Newer Strategies for the Synthesis of Five and Six Membered Heterocycles Containing N, O and S

A Dissertation Submitted to the
Indian Institute of Technology Guwahati
As Partial Fulfillment for the Degree of
Doctor of Philosophy in
Chemistry

Submitted by

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June 2009

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Dedicated to

My Family Members

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Bhisma K. Patel.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

June, 2009. Siva Murru
IIT Guwahati

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Siva Murru has been working under my supervision since July, 2005 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Newer Strategies for the Synthesis of Five and Six Membered Heterocycles Containing N, O and S**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

June, 2009.
IIT Guwahati

Prof. Bhisma K. Patel
Supervisor
Department of Chemistry
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INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE OF COURSE WORK

This is to certify that Siva Murru has satisfactorily completed all the courses required for the Ph.D degree program. These courses include

1) CH 605 : Applied crystallography
2) CH 627 : New Reagents in Organic Chemistry
3) CH 611 : Bioinorganic Chemistry
4) CH 630 : A Fundamental Approach to Physical Chemistry

Siva Murru has successfully completed his Ph.D. qualifying examination in May 2006.

Prof. A. Chattopadhyay
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Secretary
Departmental Post Graduate Committee
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ACKNOWLEDGMENT

At the very outset, with a deepest sense of gratitude, I wish to express my sincere thanks to my supervisor, Prof. Bhisma K. Patel for his proficient guidance, encouragement, inspiration and creative and scientific ideas which helped me to enhance my knowledge and have inspired me to take right decisions at crucial moments. I am also thankful to him for giving me freedom to pursue my own interests and I find myself privileged to have worked under his kind guidance.

It is my immense pleasure to express my thanks to my French host guides Dr. Jacques Muzart and Dr. Jean Le Bras, who gave me a wonderful opportunity to work in their research group for 8 months.

I would like to acknowledge my sincere gratitude to all my doctoral committee members, Dr. Manabendra Ray, Dr. Gopal das and Dr. Md. Javed for their insightful advices and valuable suggestions. I would like to thank all faculty members of Department of Chemistry of IIT Guwahati for their invaluable suggestions.

I wish to acknowledge my sincere gratitude to IIT Guwahati for all the facilities that were made available to me, the Council of Scientific and Industrial Research (CSIR), India for financial support and the French embassy for offering fellowship to carry part of my thesis work in France.

I am thankful to Mr. Babulal Das (for Single Crystal XRD) of Department of Chemistry, Mr. Chandan Borgohain and Mr. Kulakamal Senapati of Central Instruments Facility (for NMR, LC-MS) and all the non-teaching staff of Department of Chemistry for their help during my Ph.D. tenure.

I thank my seniors Dr. Sarala naik, Dr. Veerababurao Kavala and Dr. C. B. Singh for their invaluable cooperation and suggestions. I wish to thank department seniors Raju anna, Ballav da, Papori ba, Sahid da and Lokman da for lending their hands of support whenever needed.

I would like to thank all my present and past group members Hari, Ramesh, Santosh, Razzak, Alila, Jayashree, Charuta, Pravat, Ashok, Shaon, Himadri, Ines for their timely help, support and for creating a pleasant atmosphere in the lab. I am also grateful to

my French labmates and friends Chahinez, Emilie, Sahar, Jean and Nicolau for their help during my stay in France.

I also take this opportunity to thank all of my Ph.D. batchmates (july, 05), the other research scholars @ chem.iitg. and all my IITG friends, who have shared their thoughts and views with me.

I extend my sincere thanks to my best friends Saitanya, Subhash, Suri, Reddy, Rajendra, Rajesh, Paradesi, Rambo, Tirumala Prasad, Prem, Raju, Chandu, Avishek, and other close friend(CF)s for their constant unfailing support, their encouragement and all the help they extended whenever required. I also wish to thank other friends Gunin, Bolin da, Anirban, Avijit, Jashmini, Amardeep, Prasenjit, Dubey and telugu friends for the joyful moments shared with me at IITG and their support.

Finally, my Ph. D. endeavor could not have been completed without the endless love, unending support, tolerance and blessings from my family. I wish to express my sincere gratitude to my parents, sister and brother. They are the main soul and inspiration for each and every step that I achieve in my life.

Siva Murru

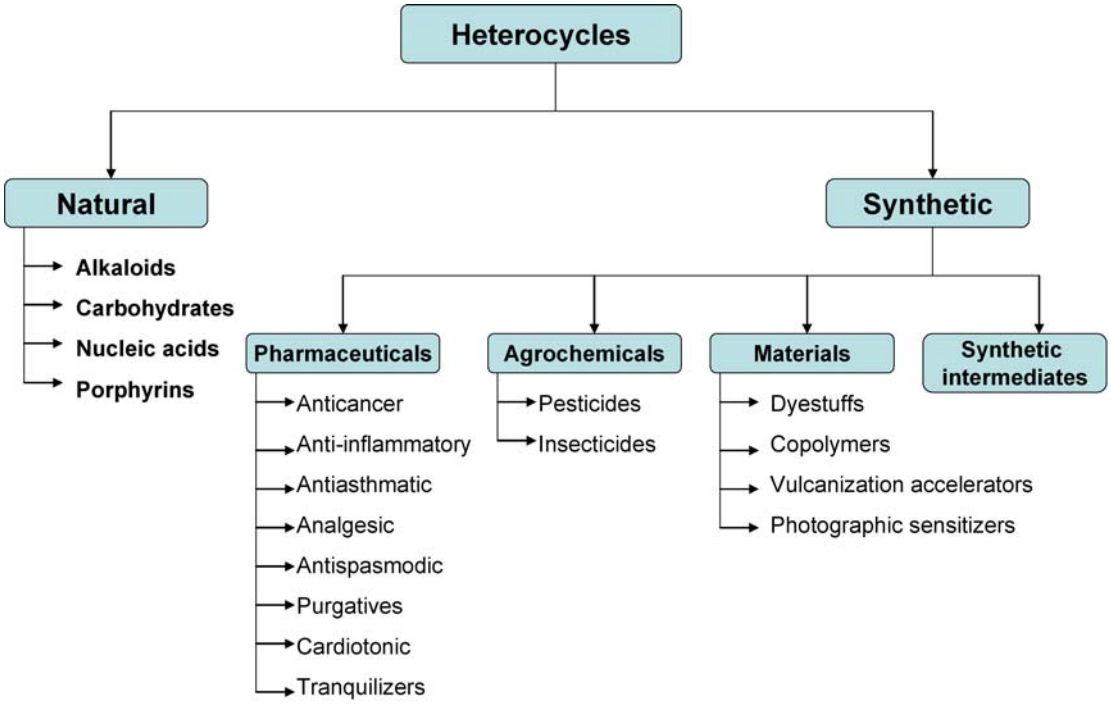
Abstract

The contents of this thesis have been divided into five chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter of the thesis presents an overview of different aspects of heterocyclic chemistry with special reference to five and six membered heterocycles and their synthesis using tribromides and copper catalysts. Chapters 2 and 3 describe the syntheses of 1, 4-dithiins and 2-iminothiazolines using a ditribromide reagent (EDPBT). Chapters 4 and 5 illustrate copper-catalyzed syntheses of substituted 2-mercapto benzimidazoles and 2-substituted benzothiazoles via inter and intramolecular hetero-arylations. Each chapter constitute four sections, describing introduction, present work, experimental work and spectral data respectively.

CHAPTER I. Introduction to Heterocyclic Chemistry

This chapter highlights the nomenclature, definition and importance of heterocycles and literature background for the synthesis of heterocycles using organic ammonium tribromides (OATBs) and copper catalysts.

Heterocycles make up an exceedingly important class of compounds. More than half of all known organic compounds are heterocycles. Almost all the compounds we know as drugs, most vitamins and many other natural products are heterocycles. The class also includes many other compounds of biological importance, such as nucleic acids, carbohydrates, hormones, and pigments. Heterocyclic compounds are key components of pharmaceutical chemistry and therefore, they have been a fruitful source of inspiration for the design of structural analogues to be used as pharmacological tools as well as new drugs. One of the reasons for the wide spread use of heterocyclic compounds as shown below, is that their structures can be subtly manipulated to achieve a required modification in function.



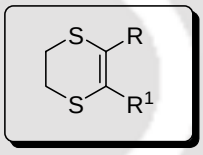
Organic ammonium tribromides are the attractive solid bromine less brominating agents. These crystalline stable solids are convenient source of bromine owing to the ease in maintenance of the desired stoichiometry and the ease in storage, transportation and handling. Apart from bromination, tribromides also can be used for several other organic transformations such as oxidation of sulphides and alcohols, brominative cyclizations, and intramolecular cyclizations. These reagents are efficient generators of anhydrous HBr in alcohols and many other organic solvents whose acidity can be tuned to a wide range of pH that can be utilizes for various acid catalyzed organic transformations.

The importance of heterocycles in many fields of science can hardly be overemphasized, and justifies a long lasting effort to work out new synthetic protocols for their production. A particularly attractive approach is based on transition-metal catalyzed heterocyclization reactions of suitably functionalized substrates which can allow the regioselective synthesis of highly functionalized heterocycles starting from readily available starting materials under mild and selective conditions. During the last few years, development of cascade and domino approaches to the synthesis of heterocycles has acquired a growing importance.

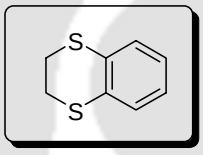
The foundation of modern cross-coupling chemistry was built at the beginning of the twentieth century with the pioneering work of Fritz Ullmann and Irma Goldberg. Their explorations into new methods for the synthesis of C–C, C–N, and C–O bonds provided the conceptual breakthrough that allowed for the use of unactivated aryl halides to supplant the electron-poor aryl halides typically required for the classical nucleophilic aromatic substitution reaction. These advancements not only expanded the scope of substrates that could be utilized in aromatic substitution reactions, it changed the way chemists thought about constructing molecules containing N, O and S–aryl bonds. With the Intramolecular Ullmann Coupling (IUC) as the strategy, the preparation of many medium- and even large-sized heterocycles can be achieved. More recently, this methodology was successfully extended to the synthesis of various bioactive heterocycles and natural products.

CHAPTER II. Synthesis of 1,4-Dithiins and 1,4-Benzodithiins

This chapter mainly focuses on the synthesis of 1,4-dithiins and 1, 4-benzodithiins via tribromide mediated ring expansion and ring expansion along with ring aromatization.



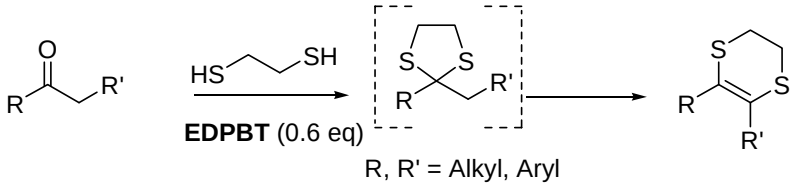
Dihydro-1,4-dithiins



Dihydro-1,4-benzodithiins

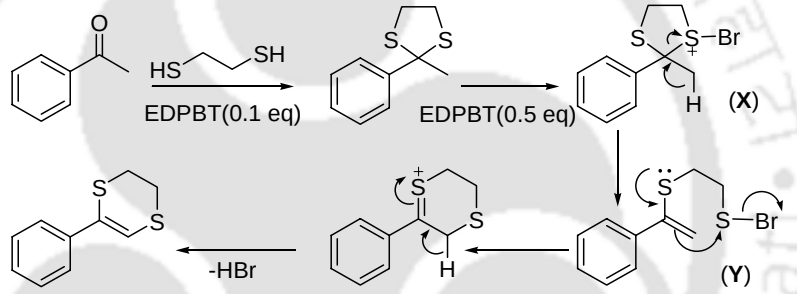
In continuation to our interest in the chemistry of cyclic thioacetals and the use of tribromides, we have further explored the chemistry of 1,4-dithiins and 1,4-benzodithiins because of their wide applications in medicinal, material and synthetic organic chemistry. We have synthesized a new ditribromide reagent, 1,1'-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT) which is superior to all known tribromides and has several advantages over molecular bromine and other tribromides.

Herein, we have utilized the acidic properties of EDPBT for the thioacetalization of carbonyl compounds and thiophilic nature of EDPBT for the ring expansion of the *in-situ* generated thioacetal to give 1,4-dithiins in one-pot (*Scheme 1*).



Scheme 1. *One-pot synthesis of 1, 4-dithiins*

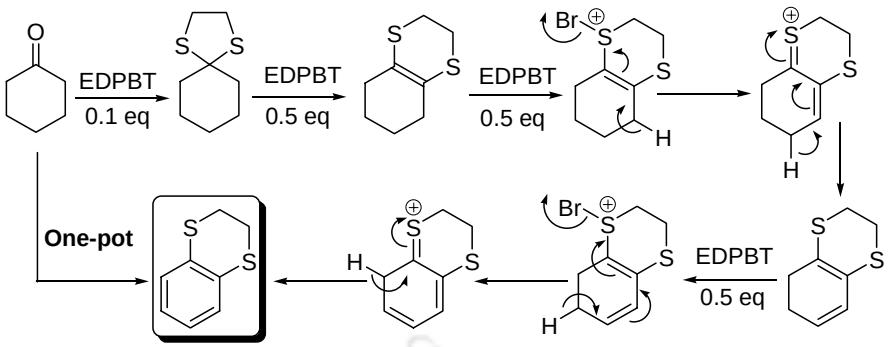
A plausible mechanism for the ring expansion is proposed in *Scheme 2.* The first step of the reaction consists of 1,3-dithiolane formation. Consumption of a further equivalent of bromine forms bromosulphonium ion (**X**). The bromosulphonium ion (**X**) loses a molecule of HBr forming sulphanyl vinylbenzene intermediate (**Y**). Finally intramolecular nucleophilic attack leads to the desired product.



Scheme 2. *Proposed mechanism for the synthesis of 1, 4-dithiin*

This method was successfully applied to a wide range of ketones containing α-methylene group. However, when the reaction was performed with *p*-hydroxy acetophenone and *p*-aminoacetophenone, the ring expanded products were not obtained, instead the starting materials along with [1,2,5,6]-tetrathiocane were obtained which can easily be rationalized.

Cyclohexanone when treated with 1.5 equivalents of EDPBT, was converted to the 1,4-dithiin derivative with concomitant aromatization of the cyclohexane ring, thus affording the valuable 1,4-benzodithiin heterocyclic ring system. In this transformation a total of three bromine equivalents are needed, one for the 1,4-dithiin ring formation and two for aromatization of the cyclohexane ring system as shown in *Scheme 3.*

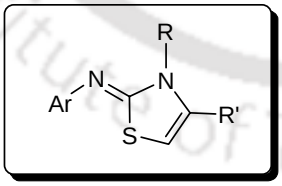


Scheme 3. *Proposed mechanism for ring expansion and aromatization.*

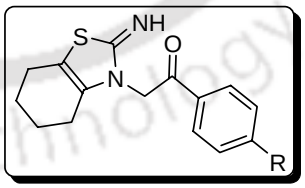
In conclusion, we have developed a one-pot transformation of acyclic ketones to 1,4-dithiins and cyclic ketones to 1,4-benzodithiins / 1,4-naphthodithiins using the recyclable reagent, 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). This method is simple, convenient, mild, and environmentally benign. An interesting aspect of this method is the EDPBT acts as promoter in the formation of 1, 3-dithiolane and as a reagent in the ring expansion step. The spent reagent can be recovered, regenerated and reused.

CHAPTER III. Structural Correction and Synthesis of 2-Iminothiazolines

This chapter mainly focuses on the synthesis of 2-iminothiazolines and pifithrin analogues.



2-Iminothiazolines

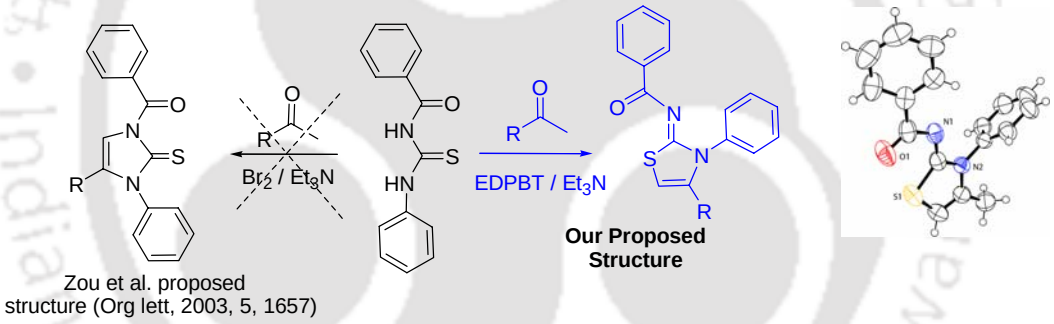


Pifithrin analogues

2-Imino-thiazoline ring system is present in several drug candidates possessing interesting biological activities and also found to have interesting applications in agriculture. The pifithrin (Pft-α), isolated by screen of chemical libraries having 2-imino-thiazoline skeleton is the leading compound of p53 inactivators.

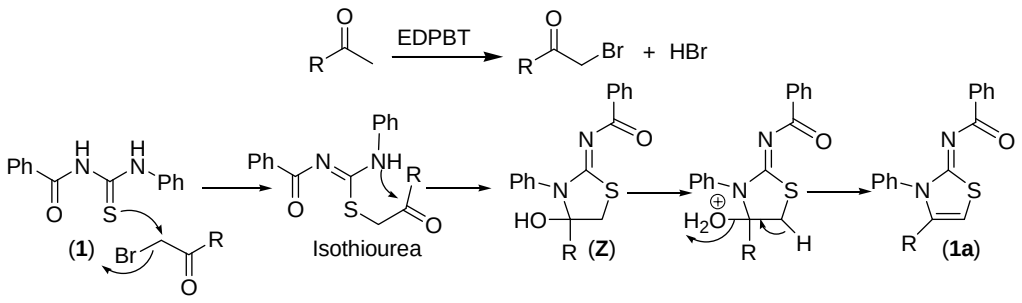
Structural Correction and Mechanistic Investigation

The reagent 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) is an excellent source of bromine capable of brominating varieties of organic substrates. Being a source of bromine we thought to utilize this for the synthesis of imidazole-2-thione derivative following the reported procedure of Zou *et. al* (*Org. Lett.* **2003**, *5*, 1657). When 1-benzoyl-3-phenylthiourea (1 equiv.) was reacted with EDPBT (0.5 equiv) in acetone (10 mL) in the presence of triethylamine (1 equiv.) the product obtained was identical in all respects (m.p, IR, ^{1}HNMR and ^{13}CNMR) to that reported by Zou *et.al*. However, X-ray crystallographic analysis of the product revealed an isomeric structure with a completely different skeleton (Scheme 4). The product obtained was not an imidazole derivative as reported, rather it is N-(4-methyl-3-phenyl-2(3H)-thiazolylidene)-benzamide or thiozole-2-imine as shown in *Scheme 4.*



Scheme 4. *Correct structure for the reaction of thiourea and ketone with EDPBT*

Having established the correct structure of 2-iminothiazoline or thiazol-2-imine or thiazolidin-2-imine as it has been named by different groups, we were further interested to study the mechanism of its formation. Based on our experimental observations, we have proposed the mechanism as shown below (*Scheme5*).



Scheme 5. *Proposed mechanism for2-iminothiazoline formation.*

As speculated earlier, EDPBT brominates enolizable ketones to α-bromoketones. The carbon of the bromomethyl group is attacked by the sulphur of thiourea, which is facilitated due to the abstraction of the NH proton flanked by a carbonyl and a thiocarbonyl moiety leading to the intermediate tertiary alcohol (**Z**). Further, the elimination of the intermediate tertiary alcohol is not by a base catalyzed E2 mechanism as proposed, rather it should be by an E1 mechanism to give the final product as shown in *Scheme 5*. This assumption of ours is confirmed by isolation of the intermediate, when 1, 3-dichloroacetone (1 equiv.) was reacted with benzoylphenyl thiourea (1 equiv.) in the presence of triethylamine (2 equiv.) a solid product was obtained after usual work up. Crystallization of the compound from ethyl acetate : hexane (4 : 1) gave a colorless crystal. X-Ray crystallographic analysis of the compound revealed the presence of 2-iminothiazoline skeleton as shown in *Figure 1*.

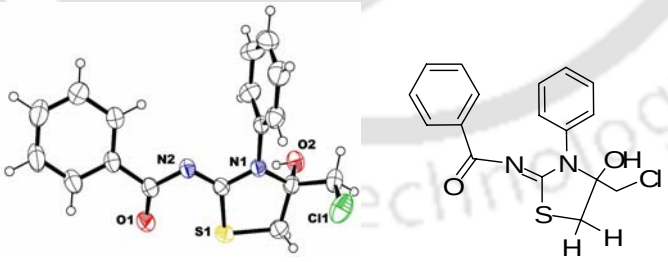


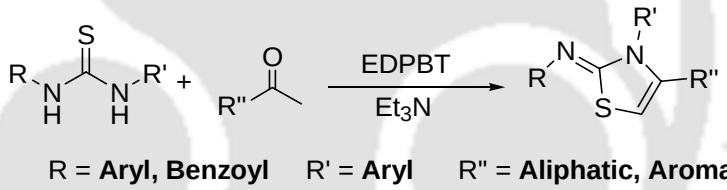
Figure 1. *X-ray structure of the isolated intermediate (**Z**).*

To confirm the mode of elimination (E1 or E2) and intermediacy of above isolated compound, it was treated with dil. HCl which rapidly gave the desired product having 2-iminothiazoline or thiazol-2-imine or thiazolidin-2-imine skeleton confirming the E1 type elimination. This observation confirms the requirement of an acidic medium for the

dehydration of the teritiary alcohol intermediate (**Z**). Since the reagent EDPBT generates one equivalent of HBr during bromination of ketones and second equivalent by the nucleophilic displacement of bromide by the sulphur to make the medium acidic even in the presence of one equivalent of triethylamine, we planned to develop a one pot procedure for the synthesis of 2-iminothiazolines from benzoylphenylthioureas and enolizable ketones.

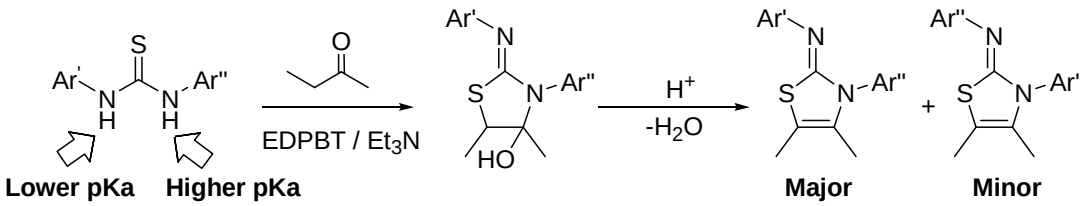
Synthesis of 2-Iminothiazolines (or thiazol-2-imine or thiazolidin-2-imine)

Having successfully established the mechanism of the reaction, our next objective was to apply this methodology to various other benzoyl phenyl thioureas and cyclic and acyclic ketones. To our delight, a wide variety of benzoyl phenyl thioureas as well as 1, 3-diaryl thioureas and a range of carbonyl compounds reacted smoothly under present reaction conditions to give a variety of substituted 2-iminothiazolines in moderate to high yields (*Scheme 6*).



Scheme 6. *Synthesis of various 2-iminothiazolines.*

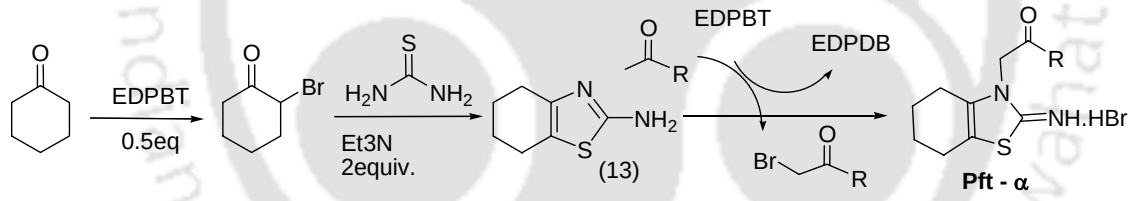
In order to study the regioselectivity of unsymmetrical thioureas such as 1-phenyl-3-*p*-tolyl-thiourea, was reacted under identical condition. The product obtained was an equimolar mixture of both the possible regioisomers as shown in *Scheme 7*, indicating the equal ease of 2-iminothiazoline formation from either side of the thiourea since the acidity of both NH protons are similar. However, when the difference in acidity is larger, exclusively one regioisomer is obtained as has been demonstrates taking 1-benzy-3-phenyl thiourea giving 3-benzyl-4-methyl-2-phenylimino-3*H*-thiazole as the exclusive product (*Scheme 7*).



Scheme 7. *Regioselectivities in 2-iminothiazolines formation*

Synthesis of Pifithrin-α and its Analogues

Further application of the reagent EDPBT and the methodology was finally demonstrated for the syntheses of neurodegenerative drug pifthrin-α and its analogues (*Scheme 8*) by one pot strategy. In this method, the *in situ* generated α-bromo cyclohexanone obtained by the reaction of cyclohexanone and EDPBT in acetonitrile reacts with thiourea to give aminothiazole. Again α-bromoketone prepared from ketone using EDPBT in acetonitrile was added to the above reaction medium containing aminothiazole and triethylamine to give various pifithrin analogues in good overall yields.

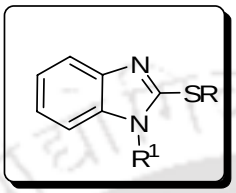


Scheme 8. *Synthesis of pifithrin-α analogues*

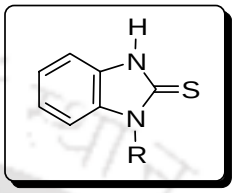
In conclusion, we have isolated the reaction intermediate and characterized it by X-ray crystallography which helped proposing the correct mechanism. We have achieved an efficient one-pot synthesis of substituted 2-iminothiazolines by the condensation of carbonyl compounds with thioureas and 1,3-disubstituted thioureas using EDPBT. The pKa's of the NH protons of thioureas dictates the regioselectivity in case of symmetrical ketones. Neurodegenerative drugs pifithrin-α and its analogues have been successfully prepared employing this methodology.

CHAPTER IV. Cu(I)-Catalyzed Synthesis of Substituted 2-Mercapto Benzimidazoles

This chapter deals with the synthesis of two heterocyclic systems viz substituted mercapto benzimidazoles and benzimidazole thiones as shown below.

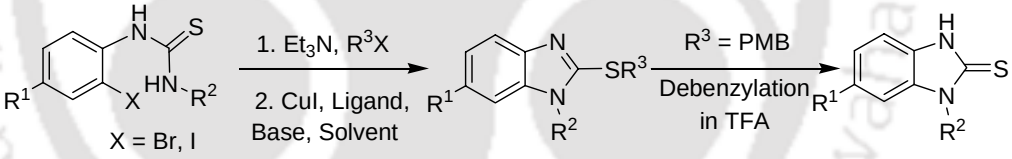


Substituted mercapto benzimidazoles



Benzimidazole thiones

2-Mercapto benzimidazoles are important class of heterocycles that are encountered in a number of natural and non-natural biologically active compounds. In continuation of our efforts and interst in developing methods for the synthesis of heterocyclic compounds from thioureas, led us to consider a Cu-catalyzed approach using 2-haloaniline derived thioureas (*Scheme 9*).



Scheme 9. *Synthesis of substituted 2-mercapto benzimidazoles.*

We envisaged that an *S*-alkylation followed by an intramolecular Cu-catalyzed aryl amination sequence from 2-haloaniline derived thioureas could lead to substituted 2-mercapto benzimidazoles as shown in *Scheme 9*. The reaction of *S*-*p*-methoxybenzyl thioethers in trifluoro acetic acid in the presence or absence of metal salts, is known to produce the corresponding thiols or thiones, therefore we expected that our approach could be extended for the preparation of benzimidazole thiones from 2-mercapto benzimidazoles substituted with a *p*-methoxy benzyl (PMB) group (*Scheme 9*).

We began our investigation using MeI and NEt_3 for S-alkylation of 2-bromo phenylthiourea, and evaluated different ligands (0.1-0.2 equiv.) (*Figure 2*), using CuI (0.05

equiv.) as precatalyst, K_2CO_3 (2 equiv.) as base, and 1,4-dioxane as solvent. The best results were obtained using 1,10-phenanthroline (**L2**) and 4,7-diphenyl 1,10-phenanthroline (**L3**) that led to nearly 95% conversion at 85 °C. 1,10-Phenanthroline (**L2**) was finally selected as the ligand due to easy availability and cost consideration. The one-pot sequence *S*-alkylation/Cu-catalyzed intramolecular *N*-arylation of 2-bromo phenylthioureas led to the corresponding cyclized products, substituted 2-mercapto benzimidazoles in good yields. Using this procedure, the scope of the method was then explored.

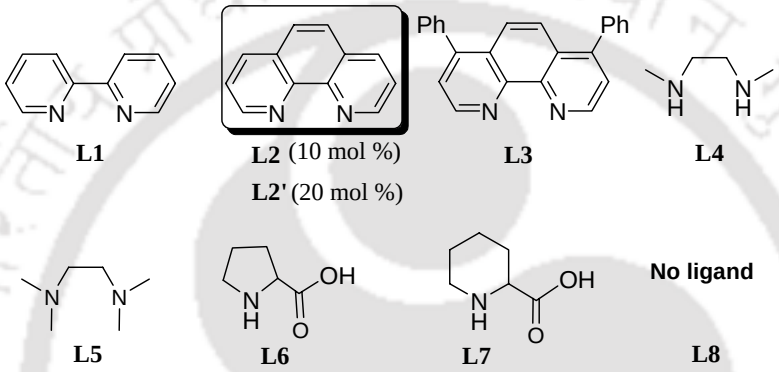
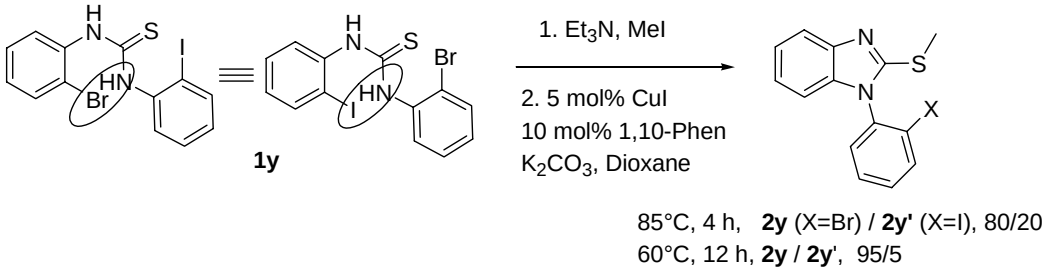


Figure 2. *Ligands tested for Cu-catalyzed intramolecular N-arylation*

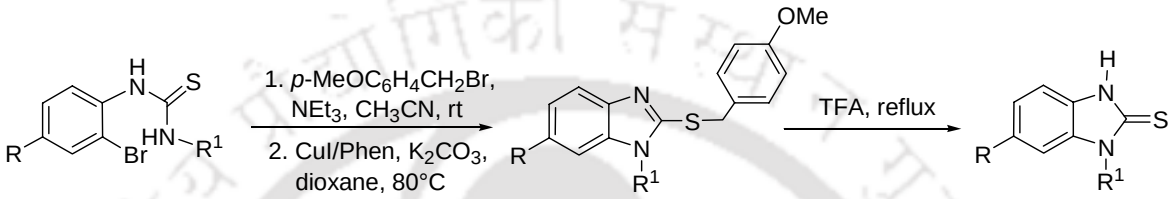
The aryl substituted thioureas, prepared from the corresponding 2-haloanilines and aryl isothiocyanate, were converted smoothly into their corresponding 2-mercapto benzimidazoles in shorter reaction times compared to their alkyl substituted analogues. 1-(2-Bromophenyl)-3-(2-iodophenyl) thiourea **1y** led, under standard conditions, to a mixture of bromo and iodo derivatives **2y**/**2y'**. However, when the reaction was performed at lower temperature, 1-(2-bromophenyl)-2-(methylthio) benzimidazole **2y** was produced with good selectivity (*Scheme 10*).



Scheme 10. *Selective intramolecular N-arylation toward iodoarene.*

Application in the Synthesis of Benzimidazole Thiones

As the general nature and the efficiency of the reaction protocol has been proven, the debenzylation of the compounds bearing a *p*-methoxy benzyl group was investigated, in order to extend our methodology to the preparation of benzimidazole thiones (*Scheme 11*). It was found that such compounds cannot be synthesized in a direct manner by a cyclization process.

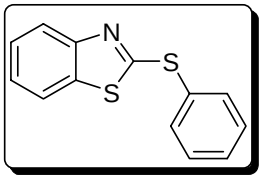


Scheme 11. *Synthesis of benzimidazole thiones*

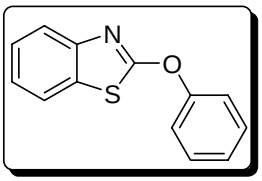
In conclusion, we have developed an alkylation/Cu-catalyzed intramolecular *N*-arylation process to synthesize substituted 2-mercapto benzimidazoles from their corresponding thioureas. A wide range of substrates were easily prepared from 2-haloanilines and were efficiently assembled into these heterocycles. The synthetic approach allows the construction of products from three different components (bromoanilines, isothiocyanates, and alkyl halides) providing a versatile access to these pharmaceutically important compounds. Benzimidazole thiones are also accessible by using a protection (PMB)/deprotection strategy.

CHAPTER V. Cu(I)-Catalyzed Cascade Synthesis of 2-Substituted Benzothiazoles

This chapter deals with the following two types of heterocycles namely 2-arylthio benzothiazoles and 2-aryloxy benzothiazoles.



Arylthiobenzothiazoles



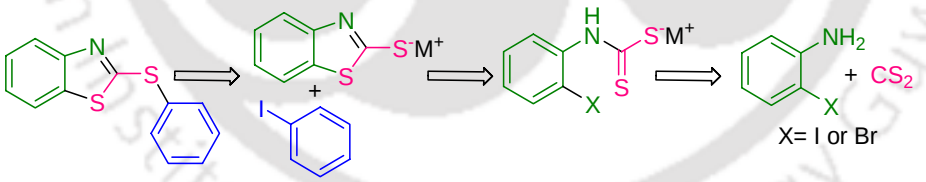
Aryloxybenzothiazoles

The benzothiazole scaffold is ubiquitous in the realms of pharmacologically active agents and natural products. Particularly, 2-mercapto and oxo-substituted analogues exhibit a wide range of biological activities.

In recent years, there has been an ever-increasing interest in the field of metal catalyzed-multi-step processes such as tandem, domino, cascade, sequential and / or concurrent catalysis in which one or more catalysts are employed for two or more transformations in one-pot. Although, the chemistry of Cu-catalyzed C–C, C–N and C–O bond formations are well explored, methods available for C–S bond formation are rather few in number because of the propensity of thiols towards oxidative dimerization and its affinity for metals, causing reduced catalytic efficiency by catalytic modifications.

As a part of our ongoing research in developing methods for the synthesis of heterocycles, we were further interested in developing newer protocols for the synthesis of heterocycles via two sequential intra and intermolecular C–S bond formation using a single catalyst (Cu) in one-pot.

In this single catalytic one-pot double arylation strategy, intramolecular S-arylation of dithiocarbamate salt would yield benzothiozole-2-thiol or 2-mercaptobenzothiazole (MBT) which is then followed by an intermolecular C-S coupling giving directly 2-arylthiobenzothiazoles as shown in *Scheme 12.*



Scheme 12. *The design of direct synthesis of arylthiobenzothiazoles*

Dithiocarbamate salt of 2-iodoaniline was prepared in quantitative yield by treating it with CS_2 and triethylamine following the literature procedure, which was used as a model substrate to optimize the reaction condition. In the absence of suitable ligand, the first step (intramolecular) of the reaction was slow and the second step (intermolecular) was not at all effective (*Figure 3*). While phenanthroline ligand (L1) was found to be most effective, an observation consistent with our previous report on intramolacular C-N bond

formation. Surprisingly, less expensive cyclohexyl-1,2-diamine (L5) was found to be even better interms of superior yield (86%) in short reaction time (4 hrs) for this sequential reaction. From a series of experiments the optimum ratios of dithiocarbamate : aryliodide : CuI : 1,2-cyclohexyl diamine ligand (L5) : base, were found to be 1 : 1 : 0.05 : 0.1 : 3. Further experimentation revealed significance of the solvent dependence for both the steps. Among various solvents (DMF, Dioxane, DMSO, DMA and toluene) tested, the reaction was found to be fastest in DMSO and K_2CO_3 to be the ideal base at 90 ^oC.

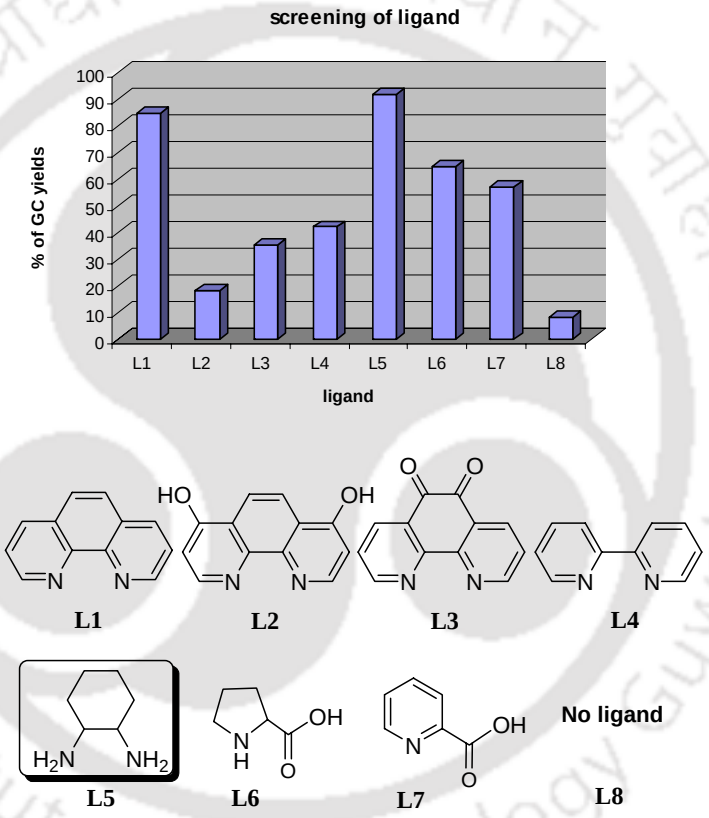
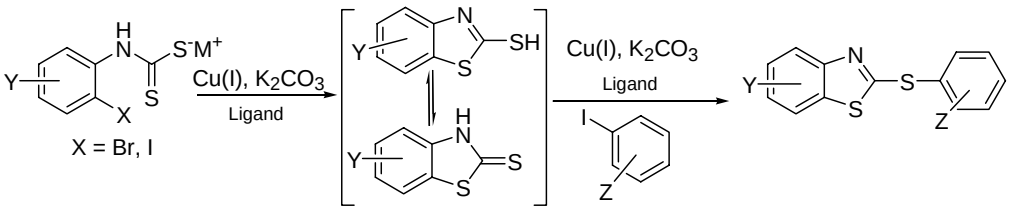


Figure 3. *Ligand effects in Cu-catalyzed sequential coupling reaction.*

It is reasonable to assume that the initial reaction proceeds by an intramolecular S-arylation to give 2-mercaptobenzothiazole (MBT), the intermediacy of which has been confirmed by its isolation (*Scheme 13*). In general, all reactions were very clean, and the 2-arylthiobenzothiazole derivatives were obtained in high yields under the optimized reaction conditions.



Scheme 13. *Synthesis of arylthiobenzothiazoles*

An interesting trend in reactivity was observed in its intermolecular coupling partner aryliodide. Presence of electron withdrawing substituents such as *p*-NO_2, *o*-NO_2, *o*-OCOR accelerate the rate of the reaction giving products in shorter reaction times, whereas electron donating substituents *p*-OMe, *p*-Me retard the reaction. Thus, from the present study we found the reactivity order in aryliodides as *p*-NO_2 > *o*-NO_2 > *o*-COOMe > *m*-Cl > H > *p*-Me > *p*-OMe. The presence of expected 2-arylthiobenzothiazole skeleton was confirmed by the X-ray structure (*Figure 4*).

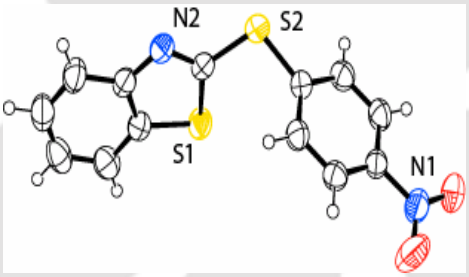


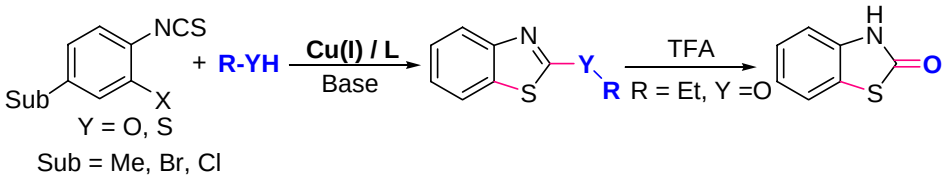
Figure 4. X-ray crystal structure *of 2-(4-Nitrophenylthio)benzo[d]thiazole.*

In summary, we have for the first time developed a single catalytic system for two sequential intra and intermolecular S-arylation leading to direct synthesis of 2-arylthiobenzothiazoles from amines / dithiocarbamates. Low catalyst loading, inexpensive metal catalyst and ligand, lower reaction temperature and shorter reaction times makes this method superior to all methods reported so far thus, of potential industrial significance.

Synthesis of 2-Substituted Oxa/Thia Benzothiazoles

Our success in the Cu-catalyzed synthesis of substituted 2-mercapto benzimidazoles and 2-arylthiobenzothiazoles via intra/intermolecular C-N and C-S bond formations and our interest in the construction of various heterocycles prompted

us to develop a Cu-catalyzed domino process for an easy access to 2-substituted benzothiazoles. The synthetic strategy is shown in *Scheme 14*.



Scheme 14. *Synthesis of 2-substituted benzothiazoles and benzothiazolones.*

This strategy involves initial nucleophilic addition of sulfur or oxygen nucleophiles to isothiocyanate followed by an intramolecular S-arylation leading to substituted 2-thia/oxa benzothiazoles in the same pot. The success of this strategy depends on the formation of thiocarbamate or dithiocarbamate esters by oxa or thia nucleophile respectively. Unlike amino nucleophile which quantitatively forms stable isolable thiourea corresponding thiocarbamate or dithiocarbamate esters derived from phenol or thiophenol are in equilibrium particularly under basic condition due to their better leaving ability and once form it undergo rapid intramolecular S-arylation

For optimization of this cascade process, *o*-bromo-phenylisothiocyanate and phenol were selected as the reaction partners. The optimum reaction condition for the present reaction was achieved using isothiocyanate (1 equiv.), phenol (1.2 equiv), CuI (5 mol%), 1,10-phenanthroline (10 mol%) and K_2CO_3 (2 equiv.) in dry dioxane.

The present Cu-catalytic system is efficient and compatible with various *o*-halo (Br and I) isothiocyanates. This intramolecular heteroarylation was equally effective either with *o*-bromo or *o*-iodo isothiocyanates. Due to easy preparation and low cost of *o*-bromo substrates, the reactions were performed mostly with *o*-bromo substrates. Wide varieties of oxa and thia nucleophiles such as phenols, alcohols, thiophenols and thiol containing electron withdrawing and donating substituents reacted well with *o*-halo arylisothiocyanates to give oxo and thio substituted benzothiazoles. Both phenols and thiophenols were found to be equally effective in this cascade process. The presence of expected 2-aryloxybenzothiazole skeleton was confirmed by the X-ray structure of 1-(4-(benzo[*d*]thiazol-2-yloxy)phenyl)ethanone (*Figure 5*).

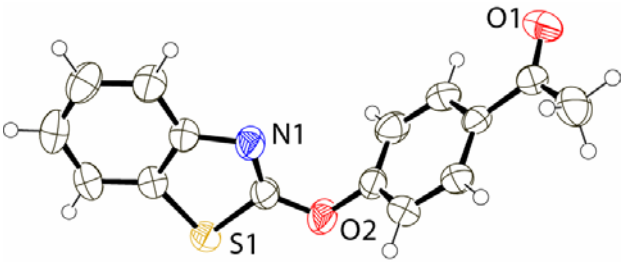
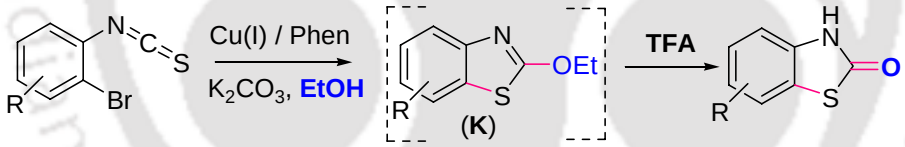


Figure 5. *X-Ray structure of 1-(4-(benzo[d]thiazol-2-yloxy)phenyl)ethanone.*

We envisaged an O-dealkylation strategy could be useful to access valuable heterocycles benzothiazolones which cannot be accessed in direct cyclization manner. Nucleophilic addition of ethanol to *o*-bromo-phenylisothiocyanate (**1**) would give thiocarbamate ester which then undergoes intramolecular *S*-arylation by CuI / L system to give 2-ethoxybenzothiazole (**Z**) (*Scheme 15*). In these reactions ethanol serves the dual purpose of nucleophile and solvent. Ethanol being a weaker leaving group and present in excess drives the reaction towards forward direction giving quantitative yields of (**K**). *o*-Dealkylation of (**Z**) using trifluoroacetic acid (TFA) provided 2-benzothiazolone in 65 % overall isolated yield.



Scheme 15. *Cascade synthesis of benzothiazolones*

In conclusion, we have developed an efficient cascade process for the preparation of 2-substituted benzothiazoles. The *in situ* generated thiocarbamate or dithiocarbamate by the reaction of 2-haloisothiocyanates with oxa- or thia- nucleophiles undergo CuI/L-catalyzed intramolecular C-S bond formation giving substituted benzothiazoles. Both phenols and thiophenols react with equal ease, on the other hand, alcohols and thiols are found to be less reactive. The rate of the reaction is faster giving better yields when electron withdrawing substituents are present in either of the coupling partners. Benzothiazolones can be prepared in one-pot using ethanol as solvent and nucleophile (oxygen source).

Contents

CHAPTER I

I. Introduction to Heterocyclic Chemistry

Heterocycles make up an exceedingly important class of compounds and more than half of all the known organic compounds are heterocycles. Almost all the compounds known as drugs, most of the vitamins and many other natural products are heterocycles. The class also includes several other compounds of biological importance, such as nucleic acids, carbohydrates, hormones, and pigments. Heterocyclic compounds are the key components of pharmaceutical chemistry and therefore they have been a fruitful source of inspiration for the design of structural analogues to be used as pharmacological tools as well as new drugs. Heterocyclic compounds are used widely because their structures can be subtly manipulated to achieve a required modification in function.

I.1. Heterocycles and their Importance

Most of the chemical compounds consist of molecules, which are classified based on their structure, type and number of atoms as well as their bonding patterns. In organic chemistry, there are two main types of frame work structures, namely cyclic and acyclic. Cyclic compounds in which the ring frame is made from only one element are called **isocyclic** compounds. If the building block is made from C-atom they are term as **carbocyclic** compound (e.g. cyclohexane, benzene). Cyclic compounds in which the ring frame is made from more than one element are called **heterocyclic compounds**. Atoms other than carbon in the ring are termed as **heteroatoms**. The most commonly found heteroatoms are **nitrogen**, **oxygen** and **sulfur**; while heterocycles containing other polyvalent elements such as boron, silicon, phosphorus, selenium and arsenic are also known. Besides type, the number of atoms present per ring is important since the ring size is dependent on it. The smallest possible is a three membered ring, whereas the most abundant and stable are the **five** and **six** membered heterocycles. There is no upper limit as far as the size of the ring is concerned.

I.1.1. Classification and Nomenclature

Heterocyclic compounds can be classified as mono, di, tricyclic heterocyclic compounds etc. based on the number of rings present in the basic skeleton. Monocyclic heterocycles can be further sub-classified as:

(i) Heterocycloalkanes (saturated, e.g. aziridine, piperidine etc.)

(ii) Heterocycloalkenes (partially unsaturated, e.g. 2H-pyran, 4H-pyran etc.)

(iii) Heteroannulenes (systems with greatest possible number of non-cumulated double bonds, e.g. pyridine, pyrilium ion)

(iv) Heteroaromatics {systems posses (4n+2) π electrons, e.g. furan, thiophene}.

Chemists have been working with heterocycles for more than two centuries, and trivial names were often applied long before the structures of the compounds were known. As a result, many heterocycles continue to retain these names. Some common five- and six-membered heterocycles that contain one oxygen, nitrogen or sulfur atom are shown in *Figure I.1.1.1.*

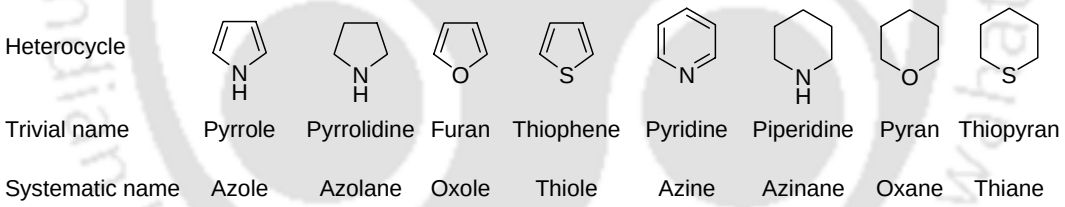


Figure I.1.1.1. *Trivial and systematic names of some common five and six membered heterocycles.*

The most widely used systematic method for naming three to ten membered monocyclic heterocycles of various degree of unsaturation containing one or more heteroatoms is **Hantzsh-Widman** system.[1] This nomenclature specifies the ring size and the nature, type and position of the heteroatom and the degree of unsaturation in the ring. In this method the ring atoms are normally numbered such that the heteroatom carries the lowest number. Hetero monocyclic compounds are named by combining one or more prefixes for the heteroatoms with a stem indicating the size of the ring. (*Table I.1.1.1* and *I.1.1.2*).

Table I.1.1.1. *Prefixes for heteroatoms (in decreasing order of priority).*

Heteroatom	**Symbol**	**Prefix**
Oxygen	O	Oxa
Sulfur	S	Thia
Nitrogen	N	Aza

Table I.1.1.2. *Stems for three to ten membered heterocycles.*

Ring size	**Unsaturated**	**Saturated**
3	-irene	-irane
4	-ete	-etane
5	-ole	-olane
6	-ine	-ane
7	-epine	-epane
8	-ocine	-ocane
9	-onine	-onane
10	-ecine	-ecane

2*H*-Pyran 4*H*-Pyran 3,4,5,6-tetrahydro-2*H*-Pyran

Figure I.1.1.2. *Systematic names having sp^3 carbon atom in heterocyclic ring.*

A problem arises with trivial names when a sp^3 hybridized atom is present in an unsaturated ring. A good example is pyran, a heterocycle that is formally the product of the addition of a single hydride ion to the pyrylium cation. However, as this addition could occur either at C-2 or C-4, two isomers of pyran are possible, which are called as 2*H*-pyran and 4*H*-pyran respectively. In these types of compounds, the position of the hydrogen/ sp^3 carbon is indicated by the number of the ring atom containing H, followed by the letter 'H' in italics (*Figure I.1.1.2.*).This system of nomenclature works reasonably well in many related cases and is widely used in the literature.[2] It is also customary to use the prefixes di-, tetra-, hexahydro- etc instead of tri-, penta- or heptahydro- while referring to

compounds that are partly (one or two double bonds) or fully reduced (three double bonds for six membered ring). It is important to note that the lowest possible number is always selected for the locant (heteroatom); for example, the fully reduced pyrylium cation is referred to as 3,4,5,6-tetrahydro-2*H*-pyran (*Figure I.1.1.2*).

Many heterocycles are fused to other ring systems, notably benzene, giving in this case benzo derivatives such as benzothiazole, benzimidazole, benzoxazole etc. Some of these compounds are known to have trivial names of their own, such as indole and isoquinoline etc. the basic heterocyclic nuclei investigated in this thesis along with their nomenclature are shown in *Figure I.1.1.3*.

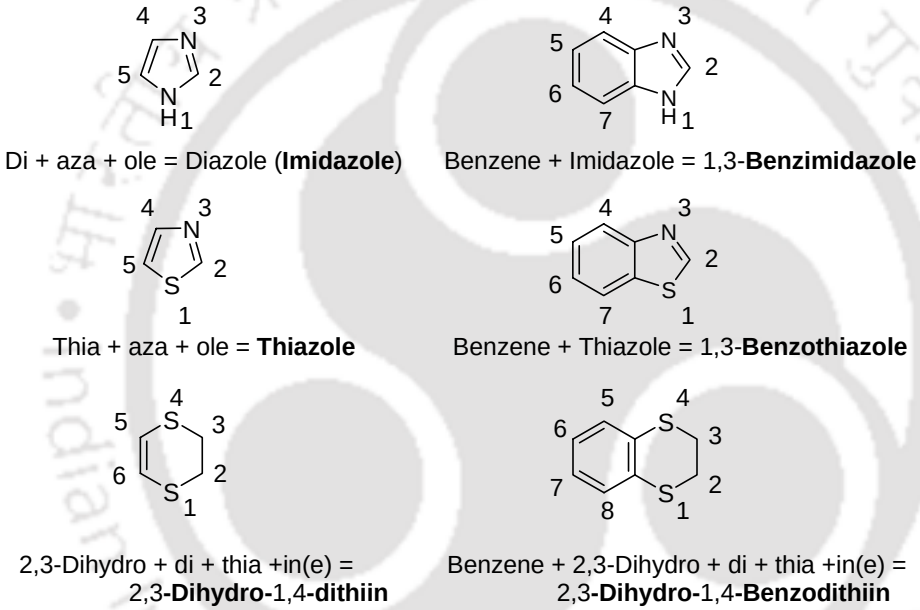
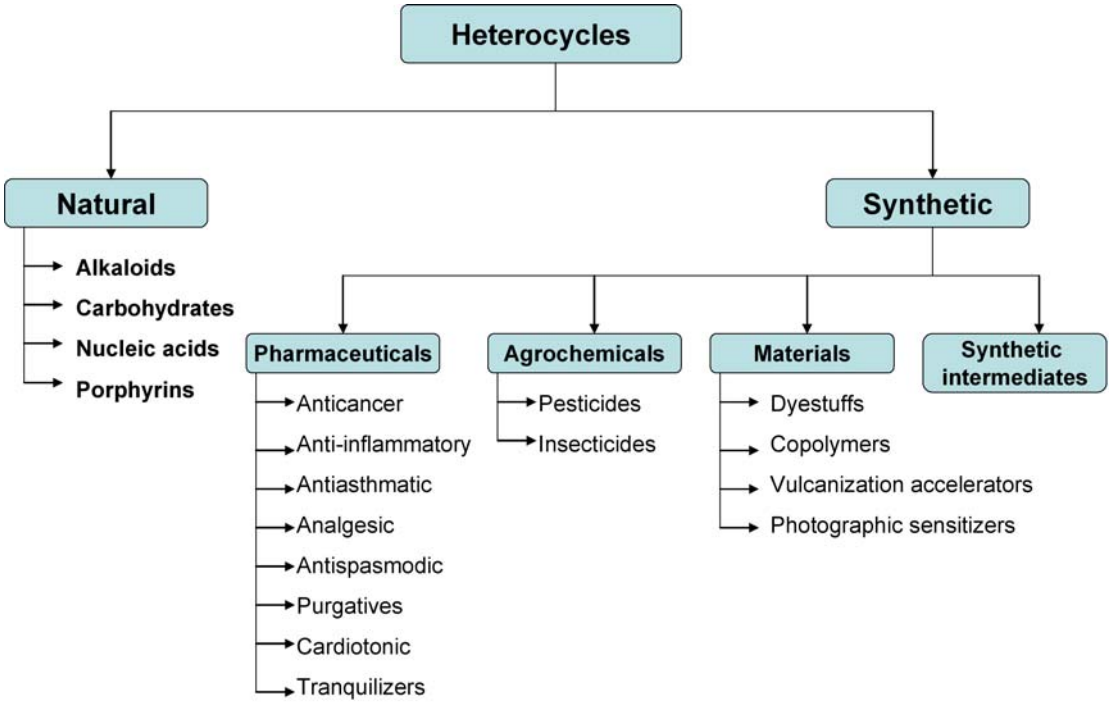


Figure I.1.1.3. *Some of the basic heterocyclic nuclei and their nomenclature.*

I.1.2. Important Applications of Heterocycles

Many heterocyclic compounds are biosynthesized by plants and animals and possess various biological activities. Over millions of years many organisms have been under intense evolutionary pressure, and their metabolites may be used to advantage; for example, as toxins toward off predators, or as coloring agents to attract mates of pollinating insects. There are many thousands of other heterocyclic compounds, both natural and synthetic, of major importance, not only in medicine but also in several other activities known to mankind (*Scheme I.1.2.1*). Heterocyclic compounds are of the utmost

importance to industry in countless ways. One cannot imagine a society without access to the benefits of synthetic heterocycles.



Scheme I.1.2.1. *Various applications of heterocycles.*

Most of the heterocycles are fundamental to life processes; for example **heme** found in hemoglobin and myoglobin, responsible for oxygen storage and transport respectively, contains a heterocyclic porphyrin system and Fe(II). The green coloring pigments **chlorophylls** in plants are porphyrins, essential for photosynthesis without which life on earth as we know it could not exist. Similarly, the purine and pyrimidine bases found in **RNA** and **DNA** are heterocycles, as are the sugars that in combination with phosphates provide the backbone and determine the topology of nucleic acids.

Indigo blue, a dyestuff of plant origin, is used to dye jeans. **Strychnine,** a natural alkaloid, is a notorious poison (LD_{50} = 10 mg) featured in many detective stories, and is used as pesticide, particularly for killing small vertebrates such as birds and rodents. The biological properties of heterocycles in general, make them of prime interests for the pharmaceutical and biotechnology industries. Considering only the drugs, one can define the whole history of medicine through heterocycles. Even in the sixteenth century, **quinine** was used to prevent and treat malaria though its structure was not known at that time. The

first synthetic drug was **antipyrine** (1887) which was used to reduce fever. The first effective antibiotic was **sulfapyridine** (1938). The first multi-million pound drug (1970s) **Tagamet**, is an anti-ulcer drug, and among the most topical of current drugs is **Viagra** (1997) for treatment of male impotence.

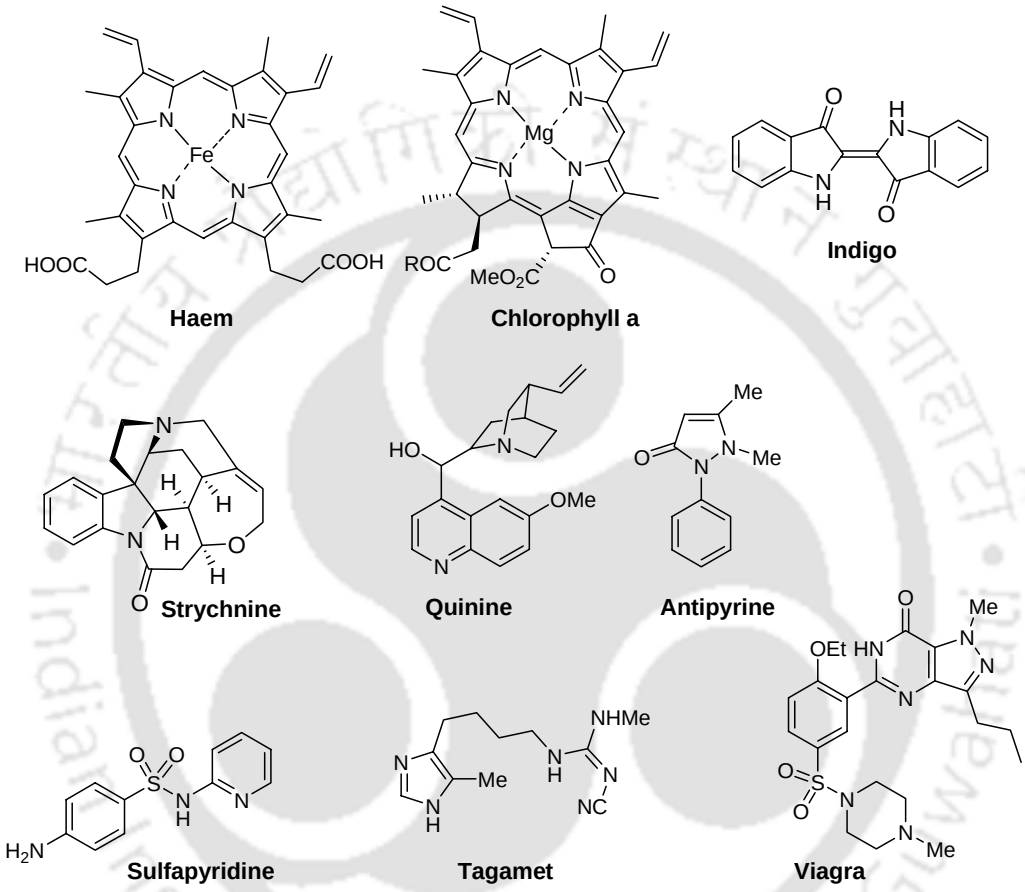


Figure I.1.2.1. *Examples of biologically active heterocycles.*

Nicotine is an alkaloid found in the nightshade family of plants which is an additive drug and acts as an insecticide. **Nifedipine** is a cardiovascular drug and is a dihydropyridine calcium channel blocker. For over thousand years, South American indigenous peoples have chewed the coca leaf, a plant that contains hallucinogenic addictive drug **cocaine**. It belongs to the class of tropane alkaloids and acts as a central nervous system (CNS) stimulant and an appetite suppressant. **Morphine** is a highly potent opiate analgesic drug and a principal active agent in opium. In the central nervous system, **serotonin** plays an important role as a neurotransmitter in the modulation of anger,

aggression, body temperature, mood, sleep, human sexuality, appetite, and metabolism**.** **Benomyl** is a fungicide which was introduced in 1968 by Du Pont. It is a systemic benzimidazole fungicide that is selectively toxic to micro-organisms and to invertebrates, especially earthworms.

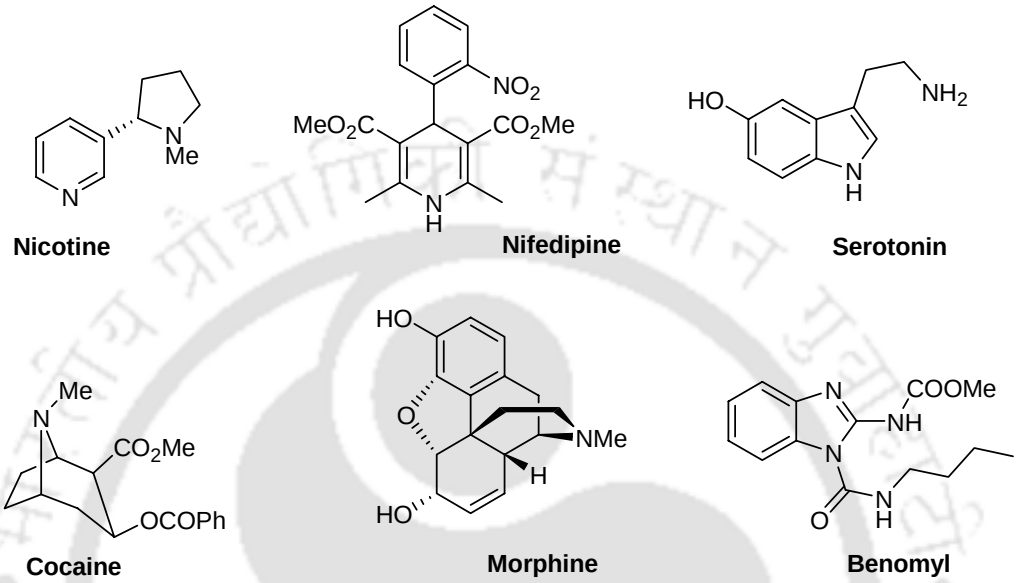


Figure I.1.2.2. *Examples of biologically active heterocycles.*

In 1929, Fleming discovered that the mould *Penicillium notatum* inhibits the growth of bacteria. In 1941 Florey and Chain succeeded in isolating the active agent, known as **penicillin**, in the form of its sodium salt. **Luciferin**, which occurs in fireflies and glow worms, upon enzymatic oxidation causes bioluminescence in these insects. The herbicide **benazoline** serves as an example of a synthetic benzothiazole derivative with biological activity. **Eprosartan** is an angiotension II inhibitor and used as antihypertensive agent. The compound 2-(4'-thiazolyl) benzimidazole (**thiabendazole**) is used extensively as a preservative for fruits and as an anthelmitic in veterinary medicine. **Pimprinin** is a natural product isolated from *Streptomyces pimprina*. The world's best selling medicine in 1998 was **omeprazole**, an anti ulcer drug from Astra. It prevents excess acid in the stomach and allows body to heal ulcers. The list is uncountable and is beyond the scope of this thesis.

