Newer Strategies for the Synthesis of Heterocycles Using Thiophilic Reagents

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

Submitted by

Ramesh Yella

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781 039

Jan 2011

Newer Strategies for the Synthesis of Heterocycles Using Thiophilic Reagents

Submitted by

Ramesh Yella

Roll No. 06612211

Department of Chemistry

Indian Institute of Technology Guwahati

Guwahati-781 039

Jan 2011

Dedicated to

My Parents

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 supervision of **Professor Mihir K. Chaudhuri** and **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.

Jan, 2011 Ramesh Yella
IIT Guwahati

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Ramesh Yella has been working under our supervision since July, 2006 as a regular registered Ph. D. student. We are forwarding his thesis entitled "**Newer Strategies for the Synthesis of Heterocycles Using Thiophilic Reagents**" being submitted for the Ph. D. (Science) Degree of this Institute. We 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.

Prof. Bhisma K. Patel
Supervisor
Department of Chemistry
IIT Guwahati

Prof. Mihir K. Chaudhuri
Co-Supervisor
Department of Chemistry
IIT Guwahati

ACKNOWLEDGMENT

First and foremost, with a deepest sense of gratitude, I wish to express my sincere thanks to my supervisors, Prof. Mihir K. Chaudhuri and Prof. Bhisma K. Patel whose timely help during my crucial phase of my career has made possible to achieve this target. My special thanks to my current supervisor Prof. Bhisma K. Patel for his valuable guidance, encouragement, inspiration, creative and scientific ideas which helped me to enhance my knowledge. I am fortunate enough to have his guidelines to cultivate scientific thought. My everlasting gratitude goes towards him.

I would like to acknowledge my sincere gratude to all my doctoral committee members Prof. Abu T. Khan, Dr. Manabendra Ray and Dr. Gopal das for their intuitive reviewing of my work, advices and suggestions. I would like to thank all faculty members of Department of Chemistry of IIT Guwahati for their invaluable suggestions.

I express my sincere gratitude and acknowledgement 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.

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 lab seniors Dr. Veerababurao Kavala, Dr. C. B. Singh, Dr. Siva Murru and Dr. Jayashreeba for their invaluable cooperation and suggestions. I would like to thank all my present and past group members Dr. Harisadhan Ghosh, Ali, Santosh, Razzak, Srimanta, Saroj, Ashok, Nipa, Charuta, Pravat, Arghya, Nilufa, Anupal, Raman for their timely help, support and for creating a pleasant atmosphere in the lab.

I wish to thank department seniors Saitanya bayya, Subash bhai, Suri, Ballav Da, Avijith Da, Amardeep bayya, Jashmini and Sonit da for lending their hands of support whenever needed. I also take this opportunity to thank all of my Ph.D. batchmates (July, 06) specially Chandramouli Reddy, Nihar, Marjit and the other research scholars@chem and all my IITG friends, who have shared their thoughts and views with me.

I extend my sincere thanks to my best friends Naresh Kasoju, Prasenjit, Gunin, Prasanta, Bimlesh, Musawwer, Badrinath, Purna, Ramu, Devender Rao, Venu, Praveen, Prashanth, Venkatswamy, Nagender, Prasad and all other close friends for their constant unfailing support, their encouragement and all the help they extended whenever required. I also wish to thank other friends@IITG Sandeep, Bedabrata, Chaitnaya, Nani, Ramana, Laxman, Nasimha for their joyful moments shared with me at IIT 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 (Padma), brother in law (Ganesh), nephew (Vijay) and niece (Chitti). I am also grateful to my cousin brother(s) (Satyanarayana and Subash), and their family members for their affection and deep concern for career. They are the main soul and inspiration for each and every step that I achieve in my life.

