed at −45 °C through a combination of *ortho* substitution and ligand and solvent effects and developed Cu catalyzed enantioselective arylation of 2-methylacetoacetate catalyzed by CuI/*trans*-4-hydroxy-L-proline at low reaction temperature (Scheme12, eq. 3). It is noteworthy that these results represent a new record low in reaction temperatures for Ullmann-type coupling reactions as only two room-temperature reactions were disclosed quite recently.[19]



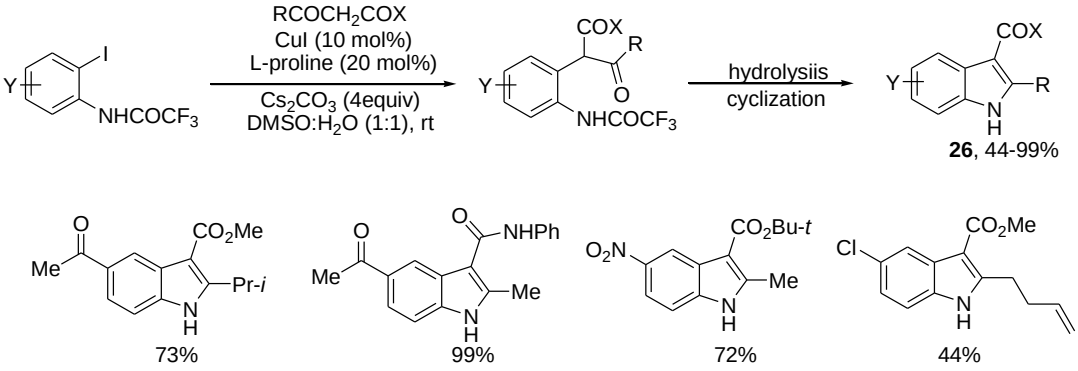
Scheme 12 continued

Kwong and coworkers have developed an effective method for the synthesis of *α*-aryl malonates involving coupling of diethyl malonates with aryl iodides in the presence of a catalytic amount of 2-picolinic acid and CuI (Scheme 12, eq. 4).[20] The reaction proceeds smoothly even at room temperature with high level of functional group compatibility.



Scheme 12

Using the above strategy, Ma and coworkers have developed an efficient and high yielding cascade process for the assembly of 2,3-substituted indoles **26** via CuI/L-proline-catalyzed coupling of 2-halotrifluoroacetanilides with *β*-ketoesters and amides followed by in situ acidic hydrolysis (Scheme 13).[21a] The 2-halotrifluorocetanilides bearing a strong electron withdrawing group in the 4-position could undergo in situ basic hydrolysis to provide the corresponding indoles **26**. A variety of functional groups such as ketones, esters, nitro, iodo, olefin, chloro, and benzoxy moieties could be tolerated under these reaction conditions, besides a range of polysubstituted indoles can be prepared from substituted 2-halotrifluoroacetanilides with high regioselectivity (Scheme 13).

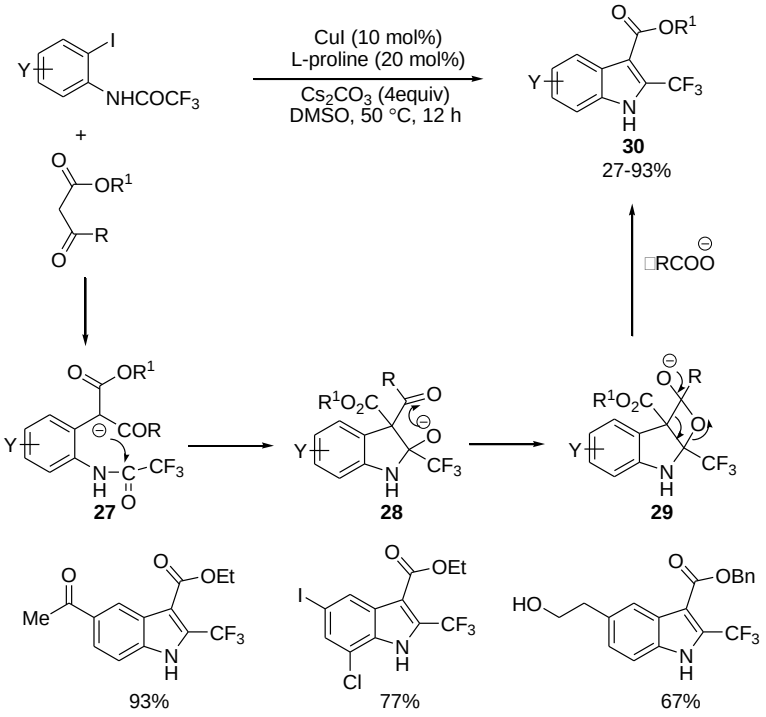


Scheme 13

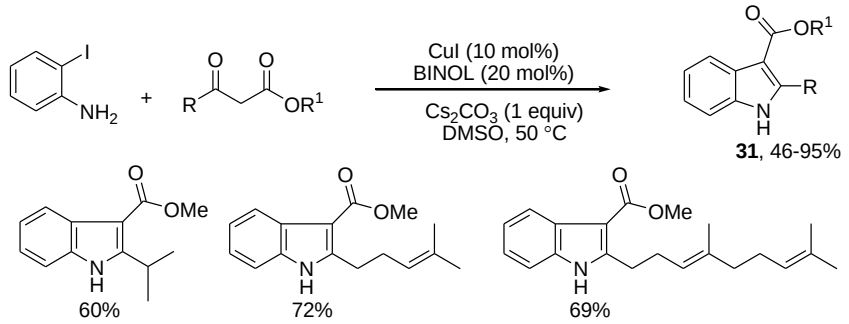
In a subsequent paper, Ma and coworkers have demonstrated that the method can be extended for the synthesis of polysubstituted 2-(trifluoromethyl)indoles **27** in good to excellent yields, when the CuI/L-proline-catalyzed cross coupling of 2-halotrifluoroacetanilides with *β*-ketoesters is carried out in anhydrous DMSO in the presence of Cs_2CO_3 at 40-80 °C (Scheme 14).[21b] A number of functional groups are tolerated under these conditions. A possible mechanism involving initial formation of coupling intermediate **27**, followed by intramolecular attack of the carbanion on the carbonyl group of the trifluoroacetamide moiety to produce intermediate **28**. Next, the alkoxy anion in **28** attacks the keto group to form a four-membered ring **29**, in which C-C bond disconnection might occur and followed by its deacylation to furnish 2-trifluoromethylindoles **30** (Scheme14).

Tanimori and co-workers have described one-step synthesis of 2,3-disubstituted indoles **31** by a copper-catalyzed domino reaction of 2-iodoaniline and *β*-keto esters (Scheme 15).[22] The reaction proceeded smoothly at 50 °C with the use of 10 mol% CuI and 20 mol% of BINOL (racemate) with Cs_2CO_3 (1 equiv) as the base in DMSO to

produce indoles **31** in moderate to high yields. A variety of *β*-keto esters including branched and bulky substituents, terminal alkenes, long chains, aromatic and heteroaromatic rings were feasible for the present reaction under the optimized conditions for the synthesis of 2-substituted indole-3-carboxylates in good yields (Scheme 15). However, no mechanistic studies of this reaction have been reported.

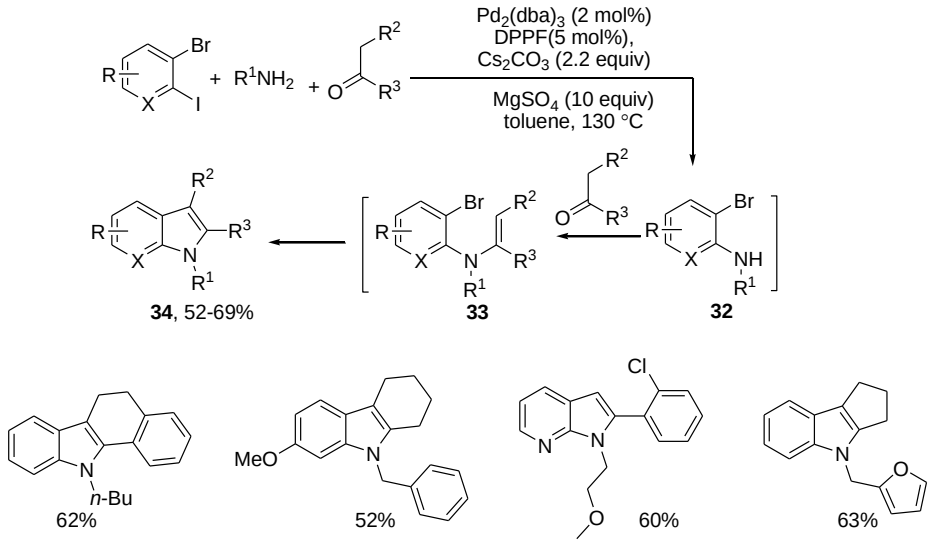


Scheme 14



Scheme 15

Kurth and coworkers have reported a general palladium-catalyzed three step multicomponent assemblies for the synthesis of highly substituted indoles that incorporates both a Buchwald–Hartwig reaction and an arene-alkene coupling reaction in a one pot three step fashion and proceeds by a single catalyst/ligand system involving three independent components (Scheme 16).[23]



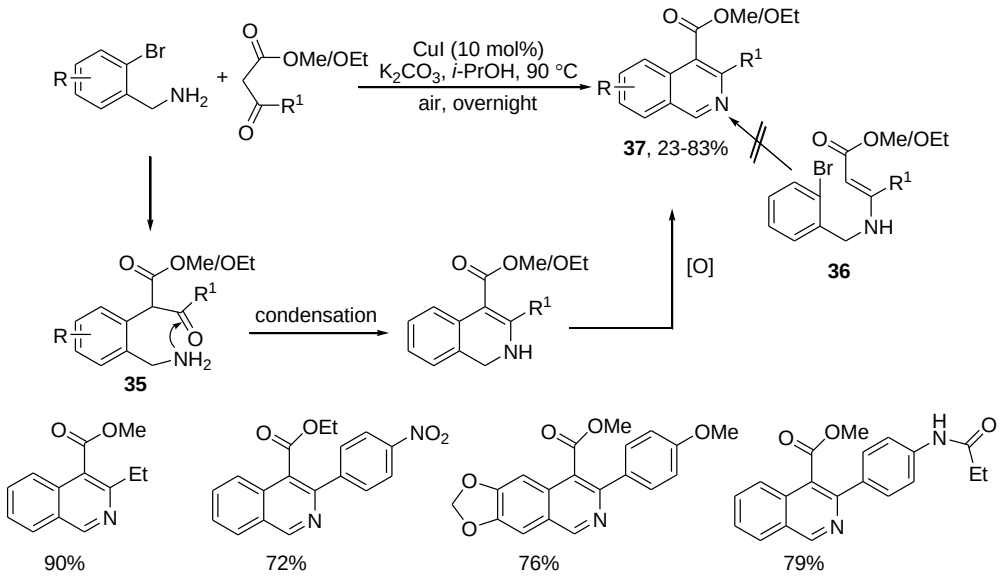
Scheme 16

Indole formation could be accomplished using suitable reaction conditions that favour in situ generation of an aniline **32**, condensation leading to an arylenamine **33**, and a subsequent arene–alkene coupling reaction to close the ring. Three bonds are formed in this transformation: an *N*–aryl bond by a Buchwald-Hartwig coupling, followed by condensation of nitrogen nucleophile with ketone to give *N*-arylenamine intermediate **33**, and a C-C bond by an intramolecular arene–alkene coupling as final step to give indoles **34** (Scheme 16).

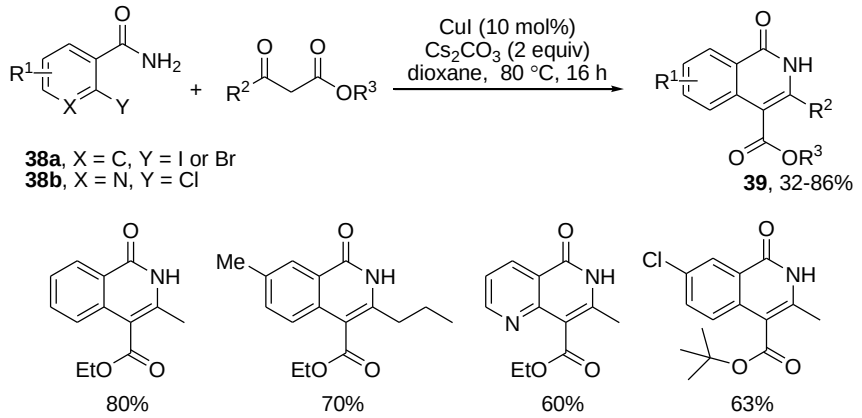
Ma and coworkers have recently reported an efficient synthesis of substituted isoquinolines **37** via CuI-catalyzed coupling-cascade condensative cyclization of *o*-halobenzylamines and *β*-keto esters or 1,3-diketones in *i*-PrOH under the action of K_2CO_3.[24a] A number of functional groups in both the benzylamine and the *β*-keto ester moieties are tolerated under the reaction conditions. The reaction is shown to involve Cu catalyzed coupling of *β*-ketoesters with *o*-bromobenzylamines followed by intramolecular condensative cyclization of the resulting adduct **35**. An alternative mechanism involving initial condensation of benzyl amine with *β*-ketoesters to give *o*-bromoenaminoester **36** followed by its intramolecular copper catalyzed cyclization to isoquinolines **37** was ruled out as **36** did not afford isoquinolines, when subjected to Cu catalyzed cyclization (Scheme 17).

Zhao and coworkers have reported an efficient one-pot copper-catalyzed approach to isoquinolin-1(2*H*)-one derivatives **39** via cascade coupling of 2-bromo and 2-iodobenzamides **38a** or 2-chloronicotinamide **38b** with *β*-ketoesters in the presence of

cuprous iodide catalyst at 80 ^{0}C without addition of any ligand under mild conditions (Scheme 18).[25] However no mechanistic studies have been reported by these co-workers.