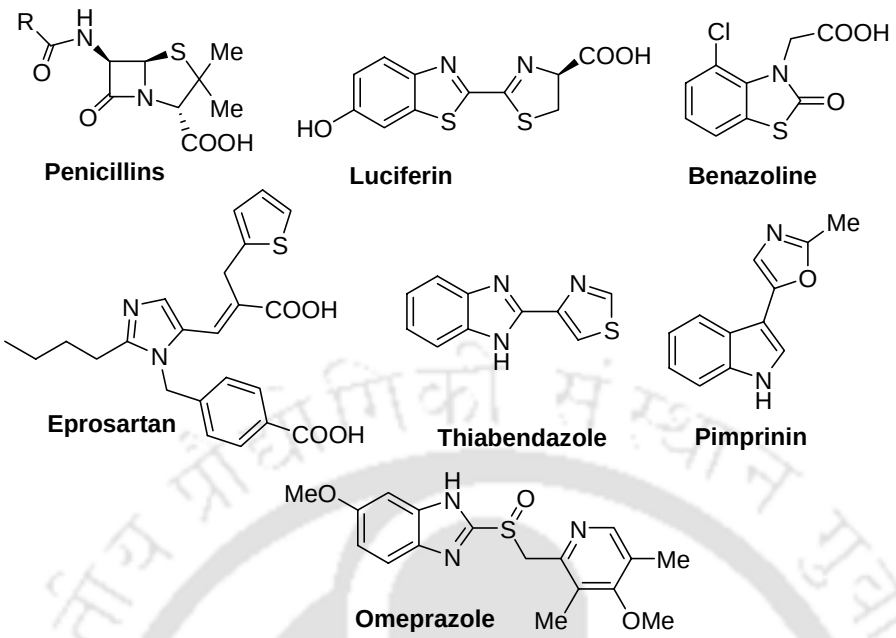


Figure I.1.2.3. *Examples of biologically active heterocycles.*

I.2. General Approaches for the Construction of Aromatic Heterocycles

Generally, the following four major strategies are applied for the construction of aromatic heterocycles.

(i) Ring construction by ionic cyclizations

(ii) Ring construction by pericyclic reactions

(iii) Modification of existing rings by electrophilic or nucleophilic aromatic substitution or by lithiation followed by reaction with electrophiles.

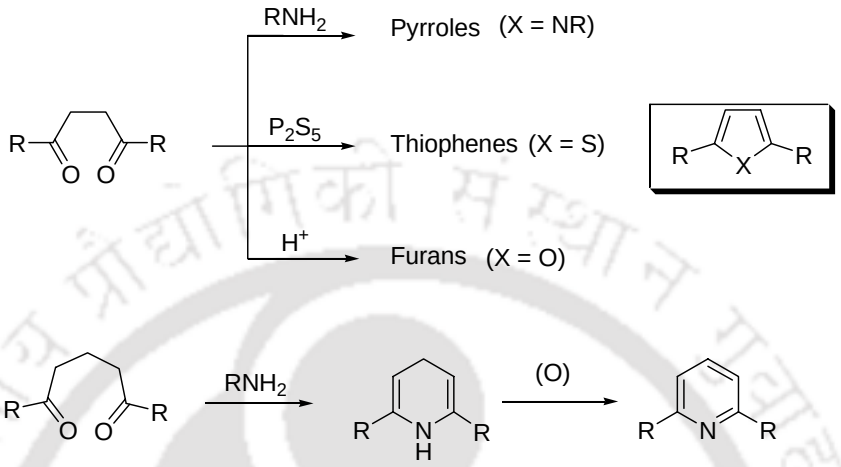
(iv) Metal catalyzed cyclizations via C-heteroatom bond formation.

This thesis deals mainly with the construction of heterocyclic involving ionic path and metal catalyzed cyclizations. A brief summary of different applications involving these two types of reactions are discussed below.

I.2.1. Ring Construction by Ionic Cyclization

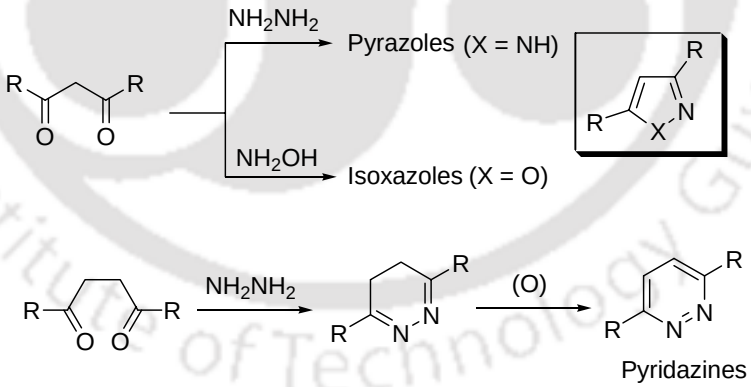
In this approach the heteroatom is used as the nucleophile and the carbon atoms as double electrophiles. The construction of five and six membered heterocycles with one hetero atom using this approach is shown in *Scheme I.2.1.1.* Five-membered rings such as

pyrroles, thiophenes, and furans are ideally made by this strategy from 1,4-dicarbonyl compounds while the six-membered rings dihydropyridine and pyridines are made from 1,5-dicarbonyl compounds in the presence of an oxidant.



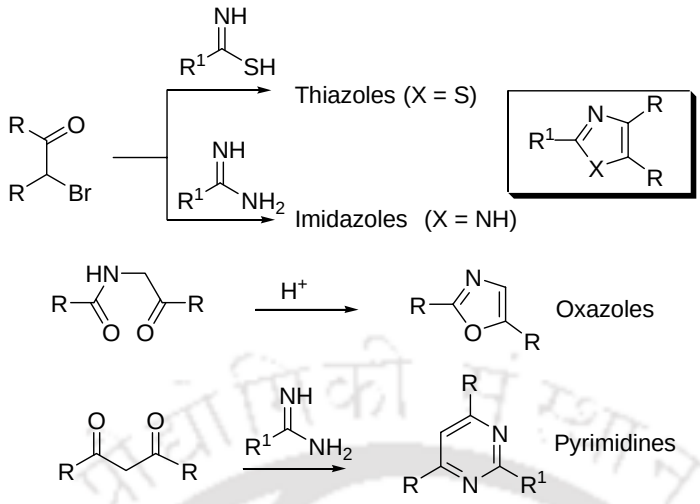
Scheme I.2.1.1. *Construction of five and six membered heterocycles with one heteroatom.*

Five and six membered heterocycles with two adjacent heteroatoms can be constructed from 1,2-bis nucleophile such as hydrazine or hydroxylamine and 1,3 or 1,4 carbonyl compounds as shown in *Scheme I.2.1.2.*



Scheme I.2.1.2. *Construction of five and six membered heterocycles with two heteroatoms.*

Heterocycles with two non-adjacent heteroatoms in five (imidazoles and thiazoles) and six (pyrimidines) membered ring, can be constructed using 1,3-bis nucleophiles and either 1,2-bis electrophile (α-haloketone) or 1,3 and 1,4-dicarbonyl compounds as shown in *Scheme I.2.1.3.*

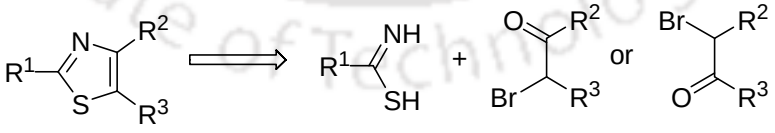


Scheme I.2.1.3. *Construction of five and six membered heterocycles with two nonadjacent heteroatoms.*

Ionic cyclizations using organic ammonium tribromides is one of the areas in heterocyclic synthesis, which is discussed in the forth coming section I.3. Their uses in heterocylic synthesis via oxidative and brominative cyclizations are reviewed.

I.2.1.1. Selectivity of Unsymmetrical *bis*-Nucleophiles toward Unsymmetrical *bis*-Electrophiles

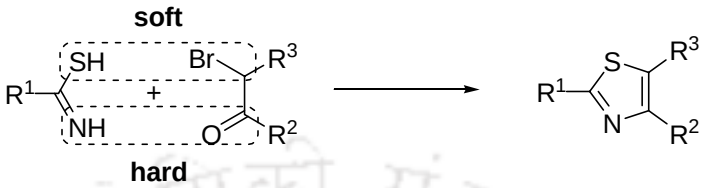
The synthesis of thiazoles from α-haloketones and thioamides is particularly interesting and challenging because of the regioselectivity problem. When thioamides react with α-haloketones, there is a problem of regioselectivity as to which of the nucleophiles (N or S) attack on which of the two possible electrophilic sites (carbonyl or alkyl halide). A possible retrosynthesis of thiazoles formation is shown in *Scheme I.2.1.1.1*.



Scheme I.2.1.1.1.

Carbonyl groups being '**hard**' electrophiles, their reactions are mainly under charge control and so they prefer to react with hard nucleophiles such as amines. Alkyl halides are '**soft**' electrophiles, so their reactions are mainly under frontier orbital control

and they react best with large uncharged nucleophiles from the lower rows of the periodic table. Thus, ketone should react with amine and the alkyl halide with sulfur nucleophile (thiol) as shown in *Scheme I.2.1.1.2.*

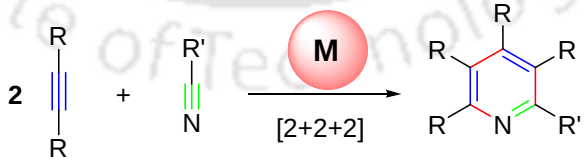


Scheme I.2.1.1.2.

I.2.2. Transition Metal Catalyzed Approaches to Heterocycles

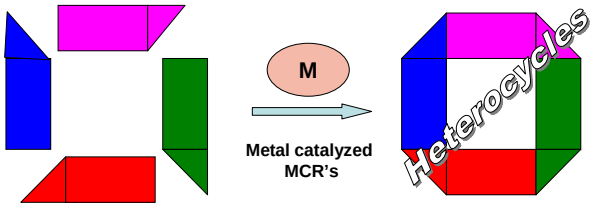
The importance of heterocycles in many fields of science can hardly be overemphasized, and justifies a long lasting effort to work out new synthetic protocols for their production. A particularly attractive approach is based on transition-metal catalyzed heterocyclization reactions of suitably functionalized substrates, which can allow the regioselective synthesis of highly functionalized heterocycles starting from readily available precursors under mild and selective conditions. During the last few years, this approach to the synthesis of heterocycles has acquired a growing importance.

Many strategies have been developed by the use of metal-mediated convergent reactions for the rapid construction of highly functionalized heterocycles. Heller and Hapke described the scope of the metal-catalyzed [2+2+2] cycloadditions for the synthesis of pyridine derivatives.[3] (*Scheme I.2.2.1.*)



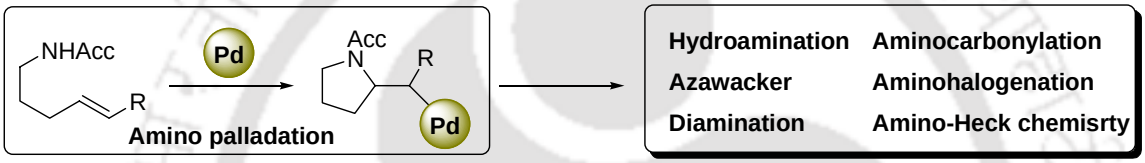
Scheme I.2.2.1.

A further development is the use of multi-component reactions (*Scheme I.2.2.2.*) for the synthesis of heterocycles by transition metal catalysis, which is recently reviewed by DSouza and Muller.[4]

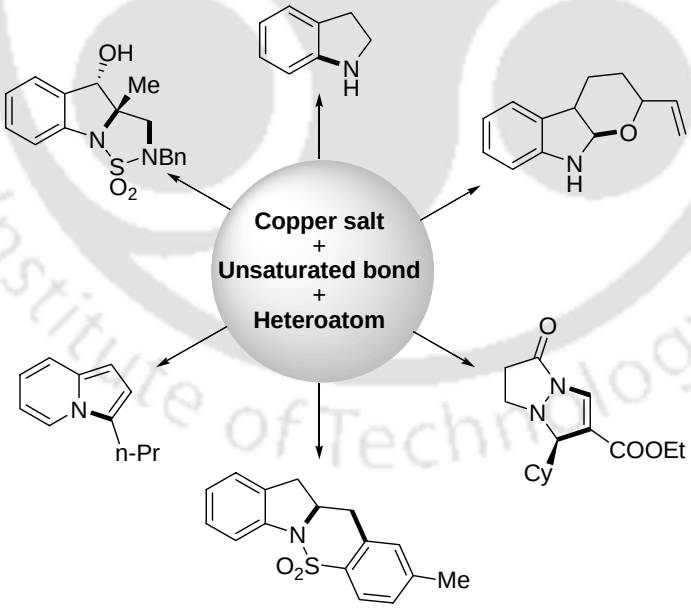


Scheme I.2.2.2.

Transition-metal catalyzed addition of nitrogen nucleophiles to alkenes is recently recognized as a powerful tool for the synthesis of saturated nitrogen heterocycles. Minatti and Muniz described the palladium-catalyzed amination of alkenes (*Scheme I.2.2.3.*),[5a] while Chemler and Fuller reviewed complimentary methods using copper catalysis (*Scheme I.2.2.4.*).[5b]



Scheme I.2.2.3.



Scheme I.2.2.4.

Metal catalyzed cross-coupling reactions are now standard methods for the synthesis of heterocycles, but very innovative variations are still being discovered. The

field is still wide-open for innovation and will continue to advance as even more versatile transformations are developed. Copper catalyzed cyclizations, intramolecular Ullmann reactions (IUCs) in particular for the synthesis of heterocycles are discussed in section **I.4.**

I.3. Heterocyclic Synthesis Using Organic Ammonium Tribromides

Organic ammonium tribromides (OATBs) are attractive solid bromine less brominating agents. These crystalline stable solids are convenient source of bromine owing to the ease in maintenance of their desired stoichiometry and the ease in storage, transportation and handling. Several organic tribromides have been reported in the literature (*Figure I.3.1.*), which includes tetramethylammonium tribromide (TMATB), tetrabutylammonium tribromide (TBATB), tetraethylammonium tribromide (TEATB), cetyltrimethylammonium tribromide (CTMATB), pyridine hydrobromide perbromide (PHPB), phenyltrimethylammonium tribromide (PTATB), benzyl trimethylammonium tribromides (BTMATB), 1,8-diazabicyclo [5.4.0]-undec-7-ene hydrobromide perbromide ($DBUHBr_3$), pentylpyridinium tribromide (PPTB), 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide and 1-butyl-3-methylimidazoliumtribromide ([bmim] Br_3).

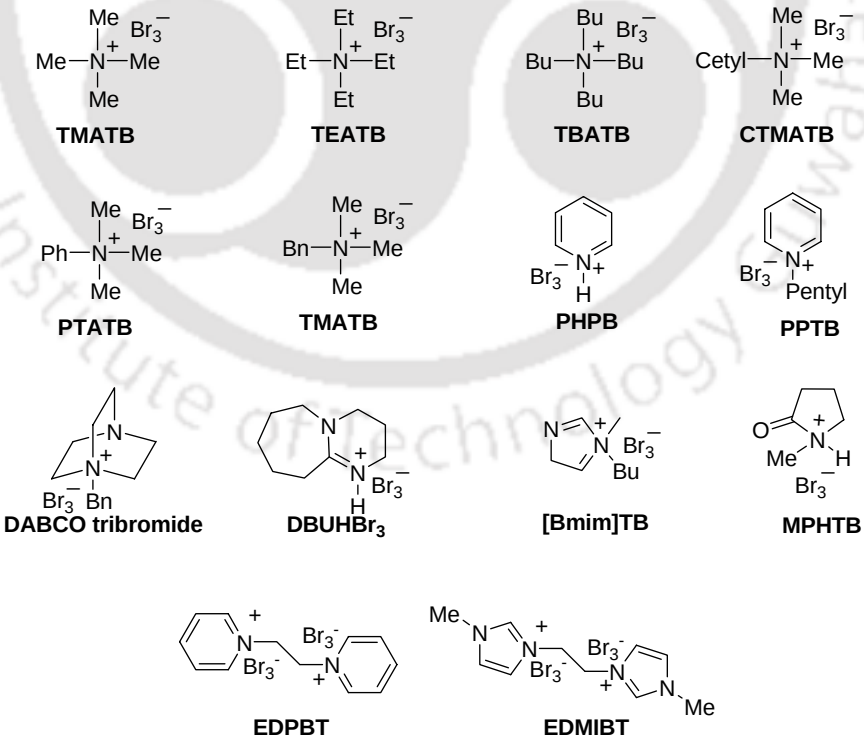
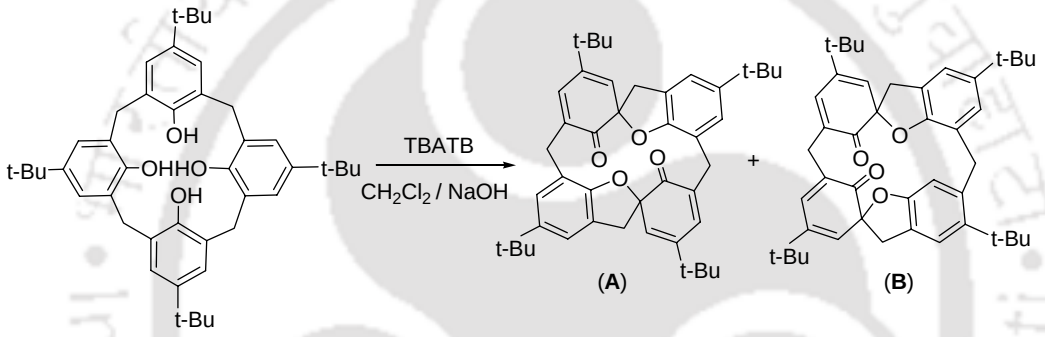


Figure I.3.1.

In addition to serving as efficient oxidizing and brominating agents various tribromides have been used for the construction of heterocycles. Their uses in heterocylic synthesis via oxidative and brominative cyclizations are reviewed below.

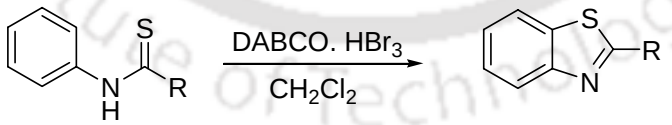
I.3.1. Tribromide Mediated Oxidative Cyclizations

Biali and coworkers have discovered that *tert*-butyl calix[4]arenes can easily be oxidized with tetrabutylammonium tribromide (TBATB) into *bis*-spirodienenones (A and B) via oxidative cyclization. This procedure converts calixarenes into molecules possessing carbonyl and ethereal oxygen which can bind to metal ions selectively, similar to the natural ionophores (*Scheme I.3.1.1*).[6a,b]



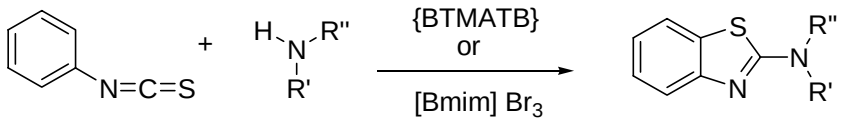
Scheme I.3.1.1.

Recently, solid brominating agent such as N-benzyl-DABCO tribromide and benzyltrimethyl ammonium tribromide (BTMATB) have been utilized as an alternative electrophilic bromine source for the efficient oxidative cyclization of thiobenzanilides and thioureas to their corresponding 2-substituted benzothiazoles under mild conditions (*Scheme I.3.1.2.*) .[6c]



Scheme I.3.1.2.

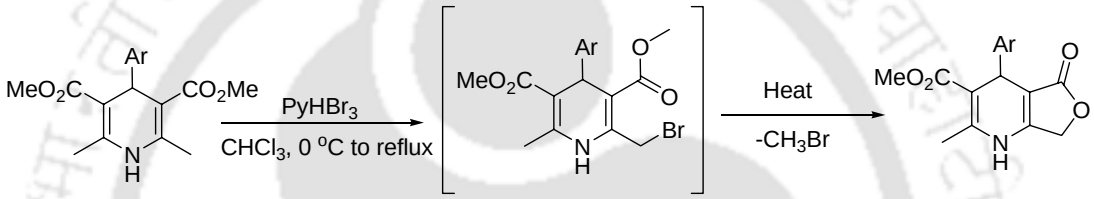
Jordan and his cowokers have used benzyltrimethylammonium tribromide (BTMATB) for the oxidative cyclization of thioureas, generated *in situ* by reacting corresponding isothiocyanates and amines.[6d] The same synthesis was achieved by Le *et al.* using 1-butyl-3-methylimidazolium tribromide ([Bmim]Br_3) (*Scheme I.3.1.3*).[6e]



Scheme I.3.1.3.

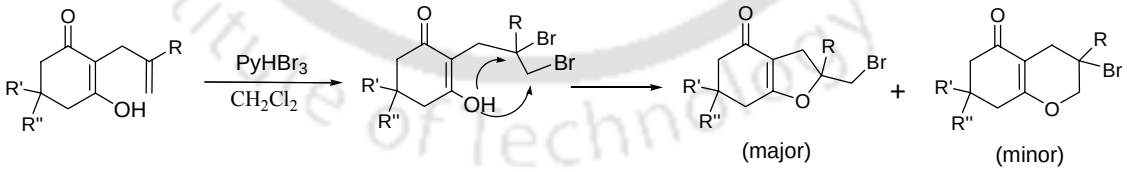
I.3.2. Brominative Cyclizations

Young reported a brominative cyclization of suitably substituted 1,4-dihydropyrimidines using pyridinium hydrobromide perbromide ($PyHBr_3$) to yield lactones as shown in *Scheme I.3.2.1.* This reaction proceeds via bromination of methyl group of 1,4-dihydro pyrimidines, followed by cyclization with the ester moiety.[7a]



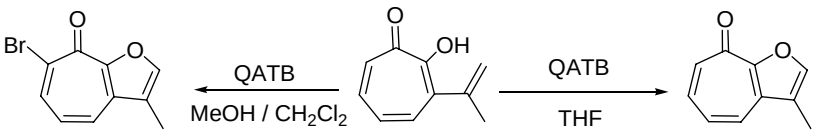
Scheme I.3.2.1.

Pyridinium tribromide ($PyHBr_3$) in dichloromethane provides an effective medium for the bromocyclization of α-allyl cyclohexane-1,3-diones to afford tetrahydrofuranones and tetrahydropyaranones (*Scheme I.3.2.2.*).[7b] This reaction proceeds through a 2-(2,3-dibromopropyl)-1,3-cyclohexanedione intermediate to form both the endo and exocyclic derivatives.



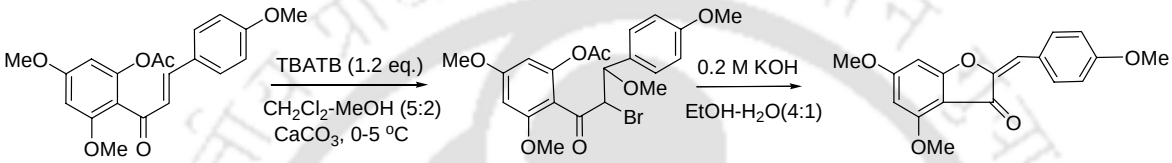
Scheme I.3.2.2.

Treatment of 3-isopropenyltropolone with different quaternary ammonium tribromides (QATB) in THF afforded 3-methyl-8H-cyclohepta[b]furan-8-one. The same reaction in MeOH-CH_2Cl_2 gave 7-bromo-3-methyl-8H-cyclohepta[b]furan-8-one as shown in *Scheme I.3.2.3.* [7c]



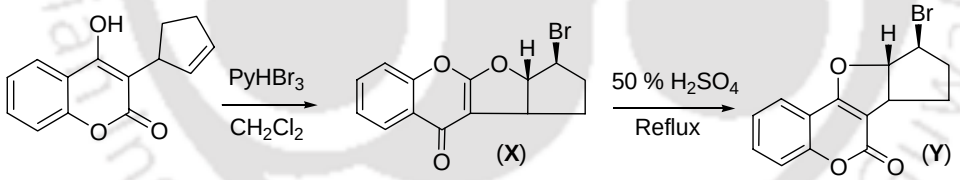
Scheme I.3.2.3.

An environmentally benign synthesis of aurones and flavones from 2'-acetoxychalcones using tetrabutylammonium tribromide has been reported by Khan *et al*. The bromination step is the decisive step which directs the formation of flavone and aurone (*Scheme I.3.2.4.*).[7d]



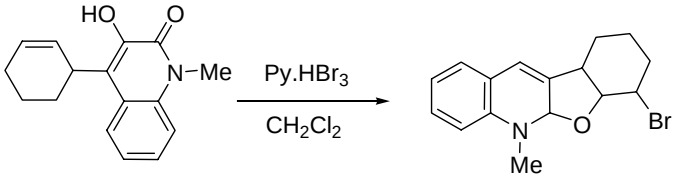
Scheme I.3.2.4.

Treatment of 4-hydroxy[1]benzopyran-2-one with pyridine hydrobromide perbromide ($PyHBr_3$) gave fused furochromone (X) in 90% yield (*Scheme I.3.2.5.*). These heterocycles undergoes rearrangement to furnish fused furocoumarin (Y) in 87% yield.[7e]



Scheme I.3.2.5.

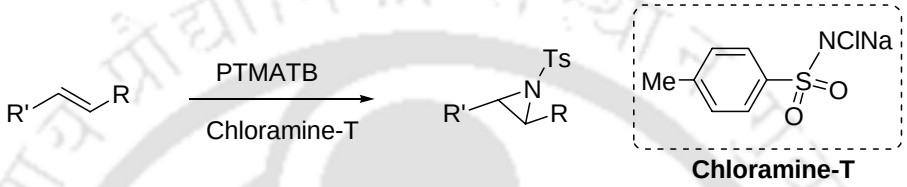
Reaction of 4-cyclohex-2-enyl-3-hydroxy-1-methyl-1H-quinolin-2-one with pyridine hydrobromide perbromide ($PyHBr_3$) in dichloromethane at 0-5 ^oC afforded benzofluorene product in excellent yield (*Scheme I.3.2.6.*).[7f]



Scheme I.3.2.6.

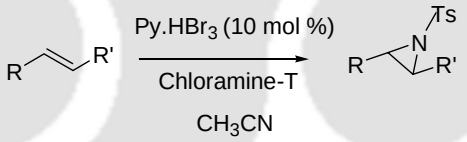
I.3.3. Tribromide Mediated Aziridinations

Sharpless *et al.* used phenyl trimethylammonium tribromide (PTAB) as catalyst for aziridination of alkenes in the presence of anhydrous chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide). The mechanism involves the formation of intermediate bromonium ion, which undergoes ring opening with TsNHCl to give the key intermediate. However, electron-deficient olefins such as α,β-unsaturated ketones, aldehydes, esters etc. failed to undergo aziridination (*Scheme I.3.3.1.*).[8a,b]



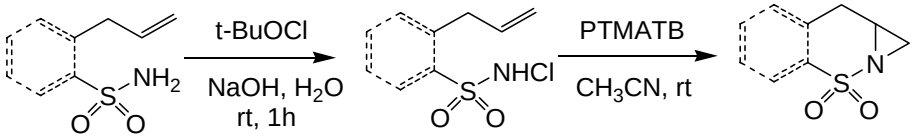
Scheme I.3.3.1.

Later on Sudalai group found that pyridinium hydrobromide perbromide ($Py.HBr_3$) acts as an efficient catalyst for the aziridination of electron-deficient as well as electron-rich olefins using chloramine-T as a nitrogen source (*Scheme I.3.3.2.*). The best feature of this method is tolerance of sensitive functional groups such as acetals and enol ethers.[8c]



Scheme I.3.3.2.

N-Chloramine salts of unsaturated sulfonamides have been prepared and used for the synthesis of bicyclic aziridines in presence of a catalytic amount of phenyl trimethylammonium tribromide (PTATB). This intramolecular procedure gave best results with the *N*-chloramine salts of vinyl sulfonamides, 2-vinylbenzenesulfonamidex (*Scheme I.3.3.3.*).[8a,b] Subsequently, other tribromides such as PHBPB, MPHTB have been used for this transformation.[8c-f]



Scheme I.3.3.3.

I.4. Copper Catalyzed Synthesis of Heterocycles

The foundation of modern cross-coupling chemistry was built at the beginning of the twentieth century with the pioneering work of Fritz Ullmann and Irma Goldberg.[9] Their explorations into new methods for the synthesis of C–C, C–N, and C–O bonds provided the conceptual breakthrough that allowed for the use of unactivated aryl halides to supplant the electron-poor aryl halides typically required for the classical nucleophilic aromatic substitution reaction. These advancements not only expanded the scope of substrates that could be utilized in aromatic substitution reactions, but also changed the way chemists thought about constructing molecules containing N-aryl and O-aryl bonds.

The formation of aryl C–X bonds (X = O, S, N etc.) via copper-catalyzed coupling between aryl halides and heterocentered nucleophiles has drawn a great deal of attention in the past few years.[10] The high stability and low costs of copper catalysts enable these transformations to be a useful complement to the more extensively investigated palladium catalyzed processes which encounter some limitations.[11] For example, N-arylation of amines containing free N-H moieties remains problematic.[12] With the intramolecular Ullmann Coupling (IUC) as the strategy, the preparation of many medium- and even large-sized heterocycles can be achieved as discussed below in section **I.4.3.** More recently, this methodology was successfully extended to the synthesis of various bioactive heterocycles and natural products.

I.4.1. Mechanistic Aspects of Copper-Catalyzed Inter and Intramolecular Heteroarylations

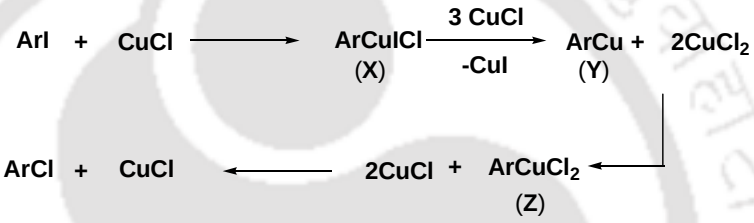
It is a well accepted fact that a reaction mechanism can never be proved, at the best, evidences can be given in the favor of or against it. The most important aspect of copper is its accessibility of four oxidation states from 0 to +3. Most likely the catalytic cycle of cross couplings with copper involves +1/+3 oxidation states. To date, three plausible mechanisms for Ullmann-type coupling reactions have been described in the literature.[13a-c]

1. Oxidative addition/reductive elimination mechanism proposed by Cohen in 1974.[13d]

2. π-complex mechanism proposed by Paine in 1987.[13e]

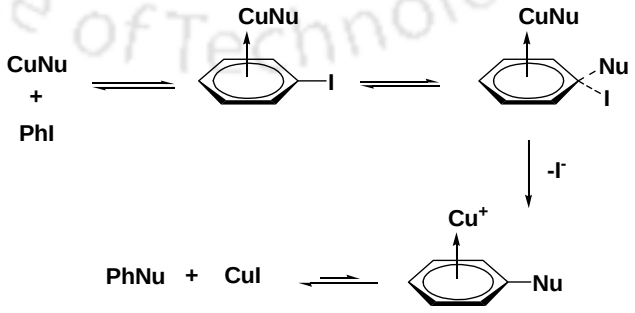
3. Radical or radical anion pathway.[13f,g]

Cohen *et al.* proposed that the oxidative addition of carbon-halogen bond to the cuprous chloride forms the Cu^{III} organometallic species (X), reduction of which by cuprous chloride leads to an organometallic of lower oxidation state written here as the Cu^{I} species (Y). Oxidation of the latter by cupric chloride presumably occurs via the Cu^{III} compound (Z) which could reductively eliminate cuprous chloride to produce the aryl chloride. Here in this a two electron reduction process occurs where Cu^{I} is directly converted to Cu^{III} intermediate (*Scheme.I.4.1.1.*).



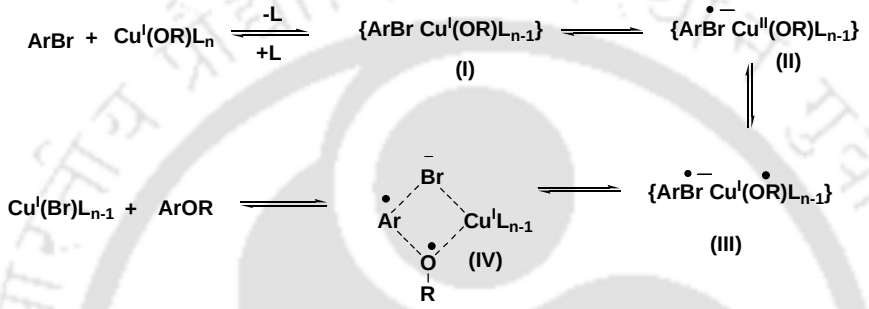
Scheme I.4.1.1.

Later on Paine has reported a mechanism for the copper catalyzed Ullmann condensation reaction which involves π-complex formation of haloarene with copper nucleophile (CuNu) as shown in *Scheme I.4.1.2.* Copper nucleophile reacts with iodoarene to form an organo cuprate intermediate followed by transfer of nucleophile from copper to arene ring and elimination of iodide. This mechanism does not deal with any benzyne, radical or radical anion intermediates and it can be considered as general copper mediated nucleophilic aromatic substitution.



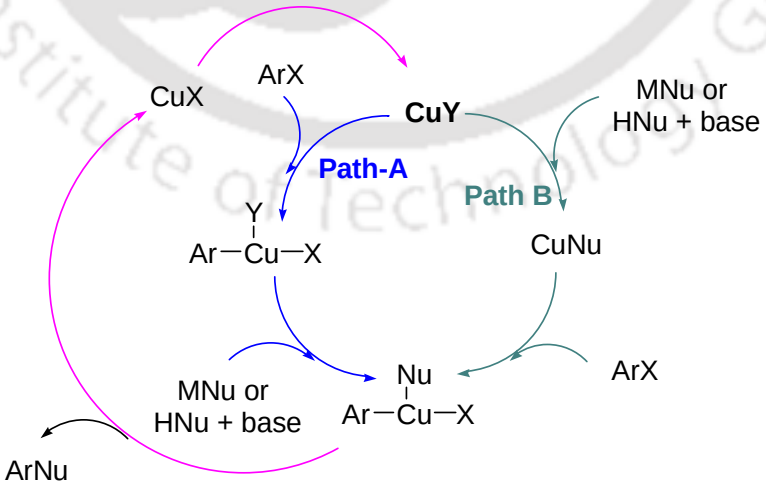
Scheme I.4.1.2.

Litwak and Shen investigated the mechanism of the copper catalyzed reaction of aryl bromide with sodium methoxide. This mechanism involves radical reaction and 4-centered substitution process. The experimental studies revealed that the chloro substitution is far more difficult in copper catalyzed reactions. This is most readily explained by the more diffuse nonbonding electrons of bromine and iodine derivatives which are able to improve the complexation step and the intimate electron transfer step leads to intermediate (*Scheme I.4.1.3.*).



Scheme I.4.1.3.

As can be seen from many examples, copper sources are diverse, but in general, the most universal starting Cu-source is a Cu^{I} or Cu^{II} species. It seems most likely that Cu^{II} is not the catalytic species in the reaction. Furthermore, it has been ascertained that radical mechanisms are ruled out as the reactions are not inhibited by radical scavenger additives.



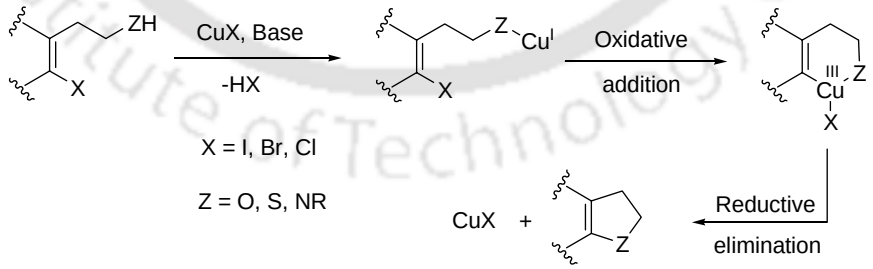
Scheme I.4.1.4.

The role of catalyst is generally believed to take part in successive oxidative addition, transmetallation, and reductive elimination. Unlike Pd-catalyzed cross coupling reactions, in which an oxidative addition step is believed to precede the transmetallation, the order of oxidative addition and transmetallation steps in the copper cycle is unknown. So, after all these considerations, the plausible mechanism for the Ullmann reaction can be either of the two probable pathways as shown in *Scheme I.4.1.4*.

The pathway involved in the transfer of an aryl moiety (R) to heteroatom (Nu) has been rationalized with the following steps.

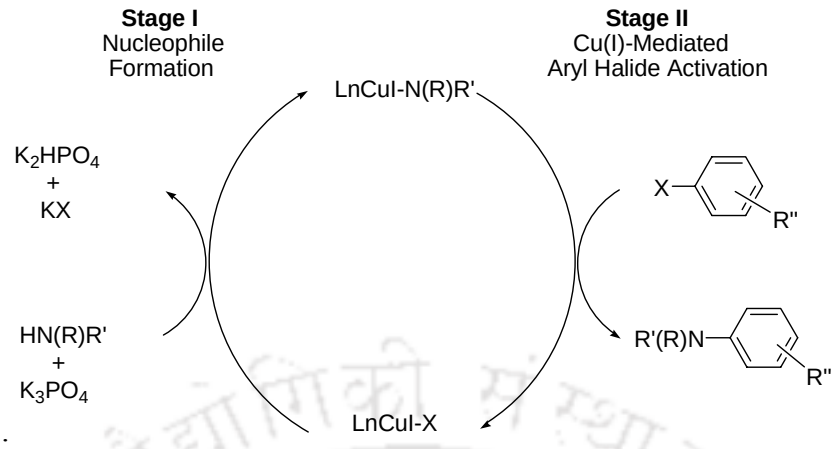
Path A	**Path B**
▪ Oxidative addition ▪ Transmetallation or nucleophilic substitution ▪ Reductive elimination	▪ Transmetallation or nucleophilic substitution ▪ Oxidative addition ▪ Reductive elimination

However, the mechanism for the intramolecular Cu^{I}-catalyzed C-heteroatom bond formation of aryl and vinyl halides with heteroatoms (N, O, S) is believed to proceed as shown in *Scheme I.4.1.5*. Ligand exchange of the heteroatom functional group with the Cu^{I}-ligand provides a new Cu^{I} intermediate that may then undergo oxidative addition into the aryl halide bond, thereby generating a Cu^{III} intermediate. Subsequent reductive elimination provides the target product and regenerates the Cu^{I} catalyst.



Scheme I.4.1.5.

Recently Buchwald *et al.* have studied the mechanistic aspects of catalytic and stoichiometric *N*-arylation of amides. In the context of the catalytic reaction, their findings reveal the importance of chelating diamine ligands in controlling the concentration of the active catalytic species.[13h]



Scheme I.4.1.6.

The consistency between the catalytic and stoichiometric results suggests that the activation of aryl halides occurs through a 1,2-diamine-ligated Cu^{I} amidate complex. Kinetic studies on the stoichiometric *N*-arylation of aryl iodides using 1,2-diamine ligated Cu^{I} amidates also provide insights into the mechanism of aryl halide activation (*Scheme I.4.1.6*.).

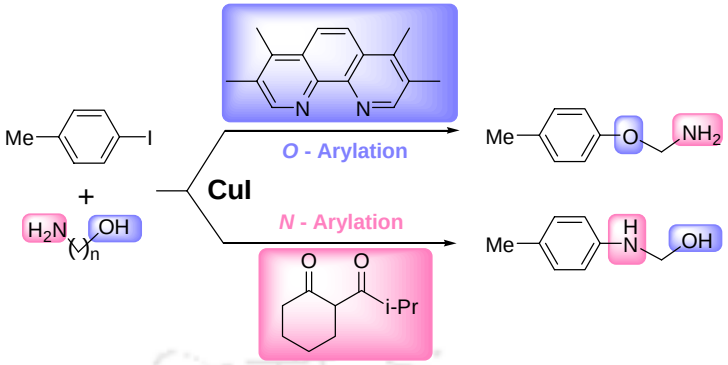
In conclusion, various studies have shown that copper sources of different oxidation states (Cu^{0}-bronze, Cu^{I}, or Cu^{II}) are catalytically active, presumably a result of their conversion into the same active species during the course of reaction. It also seems likely that a Cu^{I}-Cu^{III} redox couple is involved in most of the reactions.

I.4.2. Ligands Used in Cu-Catalyzed Intramolecular Hetero-Arylations

Sevaral ligands are known to promote the copper-assisted coupling reactions. Possible explanations for the ligands effect in Cu-catalysis include

1. Prevents the aggregation of intermediate complexes
2. Improve the solubility of in situ formed complexes
3. Inhibition of catalyst decomposition
4. Prevents multiple ligation with substrates (nucleophiles), a process which might lead to the formation of inactive copper-complexes

Here is an example which describes the tuning of reactivity of a metal catalyst by changing the ligand system. Selective *N* or *O*-arylation can be achieved using 1,3-diketone or phenanthroline based ligands as shown in the scheme shown below.[14]



Scheme I.4.2.1. *Ligand assisted selective N- and O- arylations*

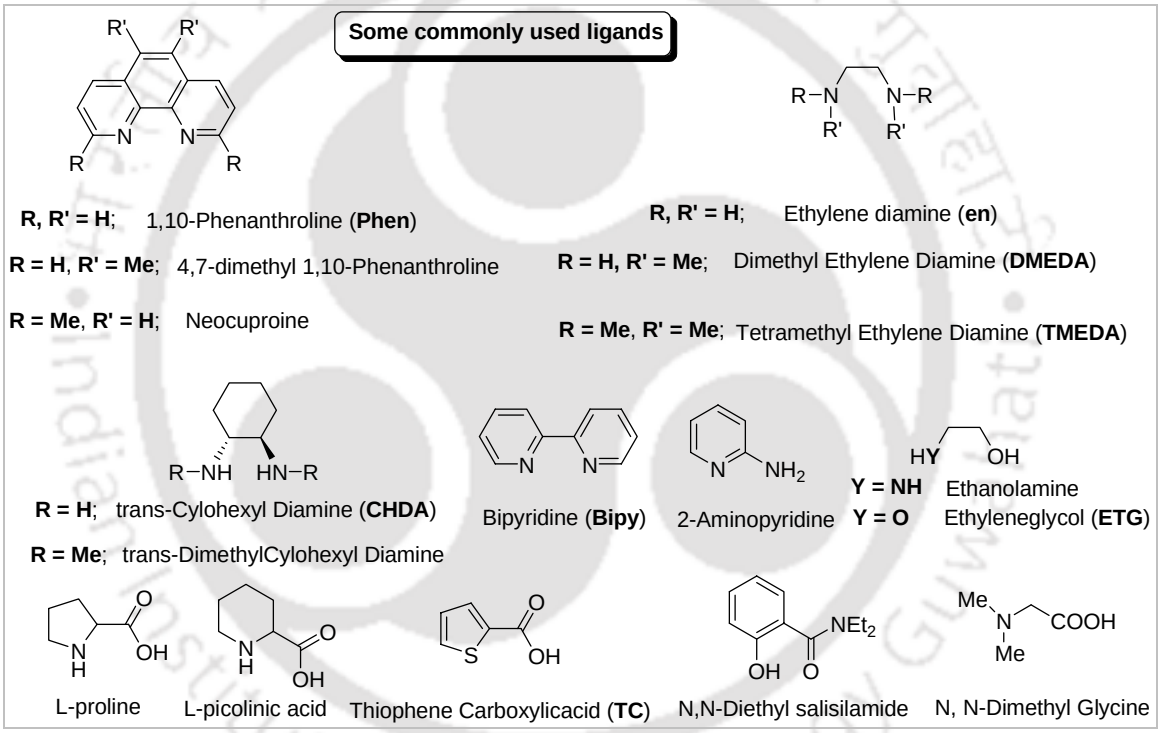
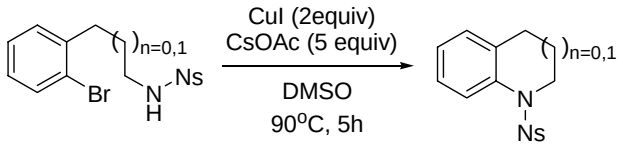


Figure I.4.2.1. *Typical ligands used in Cu-catalyzed hetero-arylations.*

I.4.3. Recent Examples of Cu-Catalyzed Intramolecular Hetero-Arylations

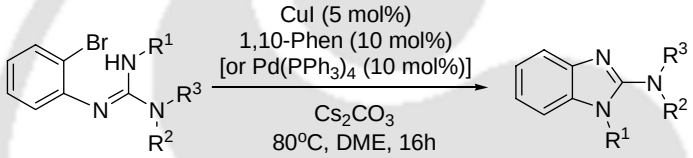
An intramolecular amination of aryl halides was found to be mediated by the combination of copper iodide and cesium acetate. The reaction works well at room temperature with primary or *N*-benzyl amines and at high temperature with other amines. The reaction has been applied to the formation of 5-, 6-, and 7-membered rings. In this

experimental condition halogens at the *meta*-positions are unaffected providing an advantage over palladium-catalyzed systems (*Scheme I.4.3.1.*).[15a]



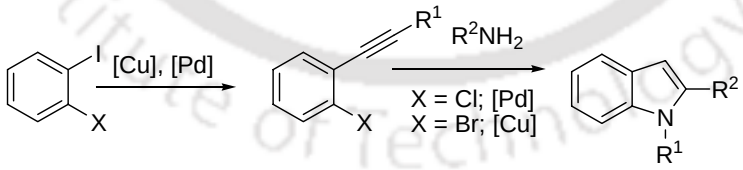
Scheme I.4.3.1.

Batey *et al.* have described an approach for the formation of 2-amino benzimidazoles via an intramolecular C-N bond formation between an aryl halide and a guanidine moiety using either copper or palladium catalysis. Remarkably, inexpensive copper salt CuI is superior to the use of palladium catalysts for this transformation (*Scheme I.4.3.2.*).[15b]



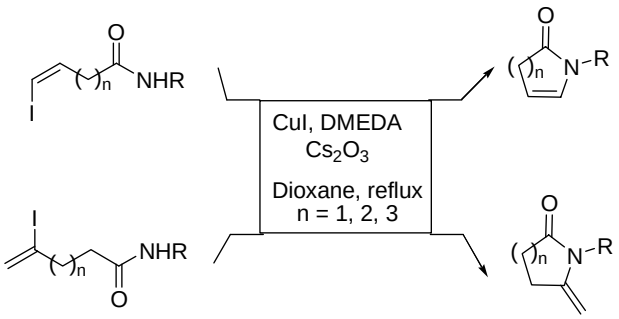
Scheme I.4.3.2.

An efficient synthesis of indoles from *o*-alkynylhaloarenes via a palladium- or a copper-catalyzed amination reaction followed by a subsequent cyclization reaction is achieved by Ackermann *et al.* In addition, a multi-catalytic one-pot indole synthesis starting from *o*-chloroiodobenzene using a single catalyst consisting of an N-heterocyclic carbene palladium complex and CuI has also been described (*Scheme 1.4.3.3.*).[15c]



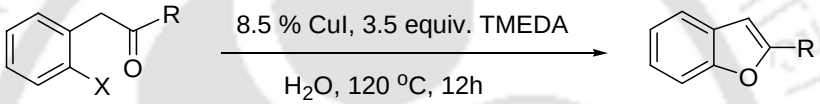
Scheme I.4.3.3.

A ligand assisted copper-catalyzed intramolecular vinylation of iodoenamides is disclosed with CuI as the precatalyst and *N*,*N*'-dimethylethylenediamine (DMEDA) as the ligand. A wide variety of iodoenamides involved in cyclization leads to the formation of five to seven membered lactams **(***Scheme I.4.3.4.*).[15d]



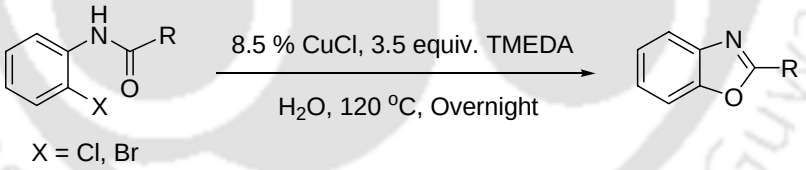
Scheme I.4.3.4.

A general protocol leading to 2-alkyl- or 2-aryl-substituted benzofurans in water was reported by Carril *et al.* involving a Cu-TMEDA complex which catalyzes the transformation of readily available ketone derivatives into the corresponding benzofurans (*Scheme I.4.3.5.*).[15e]



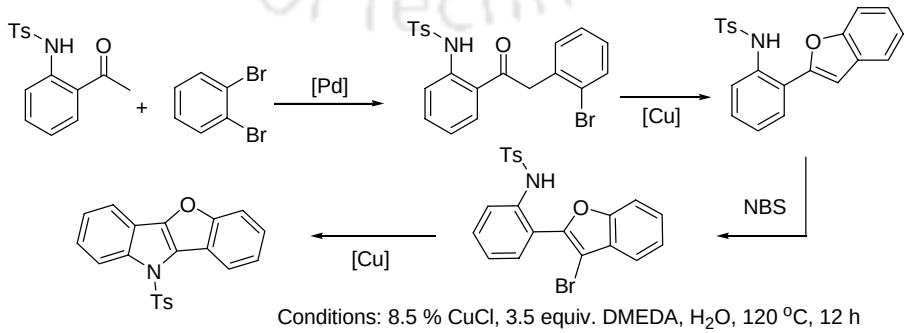
Scheme I.4.3.5.

A copper-catalyzed intramolecular O-arylation of *o*-haloanilides leading to the benzoxazole core is reported. This reaction is performed using aryl chlorides as arylating agents and water as the reaction media (*Scheme I.4.3.6.*).[15f]



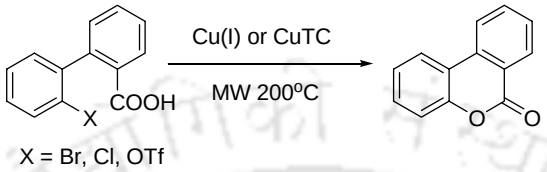
Scheme I.4.3.6.

The synthesis of the benzofuroindole skeleton by Carril *et al.* using a recyclable copper-catalytic system in water is presented in *Scheme I.4.3.7.*[15g]



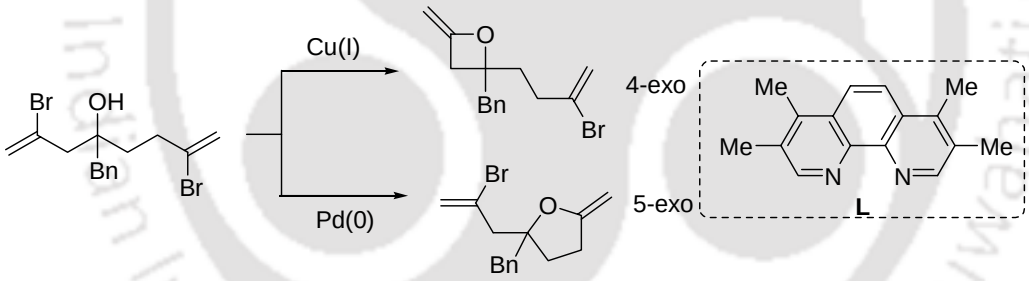
Scheme I.4.3.7.

A simple C-O carboxylic coupling reaction catalyzed by copper(I) salts has been developed to synthesize benzopyranones by Ruchiravat *et al*. Various benzopyranones were synthesized using microwave irradiation. Furthermore, a new class of pyrroloisoquinoline alkaloid, isolamellarin, was also synthesized using this methodology (*Scheme I.4.3.8.*).[15h]



Scheme I.4.3.8.

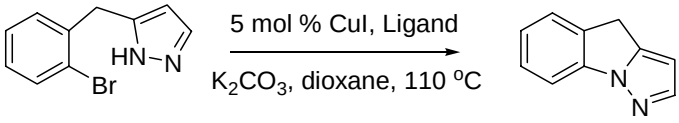
Li *et al.* have reported an uncommon 4-*exo* ring closure in the copper-catalyzed intramolecular *O*-vinylation of bromo homoallylic alcohols leading to the convenient synthesis of 2-methyleneoxetanes. The 4-*exo* mode of ring closure is preferred over other modes (5-*exo*, 6-*exo*, and 6-*endo*) of cyclization. However, this unique selectivity is different from that of palladium catalyzed processes (*Scheme I.4.3.9.*).[15i]



Cu(I)-conditions:10 mol% CuI, 20 mol% L, 2 equiv. Cs_2CO_3, MeCN, reflux

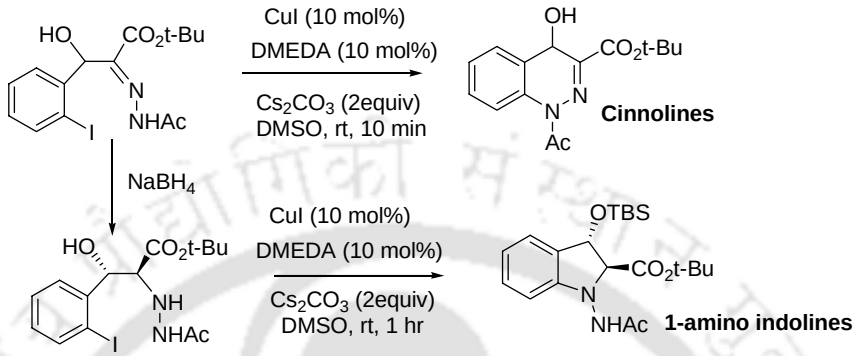
Scheme I.4.3.9.

A variety of pyrazoloindole derivatives were synthesized via Cu(I)-catalyzed intramolecular amination reactions. This method provides a general route for the synthesis of indoles fused with pyrazole rings (*Scheme I.4.3.10.*).[15j]



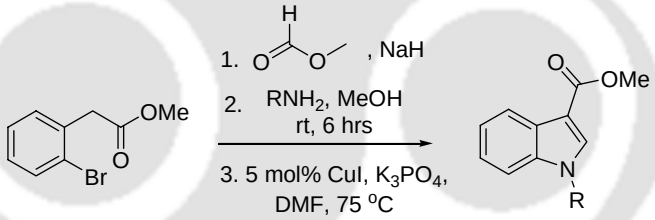
Scheme I.4.3.10.

Nishida *et al.* have demonstrated a facile access to cinnolines, dihydrocinnolines, and 1-aminoindolines by one-pot Cu-catalyzed N-arylation using hydrazines and hydrazones as cyclization precursors derived from 3-haloaryl-3-hydroxy-2-diazopropanoates (*Scheme I.4.3.11.*).[15k]



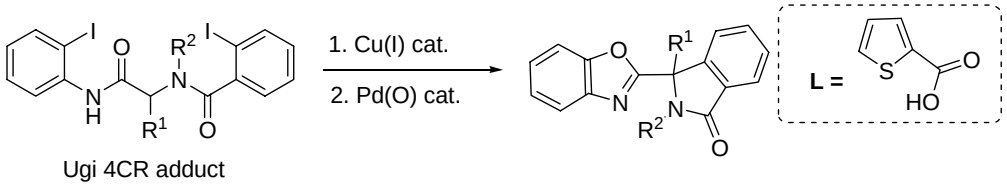
Scheme I.4.3.11.

A variety of N-alkylated and N-arylated derivatives of methyl-1*H*-indole-3-carboxylates were synthesized via Ullmann type intramolecular arylamination, using CuI-K_3PO_4-DMF system. This catalytic amination procedure can be performed under mild conditions in an air atmosphere (*Scheme I.4.3.12.*).[15l]



Scheme I.4.3.12.

Zhu *et al.* have shown that the Ugi-adduct undergoes two consecutive metal-catalyzed intramolecular reactions, namely copper-catalyzed *O*-arylation and palladium-catalyzed *C*-arylation of benzylic carbon to afford benzoxazolylisoindolinones (*Scheme I.4.3.13.*).[15m]

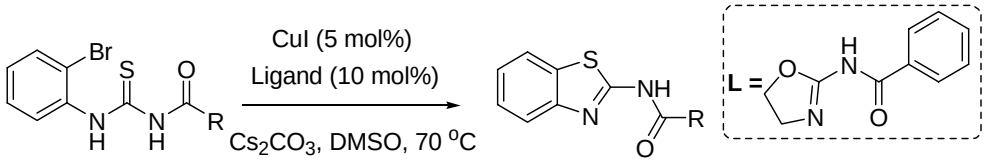


Ugi 4CR adduct

[Cu] conditions: CuI (5 mol %), L (5 mol%), K_2CO_3, DMSO, 120 °C

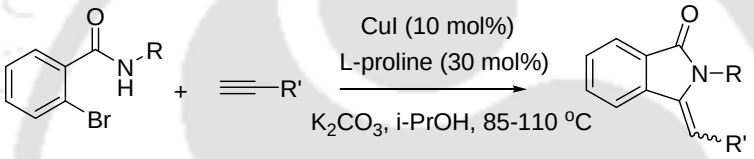
Scheme I.4.3.13.

Pan and coworkers have reported a copper-catalyzed intramolecular cyclization of various substituted 1-acyl-3-(2-bromophenyl) thioureas to yield N-benzothiazol-2-yl-amides using N-(4,5-dihydrooxazol-2-yl) benzamide as the ligand (*Scheme I.4.3.14.*).[15n]



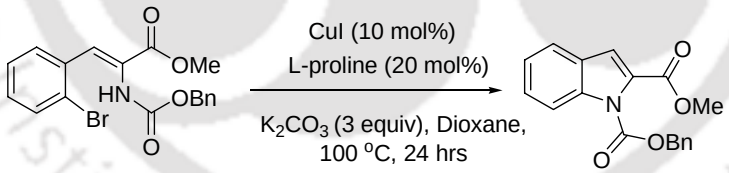
Scheme I.4.3.14.

Recently, Ma group has developed a CuI/L-proline catalyzed coupling/additive cyclization, a domino process for assembling substituted 3-methyleneisoindolin-1-ones from 2-bromobenzamides and terminal alkynes (*Scheme I.4.3.15.*).[15o]



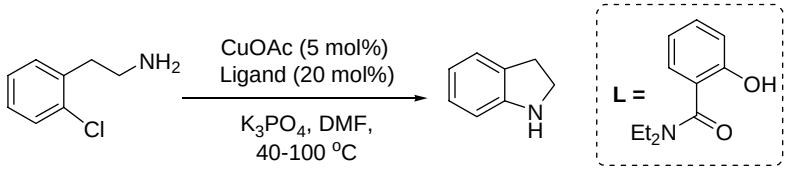
Scheme I.4.3.15.

An amino acid promoted copper-catalyzed coupling of amines with aryl halides has been depicted. This method is applicable for the synthesis of functionalized indoles and pyrrolo[2,3-c]pyridines (*Scheme I.4.3.16.*).[15p]



Scheme I.4.3.16.

Buchwald *et al.* have reported an efficient method for amination of aryl bromides with primary alkylamines using copper-catalytic system that uses commercially available diethylsalicylamide as the ligand. This amination method was extended further for the synthesis of indole derivatives (*Scheme I.4.3.17.*).[15q].

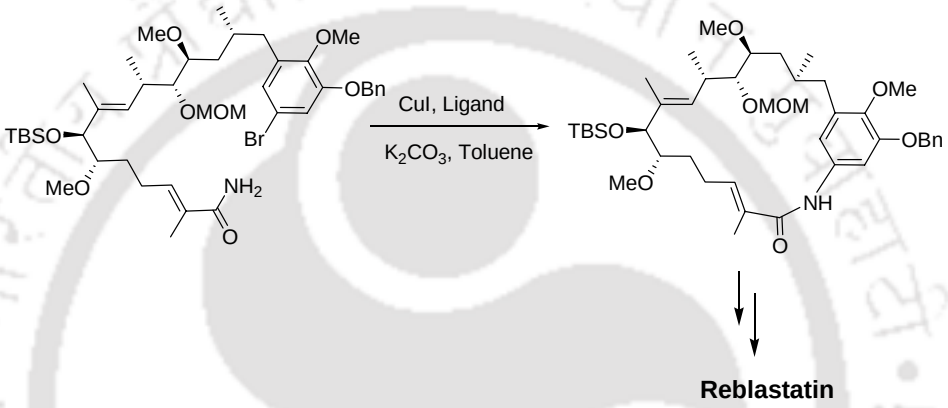


Scheme I.4.3.17.

I.4.4. Application of Copper Catalysis in Total Synthesis of Natural Products and Macrocycles

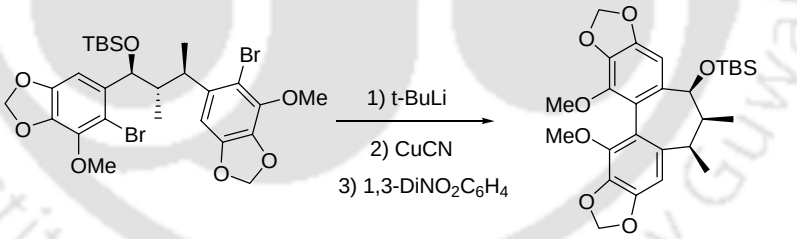
The copper catalyzed systems are not restricted for the synthesis of only a library of heterocyclic compounds but have also been widely used during the total synthesis of various natural and non natural products. Some of the natural and non natural products where they have been used are listed in *Schemes* ***I.4.4.1.*** to ***I.4.4.6.***

1. Synthesis of Reblastatin[16a]



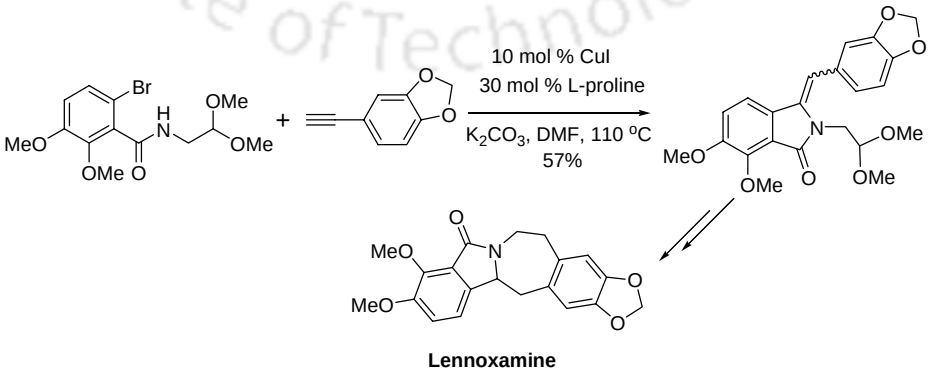
Scheme I.4.4.1.