Ramesh Yella

Abstract

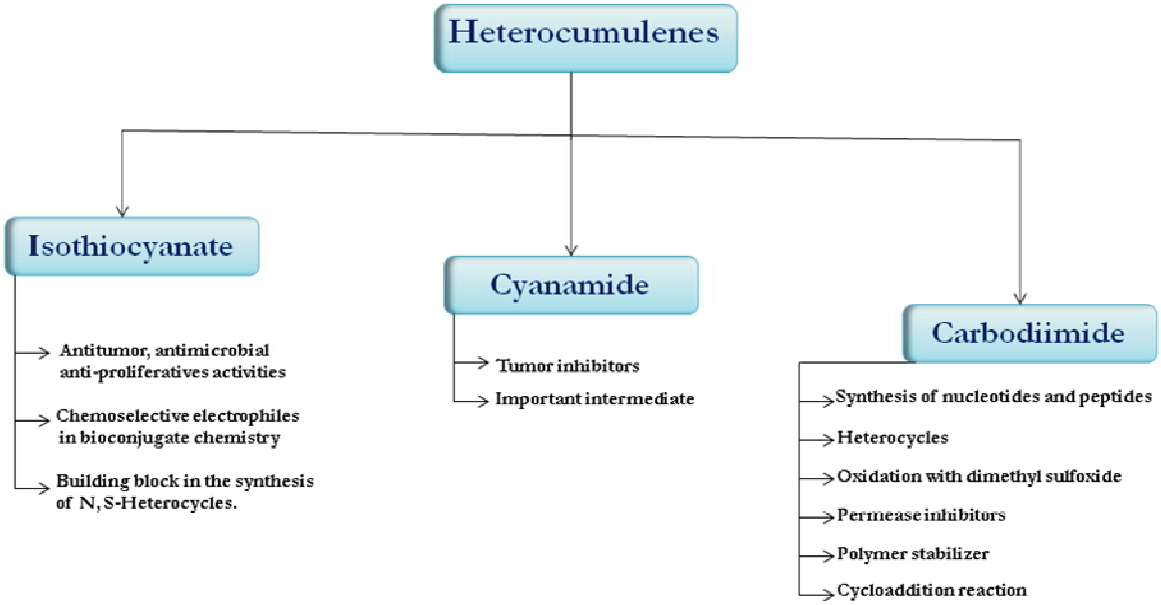
The contents of this thesis have been divided into six chapters based on the results of experimental works performed during the complete course of the research period. The introductory chapter of the thesis presents an overview of various thiophilic reagents, heterocumulenes and their importance in the synthesis of heterocycles. Chapter-II describes the preparation of isothiocyanate, cyanamide and thiazole through desulfurization of dithiocarbamic acid salt with ditribromide reagent 1,1'-(ethane-1, 2-diyl) dipyridinium bistribromide (EDPBT). Chapter-III demonstrates the syntheses of five and six membered *N*, *O*, *S* heterocycles again using EDPBT. Chapter-IV illustrates the detailed mechanistic investigation of *anti*-Hugerschoff reaction. Chapter-V and VI mainly focus on the synthesis of tetrazoles, thiadiazoles and 2-imino-4-thiazolidinones using molecular iodine and chloroacetylchloride. Each chapter consists of four sub sections, describing introduction, present work, experimental work and spectral data respectively.

CHAPTER I. Introduction to Heterocumulenes and their Applications in the Synthesis of Heterocycles

This chapter highlights the definition of thiophilic reagents, heterocumulenes and their applications. It also includes nomenclature, definition and importance of heterocycles and literature background for the synthesis of heterocycles using organic ammonium tribromides.

Thiophilic reagents such as halogens (bromine or its equivalent and iodine), hypervalent iodine are electrophilic in nature and reacts with the sulphur nucleophiles of a molecule. The sulphur nucleophiles can be part of dithiocarbamates, thioamides, mono thioureass, and 1,3-disubstituted thioureas (symmetrical and unsymmetrical).

Heterocumulenes such as isocyanate, isothiocyanate, cyanamide and carbodiimides are an important class of organic intermediates. Various compounds of biological and pharmaceutical interest have been prepared taking advantage of their electrophilicity. The uses of some of the heterocumulenes are shown below.