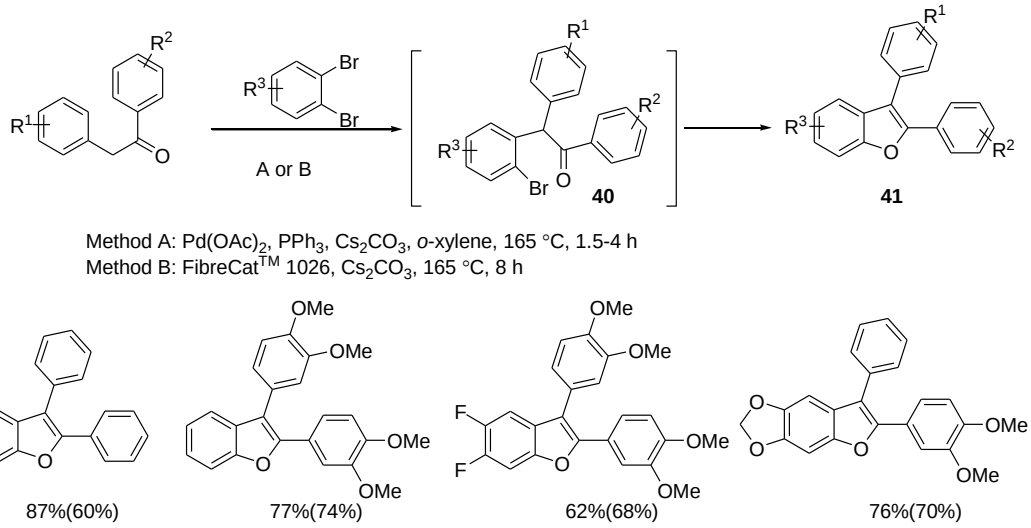


Scheme 17



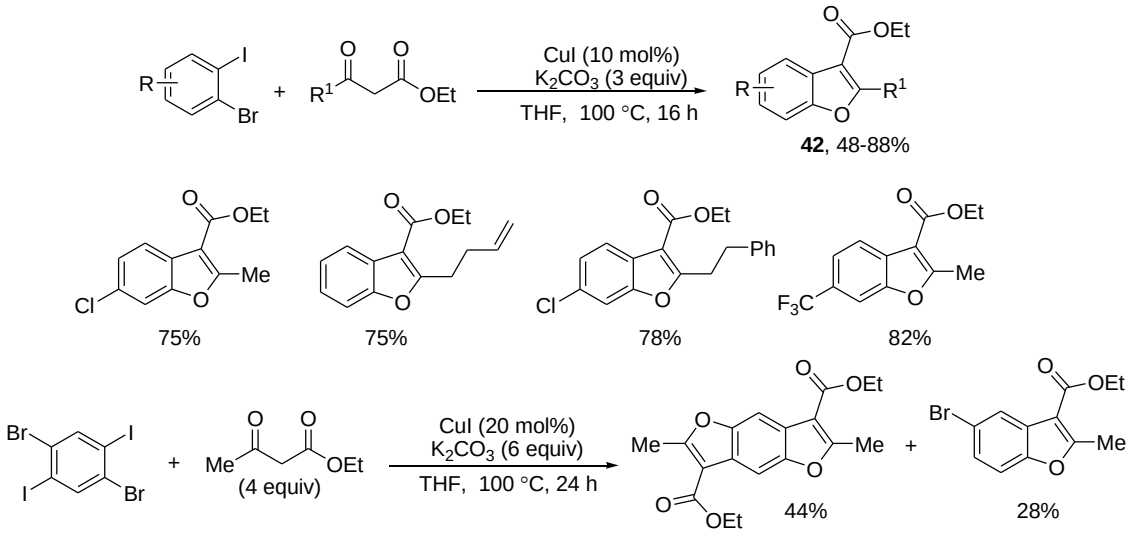
Scheme 18

Dominguez and coworkers have reported a regioselective synthesis of a series of 2,3-diarylbenzo[*b*]furans **41** by a tandem C-/O-arylation of 1,2-diarylethanones and 1,2-dibromoarenes catalyzed by homogenous and polymer anchored palladium catalysts (Scheme 19).[26] This tandem process can be effectively halted at the *C*-arylation step, thus providing key *o*-bromoarylated deoxybenzoin intermediates **40** in good yields (Scheme 19).



Scheme 19

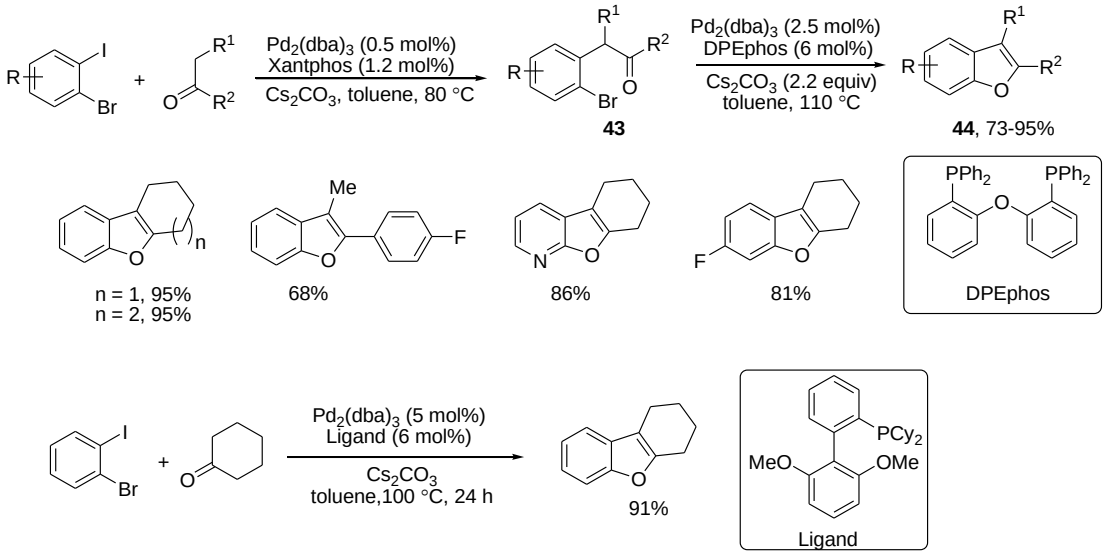
Ma and coworkers have developed a domino process leading to disubstituted benzofurans **42** via CuI catalyzed coupling of *β*-ketoesters with 1-bromo-2-iodobenzenes involving an initial intramolecular C-C bond formation and subsequent intramolecular C-O bond forming process (Scheme 20).[27] The reaction tolerates a number of functional groups including vinyl, chloro, fluoro, ester, keto, nitro, silyl ether groups thus making it versatile process for synthesis of substituted benzofurans.



Scheme 20

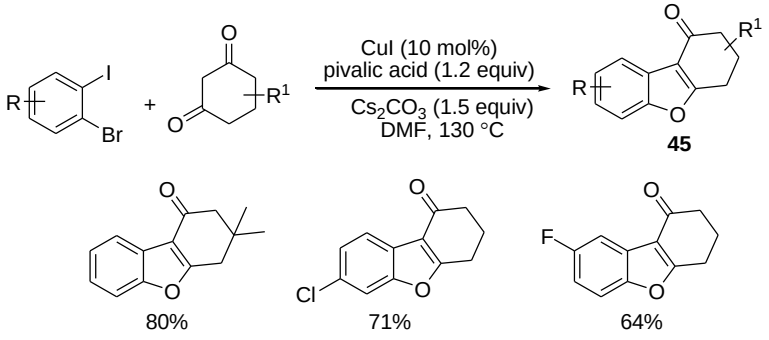
Willis and coworkers have recently demonstrated that enolates derived from *α*-(ortho-haloaryl)-substituted ketones **43** undergo palladium-catalysed intramolecular cyclization via C–O bond formation to deliver benzofuran products **44** in good yield (Scheme 21).[16a,28] A catalyst generated from $Pd_2(dba)_3$ and the ligand DPEphos effects the key bond formation to deliver a variety of substituted benzofuran products from both

cyclic and acyclic precursors. The key cyclization reaction involves coupling of enolates to palladium activated aryl halides. A cascade sequence that involving the in situ preparation of arylated ketones has also been developed, although the substrate scope is more restricted and requires optimization for individual substrates (Scheme 21).[16a]



Scheme 21

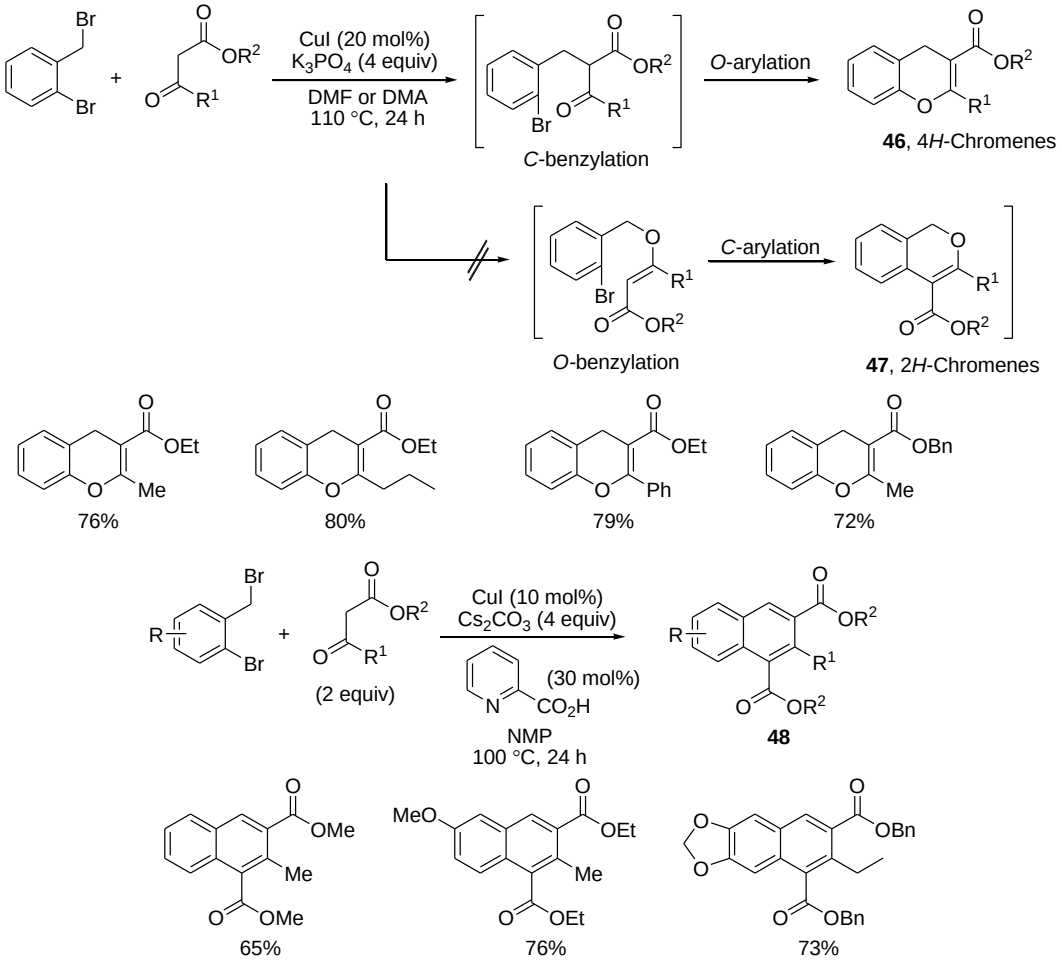
Beifuss and coworkers have recently reported Cu catalyzed domino reaction between 1-bromo-2-iodobenzenes and cyclohexane 1,3-diones leading to selective synthesis of dibenzo[*b,d*]furans **45** (Scheme 22).[29a] The highly regioselective domino process is based on an intermolecular Ullmann type C-arylation, followed by an intramolecular Ullmann-type *O*-arylation. Substituted products are accessible by employing substituted 1-bromo-2-iodobenzenes and substituted 1,3-cyclohexanediones.



Scheme 22

These workers have also reported two new and efficient Cu(I)-catalyzed domino reactions between readily available and inexpensive 2-bromobenzyl bromides and *β*-ketoesters (Scheme 23). Depending on the ratio of the substrates and the reaction

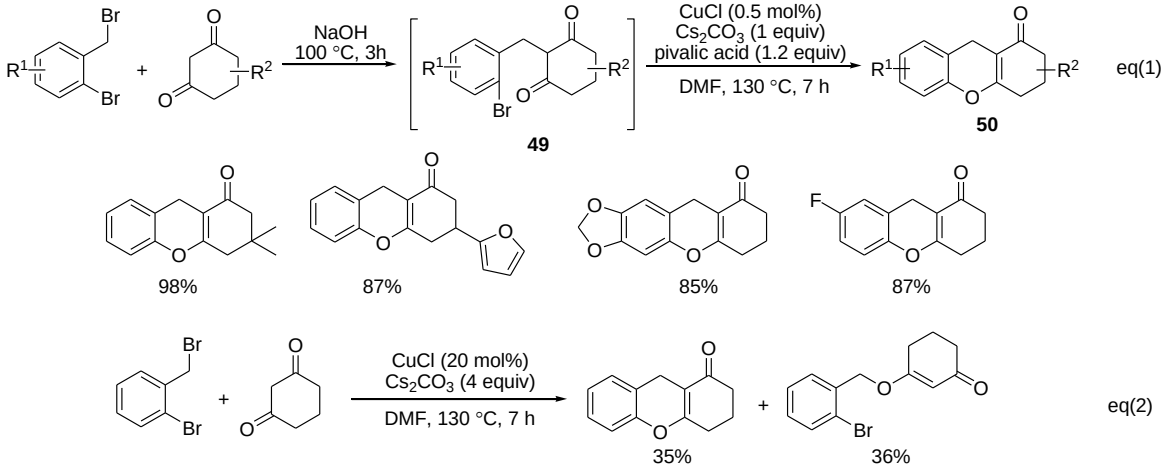
conditions employed, either 4*H*-chromenes **46** or naphthalenes **48** are formed exclusively. The formation of 4*H*-chromenes involves a domino *C*-benzylation/*O*-arylation process.[29b] Interestingly, no trace of the corresponding 2*H*-chromene **47**, which could be formed by alternate *O*-benzylation/*C*-arylation process could be isolated from reaction (Scheme 23), thus showing that former *C*-benzylation/*O*-arylation process is more favorable than the *O*-benzylation/*C*-arylation process. The formation of 4*H*-chromene is found to be highly selective, which could also be performed under ligand free conditions, which are typical of many other Cu(I) catalyzed transformations.



Scheme 23

In a subsequent paper, Beifuss and coworkers have reported an efficient two step method for the synthesis of substituted 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones **50** from easily accessible *o*-bromobenzyl bromides and cyclic 1,3-dicarbonyls as starting materials (Scheme 24, eq. 1).[30] The 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones **50** could be synthesized in a one-pot reaction between 2-bromobenzyl bromides and 1,3-cyclohexanediones via Cu(I)-catalyzed domino intermolecular *C*-benzylation/intramolecular *O*-arylation.

However the competing *O*-benzylation in the initial step, which could not be suppressed under the conditions of the Cu(I)-catalyzed domino reaction, gave rise to the formation of benzyl ethers as side products (Scheme 24, eq. 2). Therefore these workers developed the synthesis of the 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones in two steps which proved to be a valuable alternative to the domino process, as no side product formation occurred (Scheme24, eq. 1). The required *C*-benzylated 1,3-diones **49** could be obtained selectively by reacting 2-bromobenzyl bromides with 1,3-diones under basic conditions with yields ranging from 45% to 83%. Subsequently, the 2-(2-bromobenzyl)-cyclohexane-1,3-diones **49** were cyclized to the corresponding 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones by Cu(I)-catalyzed intramolecular *O*-arylation in high yields by performing the cyclizations with 0.5 mol % CuCl as the catalyst, 1.2 equiv of pivalic acid as an additive, and 1 equiv of Cs_2CO_3 as the base (Scheme 24).