2. *Synthesis of Dibenzocyclooctadiene Lignans*[16b,c]



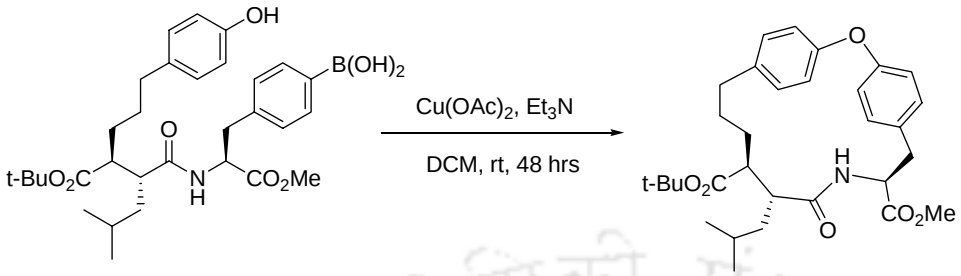
Scheme I.4.4.2.

3. *Synthesis of Lennoxamine*[16d]



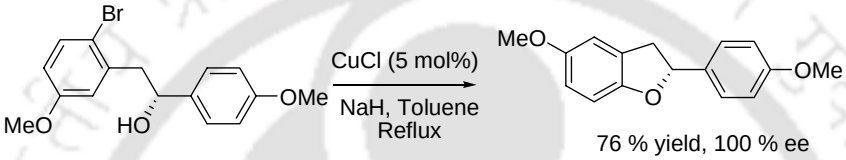
Scheme I.4.4.3.

4. *Synthesis of a Macrocyclic Ether* [16e]



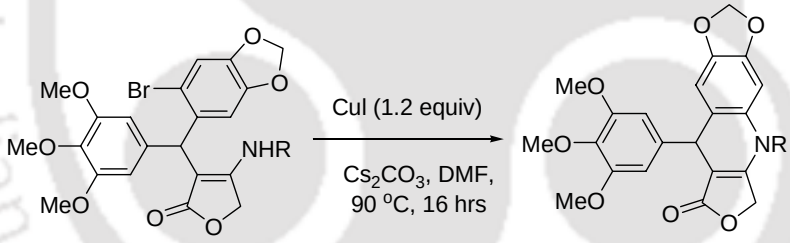
Scheme I.4.4.4.

5. *Assymmetric synthesis of Cosifuran A* [16f]



Scheme I.4.4.5.

6. *Synthesis of aza-Analogues of Podophyllotoxins* [16g]



Scheme I.4.4.6.

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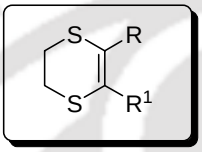
CHAPTER II

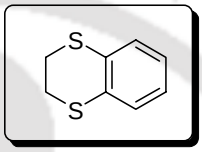
II. Synthesis of 1,4-Dithiins and 1,4-Benzodithiins

II.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I, Section I.1.1, Figure I.1.1.3. in page 3-4. This chapter deals with the following two types of heterocycles namely, dihydro-1,4-dithiins and dihydro-1,4-benzodithiins.



Dihydro-1,4-dithiins



Dihydro-1,4-benzodithiins

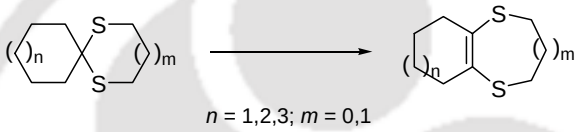
II.2. Importance and Applications

There is a great deal of interest in the chemistry of 1,4-dithiins and 1,4-benzodithiins because of their applications in synthetic organic chemistry and medicinal chemistry.[1] Derivatives of 1,4-dithiins show activities as non peptide antagonists of the human Galanin hGAL-1 receptors.[2a] Benzodithiins, benzoxathiins and benzodioxiins were found to act as estrogen receptor modulators.[2b] Recently it has also been noted that benzodithiins are the new drugs against respiratory syncitial virus (RSV) infections.[2c]

II.2.1. Applications in Organic Synthesis

1,4-Dithiins also serves as an allylic alcohol anion and acyl β-anion equivalents for three carbon homologations.[3a] 1,4-Dithiins have also attracted much attention because of their structural and electronic properties, their ability to act as electron donors and the wide variety of synthetic transformations they undergo.[3b-c] Some 1,4-dithiin derivatives can be metallated with LDA,[3d] BuLi,[3e] *t*-BuOK,[3f] and NaOMe.[3g] Further, the metallated species, when generated, can react in several ways, giving rise to substitution, ring-opening or ring contraction products.[3a-h] 1,4-Dithiins have also been transformed into derivatives of 5,6-dihydro-1,4-dithiin by the reaction of BuLi with various electrophiles.[3i-j] The 5,6-dihydro-

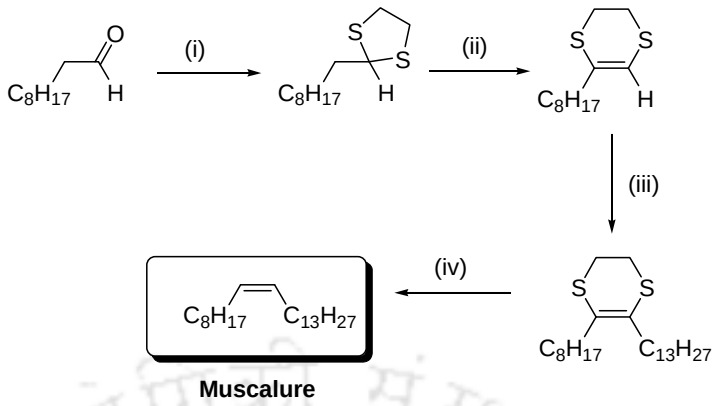
1,4-dithiin moiety has been shown to be a useful synthetic intermediate to mimic *cis* configured double bonds in the preparation of simple alkenes and other unsaturated compounds as well.[3k] Derivatives of 2,3-dihydro-1,4-dithiins are reported to be easily oxidized affording good dienophiles for use in Diels-Alder reactions.[4a] Caputo *et al*. have shown the utility of this approach for generating *cis*-configurated double bonds in the synthesis of sex pheromone (*Z*)-9-tricosene (muscalure),[4b] isolated from the common house fly *Musca domestica L*.[4c] In addition, the ring expansion reactions of 1,3-dithiolanes (m=0) and 1,3-dithianes (m=1) are useful tools for the construction of larger rings containing sulfur atoms, for the 1,2-transposition of carbonyl compounds **(***Scheme II.2.1.1*.).[4d-f]



Scheme II.2.1.1. *Ring expansion of 1,3-dithiolanes and 1,3-dithianes.*

Further, the 1,4-benzodithiin system is useful intermediate for the synthesis of aromatic compounds and for the preparation of organic ferromagnets.[4g] The 1,4-benzodithiin system itself being regarded as an appealing intermediate to obtain, after sulfur removal or replacement, aromatic compounds that cannot be prepared under the usual electrophilic substitution conditions.

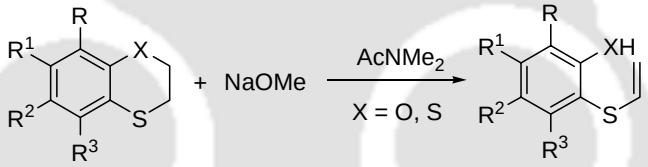
Aldehydes and methyl ketones readily afford 5,6-dihydro-1,4-dithiins that can be converted by BuLi into their corresponding sulfur stabilized carbanions. Coupling of the later with alkyl halides leads to species having a *cis*-disubstituted double bond tied up by the sulfur-containing ring which is known to be susceptible to selective removal. Thus, 2-phenyl-5,6-dihydro-1,4-dithiin was treated with BuLi in THF followed by MeI to give 2-phenyl-3-methyl-5,6-dihydro-1,4-dithiin.[5a] The same method was further extended for the chemo and stereoselective sulfur removal from 5,6-dihydro-1,4-dithiins which completes the pathway to synthesize *cis*-configured olefins from carbonyl compounds. A four step synthesis of (Z)-9-tricosene (muscalure) was achieved where dithiin moiety serving as the penultimate olefin precursor (*Scheme II.2.1.2.*).[5b]



Reaction conditions: (i) $HSCH_2CH_2SH$, AcOH, TsOH, r.t., 60 min; (ii) NBS, dry $CHCl_3$, r.t. 30 min; (iii) BuLi, dry THF, under Ar, -78 ^oC, 15 min.; (iii) $ICH_2(CH_2)_{11}CH_3$, dry THF, under Ar, 0 ^oC, 20 min.

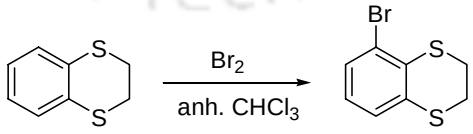
Scheme II.2.1.2. *Synthesis of (Z)-9-tricosene (muscalure).*

2,3-Dihydro-1,4-benzodithiins and 2,3-dihydro-1,4-benzoxathiins react with NaOMe in $AcNMe_2$ to give 1,3-benzodithioles and 2-(vinylthio) phenols and thiophenols (*Scheme II.2.1.3.*).[5c]



Scheme II.2.1.3. *Synthesis of 2-(vinylthio) phenols and thiophenols.*

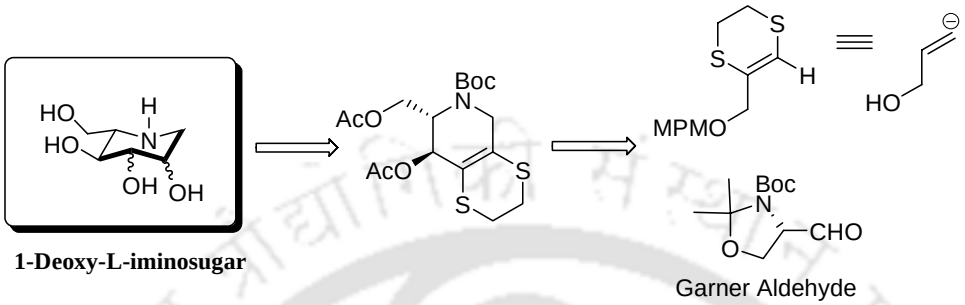
Benzodithiins, when treated with bromine in anhydrous chloroform, undergo very fast monobromination at the aromatic ring (*Scheme II.2.1.4.*). By the use of quantum mechanical semiempirical calculations, the reaction is shown to proceed most likely *via* a vicarious nucleophilic substitution of hydrogen.[5d]



Scheme II.2.1.4. *Vicarious Nucleophilic substitution of hydrogen in 1,4-benzodithiins.*

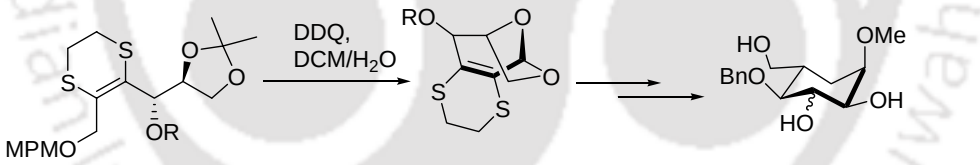
Very recently, Palumbo *et al.* have shown the synthetic utiliy of dithiins as allylic anion equivalents in the synthesis of non-natural imino sugars. A stereoselective procedure

for the preparation of non-naturally occurring deoxy iminosugars belonging to L-series has been developed (*Scheme II.2.1.5.*). The synthesis involves in the construction of the key intermediate bicyclic piperidine, available in few steps by the coupling of heterocyclic synthon 1,4-dithiin and the readily available Garner aldehyde.[6]



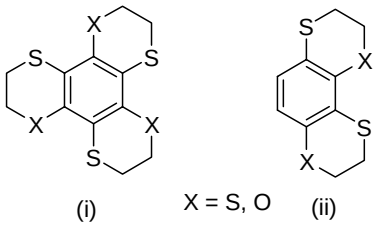
Scheme II.2.1.5. *Retrosyntheic scheme for the synthesis of 1-deoxy-L-iminosugars.*

An expeditious and efficient synthesis of 1,6-anhydro-L-hexopyranosyl derivatives as valuable building blocks for the preparation of L-sugars was reported. (*Scheme II.2.1.6.*). This method relies in the use of a domino reaction involving five synthetic steps from the 5,6-dihydro-1,4-dithiin. Dithioethylene bridge removal and double-bond dihydroxylation give access to protected L-allose and L-glucose in stereoselective fashion.[7]



Scheme II.2.1.6. *Stereoselective synthesis of protected L-allose and L-glucose.*

Benzotris(dithiin) (X=S) (i), benzobis(dithiin) (X=S) (ii), benzotris(oxathiin) (X = O) (i) and benzobis(oxathiin) (X = O) (ii) were prepared in seven steps and are used for the sythesis of organic ferromagnets (*Scheme II.2.1.7.*).[8]



Scheme II.2.1.7. *Benzodithiin derivatives as candidates for the preparation of organic ferromagnets*

II.3. Available Synthetic Methods

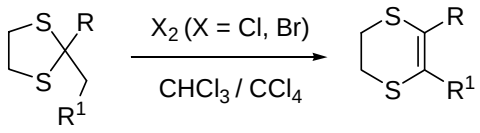
A review of the literature reveals that a little attention has been paid to synthesize these valuable six-membered heterocycles. Most of the reported methods are based on the ring-expansion of 1,3-dithiolanes to their corresponding 1,4-dithiins by various reaction path ways. The reagents and the catalysts employed in the literature are classified into four categories which are summarized below and briefly discussed in the subsequent sections.

II.3.1. Known Methods for the Synthesis of 1,4-Dithiins

- Ring expansion of 1,3-dithiolanes and 1,3-dithianes using electrophilic (thiophilic) reagents such as Br_2, Cl_2, N-substituted succinimides, PhSeCl, Trichloro Triazine, SO_2Cl_2, DBH, IBX, t-BuOCl, SiO_2Cl-DMSO, PTSA (*p*-Toluene sulfonic acid).
- Ring expansion of 1,3-dithiolanes and 1,3-dithianes using metal salts such as WCl_6-DMSO, $TeCl_4$, $MoCl_5$.
- Neutral or acid catalyzed thermal rearrangement of 1,3-dithiolan-1-oxides.
- Miscellaneous methods.

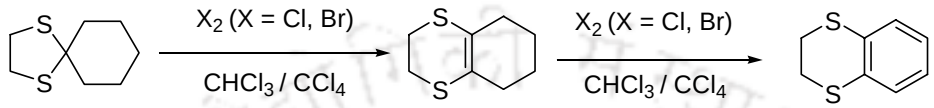
a) Ring Expansions Using Electrophilic Reagents

Caputo *et al.* reported that cyclic thioacetals and thioketals (1,3-dithiolanes) reacts smoothly with halogens such as bromine or chlorine in a 1:1 molar ratio at room temperature in anhydrous carbon tetrachloride giving 2,3-dihydro-1,4-dithiins (*Scheme II.3.1.1.*). The mechanistic aspects of the reaction are considered and evidence is shown of the intermediacy of monocationic rather than the previously postulated dicationic species in the cleavage reactions of 1,3-dithiolanes of aromatic ketones.[9a] In continuation, a one-step synthesis of the same from 1,3-dithiolane has been achieved using Br_2 in $CHCl_3$ or CCl_4. However, replacing Br_2 by Cl_2 leads to satisfactory results giving better yield in shorter reaction time.[9b]



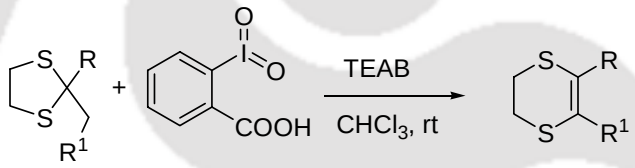
Scheme II.3.1.1.

Ethanediyl S,S-acetal derivatives of cyclohexanone and substituted cyclohexanones were reported to be converted into 1,4-benzodithiins, by concurrent aromatization of the six-membered ring and expansion of the five-membered ring, under treatment with bromine in anhydrous chloroform at room temperature (*Scheme II.3.1.2.*). This conversion represents the first reported synthesis of 1,4-benzodithiins variously substituted at the benzenoid ring.[9c]



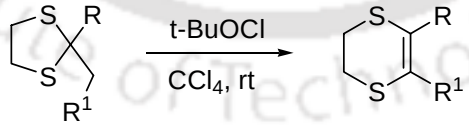
Scheme II.3.1.2.

Akamanchi *et al.* have developed a new method for the ring expansion of 1,3-dithiolanes and 1,3-dithianes to dihydro-1,4-dithiins and dihydro-1,4-dithiepines respectively, using *tert*-butyl hypochlorite at room temperature (*Scheme II.3.1.3*).[9d]



Scheme II.3.1.3.

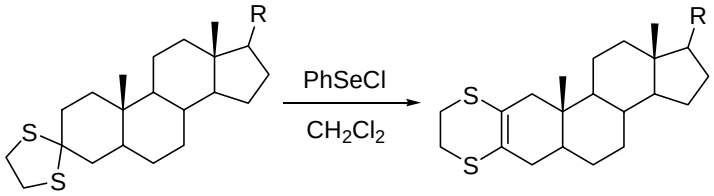
Subsequently, a rapid method for the synthesis of dihydro-1,4-dithiins and dihydro-1,4-dithiepines from the corresponding 1,3-dithiolanes and 1,3-dithianes using hypervalent iodine reagent *o*-iodoxybenzoic acid (IBX) in combination with tetraethylammonium bromide (TEAB) was explored (*Scheme II.3.1.4.*). The salient features of the protocol include mild reaction conditions and short reaction times.[9e]



Scheme II.3.1.4.

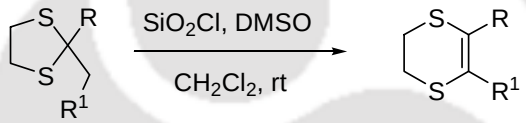
A mild and convenient method for ring expansion of 1,3-dithiolanes and 1,3-dithianes of steroid based carbonyl compounds to dihydro-1,4-dithiins and dihydro-1,4-dithiepins respectively using PhSeCl in CH_2Cl_2 is depicted (*Scheme II.3.1.5.*). A mechanism involving sulphenyl chloride derivatives as intermediates also was proposed.[9f] The same method was applied to steroid enone ethylene dithioacetals with PhSeCl in

CH_2Cl_2 to afford 3,5-dieno[3,4-b](5,6-dihydro-1,4-dithiins) in good yields.[9g]



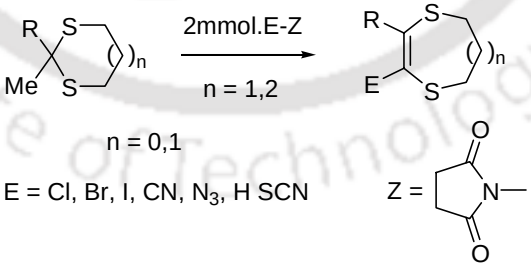
Scheme II.3.1.5.

Silica chloride (SiO_2Cl)/DMSO, as a heterogeneous system, has been efficiently used for deprotection of thioacetals into aldehydes in dry CH_2Cl_2 at room temperature. However, thioketals with enolizable methyl and methylene groups undergo ring-expansion reactions to afford 1,4-dithiepins and 1,4-dithiins (*Scheme II.3.1.6.*).[9h]



Scheme II.3.1.6.

In continuation, Firouzabadi *et al.* have developed a general method for ring expansion/substitution reaction of 1,3-dithiolanes and 1,3-dithianes, generated from different aryl methyl ketones, with different electrophilic reagents (*Scheme II.3.1.7.*). Facile preparation of monohalo-, cyano-, azido-, thiocyanato-1,4-dithiins and -1,4-dithiepins were synthesized and also proposed a general mechanism.[9i]



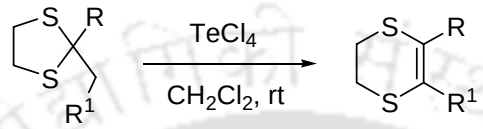
Scheme II.3.1.7.

b) Metal Mediated Ring Expansion Reactions

Tungsten hexachloride (WCl_6) and molybdenum pentachloride ($MoCl_5$) in the presence of DMSO were found to be efficient reagents for the facile deprotection of

thioacetals and one-pot ring-expansion and ring-expansion chlorination of cyclic thioacetals.[10a]

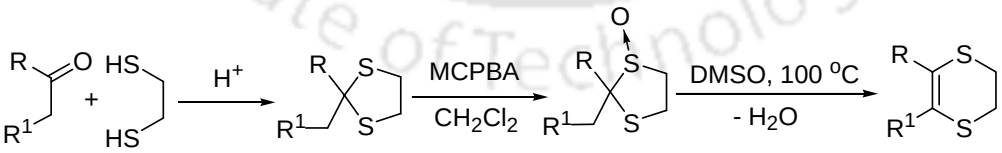
Treatment of five-membered cyclic thioacetals derived from dialkyl or alkyl aryl ketones (1,3-dithiolanes and 1,3-oxathiolanes) underwent facile ring enlargement with $TeCl_4$-CH_2Cl_2 by one carbon atom to dihydro-1,4-dithiins and dihydro-1,4-oxathiins respectively in good to moderate yields (*Scheme II.3.1.8*).[10b-c]



Scheme II.3.1.8.

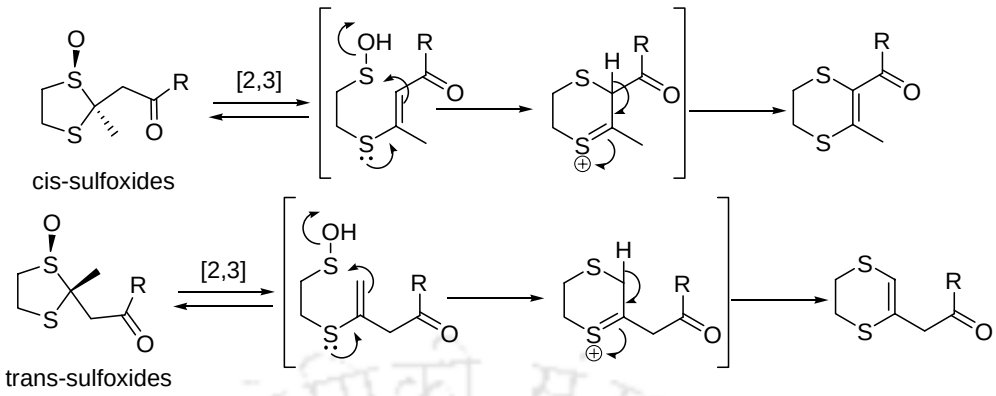
c) Neutral or Acid Catalyzed Thermal Rearrangement of 1,3-Dithiolan-1-oxides

The dithiolane oxides prepared quantitatively from RCH_2COR_1 by successive treatment with 1,2-ethanedithiol and *m*-chloroperbenzoic acid in cold dichloromethane and on heating for 6-72 hr in DMSO or DMF at 100 ^oC giving dihydro-1,4-dithiins in moderate yields (*Scheme II.3.1.9*). The reaction involves [2,3]-sigmatropic rearrangement of dithiolane 1-oxide to generate a sulfenic acid intermediate followed by ring closure through a S-stabilized carbonium ion. In view of the neutral and mild conditions employed in the ring expansion step, this method for preparing the dihydro-1,4-dithiin system from ketones is of considerable synthetic value, since the available procedures are limited, particularly that from the corresponding ketones.[11a] Annelated 5,6-dihydro-1,4-dithiins were also prepared by ring expansion of spiro-1,3-dithiolane 1-oxides, which were generated from the corresponding cyclic ketones.[11b]



Scheme II.3.1.9.

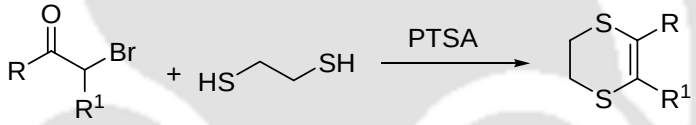
Under neutral conditions *cis*-sulfoxides undergo a sigmatropic rearrangement with 2-methylene hydrogens to give sulfenic acids, followed by cyclization to dihydro-1,4-dithiins. The *trans*-sulfoxides rearranged involving 2-methyl hydrogens to form isomeric dihydrodithiins via sulfenic acids (*Scheme II.3.1.10.*).[11c-d]



Scheme II.3.1.10.

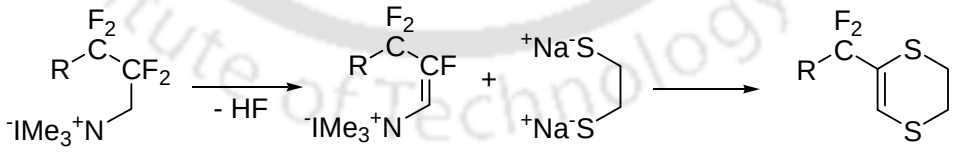
d) Miscellaneous Methods

A novel synthesis of 2,3-mono and disubstituted 5,6-dihydro-l,4-dithiins by treating ethanedithiol with an α-bromo ketone in the presence of *p*-$MeC_6H_4SO_3H$ (PTSA) was reported by Rubinstein *et al.* (*Scheme II.3.1.11.*).[2a-b]



Scheme II.3.1.11.

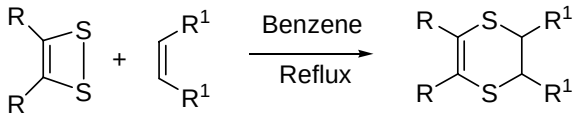
Synthesis of 5-(fluoromethyl)-2,3-dihydro-1,4-dithiins were prepared from $RCF_2CF_2CH_2N^+Me_3I^-$ by dehydrofluorination to give (Z)-$RCF_2CF{:}CHN^+Me_3I^-$ and cyclocondensation reaction with $NaSCH_2CH_2SNa$ (*Scheme II.3.1.12.*).[12c]



Scheme II.3.1.12.

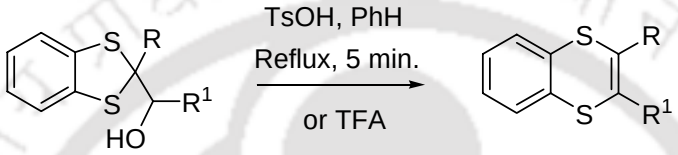
A stereospecific reaction of 3,4-bis(methoxycarbonyl)-1,2-dithiete with various alkenes to afford 2,3-dihydro-1,4-dithiins was reported (*Scheme II.3.1.13.*). This reaction proceeds between ethane-1,2-dithione, the valence isomer of the 1,2-dithiete, and alkenes

via reverse electron demand hetero Diels-Alder reaction and it was proved by experimental as well as theoritical study.[12d]



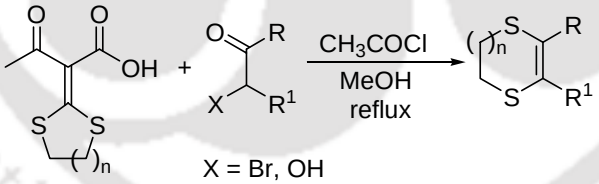
Scheme II.3.1.13.

Suitably substituted benzodithioles on treatment with *p*-toluenesulfonic acid in benzene gave the corresponding benzodithiins (*Scheme II.3.1.14.*).[12e]



Scheme II.3.1.14.

Subsequently, a facile one-step synthesis of substituted 2,3-dihydro-1,4-dithiins and 6,7-dihydro-5H-1,4-dithiepins based on the reactions of α-bromo/hydroxy ketones with α-oxoketene cyclic dithioacetals was developed (*Scheme II.3.1.15.*). Most likely the mechanism for α-bromo ketones is different from that for α-hydroxy ketones although they are finally converted to the same compounds.[12f]

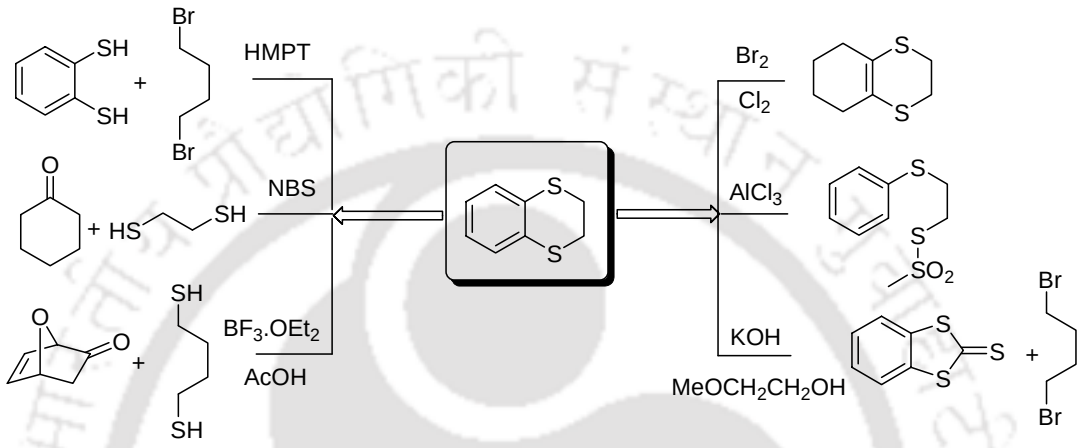


Scheme II.3.1.15.

II.3.2. Known Methods for the Synthesis of 1,4-Benzodithiins

2,3-Dihydro-1,4-benzodithiins and 2,3-dihydro-1,4-benzoxathiins have been synthesized using different reagents and catalysts as shown in *Scheme II.3.2.1.* A one-pot method was developed by the reaction of cyclohexanone derivatives with $HSCH_2CH_2SH$ or $HOCH_2CH_2SH$ in dichloromethane using *N*-bromosuccinimide at 0 ^oC.[13a] 4-Aryl(or heteroaryl)-5-heterosubstituted 1,2,3-thiadiazoles on heating in the presence of sodium hydride undergo ring opening with nitrogen elimination followed by recyclization to form

the corresponding 1,4-benzoxathiins and 1,4-benzodithiins.[13b] Benzo-1,4-dithiin and benzo-1,4-oxathiin were prepared by treating PhXNa with $Br(CH_2)_2Br$ to give $PhXCH_2CH_2Br$, reacting the later with $MeSO_2SK$ to give $PhXCH_2CH_2SSO_2Me$, cyclizing the methylsulfonylthio compound in the presence of $AlCl_3$ to afford dihydro benzodithiin or benzoxathiin.[13c]



Scheme II.3.2.1.

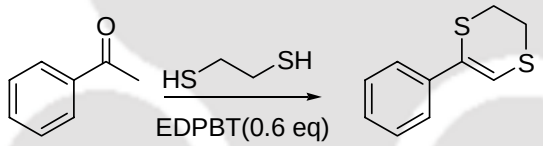
II.4. Present Work

II.4.1. One-pot Synthesis of 1,4-Dithiins and 1,4-Benzodithiins from Ketones Using 1,1'-(Ethane-1,2-diyl)Di-Pyridinium Bis-Tribromide (EDPBT).

In continuation to our interest in the chemistry of cyclic thioacetals and the use of tribromides, we have further explored the chemistry of 1,4-dithiins and 1,4-benzodithiins because of their wide applications in medicinal chemistry, material chemistry and synthetic organic chemistry in particular as discussed above. We have been utilizing tetrabutylammonium tribromide (TBATB) for bromination[14] and for various other organic transformations.[15] Recently we have synthesized a new ditribromide reagent, 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) which is superior to all known tribromides and has several advantages over molecular bromine and other tribromides.[16a] In addition to

acting as an excellent brominating agent, it has been utilized as a catalyst for the acylation of alcohols[16b] and for the synthesis of various 2-iminothiazoline derivatives.[16c] Although methods have been reported for the ring expansion of 1,3-dithiolanes and a few for ring expansion combined with aromatization, no method has been reported directly from ketones.

In spite of the several methods available in the literature, some of the procedures suffer due to the use of expensive and toxic reagents, difficulty in handling and longer reaction times. Moreover, all the reported procedures involve two steps and the synthesis usually starts from the 1,3-dithiolane. Earlier we reported the thioacetalization of various carbonyl compounds using a catalytic quantity of tetrabutylammonium tribromide (TBATB). We have utilized the acidic properties of EDPBT for the thioacetalization of carbonyl compounds followed by ring expansion of the in situ generated thioacetal to give 1,4-dithiins in one-pot (*Table II.4.1.1.*) (*Scheme II.4.1.1.*).



Scheme II.4.1.1.*Formation of 1,4-dithiins from the corresponding ketones.*

In an initial reaction acetophenone **1** (5 mmol) was treated with 1,2-ethanedithiol (5.5 mmol), and a catalytic quantity of EDPBT (0.5 mmol) in acetonitrile (10 mL) and stirred for 0.5 hrs. During this time acetophenone was converted to the corresponding 1,3-dithiolane. Although the rate of 1,3-dithiolane formation for different ketones is different, we maintained a uniform time of 0.5 hrs for all the substrates. To the reaction mixture a further quantity of EDPBT (2.5 mmol) was added and stirring continued for 15 min. The desired ring expanded product, 1,4-dithiin 1a was isolated in good yield. The structure of 1a was unambiguously confirmed by single crystal X-ray diffraction analysis as shown in *Figure II.4.1.1.* It should be mentioned here that when a similar reaction was performed with the 1,3-dithiane of ketones using methyltriphenylphosphonium tribromide deprotection of the ketone without ring expansion has been reported.[17]

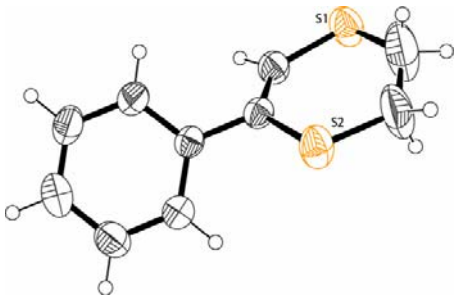
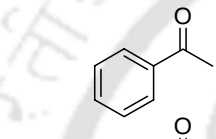
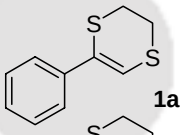
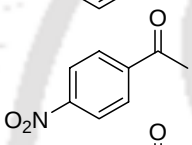
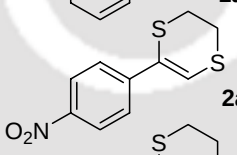
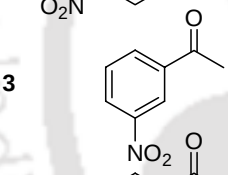
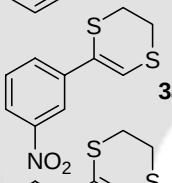
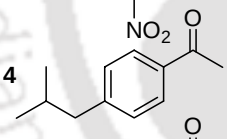
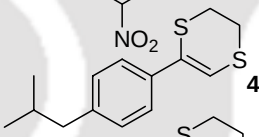
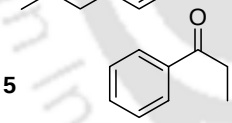
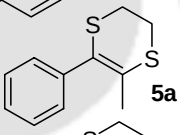
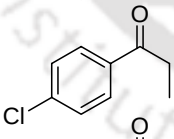
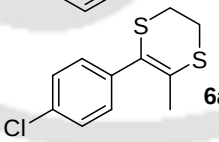
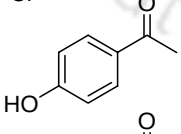
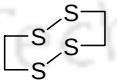
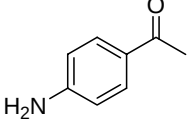
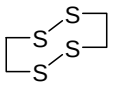
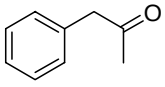
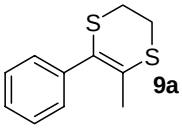
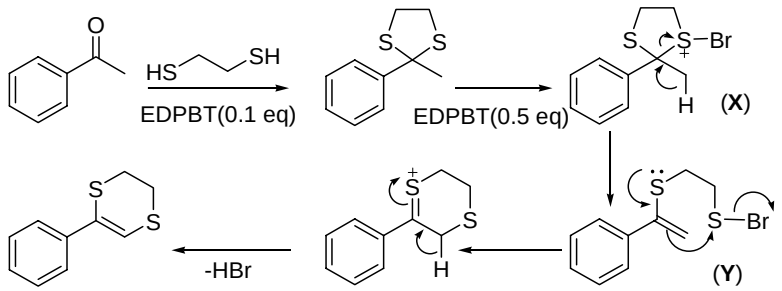


Figure II.4.1.1. *ORTEP molecular diagram with ellipsoid at 50% probability of* ***1a****.*

Table II.4.1.1. *Formation of 1,4-Dithiins from Ketones.*[a]

Entry	Substrate	Product[b]	Time (min)[c]	Yield (%)[d]
1		 **1a**	15	85
2		 **2a**	25	72
3		 **3a**	25	68
4		 **4a**	30	75
5		 **5a**	20	73
6		 **6a**	30	78
7		 **7a** + **7**	25	55 + 92
8		 **7a** + **8**	25	58 + 91
9		 **9a**	20	73

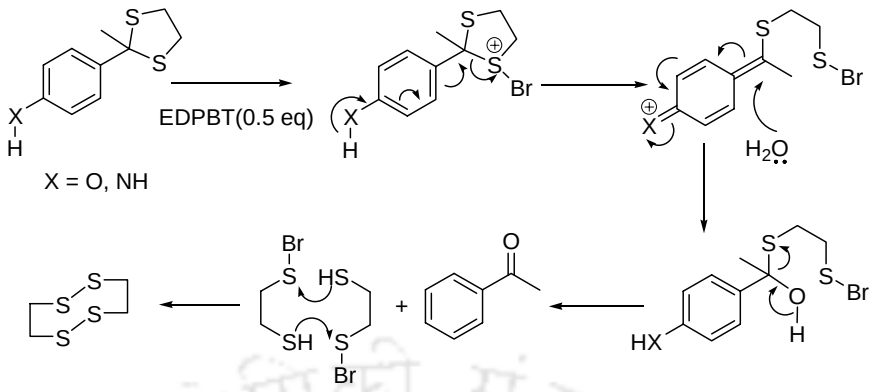
[a]Reactions were monitored by TLC. [b]Products were characterized by IR, ^{1}H and ^{13}C NMR. [c]An additional 0.5 h for 1,3-dithiolane formation in the first step was required. [d]Yield of isolated product.



Scheme II.4.1.2. *Mechanism for the formation of 1,4-dithiins.*

A plausible mechanism for the ring expansion is proposed in *Scheme II.4.1.2.* The first step of the reaction consists of 1,3-dithiolane formation.[18] Consumption of a further equivalent of bromine forms bromosulphonium ion (**X**). The bromosulphonium ion (**X**) loses a molecule of HBr forming sulphanyl vinylbenzene intermediate (**Y**). Finally intramolecular nucleophilic attack leads to the desired product. This method was successfully applied to *p*-nitroacetophenone **2** and *m*-nitroacetophenone **3** both of which gave the corresponding ring expanded 1,4-dithiins **2a** and **3a** respectively in good yields (*Table II.4.1.1.*). 4-Isobutylacetophenone **4** gave 1,4-dithiin **4a** under identical conditions. Propiophenone **5** and *p*-chloropropiophenone **6** yielded the ring expanded products **5a** and **6a**, respectively. However, when the reaction was performed with *p*-hydroxyacetophenone **7** and *p*-aminoacetophenone **8**, the ring expanded products were not obtained, instead the starting materials along with [1,2,5,6]-tetrathiocane were obtained. The formation of [1,2,5,6]-tetrathiocane is not due to oxidation of 1,2-ethanedithiol.

In the first step of the reaction of *p*-hydroxy and *p*-amino acetophenones with 1,2-ethanedithiol both were consumed forming the corresponding 1,3-dithiolanes. We have theoritically,[19a] as well as experimentally,[19b] proven that the presence of an electron donating substituent (OH, NH_2) on the aromatic ring favors thioacetalization. Thus, recovery of the starting ketones **7** and **8** along with the formation of [1,2,5,6]-tetrathiocane can be explained by the following mechanism (*Scheme II.4.1.3.*). Due to the presence of OH and NH_2 substituents in the para position of the aromatic ring, the quinone formation pathway is more favored over proton abstraction returning the carbonyl compound along with [1,2,5,6]-tetrathiocane.

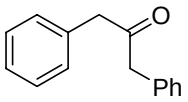
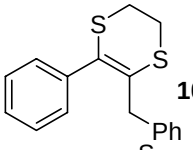
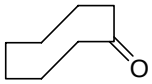
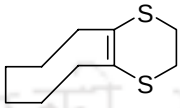
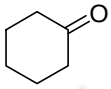
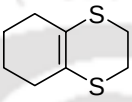
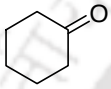
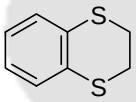
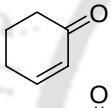
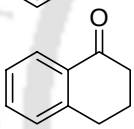
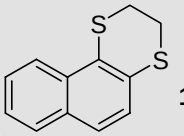
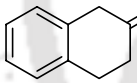
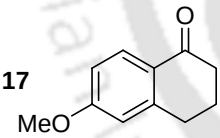
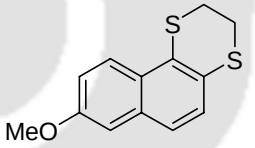


Scheme II.4.1.3. *Proposed pathway for the regeneration of carbonyl compounds.*

For ketones **1-6**, formation of the intermediate **Y** (*Scheme II.4.1.2.*) occurs via elimination of a methyl proton associated with C-S bond cleavage. In the case of phenylacetone (**9)** where the carbonyl group is flanked by a methyl and a methylene group, proton abstraction occurs from the methylene carbon because of its higher acidity, ultimately leading to the regioselective product **9a**. Symmetrical ketones such as dibenzyl ketone **10**, cyclooctanone **11** and cyclohexanone **12** were smoothly converted to 1,4-dithiins **10a**, **11a** and **12a**, respectively, with 0.6 equivalents of EDPBT (*Table II.4.1.2.*). Cyclohexanone **12** was reacted with 1.6 equivalents of EDPBT, it was converted to the 1,4-dithiin derivative with concomitant aromatization of the cyclohexane ring, thus affording the valuable 1,4-benzodithiin heterocyclic ring system **12b**. In this transformation a total of three bromine equivalents is needed, one equivalent for the 1,4-dithiin ring formation and two equivalents for aromatization of the cyclohexane ring system as shown in *Scheme II.4.1.4.* Literature revealed a few such ring expansions associated with aromatization, all starting from the corresponding 1,3-dithiolanes only.[20]

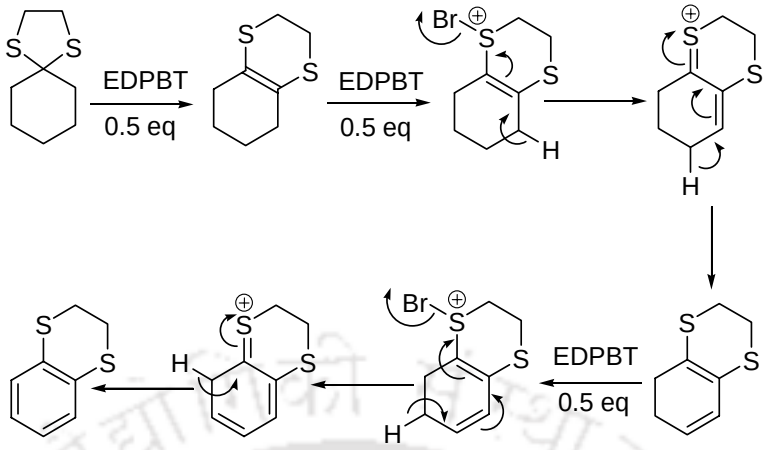
The first step of the 1,4-benzodithiin synthesis consists of the formation of dihydro-1,4-dithiin **12a** with the consumption of 1 equivalent of bromine, i.e 0.5 equivalents of **EDPBT** followed by two subsequent electrophilic attacks by bromine at one of the sulphur atoms with two sequential losses of HBr.

Table II.4.1.2. *Formation of 1,4-Dithiins and 1,4-Benzodithiins from Ketones*[a]

Entry	Substrate	Product[b]	Time (min)[c]	Yield (%)[d]
10		 **10a**	30	69
11		 **11a**	40	63
12		 **12a**	40	62
13		 **13a**	60	70[e]
14			60	73[f]
15		 **14a**	60	75
16			60	67
17		 **15a**	60	72

[a]Reactions were monitored by TLC. [b]Products were characterized by IR, ^{1}H and ^{13}C NMR. [c]An additional 0.5 h for 1,3-dithiolane formation in the first step was required. [d]Yield of isolated product. [e]1.6 equivalents of EDPBT was used. [f] 1.1 equivalents of EDPBT was used.

This process is associated with aromatization leading to **12b**. Benzodithiin **12b** was also obtained from cyclohexenone **13** with just 1.1 equivalents of EDPBT suggesting the requirement of two bromine equivalents for complete aromatization as proposed in *Scheme II.4.1.4.* Both α-tetralone **14** and β-tetralone **15** were converted to the same naphtho-1,4-dithiin **14a**. In the later case, proton abstraction occours from the benzylic carbon which is more acidic, where as in the former proton abstraction occours from the only available β-carbon. Finally, 6-methoxytetralone **16** was converted in to naphtho-1,4-dithiin derivative **16a**. The single crystal X-ray structure of **16a** is shown in *Figure II.4.1.2.*



Scheme II.4.1.4. Mechanism for the formation of 1,4-benzodithiins.

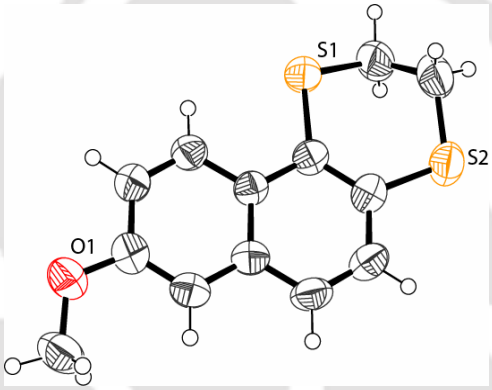


Figure II.4.1.2. *ORTEP molecular diagram with ellipsoid at 50% probability of* ***16a***.

In conclusion, we have developed a one-pot transformation of acyclic ketones to 1,4-dithiins and cyclic ketones to 1,4-benzodithiins/1,4-naphthodithiins using the recyclable reagent, 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). This method is simple, convenient, mild, and environmentally benign. An interesting aspect of this method is the EDPBT acts as promoter in the formation of 1,3-dithiolane and as a reagent in the ring expansion step. The spent reagent can be recovered, regenerated and reused.[21]

II.5. Experimental Section

II.5.1. Instrumentation and Characterization

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Gas liquid chromatography was performed using HP 6890 series II instrument and using, a cross linked methyl silicon gum capillary column (30m x 0.32mm x 0.25μm) fitted with FID, and quantification was done using HP integrator.

Melting points were recorded with a Büchi B-540 melting point apparatus. Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Fourier transform-infra red (FT-IR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pellets. Fast atom bombardments (FAB) mass were recorded using a JEOL SX-120/DA-6000 instrument using argon (6KV, 10mA) as the FAB gas. GC-MS were recorded using a capillary column (30 X 0.25 mm X 0.25 mμ) in EI mode. NMR spectra were recorded in $CDCl_3$ or [D_6] DMSO with tetramethylsilane as the internal standard for ^1H (200, 300 and 400 MHz) or $CDCl_3$ or [D_6] DMSO solvent as the internal standard for ^{13}C (50, 75 and 100 MHz). Crystal Data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

II.5.2. General Procedure for the Synthesis of 1,4-dithiins

In to a solution of carbonyl compound (5 mmol) in acetonitrile (10 mL) and 1,2-ethanedithiol (5.5 mmol) was added EDPBT (0.5 mmol). The reaction mixture was stirred at room temperature. After stirring for 30 min, an additional 2.5 mmol of EDPBT was added to the reaction mixture and stirring continued at room temperature. The reaction progress was monitored by TLC. After completion of the reaction, acetonitrile was evaporated and the reaction was quenched by adding saturated $NaHCO_3$ solution and the product was extracted with ethyl acetate (2 x 25 mL). The organic layer was separated and dried over anhydrous sodium sulfate and concentrated. Further purification was accomplished by column chromatography over a short column of silica gel using a mixture of hexane and ethylacetate as eluent. The aqueous layer containing spent reagent was kept for regeneration.

II.5.3. General Procedure for the Synthesis of 1,4-Benzodithiins

Similar to the above procedure for 1,4-dithiins (II.5.2.), except 1.6 equivalents of EDPBT for 1 equiv. of cyclohexanone and 1.1 equivalents of EDPBT for 1 equiv. of tetralone were used.

II.6. References

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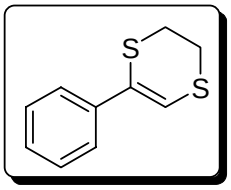
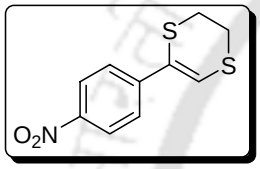
II.7. Spectral Data

2,3-Dihydro-5-phenyl-1,4-dithiine (1a):



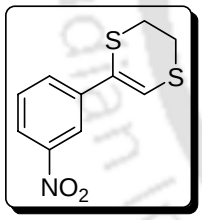
^{1}HNMR (400 MHz, $CDCl_3$): δ 3.23 (m, 2H), 3.30 (m, 2H), 6.37 (s, 1H), 7.32 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.0, 28.0, 112.4, 125.8, 127.6, 127.9, 128.3, 140.1; **IR** (KBr): 3055, 3021, 2920, 1588, .1551, 1487, 1429, 1281, 923, 749, 695 cm^{-1}; **Mass** (CI): 194 (M^+).

2,3-Dihydro-5-(4-nitrophenyl)-1,4-dithiine (2a):



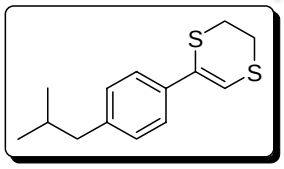
^{1}HNMR (400MHz, $CDCl_3$): δ 3.29 (m, 4H), 6.63 (s, 1H), 7.55 (d, 2H, *J* = 8.8Hz,), 8.14 (d, 2H, *J* = 8.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 27.4, 27.5, 117.6, 123.9, 126.1, 146.1, 146.7; **IR** (KBr): 3071, 2873, 1588, 1506, 1336, 1103, 945, 816, 743, 682 cm^{-1}; **Mass** (CI): 239 (M^+).

2,3-Dihydro-5-(3-nitrophenyl)-1,4-dithiine (3a):



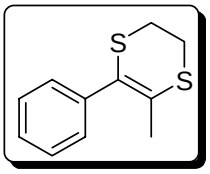
^{1}HNMR (400 MHz, $CDCl_3$): δ 3.27 (m, 2H), 3.32 (m, 2H) 6.54 (s, 1H), 7.30 (d, 1H, *J* = 8.0 Hz), 7.47 (t, 1H, *J* = 8.0 Hz), 7.80 (d, 1H, *J* = 8.0 Hz), 8.28 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.3, 27.7,116.0, 120.8, 122.3, 125.6, 129.4, 131.6, 141.8, 148.8; **IR** (KBr): 3054, 2876, 1591, 1504, 1321, 1218, 1109, 934, 815, 743, 682 cm^{-1}; **Mass** (EI): 239 (M^+).

2,3-Dihydro-5-(4-isobutylphenyl)-1,4-dithiine (4a):



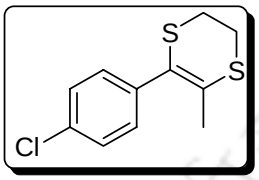
^{1}HNMR (400 MHz, $CDCl_3$): δ 0.88 (d, 6H, *J* = 6.4 Hz), 1.83 (m, 1H), 2.44 (d, 2H, *J* = 7.2 Hz), 3.20 (m, 2H), 3.27 (m, 2H), 6.33 (s, 1H), 7.06 (d, 2H, *J* = 8 Hz,), 7.31 (d, 2H, *J* = 8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.7, 27.1, 28.3, 30.5, 45.3, 111.8, 125.6, 128.1, 129.2, 137.7, 141.5; **IR** (KBr): 3021, 2953, 2921, 2867, 1567, 1546, 1504, 1464, 1412, 1286, 1168, 1121, 929, 847, 776 cm^{-1}; **Mass** (CI): 246 (M^+).

2,3-Dihydro-5-methyl-6-phenyl-1,4-dithiine (5a = 9a):



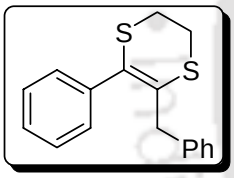
^{1}HNMR (400 MHz, $CDCl_3$): δ 1.81 (s, 3H), 3.27 (s, 4H), 7.26 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 22.2, 29.4, 29.5, 120.1, 122.3, 127.4, 128.1, 129.4, 139.7; **IR** (KBr): 3057, 3027, 2919, 2853, 1598, 1481, 1441, 1416, 1287, 1119, 1072, 925, 745, 701 cm^{-1}; **Mass** (CI): 208 (M^+).

2-(4-Chlorophenyl)-5,6-dihydro-3-methyl-1,4-dithiine (6a):



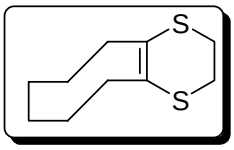
^{1}HNMR (400MHz, $CDCl_3$): δ 1.83 (s, 3H), 3.28 (s, 4H), 7.21 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 22.4, 29.5, 29.8, 121.2, 121.3, 128.5, 131.0, 133.5, 138.4; **IR** (KBr): 3049, 2921, 2853, 1586, 1486, 1441, 1416, 1395, 1287, 1236, 1119, 1084, 1015, 829, 775 cm^{-1}; **Mass** (CI): 243 (M^+).

2-Benzyl-5,6-dihydro-3-phenyl-1,4-dithiine (10a):



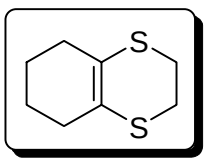
^{1}HNMR (400 MHz, $CDCl_3$): δ 3.21 (m, 2H), 3.26 (m, 2H), 3.48 (s, 2H), 7.17 (m, 5H), 7.28 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 29.8, 30.3, 41.4, 124.0, 126.4, 127.9, 128.3, 128.5, 128.6, 128.8, 129.7, 139.2, 139.7; **IR** (KBr): 3061, 3027, 2926, 2854, 1600, 1529, 1495, 1453, 1349, 1073, 962, 761, 698 cm^{-1}; **Mass** (CI): 284 (M^+).

2,3,5,6,7,8,9,10-Octahydrocycloocta[b][1,4]dithiine (11a):



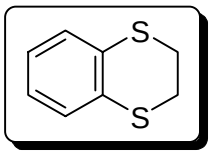
^{1}HNMR (400MHz, $CDCl_3$): δ 1.49 (m, 4H), 1.59 (m, 4H), 2.32 (t, 4H, *J* = 6.4 Hz), 3.14 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 26.6, 29.5, 30.1, 34.32, 112.5; **IR** (KBr): 2919, 2848, 1603, 1464, 1445, 1413, 1286, 1141, 1024, 927, 886, 832, 741 cm^{-1}; **Mass** (CI): 200 (M^+).

2,3,5,6,7,8-Hexahydrobenzo[b][1,4]dithiine (12a):



^{1}HNMR (400 MHz, $CDCl_3$): δ 1.68 (m, 4H), 2.10 (m, 4H), 3.16 (s, 2H), 3.27 (d, 2H, *J* = 5.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.4, 26.3, 38.4, 131.2; **IR** (KBr): 2930, 2853, 1614, 1450, 1281, 1189, 1025, 774, 707cm^{-1}; **Mass** (CI): 172 (M^+).

2,3-Dihydrobenzo[b][1,4]dithiine (13a):

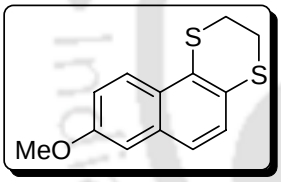


^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (m, 4H), 6.96 (m, 2H), 7.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.6, 125.2, 128.8, 131.5; **IR** (KBr): 3054, 2921, 1583, 1556, 1455, 1422, 1290, 1250, 1105, 872, 746 cm^{-1}; **Mass** (CI): 168 (M^+).

2,3-Dihydronaphtho[2,1-b][1,4]dithiine (14a):

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (m, 2H), 3.36 (m, 2H), 7.23 (d, 1H, *J* = 8 Hz), 7.50 (m, 3H), 7.73 (d, 1H, *J* = 8 Hz), 8.17 (d, 1H, *J* = 8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.9, 30.1, 122.5, 125.0, 125.4, 126.5, 126.9, 127.1, 128.4, 129.0, 131.5, 132.1; **IR** (KBr): 3042, 3008, 2915, 2856, 1604, 1552, 1494, 1388, 1349, 1053, 942, 838, 825 cm^{-1}; **Mass** (CI): 218 (M^+).

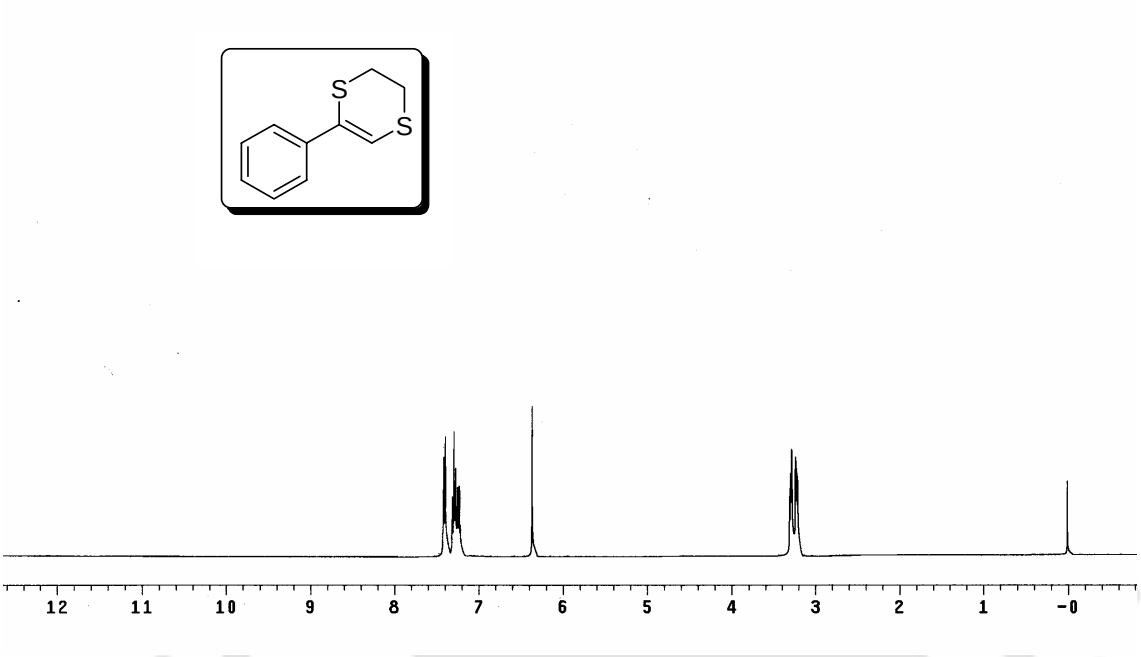
2,3-Dihydro-8-methoxynaphtho[2,1-b][1,4]dithiine (15a):



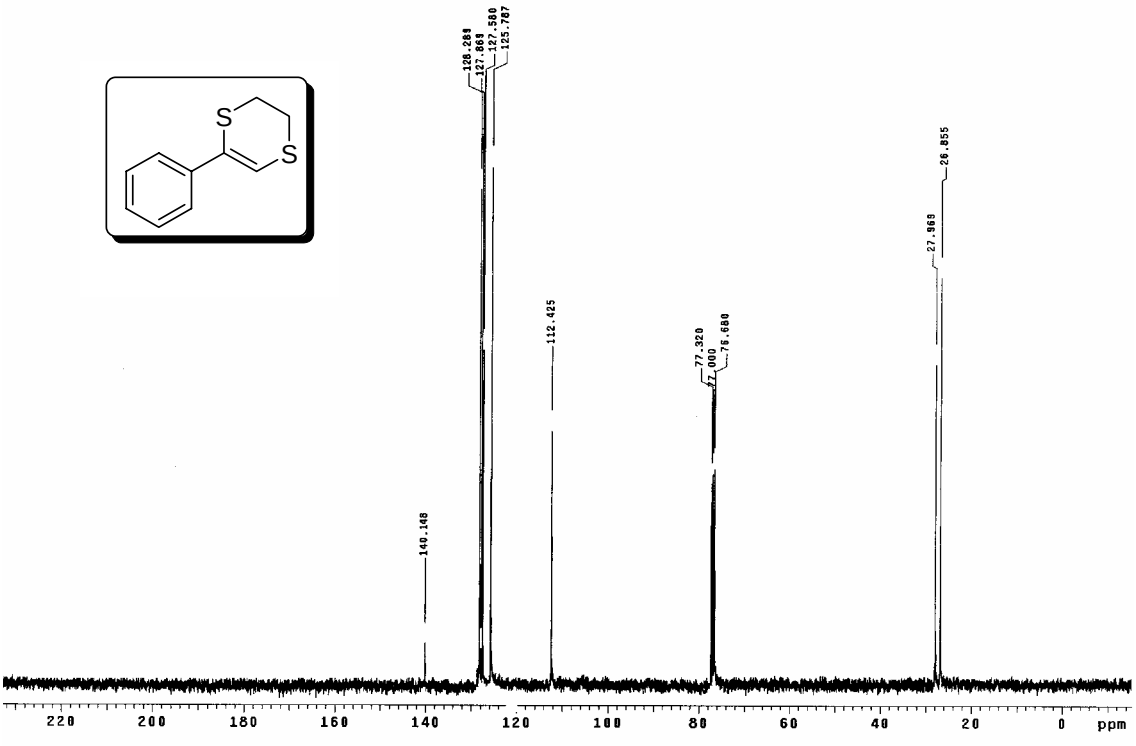
^{1}HNMR (400 MHz, $CDCl_3$): δ 3.35 (m, 4H), 3.90 (s, 3H), 7.05 (s, 1H), 7.16 (m, 2H), 7.39 (d, 1H, *J* = 8.8 Hz), 8.05 (d, 1H, *J* = 9.2 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 29.5, 30.3, 55.6, 106.6, 107.0, 118.7, 119.5, 124.2, 124.8, 126.6, 127.6, 130.8, 132.1; **IR** (KBr): 3049, 3005, 2920, 1610, 1558, 1495, 1395, 1357, 1239, 1170, 1033, 936, 851, 819 cm^{-1}; **Mass** (CI): 248 (M^+).