Heterocycles constitute the largest group of organic compounds and are becoming ever more important in all aspects of pure and applied chemistry. They are having wide range of applications such as pharmaceuticals, agrochemicals, antioxidants *etc*. The class also includes many compounds of biological importance, such as nucleic acids and certain vitamins, hormones, and pigments. One of the reasons for the wide spread use of heterocyclic compounds is their structures can be ingeniously manipulated to achieve a required modification in function. Heterocyclic compounds are key components of pharmaceutical chemistry and therefore, they have been a source of inspiration for the design of structural analogues to be used as pharmacological tools as well as in the design of new drugs.

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 which in turn, can be utilized for various acid catalyzed organic transformations.

CHAPTER II. One-Pot Synthesis of Isothiocyanates, Cyanamides and Thiazoles from Dithiocarbamic Acid Salts Using EDPBT

This chapter mainly focuses on the synthesis of isothiocyanates, cyanamides and thiazoles starting from dithiocarbates using ditribromide 1,1'-(ethane-1, 2-diyl) dipyridinium bistribromide (EDPBT) as desulfurizing agent *Figure II.1.*

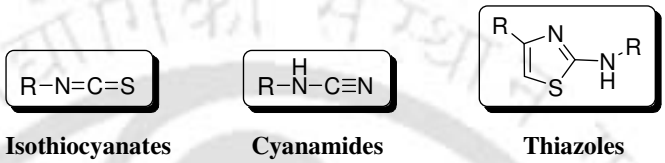


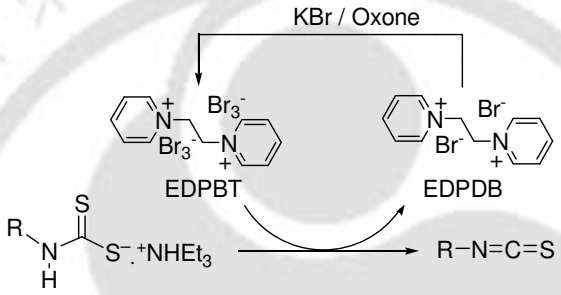
Figure II.1. *Isothiocyante, cyanamide and thiazole*

Isothiocyanates are important precursors for the construction of pharmaceutically important heterocycles and are frequently encountered in many natural products. Due to their unique reactivity towards –OH and $–NH_2$ nucleophiles present in nucleic acids and proteins, they serve as chemoselective electrophiles in bioconjugate chemistry, particularly for biological assays. Conventional method for the preparation of isothiocyanate involves the reaction of deadly toxic thiophosgene or thiocarbonyl transfer reagents with amines. In addition, they are also prepared by the decomposition of dithiocarbamates with diverse reagents such as uranium and phosphonium based coupling agents, tosylchloride, di-*tert*-butyl dicarbonate, hydrogen peroxide and ethylchlorocarbonate. The drawbacks of this reported process mainly result from the use of environmentally unsafe halogenated solvents, longer reaction times, and hazardous and toxic reagents.

Another class of heterocumulene is cyanamides which are useful precursors in the synthesis of pharmaceutically important heterocycles and *N*-alkyl or *N*-aryl imides. They also serve as a protecting group during the synthesis of secondary and tertiary amine containing heterocycles. Synthesis of biologically active compounds, such as minoxidil and some herbicides goes via cyanamide intermediates. Conventional methods of synthesis of cyanamides are by the cyanation of amine using cyanogen halides, or its synthon (CN^+). The reagents that are capable of delivering electrophilic cyanogens (CN^+) are chlorobenzyl