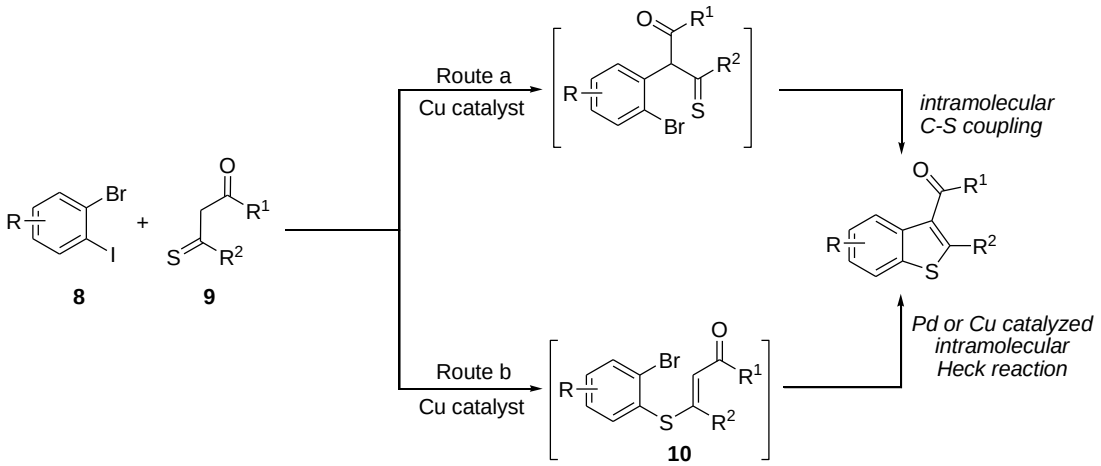


Scheme 24

In earlier work from this laboratory, our research group has reported synthesis and application of 1,3-disubstituted monothio-1,3-diketones **9**, a new class of versatile organosulfur synthons. Based on these intermediates, they have developed a novel synthesis of substituted pyrazoles with complementary regioselectivity (see Chapter 5, Scheme 18).[31a] In continuation of these studies, Anand and coworkers from our group have further elaborated a one pot, three- step synthesis of highly functionalized and fluorescent thiophenes utilizing these substituted 1,3-monothioketones as precursors (see chapter 5, Scheme 19).[31b] In chapter 5 of this thesis, we have reported a novel one pot, three-step synthesis of 2,4,5-substituted imidazoles starting from substituted 1,3-monothioketones, via sequential generation of *N*-substituted enaminones, followed by

their nitrosation and base mediated intramolecular cyclization of the resulting nitrosoenaminones.[31c]

In continuation of these studies, to further explore the synthetic applications of 1,3-monothioketones **9**, we conceived of developing an alternative convergent synthesis of benzo[*b*]thiophenes utilizing these intermediates as C-C-S coupling partners with 1-bromo-2-iodoarenes and hetarenes **8** (Scheme 25). It was envisaged that 1,3-monothioketone may undergo copper catalyze arene C-C coupling and subsequent intramolecular C-S bond formation to give benzo[*b*]thiophenes as observe by previous workers for the synthesis of few benzoheterocycles (Scheme 25, route a). Alternatively, a (C1a)-(S1) bond formation may take place as the first step via initial intermolecular attack of nucleophilic sulfur atom derived from thioenolate of 1,3-monothioketone on 1-bromo-2-iodobenzenes via Ullman type C-S coupling followed by intramolecular Heck reaction of the resulting *β*-phenylthio-*α*,*β*-unsaturated ketones **10** involving formation of (C-3)-(C-3a) bond formation via arene-alkene coupling leading to substituted benzo[*b*]thiophenes (route b, Scheme 25). Indeed, we could achieve this goal and report in this chapter, a new one-pot, two step regioselective synthesis of substituted benzo[*b*]thiophenes using 1,3-monothio-1,3-diketone precursors through latter pathway (route b, Scheme 25). The results of these studies have been reported in the following section.



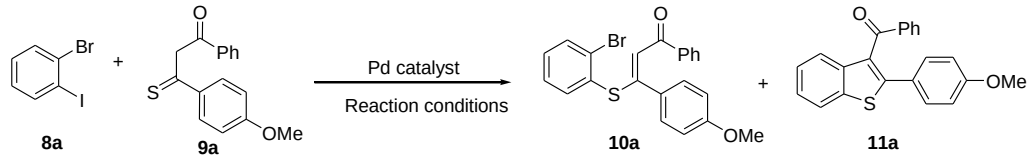
Scheme 25

6.3 Results and Discussion

6.3.1 Optimization of Reaction Conditions for the Formation of Benzo[*b*]thiophene 11a

We selected 1,3-monothioketone **9a** as model substrates for its coupling with 2-bromo-1-iodobenzene **8a** for the screening of the suitable catalyst system for the synthesis of benzothiophene **11a**. During initial studies, we first employed various Pd catalysts like $Pd(OAc)_2$, $Pd_2(dba)_3$ etc. for the coupling-cyclization of **8a** and **9a** in the presence of different phosphine ligands, bases and solvent systems for the synthesis of benzothiophene **11a** (Table 1). Unfortunately, we could not get benzothiophene **11a** from any of these reactions, except in one case, where, we were able to isolate C-S coupled thiovinyl intermediate **10a**, in presence of $Pd_2(dba)_3$ catalyst , DPEPhos ligand and Cs_2CO_3 as base in toluene (Table 1, entry 3).

Table 1. Optimization of Reaction Conditions for the Formation of Benzo[*b*]thiophene 11a with Pd Catalysts[a]



8a **9a** **10a** **11a**

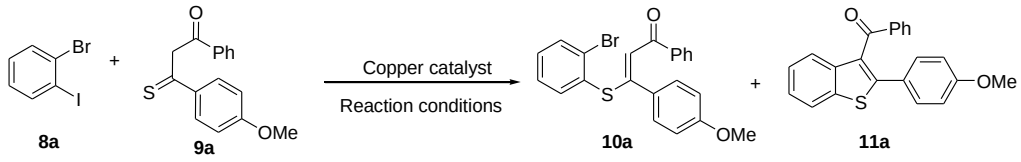
entry	Pd catlyst (mol%)	ligand (mol%)	base/additive	temp °C/time, h	solvent	%yield **10a**	%yield **11a**
1	$Pd(OAc)_2$ (10 mol%)	PPh_3 (20 mol%)	Cs_2CO_3(2.0 equiv)	100 °C, 20 h	DMF	No reaction	
2	$Pd(OAc)_2$ (10 mol%)	PPh_3 (20 mol%)	K_2CO_3 (2.0 equiv)	100 °C, 20 h	DMSO	No reaction	
3	$Pd_2(dba)_3$ (5 mol%)	DPEPhos (10 mol%)	Cs_2CO_3 (2.0 equiv)	110 °C, 12 h	Toluene	73%	—
4	$Pd_2(dba)_3$ (5 mol%)	DPEPhos (10 mol%)	Cs_2CO_3 (2.0 equiv)	100 °C, 10 h	DMF	Decomposed	
5	$Pd(OAc)_2$ (10 mol%)	DPEPhos (20 mol%)	Cs_2CO_3 (2.0 equiv)	100° C, 24 h	Toluene	No reaction	
6	$Pd(OAc)_2$ (10 mol%)	DPEPhos (20 mol%)	Cs_2CO_3 (2.0 equiv)	100 °C, 24 h	DMF	No reaction	
7	$Pd_2(dba)_3$ (5 mol%)	Xantphos (10 mol%)	Cs_2CO_3 (2.0 equiv)	100 °C, 24 h	1,4-dioxane	No reaction	
8	$Pd(OAc)_2$ (10 mol%)	PPh_3 (20 mol%)	*t*-BuOK (2.0 equiv)	100 °C, 30 h	DMF	No reaction	
9	$Pd(PPh_3)_4$ (10 mol%)	—	Cs_2CO_3(2.0 equiv)	100 °C, 20 h	DMSO	No reaction	
10	$PdCl_2$ (10 mol%)	BINAP (20 mol%)	$NaHCO_3$ (2.0 equiv)	100 °C, 24 h	1,4-dioxane	No reaction	

[a]Reactions performed with **8a** (0.5 mmol) and **9a** (0.5 mmol) in 4 mL of solvent under N_2.

With failure of Pd catalysts, we then switched our attention towards copper catalysts and tried to carry out the same reaction in presence of Cu(I) salts as catalysts in the presence of various ligands (Table 2). However we again failed to isolate

benzothiophene **11a** under these conditions, but to our delight, we found that, the reaction works very well for the formation of thiovinylketone **10a** (Table 2). Under optimal conditions, best yield of **10a** was obtained with cuprous iodide (10 mol%) as catalyst, in the presence of Cs_2CO_3 as base in DMF under ligand free conditions, yielding **10a** in 87% yield (Table 2, entry 2).

Table 2. Optimization Conditions for Benzothiophene 11a with Cu Catalysts[a]



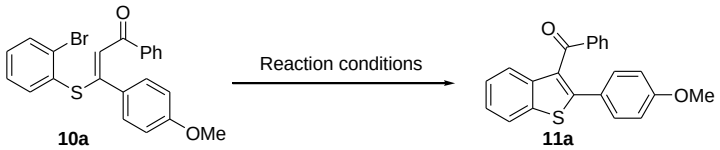
8a **9a** **10a** **11a**

entry	Copper catalyst (mol%)	ligand (mol%)	base/additive	temp °C/time, h	solvent	%yield **10a**	**10b**
1	CuI(10 mol%)	—	Cs_2CO_3(2.0 equiv) Pivalic Acid (1.5 equiv)	120 °C, 5 h	DMF	78%	
2	CuI(10 mol%)	—	Cs_2CO_3 (1.5 equiv)	100 °C, 3 h	DMF	87%	
3	CuI(10 mol%)	—	K_2CO_3 (1.5 equiv)	100 °C, 3 h	DMF	81%	
4	Cu_2O (10 mol%)		Cs_2CO_3 (1.0 equiv)	100 °C, 6 h	DMSO	63%	
5	CuI(10 mol%)	L-proline (20 mol%)	Cs_2CO_3 (1.0 equiv)	100 °C, 3 h	DMSO	80%	
6	CuBr(10 mol%)	1,10-phen (20 mol%)	Cs_2CO_3 (1.0 equiv)	100 °C, 4 h	DMSO	75%	
7	CuI(10 mol%)	DMEDA (20 mol%)	K_2CO_3 (2.0 equiv)	100 °C, 4 h	DMF	70%	
8	Cu_2O (10 mol%)	1,10-phen (20 mol%)	*t*-BuOK (1.0 equiv)	100 °C, 5 h	1,4-dioxane	69%	

[a]Reactions performed with **8a** (0.5 mmol) and **9a** (0.5 mmol) in 4 mL of solvent under N_2.

With faliure to obtain benzothiophene **11a** directly under palladium or copper catalyst from **8a** and **9a**, we next attempted cyclization thiovinyl ketone **10a** to benzothiophene **11a** in the presence of various palladium catalyst/ligand systems via intramolecular Heck reaction. (Table 3). To our delight, that intramolecular Heck reaction worked very well furnishing benzothiophene **11a** giving good to excellent yields. We tried various Pd(II) catalysts (Table 3, entries 1-7, 9-10, 12, 15-21), as well as Pd(0) catalysts (Table 3, entries 8, 11, 13-14) of which Pd(II) catalysts showed good results. Best results were obtained using 10 mol% of palladium catalysts, Cs_2CO_3 as base and DMF at 100 ^{0}C in the presence or absence of triphenyl phosphine affording **11a** in comparable yield of 81-82% (Table 3, entries 1 and 5).

Table 3. Cyclization of Intermediate 10a to Benzothiophene 11a[a]



10a **11a**

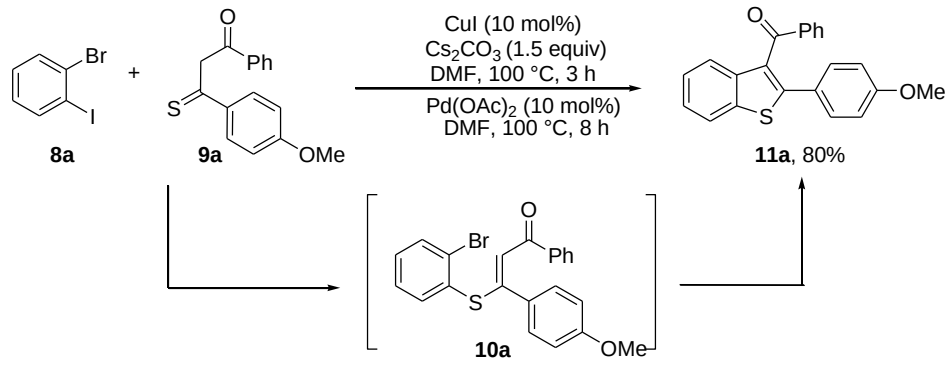
entry	Pd catlyst (mol%)	ligand (mol%)	base/additive	temp °C/time, h	solvent	%yield
1	$Pd(OAc)_2$ (10 mol%)	—	Cs_2CO_3 (1.0 equiv)	100 °C, 8 h	DMF	81%
2	$Pd(OAc)_2$ (10 mol%)	—	Cs_2CO_3 (1.0 equiv)	100 °C, 8 h	DMSO	78%
3	$Pd(OAc)_2$ (10 mol%)		Et_3N (1.0 equiv)	80 °C, 20 h	CH_3CN	No reaction
4	$Pd(OAc)_2$ (10 mol%)	PPh_3 (20 mol%)	Cs_2CO_3 (1.0 equiv)	100 °C, 8 h	DMSO	71%
5	$Pd(OAc)_2$ (10 mol%)	PPh_3 (20 mol%)	Cs_2CO_3 (1.0 equiv)	100 °C, 8 h	DMF	82%
6	$Pd(OAc)_2$ (5 mol%)	PPh_3 (10 mol%)	Ag_2CO_3 (1.0 equiv)	100 °C, 12h	DMF	55%
7	$Pd(OAc)_2$ (5 mol%)	BINAP (10 mol%)	K_2CO_3 (1.0 equiv)	100 °C, 10 h	DMF	64%
8	$Pd(PPh_3)_4$ (5 mol%)	—	Cs_2CO_3 (1.0 equiv)	100 °C, 24 h	CH_3CN	No reaction
9	$Pd(OAc)_2$ (5 mol%)	P(*o*-tol)$_3$ (10 mol%)	K_2CO_3 (1.0 equiv)	100 °C, 12 h	DMSO	68%
10	$PdCl_2$ (5 mol%)	PPh_3 (10 mol%)	Cs_2CO_3 (1.0 equiv)	100 °C, 15 h	DMF	59%
11	$Pd(PPh_3)_4$ (10 mol%)	—	Et_3N (5.0 equiv)	100 °C, 30 h	DMF	No reaction
12	$Pd(OAc)_2$ (5 mol%)	Xphos(10 mol%)	Cs_2CO_3 (1.0 equiv)	100 °C, 20 h	DME	62%
13	$Pd_2(dba)_3$ (5 mol%)	Xantphos(10 mol%)	Cs_2CO_3 (1.0 equiv)	100 °C, 18 h	DMSO	52%
14	$Pd_2(dba)_3$ (5 mol%)	DavePhos (10 mol%)	NaO*t*Bu (1.0 equiv)	100 °C, 4 h	DMF	Decomposed
15	$PdCl_2$ (5 mol%)	BINAP (10 mol%)	$NaHCO_3$ (1.0 equiv)	100 °C, 10 h	1,4-dioxane	73%
16	$Pd(OAc)_2$ (10 mol%)	PPh_3 (20 mol%)	K_2CO_3 (1.0 equiv)	100 °C, 30 h	Toluene	No reaction
17	$Pd(OAc)_2$ (10 mol%)	—	K_2CO_3 (1.0 equiv) Bu_4NBr (1.0 equiv)	100 °C, 15 h	DMF	77%
18	$Pd(OAc)_2$ (10 mol%)	—	K_2CO_3 (1.0 equiv) Bu_4NI (1.0 equiv)	100 °C, 12 h	DMF	70%
19	$Pd(OAc)_2$ (10 mol%)	—	K_2CO_3 (1.0 equiv) Bu_4NHSO_3 (1.0 equiv)	100 °C, 16 h	DMF	65%
20	$PdCl_2(PPh_3)_2$ (10 mol%)	—	K_2CO_3 (1.0 equiv) Bu_4NI (1.0 equiv)	100 °C, 20 h	DMF	48%
21	$Pd(OAc)_2$ (10 mol%)	—	$NaHCO_3$ (1.0 equiv) Bu_4NI (1.0 equiv)	130 °C, 8 h	DMF	72%

[a]Reactions performed with **10a** (0.3 mmol) in 4 mL of solvent under N_2.

6.3.2 One-Pot Synthesis of Benzo[*b*]thiophene 11a from Bromo-iodobenzene 8a and Monothioketone 9a

With two step optimized conditions for the synthesis of benzothiophene **11a** (from **8a** and **9a**) in hand, involving copper catalyzed C-S bond formation to give **10a** and its subsequent palladium catalyzed intramolecular Heck cyclization to **11a**, we next attempted one-pot, two step synthesis of **11a** via sequential addition of copper and palladium catalyst (Tables 2 and 3). Thus by combining the earlier optimized copper

catalyzed C-S bond formation conditions for the formation of **10a** (Table 2, entry 2), followed by its in situ palladium catalyzed intramolecular Heck reaction under optimal conditions (Table 3, entry 1), we could successfully obtain benzothiophene **11a** in 80% yield (Scheme 26). Use of other solvents like DMSO or in the presence of base like K_2CO_3 (in DMF) afforded the benzothiophene **11a** in reduced yield of 73% and 76% respectively. These optimized reaction conditions were followed throughout our studies to develop a general convergent synthesis of substituted benzo[*b*]thiophenes **11** from various 1,3-monothioketones **9** and substituted *o*-bromo-iodobenzenes **8**.