II.8. Spectra

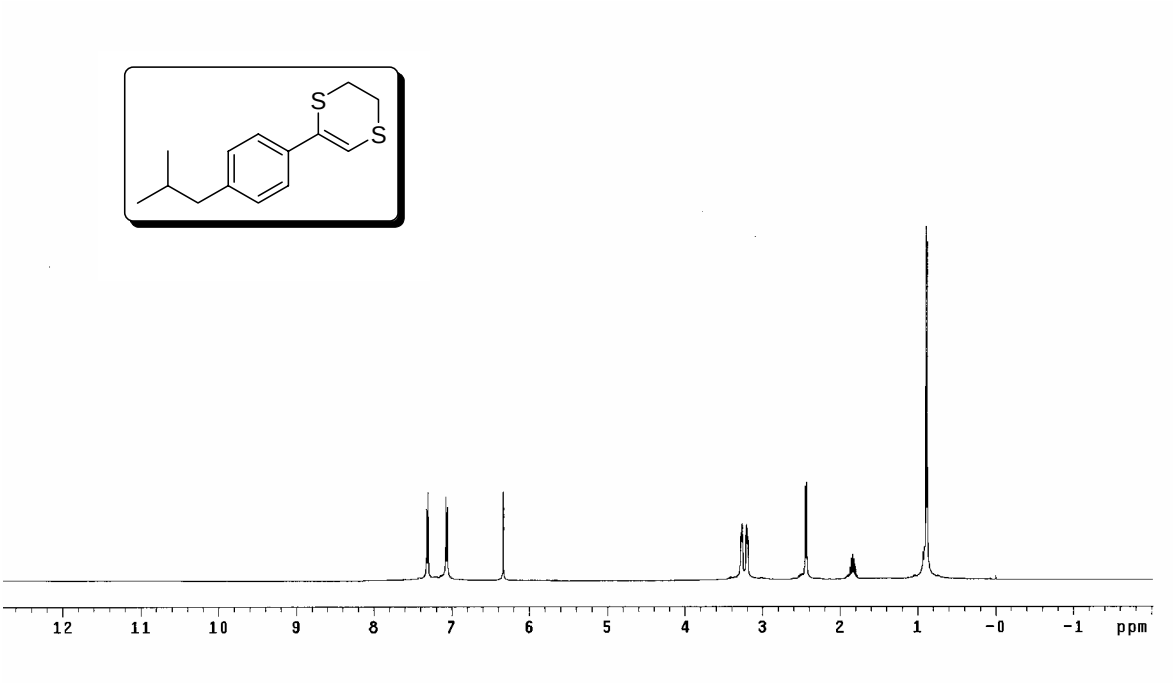
2,3-Dihydro-5-phenyl-1,4-dithiine (1a): ^{1}H NMR (400 MHz, $CDCl_3$):



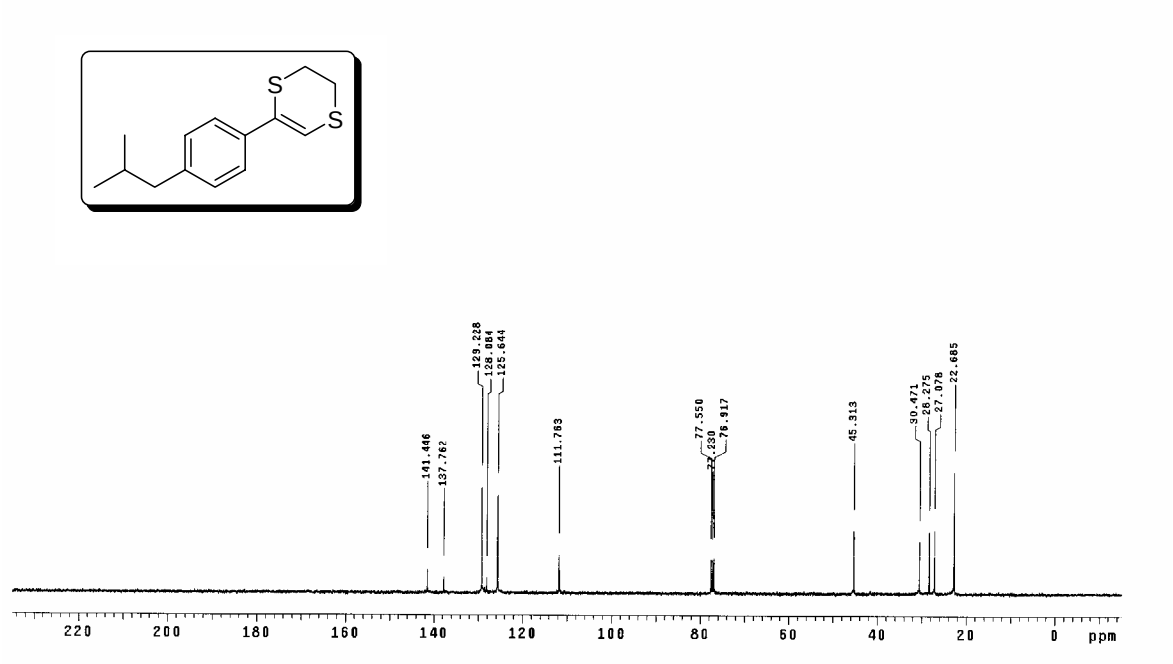
2,3-Dihydro-5-phenyl-1,4-dithiine (1a): ^{13}C NMR (100 MHz, $CDCl_3$):



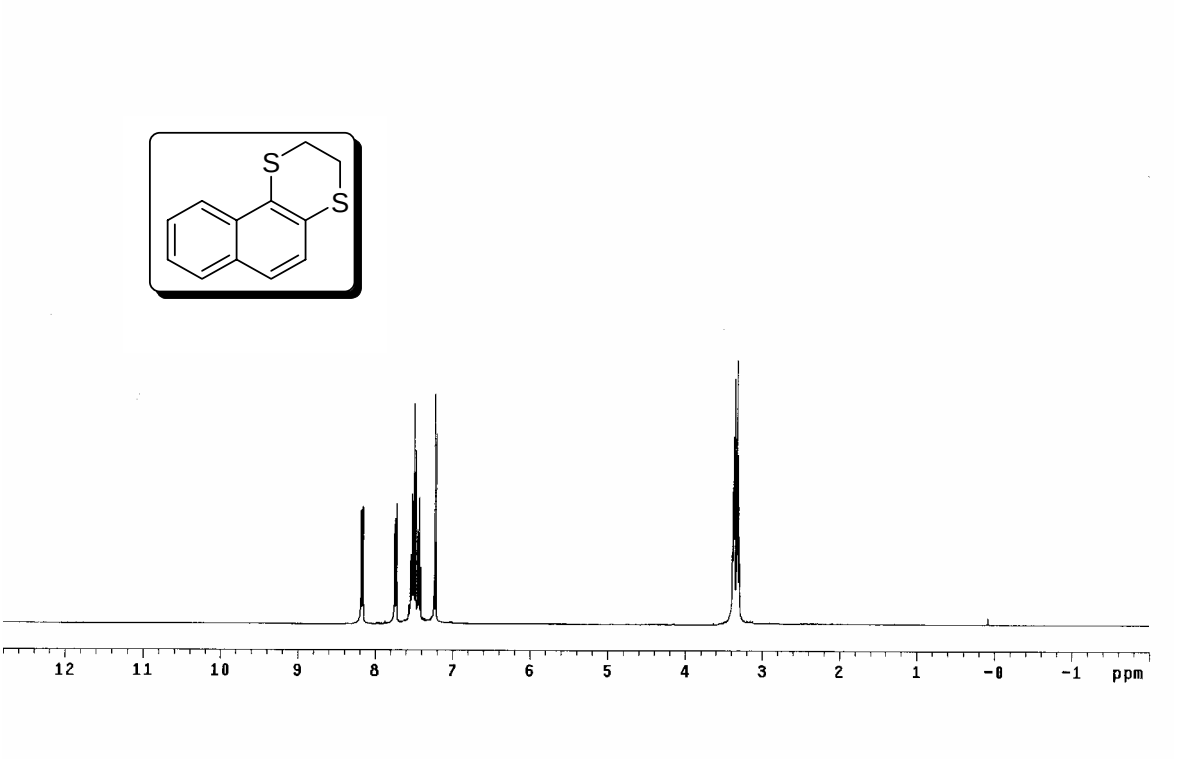
2,3-Dihydro-5-(4-isobutylphenyl)-1,4-dithiine (4a): ^{1}H NMR (400 MHz, $CDCl_3$):



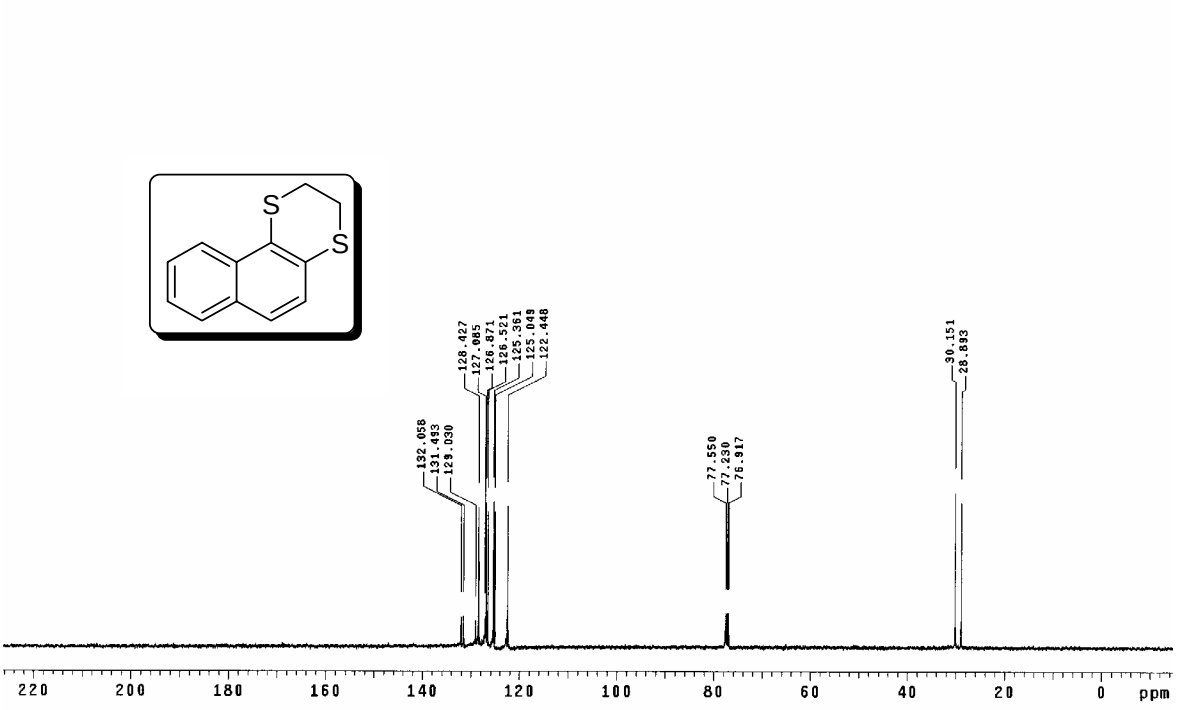
2,3-Dihydro-5-(4-isobutylphenyl)-1,4-dithiine (4a): ^{13}C NMR (100 MHz, $CDCl_3$):



2,3-Dihydronaphtho[2,1-b][1,4]dithiine (14a): ^{1}H NMR (400 MHz, $CDCl_3$):



2,3-Dihydronaphtho[2,1-b][1,4]dithiine (14a): ^{13}C NMR (100 MHz, $CDCl_3$):

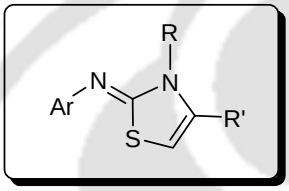


CHAPTER III

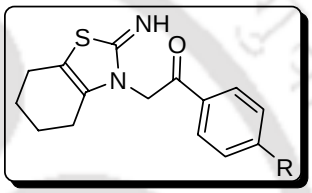
III. Structural Correction and Synthesis of 2-Iminothiazolines

III.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I., Section I.1.1., Figure I.1.1.3. in pages 3 and 4. This chapter deals with the following two types of heterocycles namely 2-iminothiazolines and pifithrin analogues.



2-Iminothiazolines



Pifithrin analogues

III.2. Importance and Applications

The thiazolidin-2-imine or thiazol-2-imine or 2-imino-thiazoline[1] ring system as has been named by different groups is present in several drug candidates possessing interesting biological activities such as muscarinomimetic, antimicotic, hypolipemic, antidiabetic, thrombopoietin agonism**,** cell adhesion antagonists**,** platelet GPIIb/IIIa receptor antagonists (*Figure III.2.1* **A**, **B**), anti-inflammatory, analgesic and kinase (CDK1, CDK5 and GSK3) inhibition, schistosomicides, cardiotonics and trichomonides.[2] Thiazoline derivatives have found interesting applications in agriculture as acricides, insecticides and plant growth regulators.[3] Recently, 2-imino-thiazolines were found to have antifungal activity[4] and skin whitening properties (*Figure 1***C**).[5] The pifithrin (Pft-α) (*Figure 1***D**) was isolated by screen of chemical libraries having 2-iminothiazoline skeleton is the lead compound of p53 inactivators and have received increasing attention due to their possible applications in several major neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, stroke, cancers therapy and other pathologies related to various signaling pathways.[6]

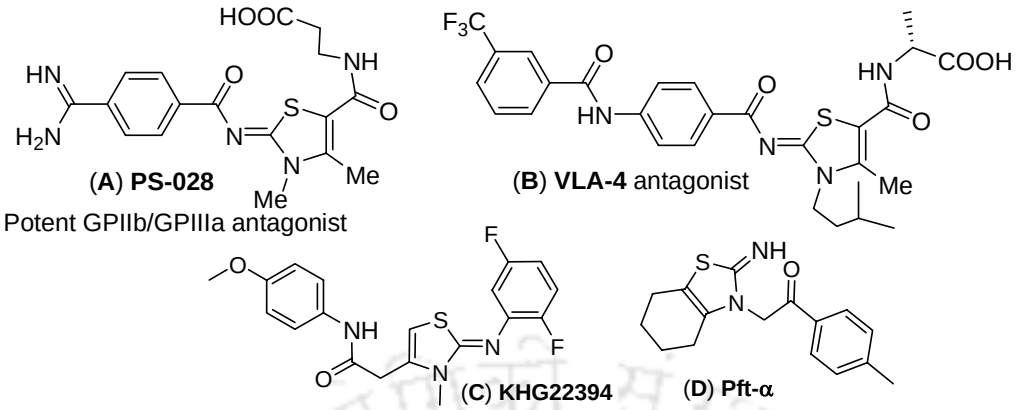


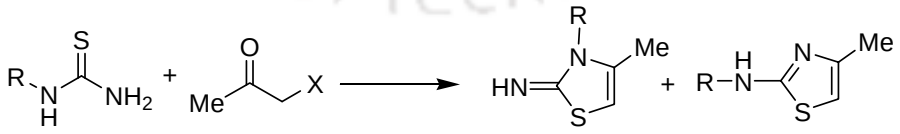
Figure III.2.1. *Structures of pharmacologically important molecules*

III.3. Available Synthetic Methods

The basic moiety 2-aminothiazole was first synthesized by Hantzsch condensation reaction involving thiourea and α-haloketone (*Scheme III.3.1.*).[7]

Scheme III.3.1.

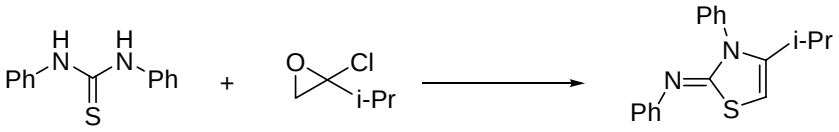
This approach was subsequently adopted for the synthesis of N-alkylated imino-thiazolines by replacing thioureas with mono-*N*-substituted thioureas.[8] The condensation of α-haloketones with mono-*N*-substituted thioureas in usual organic solvents led to the formation of 2-(*N*-substituted amino)thiazoles. However the same condensation under acidic conditions gave isomeric 2-imino-1,3-thiazolines in addition to variable amount of the aminothiazoles (*Scheme III.3.2.*).[9]



Scheme III.3.2.

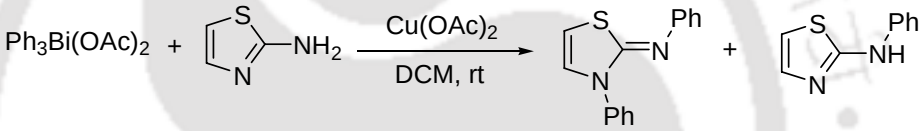
The reaction of 2-chlorooxiranes with thioamides and thioureas provides access to thiazoles, 4-hydroxy-4,5-dihydrothiazoles and 2-imino-2,3-dihydrothiazoles under mild

conditions (*Scheme III.3.3.*). In addition, 2-chlorooxiranes and selenourea also reacted under similar conditions to give selenazoles in quantitative yields.[10]



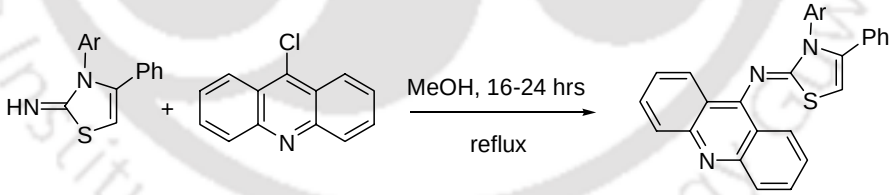
Scheme III.3.3.

Boyer *et al.* reported the copper diacetate catalyzed reaction of triphenylbismuth diacetate with 2-amino thiazoles / benzothiazoles which afforded mixtures of monophenylated and diphenylated products (*Scheme III.3.4.*). However, diphenylated product 2-(*N*-phenylamino)-3-*N*'-phenylthiazole derivatives are predominant over monophenylated 2-phenylamino derivatives.[11]



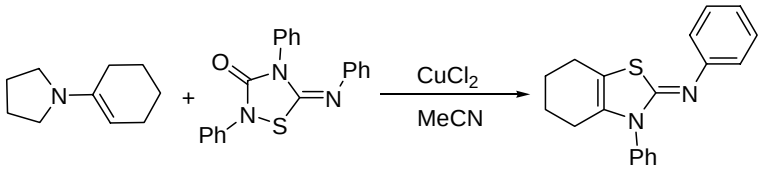
Scheme III.3.4.

Alternatively, *N*-substituted imino-thiazolines have been prepared by the *N*-arylation/alkylation of aminothiazoles with aryl/alkyl halides (*Scheme III.3.5.*).[12]



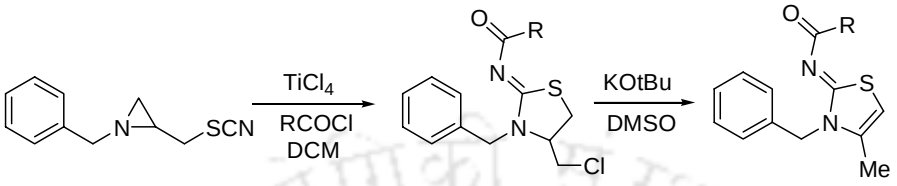
Scheme III.3.5.

Cycloadditions followed by elimination reactions of 5-imino-1,2,4-thiazolidin-3-ones and 5-imino-1,2,4-dithiazolidin-3-ones with enamines and ester enolate has been reported for the synthesis of 2-iminothiazoline (*Scheme III.3.6.*).[13]



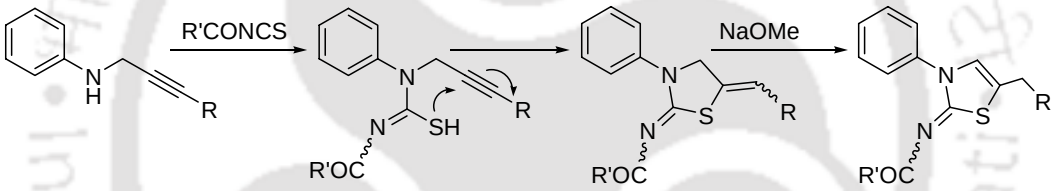
Scheme III.3.6.

Ring transformation of 1-arylmethyl-2-(thiocyanomethyl) aziridines in the presence of $TiCl_4$ and acylchloride gives 2-(*N*-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines which on treatment with potassium *tert*-butoxide afforded 2-(*N*-acylimino)-4-methyl-2,3-dihydro-1,3-thiazolines (*Scheme III.3.7.*).[14]



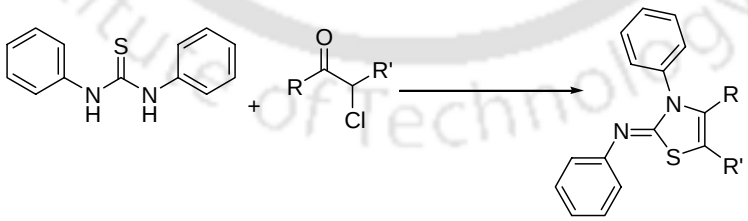
Scheme III.3.7.

Treatment of *N*-propargylaniline with acylisothiocyanates furnished 2-(*N*-acylimino)-1,3-thiazolines which gives 5-alkyl-1,3-thiazoline upon treatment with NaOMe (*Scheme III.3.8.*).[15]



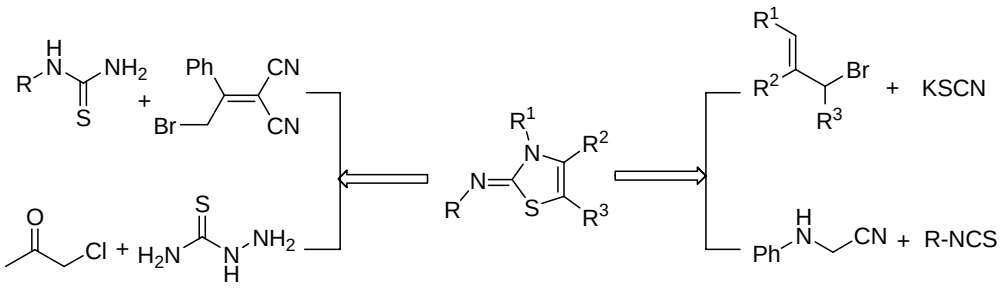
Scheme III.3.8.

The condensation of α-haloketones with *N*-benzoyl-*N*'-arylthioureas or *N*,*N*'-disubstituted thioureas is a common method for the synthesis of 2-imino-thiazolines under various reaction conditions (*Scheme III.3.9.*).[16]



Scheme III.3.9.

A novel synthesis of 2-imino-4-thiazolines has been reported by the reaction of α-bromoketimines with potassium thiocyanate in acetonitrile.[17a] Hydrobromide salts of either 2-aminothiazoles or 2-imino-3-thiazolines are obtained by the reactions of *N*-monoalkylated thioureas with 3-bromomethyl-2-cyanocinnamonitrile (*Scheme III.3.9.*).[17b,c]



Scheme III.3.10.

2-Iminothiazolines were prepared by treating phenylamino acetonitrile with alkyl isothiocynates.[17d] Less general approaches towards the synthesis of these heterocycles involve the reaction of α-chloroketones with thiosemicarbazide in an acid medium.[17e-g]

III.4. Present Work

III.4.1. Structural Correction of the Reaction Product of Thioureas with α-Haloketones

We have been utilizing tetrabutylammonium tribromide for bromination[18] and for various other organic transformations.[19] Recently we have synthesized a ditribromide reagent, 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) which is superior to all known tribromides because of its stability, higher bromine content per molecule, higher bromination efficiency, selectivity, reduced phase transfer property and quantitative recovery of the spent reagent.[20] This reagent is an excellent source of bromine capable of brominating varieties of organic substrates and is found to be an excellent catalyst for the acylation of alcohols using various anhydrides.[21] Being a source of bromine we thought to utilize this for the synthesis of imidazol-2-thione derivative following the reported procedure of Zou *et al*.[22] When 1-benzoyl-3-phenylthiourea (**1**) (1 equiv.) was reacted with 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (0.5 equiv) in acetone (10 mL) in the presence of triethylamine (1 equiv.) the product obtained was identical in all respects (m.p, IR, ^{1}HNMR and ^{13}CNMR) to that reported by Zou *et al*. However, X-ray crystallographic analysis of the product revealed an isomeric structure with a completely different skeleton. The product obtained was not an imidazole derivative (**1c**) as reported

rather it is *N*-(4-methyl-3-phenyl-2(3*H*)-thiazolylidene)-benzamide (**1a**) as shown in *Figure III.4.1.1.*

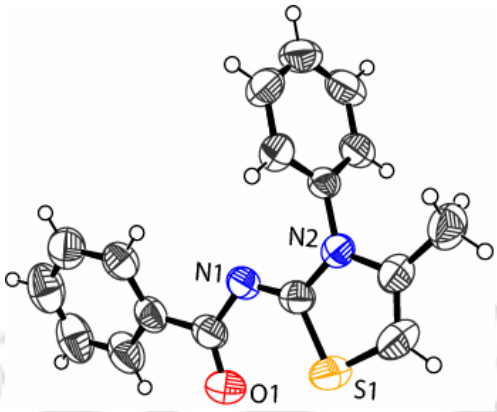


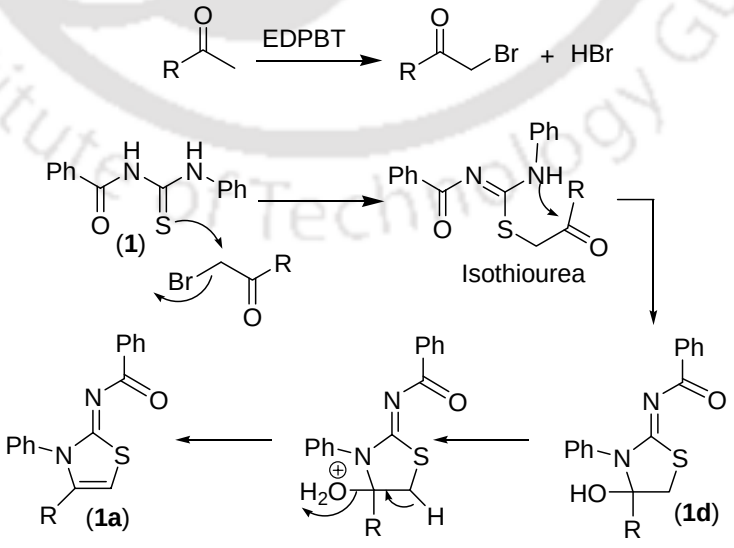
Figure III.4.1.1. *An ORTEP view with atomic numbering scheme of* ***1a.***

Our experience of working with organicammonium tribromides have never encountered such a drastic change in reactivity / selectivity, after all tribromides are just an efficient bromine carrier with similar or better reactivity. Thus there is no reason why the product obtained by Zou *et al.* using molecular bromine instead of EDPBT should be so much different? This prompted us to repeat the reaction of Zou *et al.*[22] exactly under their reported conditions using molecular bromine. Comparison of melting point, IR, ^{1}H and ^{13}CNMR of the sample prepared by us using bromine following the procedure of Zou *et al.* and using EDPBT were exactly identical. Further all the spectral, analytical and m.p. data obtained were in perfect agreement with that reported by Zou *et al*.[22]

The structure, 1-benzoyl-3-phenyl-4-methylimidazole-2-thione (**1c**) as proposed by Zou *et al.* and the structure N-(4-methyl-3-phenyl-2(3H)-thiazolylidene)-benzamide (**1a**) obtained by us are two isomeric compounds with the same molecular formula ($C_{17}H_{14}N_2OS$) which cannot be differentiated by their elemental composition and HRMS analyses. It is also difficult to differentiate the two compounds based on their ^{1}HNMR, as both have identical ethylenic, methyl and aromatic protons. The only difference in the structure is the presence of a -C*=S group in **1c** and -C*=N group in **1a**. The DEPT spectrum is of not much help in arriving at the correct structure as both the structures have identical numbers of CH_3, CH and C carbon.

Single crystal X-ray crystallography unequivocally established the structure to be N-(4-methyl-3-phenyl-2(3*H*)-thiazolylidene)-benzamide (**1a**). Based on the structure we

proposed the following mechanism for the reaction (*Scheme III.4.1.1.*). The ditribromide reagent EDPBT or bromine as the case may be brominates acetone to bromoacetone. The carbon of bromomethyl group is attacked by the sulphur of thiourea which is facilitated due to an abstraction of NH proton by triethylamine giving an isothiourea intermediate.[23] The NH proton flanked by a carbonyl and a thiocarbonyl moiety is more acidic, hence is preferentially deprotonated in the presence of other NH proton. Intramolecular attack of second NH group of isothiourea intermediate on carbonyl group would give *N*-(4-hydroxy-3,4-diphenyl-2-thiazolidinylidene)-benzamide (**1d**)[23] followed by dehydration of the tertiary alcohol leading to the formation of *N*-(4-methyl-3-phenyl-2(3*H*)-thiazolylidene)-benzamide (**1a**). This mechanism seems resonable since thiazolylidene derivative has been prepared by the condensation of acyl and arylacyl thioureas with α-haloketones.[23,24] Under basic condition several hydroxy thiazolidinylidene derivatives has been isolated.[23] When we reacted benzoyl thiourea (**1**) (1 equiv.) with phenacyl bromide (1 equiv.) in the presence of triethylamine (1.5 equiv) in acetonitrile, the corresponding 4-hydroxy thiazolidinylidene (**1d**) derivative precipitated out quantitatively which could not be converted to its final thiazolylidene (**1b**) even under reflux condition. However, on addition of two equivalents of HBr the final thiazolylidene (**1b**) was obtained in quantative yield at room temperature suggesting an acid catalyzed elimination of tertiary alcohol intermediate. In this reaction the insitu generated HBr serves as an acid for the dehydration of the intermediate tertiary alcohol (**1d**).



Scheme III.4.1.1. *Proposed mechanism of formation of* ***1a***

We believe that this may not be an isolated example and all the structures reported by Zou *et al.* are expected to have a thiazolylidene moiety and not imidazole. To further demonstrate our claim 1-benzoyl-3-phenylthiourea (**1**) was reacted under an identical condition using EDPBT but replacing acetone with acetophenone. The spectral and analytical data of the product obtained (**1b**) were again in perfect agreement with that reported by Zou *et al.*

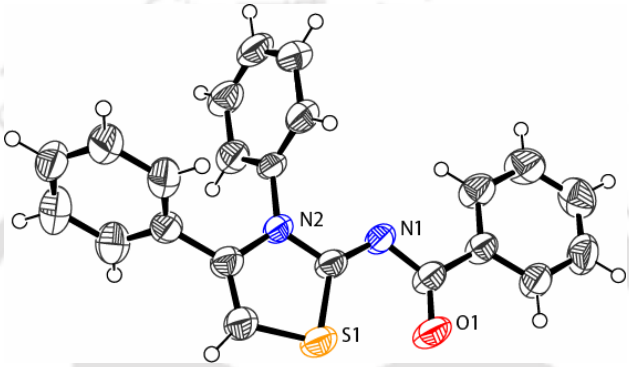


Figure III.4.1.2. *An ORTEP view with atomic numbering scheme of* ***1b.***

It may be mentioned here that replacement of bromine with EDPBT also gave the same product. Formation of thiazolylidene ring was confirmed by single crystal X-ray diffraction (*Figure III.4.1.2.*). Thiazolylidene ring formation is of general one and not specific to a particular benzoyl thiourea. When 3-bromobenzoyl-3-phenylthiourea (**6**) was reacted under above conditions separately with acetone and acetophenone both gave corresponding thiazolylidene derivatives (**6a**) and (**6b**) respectively.

In conclusion, we have unambiguously proved that the product obtained by the reaction of benzoyl-3-phenylthioureas with bromine / EDPBT and acetone /enolizable ketones in the presence of triethyl amine are thiazolylidene derivatives not imidazole-2-thiones as reported earlier.[22] We also believe that all other structures reported by Zou *et al.* are expected to have a thiazolylidene moiety and not imidazole. The wrong structure has lead to postulate an incorrect reaction mechanism.[22] Further scope of the mechanism, generalization and application of the method is discussed in next section.

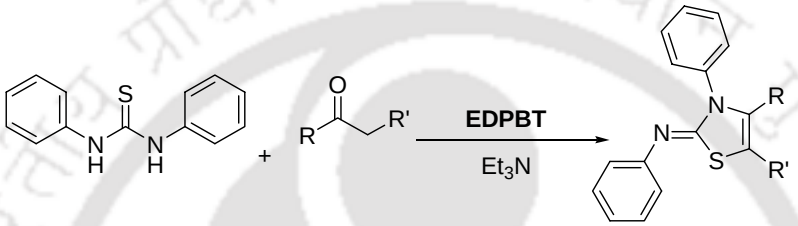
III.4.2. Synthesis of 2-Iminothiazolines

The mechanism of thiazol-2-imine formation has not been well understood leading to the proposal of wrong structures for the products by two independent research groups.[22,25] In the previous section we have unequivocally demonstrated that the reaction of benzoyl-3-phenylthioureas with bromine/1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) and acetone/enolizable ketones in the presence of triethylamine gives thiazol-2-imine derivatives and not imidazol-2-thione as reported earlier.[26,27] Further, we have established that even in aqueous medium the course of the reaction remains unaltered giving thiazol-2-imine derivatives instead of imidazole-2-thiones as reported.[26,27]

Although some methods for the preparation of 2-iminothiazolines are effective, the drawbacks associated with most of the procedures reported in literature are, arduous preparation of precursor substrates, difficulties in work up and isolation, the need for harsh reaction conditions, low yields and longer reaction time. The use of lachrymatory α-haloketones is unavoidable for methods using thioureas as starting materials. There are only two reports on one-pot procedure for the synthesis of 2-imino-thiazoline involving *N*,*N*'-dialkylthiourea and in situ generated α-bromo ketones which is limited to only symmetrical thioureas and few selected ketones thus lacking regioselectivity in 2-iminothiazoline formation.[28] The important drugs pifithrin (Pft-α) analogues have been prepared under a harsh reaction condition and at longer reaction times giving lesser yields. In this section we have revisited the reaction mechanism and developed a one- pot synthesis of thiazol-2-imine derivatives and the synthetic methodology was applied towards the synthesis of novel drug candidate pifithrin-α and its analogues.

The genesis of the work started with the two earlier reports proposing wrong reaction mechanism for the reaction of benzoylthioureas and α-haloketones, which ultimately led to the wrong interpretation of the structures of the products involved.[22,25] As stated earlier, the correct structures proposed by us[26,27] are not for the few selected ones, rather for all the other products proposed in the two earlier reports having thiazole and not imidazole rings.[22,25] In order to further delineate our objective we reinvestigated both the reactions using bromine equivalent reagent 1,1'-(ethane-1,2-diyl)dipyridinium

bistribromide (EDPBT).[29] The reagent EDPBT is capable of brominating enolizable ketones[20] as well as generating two equivalents of HBr, one equivalent during bromination of ketone and the second equivalent by the nucleophilic displacement of bromide by the sulphur thereby making the medium acidic even in the presence of one equivalent of triethylamine (*Scheme III.4.2.1.*). Acidic medium facilitates the dehydration of the intermediate tertiary alcohol. This prompted us to develop a one pot procedure for the synthesis of thiazol-2-imine derivative from benzoylphenylthioureas and enolizable ketones.

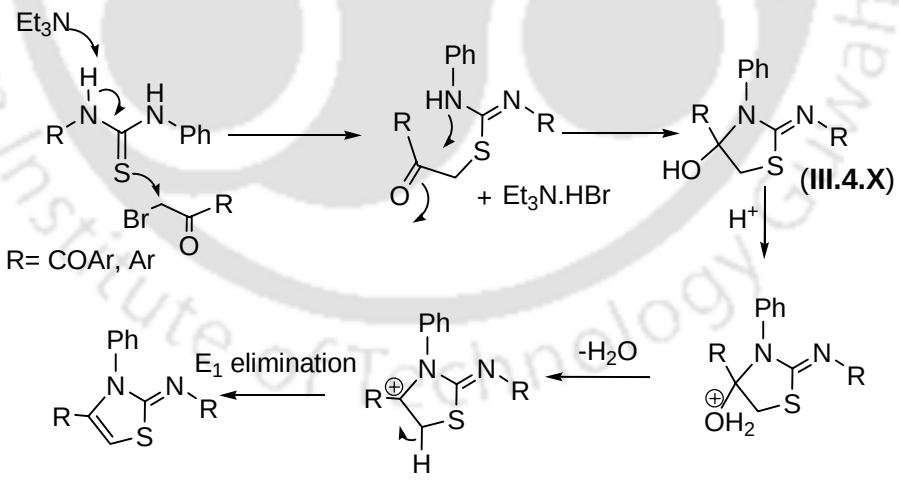


Scheme III.4.2.1.

In a typical reaction, to a solution of 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide EDPBT (0.5 mmol) in acetonitrile (2 mL) was added acetone (2 mmol) and was kept stirring for 10 minutes. During that period α-bromoacetone was formed which was clearly observed from the disappearance of the characteristic orange color of **EDPBT** precipitating out the spent reagent 1,1'-(ethane-1,2-diyl)dipyridinium dibromide (**EDPDB**). The supernatant liquid containing α-bromoacetone was then directly filtered into a solution of 1-benzoyl-3-phenyl-thiourea **1** (1 mmol) in acetonitrile (2 mL) containing triethylamine (1 mmol). The reaction was completed within an hour as can be judged from the TLC. After completion of the reaction, the solvent was evaporated and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column to give the product **1a** in 78 % isolated yield. The product **1a** obtained was found to be identical (melting point, IR, ^1H and ^{13}C NMR) to that of the product obtained earlier by Zou and by us using molecular bromine.[22, 25-27] The structure of **1a** has already being confirmed as having the thiazol-2-imine skeleton by X-ray crystallographic analysis.[26] The requirement of an inert atmosphere using bromine by

Zou *et al.* is really not necessary when bromine is replaced with EDPBT and the reaction works even under a moist condition.

As speculated earlier, this reagent brominates enolizable ketones to α-bromoketones. The carbon of the bromomethyl group is attacked by the sulphur of thiourea, which is facilitated due to the abstraction of the NH proton flanked by a carbonyl and a thiocarbonyl moiety leading to the intermediate tertiary alcohol.[26] However, Kaupp group have proposed an ionic intermediate having thiocarbenium and alkyl ammonium intermediate (thiazolium) species. We differ with the mechanism proposed by Manaka[30a,b] and by Kaupp[30c] in the sense that due to the higher acidity of the NH proton, it would prefer to exist as isothiourea rather than as thiocarbenium ion and that the thiazolium salt should exist as thiazol-2-imine. Further, the elimination of the intermediate tertiary alcohol is not by a base catalyzed E2 mechanism, rather it should be by an E1 mechanism. This assumption of ours is confirmed by isolation of the intermediate 1-benzoyl(4-hydroxy-3,4-diphenylthiazolylidene)2-imine (**III.4.X**), obtained by the reaction of benzoylthiourea (**1**) (1 equiv.) and acetophenone (1 equiv.) in the presence of EDPBT (0.5 equiv.) and triethylamine (4 equiv.).



Scheme III.4.2.1. *Proposed reaction mechanism of thiazol-2-imine formation.*

The intermediate 1-benzoyl(4-hydroxy-3,4-diphenylthiazolylidene)-2-imine obtained was identical to the product obtained earlier.[26] When 1,3-dichloroacetone (1 equiv.) was reacted with benzoylthiourea (**1**) (1 equiv.) in the presence of triethylamine (2

equiv.) a solid product (**III.4.Y**) was obtained after usual work up. Crystallization of the compound from ethylacetate : hexane (4:1) gave a colorless crystal. X-Ray crystallographic analysis of the compound revealed the presence of thiazol-2-imine skeleton as shown in *Figure III.4.2.1.*

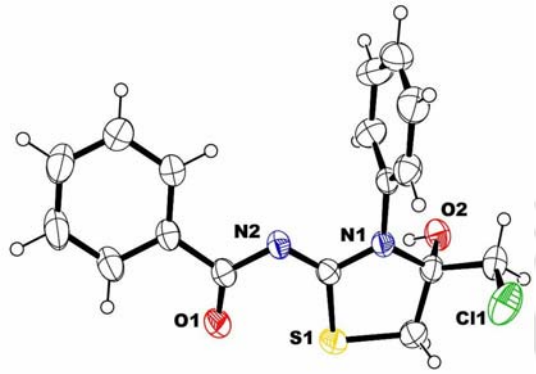
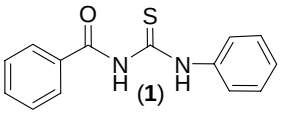
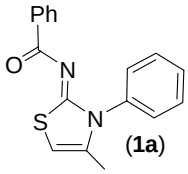
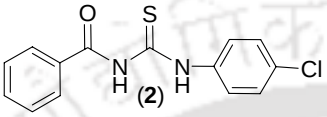
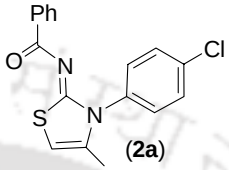
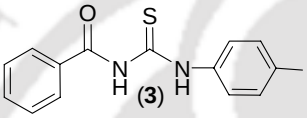
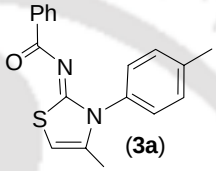
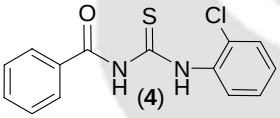
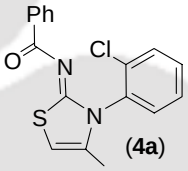
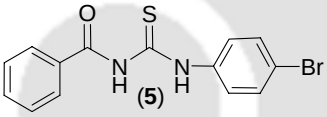
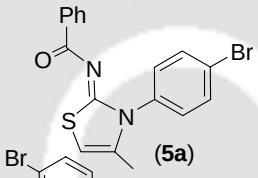
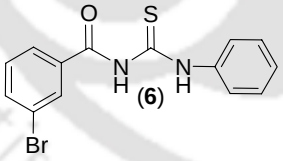
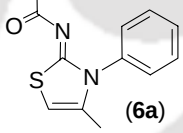


Figure III.4.2.1. *An ORTEP view with the atomic numbering scheme of* ***III.4.Y***

The NH proton flanked by a carbonyl and a thiocarbonyl is sufficiently acidic and its deprotonation by triethylamine is feasible and is essential as it enhances the nucleophilicity of the sulphur towards the attack on bromomethyl ketone forming an imine derivative. The distance between C(3)-N(3) is 1.308 Å, which is typical of an imine C-N double bond. Surprisingly, many earlier reports have proposed a base catalyzed E2 type elimination. This isolated intermediate (**III.4.Y**) is stable under basic and neutral conditions. Treatment of the intermediate (**III.4.Y**) with dilute (HCl) led to the formation of thiazol-2-imine with elimination of water, hence a base catalyzed elimination is completely ruled out. The dihedral angles for O(4)-C(24)-C(17)-H(17B) and O(4)-C(24)-C(17)-H(17A) are estimated to be -141.26^{o} and -21.97^{o} respectively. Thus, none of the hydrogens H(17A) and H(17B) adjacent to the sulphur atom is either *anti*-periplanar or *syn*-periplanar with respect to the hydroxyl group of the intermediate product (**III.4.Y**) there by diminishing any possibilities of an E2 elimination. The hydroxyl group being tertiary in nature is only susceptible to acid catalyzed E1 elimination. It may be mentioned here that the use of one equivalent of the triethylamine does not make the medium basic for an E2 elimination rather the medium remains acidic by just neutralizing one of the two equivalents of the HBr generated in the medium (*Scheme III.4.2.1.*).

Table III.4.2.1. *Reaction of benzoylthioureas with acetone and EDPBT.*[a]

Substrate	Product	Yield %[b]
 (**1**)	 (**1a**)	78
 (**2**)	 (**2a**)	72
 (**3**)	 (**3a**)	82
 (**4**)	 (**4a**)	68
 (**5**)	 (**5a**)	75
 (**6**)	 (**6a**)	85

[a]Reactions were monitored by TLC. [b] Isolated yields.

Having successfully established the mechanism of the reaction, our next objective was to apply this methodology to various other benzoylthioureas. When benzoylthiourea (**2**) was reacted under identical conditions as described above, the product (**2a**) obtained was again found to be identical (melting point, IR, ^{1}H and ^{13}C NMR) to that of the product obtained earlier by Wang group[25] and also by us in an aqueous medium.[27] The structure of (**1b**) already confirmed as having the thiazol-2-imine skeleton by X-ray crystallographic analysis.[27] Thus the course of the reaction and the reaction mechanism remains unchanged

both in the organic as well as in the aqueous medium. Benzoylthioureas **3**, **4** and **5** gave their corresponding thiazol-2-imine products **3a**, **4a** and **5a** respectively (*Table III.4.2.1.*). Thiazol-2-imine ring formation is general and not specific to a particular benzoylthiourea. When 3-bromobenzoyl-3-phenylthiourea **6** was reacted under the above conditions it gave the corresponding thiazol-2-imine derivative **6a**. The product obtained was again found to be identical (melting point, IR, ^{1}H and ^{13}C NMR) to that of the product obtained earlier by Zou group and independently by us.[22,26] The presence of thiazol-2-imine skeleton has been confirmed by X-ray.[26] It may be noted here that X-ray crystal structures of **1a**, **2a** and **6a** all revealed having *syn*-stereochemistry. The *syn*-selectivity is likely due to the steric hinderance of the acyl group and the *N*-phenyl group. This observation is consistent with the observations made by others.[30]

The acidity of NH proton of 1,3-disubstituted thiourea is expected to be less than the NH proton of benzoylthiourea. Having effectively applied to different benzoylthioureas we wished to test if this methodology can be applied to 1,3-diaryl thiourea as well. When 1,3-diphenyl thiourea (**7**) was reacted under an identical condition to that described above for benzoylthioures, a solid product was obtained. The ORTEP diagram with atom numbering scheme of **7a** is shown in *Figure III.4.2.2.* X-ray crystallographic analysis of the product **7a** again revealed the presence of thiazol-2-imine skeleton. The proposed reaction mechanism for 1,3-disubstituted thiourea is expected to be similar to the one proposed for benzoylthiourea.[26]

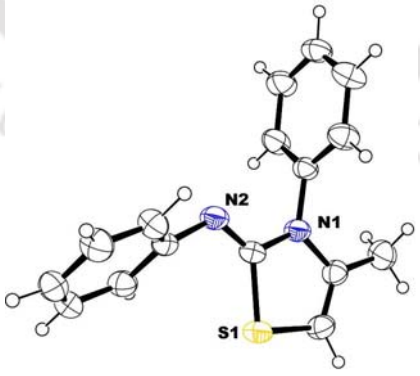
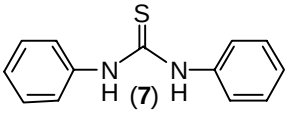
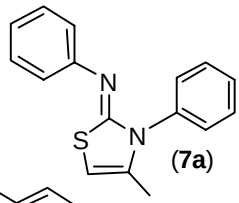
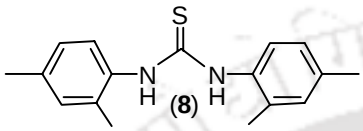
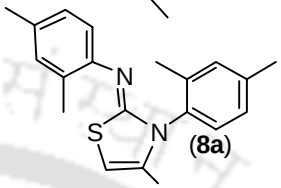
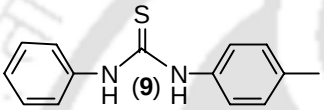
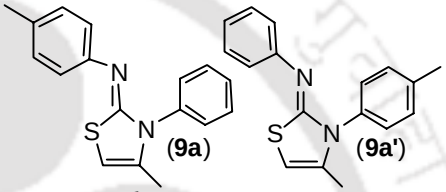
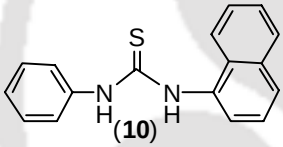
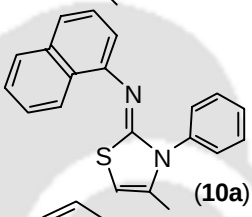
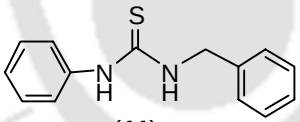
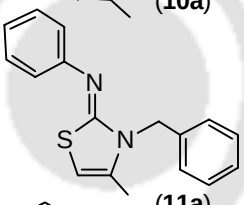
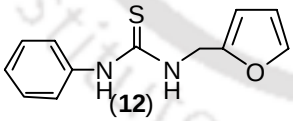
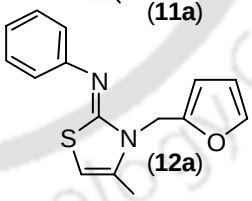


Figure III.4.2.2. *An ORTEP view with the atomic numbering scheme of* ***7a.***

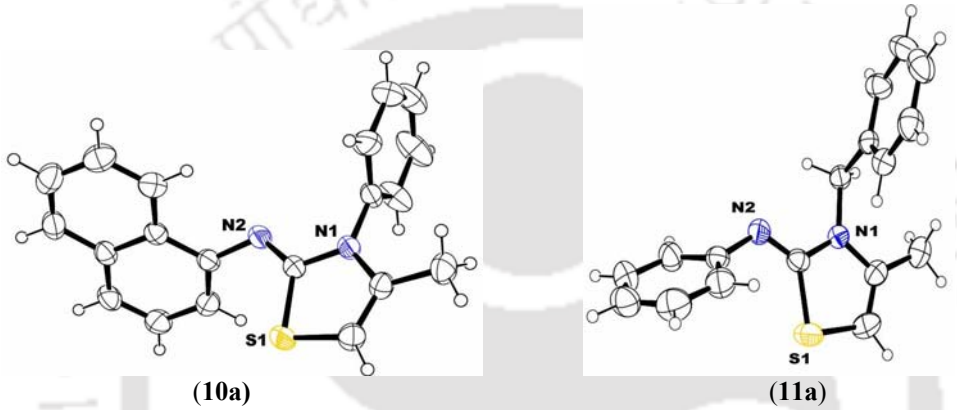
Table III.4.2.2. *Reaction of 1,3-disubstituted thiourea with acetone and EDPBT.*[a]

Substrate	Product	Yield %[b]
 (**7**)	 (**7a**)	75
 (**8**)	 (**8a**)	78
 (**9**)	 (**9a**) (**9a'**)	82 (2:3)
 (**10**)	 (**10a**)	72
 (**11**)	 (**11a**)	69
 (**12**)	 (**12a**)	66

[a]Reactions were monitored by TLC and stopped after 1.5h. [b]Isolated yields.

This methodology was successfully applied to another 1,3-disubstituted symmetrical thiourea **8** giving corresponding product **8a** in good yield. In order to study the regioselectivity, unsymmetrical thiourea 1-phenyl-3-*p*-tolyl-thiourea **9** was reacted under identical condition. The product obtained was an equimolar mixture of **9a** and **9a'** indicating the equal ease of thiazol-2-imine formation from either side of the thiourea since

the acidity of both NH protons are similar. However, when naphthyl ring is attached to one of the side in thiourea it results in exclusive regioselective product **10a** obtained via deprotonation of the NH proton from the naphthyl side of the urea **10**. The structure of the product **10a** was confirmed by X-ray crystallographic analysis. The ORTEP diagram with atom numbering scheme of product **10a** is shown in *Figure III.4.2.3.* Formation of regioselective product **10a** is because of the higher acidic character of the naphthyl NH proton. The measured pKa's of 1-naphthylamine and aniline are 3.94 and 4.61 respectively.



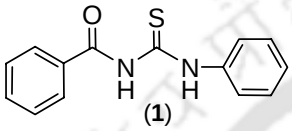
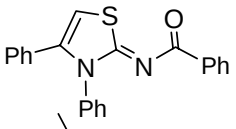
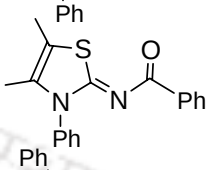
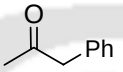
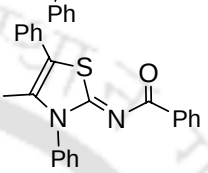
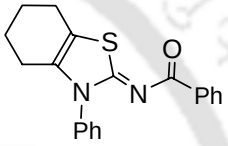
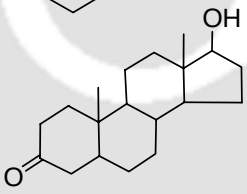
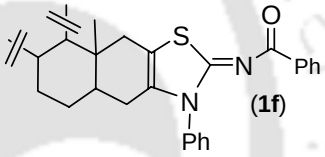
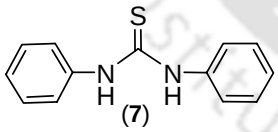
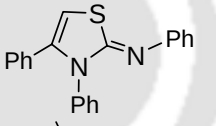
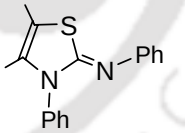
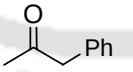
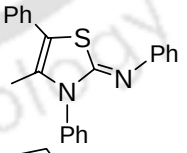
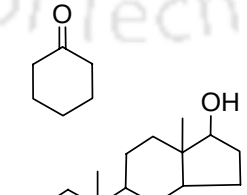
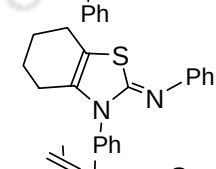
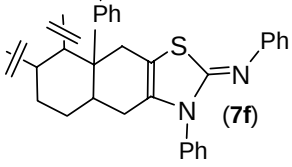
(10a) **(11a)**

Figure III.4.2.3. *An ORTEP view with the atomic numbering scheme of* ***10a*** *and* ***11a***

However, for substrate having phenylic and benzylic systems as in the case of 1-benzyl-3-phenyl-thiourea **11**, the NH proton flanked by a phenyl and a thiocarbonyl moiety is more acidic compared to the other NH proton flanked by a benzyl and a thiocarbonyl group giving product **11a** obtained by the deprotonation from the phenyl side of the thiourea. This is because of the higher basicity of the benzyl amine (pKa 9.41) compared to aniline (pKa 4.61). The structure of product **11a** is confirmed by single crystal X-ray measurement. The ORTEP diagram with atomic numbering scheme of **11a** is shown in *Figure III.4.2.3.* The ease of deprotonation from the phenyl side of the NH proton compared to the benzylic side leading to the formation of thiazol-2-imine skeleton is demonstrated for substrate **12** containing a furyl ring attached to one side.

So far the formation of thiazol-2-imine is applied to various benzoylthioureas and 1,3-disubstituted thioureas with acetone only. This approach can be applied to various other ketones as shown in *Table III.4.2.3.* Substrate 1-benzoyl-3-phenyl-thiourea **1** was reacted with acetophenone under an identical reaction condition to give the product **1b**.

Table III.4.2.3. *Reaction of 1,3-disubstituted thiourea with ketones and EDPBT.* [a]

Substrate	Ketone	Product	Yield %[b]
 (**1**)		 (**1b**)	77
		 (**1c**)	68
		 (**1d**)	71
		 (**1e**)	65
		 (**1f**)	48[c]
 (**7**)		 (**7b**)	82
		 (**7c**)	69
		 (**7d**)	66
		 (**7e**)	70
		 (**7f**)	45[c]

[a]Reactions were monitored by TLC and stopped after 1.5h. [b]Isolated yields. [c]Reaction was continued up to 6h.

The structure of product **1b** has already being confirmed as having the thiazol-2-imine skeleton by X-ray crystallographic analysis. Unsymmetrical ketones such as butan-2-one and 1-phenyl-propan-2-one gave products corresponding to the α-bromination at the highly substituted side of the ketones with the EDPBT finally leading to the formation of regioselective heterocycles thiazol-2-imine **1c** and **1d** respectively. Cyclohexanone with 1-benzoyl-3-phenyl-thiourea **1** gave the product **1e**.

Interestingly, anabolic thiazoloandrostane **1f**[31] was prepared from 17α-methyl-5α-androstan-17β-ol-3-one in moderate yield. The reactivity of 1,3-diphenyl thiourea **7** is similar to 1-benzoyl-3-phenyl-thiourea **1** as shown in *Table III.4.2.3.* The reactivity and regioselectivity of the products obtained using 1,3-diphenylthiourea **7** are similar to the product obtained using 1-benzoyl-3-phenyl-thiourea (**1**) (*Table III.4.2.3.*). The ORTEP diagram of compound **7e** having thiazol-2-imine skeleton is shown in *Figure III.4.2.4.*

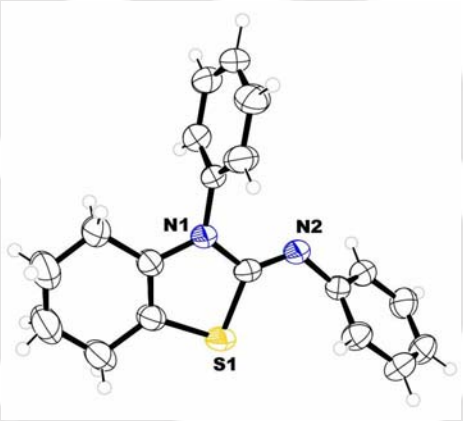
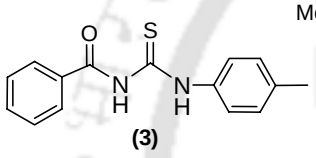
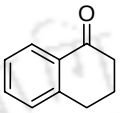
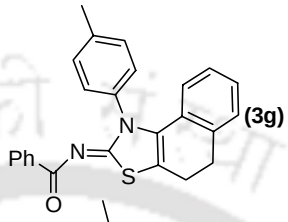
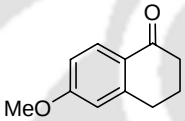
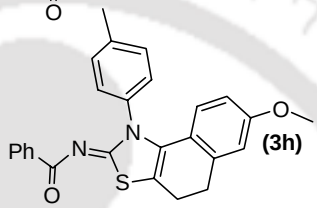
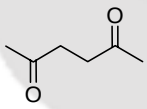
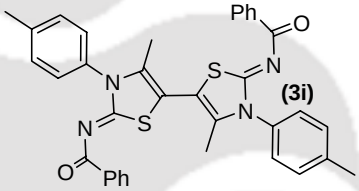
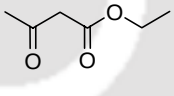
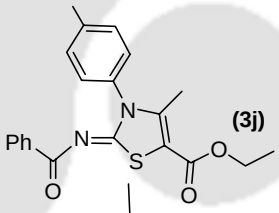
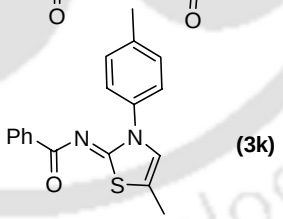


Figure III.4.2.4. *An ORTEP view with the atomic numbering scheme of* ***7e.***

The successful applications of the methodology to various ketones prompted us to test the usefulness of this synthetic strategy on other ketones and diketones. The *in situ* generated α-brominated products of cyclic ketones such as 1-tetralone and 6-methoxy-1-tertalone with EDPBT reacts with 1-benzoyl-3-(*p*-tolyl)-thiourea **3** giving thiazol-2-imine products **3g** and **3h** in good yields. The synthetic utility of this method is demonstrated in the synthesis of bis-thiazolidine product using a 1,4-diketone. Treatment of hexan-2,5-dione with one equivalent of the EDPBT possibly gave dibromo product 3,4-dibromo-hexane-2,5-dione in the reaction medium, which reacts with thiourea **3** giving bis-thiazolidin-2-imine product **3i** in 55 % isolated yield. Finally, ethylacetoacetate under the

present experimental condition gave regioselective product **3j**, which is in accordance to the reported one.[30a]

Table III.4.2.4. *Reaction of 1-benzoyl-3-p-tolyl-thiourea **3** with various ketones.*[a]

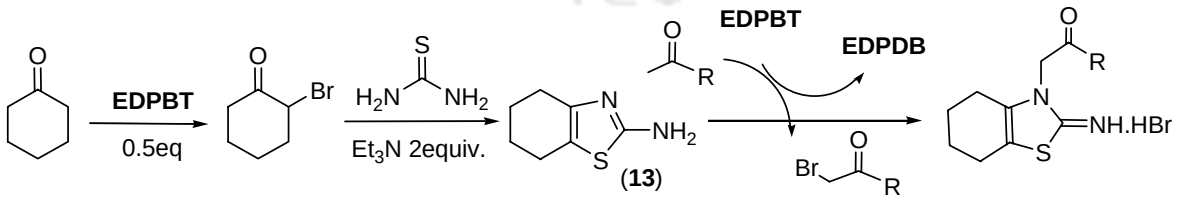
Substrate	Ketone	Product	Time	Yield %[b]
		 **(3g)**	1.5	73
		 **(3h)**	1.5	75
		 **(3i)**	2.0	55[c]
		 **(3j)**	1.5	78
		 **(3k)**	1.0	68

[a] Reactions were monitored by TLC. [b]Isolated yields. [c]0.5 equivalent of 2,4-hexan-dione was used.

III.4.3. Application in the Synthesis of Pifithrin-α Analogues

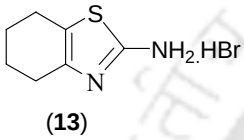
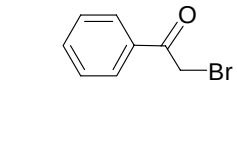
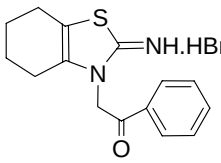
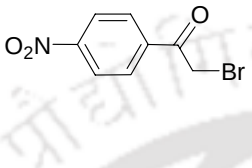
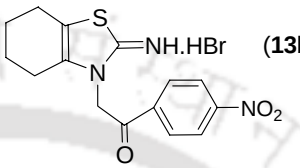
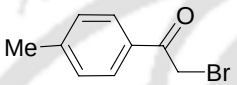
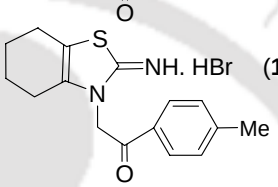
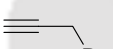
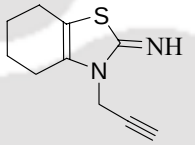
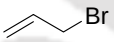
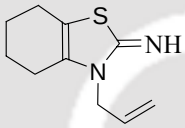
The synthetic utility of this reagent EDPBT and the methodology was finally demonstrated for the syntheses of neurodegenerative drug pifthrin-α and its analogues. Even though there are some reports for the syntheses of pifithrin analogues, almost all the reported methods use a two steps strategy. The first stage involves the iodine mediated formation of aminothiazole by the reaction of cyclic ketones and thiourea at 110 ^{o}C for 12 hrs. The product after isolation is then reacted with alkyl halide to give pifithrin-α analogues with an over all yield in the range of 30-35 %.[32a-d] This method suffers due to high reaction temperatures, longer reaction times and less yields.

As pifithrin-α analogues are very important scaffolds in medicinal chemistry, we have applied this methodology to access these biologically important compounds. The reagent EDPBT is capable of α-brominating various ketones.[20]. The *in situ* generated α-bromo cyclohexanone obtained by the reaction of cyclohexanone and EDPBT in acetonitrile reacts with thiourea to give aminothiazole. α-Bromoacetophenone prepared from acetophenone using EDPBT in acetonitrile was added to the above reaction medium containing aminothiazole and triethylamine. The pifithrin analogue **13a** was obtained in 62 % overall isolated yield. This is the highest yield reported so far. The pifithrin **13c** and its analogue **13b** were prepared using *p*-methylacetophenone and *p*-nitroacetophenone respectively. Similarly, other analogues **13d** and **13e** were also prepared using propargyl and allyl bromide showing the versatility of this method. Thus, the present method is superior to any of the reported procedure in terms of simplicity and better yield (*Scheme III.4.3.1.*).



Scheme III.4.3.1. *Synthesis of Pifithrin-α and its analogues.*

Table III.4.2.5. *Reaction of in situ generated aminothiazole with various insitu generated α-halo ketones and alkyl bromides.*[a]

Substrate	α-Halo ketone / Alkyl halide	Product	Time(h)	Yield %[b]
 (**13**)		 (**13a**)	4.5	62
		 (**13b**)	4.0	54
		 (**13c**)	4.5	57
		 (**13d**)	6.0	66[c]
		 (**13e**)	6.0	60[c]

[a] Reactions were monitored by TLC. [b]Isolated yields. [c] Propargyl and allyl bromides used were from commercial source and not generated insitu.

In conclusion, we have isolated the reaction intermediate and characterized it by X-ray crystallography. Formation of thiazol-2-imine is a two step process, the first step of the reaction requires the medium to be basic for favorable nucleophilic attack and the intermediate tertiary alcohol is stable under both neutral and basic conditions. The second step of the reaction is an acid mediated E1 elimination. We have achieved an efficient one-pot synthesis of substituted thiazol-2-imines by the condensation of carbonyl compounds with thioureas and 1,3-disubstituted thioureas using EDPBT. The pKa's of the NH protons of thioureas dictates the regioselectivity in the case of symmetrical ketones. The regioselective bromination at the more substituted side in the case of unsymmetrical ketones produces regioselective product with symmetrically 1,3-disubstituted thioureas. *Bis*-thiazolidine derivative can be prepared from dicarbonyl compound. Neurodegenerative

drugs pifithrin-α and its analogues have been successfully prepared employing this methodology. The pifithrin analogues obtained by this one-pot method is by far the best in terms of shorter reaction time and better yield. This method is simple, versatile and can be applied successfully for different 1,3-disubstituted thioureas as well as a range of carbonyl compounds.

III.5. Experimental Section

III.5.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1.