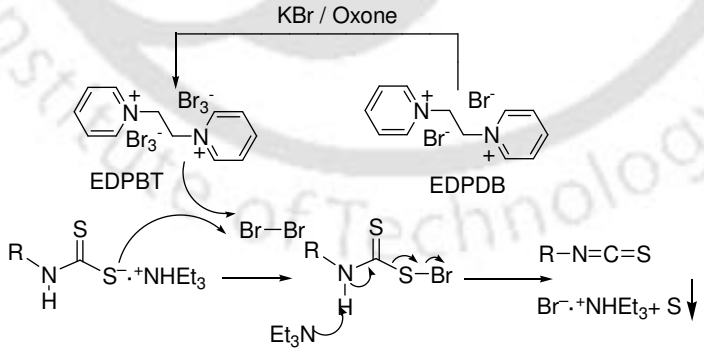
thiocyanate, 1-cyanoimidazole, 2-cyanopyridazin-3-(2*H*)-ones, 1-cyanobenzotriazole and metal cyanides, tosylcyanide, thiocyanogen and cyanogen azide. Most of the reported methods use cyano cation (CN^+) directly from highly toxic cyanogen bromide or indirectly using (CN^+) synthons which in turn are obtained using cyanogen halides.

In continuation to our interest in the chemistry of heterocyclic synthesis using tribromides, we have first time explored the thiophilic / desulfurizing ability of tribromide reagent, EDPBT in the preparation of heterocumulenes *viz.* isothiocyanates and cyanamides.



Scheme II.1. *Preparation of isothiocyanate from the dithiocarbamic acid salt.*

When dithiocarbamate (1 mmol.) was treated with EDPBT (0.5 mmol.) in the presence of triethylamine (2 mmol.) in acetonitrile, isothiocyanate was obtained in nearly quantitative yields (96% after purification) (*Scheme II.1*).



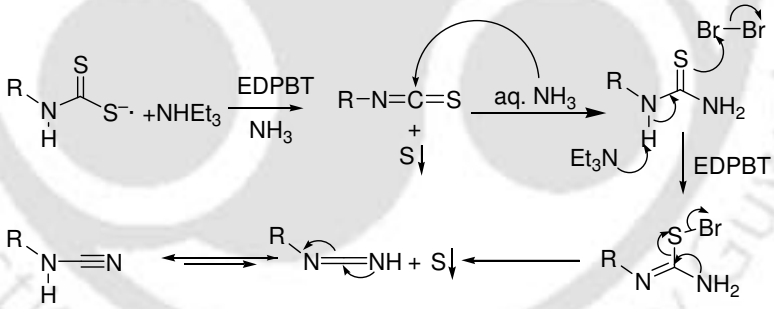
Scheme II.2. *Mechanism of formation of isothiocyanate from dithiocarbamate.*

The proposed reaction mechanism for the formation of isothiocyanate is shown in *Scheme II.2*. The formation of elemental sulfur supports the proposed mechanism. The base triethylamine is sufficiently basic (p*Ka* 10.78) to abstract the –NH proton from

dithiocarbmic acid salts derived from aromatic amines (p*Ka* range 2.46–5.63), and aliphatic amines (p*Ka* range 9.33–10.77).

The scope of this interesting transformation was evaluated with different aryl dithiocarbamates containing electron donating and withdrawing groups at *ortho*, *meta,* and *para* positions. In general, all the reactions were very clean and corresponding isothiocyanates were obtained in high yields under the optimized reaction conditions. Dithiocarbamate salts derived from chiral amines resulted in their corresponding isothiocyanates in excellent yields with retention of optical activity.

After successfully synthesizing various isothiocyanates, we focused our attention on the synthesis of cyanamides in one-pot. Taking cues from the above work, we have reasoned that isothiocyanates can be synthesized from dithiocarbamic acid salts and EDPBT. In this strategy the *in situ* generated isothiocyanates reacts with aqueous ammonia to form corresponding mono thioureas (*Scheme II.3.*). The use of aqueous ammonia serves the dual purpose, as a base in the first step to generate isothiocyanate from dithiocarbamate salt, and as a nucleophile to form alkyl / aryl thioureas thereafter.