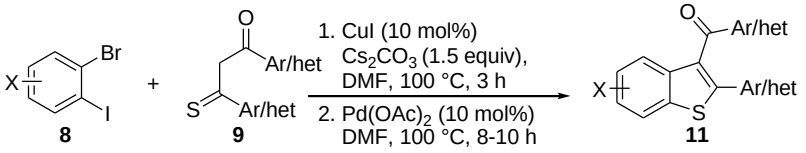


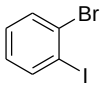
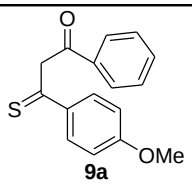
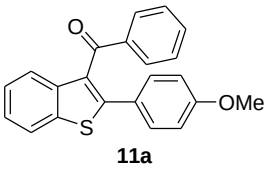
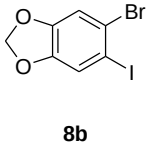
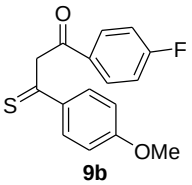
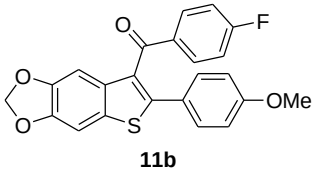
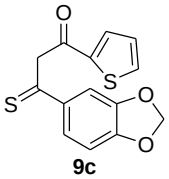
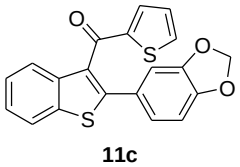
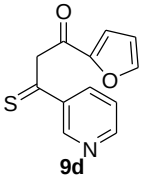
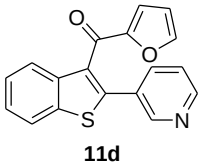
Scheme 26

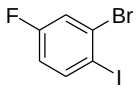
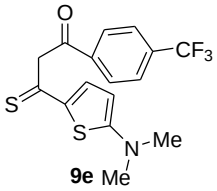
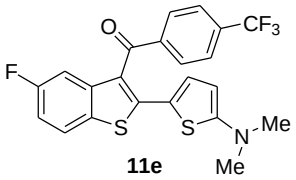
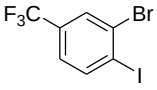
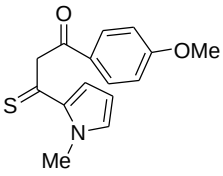
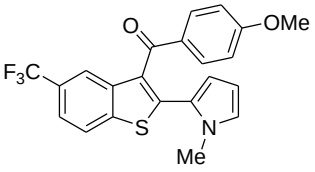
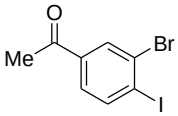
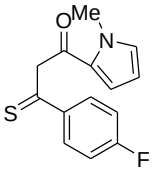
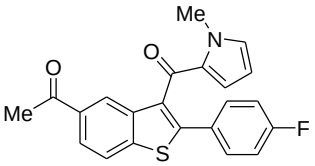
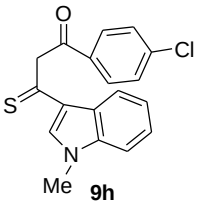
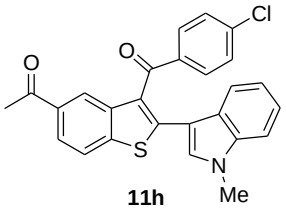
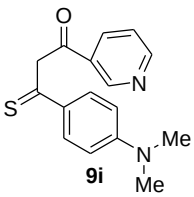
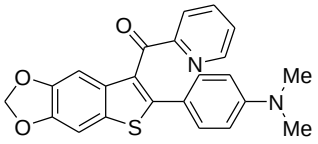
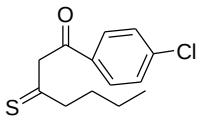
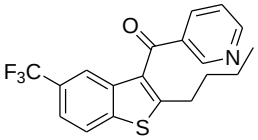
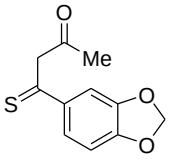
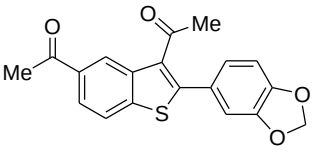
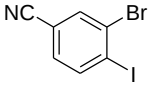
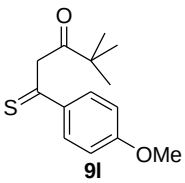
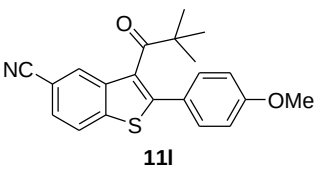
With optimized one-pot conditions for this novel convergent synthesis of benzo[*b*]thiophenes **11a** in hand, we next examined generality of this reaction with various monothioketones and 1,2-halobenzenes carrying various substituents, these results are depicted in Table 4. Thus the reaction proceeded smoothly with 1,3-bis(aryl)monothioketones **9a-b** carrying both electron donating and withdrawing groups to afford 2-aryl-3-aroylbenzothiophenes **11a-b** in good yields (Table 4, entries 1-2). Similarly, 1,3-monothioketones **9c-h**, bearing various hetaryl groups such as 2-thienyl-, 2-furyl- or 2-(N-methylpyrrolyl-) or 3-(N-methylindolyl-) moieties either at carbonyl or thiocarbonyl groups, afforded the corresponding 2-(het)aryl or 3-het(aroyl)benzothiophenes **11c-g** in good yields (Table 4, entries 3- 8). It was also possible to introduce a (3-pyridyl) or (3-pyridoyl) group at 2- and 3- positions of benzothiophenes **11d** and **11i** respectively (Table 4, entries 4 and 9). Entry 10 depicts the example of synthesis of benzothiophene (**11j**) bearing an alkyl chain such as *n*-butyl group at 2-position (Table 4, entry10). Similarly by employing the 1,3-monothioketones such as **9k** and **9l** carrying an acetyl or (*t*-butyroyl) groups, it was possible to synthesize 3-acetyl-, and 3-(*t*-butyroyl)benzothiophenes **11k** and **11l** respectively in good to

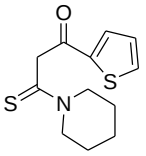
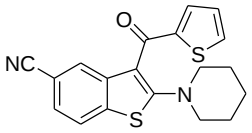
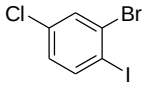
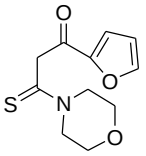
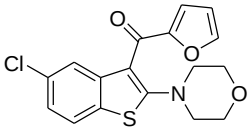
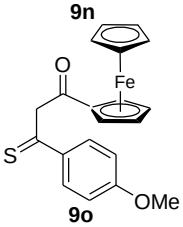
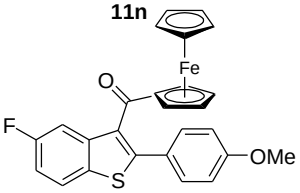
moderate yields (Table 4, entries 11-12). Also, further diversity at 2-position of the benzothiophene could be achieved by employing tertiary *β*-ketothioamides such as **9m-n** as coupling partners affording the corresponding 2-(N-piperidino)- and 2-(N-morphilino)benzothiophenes **11m-n** in moderate to good yields (Table 4, entries 13-14). Also, it was possible to introduce both electron donating (Table 4, entries 2 and 9) and withdrawing groups such as fluoro (Table 4, entry 5), trifluoromethyl (entry 6), acetyl (entries 7 and 8) and cyano (entry 12) groups at various positions of benzene ring of benzothiophenes by using various substituted 2-bromo-1-iodobenzenes **8b-f**. Entry 14 demonstrates the example of a synthesis of 5-chloro- substituted benzothiophenes **11n** without formation of any side products. However, when we have reacted 1,3-monothioketone **9o** bearing 2-ferrocenoyl group at carbonyl with **8c** under similar reaction conditions, we did not observe the formation of benzothiophene **11o** (Table 4, entry 15), instead some unidentified product obtained, which we could not be characterized.

Table 4. Synthesis of Benzo[*b*]thiophene 11 from Bromoiodobenzene 8 and Monothioketone 9[a]



entry	8	9	11	yield (%)[a]
1	 **8a**	 **9a**	 **11a**	80
2	 **8b**	 **9b**	 **11b**	88
3	**8a**	 **9c**	 **11c**	82
4	**8a**	 **9d**	 **11d**	77

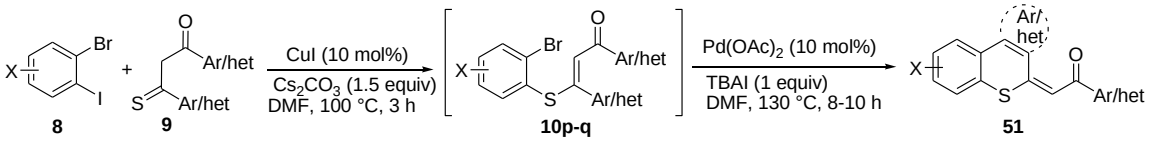
entry	8	9	11	yield (%)[a]
5	 **8c**	 **9e**	 **11e**	76
6	 **8d**	 **9f**	 **11f**	81
7	 **8e**	 **9g**	 **11g**	73
8	**8e**	 **9h**	 **11h**	70
9	**8b**	 **9i**	 **11i**	78
10	**8d**	 **9j**	 **11j**	65
11	**8e**	 **9k**	 **11k**	79
12	 **8f**	 **9l**	 **11l**	58

entry	8	9	11	yield (%)[a]
13	**8f**	 **9m**	 **11m**	55
14	 **8g**	 **9n**	 **11n**	62
15	**8c**	 **9o**	 **11o**	0

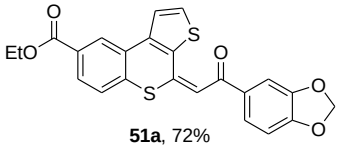
[a]Reaction conditions: **8a** (0.5 mmol), **9a** (0.5 mmol), CuI (0.05 mmol), $Pd(OAc)_2$ (0.05 mmol) and Cs_2CO_3 (0.75 mmol) in DMF (4 mL) heated under N_2 atm at 100 °C for 11-12 h

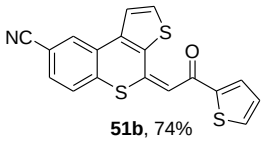
6.3.3 Synthesis of Thieno-Fused Benzothiopyran 51 from Bromoiodobenzene 8 and Monothioketone 9

When we tried to cyclize intermediate **10p** obtained by monothioketone with a thiophene moiety attached to thione part, we found that the reaction was forming thiochromene/thieno-fused benzothiopyran **51a** via direct C-H arylation at 3-position of thiophene motif, rather than intramolecular Heck reaction (Scheme 27).



8 **9** **10p-q** **51**


51a, 72%

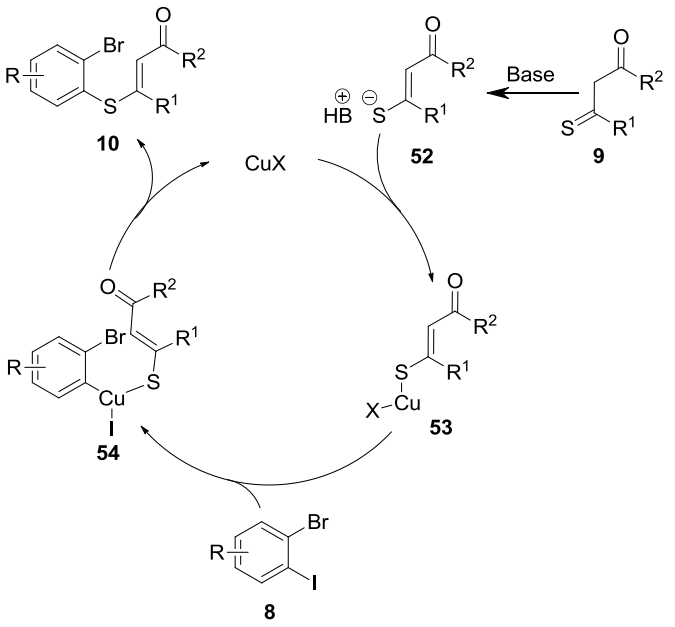

51b, 74%

Scheme 27

6.3.4 Proposed Mechanism for Cu(I) Catalyzed Formation of Arylthiovinyl ketones 10 from 1,3-Monothioketones 9 and *o*-Bromoiodobenzenes

The probable mechanism for the formation of arylthiovinyl ketones **10** via copper catalyzed C-S coupling of monothioketones **9** and *o*-iodobromobenzenes **8** is shown in the Scheme 28. Thus, in the presence of base, the generated thioenolate anion **52** couples

with copper iodide to afford thioenolate coordinated copper complex **53**, which on insertion into more reactive aryl C-I bond of *o*-bromoiodobenzene, furnishes arylcopperthioenolate intermediate **54**. Subsequent reductive elimination of **54** gives arylthiovinyl ketone **10** along with the generation of Cu(I) catalyst. Interstingly, the formation of C-S bond is very facile in this case, which proceeds in the absence of any ligand (Scheme 28).