III.5.2. Procedure for the Preparation of N-benzoyl[4-(chloromethyl)-4-hydroxy -3-phenylthiazolidine] -2-imine (Y) :

(See figure ***Figure III.4.2.1.***, page 72)

To a solution of 1-benzoyl-3-phenyl-thiourea **1** (1 mmol) in acetonitrile (2 mL) containing triethylamine (2 mmol) was added a solution of 1,3-dichloroacetone (1 mmol) in acetonitrile (2 mL). The reaction was completed with in 1 hr as can be judged from the TLC. After completion of the reaction, solvent was evaporated and admixed with ethylacetate (20 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column to give 85 % of the product **I.** Compound **I** was recrystallized from a mixture of EtOAc: hexane (8 : 2) to give colorless crystal. m.p 137-138 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 3.04 (d, 1H, J =12.8 Hz), 3.55 (d, 2H, J =12.8 Hz), 3.78 (d, 1H, J = 12.8 Hz), 7.10-7.65 (m, 7H), 7.85 (d, 1H, J = 7.2 Hz), 7.93 (d, 2H, J = 7.2 Hz). ^{13}C (400 MHz, $CDCl_3$): δ 137.9, 46.9, 92.7, 120.6, 127.3, 128.3, 129.0, 129.3, 130.1, 132.6, 137.2, 174.0, 177.5. IR (KBr): 3334, 3191, 3165, 3063, 2945, 2848, 1655, 1609, 1486, 1025, 702 cm^{-1}. Crystallographic description of (I): Crystal dimension (mm): 0.48 x 0.27 x 0.19; $C_{17}H_{14}ClN_2OS$, Mr = 329.81; triclinic, space group P_1; a = 11.3616(3) Å, b = 12.2735(2) Å, c = 14.1624(2) Å; α = 114.3440(10), β = 104.7900(10), γ = 99.1230(10), V = 1659.86(6) (A^3); Z = 4; ρ_{cal} = 1.320 mg/m^3; μ (mm^{-1}) = 0.358; *F (000)* = 684; reflection collected / unique = 15148 / 3901; refinement method = full-matrix least-squares on F^2;

final R indices [I > $2\sigma_I$] R_1 = 0.0419, wR2 = 0.0940, R indices (all data) R1 = 0.0671; wR2 = 0.1067; goodness of fit = 1.024.

III.5.2. Preparation of 1-benzoyl-3-phenyl-4-methyl-thiazolidene-2-imine (1a) using EDPBT.

To a solution of 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide EDPBT (0.5 mmol) in acetonitrile (2 mL) was added acetone (2 mmol) and kept stirring for 10 minutes during this period the bromination of acetone was complete as judged from the disappearance of the orange color of EDPBT separating out the spent reagent 1,1'-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB). The supernatant containing bromo ketone was then directly filtered into a solution of 1-benzoyl-3-phenyl-thiourea **1** (1 mmol) in acetonitrile (2 mL) containing triethylamine (1 mmol) and kept for heating at 60°C. The reaction was completed with in 1 h as can be judged from the TLC. After completion of the reaction, solvent was evaporated and admixed with ethylacetate (20 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column to give 78 % of the product **1a**.

III.5.3. General Procedure for the Preparation of Pifithrin-α analogues

To a solution of cyclohexanone (2 mmol) in acetonitrile (2 mL) was added 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (1 mmol) and left stirring for 10 minutes. This reaction mixture was then filtered into a solution of thiourea (2 mmol), triethylamine (2 mmol) in acetonitrile (5 mL) and was heated at 80°C for 5 hrs to give aminothiazole hydrobromide. The free aminothiazole was obtained by treating it with triethylamine (2 mmol). Separately, acetophenone (2 mmol) was brominated with EDPBT (1 equiv) using our solvent free method to give bromoacetophenone.[8] The crude aminothiazole was then filtered into the crude bromo acetophenone and the reaction mixture was stirred for 4.5 hrs. The desired product precipitated out from the reaction mixture was filtered and washed with acetonitrile to obtain the pure product.

III.6. References

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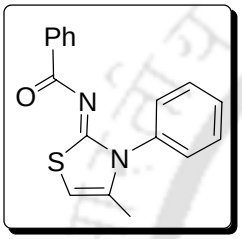
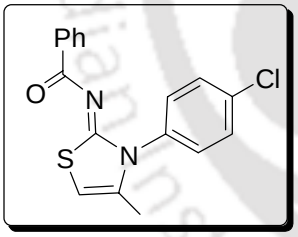
III.7. Spectral Data

2-Benzoylimino-3-phenyl-4-methyl-3H-thiazole (1a):



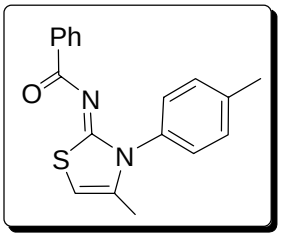
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H) 6.39 (s, 1H), 7.31 (m, 5H), 7.54 (m, 3H), 8.01 (m, 2H). ^{13}C (400 MHz, $CDCl_3$): δ 15.2, 104.7, 128.0, 128.2, 128.5, 129.4, 129.6, 131.5, 134.5, 137.0, 137.6, 170.2, 174.5. IR (KBr): 3050, 2948, 1598, 1564, 1491, 1458, 1364, 1342, 1275, 1171, 1066, 1017, 903 cm^{-1}.

2-Benzoylimino-3-(4-Chloro-phenyl)-4-methyl-3H-thiazole (2a):



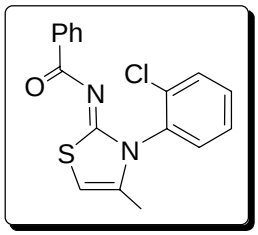
M.p. 199-201 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 6.37 (s 1H), 7.40 (m, 5H), 7.55 (d, 2H, J = 7.6 Hz), 8.03 (d, 2H, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 104.9, 128.1, 129.3, 129.6, 129.8, 131.6, 134.0, 135.2, 135.9, 136.7, 170.1, 174.4. IR (KBr): 3054, 2912, 1599, 1561, 1489, 1459, 1344, 1270, 902, 705 cm^{-1}.

N-(4-Methyl-3-p-tolyl-3H-thiazol-2-ylidene]-benzamide (3a):



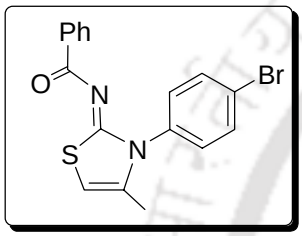
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.41 (s, 3H), 6.63 (s, 1H), 7.25 (m, 7H), 7.83 (d, 2H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 20.9, 105.1, 127.2, 127.7, 128.6, 129.9, 131.3, 133.7, 135.1, 135.7, 139.1, 168.4, 172.3. IR (KBr): 3032, 2917, 1596, 1561, 1456, 1341, 1267, 905, 707 cm^{-1}.

2-Benzoylimino-3-(2-chlorophenyl)-4-methyl-3H-thiazole (4a):



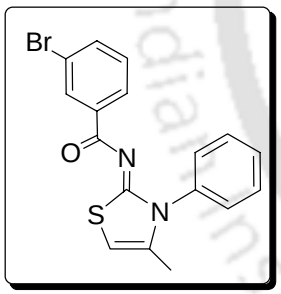
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 3H), 6.37 (s, 1H), 7.42 (m, 7H), 7.98 (d, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ14.3, 104.4, 127.9, 128.0, 129.3, 130.1, 130.5, 130.9, 131.4, 132.6, 133.8, 135.1, 136.8, 169.7, 174.4. IR (KBr): 3065, 2917, 1602, 1566, 1481, 1344, 1281, 908, 716, 705 cm^{-1}. $C_{17}H_{13}ClN_2OS$ (328.82): calcd. C 62.10, H 3.99, N 8.52, S 9.75; found C 62.38, H 4.08, N 8.31, S 9.78.

N-[3-(4-Bromo-phenyl)-4-methyl-3H-thiazol-2-ylidene]-benzamide (5a):



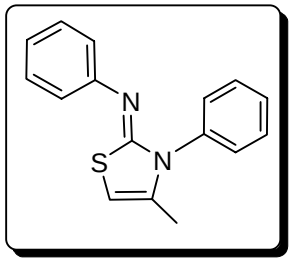
^{1}H NMR (400 MHz, $CDCl_3$): δ1.96 (s, 3H), 6.29 (s, 1H), 7.25 (m, 5H), 7.64 (m, 2H), 7.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ15.2, 104.9, 128.1, 129.4, 129.5, 130.0, 131.7, 132.9, 134.0, 136.5, 136.7, 170.2, 174.5. IR (KBr): 3065, 1591, 1561, 1476, 1377, 1168, 1012, 718, 694 cm^{-1}.

2-(3-Bromobenzoylimino)-4-methyl-3-phenyl-3H-thiazole (6a):



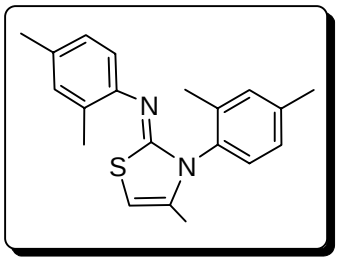
^{1}H NMR (400 MHz, $CDCl_3$): δ2.06 (s, 3H), 6.40 (s 1H), 7.17 (t, 1H, J = 8.0 Hz), 7.32 (d, 2H, J = 7.6 Hz), 7.54 (m, 4H), 7.93 (d, 1H, J = 6.8 Hz), 8.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ15.2, 104.9, 122.2, 127.9, 128.1, 128.5, 129.6, 129.7, 132.5, 134.2, 134.7, 137.3, 139.1, 170.3, 172.9. IR (KBr): 3086, 2923, 1596, 1557, 1496, 1459, 1450, 1337, 1255, 1127, 1033, 907, 739 cm^{-1}.

4-Methyl-(3-phenyl-3H-thiazol-2-ylidene)-phenyl-amine (7a):



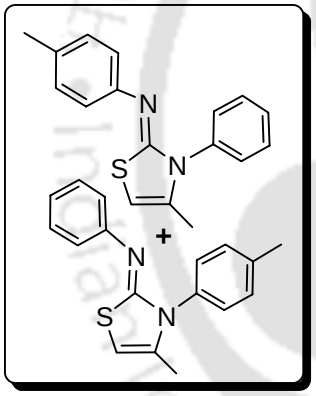
^{1}H NMR (400 MHz, $CDCl_3$): δ1.86 (s, 3H), 5.62 (s, 1H), 6.97 (m, 3H), 7.37 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ15.8, 93.5, 121.8, 123.1, 128.6, 129.2, 129.4, 129.7, 135.1, 137.8, 152.2, 161.0. IR (KBr): 3109, 2863, 1615, 1572, 1492, 1355, 1163, 768, 694 cm^{-1}.

3-(2',4'-Dimethylphenyl)-2-(2',4'-dimethylphenylimino)-4-methyl-3H-thiazole (8a):



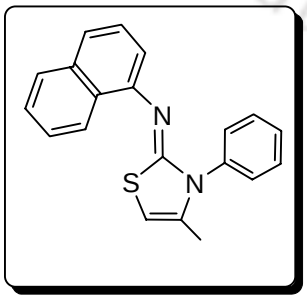
M.p. 134-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ1.76 (s, 3H), 2.07 (s, 3H), 2.24 (s, 3H), 2.26 (s, 3H), 2.36 (s, 3H), 5.57 (s, 1H), 6.93 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ15.3, 17.7, 17.9, 21.1, 21.4, 93.2, 120.7, 127.4, 128.1, 129.2, 130.1, 131.4, 132.1, 132.4, 134.2, 135.0, 136.9, 139.1, 148.7, 159.8. IR (KBr): 3056, 2912, 1615, 1585, 1497, 1358, 861, 749 cm^{-1}. $C_{20}H_{22}N_2S$ (322.48): calcd. C 74.49, H 6.88, N 8.69, S 9.94; found C 74.26, H 6.93, N 8.75, S 9.89.

4-Methyl-3-phenyl-2-(p-tolylimino)-3H-thiazole and 4-Methyl-2-phenylimino-3-(p-tolyl)-3H-thiazole (9a + 9a'):



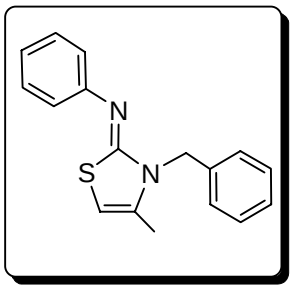
^{1}H NMR (400 MHz, $CDCl_3$): δ1.82 (brs, 6H), 2.28 (s, 3H), 2.39 (s, 3H), 5.59 (m, 2H), 6.98 (m, 8H), 7.36 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ15.5, 20.9, 21.2, 92.9, 93.3, 121.4, 121.6, 121.7, 122.8, 122.9, 128.4, 128.6, 128.9, 129.1, 129.2, 129.5, 129.7, 129.8, 130.2, 132.1, 132.2, 134.9, 135.1, 137.6, 138.3, 149.5, 152.1, 160.9, 161.0. IR (KBr): 3027, 2920, 1621, 1574, 1506, 1356, 1296, 1244, 1167, 1112, 1037, 879, 696, 533 cm^{-1}. $C_{17}H_{16}N_2S$ (280.39): calcd. C 72.82, H 5.75, N 9.99; S 11.44; found C 72.73, H 5.81, N 10.08, S 10.91.

4-Methyl-2-(1'-naphthylimino)-3-phenyl-3H-thiazole (10a):



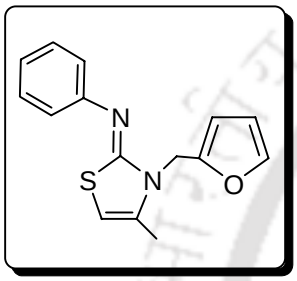
M.p. 128-129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ1.89 (s, 3H), 5.65 (s, 1H), 7.19 (d, 1H, J = 7.6 Hz), 7.47 (m, 9H), 7.78 (d, 1H, J = 8 Hz), 7.98 (d, 1H, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8, 93.9, 115.0, 123.1, 124.0, 125.2, 126.2, 126.5, 128.0, 128.8, 128.9, 129.3, 130.0, 135.0, 135.1, 138.1, 148.5, 160.9. IR (KBr): 3043, 2916, 1620, 1600, 1567, 1492, 1359, 1264, 777, 695, 545 cm^{-1}. $C_{20}H_{16}N_2S$ (316.43): calcd. C 75.92, H 5.10, N 8.85, S 10.13; found C 75.49, H 4.96, N 8.69, S 10.16.

3-Benzyl-4-methyl-2-phenylimino-3H-thiazole (11a):



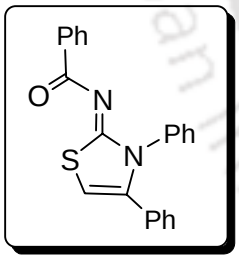
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 5.16 (s, 2H), 5.52 (s, 1H), 7.03 (m, 3H), 7.30 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9, 47.2, 92.6, 121.7, 122.8, 126.8, 127.5, 128.8, 129.5, 135.1, 137.5, 151.6, 160.2. IR (KBr): 3060, 3021, 2923, 1610, 1577, 1358, 1220, 913, 768, 696 cm^{-1}. $C_{17}H_{16}N_2S$ (280.39): calcd. C 72.82, H 5.75, N 9.99, S 11.44; found C 72.87, H 5.82, N 9.91, S 11.52.

3-(Furfuryl)-4-methyl-2-phenylimino-3H-thiazole (12a):



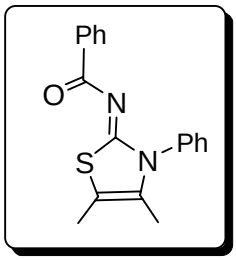
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 5.08 (s, 2H), 5.51 (s, 1H), 6.36 (t, 1H, *J* = 2.8 Hz), 6.42 (d, 1H, *J* = 3.6 Hz), 7.08 (m, 3H), 7.36 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.9, 40.6, 92.7, 108.8, 110.9, 121.8, 123.1, 129.6, 134.9, 142.2, 150.6, 151.7, 159.5. **IR (KBr):** 3056, 3027, 2924, 2954, 1614, 1580, 1488, 1396, 1317, 1221, 1189, 1146, 1067, 1011, 931, 801, 767, 747, 696 cm^{-1}. $C_{15}H_{14}N_2OS$ (270.36): calcd. C 66.64, H 5.22, N 10.36; S 11.86; found C 66.73, H 5.34, N 10.21, S 12.41.

2-Benzoylimino-3,4-diphenyl-3H-thiazole (1b):



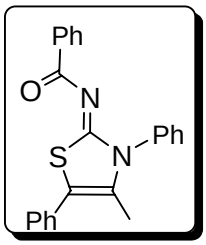
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (s, 1H), 7.12 (d, 2H, *J* = 8.4 Hz), 7.23 (m, 6H), 7.33 (t, 2H, *J* = 7.6 Hz), 7.39 (d, 3H, *J* = 7.0 Hz), 8.10 (d, 2H, *J* = 8.4 Hz). **^{13}CNMR (100 MHz, $CDCl_3$):** δ 107.6, 128.1, 128.5, 128.6, 128.9, 129.0, 129.4, 130.7, 131.6, 136.8, 137.7, 139.2, 170.0, 174.7. **IR (KBr):** 3064, 2927, 1598, 1566, 1492, 1466, 1450, 1435, 1337, 1279, 1200, 1166, 1024, 899, 713 cm^{-1}.

2-Benzoylimino-4,5-dimethyl-3-phenyl-3H-thiazole (1c):



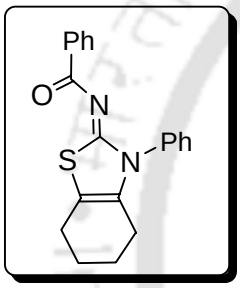
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.28 (s, 3H), 7.31 (m, 5H), 7.54 (m, 3H), 8.01 (d, 2H, *J* = 7.2 Hz). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 12.1, 12.4, 115.0, 128.0, 128.2, 128.3, 129.0, 129.4, 129.6, 131.4, 137.1, 138.2, 168.4, 174.1. **IR (KBr):** 3054, 2923, 1596, 1558, 1481, 1349, 905, 713 cm^{-1}. $C_{18}H_{16}N_2OS$ (308.41): calcd. C 70.10, H 5.23, N 9.08; S 10.40; found C 70.37, H 5.31, N 9.23, S 10.26.

2-Benzoylimino-3,5-diphenyl-4-methyl-3H-thiazole (1d):



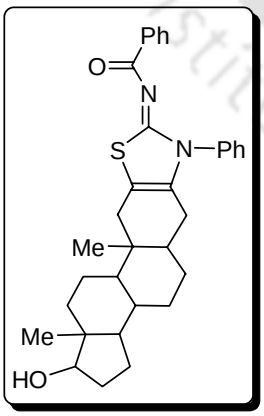
^{1}H NMR (400 MHz, $CDCl_3$): δ2.11 (s, 3H), 7.41 (m, 13H), 8.03 (d, 2H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ13.7, 120.5, 128.0, 128.2, 128.3, 129.1, 129.2, 129.3, 129.4, 129.6, 131.5, 132.0, 136.9, 137.9, 168.7, 174.5. IR (KBr): 3054, 2857, 1596, 1462, 1338, 1174, 902, 718, 691cm^{-1}. $C_{23}H_{18}N_2OS$ (370.48): calcd. C 74.57, H 4.90, N 7.56, S 8.65; found C 74.73, H 5.08, N 7.38, S 8.83.

N-(3-Phenyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylidene)-benzamide (1e):



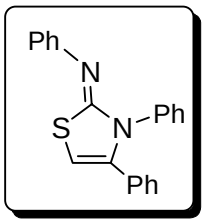
^{1}H NMR (400 MHz, $CDCl_3$): δ1.75 (q, 4H, J = 6.0 Hz), 2.15 (s, 2H), 2.55 (s, 2H), 7.24 (m, 4H), 7.46 (m, 3H), 7.96 (d, 2H, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 23.0, 23.5, 24.1, 118.0, 120.5, 124.8, 127.3, 127.6, 128.1, 128.8, 129.1, 129.3, 129.4, 131.4, 131.6, 137.2, 168.5, 174.3. IR (KBr): 3049, 2939 , 2835, 1604, 1572, 1489, 1374, 1141, 762, 694 cm^{-1}.

N-(1-Hydroxy-10a,12a-dimethyl-7-phenyl-1, 2, 3, 3a, 3b, 4, 5, 5a, 6, 7, 10, 10a, 10b, 11,12,12a-hexadecahydro-9-thia-7-aza-dicyclopenta[a,h]phenanthren-8-ylidene)-benzamide (1f):



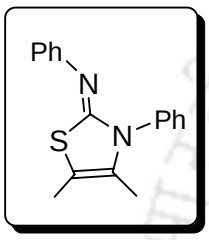
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (s, 3H), 0.86 (s, 3H), 0.80-2.00 (m, 19H), 2.31 (d, 1H, J = 8.0 Hz), 2.60 (d, 1H, J = 16.0 Hz), 3.65 (t, 1H, J = 8.4 Hz), 4.15 (m, 1H), 7.42 (m, 7H), 7.81 (d, 1H, J = 7.2 Hz), 8.03 (d, 2H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ11.2, 12.0, 21.0, 23.5, 28.5, 30.5, 31.2, 34.1, 35.7, 36.5, 36.7, 37.0, 37.8, 42.0, 43.0, 51.0, 53.8, 81.9, 117.2, 127.6, 128.0, 128.7, 129.1, 129.3, 129.4, 130.1, 131.3, 132.1, 137.2, 137.3, 168.6, 169.7, 174.2. IR (KBr) : 3131, 2923, 2878, 1654, 1608, 1580, 1376, 1243, 1149, 764, 695 cm^{-1}. $C_{33}H_{38}N_2O_2S$ (526.75): calcd. C 75.25, H 7.27, N 5.32, S 6.09; found C 75.41, H 7.36, N 5.26, S 6.18.

3,4-Diphenyl-2-phenylimino-3H-thiazole (7b):



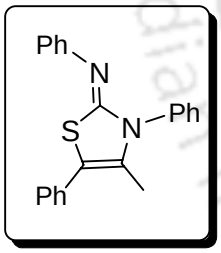
^{1}H NMR (400 MHz, $CDCl_3$): δ5.94 (s, 1H), 6.95-7.40 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 97.4, 121.8, 123.4, 127.7, 128.3, 128.4, 128.5, 129.0, 129.1, 129.6, 131.8, 138.1, 140.1, 152.1, 160.4. IR (KBr): 3049, 2923, 1618, 1577, 1486, 1360, 1138, 710, 694 cm^{-1}. $C_{21}H_{16}N_2S$ (328.44): calcd. C 76.80, H 4.91, N 8.53, S 9.76; found C 76.68, H 5.04, N 8.62, S 9.58.

4,5-Dimethyl-3-phenyl-2-phenylimino-3H-thiazole (7c):



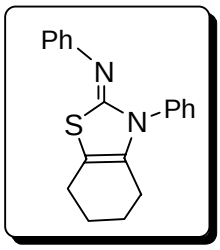
^{1}H NMR (400 MHz, $CDCl_3$): δ1.74 (s, 3H), 2.04 (s, 3H), 6.95 (m, 3H), 7.34 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ12.4, 12.8, 92.4, 104.0, 122.1, 123.2, 128.7, 129.1, 129.4, 129.7, 138.6, 152.7, 160.1. IR (KBr): 3102, 2912, 1648, 1610, 1569, 1489, 1341, 1155, 762, 691 cm^{-1}.

4-Methyl-3,5-diphenyl-2-phenylimino-3H-thiazole (7d):



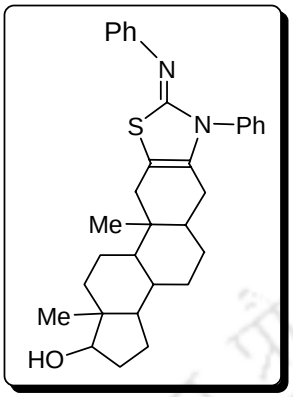
^{1}H NMR (400 MHz, $CDCl_3$): δ1.93 (s, 3H), 7.01 (m, 2H), 7.26 (m, 3H), 7.33 (m, 4H), 7.43 (m, 3H), 7.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ14.2, 109.6, 121.8, 123.2, 127.3, 128.7, 128.8, 129.2, 129.4, 129.7, 130.3, 132.8, 138.0, 152.2, 159.4. IR (KBr): 3021, 2854, 1618, 1577, 1489, 1352, 1141, 760, 688 cm^{-1}. $C_{22}H_{18}N_2S$ (342.47): calcd. C 77.16, H 5.30, N 8.18, S 9.36; found C 77.23, H 5.26, N 8.31, S 9.24.

Phenyl-(3-phenyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylidene)-amine (7e):



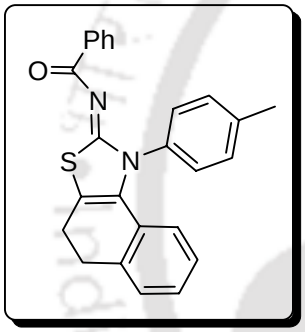
^{1}H NMR (400 MHz, $CDCl_3$): δ1.75 (m, 4H), 2.03 (m, 2H), 2.35 (m, 2H), 6.98 (m, 3H), 7.38 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ22.4, 23.2, 23.8, 24.4, 107.0, 122.0, 123.0, 128.2, 129.0, 129.4, 129.5, 131.9, 137.5, 152.6, 159.9. IR (KBr): 2939, 2835, 1648, 1607, 1572, 1489, 1374, 1141, 762, 694 cm^{-1}.

10a,12a-Dimethyl-8-phenylimino-7-phenyl- l, 2, 3, 3a, 3b, 4, 5, 5a, 6, 7, 8, 10, 10a, 10b, 11, 12, 12a-hexadecahydro-1H-9-thia-7-aza-dicyclopenta[a,h] phenanthren-1-ol (7f):



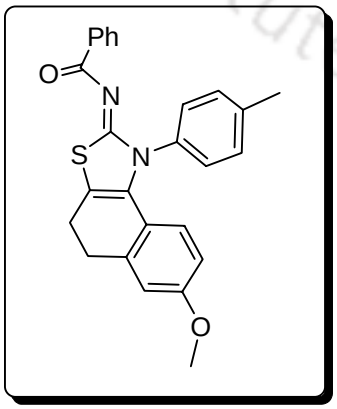
^{1}H NMR (400 MHz, $CDCl_3$): δ0.73 (s, 3H), 0.86 (s, 3H), 0.82-2.30 (m, 20H), 3.60 (t, 1H, *J* = 8.8 Hz), 4.18 (m, 1H), 7.03 (m, 2H), 7.37 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ11.2, 12.0, 20.9, 23.5, 28.5, 28.9, 30.5, 31.2, 35.7, 36.7, 37.0, 38.2, 41.8, 42.9, 50.9, 53.8, 81.9, 106.3, 121.9, 123.2, 125.2, 126.8, 128.3, 128.8, 129.4, 129.5, 137.5, 152.2, 160.8. IR (KBr): 3133, 2928, 2886, 1609, 1577, 1378, 1149, 764, 695 cm^{-1}. m/z :499 (M+1). $C_{32}H_{38}N_2OS$ (498.74): calcd. C 77.07, H 7.68, N 5.62, S 6.43; found C 76.84, H 7.71, N 5.57, S 6.50.

2-Benzoylimino-4,5-dihydro-1H-naphtho[1,2-d]-3-(p-tolyl)-thiazole (3g):



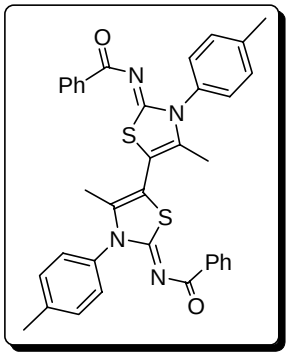
M.p. 196-197 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ2.49 (s, 3H), 2.81 (t, 2H, *J* = 7.2 Hz), 3.03 (t, 2H, *J* = 7.2 Hz), 6.35 (d, 1H, *J* = 8 Hz), 6.88 (t, 1H, *J* = 7.2 Hz), 7.09 (t, 1H, *J* = 7.2 Hz), 7.23 (t, 2H, *J* = 6.8 Hz), 7.36 (m, 6H), 8.11 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.6, 23.0, 30.0, 122.3, 123.2, 126.5, 126.6, 127.5, 128.0, 128.1, 128.5, 129.5, 130.0, 131.3, 131.5, 136.3, 136.4, 137.1, 139.0, 169.0, 174.5. IR (KBr): 3025, 3002, 2927, 2837, 1651, 1597, 1563, 1470, 1340, 1316, 1163, 905, 758, 714 cm^{-1}. $C_{25}H_{20}N_2OS$ (396.51): calcd. C 75.73, H 5.08, N 7.06, S 8.09; found C 75.79, H 5.18, N 7.18, S 8.23.

2-Benzoylimino-4,5-dihydro-7-methoxy-1H-naphtho [1,2-d]-3-(p-tolyl)-thiazole (3h):



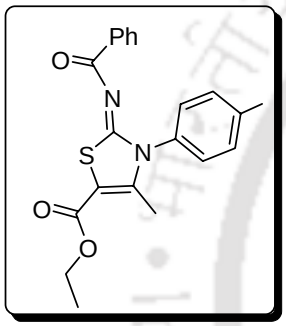
^{1}H NMR (400 MHz, $CDCl_3$): δ2.50 (s, 3H), 2.80 (t, 2H, *J* = 6.8 Hz), 3.02 (t, 2H, *J* = 6.8 Hz), 3.74 (s, 3H), 6.25 (d, 1H, *J* = 8.8 Hz), 6.41 (d, 1H, *J* = 8.8 Hz), 6.79 (s, 1H), 7.34 (m, 7H), 8.09 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ21.6, 22.9, 30.2, 55.4, 111.0, 114.9, 124.6, 127.8, 128.1, 129.4, 129.7, 130.0, 131.5, 136.4, 137.1, 138.6, 139.0, 159.9, 168.9, 174.4. IR (KBr): 3021, 2924, 2841, 1649, 1602, 1563, 1468, 1339, 1318, 1268 , 1165, 905, 756, 694 cm^{-1}. $C_{26}H_{22}N_2O_2S$ (426.54): calcd. C 73.21, H 5.20, N 6.57, S 7.52; found C 73.14, H 5.09, N 7.58, S 7.67.

5,5'-Bis-[2-benzoylimino-4-methyl-3-(p-tolyl)-3H-thiazole] (3i):



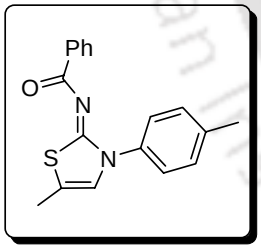
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 6H), 2.51 (s, 6H), 7.30 (m, 8H), 7.41 (m, 6H), 8.05 (d, 4H, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.6, 109.5, 127.9, 128.1, 129.6, 130.5, 131.8, 134.6, 135.1, 136.7, 139.7, 169.1, 174.9. IR (KBr): 3063, 2909, 1602, 1572, 1475, 1242, 818. cm^{-1} m/z : 615 (M+1). $C_{36}H_{30}N_4O_2S_2$ (614.79): calcd. C 70.33, H 4.92, N 9.11, S 10.43; found C 70.42, H 5.08, N 9.03, S 10.52.

2-Benzoylimino-4-methyl-3-(p-tolyl)-5-ethoxy carbonylcarboxylic acid ethyl ester-3H-thiazole (3j):



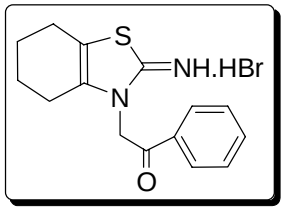
M.p. 165-167 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ1.36 (t, 3H, J = 7.2 Hz), 2.40 (s, 3H), 2.48 (s, 3H), 4.32 (q, 2H, J = 7.2 Hz), 7.28 (m, 7H), 8.00 (d, 2H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ14.2, 14.4, 21.5, 61.4, 127.8, 128.1, 129.1, 129.5, 130.5, 131.9, 134.2, 136.4, 139.8, 144.6, 162.2, 169.2, 175.2. IR (KBr): 3061, 2997, 2926, 1678, 1608, 1514, 1465, 1317, 1299, 1096, 720 cm^{-1}. $C_{21}H_{20}N_2O_3S$ (380.47): calcd. C 66.30, H 5.30, N 7.36, S 8.43; found C 66.28, H 5.18, N 7.28, S 8.38.

2-Benzoylimino-5-methyl-3-(p-tolyl)-3H-thiazole (3k):



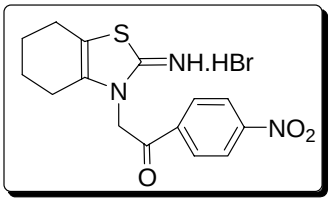
M.p. 106-107 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.39 (s, 3H), 6.80 (s, 1H), 7.34 (m, 7H), 8.10 (d, 2H, J = 8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ12.7, 21.2, 121.6, 122.7, 125.5, 127.9, 129.3, 129.6, 131.3, 136.0, 136.8, 138.2, 167.2, 174.0. IR (KBr): 3066, 2913, 1630, 1600, 1570, 1474, 1384, 1344, 1240, 902, 816, 703 cm^{-1}. $C_{18}H_{16}N_2OS$ (308.41): calcd. C 70.10, H 5.23, N 9.08, S 10.40; found C 69.92, H 5.28, N 9.23, S 10.51.

2-(2-Imino-4,5,6,7-tetrahydro-benzothiazol-3-yl)-1-phenyl-ethanone hydrobromide (13a):



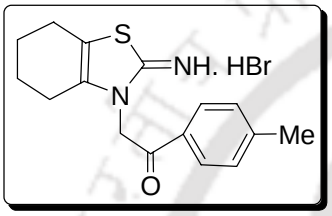
^{1}H NMR (400 MHz, $CDCl_3$): δ1.73 (s, 4H), 2.30 (s, 2H), 2.50 (s, 2H), 5.73 (s, 2H), 7.53 (m, 2H), 7.62 (m, 1H), 8.03 (m, 2H), 9.53 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.8, 22.2, 22.4, 52.2, 114.5, 128.4, 128.6, 133.5, 134.2, 134.3, 167.8, 190.2. IR (KBr): 3273, 3174, 2998, 1690, 1623, 1560, 1411, 1233, 991, 749, 688 cm^{-1}.

2-(2-Imino-4,5,6,7-tetrahydro-benzothiazol-3-yl)-1-(4-nitro-phenyl)-ethanone hydrobromide (13b):



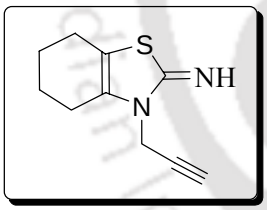
^{1}H NMR (400 MHz, $CDCl_3$): δ1.73 (s, 4H), 2.40 (m, 4H), 5.96 (s, 2H), 8.29 (s, 2H), 8.94 (s, 2H), 9.59 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.3, 23.5, 23.7, 52.5, 108.6, 123.0, 123.6, 124.9, 125.9, 126.7, 168.6, 191.9. IR (KBr): 3224, 3169, 2998, 1695, 1619, 1561, 1415, 1346,1228, 752 cm^{-1}.

2-(2-Imino-4,5,6,7-tetrahydro-benzothiazol-3-yl)-1-p-tolyl-ethanone hydrobromide (13c):



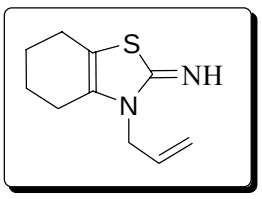
^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ1.57 (s, 4H), 1.99 (s, 3H), 2.25 (m, 4H), 5.42 (s, 2H), 7.01 (d, 2H, J = 8.0 Hz), 7.69 (d, 2H, J = 8.0 Hz), 9.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 20.7, 21.6, 22.1, 22.2, 23.5, 51.8, 114.8, 125.0, 128.1, 129.1, 129.5, 131.0, 167.8, 189.1. IR (KBr): 3273, 3169, 2984, 2849, 1688, 1627, 1554, 1228, 986, 749 cm^{-1}.

3-Prop-2-ynyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylideneaminehydrobromide (13d):



^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 4H), 1.52 (s, 2H), 1.61 (s, 2H), 2.12 (m, 1H), 3.56 (brs, 1H), 3.90 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 20.5, 20.9, 21.0, 44.6, 73.7, 75.2, 113.8, 132.4, 165.6. IR (KBr): 3269, 3109, 2941, 2844, 2124, 1649, 1622, 1558, 1396, 1120, 1024, 900, 720, 707, 591cm^{-1}. $C_{10}H_{12}N_2S$ (192.28): calcd. C 62.47, H 6.29, N 14.57, S 16.68; found C 62.56, H 6.31, N 14.52, S 16.71.

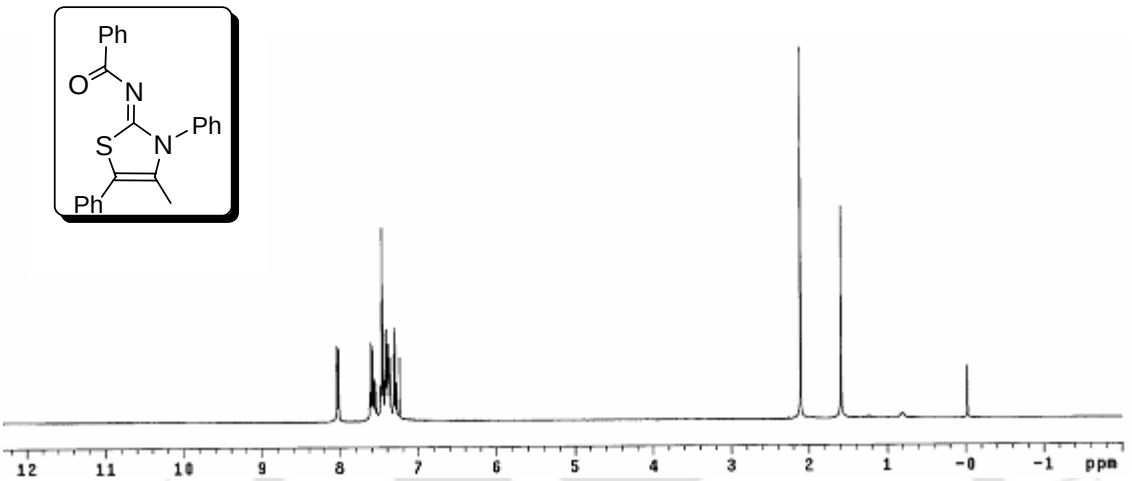
3-Allyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylideneamine (13e):



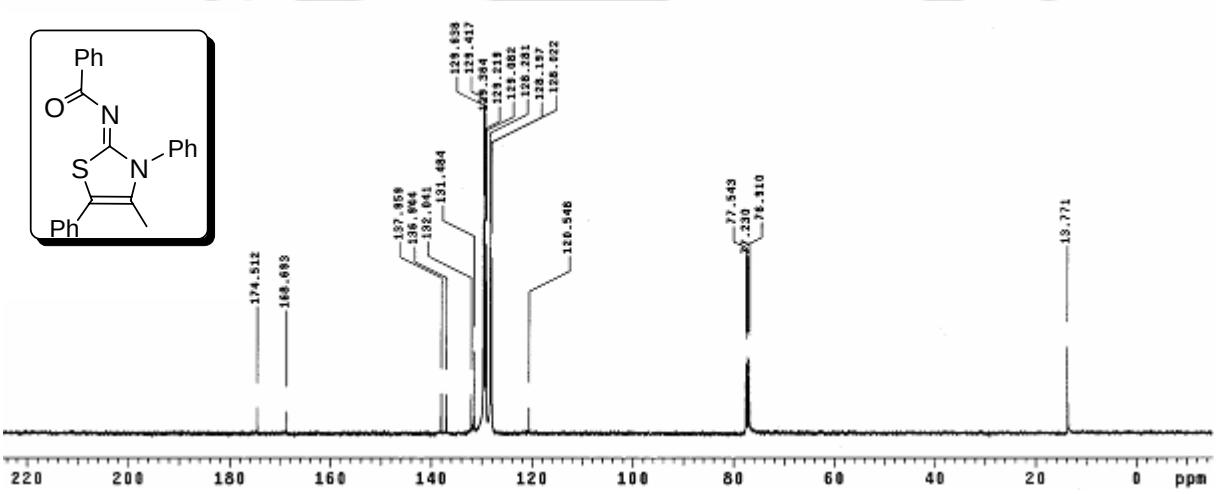
^{1}H NMR (400 MHz, $CDCl_3$): δ1.78 (s, 4H), 2.30 (s, 4H), 3.60 (brs, 1H), 4.36 (d, 2H, J = 2.8 Hz), 5.10 (d, 1H, J = 17.2 Hz), 5.16 (d, 1H, J = 10.4 Hz), 5.87 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 22.4, 22.9, 23.0, 48.2, 116.6, 118.5, 129.3, 133.8, 166.9. IR (KBr): 3221, 3176, 3010, 1623, 1556, 1423, 688 cm^{-1}. $C_{10}H_{14}N_2S$ (194.30): calcd. C 61.82, H 7.26, N 14.42, S 16.50; found C 61.87, H 7.19, N 14.51, S 16.46.

III.8. Selected Spectra

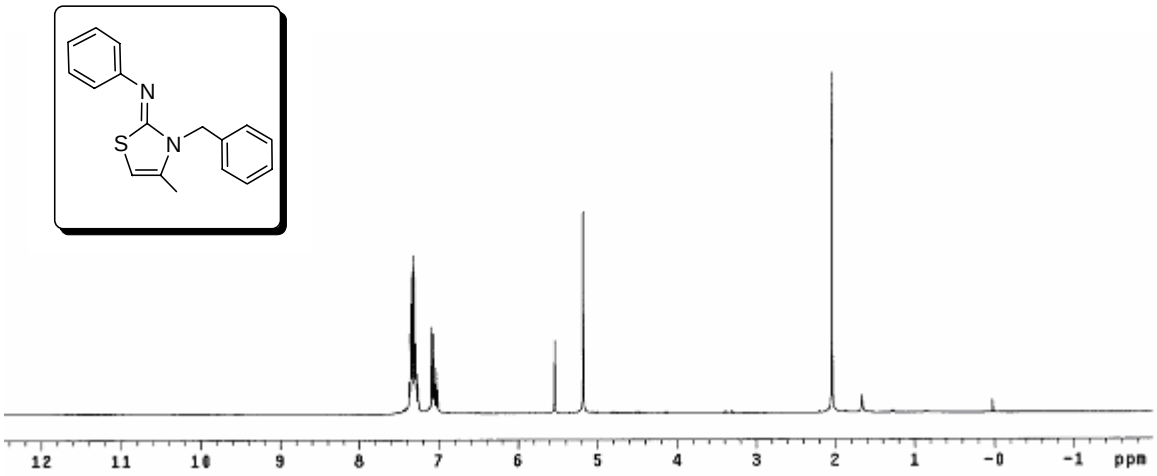
2-Benzoylimino-3,5-diphenyl-4-methyl-3H-thiazole (1d): ^{1}H NMR (400 MHz, $CDCl_3$):



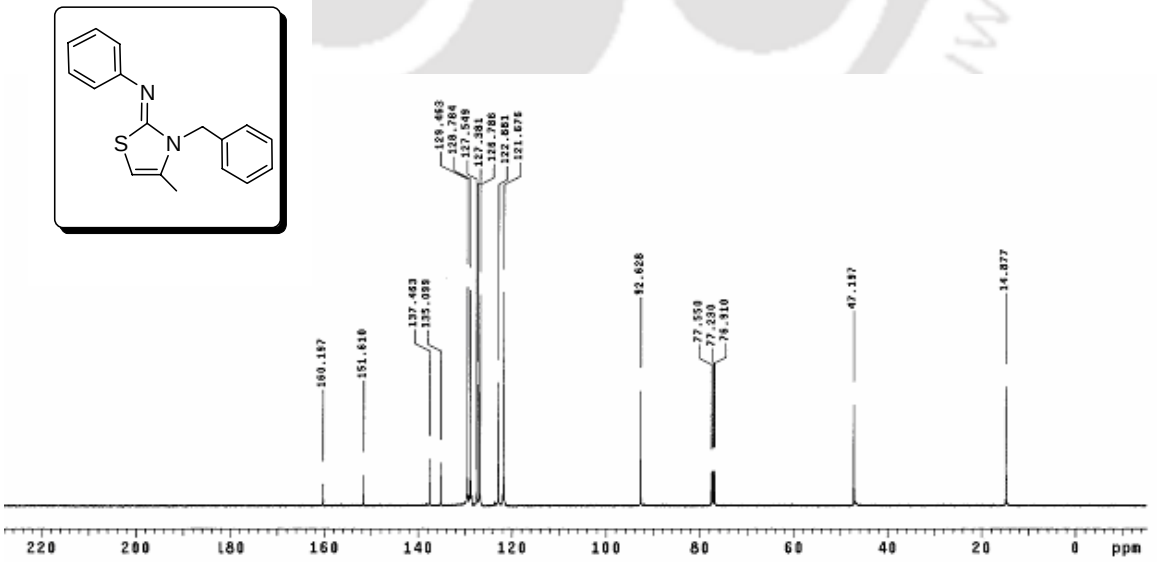
2-Benzoylimino-3,5-diphenyl-4-methyl-3H-thiazole (1d): ^{13}C NMR (100 MHz, $CDCl_3$):



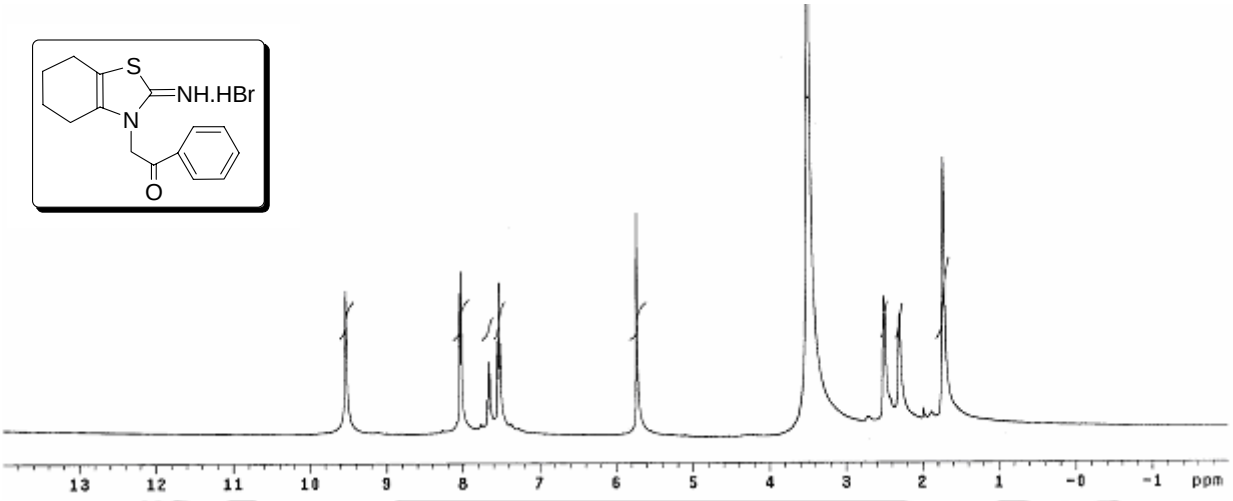
3-Benzyl-4-methyl-2-phenylimino-3H-thiazole (11a): ^{1}H NMR (400 MHz, $CDCl_3$):



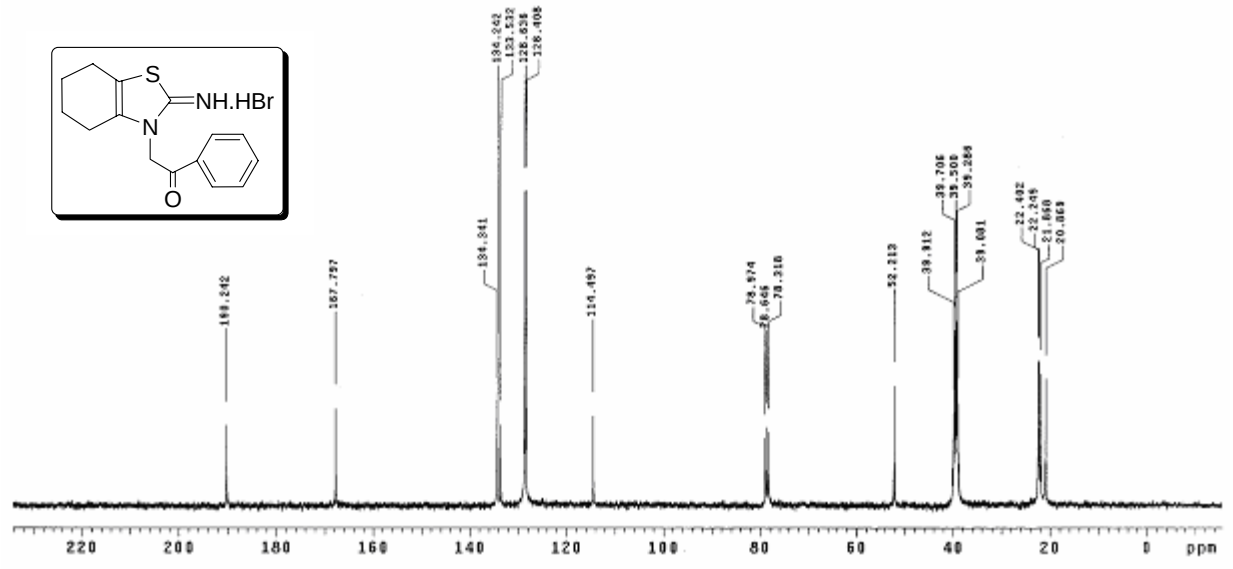
3-Benzyl-4-methyl-2-phenylimino-3H-thiazole (11a): ^{13}C NMR (100 MHz, $CDCl_3$):



2-(2-Imino-4,5,6,7-tetrahydro-benzothiazol-3-yl)-1-phenyl-ethanone hydrobromide (13a): ^{1}H NMR (400 MHz, DMSO-d$_6$):



2-(2-Imino-4,5,6,7-tetrahydro-benzothiazol-3-yl)-1-phenyl-ethanone hydrobromide (13a): ^{13}C NMR (100 MHz, DMSO-d$_6$):

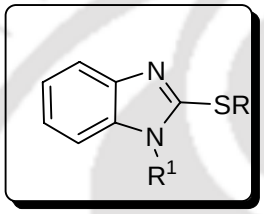


CHAPTER IV

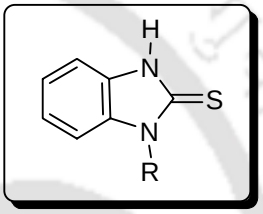
IV. Cu(I)-Catalyzed Synthesis of Substituted 2-Mercapto Benzimidazoles

IV.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I., Section I.1.1., Figure I.1.1.3. in pages 3 and 4. This chapter deals with the following two types of heterocycles namely substituted mercapto benzimidazoles and benzimidazole thiones.



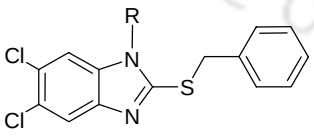
Substituted mercapto benzimidazoles



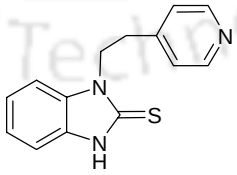
Benzimidazole thiones

IV.2. Importance and Applications

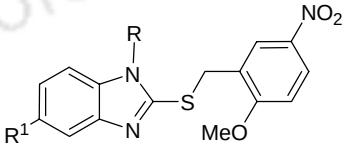
2-Mercapto benzimidazoles are important class of heterocycles that are encountered in a number of natural and non-natural biologically active compounds. For example, medicinal chemistry applications of such compounds include 2-(benzylthio)-4,6-dichloro-1-[(2-hydroxyethoxy)methyl]-benzimidazole as antiviral compound,[1a] 2-mercapto-1-(*β*-4-pyridethyl) benzimidazole (MPB) as antitumor agent,[1b] and luteinizing hormone-releasing hormone (LHRH) antagonists (*Figure IV.2.1.*).[1c]



Antiviral compound



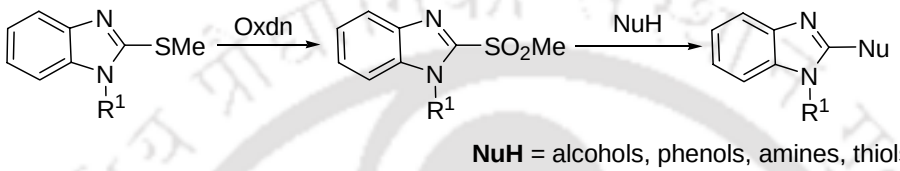
Antitumor agent (known as MPB)



Potent LHRH antagonist

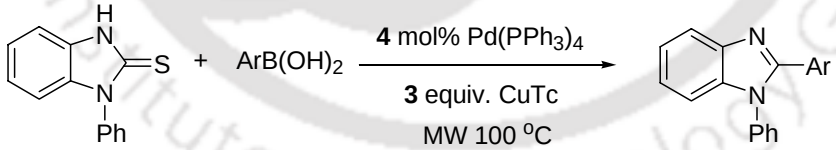
Figure IV.2.1. *Structures of some biologically active substituted 2-mercapto benzimidazoles*

The cyclic thioureide structure is recognized for its antithyroid action,[2] and has shown atypical antipsychotic potency when linked to aryl piperazines.[3] Substituted 2-mercapto benzimidazoles can be oxidized into sulfinyl derivatives, which belong to another class of pharmaceutically important molecules.[4] Finally, the mercapto group can be oxidized into sulfonyl, which can act as a leaving group for the synthesis of 2-substituted benzimidazoles (*Scheme IV.2.1.*).[5]



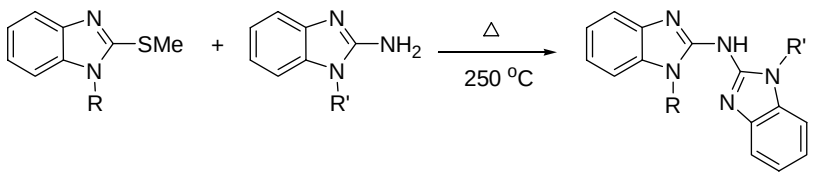
Scheme IV.2.1.

Benzimidazole thiones were used as coupling partners in Pd-catalyzed desulfurative carbon–carbon cross-coupling protocol, which leads to 2-aryl benzimidazoles (*Scheme IV.2.2.*). An advantage of using thioamides as starting materials is the fact that the system can be tuned to an alternative carbon-sulfur cross-coupling pathway by changing to stoichiometric copper (II) under oxidative conditions. Both types of thioamide cross-couplings are orthogonal to the traditional base-catalyzed Suzuki-Miyaura cross-coupling of aryl halides with boronic acids.[6]



Scheme IV.2.2.

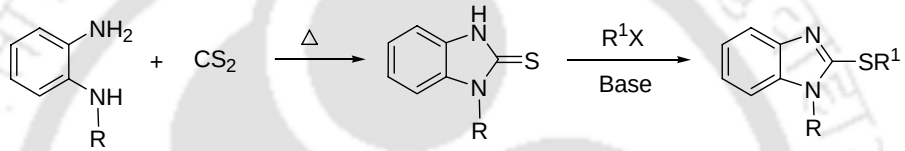
S-methyl 2-mercapto benzimidazoles were used in the synthesis of novel bis(benzimidazole-2-yl) amine derivatives for the in vitro study of antitrichinellosis activity against *Trichinelle spiralis larvae* in regard to the activity of albendazole (*Scheme IV.2.3.*).[7]



Scheme IV.2.3.

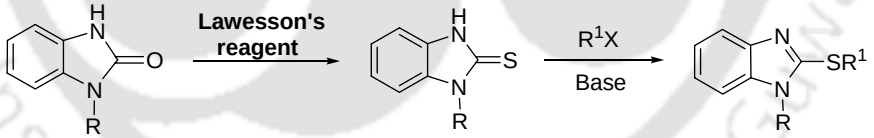
IV.3. Available Synthetic Methods

The main methodology for the synthesis of unsymmetrically substituted 2-mercapto benzimidazoles involves the reaction of *o*-phenylene diamine precursors with CS_2, followed by alkylation (*Scheme IV.3.1.*).[2c,3,5b,8]



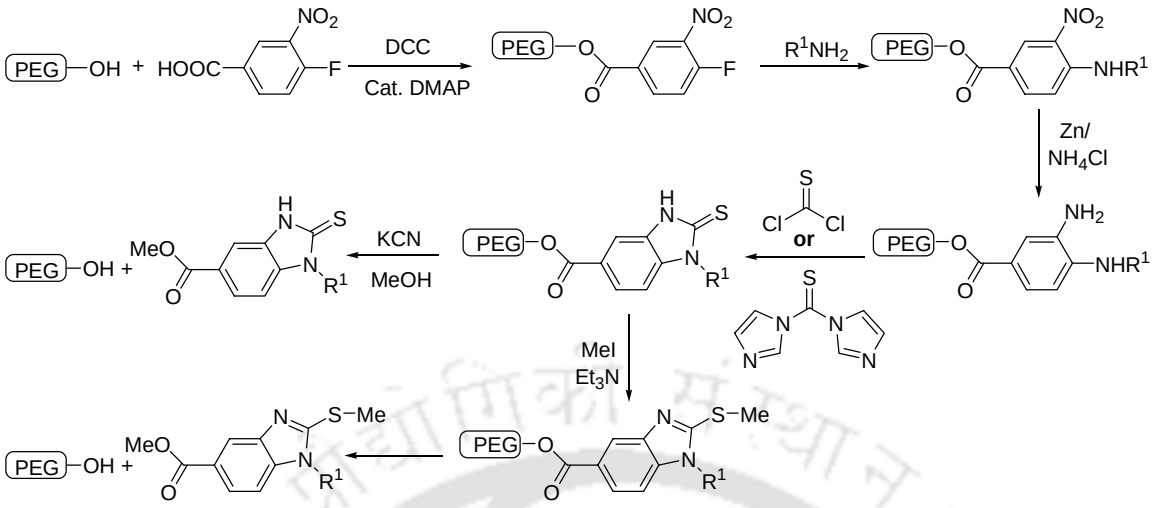
Scheme IV. 3.1.

Similarly, 2-benzimidazole thiones are prepared from *o*-phenylene diamine via the formation of benzimidazolones, and thionation of the later using Lawesson's reagent (*Scheme IV.3.2.*).[9]



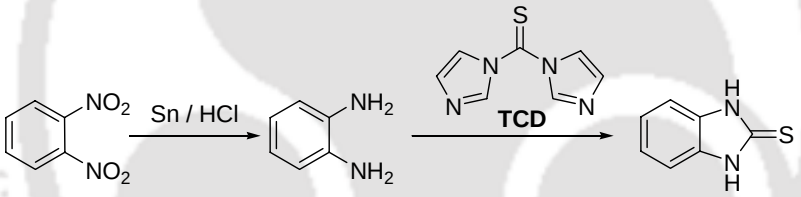
Scheme IV.3.2.

Sun *et al.* have developed a liquid phase method for the synthesis of diverse benzimidazole libraries. Nucleophilic aryl substitution of poly ethylene glycol (PEG)-supported with primary amines under basic condition, followed by Zn-mediated reduction gave PEG bound diamines. Subsequent cyclization using CS_2 equivalents provides benzimidazole thiones which were further alkylated to get a library of substituted mercaptobenzimidazoles (*Scheme IV.3.3.*). The same methodology was extended for the synthesis of 2-sulphanylated *bis*-benzimidazoles (*Scheme IV.3.3.*).[10]



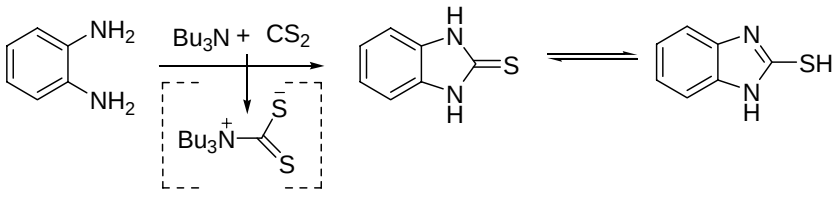
Scheme IV.3.3.

Benzimidazole 2-thiones were synthesized in two steps by the condensation *o*-phenylene diamines and thiocarbonyl diimidazole (TCD). *o*-Phenylene diamine precursors can be accessed from the corresponding *o*-dinitrobenzene as shown in *Scheme IV.3.4.*[11]



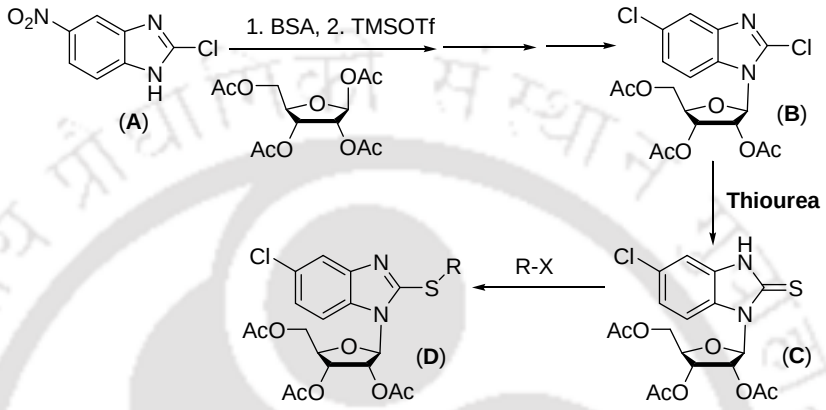
Scheme IV.3.4.

Reaction of carbon disulfide and *o*-phenylene diamine catalyzed by tertiary amines in homogeneous solution to access 2-mercapto benzimidazole (MBI) or benzimidazole thiones was reported. A kinetic model also was proposed to explain the formation of active intermediate (R_3N-CS_2) from the reaction of tertiary amine and carbondisufide (*Scheme IV.3.5.*).[12]



Scheme IV.3.5.

Ribosylation of 2-chloro-5-nitrobenzimidazole (**A**) gave 2-chloro-5-nitro-1-(2,3,5-tri-*o*-acetyl-D-ribofuranosyl) benzimidazole (**B**). Subsequent steps including chlorination and thionation with thiourea afforded 6-chloro-1-(D-ribofuranosyl)benzimidazol-2-thione (**C**) which is then alkylated using methyl iodide or benzyl bromide to give the corresponding 2-methylthio and 2-benzylthio analogues (**D**) (*Scheme IV.3.6.*).



Scheme IV.3.6.

Evaluation of these compounds for activity against human cytomegalovirus (HCMV) and herpes simplex virus type 1 revealed that these heterocycles are active against both viruses but were found to be cytotoxic.[13]

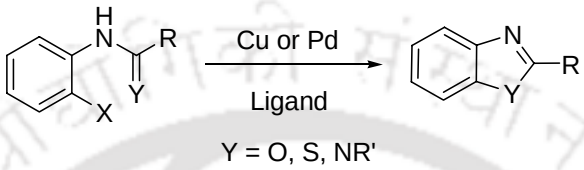
These methods suffer from a limited number of suitable substrates for diverse synthesis. We felt that a catalytic approach involving C–N bond formation would overcome this drawback.

IV.4. Present Work

IV.4.1. Cu(I)-Catalyzed Synthesis of Substituted 2-Mercapto Benzimidazoles

In the last decade, a great effort has been devoted towards the development of efficient methods for the synthesis of heterocyclic compounds from aryl halides using copper-catalysts.[14] Buchwald et al. have reported the synthesis of indolines,[15] 2-aryl-4-

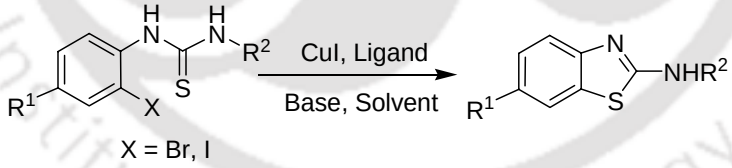
quinolones,[16] and *N*-alkylbenzimidazoles.[17] The group of Ma developed cascade processes for the preparation of isoquinolines,[18] benzofurans,[19] benzimidazoles,[20] dihydrobenzimidazole-2-ones,[21] indoles,[22] and pyrrolo[1,2-*a*]quinoxaline.[23] Batey's group reported copper or palladium-catalyzed intramolecular C–X (O, S and N) bond formation to synthesize benzoxazoles,[24] benzothiazoles,[24b] and aminobenzimidazoles[25] (*Scheme IV.4.1.1.*).



Scheme IV.4.1.1.