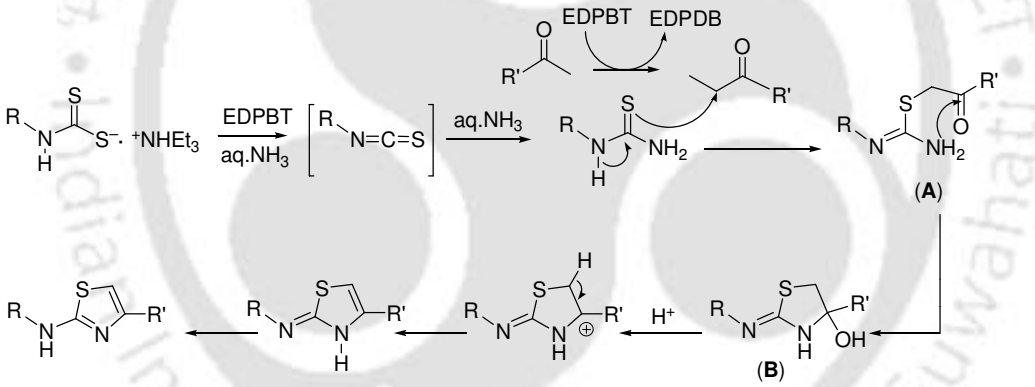


Scheme II.3. *One-pot preparation of cyanamide from dithiocarbamate.*

However, in the second step ammonia was not that effective as a base to convert the *in situ* generated mono thiourea to cyanamide and had to be replaced with a relatively stronger base triethylamine. This may be, in part, due to the relatively lesser acidity of NH proton of an alkyl/aryl thiourea, compared to the NH proton of a dithiocarbamate salt and hence, a stronger base is required for the later.

Employing this one pot strategy several aromatic cyanamides could be successfully prepared from their dithiocarbamate salts. This strategy was successful for aryl amines having electron donating and withdrawing substituents giving corresponding cyanamides in good to excellent yields. Substrates amenable to ring bromination and α-bromination gave their corresponding cyanamides without undergoing bromination. Cyanamides of aliphatic amines and benzylic amines were also successfully obtained from their dithiocarbamate salts in one pot. Dithiocarbamate salts derived form chiral amines yielded their chiral cyanamides, in excellent yields with complete retention of optical activity.

We then extended the *in situ* generated mono thiourea for the construction of substituted thiazoles, an important class of heterocycles by treating it with the *in situ* generated α-bromoketones. In this strategy, both these precursors *viz.* 1-arylthioureas and α-bromoketones can be easily synthesized using single recyclable reagent EDPBT as shown in *Scheme II.4*.



Scheme II.4*. Proposed mechanism for the formation of thiazole.*

The thiourea being an *S*-based nucleophile particularly towards softer electrophiles attacks on the bromomethyl carbon forming *S*-alkylated product (**A**). Intramolecular attack of the NH_2 group of the intermediate on the carbonyl group would give the intermediate tertiary alcohols (**B**) which undergo an acid catalyzed E1-elimination. Thus the removal of the excess ammonia is essential in the previous step to facilitate an acid mediated E1 process. Several thiazoles were successfully prepared utilizing this protocol.

In summary, EDPBT has been used as an efficient thiophilic reagent for the preparation of alkyl, aryl isothiocyanates and cyanamides from their dithiocarbamates in one pot. Subsequently, 2-amino thiazoles were synthesized by the condensation of the *in situ* generated α-bromoketones and thioureas.

CHAPTER III. Synthesis of Five and Six Membered *N*, *O*, *S*-Heterocycles Using a Ditribromide Reagent

This chapter deals with the synthesis of five types of heterocycles *viz.* 2-aminobenzimidazole, aminobenzoxazole, aminobenzothiazole, benzoxazine and 1-imidazolidinecarbothioamide (*Figure III.1*) using a desulfurization strategy mediated again by the ditribromide reagent (EDPBT).