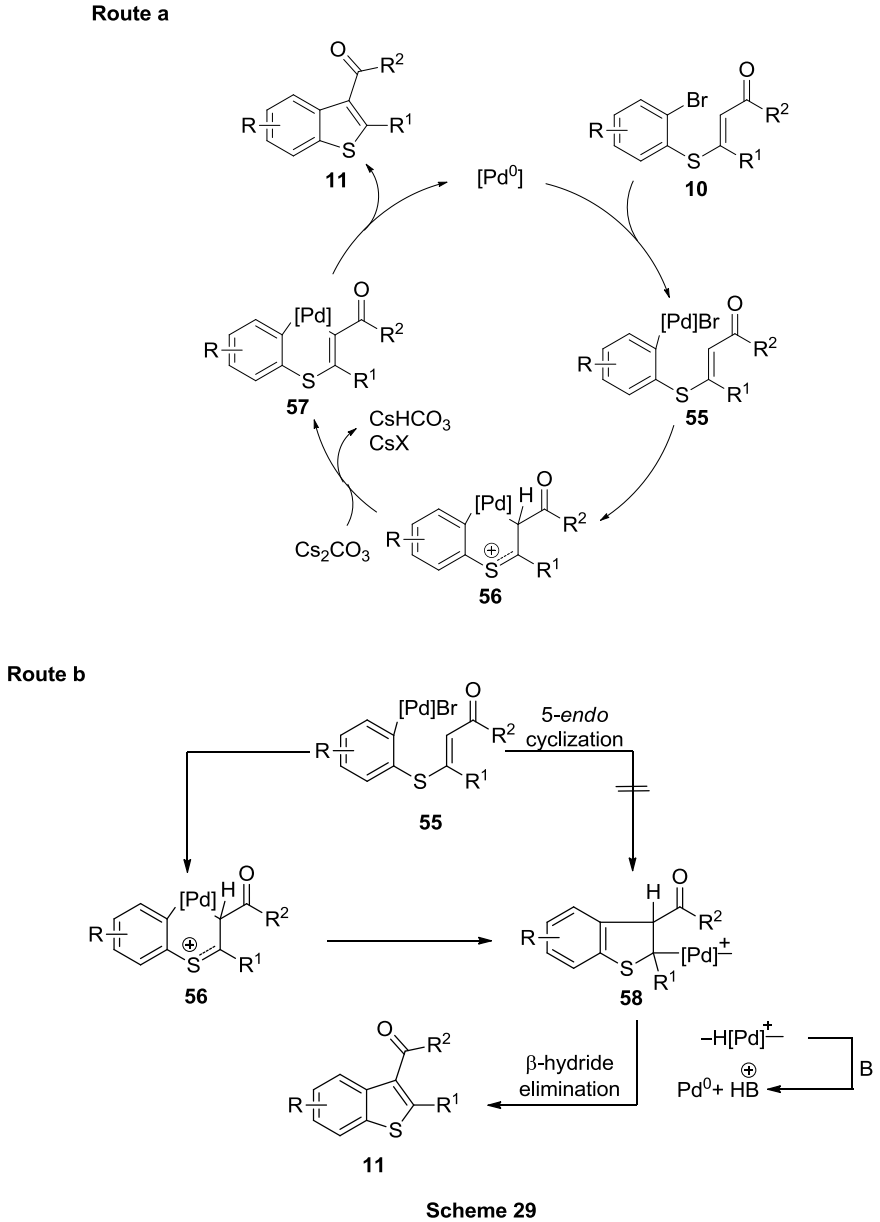


Scheme 28

6.3.5 Proposed Mechanism for Palladium Catalyzed Intramolecular Heck Type Arylation of Arylthiovinyl ketone 10 to Benzothiophene 11

The probable mechanisms for the palladium catalyzed intramolecular Heck type arene-alkene coupling of the arylthiovinylketone **10** leading to benzothiophene **11** are depicted in the Scheme 29. Thus oxidative insertion of Pd(0) into bromoarene affords the insertion intermediated **55**, which could be transformed into resonance stabilized intermediate metalllacycle **56** formed by attack of electron rich thiovinyl double bond on electrophilic metal center (with or without prior Br- loss). Subsequent deprotonation of acidic proton in the palladacycle **56** would lead to intermediate **57**, which could undergo reductive elimination to form benzothiophene **11** (Route a). A mechanism involving direct Heck type insertion in the intermediate **55** leading to intermediate **58** followed by subsequent β-hydride elimination to benzothiophene **11**(**55→58→11**) is likely disfavored energetically owing to the strain associated with the 5-*endo* cyclization. Alternatively, the intermediate **58** could be formed by a two step alkene insertion process from the **55** via

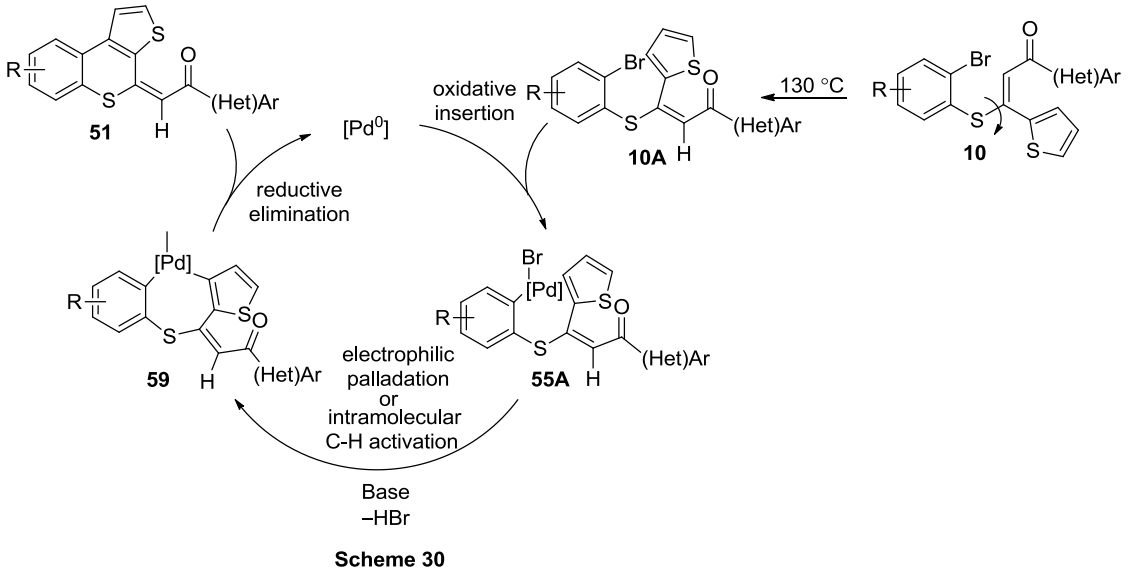
intermediate palladacycle **56** (**55→56→58→11**) (an interrupted Heck reaction). The intermediate **58** can readily undergo subsequent β- hydride elimination to give benzothiophene **11** (route b). The proposed mechanisms are similar to one suggested by Kurth and coworkers[23] for the palladium catalyzed intramolecular cyclization of N-arylenamines to 2,3- substituted/annulated indoles on the basis of quantum chemical calculations offering an alternative to previously suggested direct Heck coupling mechanisms.[32]



Scheme 29

6.3.6 Probable Mechanism for the Formation of Thieno-Fused Benzothiopyran

The probable mechanism for the unexpected formation of thieno- fused benzothiopyrans **51a-b** from arylthiovinylketones **10p-q**, in the presence of palladium acetate catalyst and tetrabutylammonium iodide at higher temperature (130 °C) (Scheme 27) is shown in the Scheme 30. Thus the thiovinylketones **10p-q** appear to undergo conformational change at higher temperature by rotation around C-S bond to **10A** with a proximal 2-thienyl ring, which on oxidative insertion on C-Br bond affords the intermediate **55A**. The arylpalladium intermediate in conformation **55A** appears to undergo intramolecular C-C bond formation through direct arylation at electron rich C-3 position of thiophene ring to afford seven membered palladacycle **59** (Scheme 30). The palladacycle **59** may be formed either by electrophilic palladation of thiophene ring in **55A**[33a] or by C-H activation involving intramolecular oxidative addition of (Aryl)Pd species **55A** to neighbouring thienyl C-H bond[33b] as proposed by Fagnou and others. Subsequent reductive elimination in palladacycle **59** gives product thieno- fused benzothiopyrans **51**, regenerating the catalyst (Scheme 30). However further work is needed to establish this mechanism by examining the generality of this reaction with thiovinyl ketones bearing a other heterocyclic moieties such as 2-pyrrolyl(**9f**), 2-furyl and 3-indolyl(**9h**) groups.



Scheme 30

6.4 Conclusion

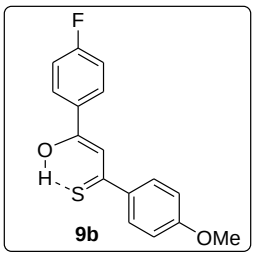
In summary, we have developed a novel, convergent highly regioselective one-pot synthesis of substituted 2-(het)aryl/alkyl-3-acylbenzo[*b*]thiophenes incorporating both a

sequential intermolecular copper catalyzed C-S bond formation and an intramolecular palladium catalyzed Heck type arene-alkene coupling. Benzothiophene formation could be accomplished by employing a range of 1,3-monothioketones **9** and substituted *o*-bromoiodobenzenes **8** as coupling partners under suitable optimized reaction conditions. We have also observed unexpected formation of thieno- fused benzothiopyrans **51a-b** by intramolecular palladium catalyzed cyclization of arylthiovinyl ketones **10p-q** bearing a (2-thienyl) moiety at β-position under different reaction conditions at higher temperature (Scheme 27). Probable mechanisms for the formation of benzothiophenes **11** and thieno-fused benzothiopyran products **51a-b** under palladium catalysis has been suggested. Further work to establish generality of these two palladium catalyzed process by employing various 1,3-monothioketones as well as β-thioxo-esters along with detailed mechanistic studies are under progress in our laboratory.

6.5 Experimental Section

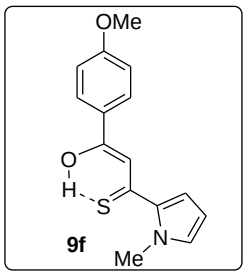
6.5.1 General Information. All reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using standard TLC silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100–200 mesh). Nuclear magnetic resonance spectra were recorded on (400 MHz) FT–NMR spectrometer with $CDCl_3$ or DMSO–d_6 as solvent. Chemical shifts were reported in δ ppm using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO–d_6 in ^{1}H–NMR, δ 77.16 for $CDCl_3$ and δ 39.52 for DMSO–d_6 in ^{13}C–NMR). Coupling constants were reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet) and br (broad). Infrared spectra of neat samples were recorded in ATR (attenuated total reflectance) mode using FT–IR instrument and HRMS on Q–TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

The desired 1,3-bishet(aryl)-monothio-1,3-diketones **9** were prepared following our earlier reported procedure,[31a,c] and the spectral and analytical data of unknown ,3-bishet(aryl)-monothio-1,3-diketones **9b**, **9f** are given below, the required *o*-bromoiodobenzenes **8** were prepared according to the reported procedures.[34]



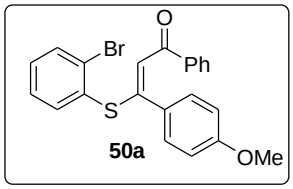
(*Z*)-3-(4-fluorophenyl)-3-hydroxy-1-(4-methoxyphenyl)prop-2-ene-1-thione (9b). Obtained as a red solid (1.08 g, 75%): mp 65-67 °C; R_f 0.3 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2903, 1557, 1448, 1245, 794; ^1H NMR (400 MHz, $CDCl_3$) δ 15.70 (s, 1H), 8.03-8.0 (m, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.38 (s, 1H), 7.17 (t, J = 8.4 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.6, 177.2, 166.5, 164.0, 162.7, 138.1, 132.0, 131.9, 129.5, 129.4, 128.6, 116.1, 115.9, 113.8, 108.5, 55.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}FO_2S$ $[M + H]^+$ 289.0699, found 289.0694.

(*Z*)-3-hydroxy-3-(4-methoxyphenyl)-1-(1-methyl-1H-pyrrol-2-yl)prop-2-ene-1-thione (9f). Obtained as a red solid (1.07 g, 79%): mp 75-77 °C; R_f 0.4 (1:4 EtOAc/hexane); IR



(neat, cm^{-1}) 2932, 1546, 1432, 1228, 812; ^1H NMR (400 MHz, $CDCl_3$) δ 16.13 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.24 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.90-6.89 (m, 1H), 6.86 (dd, J = 4.4 Hz, 2.0 Hz, 1H), 6.17 (dd, J = 4.4 Hz, 2.0 Hz, 1H), 4.05 (s, 3H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.0, 174.2, 162.8, 140.4, 132.8, 128.6, 127.7, 114.4, 114.1, 108.3, 107.1, 55.4, 38.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{16}NO_2S$ $[M + H]^+$ 274.0902, found 274.0894.

6.5.2 General Procedure for the Synthesis of (*E*)-3-((2-Bromophenyl)thio)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (50a). A mixture of 1,3 monothioketone (135.0 mg, 0.5 mmol) **9a** and 2-bromoiodobenzene (141.0 mg, 0.5 mmol) **8a** were taken in dry DMF (4 mL). To this copper catalyst (CuI) (9.5 mg, 10 mol%) and base (244.3 mg, 1.5 equiv) were added at room temperature, followed by heating at 100 °C for 3 h under N_2 atmosphere (monitored by TLC). It was then poured into saturated NH_4Cl (25 mL) solution, extracted with EtOAc (2 x 25 mL), washed with water (2 x 25 mL), brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude product, which was purified by column chromatography using EtOAc/hexane (2:8) as eluent.

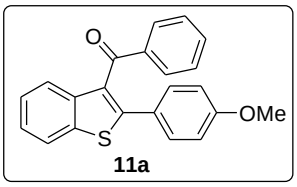


Obtained as a yellow solid (184.4 mg, 87%): mp 68-70 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2935, 1630, 1531, 1243, 744; ^1H NMR (400 MHz, DMSO-d_6) δ 8.11-8.09 (m, 2H), 7.67-7.64 (m, 1H), 7.63-7.56 (m, 2H), 7.51 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.50 (s, 1H), 7.37-7.34 (m, 3H), 7.14 (td, J = 7.2 Hz, 1.6 Hz, 1H),

7.09 (td, J = 8.0 Hz, 2.0 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 2H), 3.68 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 188.7, 160.6, 160.2, 138.5, 136.9, 135.0, 133.1, 132.6, 131.3, 130.4, 129.7, 128.8, 128.7, 128.4, 127.3, 120.6, 113.4, 55.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}BrO_2S$ $[M + H]^+$ 425.0211and 427.0190, found 425.0176 and 427.0166.

6.5.3 General Procedure for the Synthesis of Benzo[*b*]thiophene 11a from 10a Under Palladium Catalyst. A mixture of thiovinylketone **10a** (127.2 mg), $Pd(OAc)_2$ (6.7 mg, 10 mol%) and base (97.74 mg, 1.0 equiv) were taken in dry DMF (4 mL) under N_2 atmosphere and then heated at 100 °C for 8 h (monitored by TLC). It was then poured into saturated NH_4Cl (25 mL) solution, extracted with EtOAc (2 x 25 mL), washed with water (2 x 25 mL), brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude product, which was purified by column chromatography using EtOAc/hexane (1:9) as eluent.

(2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl)(phenyl)methanone (11a). Obtained as a yellow solid (83.5 mg, 81%): mp 84-86 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2945, 1658, 1434, 1217, 823; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 1H), 7.84-7.76 (m, 2H), 7.72-7.70 (m, 1H), 7.42-7.40 (m, 1H), 7.39-7.34 (m, 4H), 7.30-7.27 (m, 2H), 6.74 (d, J = 8.8 Hz, 2H), 3.74 (s, 3H)); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.6, 160.2, 146.6, 140.0, 138.8, 137.7, 133.3, 130.8, 130.7, 130.1, 128.5, 125.9, 125.2, 125.0, 123.6, 122.0, 114.2, 55.4; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}O_2S$ $[M + H]^+$ 345.0949, found 345.0932.

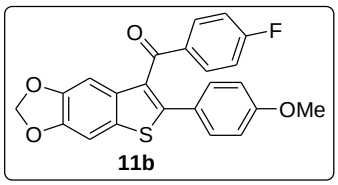


11a

6.5.4 General Procedure for Sequential One-Pot Synthesis of Benzo[*b*]thiophenes 11 from *o*-bromoiodobenzenes 8 and monothioketones 9. A mixture of 1,3 monothioketones **9** (0.5mmol) and *o*-bromoiodobenzenes **8** (0.5 mmol) were taken in dry DMF (4 mL), to this reaction mixture CuI (9.5 mg, 10 mol%) and cesiumcarbonate (244.3 mg, 1.5 equiv) were added at room temperature, followed by heating at 100 °C for 3 h under N_2 atmosphere. After complete consumption starting materials (monitored by TLC), $Pd(OAc)_2$ (11.2 mg, 10 mol%) was added and then stirred at 100 °C for 8-10 h under N_2 atmosphere (monitored by TLC). After cooling to room temperature, it was then poured into saturated NH_4Cl (25 mL) solution, extracted with EtOAc (2 x 25 mL), washed with water (2 x 25 mL), brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude products, which on purification by

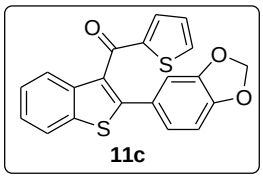
column chromatography (EtOAc/hexane as eluent) afforded the pure benzo[*b*]thiophenes **11**. The spectral and analytical data for all newly synthesized benzo[*b*]thiophenes **11b-n** is given below.