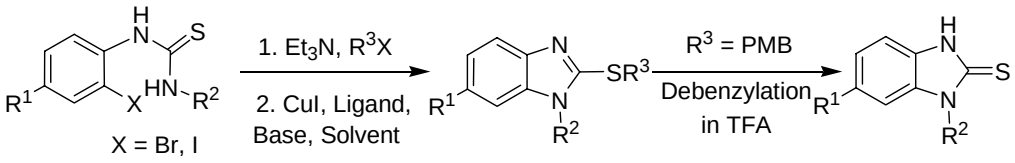
Although C–N bond formation has been well explored for the construction of various heterocycles, there is no report for the preparation of substituted 2-mercapto benzimidazoles employing this strategy.

Our interest in developing methods for the synthesis of heterocyclic compounds from thioureas,[26] led us to consider a Cu-catalyzed approach using 2-haloaniline derived thioureas. Recently, Batey and Pan have shown that the cyclization of 2-bromophenylthioureas derivatives leads to substituted 2-aminobenzothiazoles (*Scheme IV.4.1.2.*).[27]



Scheme IV.4.1.2.

We envisaged that an *S*-alkylation followed by an intramolecular Cu-catalyzed aryl amination sequence from 2-haloaniline derived thioureas could lead to substituted 2-mercapto benzimidazoles as shown in *Scheme IV.4.1.3.* The reaction of *S*-*p*-methoxybenzyl thioethers in trifluoro acetic acid in the presence or in the absence of metal salts, is known to produce the corresponding thiols or thiones,[28] therefore we expected that our approach could be extended for the preparation of benzimidazole thiones from 2-mercapto benzimidazoles substituted with a *p*-methoxy benzyl (PMB) group (*Scheme IV.4.1.3.*).



Scheme IV.4.1.3.

1-(2-Bromophenyl)-3-phenylthiourea (**1a**), (*Table IV.4.1.1*) prepared quantitatively from 2-bromoaniline and phenyl isothiocyanate, was first evaluated as a model substrate. *S*-Alkylation of 1,3-disubstituted thioureas is known to occur selectively on the sulphur atom, using alkyl halides and bases at room temperature.[26,29]

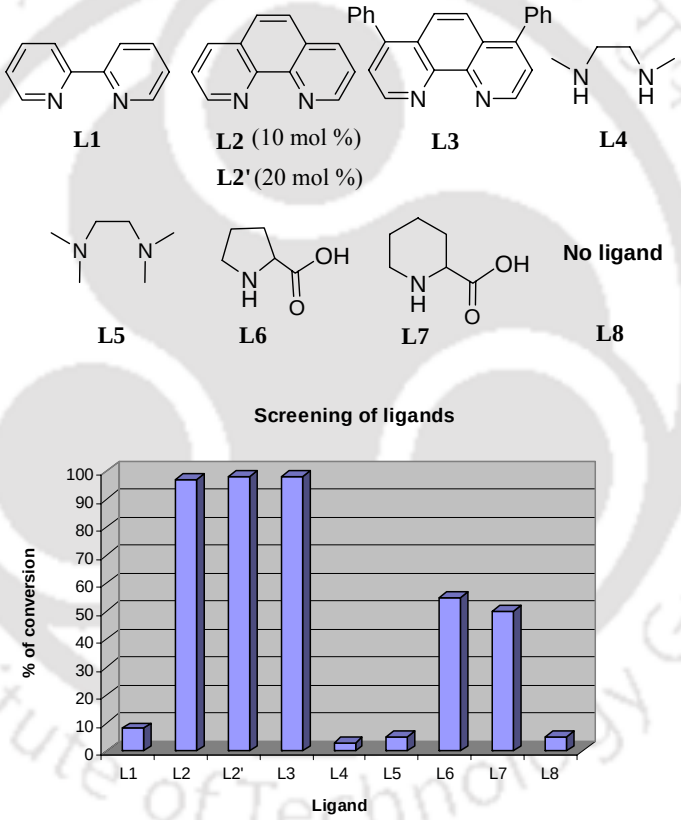
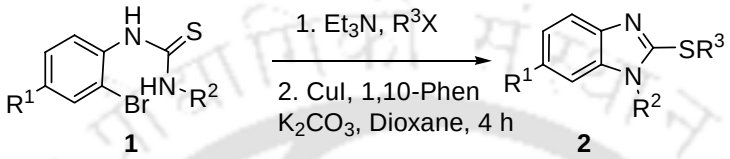


Figure IV.4.1.1. *Ligands examined for Cu-Catalyzed Intramolecular Amination*

We began our investigation using MeI and NEt_3 for alkylation, and by evaluating different ligands (0.1-0.2 equiv.) (*Figure IV.4.1.1.*), using CuI (0.05 equiv.) as precatalyst, K_2CO_3 (2 equiv.) as base, and 1,4-dioxane as solvent. The reaction was inefficient in the absence of ligand or in the presence of diamine and bipyridine ligands. Low conversion

(<50%) was observed using L-proline and L-pipecolinic acid. The best results were obtained using 1,10-phenanthroline (**L2**) and 4,7-diphenyl 1,10-phenanthroline (**L3**) that led to nearly 95% conversion at 85 °C. 1,10-Phenanthroline (**L2**) was finally selected as the ligand due to easy availability and cost consideration.

Table IV.4.1.1. *Synthesis of Substituted 2-Mercapto Benzimidazoles* ***2***[a]



1 **2**

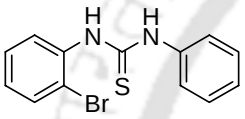
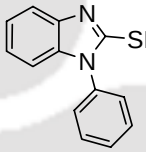
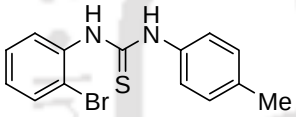
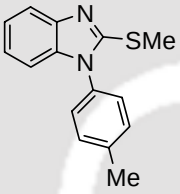
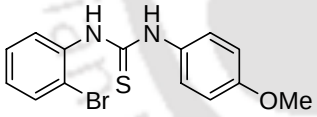
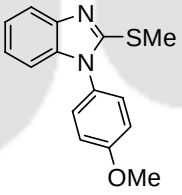
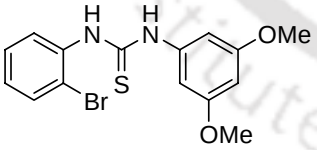
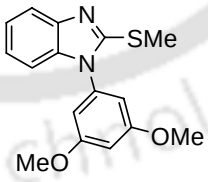
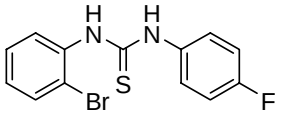
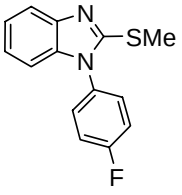
Substrate	R^3	Product		Yield %[b]
	Me		(**2a**)	75
	Me		(**2b**)	91
	Me		(**2c**)	93
	Me		(**2d**)	88
	Me		(**2e**)	83

Table IV.4.1.1. continued…

Table IV.4.1.1. continued…

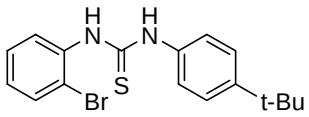
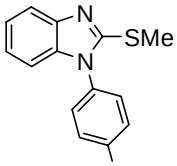
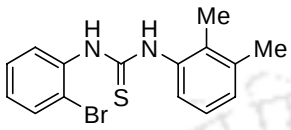
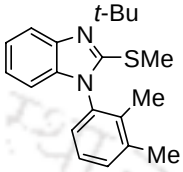
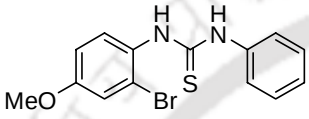
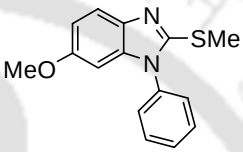
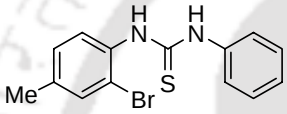
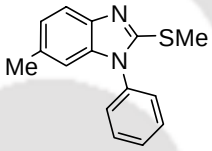
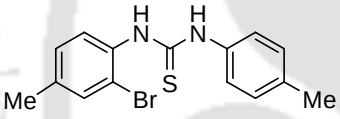
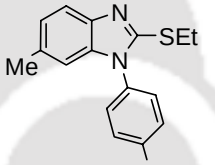
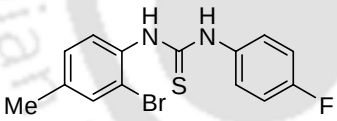
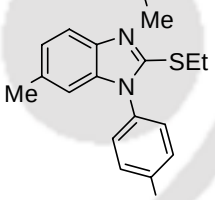
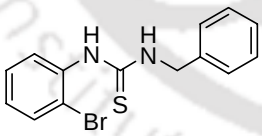
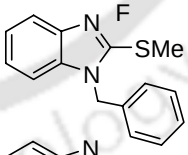
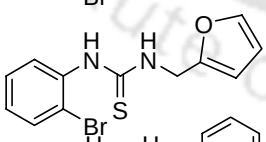
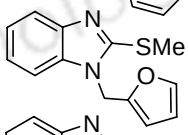
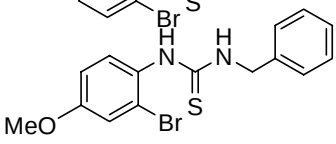
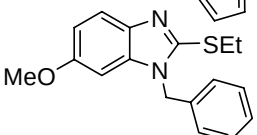
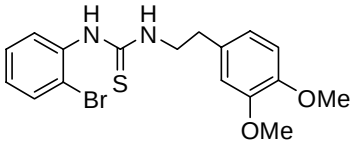
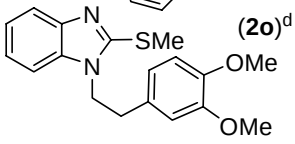
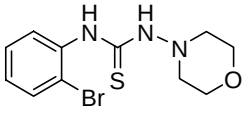
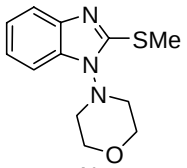
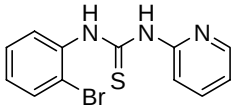
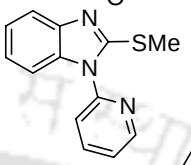
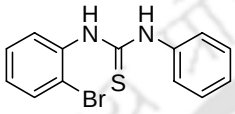
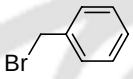
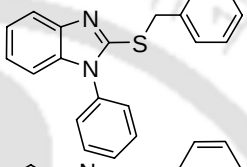
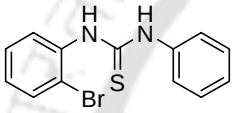
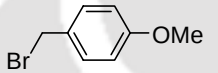
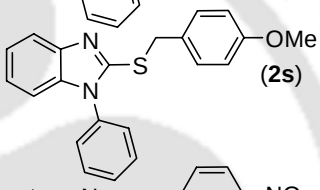
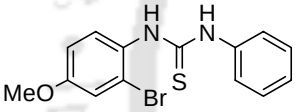
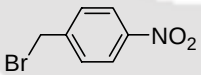
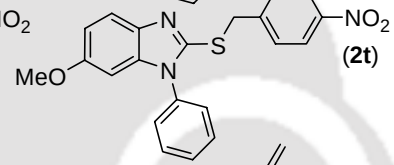
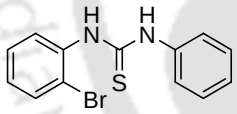
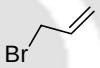
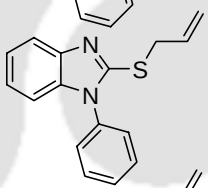
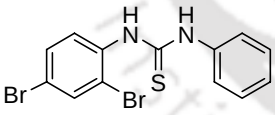
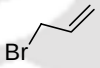
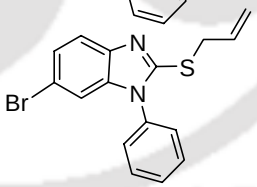
Substrate	R^3	Product		Yield %[b]
	Me		(**2f**)	78
	Me		(**2g**)	74
	Me		(**2h**)	82
	Me		(**2i**)	85
	Et		(**2j**)	78
	Et		(**2k**)	81
	Me		(**2l**)[b]	81
	Me		(**2m**)[c]	78
	Et		(**2n**)[c]	74
	Me		(**2o**)[d]	48

Table IV.4.1.1. continued…

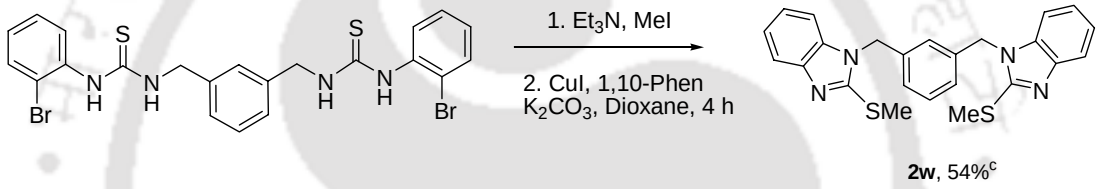
Table IV.4.1.1. continued…

Substrate	R^3X	Product		Yield %[b]
	MeI		(**2p**)[b]	86
	MeI		(**2q**)[b]	79
			(**2r**)	87
			(**2s**)	92
			(**2t**)	84
			(**2u**)	88
			(**2v**)	81

[a]Reaction conditions: 1 (1.0 mmol), Et_3N (1.5 equiv.), R^3X (1.0-1.5 equiv.), CH_3CN (5 mL); CuI (0.05 equiv.), 1,10-phenanthroline (0.1 equiv.), K_2CO_3 (2 equiv.), dioxane (5 mL), 4 h. R^3X: MeI, EtI, allyl iodide (1.5 equiv) or BnBr, *p*-(MeO)$C_6H_4CH_2Br$, *p*-(NO_2)$C_6H_4CH_2Br$ (1 equiv). [b]performed over 8 h.[c]performed over 12 h. [d]performed over 20 h.

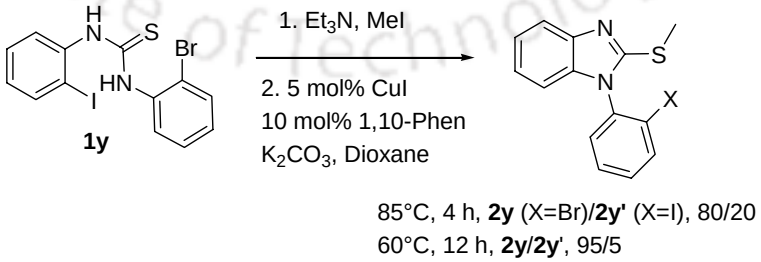
The one-pot sequence *S*-alkylation/Cu-catalyzed intramolecular *N*-arylation of **1a** led to **2a** in 75% yield within 4 hours *(TableIV.4.1.1.).* Using this procedure, the scope of the method was then explored. As shown in *Table IV.4.1.1*. a variety of aryl and alkyl groups in diversified positions are well tolerated. The aryl substituted thioureas **1b-1k**,

prepared from the corresponding 2-haloanilines and aryl isothiocyanate, were converted smoothly into their corresponding 2-mercapto benzimidazoles **2b**-**2k** in shorter reaction times compared to their alkyl substituted analogues **2l**-**2o**. The relevance of *bis*-heterocycles in drug discovery has been recently notified.[30] Thus, we have explored the reactivity of thioureas bearing heterocycles such as furan, morpholine, and pyridine. Noteworthy, the Cu-catalyzed cyclization is compatible with such compounds and *bis*-heterocycles **2m**, **2p**, and **2q** were obtained in good yields. In addition, cyclization of *bis*-thiourea **1w** prepared from 1,3-*bis*(isothiocyanatomethyl)benzene was also achieved and afforded **2w** in moderate yield (*Scheme IV.4.1.4.*). *S*-Alkylations have been performed with different electrophiles such as alkyl, benzyl, and allyl halides leading to **2b**-**2q**, **2r**-**2t**, and **2u**-**2v** respectively (*Table IV.4.1.1.*).



Scheme IV.4.1.4.

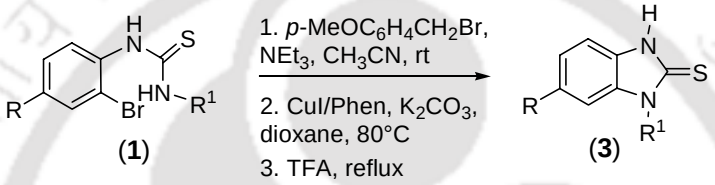
1-(2-Bromophenyl)-3-(2-iodophenyl)thiourea **1y** led, under standard conditions, to a mixture of bromo and iodo derivatives **2y**/**2y'**. However, when the reaction was performed at lower temperature, 1-(2-bromophenyl)-2-(methylthio)benzimidazole **2y** was produced with good selectivity (*Scheme IV.4.1.5.*).



Scheme IV.4.1.5.

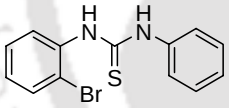
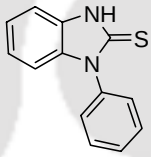
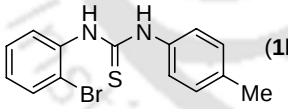
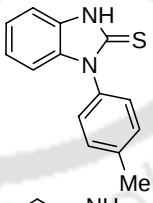
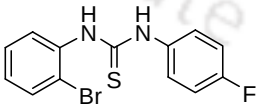
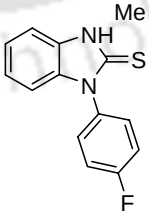
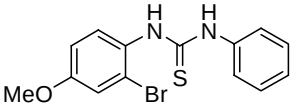
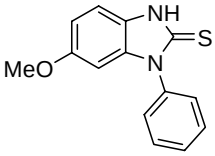
IV.4.2. Application in the Synthesis of Benzimidazole Thiones

As the general nature and the efficiency of the above reaction protocol has been proven, the debenzylation of the compounds bearing a *p*-methoxy benzyl group was investigated, in order to extend our methodology for the preparation of benzimidazole thiones **3**. Such compounds cannot be synthesized in a direct manner by a cyclization process,[27] Alkylation of **1a**, **1b**, **1e**, and **1h** with 4-methoxybenzyl bromide, followed by Cu-catalyzed cyclization, and debenzylation in TFA afforded **3a**, **3b**, **3e**, and **3h** in fair yields (*Scheme IV.4.2.1.*) (*Table IV.4.2.1.*).[31]



Scheme IV.4.2.1.

Table IV.4.2.1. *Synthesis of Substituted Benzimidazole Thiones **3**.*

Substrate		Product		Yield %
	(**1a**)		(**3a**)	68
	(**1b**)		(**3b**)	72
	(**1e**)		(**3e**)	71
	(**1h**)		(**3h**)	75

[a]Reaction conditions: 1 (1.0 mmol), Et_3N (1.5 equiv.), *p*-(MeO)$C_6H_4CH_2Br$ (1.0-1.5 equiv.), CH_3CN (5 mL); CuI (0.05 equiv.), 1,10-phenanthroline (0.1 equiv.), K_2CO_3 (2 equiv.), dioxane (5 mL), 4 h.

In conclusion, we have developed an alkylation/Cu-catalyzed intramolecular *N*-arylation process to synthesize substituted 2-mercapto benzimidazoles from their corresponding thioureas. A wide range of substrates were easily prepared from 2-haloanilines and were efficiently assembled into these heterocycles. The synthetic approach allows the construction of products from three different components (bromoanilines, isothiocyanates, and alkyl halides) providing a versatile access to these pharmaceutically important compounds. Benzimidazole thiones are also accessible by using a protection (PMB)/deprotection strategy.

IV.5. Experimental Section

IV.5.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1.

IV.5.2. General Procedure for the Synthesis of Substituted 2-Mercapto Benzimidazoles (2).

To a solution of thiourea **1** (1.0 mmol) in acetonitrile (5 mL), NEt_3 (1.5 mmol, 210 μL) and alkyl halide (1.5 mmol) were successively added and the resulting solution was stirred for 10 minutes at room temperature. Solvent was evaporated; the residue was washed with water and extracted with ethyl acetate (2 x 15 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum to give thioether *S*-alkylated product up to 98 % yield, which was used for the next step without any further purification. (In the case of BnBr, *p*-$(MeO)C_6H_4CH_2Br$, *p*-$(NO_2)C_6H_4CH_2Br$, 1 mmol of halide was used and the reaction time was extended to 20 min).

A round bottom flask was charged with thioether *S*-alkylated product (~1 mmol), CuI (0.05 mmol, 9.5 mg), 1,10-phenanthroline (0.1 mmol, 18 mg), K_2CO_3 (2 mmol, 276 mg) and 1,4-dioxane (5 mL). The resulting solution was heated at 85 °C until the disappearance of the starting material (TLC). The reaction mixture was then cooled, filtered over Celite using ethyl acetate. Solvent was evaporated and further purification was achieved by column chromatography.

IV.5.3. General Procedure for Synthesis of Benzimidazole Thiones (3).

Thiourea **1** (1.0 mmol) was first alkylated as described above. A round bottom flask was charged with the corresponding thioether *S*-alkylated product (~1.0 mmol), CuI (0.05 mmol, 9.5 mg), 1,10-phenanthroline (0.1 mmol, 18 mg), K_2CO_3 (2.0 mmol, 276 mg) and 1,4-dioxane (5 mL). The resulting solution was heated at 85 °C until the disappearance of the starting material (TLC). The reaction mixture was then cooled, filtered over Celite with ethyl acetate, and solvent was evaporated. TFA (3-5 mL) was added, and the reaction mixture was heated at 85 °C for 2 h. After completion, TFA was removed under vacuum and the residue was treated with sodium bicarbonate solution. The product was extracted with ethylacetate (2 x 15 mL). The organic phase was dried over $MgSO_4$, and then evaporated. The crude product was purified with a short chromatography column.

IV.6. References

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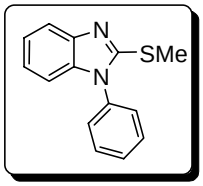
31. Benzimidazole thiones have two tautomeric forms and can be drawn as either thioenol or as thione. It is believed that these compounds exist primarily in the thione form. Therefore, for the purposes of this publication, we will refer to and draw the products as thiones. For discussions on the tautomerism of thiones, see: (a) Khan, H.; Badshah, A.; Shaheen, F.; Gieck, C.; Qureshi, R. A. *Acta Cryst.* **2008**, E64, o1141. (b) Öğretir, C.; Öztürk, İ. İ.; Tay, N. F. *Arkivoc* **2007**, *(xiv)*, 75. (c) Elzbieta, B.-O.; Lech, S.; Graham A, W.; Ian H, S.; B. *Pol. Acad. Sci-Chem.* **1987**, *35*, 81.

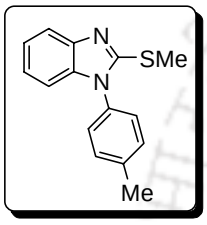
IV.7. Spectral Data

2-(Methylthio)-1-phenylbenzimidazole (2a).



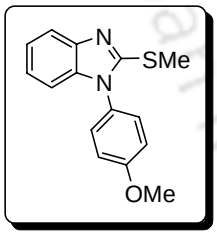
Colorless gum; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.63 (s, 3H), 7.06 (m, 3H), 7.36 (m, 5H), 7.64 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 108.4, 117.2, 121.4, 126.0, 128.1, 129.0, 134.4, 136.6, 142.7, 152.6; IR (KBr): 3052, 2928, 2853, 1596, 1499, 1369, 1270, 1011, 741 cm^{-1}. Calcd for $C_{14}H_{12}N_2S$: C 69.97; H 5.03; N 11.66; S 13.34. Found: C 69.81; H 5.02; N 12.02; S 13.25.

2-(Methylthio)-1-*p*-tolylbenzimidazole (2b).



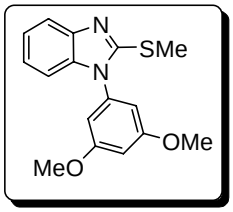
White solid; mp 72-74 ºC; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.66 (s, 3H), 7.04-7.29 (m, 7H), 7.65 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 19.7, 107.7, 116.3, 120.6, 125.1, 128.8, 136.0, 137.6, 141.9, 152.1; IR (KBr): 3056, 3029, 2922, 2858, 1604, 1514, 1445, 1270, 811, 744 cm^{-1}. Calcd for $C_{15}H_{14}N_2S$: C 70.83; H 5.55; N 11.01; S 12.61. Found: C 70.97; H 5.57; N 11.06; S 12.69.

2-(Methylthio)-1-(4-methoxy-phenyl)- 1*H*-benzo[*d*]imidazole (2c).



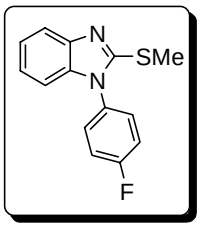
White solid; mp 129–131^o C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.66 (s, 3H), 3.79 (s, 3H), 6.94–7.26 (m, 7H), 7.64 (d, 1H, J = 7.75 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 57.4, 111.1, 116.8, 119.9, 123.9, 124.0, 130.2, 139.7, 145.4, 155.8, 161.8; IR (KBr): 3003, 2933, 2839, 1608, 1512, 1444, 1272, 1183, 1029, 844, 744 cm^{-1}. Calcd for $C_{15}H_{14}N_2OS$ (270.35): C 66.64; H 5.22; N 10.36; S 11.86. Found C 66.72; H 5.20; N 10.32; S 11.70.

2-(Methylthio)-1-(3,5-dimethoxy-phenyl)- 1*H*-benzo[*d*]imidazole (2d).



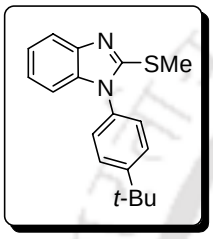
White solid; mp 88–90 ^{o}C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.75 (s, 3H), 3.80 (s, 6H), 6.58 (d, 3H, J = 2.25 Hz), 7.14–7.22 (m, 3H), 7.72 (d, 1H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 55.5, 100.8, 104.8, 109.4, 117.9, 122.1, 136.6, 137.1, 143.4, 153.2, 161.4; IR (KBr): 3050, 2961, 2931, 2836, 1616, 1588, 1447, 1305, 1270, 1157, 856, 741 cm^{-1}. Calcd for $C_{16}H_{16}N_2O_2S$ (300.09): C 63.98; H 5.37; N 9.33; S 10.67. Found C 63.90; H 5.38; N 9.40; S 10.58.

2-(Methylthio)-1-(4-fluoro-phenyl)- 1*H*-benzo[*d*]imidazole (2e).



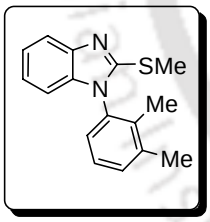
Reddish yellow liquid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.74 (s, 3H), 7.04–7.43 (m, 7H), 7.72 (d, 1H, *J* = 7.75 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 13.4, 107.9, 115.6, 115.9, 117.0, 121.2, 127.7, 127.9, 136.4, 142.3, 152.4, 159.4, 163.4; IR (KBr): 3054, 2930, 1611, 1556, 1504, 1423, 1266, 1154, 847, 748 cm^{-1}. Calcd for $C_{14}H_{11}N_2SF$ (258.31): C 65.10; H 4.29; N 10.84; S 12.41. Found C 65.28; H 4.31; N 10.90; S 12.56.

2-(Methylthio)-1-(4-*tert*-butyl-phenyl)- 1*H*-benzo[*d*]imidazole (2f).



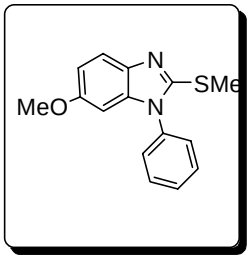
White crystalline solid; mp 153 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.26 (s, 9H), 2.61 (s, 3H), 6.99 - 7.13 (m, 3H), 7.22 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 2H, *J* = 8.5 Hz), 7.62 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.6, 31.4, 34.9, 109.4, 118.0, 122.1, 126.4, 126.7, 132.5, 137.6, 143.6, 152.1, 153.5; IR (KBr): 3050, 2962, 2927, 2867, 1608, 1515, 1441, 1373, 1272, 855, 743 cm^{-1}. Calcd for $C_{18}H_{20}N_2S$ (296.13): C 72.93; H 6.80; N 9.45; S 10.82. Found C 72.87; H 6.78; N 9.48; S 10.65.

2-(Methylthio)-1-(2,3-dimethyl-phenyl)- 1*H*-benzo[*d*]imidazole (2g).



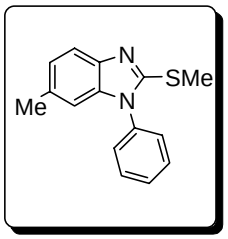
White solid; mp 88-89 ºC; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.79 (s, 3H), 2.30 (s, 3H), 2.66 (s, 3H), 6.79 (d, 1H, *J* = 7.75 Hz), 7.01–7.27 (m, 5H), 7.67 (d, 1H, *J* = 7.75 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.5, 14.8, 20.8, 109.8, 118.4, 122.4, 122.5, 126.7, 127.0, 131.7, 134.1, 135.9, 138.1, 139.4, 144.0, 154.5; IR (KBr): 3052, 2994, 2928, 1611, 1579, 1480, 1440, 1304, 1273, 981, 743 cm^{-1}. Calcd for $C_{16}H_{16}N_2S$ (268.38): C 71.61; H 6.01; N 10.44; S 11.95. Found C 71.50; H 5.98; N 10.38; S 11.82.

6-Methoxy-2-(methylthio)-1-phenyl-1*H*-benzo[*d*]imidazole (2h).



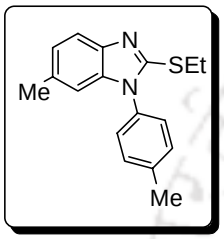
Colorless gum; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.62 (s, 3H), 3.66 (s, 3H), 6.51-6.80 (m, 2H), 7.33-7.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.2, 56.3, 94.1, 111.2, 118.9, 127.4, 129.5, 130.3, 135.7, 138.5, 152.5, 156.8; IR (KBr): 3054, 2930, 2833, 1619, 1596, 1487, 1444, 1266, 1150, 738 cm^{-1}. HRMS : Calcd 271.0905; Found 271.0900.

6-Methyl-2-(methylthio)-1-phenyl-1*H*-benzo[*d*]imidazole (2i).



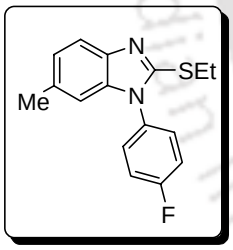
White solid; mp 80-82 ºC; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.62 (s, 3H), 6.80-6.96 (m, 2H), 7.29-7.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 22.1, 109.8, 118.0, 124.1, 127.4, 129.4, 130.2, 132.7, 135.7, 138.1, 142.1, 153.1; IR (KBr): 3053, 3012, 2924, 2857, 1611, 1594, 1497, 1434, 1365, 1271, 807, 762, 698 cm^{-1}. Calcd for $C_{15}H_{14}N_2S$ (254.35): C 70.83; H 5.55; N 11.01; S 12.61. Found C 70.65; H 5.54; N 11.07; S 12.52.

6-Methyl-2-(ethylthio)-1-*p*-tolyl-1*H*-benzo[*d*]imidazole (2j).



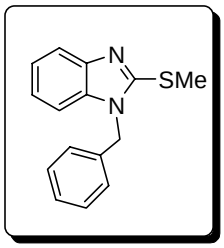
Colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.32 (t, 3H, *J* = 7.5 Hz), 2.29 (s, 3H), 2.35 (s, 3H), 3.24 (q, 2H, *J* = 7.5 Hz), 6.80 (s, 1H), 6.95 (d, 1H, *J* = 8.25 Hz), 7.17-7.27 (m, 4H), 7.51 (d, 1H, *J* = 8.25 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9, 22.6, 22.9, 27.9, 110.6, 118.8, 124.7, 128.8, 131.6, 133.4, 134.0, 138.9, 140.2, 143.0, 153.2; IR (KBr): 3033, 2969, 2925, 2868, 1608, 1515, 1439, 1366, 1270, 1209, 805, 714 cm^{-1}. Calcd for $C_{17}H_{18}N_2S$ (282.12): C 72.30; H 6.42; N 9.92; S 11.35. Found C 72.53; H 6.43; N 10.01; S 11.46.

6-Methyl-2-(ethylthio)-1-(4-fluoro-phenyl)- 1*H*-benzo[*d*]imidazole (2k).



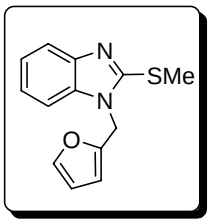
Colorless gum; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (t, 3H, *J* = 7.5 Hz), 2.31 (s, 3H), 3.25 (q, 2H, *J* = 7.5 Hz), 6.78 (s, 1H), 6.98 (d, 1H, *J* = 8.0 Hz), 7.16-7.34 (m, 4H), 7.51 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 22.1, 27.1, 109.6, 117.1, 117.5, 118.1, 124.2, 129.5, 129.6, 132.8, 134.8, 138.0, 142.1, 152.3, 161.0, 164.9. IR (KBr): 3055, 2987, 2923, 1633, 1504, 1424, 1265, 1026, 739 cm^{-1}. Calcd for $C_{16}H_{15}N_2SF$ (286.09): C 67.11; H 5.28; N 9.78; S 11.20. Found C 67.26; H 5.45; N 9.85; S 11.39.

2-(Methylthio)-1-benzylbenzimidazole (2l).



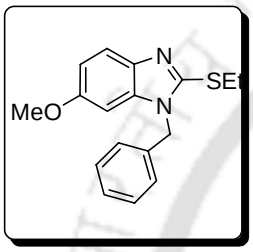
White crystalline solid; mp 77-79 ºC; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.70 (s, 3H), 5.16 (s, 2H), 7.07-7.21 (m, 8H), 7.62 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 48.0, 109.4, 118.6, 122.4, 122.4, 127.4, 128.4, 129.3, 136.0, 136.9, 144.1, 153.6; IR (KBr): 3031, 2932, 2858, 1606, 1493, 1453, 1427, 1374, 1243, 995, 734 cm^{-1}. Calcd for $C_{15}H_{14}N_2S$: C 70.83; H 5.55; N 11.01; S 12.61. Found: C 70.98; H 5.58; N 11.08; S 12.76.

2-(Methylthio)-1-(furan-2-ylmethyl)benzimidazole (2m).



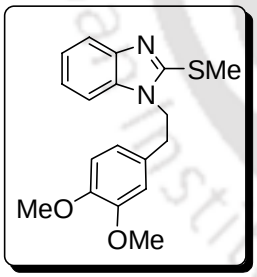
Brown oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.70 (s, 3H), 5.11 (s, 2H), 6.20 (s, 2H), 7.09–7.23 (m, 4H), 7.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 39.1, 108.0, 109.6, 117.2, 121.0, 121.1, 127.0, 131.6, 135.2, 142.0, 147.7, 153.6; IR (KBr): 3118, 3055, 2930, 1612, 1518, 1444, 1367, 1258, 1147, 1012, 923, 740 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{13}N_2OS$ $(M + H)^+$ 245.0749, Found 245.0754.

6-Methoxy-2-(ethylthio)-1-benzyl-1*H*-benzo[*d*]imidazole (2n).



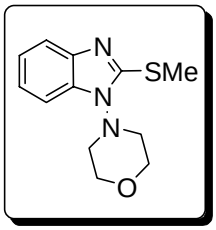
Colorless oil ; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (t, 3H, *J* = 7.25 Hz), 3.26 (q, 2H, *J* = 7.25 Hz), 3.69 (s, 3H), 5.18 (s, 2H), 6.57–6.78 (m, 2H), 7.07–7.23 (m, 5H), 7.51 (d, 1H, *J* = 8.75 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 26.0, 46.2, 54.5, 92.4, 109.0, 117.4, 125.5, 126.6, 127.6, 134.4, 135.5, 137.0, 149.4, 154.8; IR (KBr): 3062, 2962, 2930, 2834, 1621, 1488, 1445, 1368, 1266, 1214, 1029, 815, 714 cm^{-1}. Calcd for $C_{18}H_{20}N_2S$ (296.10): C 72.94; H 6.82; N 9.43; S 10.54. Found C 73.09; H 6.84; N 9.48; S 10.63.

2-(Methylthio)-1-(3,4-dimethoxyphenethyl)- 1*H*-benzo[*d*]imidazole (2o).



Colorless gum; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.68 (s, 3H), 2.94 (t, 2H, *J* = 7.25 Hz), 3.65 (s, 3H), 3.77 (s, 3H), 4.20 (t, 2H, *J* = 7.25 Hz), 6.39 (s, 1H), 6.57–6.71 (m, 3H), 7.09 (m, 2H), 7.61 (d, 1H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 34.1, 44.8, 54.8, 54.9, 107.6, 110.4, 111.1, 117.1, 119.8, 120.7, 129.1, 135.0, 142.4, 147.0, 148.0, 151.8; IR (KBr): 3054, 2933, 2834, 1613, 1591, 1514, 1454, 1263, 1157, 1027, 742 cm^{-1}. HRMS : Calcd 329.1324; Found 329.1321.

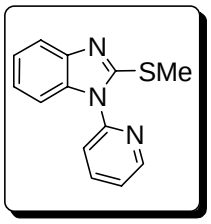
2-(Methylthio)-1-morpholino-1H-benzo[d]imidazole (2p).



White crystalline solid ; mp 156–158 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.66 (s, 3H), 3.02 (d, 2H, *J* = 10.0 Hz), 3.73 (m, 4H), 3.95 (d, 2H, *J* = 11.0 Hz), 7.15 (m, 2H), 7.47 (d, 1H, *J* = 7.25 Hz), 7.66 (d, 1H, *J* = 6.75 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 52.7, 67.1, 110.0, 119.0, 121.5, 121.9, 133.3, 142.8, 155.0; IR (KBr): 3048, 2950, 2919, 2861,

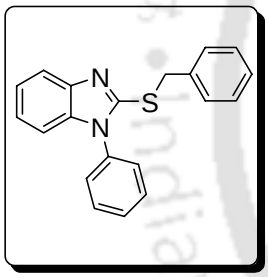
1450, 1375, 1315, 1288, 1112, 899, 743 cm^{-1}. Calcd for $C_{12}H_{15}N_3OS$ (249.33): C 57.81; H 6.06; N 16.85; S 12.86. Found C 57.58; H 6.06; N 16.78; S 12.74.

2-(Methylthio)-1-(pyridin-2-yl)-1H-benzo[d]imidazole (2q).



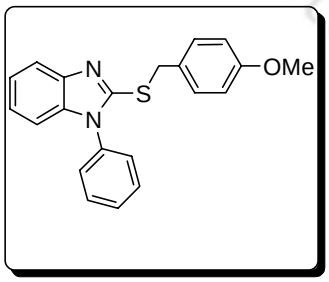
Brown gum ; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.66 (s, 3H), 7.06–7.26 (m, 3H), 7.35 (d, 1H, *J* = 7.5 Hz), 7.45 (d, 1H, *J* = 8.0 Hz), 7.64 (d, 1H, *J* = 7.5 Hz), 7.75-7.82 (m, 1H), 8.55 (d, 1H, *J* = 4.75 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.6, 110.6, 118.7, 119.3, 123.0, 123.2, 123.3, 136.1, 139.2, 144.2, 149.6, 149.9, 153.5; IR (KBr): 3054, 2926, 1584, 1461, 1441, 1313, 1264, 1017, 739 cm^{-1}. HRMS: Calcd 242.0752; found 242.0746.

2-(Benzylthio)-1-phenylbenzimidazole (2r).



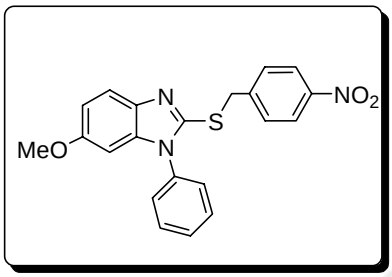
Yellow gum; ^{1}H NMR (250 MHz, CDCl3): δ 4.52 (s, 2H), 7.02-7.38 (m, 13H), 7.67 (d, 1H, *J* = 8.0 Hz); 13C NMR (100 MHz, $CDCl_3$): δ 37.0, 109.5, 118.3, 122.4, 122.5, 127.0, 127.7, 128.7, 129.1, 135.2, 136.5, 137.4, 143.6, 152.3; IR (KBr): 3060, 3030, 1595, 1498, 1434, 1267, 1072, 744 cm^{-1}. Calcd for $C_{20}H_{16}N_2S$: C 75.92; H 5.10; N 8.85; S 10.13. Found: C 75.76; H 5.08; N 8.78; S 10.05.

2-(4-Methoxy-benzylthio)-1-phenylbenzimidazole (2s).



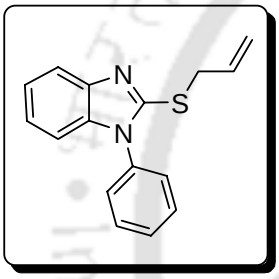
Colorless gum; ^{1}H NMR (250 MHz, $CDCl_3$): *δ* 3.63 (s, 3H), 4.48 (s, 2H), 6.67–6.71 (d, 2H, *J* = 8.6 Hz), 7.04–7.40 (m, 10H), 7.67 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 41.5, 60.4, 114.7, 119.2, 123.3, 124.0, 127.5, 127.6, 132.0, 134.2, 135.0, 135.6, 137.6, 140.3, 142.4, 148.7, 157.4, 164.3; IR (KBr): 3062, 2955, 2933, 2834, 1610, 1513, 1434, 1269, 1244, 1028, 832, 744 cm^{-1}. Calcd for $C_{21}H_{18}N_2OS$: C 72.80; H 5.24; N 8.09; S 9.26. Found C 73.02; H 5.25; N 8.14; S 9.32.

6-Methoxy-2-(4-nitrobenzylthio)-1-phenyl-1*H*-benzo[*d*]imidazole (2t).



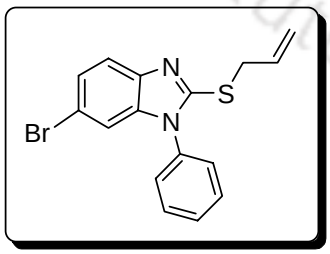
Brown gum; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.66 (s, 3H), 4.50 (s, 2H), 6.51-6.82 (m, 2H), 7.24-7.54 (m, 8H), 8.01 (d, 2H, *J* = 8.75 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.8, 54.8, 92.6, 110.3, 117.8, 122.7, 125.8, 128.1, 128.9, 133.9, 136.8, 136.9, 143.9, 146.1, 148.1, 155.6; IR (KBr): 3055, 2940, 2835, 1612, 1597, 1518, 1441, 1345, 1266, 1150, 1027, 736 cm^{-1}. HRMS : Calcd 392.1069; found 392.1064.

2-(Allylthio)-1-phenyl-1H-benzo[d]imidazole (2u).



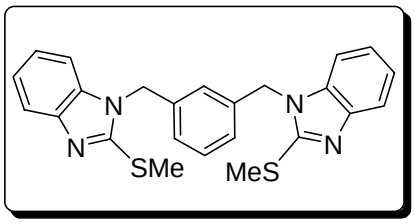
White solid ; mp 78-79 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.99 (d, 2H, *J* = 7Hz), 5.10 (d, 1H, *J* = 10Hz), 5.27 (dd, 1H, J_1 = 17.25, J_2 = 1.25 Hz), 5.91–6.08 (m, 1H), 7.09–7.25 (m 3H), 7.36–7.49 (m, 5H), 7.72 (d, 1H *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.6, 107.8, 116.7, 117.2, 120.8, 125.4, 127.4, 128.2, 131.2, 133.6, 135.8, 142.0, 150.3; IR (KBr): 3083, 3061, 2979, 2924, 1595, 1498, 1440, 1303, 1273, 1069, 928, 740, 698 cm^{-1}. Calcd for $C_{16}H_{14}N_2S$ (266.36): C 72.15; H 5.30; N 10.52; S 12.04; found C 72.34; H 5.31; N 10.58; S 12.12.

2-(Allylthio)-6-bromo-1-phenyl-1H-benzo[d]imidazole (2v).



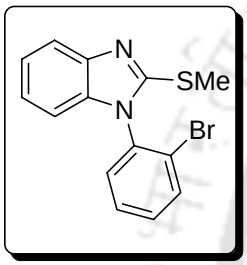
White crystalline solid ; mp 104–105 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.99 (d, 2H, *J* = 6.75 Hz), 5.13 (d, 1H, *J* = 10Hz), 5.30 (d, 1H, *J* = 17.0 Hz), 5.91–6.08 (m, 1H), 7.25–7.41 (m, 4H), 7.48–7.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.6, 112.9, 116.0, 119.4, 119.8, 126.0, 127.4, 129.8, 130.4, 133.0, 135.1, 138.8, 143.0, 153.5; IR (KBr): 3066, 3044, 3010, 2932, 1607, 1593, 1496, 1435, 1277, 1217, 935, 811, 695 cm^{-1}. Calcd for $C_{16}H_{13}N_2SBr$ (344.00): C 55.66; H 3.80; N 8.11; S 9.29. Found C 55.81; H 3.82; N 8.17; S 9.36.

1,3-*Bis*((2-(methylthio)-1*H*-benzo[*d*]imidazol-1-yl)methyl)benzene (2w).



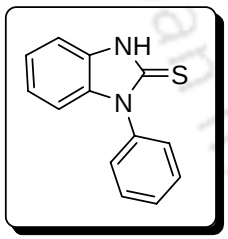
White solid; mp 146–148 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.66 (s, 3H), 5.08 (s, 2H), 6.91–7.17 (m, 5H), 7.61 (d, 1H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.9, 47.36, 109.0, 118.3, 122.1, 125.8, 126.7, 129.6, 136.4, 136.5, 143.7, 153.2; IR (KBr): 3048, 2927, 1609, 1578, 1435, 1370, 1279, 1187, 974, 735 cm^{-1}. HRMS : Calcd 431.1364; found 431.1360.

1-(2-Bromophenyl)-2-(methylthio)-1H-benzo[d]imidazole (2y).



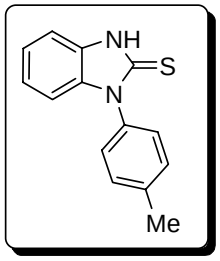
White crystalline solid; mp 119-120 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.76 (s, 3H), 6.90 (d, 1H, *J* = 7.75 Hz), 7.13–7.29 (m, 2H), 7.40–7.52 (m, 3H), 7.74–7.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.1, 109.8, 118.6, 122.7, 122.8, 123.8, 129.2, 131.0, 131.8, 134.6, 134.8, 137.5, 143.9, 154.0 ; IR (KBr): 3050, 2932, 1607, 1578, 1485, 1433, 1303, 1270, 1058, 759, 745 cm^{-1}. HRMS (ESI) Calcd for $C_{14}H_{12}BrN_2S$ ($M+H^+$) 318.9905, found 318.9915.

1-Phenylbenzimidazole-2-thione (3a).



White solid; mp 160–163 °C; ^{1}H NMR (250 MHz, $CDCl_3$ /DMSO-d_6): *δ* 6.96 (d, 1H, *J* = 7.5 Hz), 7.21–7.34 (m, 3H), 7.58–7.71 (m, 5H), 13.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): *δ* 109.0, 122.1, 122.8, 126.8, 128.2, 128.6, 134.1, 136.4, 137.6, 138.8, 167.7 ; IR (KBr): 3138, 3052, 2985, 2926, 1595, 1500, 1462, 1445, 1217, 735 cm^{-1}. Calcd for $C_{13}H_{10}N_2S$: C 69.00; H 4.45; N 12.38; S 14.17. Found: C 69.14; H 4.46; N 12.43; S 14.26.

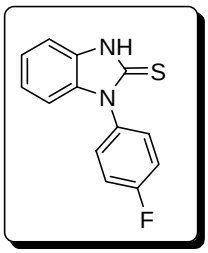
1-*p*-Tolyl-1H-benzo[d]imidazole-2(3H)-thione (3b).



White solid; mp 246-248 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.33 (s, 3H), 6.89 (d, 1H, *J* = 7.5 Hz), 7.02–7.16 (m, 3H), 7.31 (brs, 4H), 12.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.8, 110.5, 110.7, 123.5, 124.2, 128.0, 130.8, 131.3, 133.0, 134.7, 139.8, 169.1; IR (KBr): 3132, 3087, 3045, 2981, 2926, 1597, 1514, 1452, 1371, 1223,

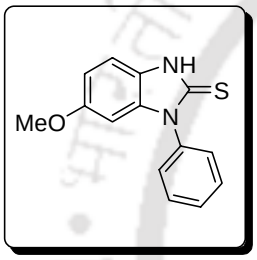
997, 746 cm^{-1}. Calcd for $C_{14}H_{12}N_2S$ (240.07): C 69.97; H 5.03; N 11.66, S 13.34; Found C 69.84 H 5.02 N 11.60 S 13.25.

1-(4-Fluorophenyl)-1H-benzo[d]imidazole-2(3H)-thione (**3e**)**.**



White solid; mp 208-210 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.91 (d, 1H, *J* = 7.75 Hz), 7.14–7.26 (m, 3H), 7.42–7.61 (m, 4H), 12.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ110.1, 110.4, 116.9, 117.2, 123.4, 124.2, 131.0, 131.1, 132.2, 134.4, 146.5, 160.4, 164.3, 170.0; IR (KBr): 3137, 3086, 2986, 2937, 1616, 1511, 1457, 1313, 1217, 1149, 833, 741 cm^{-1}. HRMS : Calcd 245.0549; found 245.0544.

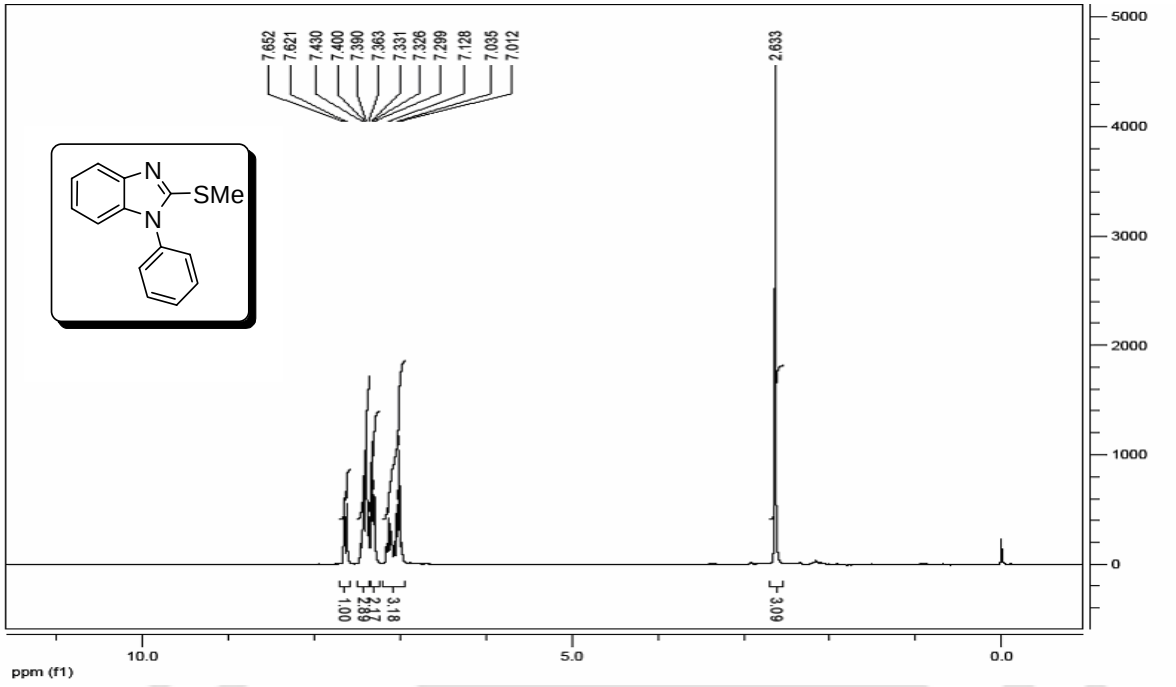
6-Methoxy-1-phenyl-1H-benzo[d]imidazole-2(3H)-thione (**3h**).



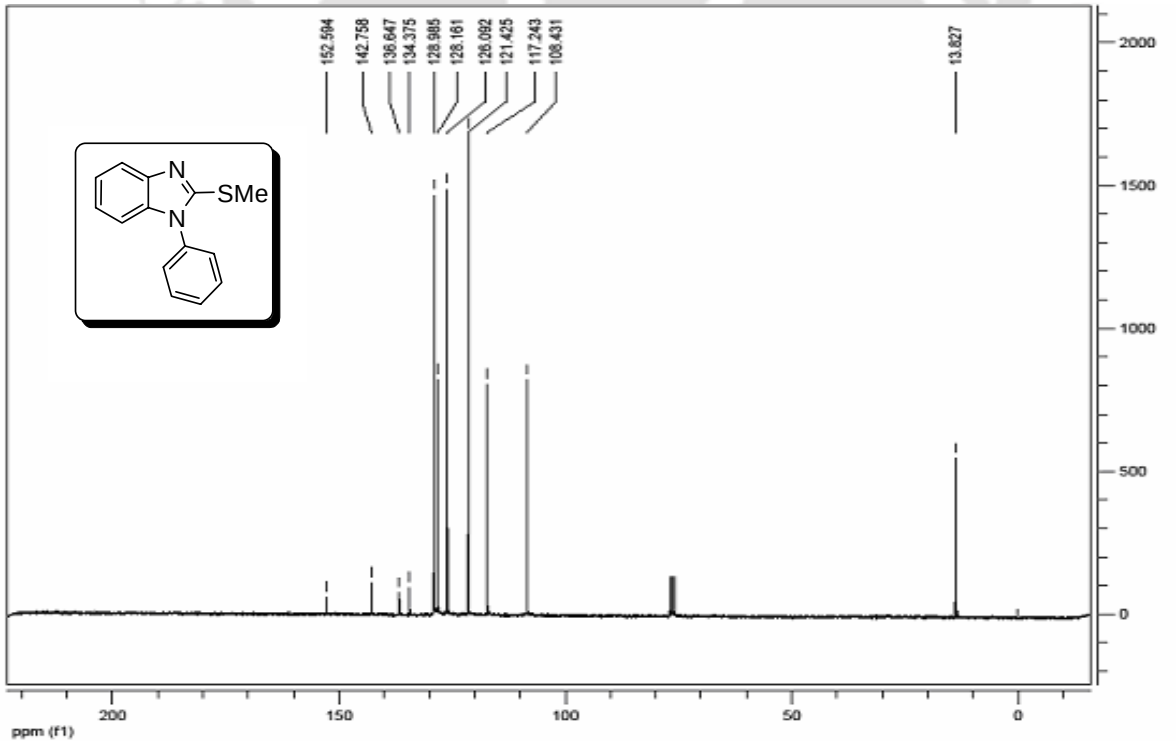
White solid; mp 176–178 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.70 (s, 3H), 6.41 (s, 1H), 6.87 (d, 1H, *J* = 8.5 Hz), 7.20 (d, 1H, *J* = 8.75 Hz), 7.53–7.64 (m, 5H), 12.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ57.6, 96.6, 112.5, 112.6, 127.2, 130.0, 130.8, 131.5, 136.5, 137.3, 158.0, 170.9; IR (KBr): 3150, 3078, 2959, 1616, 1597, 1505, 1493, 1349, 1148, 1026, 695 cm^{-1}. Calcd for $C_{14}H_{12}N_2OS$ (256.32): C 65.60; H 4.72; N 10.93; S 12.51. Found C 65.78; H 4.75; N 11.01; S 12.62.

IV.8. Selected Spectra

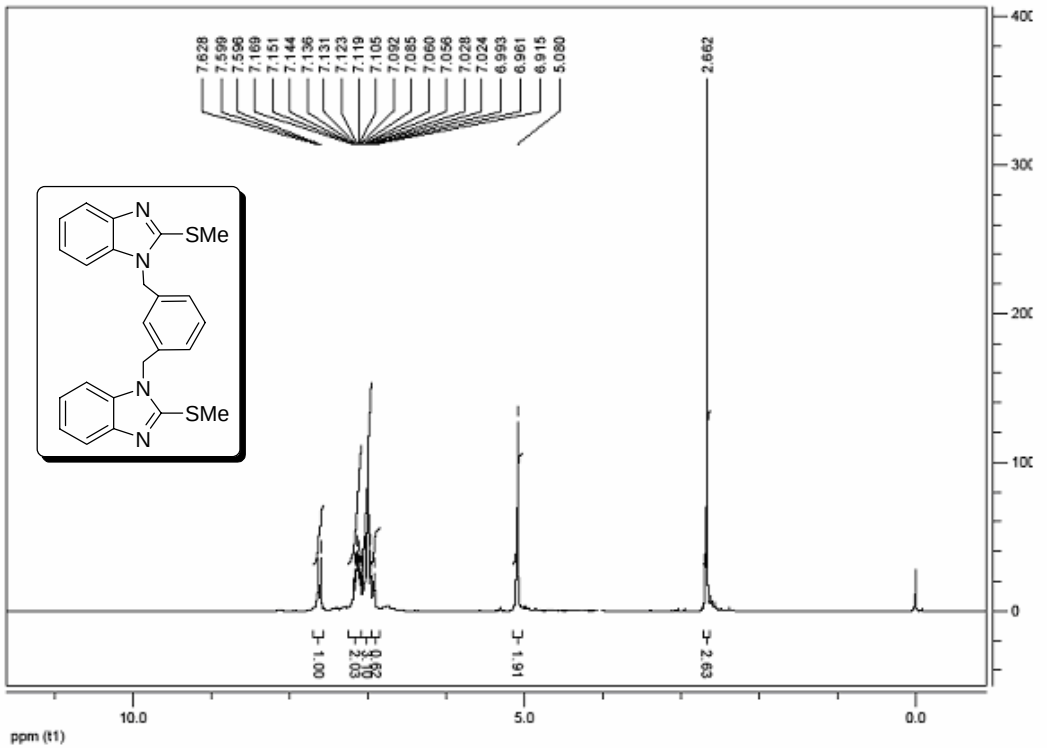
2-(Methylthio)-1-phenylbenzimidazole (2a). ^{1}H NMR (250 MHz, $CDCl_3$):



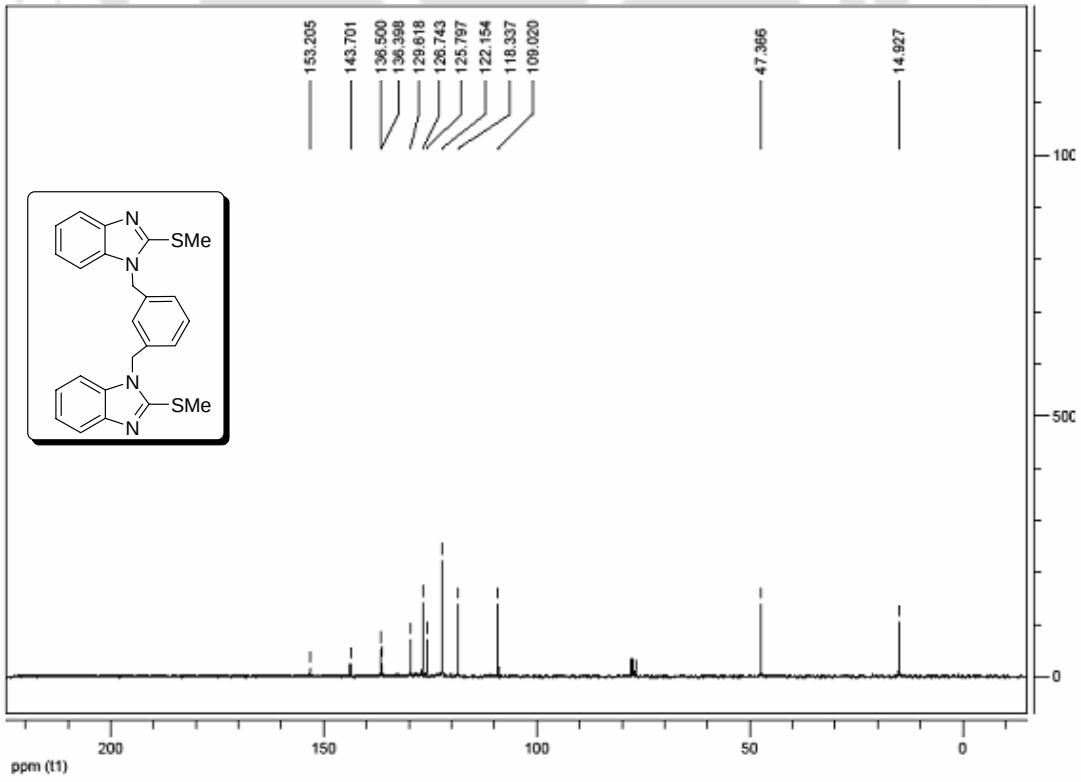
2-(Methylthio)-1-phenylbenzimidazole (2a). ^{13}C NMR (100 MHz, $CDCl_3$):



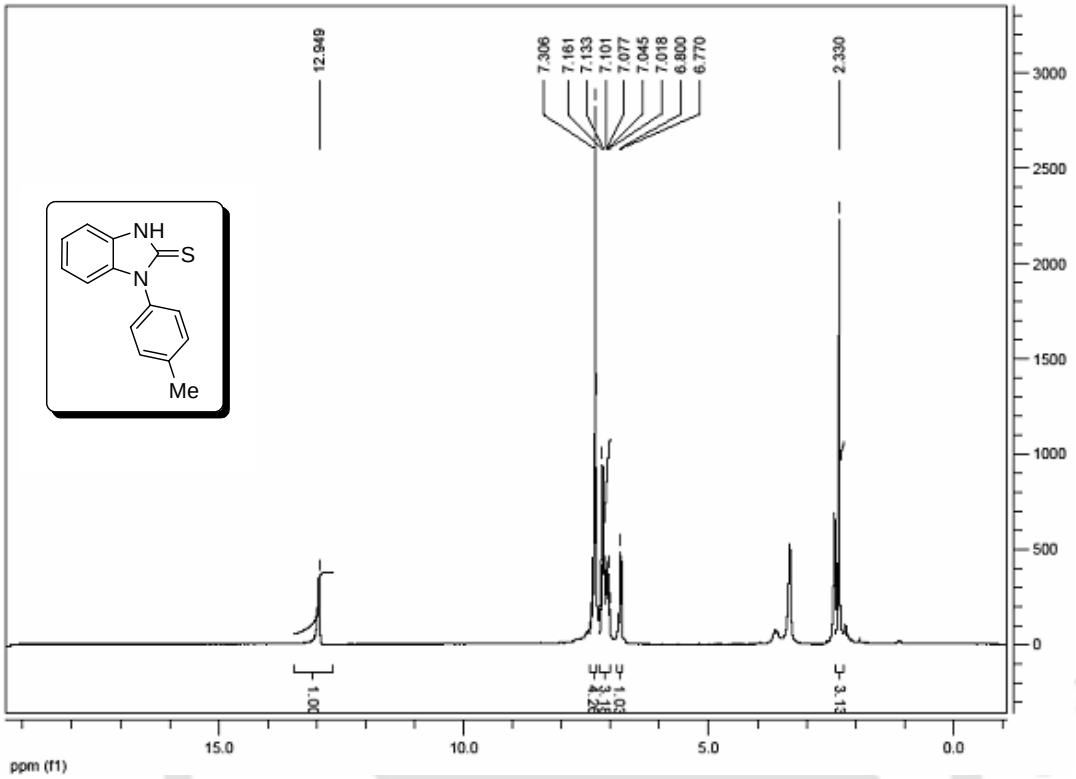
1,3-*Bis*((2-(methylthio)-1*H*-benzo[*d*]imidazol-1-yl)methyl)benzene (2w).
^{1}H NMR (250 MHz, $CDCl_3$):



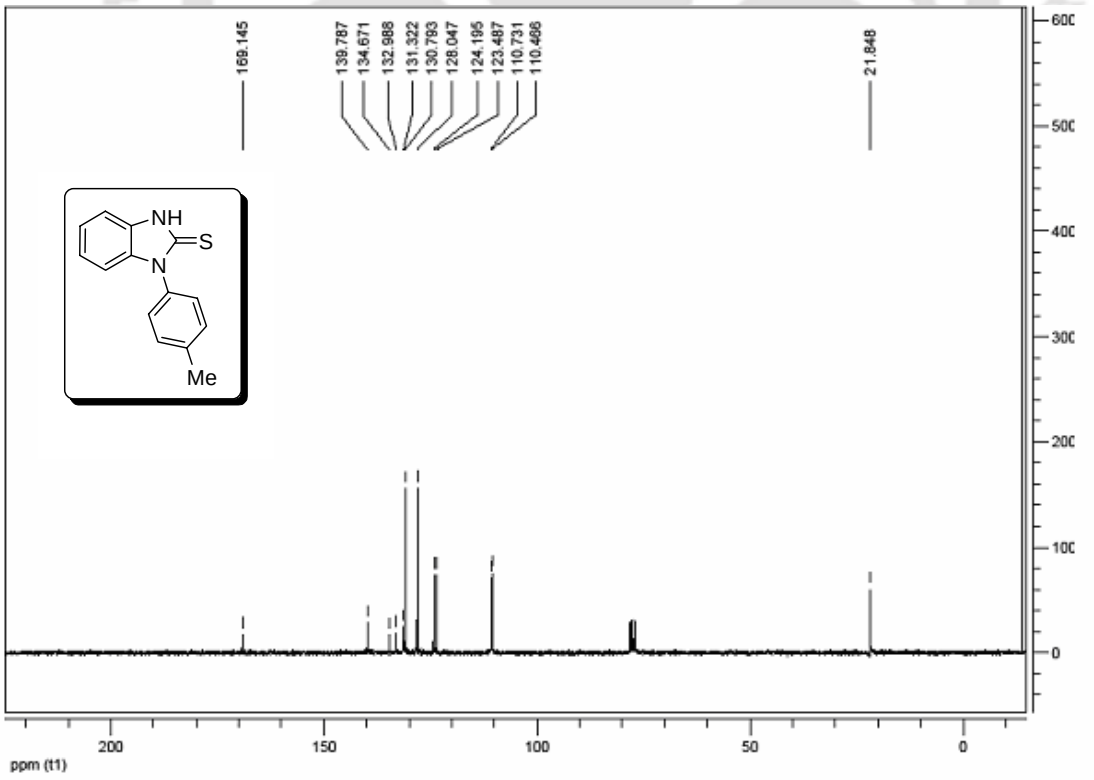
1,3-*Bis*((2-(methylthio)-1*H*-benzo[*d*]imidazol-1-yl)methyl)benzene (2w).
^{13}C NMR (100 MHz, $CDCl_3$):



1-*p*-Tolyl-1H-benzo[d]imidazole-2(3H)-thione (3b). ^{1}H NMR (250 MHz, $CDCl_3$ + DMSO):



1-*p*-Tolyl-1H-benzo[d]imidazole-2(3H)-thione (3b). ^{13}CNMR (100 MHz, $CDCl_3$ + DMSO):

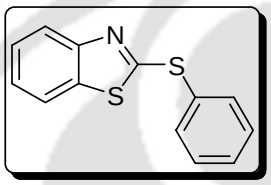


CHAPTER V

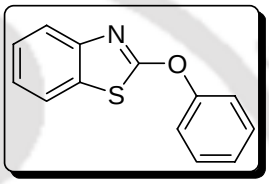
V. Cu(I)-catalyzed Cascade Synthesis of 2-Substituted Benzothiazoles

V.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I., Section I.1.1., Figure I.1.1.3. in pages 3 and 4. This chapter deals with the following two types of heterocycles namely 2-arylthio benzothiazoles and 2-aryloxy benzothiazoles.