(4-Fluorophenyl)(6-(4-methoxyphenyl)thieno[2',3':4,5]benzo[1,2-*d*][1,3]dioxol-7-yl)methanone (11b). Obtained as a pale yellow semisolid (178.6 mg, 88%): R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2932, 1631, 1467, 1227, 814; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.27 (s, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.09 (s, 1H), 6.85-6.80 (m, 2H), 6.75 (d, *J* = 8.8 Hz,, 2H), 6.05 (s, 2H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 187.1, 166.8, 164.3, 162.3, 160.2, 149.0, 147.3, 134.9, 134.9, 131.3, 130.9, 130.8, 130.2, 126.4, 121.0, 119.6, 115.9, 115.8, 115.7, 113.4, 113.0, 102.2, 55.4; HRMS (ESI) *m/z* calcd for $C_{23}H_{16}FO_4S$ $[M + H]^+$ 407.0753, found 407.0747.



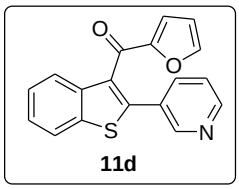
11b

(2-(Benzo[*d*][1,3]dioxol-5-yl)benzo[*b*]thiophen-3-yl)(thiophen-2-yl)methanone (11c). Obtained as a yellow semisolid (149.2 mg, 82%): R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2954, 1606, 1478, 1231, 803; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.77 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 7.64 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.43 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.29 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.15 (dd, *J* = 4.8 Hz, 3.2 Hz, 1H), 7.04 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.98 (*J* = 8.0 Hz, 2.0 Hz, 1H), 6.84-6.79 (m, 2H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.88 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 181.1, 160.1, 148.2, 147.2, 145.9, 136.9, 134.7, 133.4, 133.2, 132.6, 131.1, 129.9, 128.9, 128.3, 127.4, 123.3, 120.4, 109.4, 107.8, 101.4; HRMS (ESI) *m/z* calcd for $C_{20}H_{13}O_3S_2$ $[M + H]^+$ 365.0306, found 365.0304.



11c

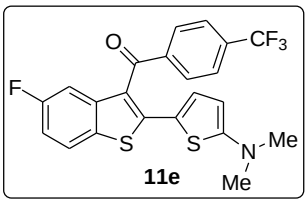
Furan-2-yl(2-(pyridin-3-yl)benzo[*b*]thiophen-3-yl)methanone (11d). Obtained as a yellow semisolid (117.4 mg, 77%): R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2932, 1630, 1464, 1266, 749; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.54 (d, *J* = 2.0 Hz, 1H), 8.36 (dd, *J* = 5.2 Hz, 1.6 Hz, 1H), 7.61 (dd, *J* = 1.6 Hz, 0.8 Hz, 1H), 7.55 (dt, *J* = 5.6 Hz, 2.0 Hz, 1H), 7.39 (dd, *J* = 3.6, Hz, 1.6 Hz, 1H), 7.37 (dd, *J* = 3.2 Hz, 1.6 Hz, 1H), 7.30 (dd, *J* = 3.6 Hz, 0.4 Hz, 1H), 7.08-7.05 (m, 1H), 7.05-7.01 (m, 1H), 7.0- 6.96 (m, 1H), 6.58 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 176.9, 157.3, 153.7, 149.5, 149.0,



11d

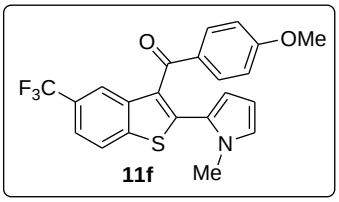
146.1, 137.3, 136.0, 134.4, 133.4, 133.3, 130.4, 129.5, 127.6, 122.3, 120.5, 116.9, 112.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{12}NO_2S$ $[M + H]^+$ 306.0589, found 306.0582.

(2-(5-(Dimethylamino)thiophen-2-yl)-5-fluorobenzo[*b*]thiophen-3-yl)(4-(trifluoromethyl)phenyl)methanone (11e). Obtained as a yellow semisolid (170.6 mg, 76%): R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2953, 1642, 1462, 1284, 813; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.68 (dd, *J* = 8.8 Hz, 4.8 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 10.0 Hz, 2.4 Hz, 1H), 7.06 (td, *J* = 8.8 Hz, 2.8 Hz, 1H), 6.79 (d, *J* = 4.0 Hz, 1H), 5.61 (d, *J* = 4.4 Hz, 1H), 2.88 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 192.3, 162.7, 162.5, 160.3, 145.2, 140.9, 140.8, 140.6, 134.2, 133.9, 132.8, 131.3, 130.0, 126.8, 126.7, 125.5, 125.44, 125.40, 125.37, 122.8, 122.7, 116.8, 113.4, 113.2, 109.0, 108.7, 102.8, 42.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}F_4NOS_2$ $[M + H]^+$ 450.0609, found 450.0602.



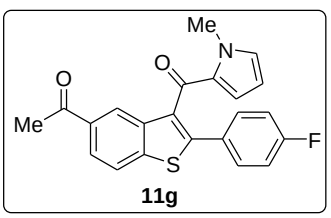
11e

(4-Methoxyphenyl)(2-(1-methyl-1*H*-pyrrol-2-yl)-5-(trifluoromethyl)benzo[*b*]thiophen-3-yl)methanone (11f). Obtained as a pale yellow semisolid (168.0 mg, 81%): R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2967, 1638, 1306, 1125, 820; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.04 (d, *J* = 8.8 Hz, 2H), 7.74 (s, 1H), 7.27-7.26 (m, 2H), 7.0 (d, *J* = 8.8 Hz, 2H), 6.48 (t, *J* = 2.4 Hz, 1H), 6.28 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H), 5.98 (dd, *J* = 3.6 Hz, 2.8 Hz, 1H), 3.92 (s, 1H), 3.59 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 187.5, 163.6, 147.4, 134.9, 131.2, 130.7, 129.83, 129.80, 129.76, 129.72, 129.6, 126.9, 125.9, 123.7 (q, J_{C-F} = 4.0 Hz), 122.5, 114.3, 114.0, 108.4, 55.7, 34.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}F_3NO_2S$ $[M + H]^+$ 416.0932, found 416.0942.



11f

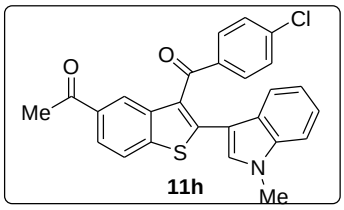
1-(2-(4-Fluorophenyl)-3-(1-methyl-1*H*-pyrrole-2-carbonyl)benzo[*b*]thiophen-5-yl)ethanone (11g). Obtained as a pale yellow solid (137.6 mg, 73%): mp 148-150 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2983, 1674, 1616, 1379, 1227, 743; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.96 (d, *J* = 1.6 Hz, 1H), 7.52 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.36-7.32 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.01 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.90-6.84 (m, 3H), 6.18 (dd, *J* = 4.0 Hz, 2.4 Hz, 1H), 4.07 (s, 3H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 195.9, 179.3, 164.0, 161.5, 152.0, 141.3, 137.1,



11g

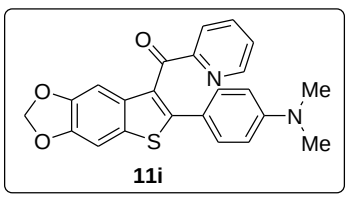
135.5, 134.7, 134.6, 132.7, 131.9, 131.7, 130.6, 130.5, 127.6, 126.5, 125.3, 118.9, 115.3, 115.1, 108.4, 37.8, 26.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}FNO_2S$ $[M + H]^+$ 378.0964, found 378.0969.

1-(3-(4-Chlorobenzoyl)-2-(1-methyl-1*H*-indol-3-yl)benzo[*b*]thiophen-5-yl)ethanone (11h). Obtained as a yellow semisolid (155.0 mg, 70%): R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2943, 1683, 1549, 1377, 811; ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.78 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.55 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.22-7.12 (m, 2H), 3.73 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 195.9, 187.6, 148.3, 143.1, 138.8, 137.4, 137.0, 136.3, 132.9, 132.6, 132.2, 129.7, 129.6, 128.9, 128.3, 126.5, 126.0, 125.4, 123.0, 121.3, 121.1, 119.9, 114.4, 110.1, 33.2, 26.4; HRMS (ESI) *m/z* calcd for $C_{26}H_{19}ClNO_2S$ $[M + H]^+$ 444.0825 and 446.0796, found 444.0830 and 446.0808.



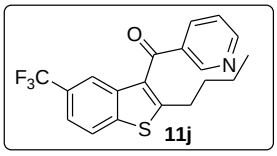
11h

(6-(4-(Dimethylamino)phenyl)thieno[2',3':4,5]benzo[1,2-*d*][1,3]dioxol-7-yl)(pyridin-2-yl)methanone (11i). Obtained as a pale yellow solid (156.7 mg, 78%): mp 132-134 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2946, 1602, 1470, 1231, 794; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.67 (m, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 7.853 (td, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.43-7.40 (m, Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 6.88 (s, 1H), 6.74 (s, 1H), 6.50 (d, *J* = 8.8 Hz, 2H), 5.87 (s, 2H), 2.93 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 187.8, 163.0, 155.0, 151.0, 148.8, 148.5, 147.2, 137.1, 130.4, 127.6, 126.7, 126.3, 122.8, 120.1, 118.7, 115.4, 112.9, 111.3, 102.0, 40.4; HRMS (ESI) *m/z* calcd for $C_{23}H_{19}N_2O_3S$ $[M + H]^+$ 403.1116, found 403.1112.



11i

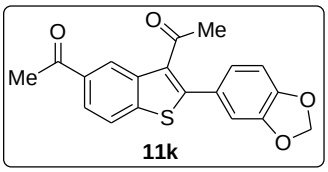
(2-Butyl-5-(trifluoromethyl)benzo[*b*]thiophen-3-yl)(pyridin-3-yl)methanone (11j). Obtained as a yellow semisolid (117.9 mg, 65%): R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2965, 1628, 1442, 1238, 810; ^1H NMR (400 MHz, $CDCl_3$) *δ* 9.21 (br s 1H), 8.78 (br s 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.96-7.95 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.61 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.45 (br s, 1H), 2.26 (t, *J* = 7.6 Hz, 2H), 1.46 (quintet, *J* = 7.6 Hz, 2H), 1.18 (sextet, *J* = 7.6 Hz, 2H), 0.75 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 187.0, 164.3, 152.7, 149.3, 137.7, 135.6, 133.3, 132.9, 131.2, 130.5 (q, J_{C-F} = 4.0 Hz), 124.1,



11j

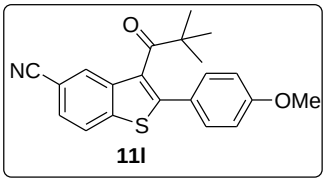
121.4, 116.4, 37.4, 31.4, 21.9, 13.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}F_3NOS$ $[M + H]^+$ 364.0983, found 364.0989.

1,1'-(2-(benzo[*d*][1,3]dioxol-5-yl)benzo[*b*]thiophene-3,5-diyl)diethanone (11k). Obtained as a yellow semisolid (133.5 mg, 79%): mp 128-130 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2932, 1686, 1662, 1480, 1251, 813; ^1H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 8.8 Hz, 1H), 8.11 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 7.15-7.13 (m, 2H), 6.97 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 6.18 (s, 2H), 2.58 (s, 3H), 2.12 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.2, 195.9, 153.6, 148.4, 147.4, 141.1, 137.0, 134.9, 132.7, 131.9, 127.0, 126.4, 126.2, 123.1, 108.8, 107.9, 101.4, 30.7, 26.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}O_4S$ $[M + H]^+$ 339.0691, found 339.0676.



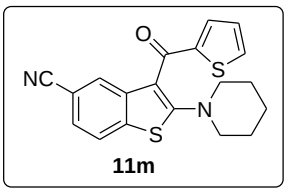
11k

2-(4-Methoxyphenyl)-3-pivaloylbenzo[*b*]thiophene-5-carbonitrile (11l). Obtained as a yellow semisolid (101.2 mg, 58%): mp 80-82 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2926, 2227, 1682, 1498, 1251, 811; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.63 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 1.14 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 206.2, 159.8, 142.6, 138.8, 137.1, 130.95, 128.9, 127.5, 125.6, 123.3, 119.0, 114.3, 108.8, 55.3, 26.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{20}NO_2S$ $[M + H]^+$ 350.1215, found 350.1216.



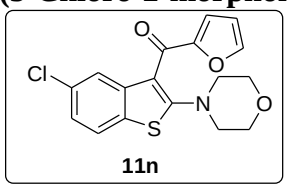
11l

2-(Piperidin-1-yl)-3-(thiophene-2-carbonyl)benzo[*b*]thiophene-5-carbonitrile (11m). Obtained as a pale yellow semisolid (96.8 mg, 55%): mp 135-137 °C; R_f 0.7 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2918, 2223, 1644, 1487, 1232, 966; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-8.01 (m, 1H), 7.69 (d, J = 4.8 Hz, 1H), 7.67-7.64 (m, 2H), 7.36 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.12 (t, J = 4.4 Hz, 1H), 3.25-3.22 (m, 4H), 1.48-1.45 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 183.9, 163.9, 144.2, 139.5, 135.9, 135.3, 134.1, 127.9, 126.5, 125.1, 124.8, 120.9, 119.5, 116.8, 54.8, 25.0, 23.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}N_2OS_2$ $[M + H]^+$ 353.0782, found 353.0766.



11m

(5-Chloro-2-morpholinobenzo[*b*]thiophen-3-yl)(furan-2-yl)methanone (11n).

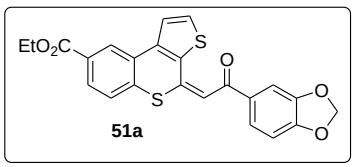


11n

Obtained as a yellow semisolid (107.5 mg, 62%): R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2945, 1632, 1432, 1244, 811; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 2.0 Hz, 1H), 7.657-7.655 (m, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 3.6 Hz, 1H), 7.17 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.59 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 3.63-3.61 (m, 4H), 3.23-3.21 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.7, 161.3, 154.7, 147.3, 144.6, 134.7, 133.4, 128.6, 126.8, 113.8, 112.7, 111.9, 98.9, 66.33, 52.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}ClNO_3S$ $[M + H]^+$ 348.0461and 350.0432, found 348.04448 and 350.0420.

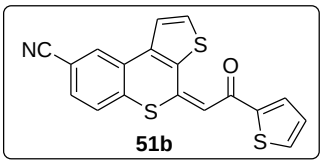
6.5.5 General Procedure for Sequential One-Pot Synthesis of thieno- fused benzothiopyrans from *o*-bromoiodobenzenes 8 and monothioketones 9. A mixture of 1,3 monothioketones **9** (0.5 mmol) and *o*-bromoiodobenzenes **8** (0.5 mmol) were taken in dry DMF (4 mL), to this reaction mixture CuI (9.5 mg, 10 mol%) and cesiumcarbonate (244.3 mg, 1.5 equiv) were added at room temperature, followed by heating at 100 °C for 3 h under N_2 atmosphere. After complete consumption starting materials (monitored by TLC), $Pd(OAc)_2$ (11.2 mg, 10 mol%) and TBAI (184.7 mg, 1.0 equiv) were added and then stirred at 130 °C for 8-10 h under N_2 atmosphere (monitored by TLC). After cooling to room temperature, it was then poured into saturated NH_4Cl (25 mL) solution, extracted with EtOAc (2 x 25 mL), washed with water (2 x 25 mL), brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude products, which were purified by column chromatography using EtOAc/hexane as eluent.

(*E*)-Ethyl 4-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoethylidene)-4*H*-thieno[2,3-c]thiochromene-8-carboxylate (51a). Obtained as a yellow solid (156.9 mg, 72%): mp 150-152 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2965, 1709, 1599, 1357, 1243, 830; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 1.6 Hz, 1H), 8.01 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.85 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.65-7.62 (m, 2H), 7.55 (d, J = 1.6 Hz, 1H), 7.40 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.06 (s, 2H), 4.44 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.8, 165.9, 151.1, 148.3, 146.8, 138.8, 138.1, 133.8, 133.7, 129.0, 128.9, 128.4, 126.7, 126.3, 126.2, 125.4, 123.5, 108.1, 108.0, 107.6, 101.8, 61.5, 14.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{17}O_5S_2$ $[M + H]^+$ 437.0517, found 437.0511.



51a

(*E*)-4-(2-Oxo-2-(thiophen-2-yl)ethylidene)-4*H*-thieno[2,3-*c*]thiochromene-8-carbonitrile (51b). Obtained as a yellow solid (129.8 mg, 74%): mp 182-184 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2945, 2228, 1605, 1414, 1258, 896; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 1.6 Hz, 1H), 7.80 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.72-7.12 (m, 1H), 7.68 (t, J = 5.6 Hz, 1H), 7.64 (dd, J = 4.8 Hz, 0.8 Hz, 1H), 7.58 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.32 (s, 1H), 7.17 (dd, J = 4.8 Hz, 3.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 180.3, 145.7, 145.6, 138.3, 137.3, 134.1, 132.8, 130.1, 129.6, 128.5, 128.2, 127.2, 127.0, 124.8, 118.2, 110.3, 108.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{10}NOS_3$ $[M + H]^+$ 351.9925, found 351.9917.



51b

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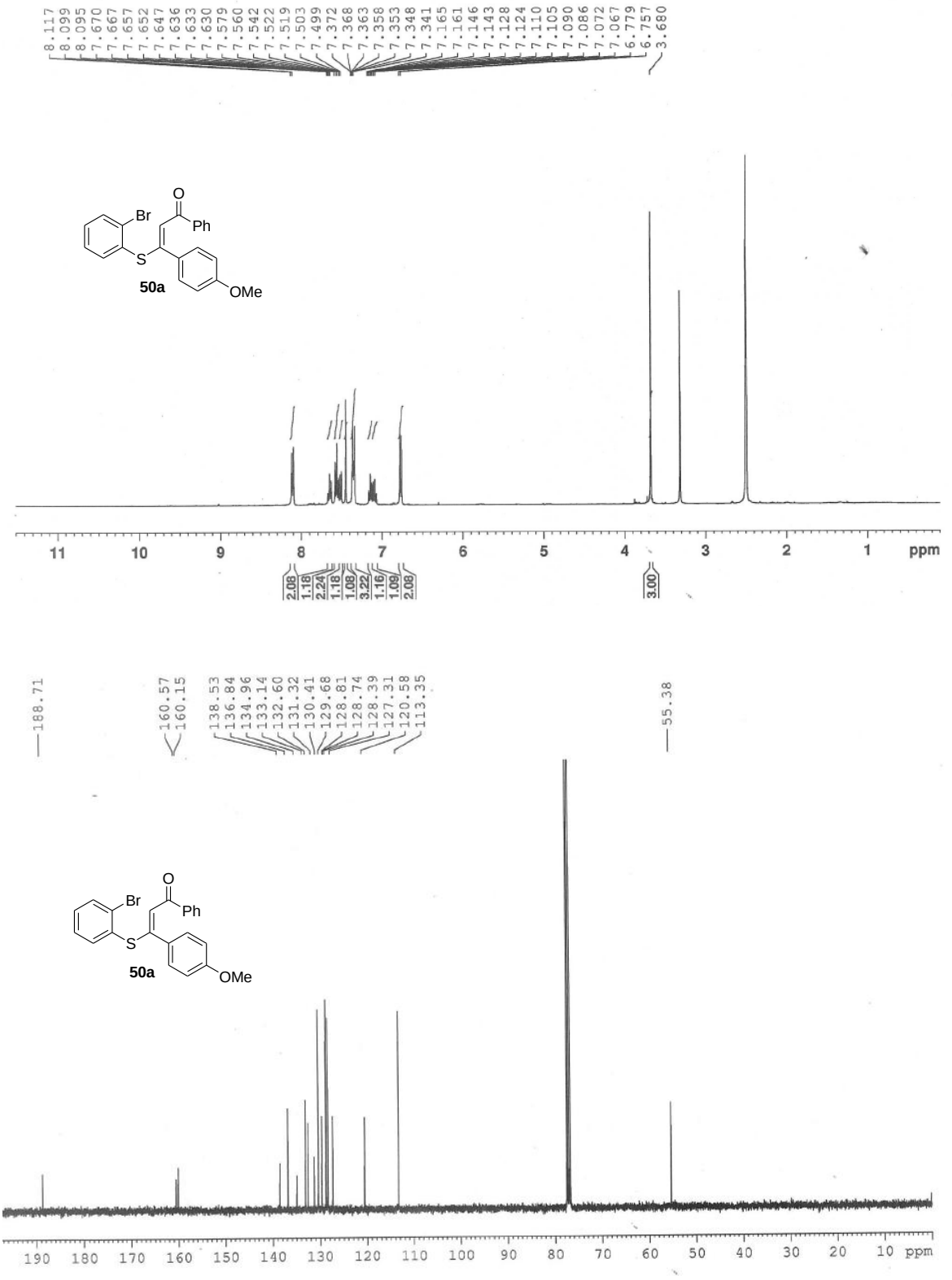
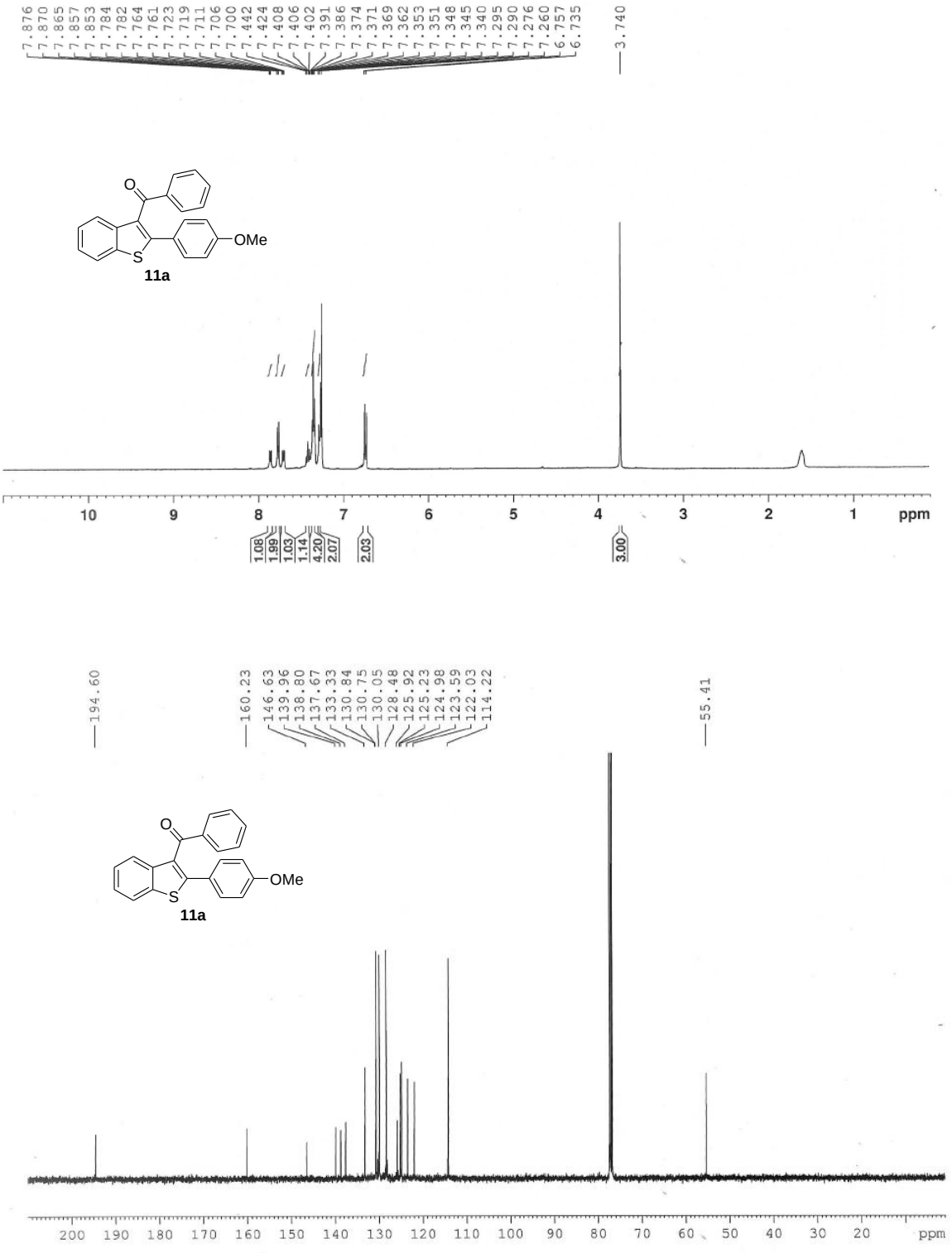
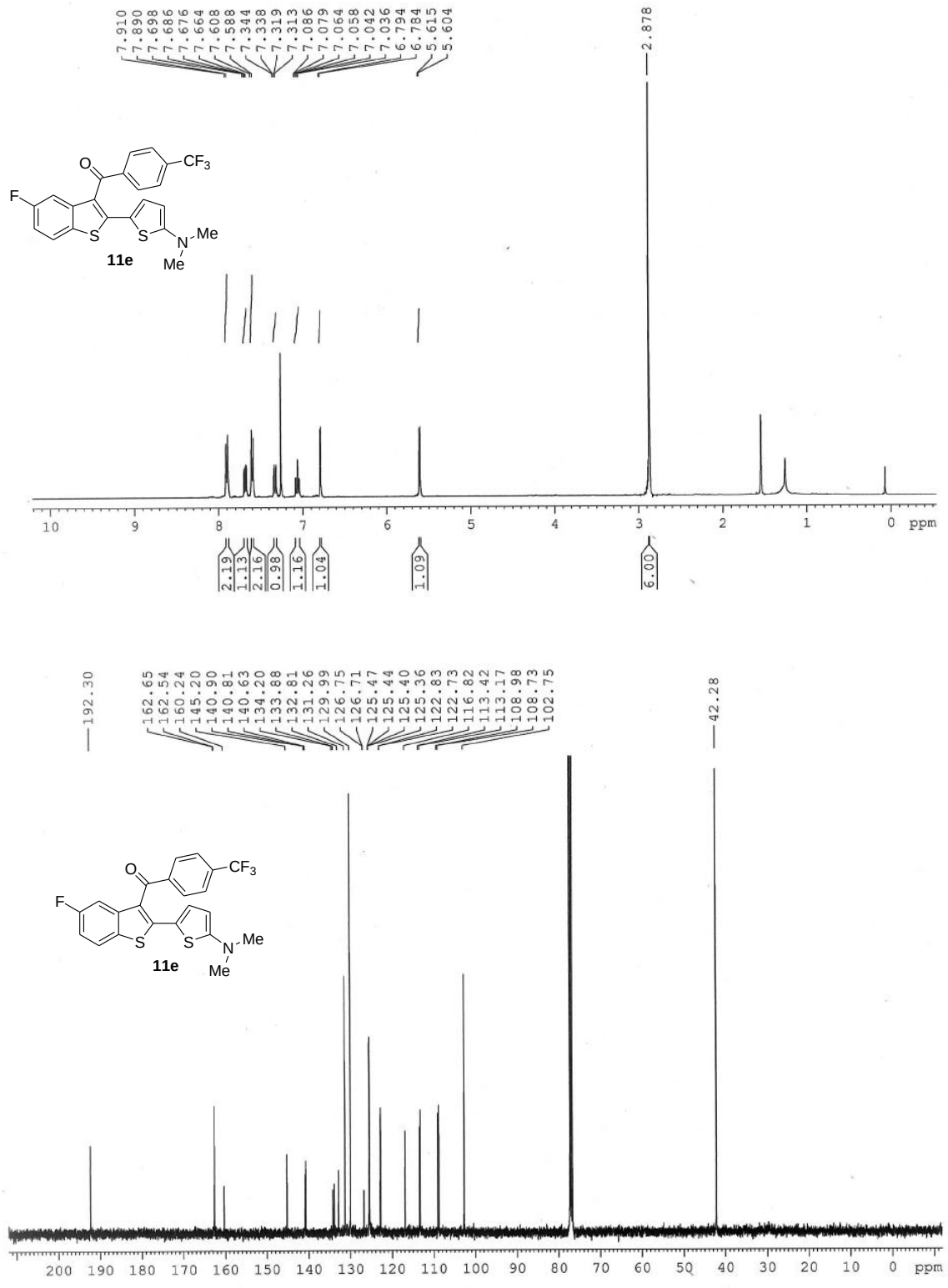
6.7 Representative Spectra



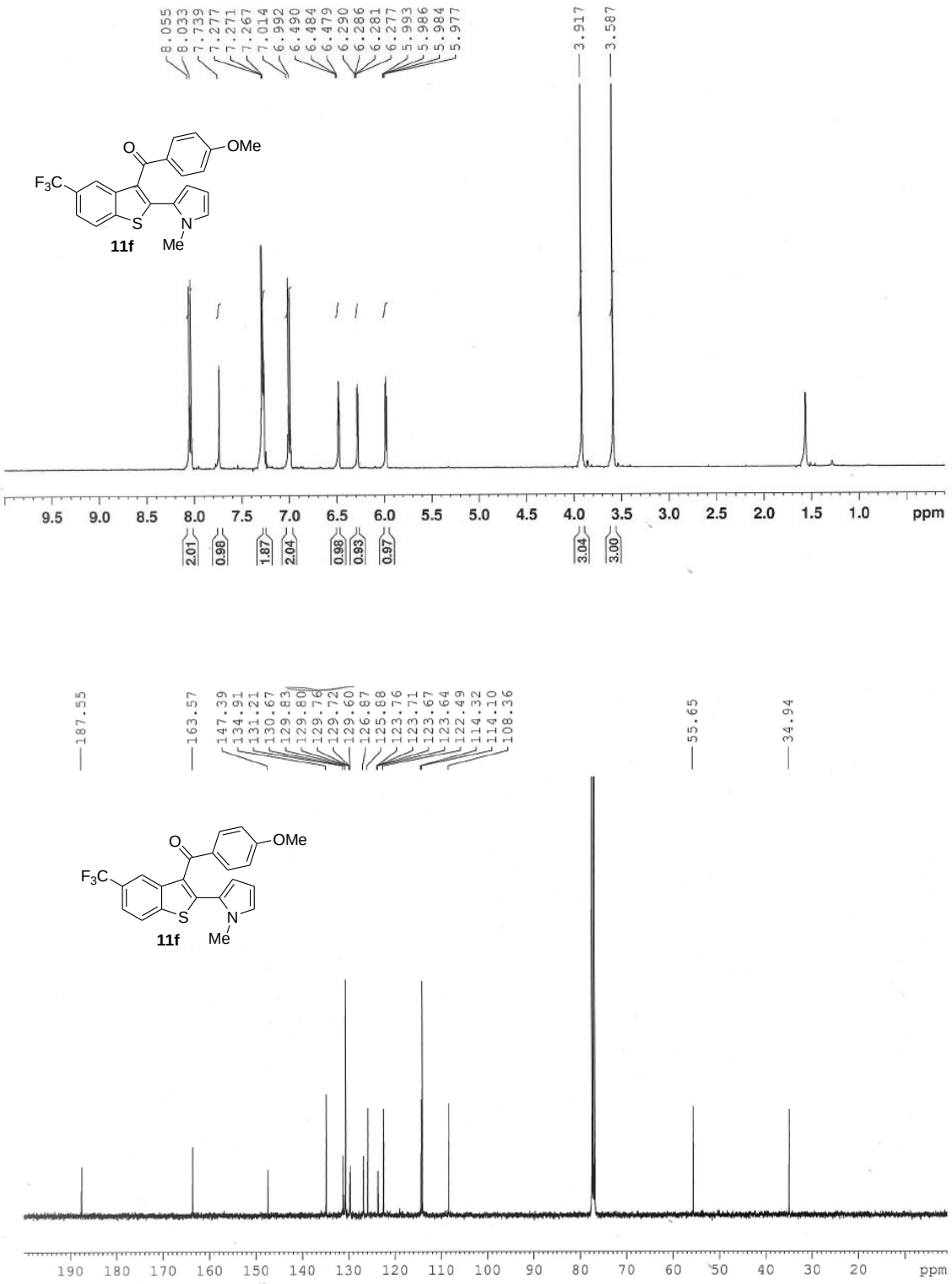
^{1}H and ^{13}C NMR Spectra of compound **50a**