Arylthiobenzothiazoles



Aryloxybenzothiazoles

V.2. Importance and Applications

The benzothiazole scaffold is ubiquitous in the realms of pharmacologically active agents and natural products. Particularly, 2-mercapto and oxo-substituted analogues exhibits wide range of biological activities such as antimycobacterial,[1a] antimicrobial,[1b,c,d] antifouling,[1e] and antiviral agents.[1f] Several 2-alkoxy- and 2-alkylthio-benzothiazole derivatives showed excellent anti-HRV (human rhinovirus) activity.[1g] A few substituted thiobenzothiazole derivatives have been screened for human cyclooxygenase-1 (COX-1) and cyclooxygenase-2 enzyme (COX-2) inhibition which shows encouraging results.[1h] Novel 6-aryl benzothiazolones were examined and found to be effective for progesterone receptor (PR) antagonist activities.[1i] Some therapeutic agents containing this core structure include leukotriene A4 (LTA4) hydrolase inhibitors, (**A**)[2a,b] aldolase reductase inhibitors (ARIs) (**B**)[2c] and as dual antagonists for the human CCR1 and CCR3 receptors (**C**),[2d] inhibitor of Cathepsin-D (**D**)[2e] and potent heat shock protein-90 inhibitors (**E**),[2f] Benazoline (**F**) as herbicide, Chlobenthiazone, (**G**) and 2-(thiocyanatomethylthio)-1,3-

benzothiazole (TCMTB) (**H**) are widely used as commercial fungicides in agriculture, are benzothiazole derivatives (*Figure V.2.1.*).[3]

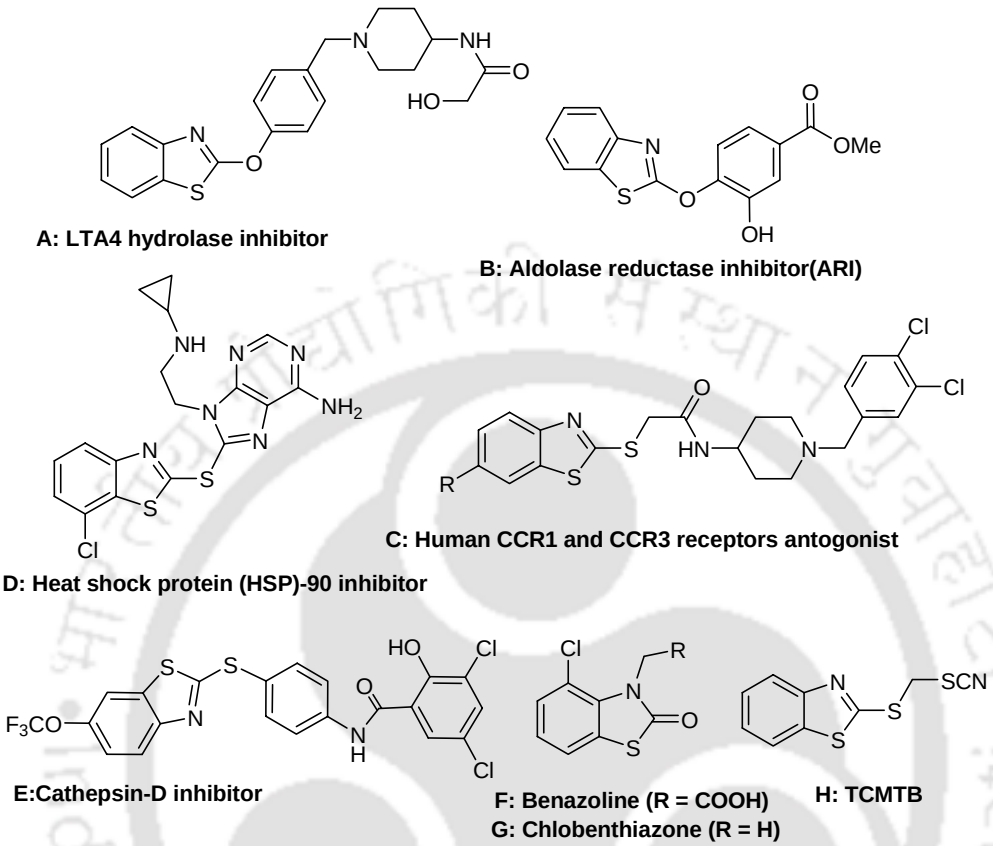
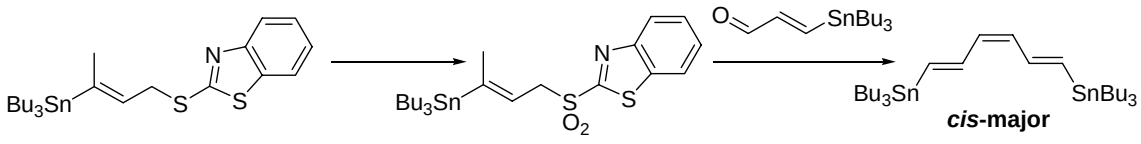


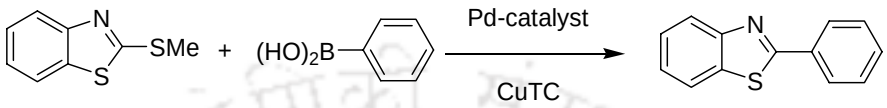
Figure V.2.1. *Structures of some biologically important molecules containing 2-oxa/thiabenzothiazole moieties.*

Some 2-substituted mercapto benzothiazoles have found applications in organic synthesis in Julia-olefinations[4a,b] and as reagents in Pd-catalyzed cross-coupling reactions.[4c] Allyl benzothiazolyl sulfones containing Bu_3Sn were used in Julia olefinations for the synthesis of stereoselective 1,3-butadienyl- and 1,3,5-hexatrienylstannanes (*Scheme V.2.1.*).[4a,b]



Scheme V.2.1.

Sigma-deficient heteroaromatic thioethers undergo efficient palladium-catalyzed cross-coupling with boronic acids mediated by copper(I) thiophene-2-carboxylate. The Cu(I) carboxylate serves the dual role of simultaneously polarizing the Pd-S bond through Cu(I)-coordination to Sulfur while activating the trivalent boron through coordination of carboxylate to Boron (*Scheme V.2.2.*).[4c]



Scheme V.2.2.

A new set of 2-mercaptobenzothiazole benzoates for highly sensitive fluorescent chemosensors of transition metal ions was synthesized and their fluorescence enhancement was obtained in the presence of transition metal ions such as Cd^{2+} and Hg^{2+}, especially Zn^{2+}, which results from the suppression of radiation less transitions from the n* state in the chemosensors.[5]

V.3. Domino Catalysis

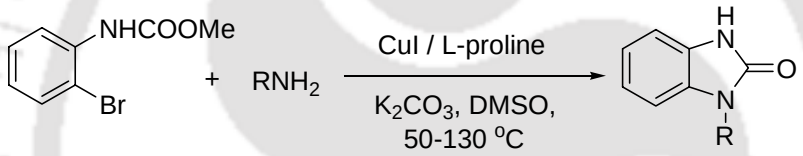
In recent years, there has been an ever-increasing interest in the field of metal catalyzed-multi-step processes such as tandem, domino, cascade, sequential and / or concurrent catalysis in which one or more catalysts are employed for two or more transformations in one-pot.[6]

A **cascade reaction** or **tandem reaction** or **domino reaction** is a consecutive series of intramolecular organic reactions which often proceed via highly reactive intermediates. It allows the organic synthesis of complex multinuclear molecules from a single acyclic precursor. The substrate contains several functional groups that take part during chemical transformations one at a time. Often a functional group is generated in situ from the previous chemical transformation. The definition includes the prerequisite intramolecular in order to distinguish this reaction type from a multi-component reaction. The main advantage of a cascade reaction in organic synthesis is that the reaction is often fast due to its intramolecular nature.

"A domino reaction is a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step" -L. F. Tietze.[7a]

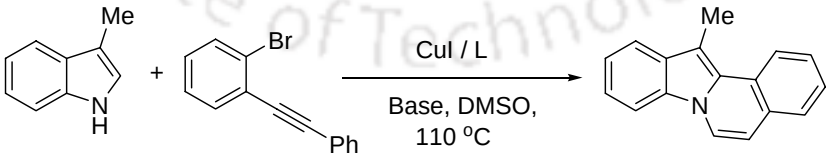
Domino reactions are such examples with high potential in organic synthesis. They have several advantages such as (a) rapid transformations, (b) minimizing the number of reaction steps and chemical waste, and displays high atom economy and (c) the occurrence of two or more bond-forming reactions under identical reaction conditions.

An example of Cu-catalyzed cascade reaction was reported by Ma *et al.* where *N*-substituted 1,3-dihydrobenzimidazol-2-ones are achieved starting from methyl *o*-haloarylcarbamates via a CuI/amino acid catalyzed coupling with amines and subsequent condensative cyclization (*Scheme V.3.1.*).[7b]



Scheme V.3.1.

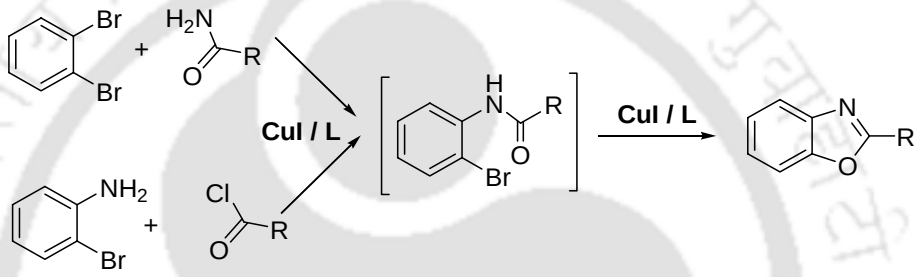
Recently a tandem process has been reported by Larock *et al.* which describes the synthesis of indolo- and pyrrolo-isoquinolines from the corresponding *ortho*-haloarylalkynes and indoles. This chemistry appears to involve the preferential nucleophilic addition of indoles and pyrroles onto the ortho-haloarylalkynes over *N*-arylation of the aryl halide (*Scheme V.3.2.*).[7c]



Scheme V.3.2.

Batey group has reported two domino annulation approaches for benzoxazole synthesis. The first approach involved in copper-catalyzed intermolecular cross-coupling

of 1,2-dihaloarenes with primary amides, followed by copper-catalyzed intramolecular cyclization to form the Ar-O bond. Benzoxazoles were formed in good yields from the reaction of 1,2-dibromobenzene, but the reaction was not regioselective in the case of 3,4-dibromotoluene. As a result of this limitation, an alternative one-pot domino annulation strategy was developed involving reaction of 2-bromoanilines with acyl chlorides in the presence of Cs_2CO_3, CuI as pre-catalyst, and 1,10-phenanthroline as the ligand. Under these conditions initial acylation of the aniline is followed by a copper-catalyzed intramolecular cyclization of the resultant 2-haloanilide to form the Ar-O bond of the benzoxazole ring (*Scheme V.3.3.*).[7d]



Scheme V.3.3.

V.4. Intra and Intermolecular C–S Bond Formation Using a Single Catalytic System: First Direct Access to 2-Arylthiobenzothiazoles

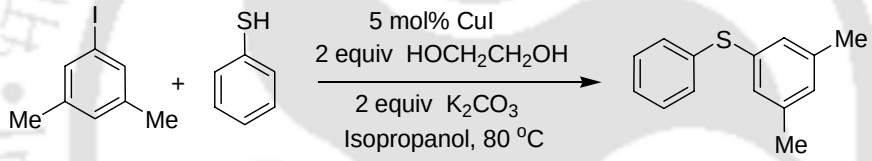
Great efforts and progress have been made in the development of Pd- and Cu-catalyzed inter- and intramolecular domino reactions involving carbon-heteroatom (N, O and S) bond formation or hetero-arylations for the synthesis of a wide variety of heterocycles.[8] However, Cu-catalyzed hetero-arylation has proved to be much more advantageous over Pd and other metal catalysts in terms of efficiency, selectivity, low costs and high functional group tolerance.[9]

Although, the chemistry of Cu-catalyzed C–C, C–N and C–O bond formations are well explored,[10a,b] methods available for C–S bond formation[11] are rather few in number because of the propensity of thiols towards oxidative dimerization and its affinity for metals, causing reduced catalytic efficiency by catalytic modifications. All intramolecular

S-arylations led to sulfur containing heterocycles whereas intermolecular reaction leads to thioethers. Traditional methods for the C–S bond formation often require harsh reaction conditions, which limit their application in industry. Thus, considerable attention has been recently focused to develop catalytic systems based on Pd, Cu, Ni and Co metals, for inter and intramolecular *S*-arylations. Although palladium based catalysts are widely used, a considerable number of reports have appeared using copper catalysts and a few with other metals.

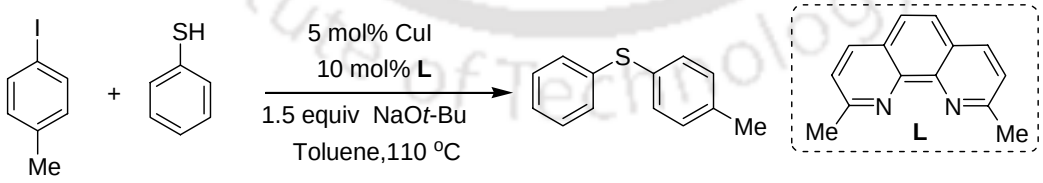
V.4.1. Known methods for Copper-Catalyzed Intermolecular *S*-Arylation

Buchwald *et al.* have developed an efficient copper-catalyzed C–S bond forming reaction. The reaction of aryl iodides having electron withdrawing and donating groups is demonstrated (*Scheme V.4.1.1.*).[12a]



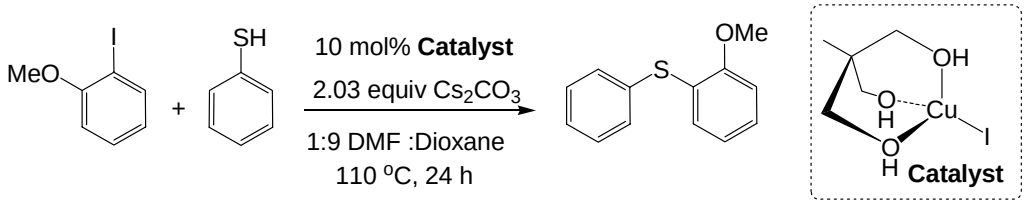
Scheme V. 4.1.1.

Venkataraman and co-workers showed the coupling of aryl thiols with aryl iodides using CuI and neocuproine in the presence of NaO*t*-Bu in toluene. Using this procedure the coupling of thiophenol with 4-methyliodobenzene is accomplished in 94% yield (*Scheme V.4.1.2.*).[12b]



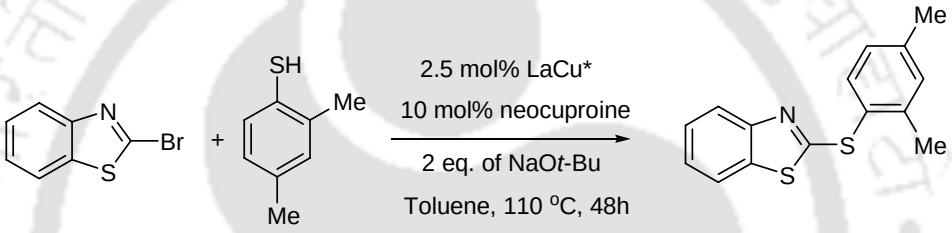
Scheme V.4.1.2.

More recently, a copper (I) complex (*Scheme V.4.1.3.*) is used for the coupling of aromatic thiols with aryl iodides in the presence of Cs_2CO_3 in 1:9 DMF:dioxane. These reaction conditions are also equally effective for C–O cross-coupling reactions.[12c]



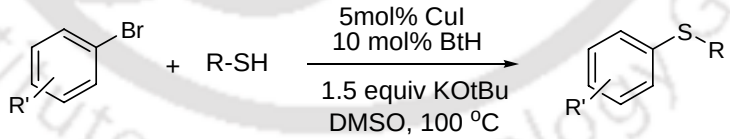
Scheme V.4.1.3.

Lohmann and co-workers have shown the utility of perovskite-based materials in organic synthesis is explored through examination of a series of copper- and palladium-containing perovskites in Ullmann type reactions. $La(0.9)Ce(0.1)Co(0.6)Cu(0.4)O_3$ is identified as an effective catalyst for the synthesis of a range of biaryl ether and thioether functionalities (*Scheme V.4.1.4.*).[12d]



Scheme V.4.1.4.

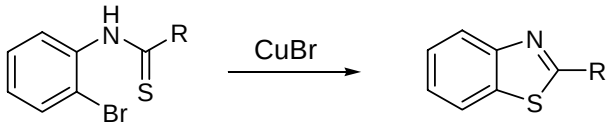
Verma *et al.* reported a mild, general and efficient copper catalyzed cross coupling reaction of aryl bromides and thiols using 0.5 mol % CuI and 1 mol % benzotriazole. Experimental simplicity, generality, functional group tolerance and low cost of the catalyst are advantages of the protocol (*Scheme V.4.1.5.*).[12e]



Scheme V.4.1.5

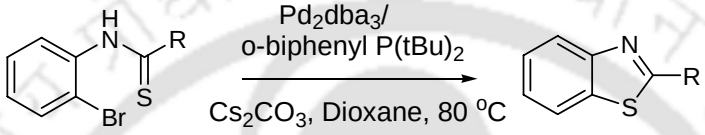
V.4.2. Copper and Palladium Catalyzed Intramolecular *S*-Arylations

In 1982 Bowmann *et al.* reported an intramolecular aromatic SRN^1 substitution for the preparation of 2-phenyl- and 2-methyl-1,3-benzothiazole from *o*-iodo thiobenzanilide and *o*-iodo thioacetanilide which however found to be much more efficient under Cu(I)-catalyzed conditions (*Scheme V.4.2.1.*).[13a]



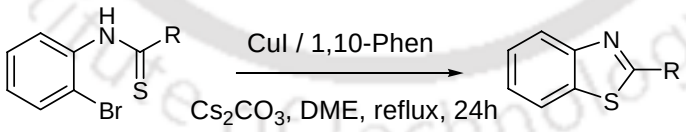
Scheme V.4.2.1.

Castillon group have developed a palladium-catalyzed intramolecular cyclization of *o*-bromophenylthioureas and *o*-bromo-phenylthioamides for synthesizing 2-amino-, and 2-alkyl-benzothiazoles. Highly hindered alkyl monophosphines proved to be the most efficient ligands (*Scheme V.4.2.2.*).[13b]



Scheme V.4.2.2.

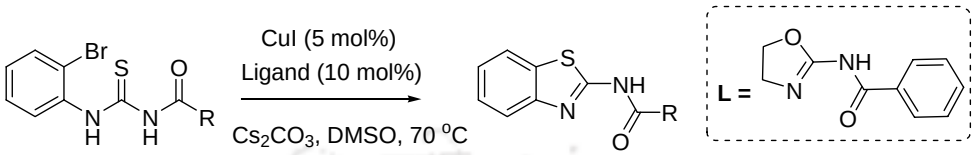
In continuation of these efforts, Batey group has extensively studied the intramolecular *S*-arylation of thioamides and amides. A general method for the formation of benzoxazoles and benzothiazoles via a copper or palladium-catalyzed cyclization of *o*-haloanilides is reported. This approach complements the more commonly used strategies for benzoxazole and benzothiazole formation which require 2-aminophenols or 1,2-phenylene diamines as precursors. A variety of ligands including 1,10-phenanthroline and *N*,*N*′-dimethylethylenediamine were shown to provide ligand acceleration / stabilization in the reaction. The rate of reaction of the *o*-haloanilides follows the order I > Br > Cl, consistent with oxidative addition being the rate-determining step (*Scheme V.4.2.3.*).[13c]



Scheme V.4.2.3.

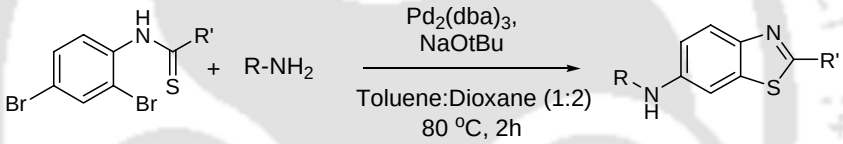
Oxazolidin-2-one was found to be a versatile and efficient ligand for the CuI-catalyzed amidation and the cyclization of *o*-halobenzanilides for the above mentioned transformation. Notably, the less active halides could also be applied successfully in the synthesis of benzoxazoles and benzothiazoles.[13d]

Most recently, a similar method has been reported using CuI/*N*-(4,5-dihydrooxazol-2-yl)benzamide as an efficient catalytic system for an intramolecular cyclization of substituted 1-arylacyl-3-(2-bromophenyl)thioureas to yield *N*-benzothiazol-2-yl-amides (*Scheme V.4.2.4.*).[13e]



Scheme V.4.2.4.

A tandem palladium-catalyzed *S*- and *N*-arylation reaction of dibromothioamides to amino-substituted benzothiazoles has been developed in one-pot. Noteworthy, the immediate combination of all reagents at the outset of the reaction is preferable to stepwise addition in terms of product conversion, operational simplicity, and purification requirements (*Scheme V.4.2.5.*).[13f]



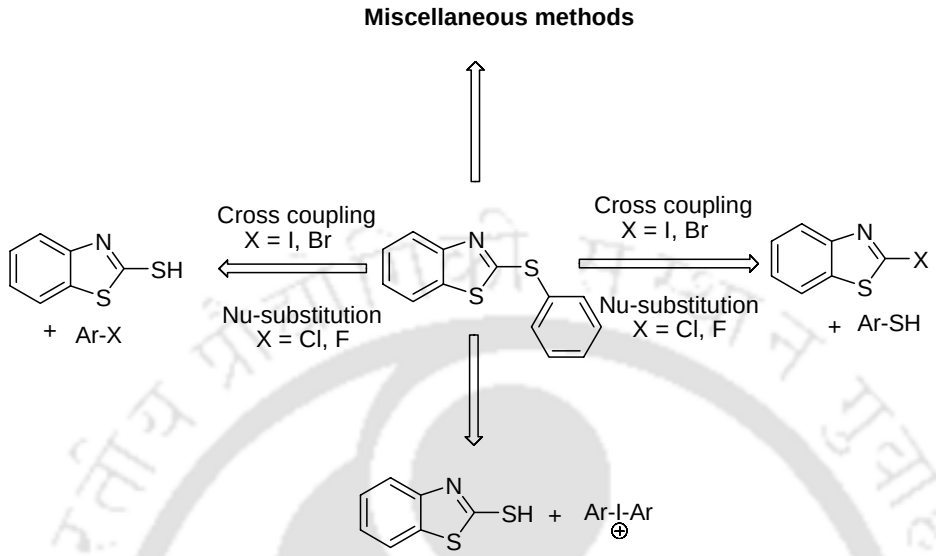
Scheme V.4.2.5.

Despite the plethora of C-heteroatom bond formation reported, involving Pd, Cu-catalyzed multi catalytic processes, there is no report on any tandem, domino, cascade, sequential and / or concurrent catalytic methods involving intra and intermolecular S-arylation. As a part of our ongoing research in developing methods for the synthesis of heterocycles,[14] we were further interested in developing newer protocols for the synthesis of heterocycles via two sequential intra and intermolecular C–S bond formation using a single catalyst (Cu) in one-pot.

V.4.3. Available Methods for the Synthesis of 2-Arylthiobenzothiazoles

Classical methods for the synthesis of 2-arylthiobenzothiazoles involve mainly two types of nucleophilic substitution reactions (*Scheme V.4.3.1.*). One by the nucleophilic attack of arylthiols with a preformed 2-halobenzothiazoles and the second one by the

nucleophilic attack of mercapto-benzothiazole with haloarenes containing deactivating substituents such as -NO_2 and -CN under strong basic condition.[15]

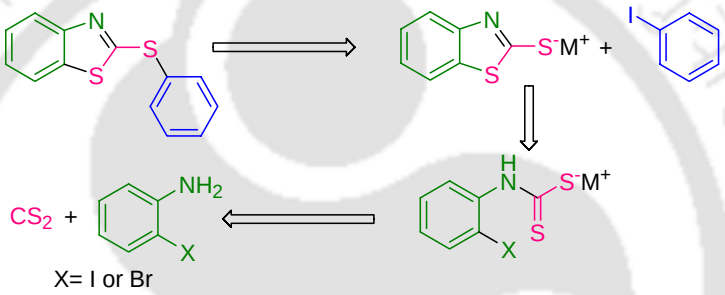


Scheme V.4.3.1. *Available synthetic routes for the synthesis of 2-arylthiobenzothiazoles*

Alternatively, several cross coupling reactions were developed with similar coupling partners to include a wide range of substrates (*Scheme V.4.3.1.*).[16] Pd-catalyzed synthesis of thioethers from aryliodides and arylthiols[16a,b] as well as Cu-catalyzed reaction of boronic acids with aryl, hetero aryl, and alkyl *N*-thioimides to yield thioethers has been reported.[16c] Recently, Bolm *et al.* reported Fe-catalyzed S-arylation protocol of aromatic and heteroaromatic thiols.[16d] A Pd-catalyzed, Cu-mediated coupling of hetero-aromatic thioethers with aryl, hetero aryl, and alkenyl stannanes has been described.[16e] Alternatively, Wang *et al.* developed a method for the synthesis of 2-arylthiobenzothiazoles by the *S*-arylation of benzothiazol-2-thiol with diaryliodonium salts in ioinic liquid ([bmim]BF_4.[16f] In addition, there exist methods for the syntheses of arylthiobenzothiazoles.[17] However, the preparation of 2-arylthiobenzothiazoles using these methods depends largely on the availability of the requisites, suitably substituted 2-halo-benzothiazole or mercapto-benzothiazoles which are often difficult to prepare.

V.4.4. Present Work

Previously, Batey and others have developed methods for the synthesis of 2-substituted benzothiazoles from the corresponding 2-halothioanilides and 2-halothioureas *via* Pd and Cu-catalyzed intramolecular S-arylation.[13] Taking cues from the Cu-catalyzed intramolecular C–S and C–N bond forming reactions,[14a] we envisioned that it would be possible to combine both intra and intermolecular S-arylations using a single catalytic system (Cu) in one-pot for the synthesis of 2-arylthiobenzothiazoles. Herein, we describe our efforts towards this target, resulting in first direct access to 2-arylthiobenzothiazoles in one-pot (*Scheme V.4.4.1.*).



Scheme V.4.4.1. *The design of direct synthesis of arylthiobenzothiazoles via two sequential C-S bond formations.*

In this single catalytic one-pot double arylation strategy, intramolecular *S*-arylation of dithiocarbamate salt would yield benzothiozole-2-thiol or 2-mercaptobenzothiazole (MBT) which is then followed by an intermolecular C–S coupling giving directly 2-arylthiobenzothiazoles as shown in *Scheme V.4.4.1.*

Dithiocarbamate salt of 2-iodoaniline **1a** was prepared in quantitative yield by treating it with CS_2 and triethylamine following the literature procedure,[18] which was used as a model substrate to optimize the reaction condition. Initially, the coupling of dithiocarbamate **1a** and iodobenzene **1b** were selected to optimize the reaction conditions taking CuI as the pre-catalyst and K_2CO_3 as the base. In the absence of suitable ligand, the first step (intramolecular) of the reaction was slow and the second step (intermolecular) was not at all effective. While phenanthroline ligand (L1) (*Figure V.4.4.1*) was found to be most effective, an observation consistent with our previous report on intramolecular C–N

bond formation.[14a] Surprisingly, less expensive cyclohexyl-1,2-diamine (L5) was found to be even better in terms of superior yield (86%) in short reaction time (4 hrs) for this sequential reaction (*Figure V.4.4.1.*).

Thus from a series of experiments the optimum ratios of dithiocarbamate : aryliodide : CuI : ligand (L5) : base, were found to be 1 : 1 : 0.05 : 0.1 : 3. Further experimentation revealed significance of the solvent dependence for both steps. Among various solvents (DMF, Dioxane, DMSO, DMA and toluene) tested, the reaction was found to be fastest in DMSO and K_2CO_3 to be the ideal base. Although the reaction works faster at high temperature we maintained a uniform temperature of 90 ^oC for both transformations in case of all the reactions. These reactions can even be carried out at lower temperature (80 ^oC) but relatively longer reaction times are required (14-18 hrs). In sharp contrast to absolute requirement for an inert atmosphere for similar reactions, there is no such necessity and it can be performed in air atmosphere without compromising the overall yield. Further, the reaction are much faster (4-8 hrs) compared to several similar intermolecular C–S bond forming reaction reported to be taking place above 100 ^oC for several hours.

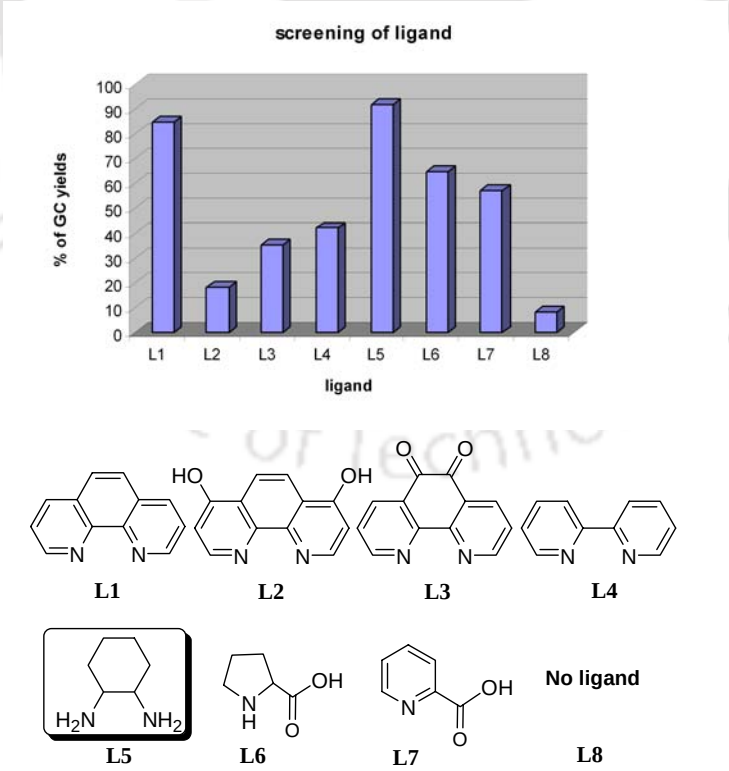
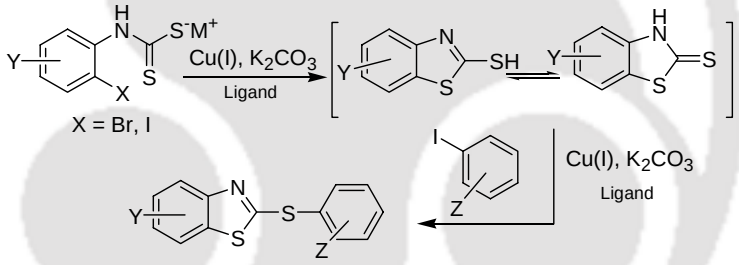


Figure V.4.4.1. *Ligand effects in Cu-catalyzed sequential coupling reaction.*

It is reasonable to assume that the initial reaction proceeds by an intramolecular *S*-arylation to give 2-mercaptobenzothiazole (MBT), the intermediacy of which has been confirmed by its isolation. Since MBT have found wide range of applications in different fields and their synthesis involves arduous reaction conditions, the reaction can be stopped to isolate MBT in quantitative yields in the absence of iodoarenes.[19] In the absence of any ligand or with less efficient ligands, 2-mercaptobenzothiazole (MBT) was obtained as the major product confirming the faster intramolecular over intermolecular S-arylation (*Scheme V.4.4.2.*).

For aryldithiocarbamates having *o*-halo (I or Br) substituents, no initial intermolecular S-arylation was observed. However, in the absence of 2-halo substituents Cu-nanoparticle catalyzed intermolecular S-arylation has been reported.[11n] The intramolecular *S*-arylation is then followed by intermolecular *S*-arylation giving arylthiobenzothiazole in excellent yield as shown in *Scheme V.4.4.2.* and *Table V.4.4.1.*



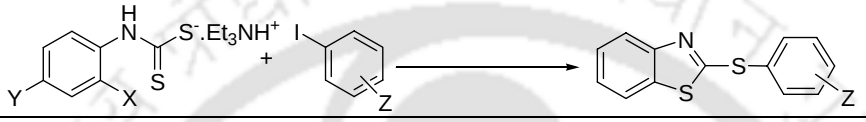
Scheme V.4.4.2. *Synthesis of 2-arylthiobenzothiazoles via sequential Cu-catalyzed intra and intermolecular S-arylations.*

Even though the reaction is carried out in an air atmosphere because of the isolation of intermediate 2-mercaptobenzothiazole (and not its disulfide) oxidative path involving dithiocarbamate disulfide is ruled out in the first step (*Scheme V.4.4.2.*). On a similar logic disulfide path can be ruled out for the second step as well, as observed recently using Fe-catalyzed C–S bond formation.[16d]

Next, the scope of the reaction with various dithiocarbamates of 2-halo anilines and substituted anilines such as 2-iodoaniline **1a**, 2-bromoaniline **1a'**, 2-iodo-4-methylaniline **2a**, 2-bromo-4-methylaniline **2a'**, and 4-chloro-2-iodoaniline **3a** was evaluated with various iodoarenes as their intermolecular coupling partners. In general, all reactions were

very clean, and the 2-arylthiobenzothiazole derivatives were obtained in high yields under the optimized reaction conditions (*Table V.4.4.1.*). The current catalytic system for double *S*-arylation is effective for aryliodide and substituted aryliodides containing activating (**2b**, **3b**, and **6b**) and deactivating (**4b**, **5b**, **7b**, and **8b**) substituents. So far intramolecular *S*-arylation is concerned dithiocarbamate salts of both 2-bromoanilines **1a'** and **2a'** and 2-iodoanilines **1a**-**3a** are equally effective.

Table V.4.4.1. *Synthesis of 2-arylthiobenzothiazoles via sequential Cu-catalyzed intra and intermolecular S-arylations.*



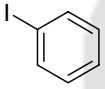
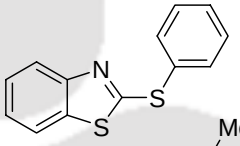
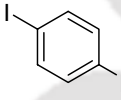
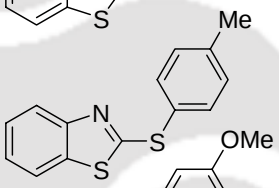
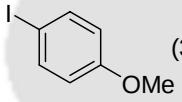
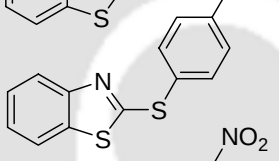
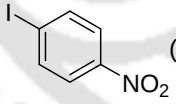
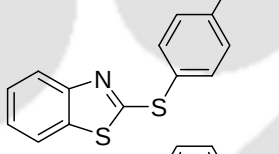
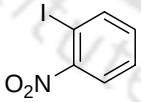
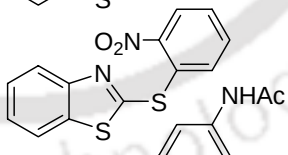
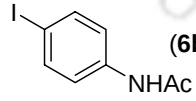
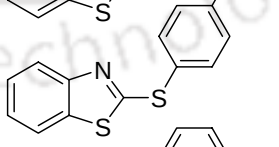
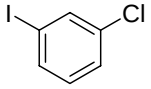
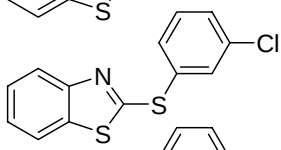
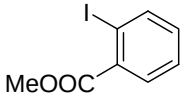
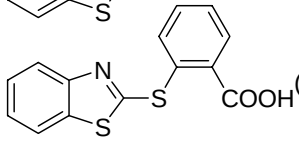
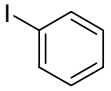
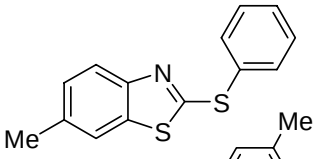
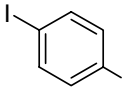
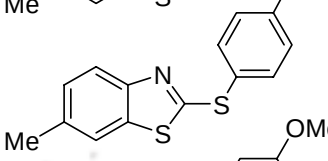
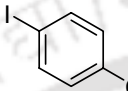
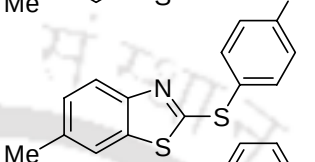
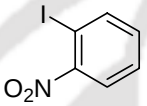
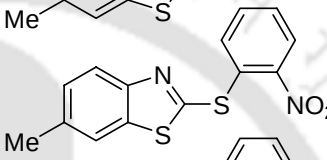
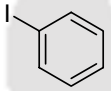
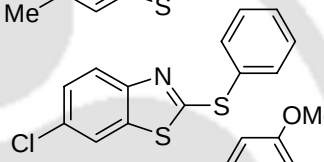
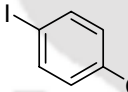
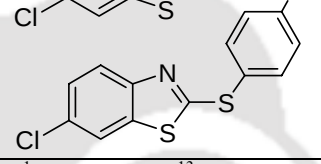
Dithiocarbamate	Iodoarene	Product	Yield (%)
X=I, Y=H (**1a**)	 (**1b**)	 (**1c**)[k]	86
X=Br, Y=H (**1a'**)			(**1c**)[k] 82
X=I, Y=H (**1a**)	 (**2b**)	 (**2c**)[m]	85
X=Br, Y=H (**1a'**)			(**2c**)[m] 79
X=I, Y=H (**1a**)	 (**3b**)	 (**3c**)[m]	74
X=I, Y=H (**1a**)	 (**4b**)	 (**4c**)[k]	92
X=Br, Y=H (**1a'**)			(**4c**)[l] 87
X=I, Y=H (**1a**)	 (**5b**)	 (**5c**)[k]	90
X=I, Y=H (**1a**)	 (**6b**)	 (**6c**)[l]	72
X=I, Y=H (**1a**)	 (**7b**)	 (**7c**)[l]	86
X=I, Y=H (**1a**)	 (**8b**)	 (**8c**)[k]	89

Table V.4.4. 1. *Contd...*

Table V.4.4. 1. *Contd...*

Dithiocarbamate	Iodoarene	Product	Yield (%)
X=I, Y=Me (**2a**)	 (**1b**)	 (**9c**)[l]	84
X=I, Y=Me (**2a**)	 (**2b**)	 (**10c**)[m]	79
X=Br, Y=Me (**2a'**)			(**10c**)[m] 76
X=I, Y=Me (**2a**)	 (**3b**)	 (**11c**)[m]	72
X=I, Y=Me (**2a**)	 (**5b**)	 (**12c**)[k]	85
X=I, Y=Cl (**3a**)	 (**1b**)	 (**13c**)[l]	66
X=I, Y=Cl (**3a**)	 (**3b**)	 (**14c**)[l]	71

[a]Reactions were monitored by TLC. [b]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [c]Isolated yield. [k]Reactions were carried out for 4hrs. [l]Reactions were carried out for 6 hrs, [m]Reactions were carried out for 8hrs.

However, only aryliodides were found to be effective for intermolecular *S*-arylation and neither aryl bromides nor aryl chlorides were reactive under this condition. The reactions are equally effective irrespective of the nature of the substituents (Y) present in the dithiocarbamate salt. However, an interesting trend in reactivity was observed in its intermolecular coupling partner aryliodide. Presence of electron withdrawing substituents *p*-NO_2 (**4b**), *o*-NO_2 (**5b**), *o*-OCOR (**8b**) accelerate the rate of the reaction giving products in shorter reaction times, whereas electron donating substituents *p*-OMe (**3b)**, *p*-Me (**2b**) retards the reaction. This fact has been further verified with a substrate containing strongly activating group (-NH_2), where no desired product was observed. However when NH_2 group was protected as NHAc (**6b**) a moderately activating group, good conversion was observed giving product **6** in 72 % yield. Thus, from the present study we found the following reactivity order in aryliodides *p*-NO_2 > *o*-NO_2 > *o*-COOMe > *m*-Cl > H > *p*-Me

> *p*-OMe. Structural characterization was done by IR, ^{1}H and ^{13}C NMR. The presence of expected 2-arylthiobenzothiazole skeleton was confirmed by the X-ray structure of **4** (*Figure V.4.4.2.*).

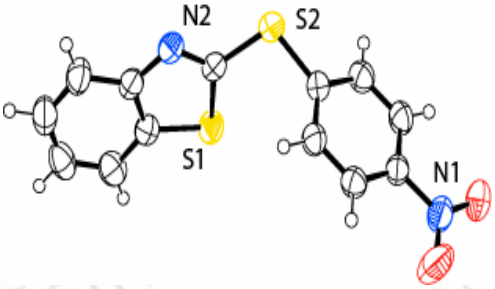


Figure V.4.4.2. ORTEP molecular diagram with ellipsoid at 50% probability of **4c**.

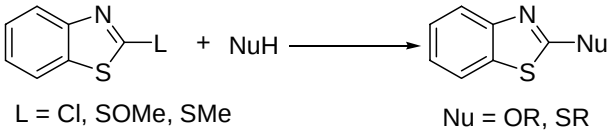
In summary, we have for the first time developed a single catalytic system for two sequential intra and intermolecular *S*-arylation leading to direct synthesis of 2-arylthiobenzothiazoles from amines / dithiocarbamates. Low catalyst loading, inexpensive metal catalyst and ligand, lower reaction temperature and shorter reaction times makes this method superior to all methods reported so far thus, of potential industrial significance.

V.5. Synthesis of 2-Substituted Oxa/Thia Benzothiazoles

Regarding Cu-catalyzed hetero-arylations, domino reactions for the synthesis of heterocycles, and intramolecular *S*-arylations leading to benzothiazoles were discussed in the previous sections **V.3.**, **V.4.** and **V.4.2.**

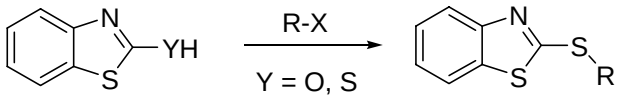
V.5.1. Known Methods for 2-Substituted Oxa/Thia Benzothiazoles

Although 2-mercapto and oxo-substituted benzothiazoles play an important role in the field of pharmaceutical science, the available synthetic methods for these compounds are very limited. Traditional methods for the synthesis of this structural moiety, include nucleophilic substitution of 2-chlorobenzothiazole or it's equivalents with either oxa (alcohols and phenols) or thia (thiols) nucleophiles (*Scheme V.5.1.1.*).[20]



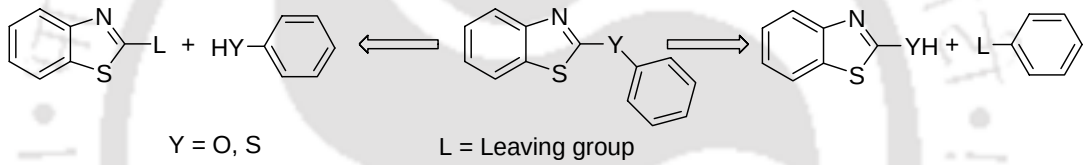
Scheme V.5.1.1.

Alternatively, *S*-alkylation of pre-formed 2-mercapto benzothiazole with alkylating agents is the common strategy to prepare *S*-alkyl mercapto benzothiazoles. (*Scheme V.5.1.2.*) [21]



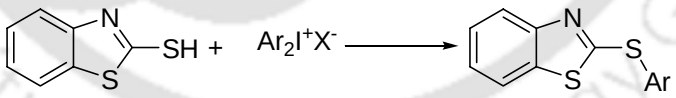
Scheme V.5.1.2.

However, by this strategy synthesis of *S*-arylthiobenzothiazoles are impossible and are generally prepared by two types of nucleophilic substitution reactions. One by the nucleophilic attack of arylthiols with a preformed 2-halobenzothiazoles and the second is by the nucleophilic attack of mercapto-benzothiazole with haloarenes containing deactivating substituents such as -NO_2 and -CN under strong basic condition. (*Scheme V.5.1.3.*).[22]



Scheme V.5.1.3.

Alternatively, a method for the synthesis of 2-arylthiobenzothiazoles by the *S*-arylation of benzothiazole-2-thiol with diaryliodonium salts in an ioinic liquid is reported. (*Scheme V.5.1.4.*)[23]



Scheme V.5.1.4.

Many of these methods rely on harsh conditions with limited functional group tolerance. Recent approaches have focused on the use of transition metals (Cu, Pd and Fe)-catalyzed intermolecular C–S bond formations in relatively milder conditions with better efficiency and selectivity.[24] However, the preparation of substituted 2-oxo and mercapto benzothiazoles using these methods depends largely on the availability of the prerequisites, suitably substituted 2-halobenzothiazole or mercapto-benzothiazoles which are often difficult to prepare and involves tedious multi-step processes.

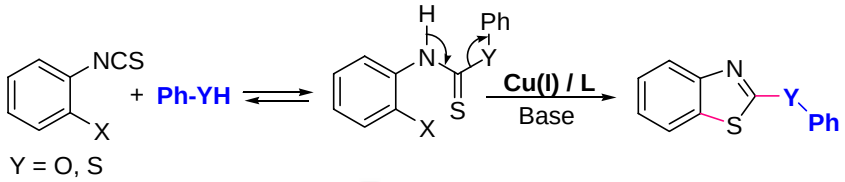
Recent advances in the field of transition metal catalyzed carbon-heteroatom bond formation, proved to be the most efficient way for the construction of various heterocycles.[25a-e] In general, the one-pot tandem, cascade or domino strategies are used to improve the efficiency of a chemical reaction whereby multiple bonds can be constructed in a single reaction without the need to isolate the intermediates.[25f-i]

Numerous heterocycles have been synthesized via one-pot Cu-catalyzed C-heteroatom (N, O, S) bond formations. As compared to C–N and C–O bond formations, C–S bond formations are comparatively less explored because of the oxidative dimerization (S–S bond formation) and its affinity for metal making the catalyst less efficient.[26] Intramolecular Cu-catalyzed *S*-arylation of thioacetanilides or thiobenzanilides to produce 2-alkyl or arylbenzothiazoles was first reported by Bowmann *et al.*[27a] Later the same synthesis was achieved by a Pd-catalyzed process in more efficient manner.[27b]. Batey *et al.* have explored the intra molecular C–S bond formation for the synthesis of 2-arylbenzothiazoles and 2-aminobenzothiazoles using either Cu or Pd-catalytic systems from the corresponding *o*-halo thiobenzanilides and thioureas respectively.[27c,d] Other groups have made further perfection in the Cu-catalytic system for similar reactions.[27e,f]. Recently, Bao et al. have reported a Cu(I)-catalyzed synthesis of 2-iminobenzo-1,3-oxathioles from aryl isothiocyanates and *o*-iodophenols in one-pot.[27g]. This aspect has been discussed in detail in the previous section (**V.4.2.**).

V.5.2. Present Work

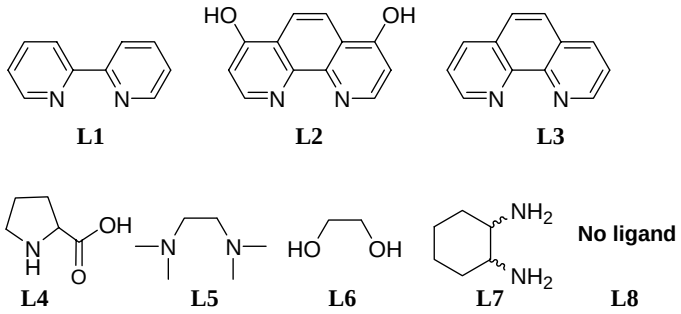
Our recent success in the Cu-catalyzed synthesis of substituted 2-mercapto benzimidazoles and 2-arylthiobenzothiazoles via intra/intermolecular C–N and C–S bond formations and our interest in the construction of various heterocycles prompted us to develop a Cu-catalyzed domino process for an easy access to 2-substituted benzothiazoles.[28] This strategy involves initial nucleophilic addition of sulfur or oxygen nucleophiles to isothiocyanate followed by an intramolecular *S*-arylation leading to substituted 2-thia/oxa benzothiazoles in the same pot. The success of this strategy depends on the formation of the thiocarbamate or the dithiocarbamate esters by oxa or thia nucleophile respectively. Unlike amino nucleophile which quantitatively forms stable isolable thiourea corresponding thiocarbamate or dithiocarbamate esters derived from

phenol or thiophenol are in equilibrium particularly under basic condition due to their better leaving ability and once formed they undergo rapid intramolecular *S*-arylation. (*Scheme V.5.2.1.*)



Scheme V.5.2.1. *Reaction pathway for the formation of 2-substituted benzothiazoles*

For optimization of this one-pot domino process, *o*-bromo-phenylisothiocyanate (**1**) and phenol (**a**) was selected as the reaction partners. In the absence of any ligand the desired product (**1a**) was not observed. Therefore an initial ligand screen was carried out with different *N*,*N*-, *N*,*O*- and *O*,*O*-donor ligands by taking CuI as precatalyst and K_2CO_3 as the base. To our delight, 1,10-phenanthroline (**L3**) was found to be the most effective ligand for the present transformation (*Scheme V.5.2.2.*, *Figure V.5.2.1.*). This observation is consistent with our previous intramolecular C–N bond formation and similar intramolecular C-heteroarylation observed by others.[28a,27c,d] In contrast to our above finding involving inter and intramolecular C–S bond formation the 1,2-cyclohexyldiamine (**L7**) ligand was totally ineffective, possibly because of the competitive thiourea formation with isothiocyanate (**1**) over metal complexation. Similar bipyridyl (**L1**) and substituted phenanthroline (**L2**) and TMEDA (**L5**) ligands were not very effective but L-proline (**L4**) and ethyleneglycol (**L6**) ligands provided the cyclized product (**1a**) in moderate yields. This cascade reaction was equally effective in a range of high boiling polar aprotic solvents (DMSO, DMF, DMA) as well as non polar solvents (dioxane and toluene). However, the use of anhydrous dioxane provided superior conversion compared to other solvents tested. The optimum reaction temperature was found to be 90 ^oC, although faster conversion was achieved at higher temperature 100 ^oC, formation of undesirable products were also observed. From further experimentation the optimum conversion was achieved using isothiocyanate (**1**) (1 equiv.), phenol (**a**) (1.2 equiv), CuI (5 mol%), **L3** (10 mol%) and K_2CO_3 (2 equiv.) in dry dioxane at 90 ^oC.



Scheme V.5.2.2. *Ligands studied for Cu-catalyzed intramolecular S-arylation.*

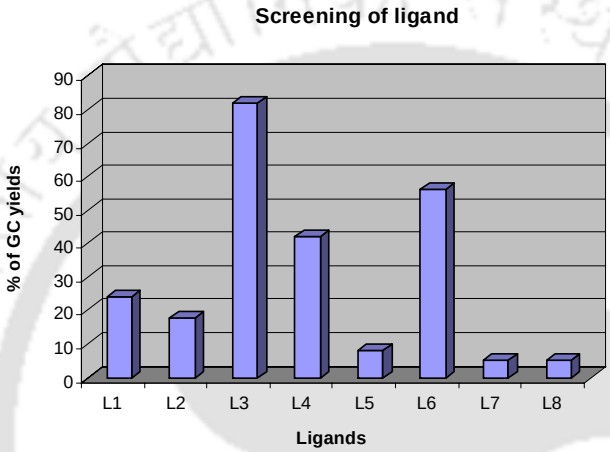
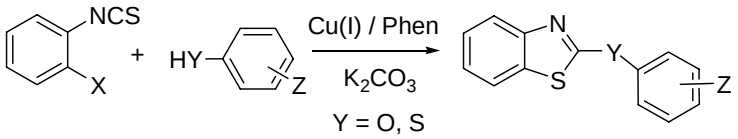


Figure V.5.2.1. *Ligands comparison for Cu-catalyzed intramolecular S-arylation.*

With the optimized catalytic conditions in hand, we then scrutinize the scope and generality of the method. We were delighted to find, a series of oxygen and sulfur nucleophiles reacts with *o*-bromo/iodo phenylisothiocyanates smoothly to give 2-oxo/thia substituted benzothiazoles in moderate to high yields (*Table V.5.2.1.*). *o*-Haloaryl isothiocyanates (**1-4**) were prepared in excellent yields following our recently reported green protocol.[29] The present Cu-catalytic system is efficient and compatible with various *o*-halo (Br and I) isothiocyanates (**1'**,**1-4**). This intramolecular heteroarylation was equally effective either with *o*-bromo (**1**) or *o*-iodo (**1'**) isothiocyanates. Due to easy preparation and low cost of *o*-bromo substrates the reaction were performed mostly with *o*-bromo substrates (**1-3**). Wide varieties of oxa and thia nucleophiles such as phenols (**a-g**), alcohols (**k**, **l**), thiophenols (**h**, **i**) and thiol (**j**) containing electron withdrawing (**b**, **c**, **g**) and donating substituents (**d**, **e**, **f**, and **i**) reacted with *o*-halo isothiocyanates (**1'**, **1-4**) giving oxa and thia substituted benzothiazoles (*Table V.5.2.1.*).

Table V.5.2.1. *Synthesis of substituted 2-oxa/thio benzothiazoles.*



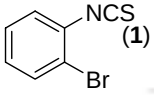
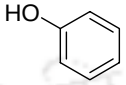
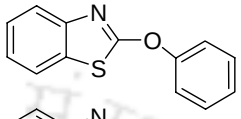
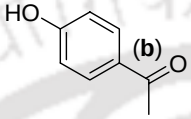
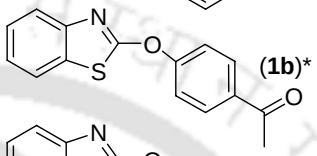
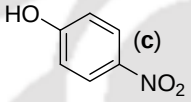
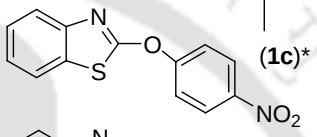
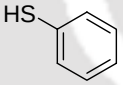
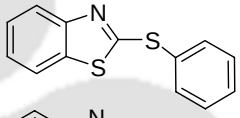
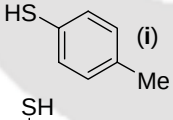
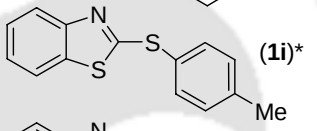
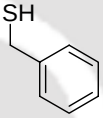
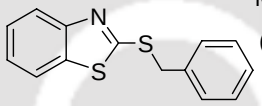
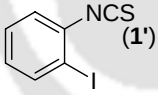
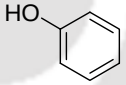
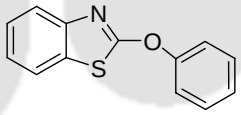
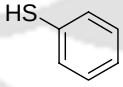
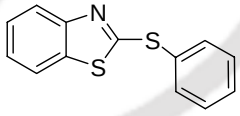
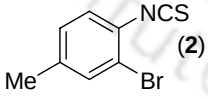
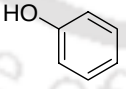
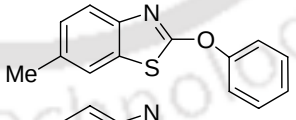
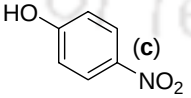
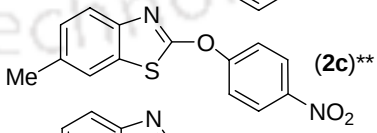
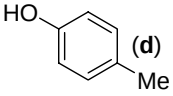
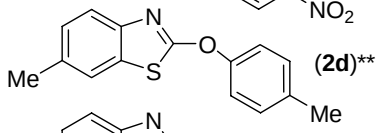
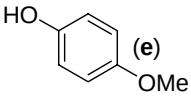
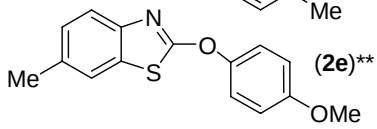
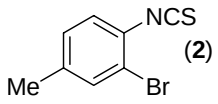
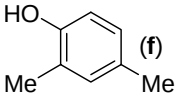
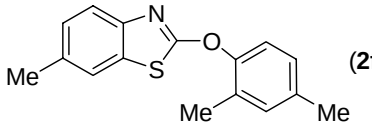
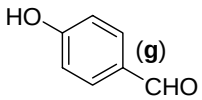
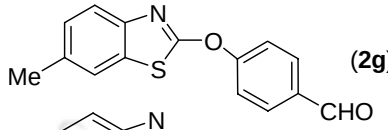
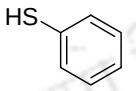
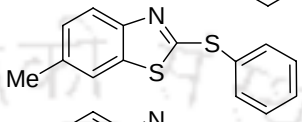
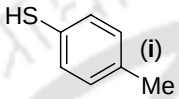
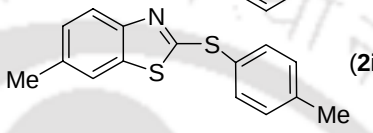
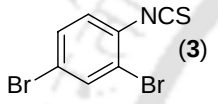
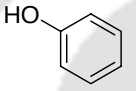
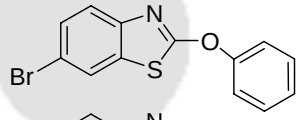
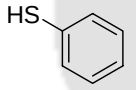
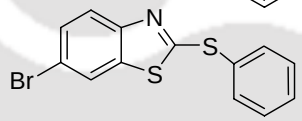
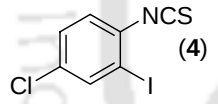
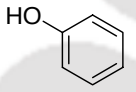
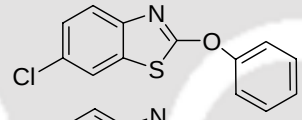
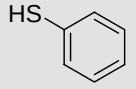
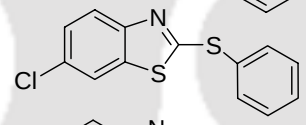
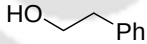
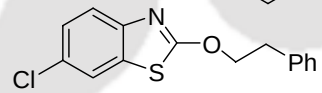
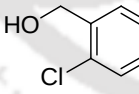
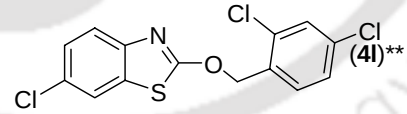
Isothiocyanate	Nucleophile	Product	Yield (%)
 (**1**)	 (**a**)	 (**1a**)*	73
	 (**b**)	 (**1b**)*	81
	 (**c**)	 (**1c**)*	85
	 (**h**)	 (**1h**)*	76
	 (**i**)	 (**1i**)*	79
	 (**j**)	 (**1j**)**	69
 (**1'**)	 (**a**)	 (**1a**)*	74
	 (**h**)	 (**1h**)*	75
 (**2**)	 (**a**)	 (**2a**)*	64
	 (**c**)	 (**2c**)**	83
	 (**d**)	 (**2d**)**	72
	 (**e**)	 (**2e**)**	78

Table V.5.2.1. contd…

Table V.5.2.1. contd…

Isothiocyanate	Nucleophile	Product	Yield (%)
 (**2**)	 (**f**)	 (**2f**)**	65
	 (**g**)	 (**2g**)*	91
	 (**h**)	 (**2h**)*	68
	 (**i**)	 (**2i**)**	70
 (**3**)	 (**a**)	 (**3a**)*	76
	 (**h**)	 (**3h**)*	75
 (**4**)	 (**a**)	 (**4a**)*	78
	 (**h**)	 (**4h**)**	80
	 (**k**)	 (**4k**)**	54
	 (**l**)	 (**4l**)**	40

*Reactions were performed for 12 h at 90 °C, **Reactions were performed for 16 h at 90 °C.

Both phenols and thiophenols were found to be equally effective in this cascade process. Aliphatic thiol (**1**) and aliphatic and benzylic alcohols (**k** and **l**) were not that efficient as compared to phenols and thiophenols. On closer look at table-1 revealed phenols having electron-withdrawing groups (**b**, **c**, **g**) giving higher yields. This is due to the facile deprotonation to their corresponding phenolate ion under basic (K_2CO_3) condition hence serving as a better nucleophile. This also explains why alcohols (**k** and **l**) and thiol (**1**) are less reactive. Further there seems to be a good correlation between the

substituents (*p*-Me, *p*-Cl, *p*-Br) attached to isothiocyanates ((**1'**, **1-4**) and reactivity. Weakly electron donating substituent (*p*-Me) when present retards the reaction giving lower yield (**2a** and **2h**) where as weakly electron withdrawing substituents (*p*-Cl, *p*-Br) gave better yields of the products (**3a**, **3h**, **4a** and **4h**). The presence of expected 2-aryloxybenzothiazole skeleton was confirmed by the X-ray structure of **1b** (*Figure V.5.2.2.*).