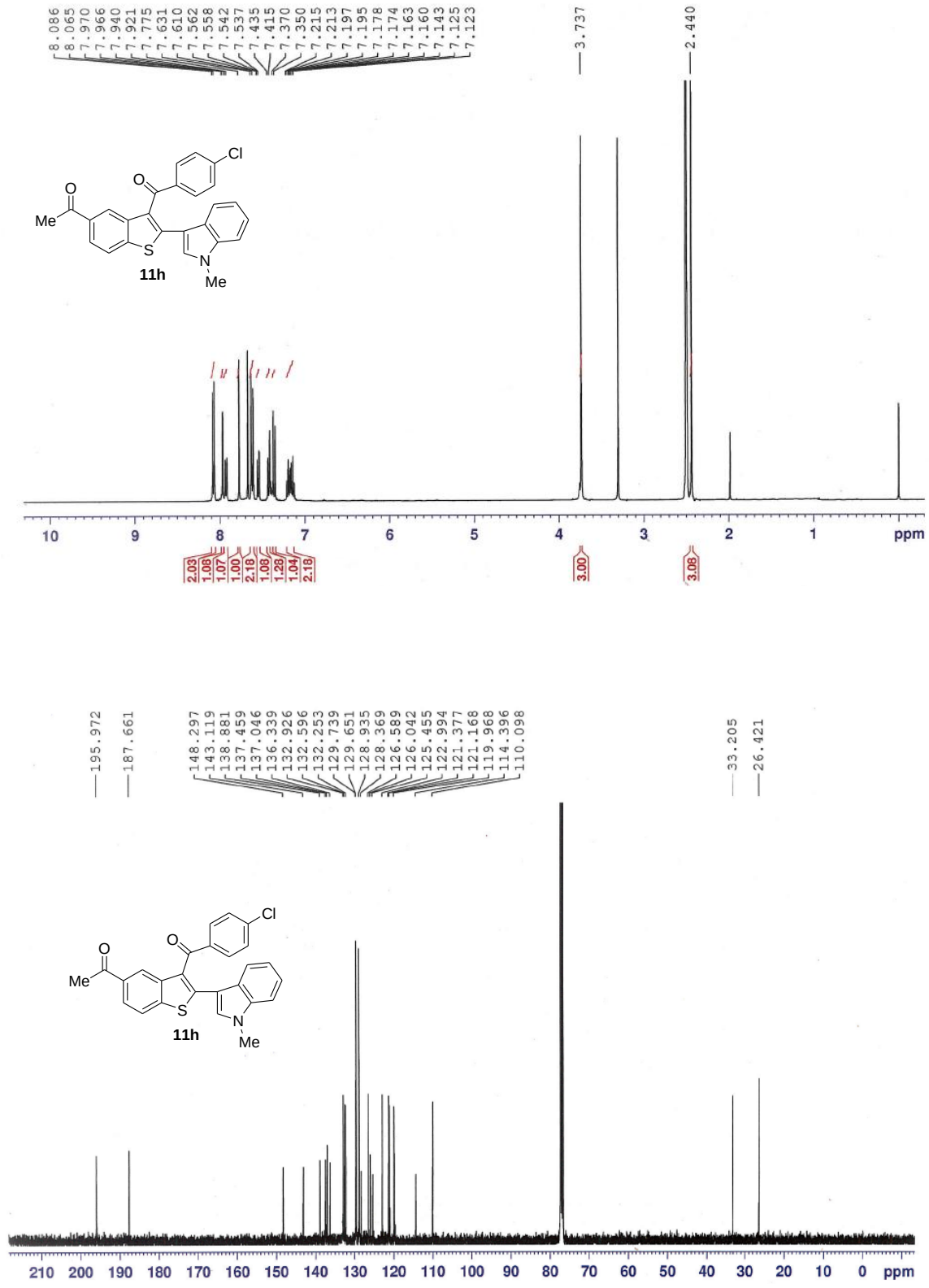
^{1}H and ^{13}C NMR Spectra of compound **11a**



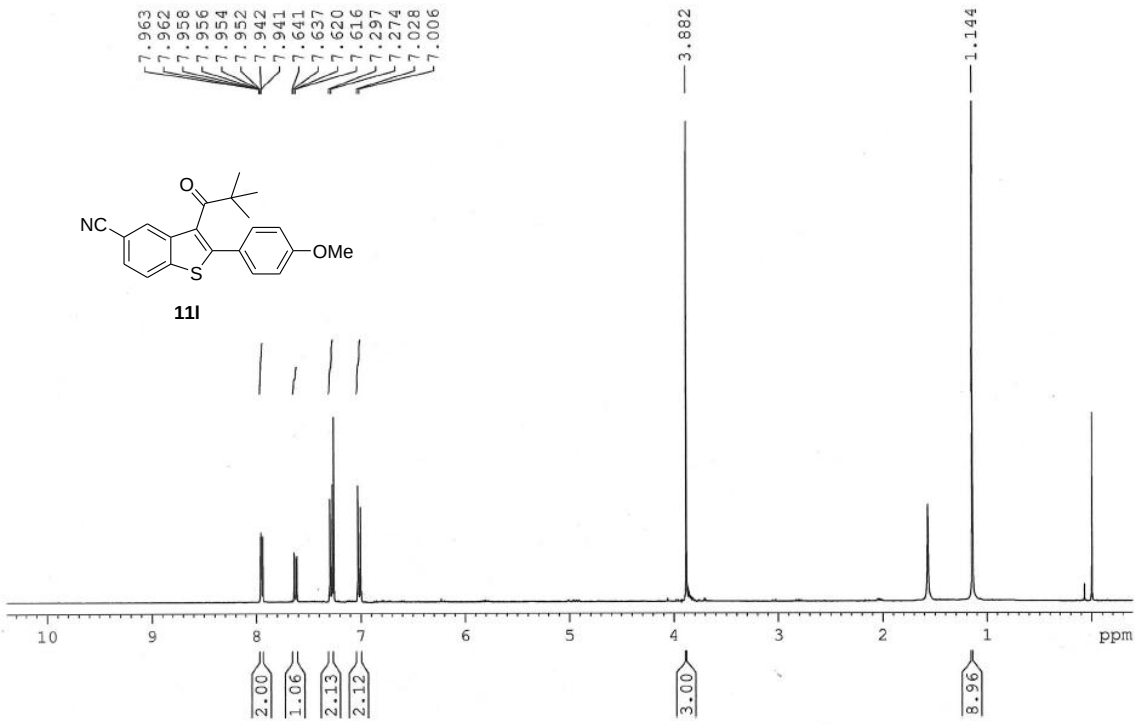
^{1}H and ^{13}C NMR Spectra of compound **11e**

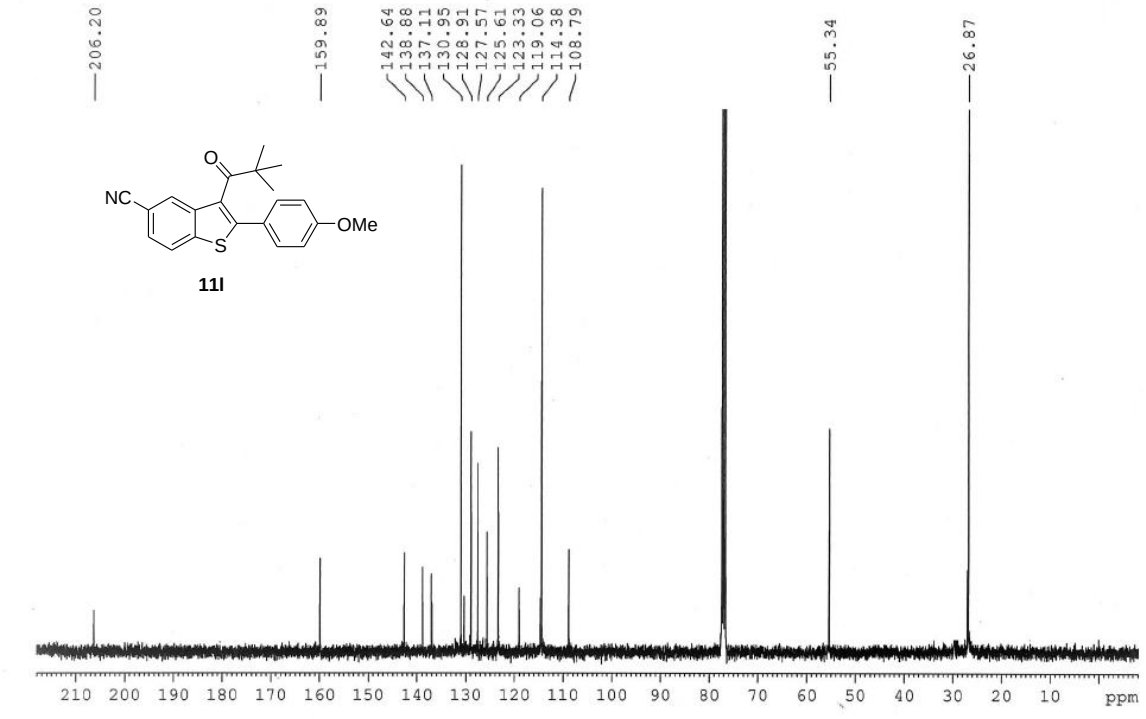


^{1}H and ^{13}C NMR Spectra of compound **11f**

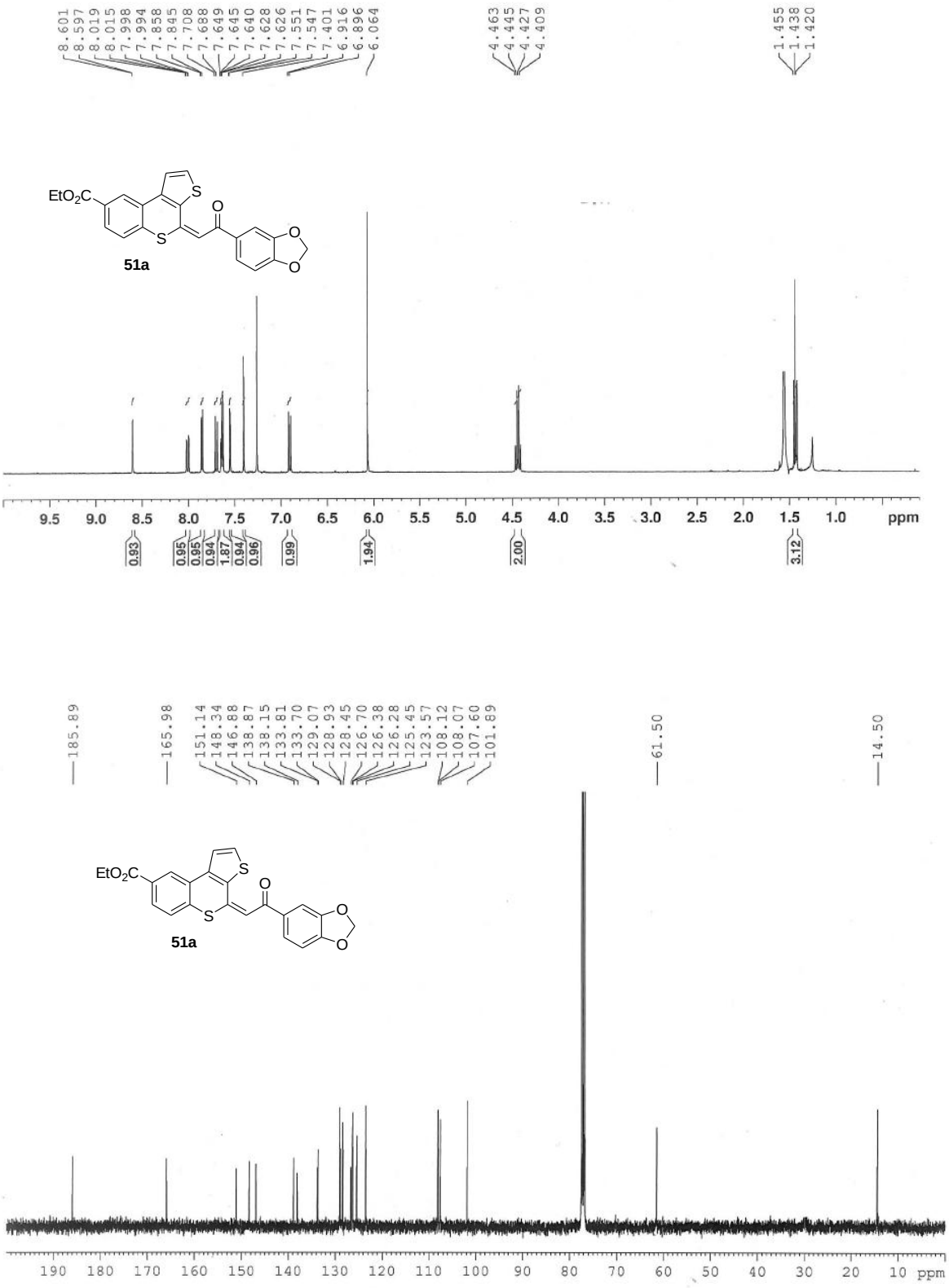


^{1}H and ^{13}C NMR Spectra of compound **11h**





^{1}H and ^{13}C NMR Spectra of compound **11l**



^{1}H and ^{13}C NMR Spectra of compound **51a**

List of Publications

1. "Reaction of Cyclic α-Oxoketene Dithioacetals with Methylene Isocyanides: A Novel Pyrrole Annulation-Ring Expansion Domino Process"
   S. Yugandar, N. C. Misra, G. Parameshwarappa, K. Panda, H. Ila, *Org. Lett.* **2013**, *15*, 5250.

2. "Synthesis of 2,5-Bis(hetero)aryl 4'-Substituted 4,5'-Bisoxazoles via Copper(I)-Catalyzed Domino Reactions of Activated Methylene Isocyanides with 2-Phenyl- and 2-(2-Thienyl)-4-[(het)aryl)(methylthio)methylene]oxazol-5(4*H*)ones"
   S. Yugandar, A. Acharya, H. Ila, *J. Org. Chem.* **2013**, *78*, 3948.

3. "Amine Directed Pd(II) Catalyzed C-H Activation-Intramolecular Amination of N-Het(aryl)/Acyl Enaminonitriles and Enaminones: An Approach towards Multisubstituted Indoles and Heterofused Pyrroles"
   S. Yugandar, S. Konda, H. Ila, *J. Org. Chem.* **2016**, *81*, 2035.

4. "One-Pot Synthesis of 2,4,5-Trisubstituted Imidazoles via [2+2+1] Cycloannulation of 1,3-Bishet(aryl)-monothio-1,3-diketones, *α*-Substituted Methylamines and Sodium Nitrite through *α*-Nitrosation of Enaminones"
   S. Yugandar, S. Konda, G. Parameshwarappa. H. Ila, *J. Org. Chem.* **2016**, *81*, 5606.

5. "A Novel One-Pot, Two Step Synthesis of Multisubstituted Benzo[*b*]thiophenes via Sequential Copper Catalyzed C-S Bond formation and Palladium Catalyzed Arene-Alkene Coupling via Intramolecular Heck Reaction"
   S. Yugandar, S. Konda, H. Ila (Unpublished Results).