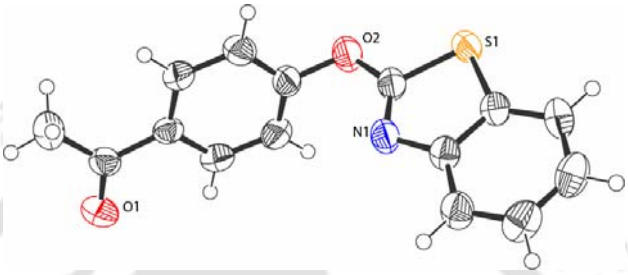


Figure V.5.2.2. *ORTEP molecular diagram with ellipsoid at 50% probability of* ***1b.***

It is worth mentioning here that derivatives of compound (**1j**) were notified as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 enzyme (COX-2) inhibitors,[30a] and have antimicobacterial activity.[30b]

V.5.3. Application in the Synthesis of Benzothiazolones

Benzothiazolone core structure can be found in a large number of compounds having a range of biological activities such as progesterone receptor (PR) antagonists,[30c] as fungicides[30d-f] and herbicides[3] and also serves as useful synthetic intermediates for the construction of complex molecules. Therefore, we envisage an *o*-dealkylation strategy could be useful to access some of these derivatives. Nucleophilic addition of ethanol to *o*-bromo-phenylisothiocyanate (**1**) gives thiocarbamate ester which then undergoes intramolecular *S*-arylation by CuI / L system to furnish 2-ethoxybenzothiazole (**m**). This is followed by *O*-dealkylation using TFA to provide 2-benzothiazolone (**5m**). In an analogous approach other benzothiazolones (**5n** and **5o**) can be prepared in moderate yield (*Scheme V.5.3.1*). The presence of benzothiazolone skeleton was confirmed by the X-ray structure of **5m** (*Figure V.5.3.1*).

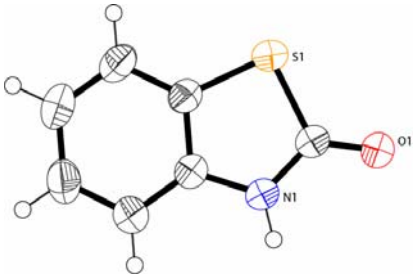
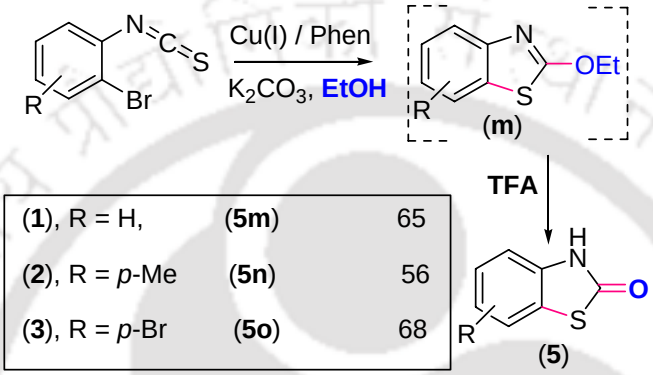


Figure V.5.3.1. *ORTEP molecular diagram with ellipsoid at 50% probability of* ***5m***



(**1**), R = H,	(**5m**)	65
(**2**), R = *p*-Me	(**5n**)	56
(**3**), R = *p*-Br	(**5o**)	68

Scheme V.5.3.1.

In conclusion, we have developed an efficient cascade process for the preparation of 2-substituted benzothiazoles wherein the *in situ* generated thiocarbamate or dithiocarbamate by the reaction of 2-haloisothiocyanates with oxa- or thia- nucleophiles undergo CuI/L catalyzed intramolecular C–S bond formation. Both phenols and thiophenols reacts equally well on the other hand, alcohols and thiols are found to be less reactive. The rate of the reaction is faster giving better yields when electron withdrawing substituents are present in either of the coupling partner's phenols / thiophenols and isothiocyanates and an opposite effect is observed when electron donating substituents are present. Benzothiazolones can also be achieved in one-pot by using ethanol as a nucleophile (oxygen source) via Cu-catalyzed intramolecular *S*-arylation followed by *O*-dealkylation strategy.

V.6. Experimental Section

V.6.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1.

V.6.2. General Procedure for the Synthesis of Substituted 2-Arylthiobenzothiazoles

An oven-dried flask was charged with CuI (5 mol %), L5 (10 mol %), dithiocarbamate (**1a**, 1 mmol), iodobenzene (**1b,** 1.1 equiv), K_2CO_3 (3 equiv), and solvent DMSO (1 mL). The flask was kept in a pre-heated oil bath at 90 ^oC. Heating was continued for 4 hrs after which the reaction mixture was cooled and admixed with water (5 mL). The product was extracted with ethylacetate (2 x 10 mL), organic layer dried over anh.Na_2SO_4, concentrated under reduced pressure, and purified over column of silica gel (EtOAc: Hexane as eluents) to give product **1b** in 86 % isolated yield. The identity and purity of the products were confirmed by spectroscopic analysis.

V.6.3. General Procedure for the Synthesis of Substituted 2-oxa / thia Benzothiazoles

A round bottom flask with a magnetic stir bar and fitted with a reflux condenser was charged with 2-bromophenylisothiocyanate (1 mmol), phenol (1.1 mmol), CuI (0.05 mmol, 9.5 mg), 1,10-phenanthroline (0.1 mmol, 18 mg), K_2CO_3 (2 mmol, 276 mg) and dry 1,4-dioxane (3 mL). The mixture was heated at 90 °C for 12 hrs protecting it with a guard tube. The reaction mixture was then cooled, filtered over Celite using ethylacetate. Filtrate was evaporated to dryness and product purified by column chromatography giving compound.

V.6.4. General Procedure for Synthesis of Benzothiazolones

A round bottom flask with a magnetic stir bar and fitted with a reflux condenser was charged with 2-bromophenylisothiocyanate (x) (1 mmol), CuI (0.05 mmol, 9.5 mg), 1,10-phenanthroline (0.1 mmol, 18 mg), K_2CO_3 (2 mmol, 276 mg) and dry ethanol (3 mL). The resulting solution was kept under reflux for 12 hrs protecting it with a guard tube. The

reaction mixture was then cooled, added TFA (2 mL), and continued under reflux for 5 h. After completion, solvent was removed under vacuum and treated with sodium bicarbonate solution. The product was extracted with ethylacetate (2 x 15 mL). The organic phase was dried over Na_2SO_4, and then evaporated. The crude product was purified using a short chromatography column.

V.7. References

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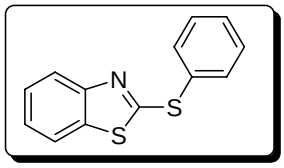
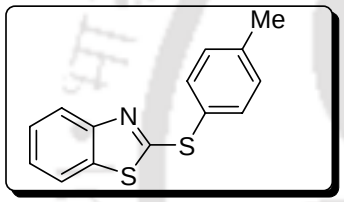
V.8. Spectral Data

2-(Phenylthio)benzo[*d*]thiazole or 2-Phenylsulfanyl-benzothiazole (1):



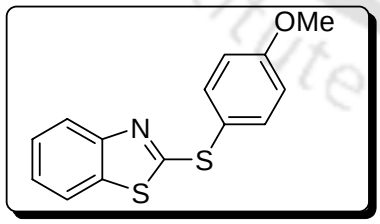
Colourless gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, 1H, *J* = 8.0 Hz), 7.33 – 7.46 (m, 4H), 7.58 (d, 1H, *J* = 7.6 Hz), 7.69 (m, 2H), 7.87 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ120.7, 121.8, 124.2, 126.0, 129.7, 129.8, 130.4, 135.2, 135.4, 153.8, 169.5.; IR (KBr): 3060, 1582, 1455, 1426, 1310, 1237, 1020, 1007, 752 cm^{-1}. Anal. Calcd for $C_{13}H_9NS_2$ (243.35): C 64.16, H 3.73, N 5.76, S 26.35; found C 64.23, H 3.75, N 5.81, S 26.31. HRMS (ESI) calcd for $C_{13}H_9NS_2$ (M + H^+) 244.0255, found 244.0259.

2-(*p*-Tolylthio)benzo[*d*]thiazole or 2-*p*-Tolylsulfanyl-benzothiazole (2).



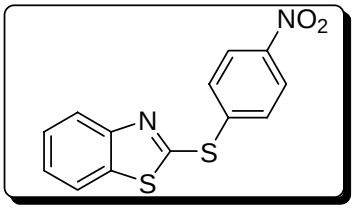
White solid; M.p. 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 7.17 – 7.24 (m, 3H), 7.34 (t, 1H, *J* = 8.0 Hz), 7.57 (d, 3H, *J* = 8.0 Hz), 7.84 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ21.5, 120.8, 121.8, 124.2, 126.1, 126.2, 130.8, 135.4, 135.6, 141.1, 154.0, 170.8.; IR (KBr): 3059, 2916, 1592, 1455, 1422, 1310, 1235, 1005, 816, 757 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NS_2$ (257.38): C 65.33, H 4.31, N 5.44, S 24.92.; found C 65.41, H 4.29, N 5.49, S 24.90.

2-(4-Methoxyphenylthio)benzo[*d*]thiazole or 2-*p*-Methoxyphenylsulfanyl-benzothiazole (3).



White solid; M.p. 61 – 63 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.98 (d, 2H, *J* = 6.8 Hz), 7.22 (t, 1H, *J* = 8.0 Hz), 7.37 (t, 1H, *J* = 7.6 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 7.64 (d, 2H, *J* = 6.8 Hz), 7.84 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ55.8, 115.7, 120.3, 121.0, 121.9, 124.3, 126.3, 135.6, 137.8, 154.4, 161.9, 172.3.; IR (KBr): 3056, 2922, 1588, 1493, 1454, 1427, 1290, 1257, 1002, 830, 758 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NOS_2$ (273.38): C 61.51, H 4.06, N 5.12, S 23.46; found C 61.47, H 4.03, N 5.14, S 23.39.

2-(4-Nitrophenylthio)benzo[*d*]thiazole or 2-*p*-Nitrophenylsulfanyl-benzothiazole (4).

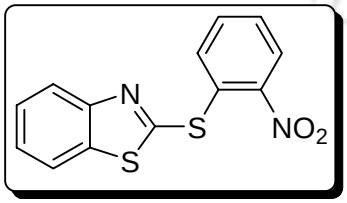


Yellow solid; Mp. 105 – 107 °C (Lit[9d] M.p.95-96 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, 1H, *J* = 7.6 Hz), 7.48 (t, 1H, *J* = 7.6 Hz), 7.77 (d, 2H, *J* = 7.6 Hz), 7.96 (d, 2H, *J* = 8.2 Hz), 8.23 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ121.3, 122.9, 124.6, 125.6, 126.8, 132.8, 136.3, 140.1, 147.9, 153.5, 163.0; IR (KBr): 3094, 2840, 1597, 1518, 1455, 1340, 1002, 843, 765 cm^{-1}. Anal. Calcd for $C_{13}H_8N_2O_2S_2$ (288.35): C 54.15, H 2.80, N 9.72, S 22.24; found C 54.08, H 2.79, N 9.68, S 22.16.

CCDC number for compound 4: CCDC 722709. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

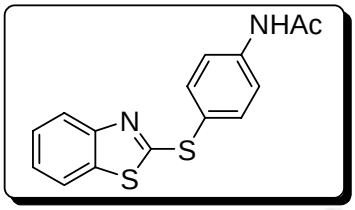
Crystallographic description of 4: Crystal dimension (mm): 0.29 x 0.21 x 0.16. $C_{13}H_8N_2O_2S_2$, Mr = 288.33. Monoclinic, space group P2(1)/n; a = 7.4427(6) Å, b = 9.3482(7) Å, c = 18.2369(14) Å; α = 90.00°, β = 95.639(4) °, γ = 90.00°, V = 1262.71(17) Å^3; Z = 4; ρ_{cal} = 1.517 mg/m^3; μ(mm^{-1}) = 0.419; *F (000)* = 592; Reflection collected / unique = 4090 / 3019; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0909, wR2 = 0.2170, R indices (all data) R1 = 0.0711, wR2 = 0.1839; goodness of fit = 1.192.

2-(2-Nitrophenylthio)benzo[*d*]thiazole or 2-*o*-Nitrophenylsulfanyl-benzothiazole (5).



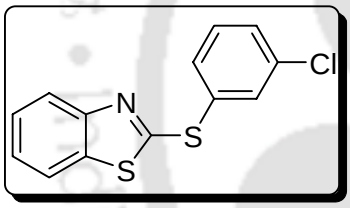
Yellow solid; M.p. 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.57 (m, 5H), 7.89 (d, 1H, *J* = 8.0 Hz), 8.10 (d, 1H, *J* = 8.0 Hz), 8.22 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ121.6, 123.7, 125.7, 126.3, 126.8, 127.5, 130.6, 130.7, 133.2, 133.9, 137.6, 153.6, 160.9; IR (KBr): 3095, 1589, 1519, 1338, 1105, 988, 754, 734 cm^{-1}. Anal. Calcd for $C_{13}H_8N_2O_2S_2$ (288.35): C 54.15, H 2.80, N 9.72, S 22.24; found C 54.21, H 2.82, N 9.76, S 22.20.

_N_-(4-Benzo[_d_]thiazole-2-ylthio)phenyl)acetamide or 2-_p_-Acetamidophenylsulfanyl-benzothiazole (6).



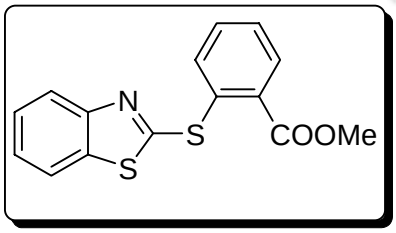
White solid; M.p. 168–170 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 7.24 (t, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 7.2 Hz), 7.60 – 7.64 (m, 3H), 7.72 (d, 2H, *J* = 8.4 Hz), 7.80 (d, 1H, *J* = 8.0 Hz), 9.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 121.0, 121.1, 121.5, 123.5, 124.5, 126.4, 135.3, 136.6, 140.9, 153.7, 169.6, 171.3.; IR (KBr): 3240, 3170, 3098, 3052, 1661, 1588, 1537, 1492, 1423, 1311, 1005, 831, 755 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2OS_2$ (300.40): C 59.97, H 4.03, N 9.33, S 21.35; found Calcd. C 60.01, H 4.07, N 9.39, S 21.28.

2-(3-Chlorophenylthio)benzo[_d_]thiazole or 2-_m_-Chlorophenylsulfanyl-benzothiazole (7).



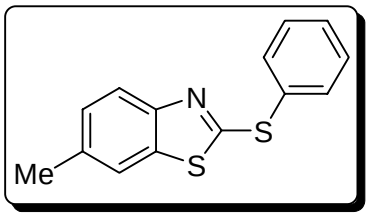
Yellow Gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, 1H, *J* = 8.0 Hz), 7.36 – 7.47 (m, 3H), 7.59 (d, 1H, *J* = 7.6 Hz), 7.67 – 7.72 (m, 2H), 7.89 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.2, 122.4, 124.9, 126.6, 130.7, 131.1, 132.0, 133.2, 134.7, 135.6, 135.9, 153.9, 162.0, 167.8; IR (KBr): 3060, 2924, 1574, 1455, 1426, 1310, 1237, 1007, 780, 756 cm^{-1}. Anal. Calcd for $C_{13}H_8NS_2Cl$ (277.80): C 56.21, H 2.90, N 5.04, S 23.09; found C 56.16, H 2.87, N 4.99, S 23.01.

Methyl 2-(benzo[_d_]thiazol-2-ylthio)benzoate or 2-_o_-Methylbenzoatesulfanyl-benzothiazole (8).



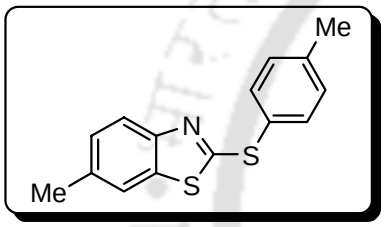
Gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 7.32–7.49 (m, 5H), 7.75 (d, 1H, *J* = 8.0 Hz), 7.99 (t, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.5, 121.2, 122.8, 125.4, 126.4, 127.7, 130.4, 131.1, 131.9, 132.7, 135.5, 136.9, 153.6, 164.6, 166.6.; IR (KBr): 3061, 2949, 1714, 1455, 1426, 1258, 1056, 755 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO_2S_2$ (301.39): C 59.78, H 3.68, N 4.65, S 21.28; found C 59.86, H 3.71, N 4.72, S 21.39.

6-Methyl-2-(phenylthio)benzo[*d*]thiazole or 2-Phenylsulfanyl-6-methylbenzothiazole (9).



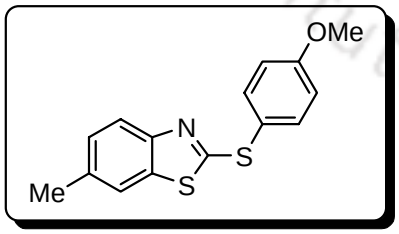
Gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.19 (d, 1H, *J* = 8.4 Hz), 7.41 – 7.47 (m, 4H), 7.70 – 7.76 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.7, 120.9, 121.7, 127.9, 130.1, 130.4, 130.6, 134.7, 135.4, 136.0, 152.2, 168.3.; IR (KBr): 3056, 2919, 1582, 1468, 1439, 1242, 1012, 813, 749, 689 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NS_2$ (257.38): C 65.33, H 4.31, N 5.44, S 24.92.; found C 65.25, H 4.29, N 5.38, S 24.79.

2-(*p*-Tolylthio)-6-methylbenzo[d]thiazole or 2-*p*-Tolylsulfanyl-6-methylbenzothiazole (10).



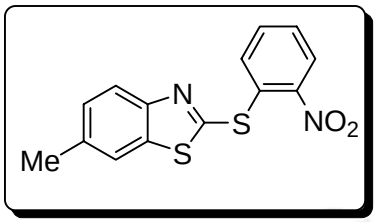
White solid; M.p. 80–81 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 2.43 (s, 3H), 7.20 (d, 1H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.41 (s, 1H), 7.61 (d, 2H, *J* = 8.0 Hz), 7.74 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.6, 120.8, 121.5, 126.7, 127.7, 130.8, 134.5, 135.6, 135.8, 141.1, 152.3, 169.3.; IR (KBr): 2918, 2852, 1594, 1438, 1003, 810, 504 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NS_2$ (271.41): C 66.38, H 4.83, N 5.16, S 23.63; found C 66.46, H 4.84, N 5.20, S 23.56.

2-(4-Methoxyphenylthio)-6-methylbenzo[*d*]thiazole or 2-*p*-Methoxyphenylsulfanyl-6-methylbenzothiazole (11).



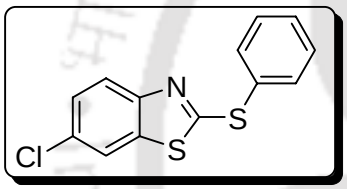
White solid; M.p. 91–93 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.86 (s, 3H), 6.98 (d, 2H, *J* = 8.4 Hz), 7.18 (d, 1H, *J* = 8.4 Hz), 7.40 (s, 1H), 7.64 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.6, 55.6, 115.6, 120.5, 120.7, 121.4, 127.7, 134.3, 135.7, 137.7, 152.4, 161.7, 170.6.; IR (KBr): 3016, 2920, 1587, 1461, 1436, 1251, 1013, 1002, 820 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NOS_2$ (287.41): C 62.69, H 4.56, N 4.87, S 22.31; found C 62.74, H 4.59, N 4.84, S 22. 25.

2-(2-Nitrophenylthio)-6-methylbenzo[*d*]thiazole or 2-*o*-Nitrophenylsulfanyl-6-methylbenzothiazole (12).



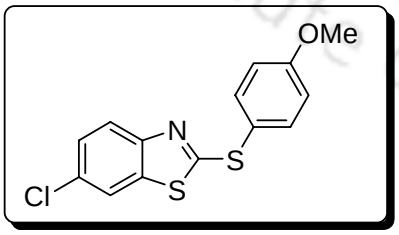
Yellow solid; M.p. 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H), 7.34–7.40 (m, 3H), 7.45–7.49 (m, 1H), 7.68 (s, 1H), 7.98 (d, 1H, J = 8.4 Hz), 8.23 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ21.8, 121.4, 123.4, 125.8, 127.4, 128.6, 130.4, 134.1, 136.9, 138.2, 146.4, 152.0, 159.2; IR (KBr): 3090, 2920, 2852, 1589, 1518, 1335, 1304, 991, 815 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2O_2S_2$ (302.38): C 55.61, H 3.33, N 9.26, S 21.21; found C 55.53, H 3.29, N 9.20, S 21.12.

6-Chloro-2-(phenylthio)benzo[d]thiazole or 2-Phenlsulfanyl-6-chlorobenzothiazole (13).



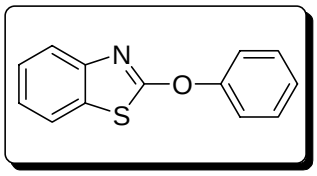
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, 1H, J = 8.8 Hz), 7.47–7.53 (m, 2H), 7.58 (s, 1H), 7.71–7.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.5, 122.7, 127.0, 129.5, 130.2, 130.3, 130.9, 135.6, 136.7, 152.6, 161.9, 170.8.; IR (KBr): 3059, 2924, 1587, 1458, 1432, 1260, 1104, 1015, 815, 749 cm^{-1}. Anal. Calcd for $C_{13}H_8NS_2Cl$ (277.80): C 56.21, H 2.90, N 5.04, S 23.09; found C 56.30, H 2.93, N 5.11, S 23.12.

2-(4-Methoxyphenylthio)-6-chlorobenzo[*d*]thiazole or 2-*p*-Methoxyphenylsulfanyl-6-chlorobenzothiazole (14).



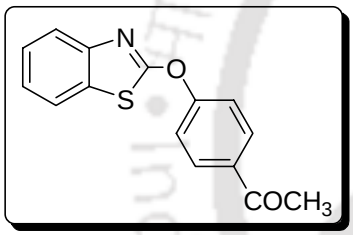
Gummy liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.98 (d, 2H, J = 8.4 Hz), 7.31 (d, 1H, J = 8.8 Hz), 7.55 (s, 1H), 7.62 (d, 2H, J = 8.4 Hz), 7.72 (d, 1H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 115.7, 120.7, 122.5, 126.9, 130.1, 137.7, 148.7, 152.8, 161.9, 172.9; IR (KBr): 3065, 2926, 1592, 1529, 1493, 1445, 1251, 1101, 814 cm^{-1}. Anal. Calcd for $C_{14}H_{10}NOS_2Cl$ (307.82): C 54.63, H 3.27, N 4.55, S 20.83; found C 54.58, H 3.23, N 4.49, S 20.75.

2-phenoxybenzo[*d*]thiazole(1a):



Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.45 (m, 7H), 7.63 (d, 1H, J = 8.0 Hz), 7.73 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.8, 121.4, 121.8, 124.2, 126.3, 126.4, 130.1, 132.4, 149.2, 154.8, 172.1; IR (KBr): 3064, 2753, 1942, 1784, 1683, 1598, 1562, 1528, 1487, 1456, 1440, 1310, 1285, 1230, 1158, 1126, 1066, 1017, 1004 cm^{-1}. $C_{13}H_9NOS$ (227.28): Calcd. C 68.69, H 3.99, N 6.16, S 14.11; found C 68.78, H 4.03, N 6.21, S 13.72.

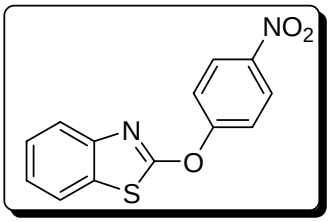
1-(4-(benzo[*d*]thiazol-2-yloxy)phenyl)ethanone(1b):



White solid; Mp. 106-108°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.27 (t, 1H, *J* = 7.4 Hz), 7.38 (t, 1H, *J* = 7.8 Hz), 7.45 (d, 2H, *J* = 8.5 Hz), 7.67 (d, 1H, *J* = 8.0 Hz), 7.73 (d, 1H, *J* = 8.0 Hz), 8.02 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6, 120.2, 121.4, 121.9 124.5, 126.4, 130.4, 132.3, 134.6, 148.7, 157.9, 170.4, 196.6; IR (KBr): 3057, 3007, 2913, 1674, 1598, 1520, 1500, 1460, 1442, 1440,1361, 1300, 1265, 1249, 1226, 1203, 1160, 1105, 1066, 1013, 959, 910, 855, 844 cm^{-1}. $C_{15}H_{11}NO_2S$ (269.32): Calcd. C 66.89, H 4.11, N 5.20, S 11.90; found C 66.82, H 4.08, N 5.09, S 11.69.

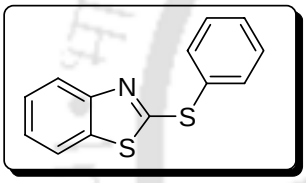
Crystallographic data for 1b: Crystal dimension (mm): 0.31 x 0.26 x 0.21. $C_{15}H_{11}NO_2S$, Mr = 269.31. Monoclinic, space group P2(1); a = 5.42480(10) Å, b = 12.5880(3) Å, c = 9.4882(2) Å; α = 90.00°, β = 97.728(10) °, γ = 90.00°, V = 642.04(2) $Å^3$; Z = 2; ρ_{cal} = 1.393 mg/m^3; μ(mm^{-1}) = 0.248; *F (000)* = 280; Reflection collected / unique = 4204 / 3581; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0411, wR2 = 0.0719, R indices (all data) R1 = 0.0338, wR2 = 0.0693; goodness of fit = 1.137.

2-(4-nitrophenoxy)-benzo[*d*]thiazole(1c):



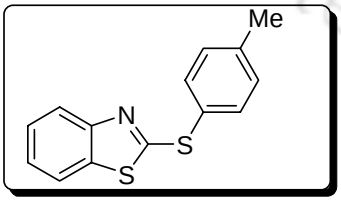
White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, 1H, J = 8Hz), 7.42 (t, 1H, J = 8Hz), 7.57 (d, 2H, *J* = 8.8 Hz), 7.74 (t, 2H, J = 8Hz), 8.30 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 120.7, 121.6, 122.2, 125.0, 125.8, 126.7, 132.5, 145.0, 148.6, 159.0, 169.7; IR (KBr): 3077, 2920, 2851, 1591, 1516, 1488, 1440, 1351, 1250, 1235, 1160, 853, 751 cm^{-1}. $C_{13}H_8N_2O_3S$ (272.02): Calcd. C 57.35, H 2.96, N 10.29, S 11.78; found. C 57.24, H 2.93, N 5.28, S 11.69.

2-(Phenylthio)benzo[*d*]thiazole or 2-Phenylsulfanyl-benzothiazole (1h).



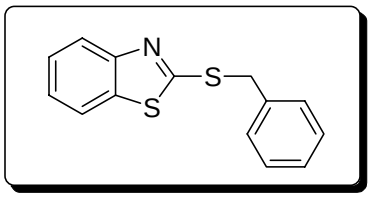
Colourless gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, 1H, *J* = 8.0 Hz), 7.33–7.46 (m, 4H), 7.58 (d, 1H, *J* = 7.6 Hz), 7.69 (m, 2H), 7.87 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 120.7, 121.8, 124.2, 126.0, 129.7, 129.8, 130.4, 135.2, 135.4, 153.8, 169.5.; IR (KBr): 3060, 1582, 1455, 1426, 1310, 1237, 1020, 1007, 752 cm^{-1}. Anal. Calcd for $C_{13}H_9NS_2$ (243.35): C 64.16, H 3.73, N 5.76, S 26.35; found C 64.23, H 3.75, N 5.81, S 26.31. HRMS (ESI) calcd for $C_{13}H_9NS_2$ ($M + H^+$) 244.0255, found 244.0259.

2-(*p*-Tolylthio)benzo[*d*]thiazole or 2-*p*-Tolylsulfanyl-benzothiazole (1i).



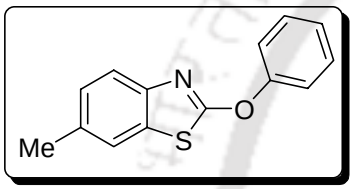
White solid; M.p. 70–72 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 7.17 – 7.24 (m, 3H), 7.34 (t, 1H, *J* = 8.0 Hz), 7.57 (d, 3H, *J* = 8.0 Hz), 7.84 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.5, 120.8, 121.8, 124.2, 126.1, 126.2, 130.8, 135.4, 135.6, 141.1, 154.0, 170.8.; IR (KBr): 3059, 2916, 1592, 1455, 1422, 1310, 1235, 1005, 816, 757 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NS_2$ (257.38): C 65.33, H 4.31, N 5.44, S 24.92.; found C 65.41, H 4.29, N 5.49, S 24.90.

2-(benzylthio)benzo[*d*]thiazole or 2-benzylsulfanyl-benzothiazole (1j).



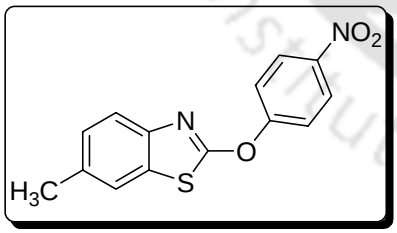
Colorless gum;^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (s, 2H), 7.26–7.34 (m, 4H), 7.39–7.46 (m, 3H), 7.74 (d, 1H, *J* = 8.2 Hz), 7.90 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ37.8, 121.2, 121.7, 124.5, 126.2, 127.9, 128.9, 129.3, 135.5, 136.3, 153.3, 166.6; IR (KBr): 3065, 3027, 2923, 2846, 1494, 1455, 1427, 1309, 1239, 1073, 1017, 993, 754 cm^{-1}. $C_{14}H_{11}NS_2$ (257.37): Calcd. C 65.33, H 4.30, N 5.44, S 25.21; found C 65.25, H 4.25, N 5.39, S 25.08.

6-methyl-2-phenoxybenzo[*d*]thiazole(2a):



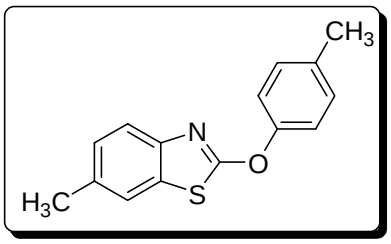
Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.16 (d, 1H, *J* = 8.0 Hz), 7.26 (t, 1H, *J* = 7.2 Hz), 7.33 (d, 2H, *J* = 8.8 Hz), 7.39-7.44 (m, 3H), 7.61 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ21.6, 120.7, 121.3, 121.4, 126.3, 127.7, 130.1, 132.4, 134.1, 147.0, 154.9, 171.3; IR (KBr): 3057, 2921, 1593, 1533, 1488, 1464, 1406, 1306, 1234, 1203, 1157, 1004, cm^{-1}. $C_{14}H_{11}NOS$ (241.31): Calcd. C 69.68, H 4.59, N 5.80, S 13.29; found C 69.73, H 4.61, N 5.84, S 13.12.

2-(4-nitrophenoxy)-6-methylbenzo[*d*]thiazole(2c):



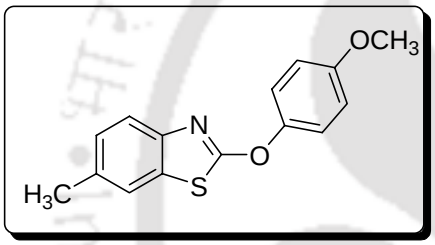
White solid; Mp. 140-142^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 7.22 (d, 1H, *J* = 8.4 Hz), 7.50 (s, 1H), 7.54 (d, 2H, *J* = 9.2 Hz), 7.62 (d, 1H, *J* = 8.4 Hz), 8.27 (d, 2H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 120.5, 121.4, 121.7 125.7, 128.0, 132.5, 135.0, 144.8, 146.3, 159.0, 168.8; IR (KBr): 3118, 2924, 2850, 1614, 1591, 1532, 1515, 1488, 1458, 1380, 1349, 1326, 1307, 1294, 1253, 1210, 1182, 1161, 1109, 1057, 862 cm^{-1}. $C_{14}H_{10}N_2O_3S$ (286.30): Calcd. C 58.73, H 3.52, N 9.78, S 11.19; found C 58.79, H 3.54, N 9.84, S 11.02. HRMS (ESI) calcd for $C_{14}H_{10}N_2O_3S$ (M + H^{+}) 287.0490, found 287.0463.

2-(*p*-tolyloxy)-6-methylbenzo[*d*]thiazole(2d):



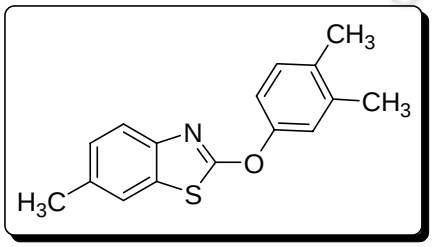
Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.38 (s, 3H), 7.15 (m, 1H), 7.19 (s, 4H), 7.38 (s, 1H), 7.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ21.0, 21.5, 120.5, 121.2, 121.3, 127.6, 130.5, 132.3, 133.9, 136.0, 147.0, 152.7, 171.7; IR (KBr): 3032, 2922, 1605, 1535, 1466, 1234, 1200, 1017, 813 cm^{-1}. $C_{15}H_{13}NOS$ (255.33): Calcd. C 70.55, H 5.13, N 5.48, S 12.55; found C 70.46, H 5.11, N 5.32, S 12.29. HRMS (ESI) calcd for $C_{15}H_{13}NOS$ (M + H^+) 256.0796, found 256.0734.

2-(4-methoxyphenoxy)-6-methylbenzo[*d*]thiazole(2e):



Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.80 (s, 3H), 6.92 (d, 2H, *J* = 9.0 Hz), 7.16 (d, 1H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 9.0 Hz), 7.41 (s, 1H), 7.60 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 55.9, 115.1, 121.4, 122.1, 127.8, 132.5, 134.1, 147.3, 148.7, 157.9, 172.4; IR (KBr): 3049, 3000, 2928, 2835, 1663, 1609, 1535, 1498, 1459, 1409, 1306, 1229, 1101, 1057, 1033, 920, 850, 816 cm^{-1}. $C_{15}H_{13}NO_2S$ (271.33): Calcd. C 66.39, H 4.83, N 5.16, S 11.81; found C 66.45, H 4.79, N 5.06, S 11.64. HRMS (ESI) calcd for $C_{15}H_{13}NO_2S$ (M + H^+) 272.0745, found 272.0705.

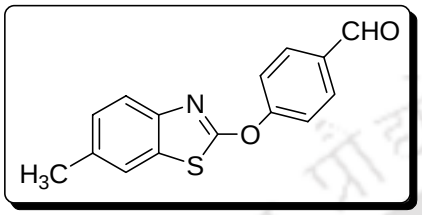
2-(3,4-dimethylphenoxy)-6-methylbenzo[*d*]thiazole(2f):



Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.26 (s, 3H), 2.40 (s, 3H), 7.03-7.09 (m, 2H), 7.16 (d, 2H, *J* = 8.0 Hz), 7.40 (s, 1H), 7.60 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ19.4, 20.1, 21.5, 117.9, 121.2, 121.3, 127.6, 130.9, 132.4, 133.9, 134.9, 138.6, 147.1, 152.9, 171.9; IR (KBr): 2924, 2857, 1604, 1537, 1496, 1466, 1244, 1225, 1195, 1146, 1056, 1021, 872, 813 cm^{-1}.

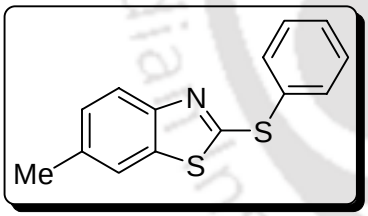
$C_{16}H_{15}NOS$ (269.36): Calcd. C 71.34, H 5.61, N 5.19, S 11.90; found C 71.43, H 5.59, N 5.28, S 11.48. HRMS (ESI) calcd for $C_{16}H_{15}NOS$ (M + H^+) 270.0953, found 270.0897.

4-(6-methylbenzo[*d*]thiazol-2-yloxy)benzaldehyde(2g):



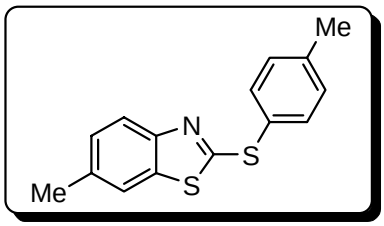
White solid; Mp. 99-100°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.21 (d, 1H, *J* = 8.0 Hz), 7.48 (s, 1H), 7.53 (d, 2H, *J* = 8.6 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 7.94 (d, 2H, *J* = 8.6 Hz), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.6, 120.6, 121.4, 121.6 127.9, 131.8, 132.5, 133.7, 134.8, 146.5, 159.1, 169.3, 190.8; IR (KBr): 2920, 2833, 1693, 1585, 1534, 1499, 1466, 1455, 1385, 1301, 1231, 1205, 1180, 1157, 1101, 1056, 1010, 963, 917, 851, 823 cm^{-1}. $C_{15}H_{11}NO_2S$ (269.32): Calcd. C 66.89, H 4.11, N 5.20, S 11.90; found. C 66.93, H 4.15, N 5.31, S 11.78.

6-Methyl-2-(phenylthio)benzo[*d*]thiazole (2h).



Gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.19 (d, 1H, *J* = 8.4 Hz), 7.41 – 7.47 (m, 4H), 7.70 – 7.76 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*21.7, 120.9, 121.7, 127.9, 130.1, 130.4, 130.6, 134.7, 135.4, 136.0, 152.2, 168.3.; IR (KBr): 3056, 2919, 1582, 1468, 1439, 1242, 1012, 813, 749, 689 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NS_2$ (257.38): C 65.33, H 4.31, N 5.44, S 24.92.; found C 65.25, H 4.29, N 5.38, S 24.79.

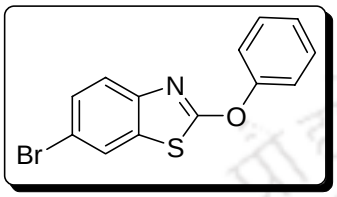
2-(*p*-Tolylthio)-6-methylbenzo[d]thiazole (2i).



White solid; M.p. 80–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 2.43 (s, 3H), 7.20 (d, 1H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.41 (s, 1H), 7.61 (d, 2H, *J* = 8.0 Hz), 7.74 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.6, 120.8, 121.5, 126.7, 127.7, 130.8, 134.5, 135.6,

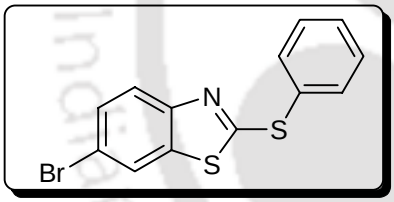
135.8, 141.1, 152.3, 169.3.; IR (KBr): 2918, 2852, 1594, 1438, 1003, 810, 504 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NS_2$ (271.41): C 66.38, H 4.83, N 5.16, S 23.63; found C 66.46, H 4.84, N 5.20, S 23.56.

6-bromo-2-phenoxybenzo[*d*]thiazole(3a):



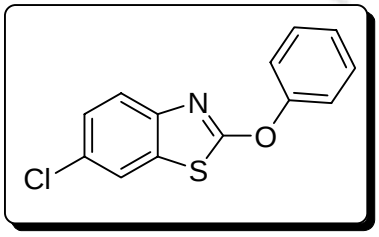
White solid; Mp. 109-111°C;^{1}H NMR (400 MHz, $CDCl_3$): 7.26 (s, 1H), 7.31-7.37 (m, 2H), 7.45-7.50 (m, 3H), 7.59 (d, 1H, J = 8.8Hz), 7.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ117.1, 120.8, 123.1, 124.0, 126.7, 129.9, 130.2, 134.0, 148.2, 154.7, 172.4; IR (KBr): 3056, 2924, 1589, 1522, 1489, 1440, 1393, 1303, 1250, 1234, 1202, 1153, 1050, 915, 807 cm^{-1}. $C_{13}H_8BrNOS$ (306.17): Calcd. C 50.99, H 2.63, N 4.57, S 10.47; found C 50.76, H 2.57, N 4.54, S 10.35.

6-bromo-2-(Phenylthio)benzo[*d*]thiazole (3h).



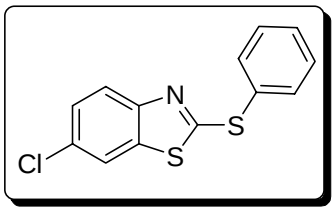
Colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49(m, 3H), 7.69 (s, 1H), 7.20 (m, 2H), 7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ118.0, 122.8, 123.1, 123.5, 129.5, 129.8, 130.3, 131.0, 135.7, 137.2, 153.0, 171.0; IR (KBr): 3059, 2924, 2851, 1581, 1528, 1494, 1456, 1429, 1390, 1093, 1013, 813, 748 cm^{-1}. $C_{13}H_8NS_2Br$ (320.93): Calcd. C 48.45, H 2.50, N 4.35, S 19.90; found C 48.51, H 4.27, N 5.45, S 24.96.

6-chloro-2-phenoxybenzo[*d*]thiazole(4a):



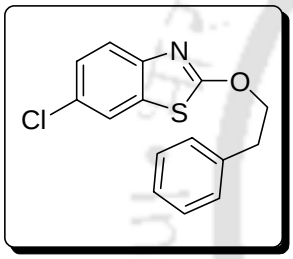
White solid; Mp. 88-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.26-7.34 (m, 4H), 7.40-7.46 (m, 2H), 7.58-7.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.7, 121.0, 122.6, 126.6, 127.0, 129.6, 130.1, 133.4, 147.7, 154.6, 172.2; IR (KBr): 3057, 2962, 1672, 1598, 1529, 1490, 1445, 1399, 1304, 1255, 1155, 1097, 915 cm^{-1}. $C_{13}H_8ClNOS$ (261.72): Calcd. C 59.66, H 3.08, N 5.35, S 12.25; found C 59.71, H 3.13, N 5.40, S 12.17.

6-chloro-2-(Phenylthio)benzo[*d*]thiazole or 6-chloro-2-Phenylsulfanyl-benzothiazole (4h).



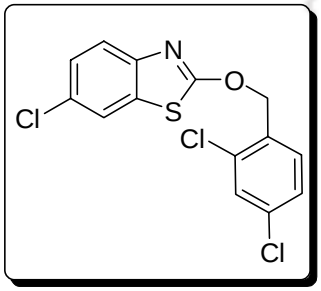
White solid; Mp. 72-74°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, 2H, *J* = 8.6 Hz), 7.40-7.52 (m, 2H), 7.56 (d, 1H, *J* = 2.0 Hz), 7.70-7.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ120.5, 122.6, 126.9, 129.5, 130.2, 130.9, 135.6, 136.6, 152.6, 170.7.; IR (KBr): 3064, 2967, 2922, 2851, 1585, 1542, 1456, 1431, 1397, 1300, 1260, 1172, 1061, 1103, 1061, 1013, 851, 829 cm^{-1}. $C_{13}H_8NS_2Cl$ (277.79): Calcd. C 56.21, H 2.90, N 5.04, S 23.08; found Calcd. C 56.27, H 2.89, N 5.11, S 22.93.

6-chloro-2-(phenethyloxy)-benzo[*d*]thiazole(4k):



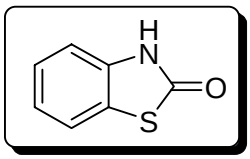
White solid; Mp. 96-98°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.16 (t, 2H, *J* = 6.8 Hz), 4.75 (t, 2H, *J* = 6.8 Hz), 7.24-7.33 (m, 5H), 7.50-7.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.3, 72.6, 121.1, 121.7 126.7, 126.9, 128.8, 129.0, 129.1, 133.2, 137.4, 148.0, 172.9; IR (KBr): 3061, 2921, 1595, 1536, 1498, 1452, 1436, 1402, 1371, 1303, 1254, 1242, 1217,1198, 1096, 1052, 977, 816cm^{-1}. $C_{15}H_{12}NOSCl$ (289.78): Calcd. C 62.17, H 4.17, N 4.83, S 11.06; found C 62.10, H 4.13, N 4.78, S 10.91.

2-(3,4-dichlorobenzyloxy)-6-chlorobenzo[*d*]thiazole(4l):



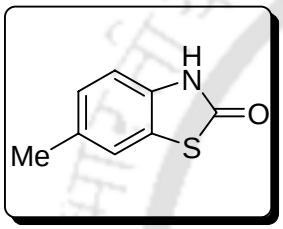
White solid; Mp. 220-222 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62(s, 2H), 7.29 (dd, 2H, *J* = 8.4 Hz), 7.42 (d, 1H, *J* = 1.6 Hz), 7.48 (d, 1H, *J* = 8.4 Hz), 7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.1, 121.2, 121.9, 126.9, 127.5, 129.3, 131.0, 131.6, 133.4, 134.6, 135.4, 147.8, 172.4; IR (KBr): 3088, 2922, 2852, 1682, 1599, 1565, 1540, 1509, 1458, 1447, 1336, 1253, 1232, 1211, 1187,1148, 1096, 1052, 1006, 812 cm^{-1}. $C_{14}H_8NOSCl_3$ (344.64): Calcd. C 48.78, H 2.34, N 4.06, S 9.30; found C 48.82, H 2.35, N 4.11, S 9.23.

3*H*-benzo[*d*]thiazol-2-one (5p).



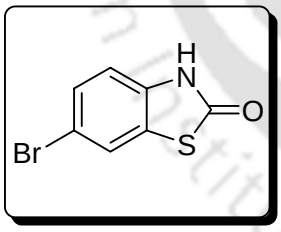
White solid; Mp. 136-137 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (m, 2H), 7.28 (t, 1H, J = 7.6 Hz), 7.40 (d, 1H, J = 7.6 Hz), 10.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ112.1, 122.7, 123.4, 124.1, 126.7, 135.7, 173.7; IR (KBr): 3154, 3110, 3054, 2922, 2853, 1666, 1591, 1463, 1214, 743, 642 cm^{-1}. C_7H_5NOS (151.01): Calcd. C 55.61, H 3.33, N 9.26, S 21.21; found C 55.53, H 3.29, N 9.21, S 21.12.

6-methyl-3*H*-benzo[*d*]thiazol-2-one (5q).



White solid; Mp. 169-170 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 6.93 (m, 2H), 7.04 (s, 1H), 10.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ20.4, 110.9, 121.7, 123.2, 126.4, 131.6, 133.4, 170.9; IR (KBr): 3148, 3070, 3017, 2915, 2850, 1660, 1485, 1229, 802, 665 cm^{-1}. C_8H_7NOS (165.02): Calcd. C 58. 16, H 4.27, N 8.48, S 19.41; found C 58.23, H 4.25, N 8.51, S 19.32.

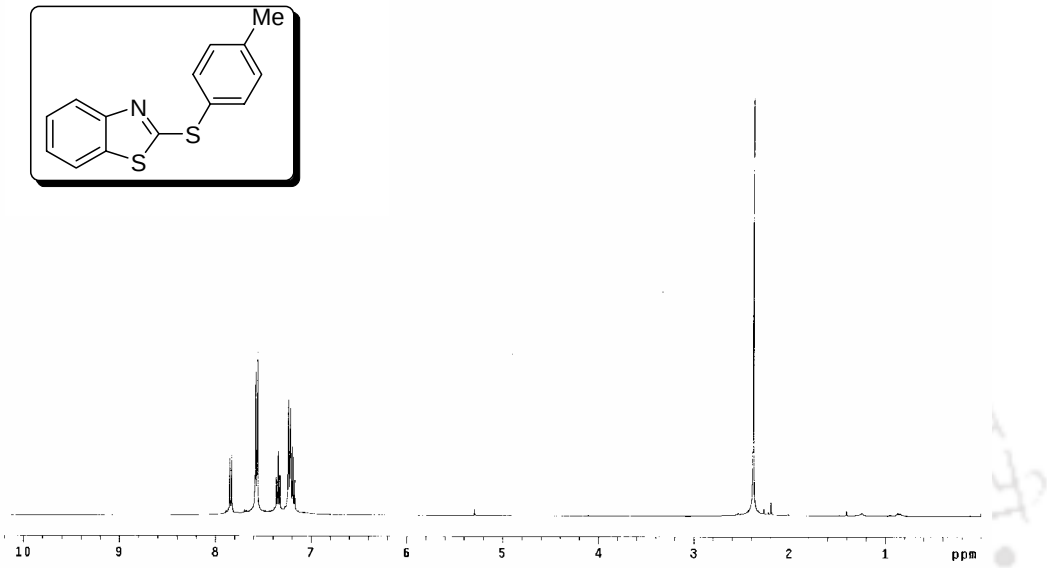
6-bromo-3*H*-benzo[*d*]thiazol-2-one (5r).



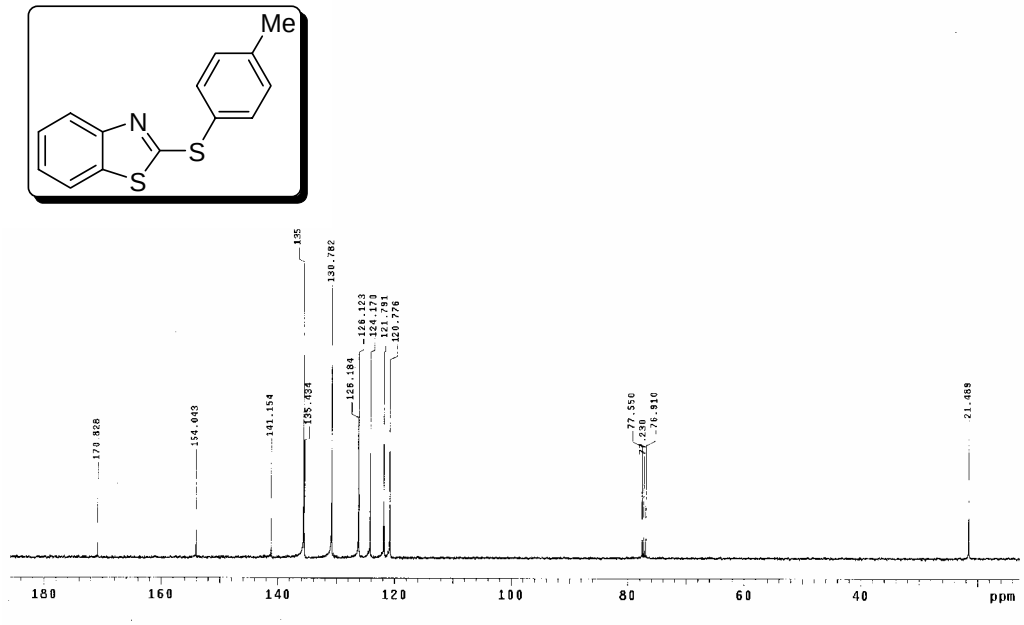
White solid; Mp. 230-231 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02(d, 1H, *J* = 8.8 Hz), 7.32(d, 1H, *J* = 8.8 Hz), 7.49 (s, 1H), 11.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ112.5, 114.0, 124.0, 125.4, 128.4, 134.9, 170.2; IR (KBr): 3139, 3074, 3013, 2890, 1673, 1597, 1463, 1210, 801, 648 cm^{-1}. C_7H_4BrNOS (228.92): Calcd. C 36.54, H 1.75, N 6.09, S 13.94; found C 36.48, H 1.73, N 5.98, S 24.98.

V.9. Selected Spectra

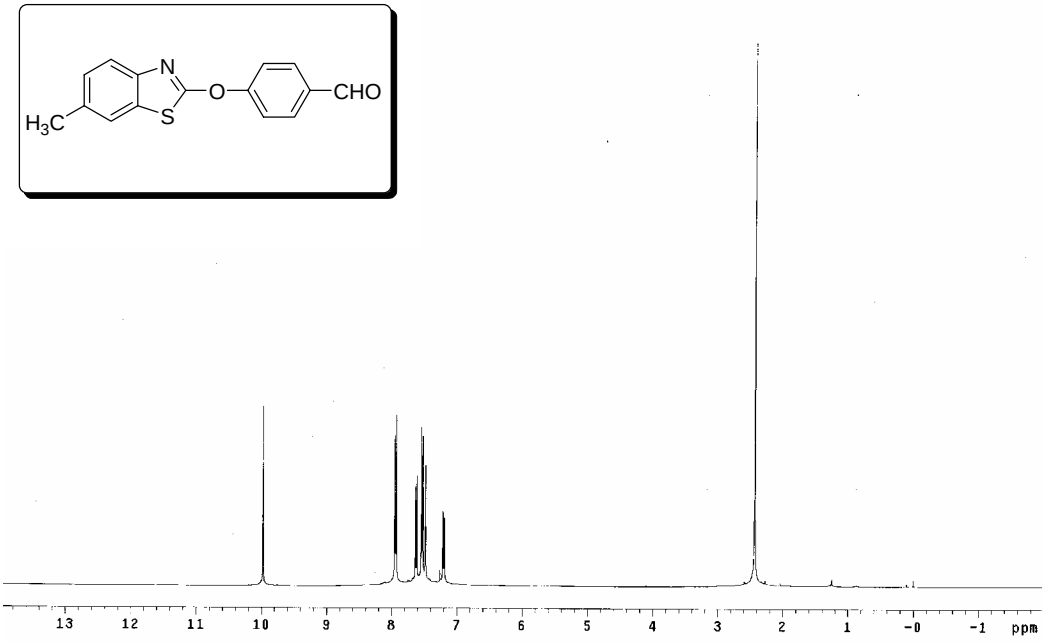
2-(*p*-Tolylthio)benzo[*d*]thiazole(2c): **^{1}H NMR (400 MHz, $CDCl_3$):**



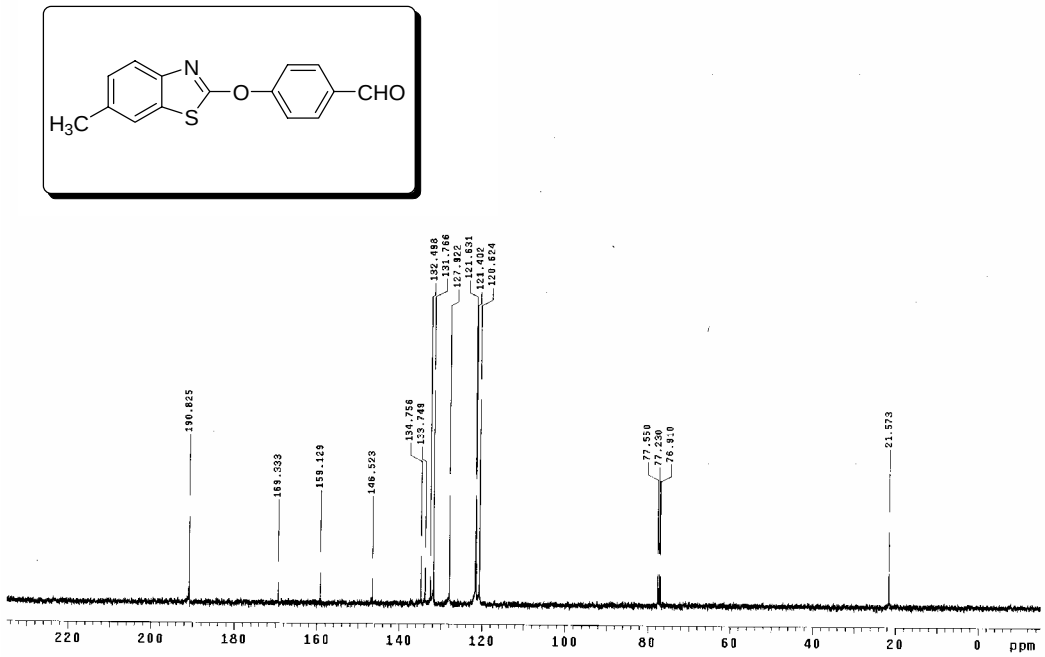
2-(*p*-tolylthio)benzo[*d*]thiazole(2c): ^{13}C NMR (100 MHz, $CDCl_3$):



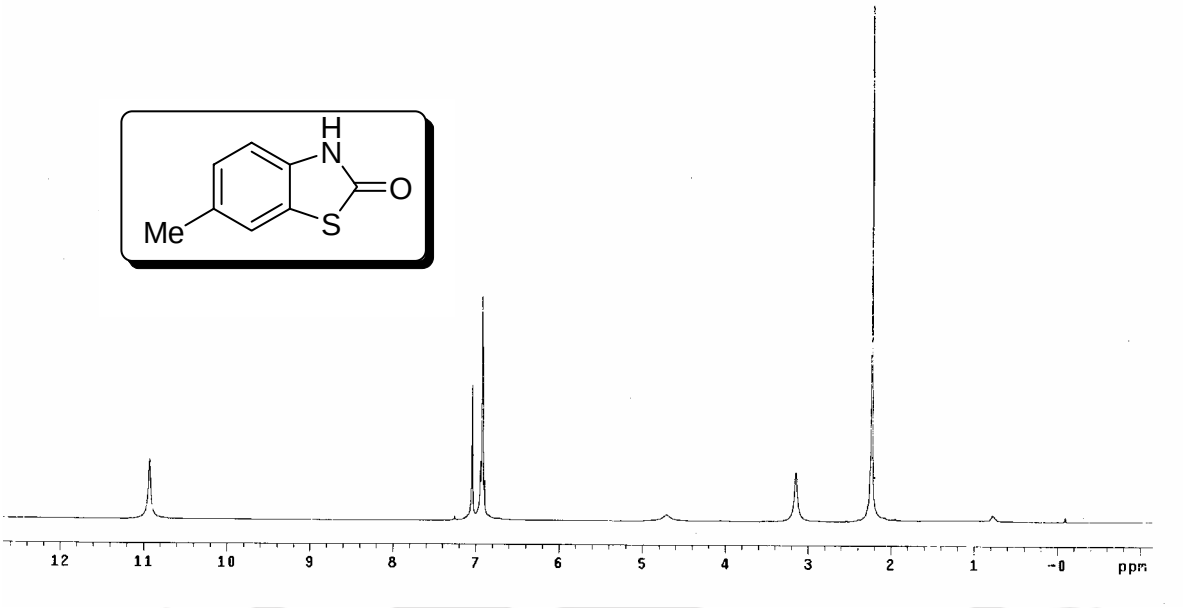
4-(6-Methylbenzo[*d*]thiazol-2-yloxy)benzaldehyde (2g): ^{1}H NMR (400 MHz, $CDCl_3$):



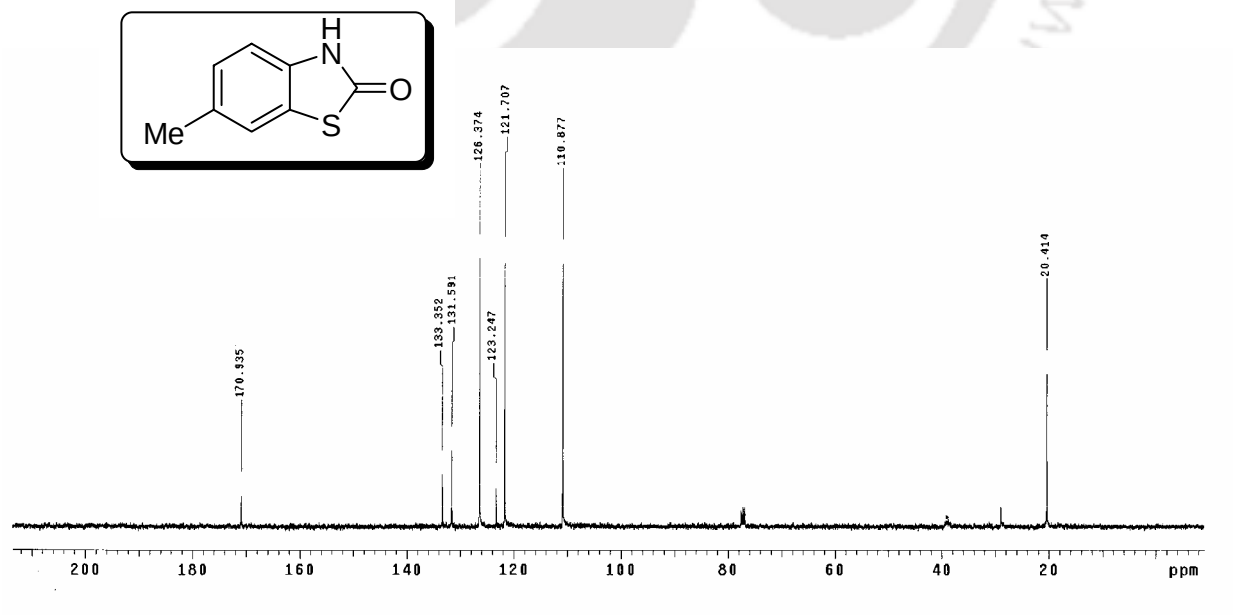
4-(6-Methylbenzo[*d*]thiazol-2-yloxy)benzaldehyde (2g): ^{13}C NMR (100 MHz, $CDCl_3$):



6-Methyl-3*H*-benzo[*d*]thiazol-2-one (5q): ^{1}H NMR (400 MHz, $CDCl_3$):



6-Methyl-3*H*-benzo[*d*]thiazol-2-one (5q): ^{13}C NMR (100 MHz, $CDCl_3$):



List of Publications

1. "It is Thiazolylidene and not Imidazole-2-thione as the Reaction Product of 1-Benzoyl-3-phenylthiourea with Br_2 / Acetone" C. B. Singh; **Siva Murru**; Veerababurao Kavala; Bhisma. K. Patel. *Org. Lett.* **2006**, *8*, 5397.
2. "A One-pot Synthesis of 1, 4-Dithiins and 1, 4-Benzodithiins from Ketones using Recyclable Reagent 1, 1'-(ethane-1, 2-diyl) dipyridinium bistribromide (EDPBT)" **Siva Murru**; Veerababurao Kavala; C. B. Singh; Bhisma K. Patel. *Tetrahedron Lett.* **2007**, *48*, 1007.
3. "3-Aryl-1-benzoylthioureas with α-Bromoketones in Water form 2-N-Benzoyl-3-arylthiazol-2(3H)-imines, not 3-Aryl-1-benzoylimidazoline-2-thiones." C. B. Singh; **Siva Murru**; Veerababurao Kavala; Bhisma K. Patel. *J. Chem. Res.* **2007**, 136.
4. "Self-Assembled Superstructure of Xanthene Derivatives" Veerababurao Kavala; **Siva Murru**; Gopal Das; Bhisma K. Patel. *J. Chem. Crystall.* **2007,** 527.
5. "Syntheses and Regiochemistry of Enolate Addition to Xanthene". Veerababurao Kavala; **Siva Murru**; Gopal Das; Bhisma K. Patel. *Tetrahedron* **2008**, *64*, 3960.
6. "Synthesis Thiazolidene-2-imine derivatives using recyclable reagent EDPBT" **Siva Murru**, C. B. Singh, Veerababurao Kavala, and Bhisma K Patel. *Tetrahedron* **2008**, 64, 1931.
7. "A New Facile synthetic Method for the Construction of 1,3-Oxathiolane-2-ylidenes" Harisadan Ghosh, **Siva Murru**; Singh, C. B.; Veerababurao Kavala; Bhisma K. Patel. *Tetrahedron Lett.* **2008**, *49*, 2601.
8. "Hypervalent Iodine (III) Mediated Regioselective N-Acylation of 1,3-Disubstituted Thioureas" Singh, C. B.; Harisadan Ghosh; **Siva Murru**; Bhisma K. Patel. *J. Org. Chem.* **2008**, *73*, 2924.
9. "Copper(I)-Catalyzed Synthesis of Substituted 2-Mercapto Benzimidazoles" **Siva Murru**; Bhisma K. Patel; Jean Le Bras; Jacques Muzart. *J. Org. Chem.* **2009**, *74*, 2217.
10. "Intra and Intermolecular C-S Bond Formation Using a Single Catalytic System: First Direct Access to Arylthiobenzothiazoles" **Siva Murru**; Harisadan Ghosh; Santosh K. Sahoo; Bhisma K. Patel. (*Under Communication*).
11. "Copper (I)-Catalyzed Cascade Synthesis of 2-Substituted Benzothiazoles: An Easy Access to Benzothiazolones" **Siva Murru;** Pravat Mondal; Ramesh Yella; Bhisma K. Patel. (*Under Communication*).
12. "Acyl isothiocyanates as efficient thiocyanate transfer agents" Charuta C. Palsuledesai; **Siva Murru;** Santosh K. Sahoo; Bhisma K. Patel. (*Under Communication*).