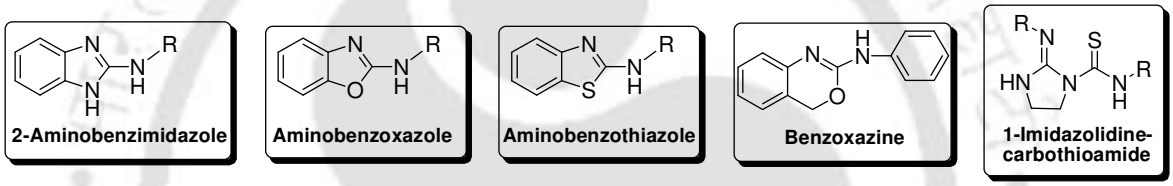
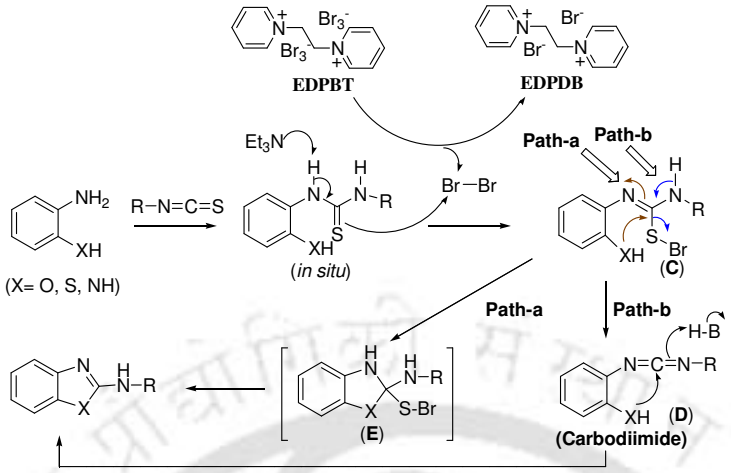


Figure III.1. *Various N, O and S heterocycles.*

After successfully synthesizing various isothiocyanates in the previous section (*Chapter II*) we have utilized them for the synthesis of various heterocycles in this section. Benzimidazoles are widely used structural motifs in drug discovery and can be found in a number of biologically active molecules. The most commonly adopted method for the synthesis involves the cyclodesulfurization of preformed mono thioureas. The reported desulfurization agents include carbodiimides, tosyl chloride, methyl iodide, mercury(II) oxide, mercury(II) chloride, and copper(I) salts.

The *in situ* generated thiourea which in turn obtained from phenyl isothiocyanate and *o*-phenylenediamine on treatment with EDPBT produced the desired aminobenzimidazole. The formation of benzimidazole can be explained through the intramolecular attack of the amino nucleophile (where X = NH) on S-Br type species **C** (path a) or through the intermediacy of carbodiimide **D** followed by intramolecular nucleophilic attack (path-b) as shown in *Scheme III.1*.

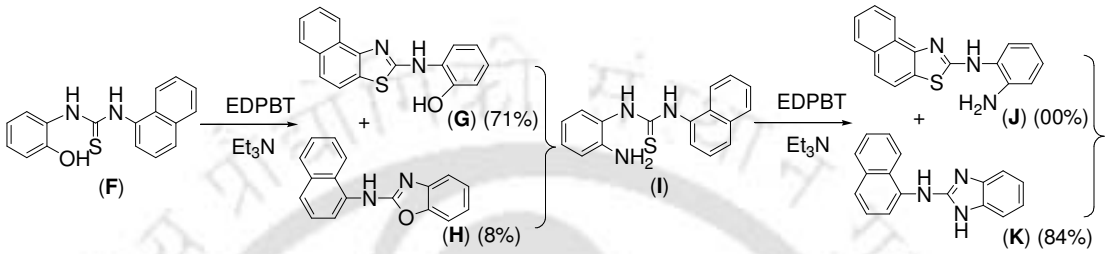


Scheme III.1. *Mechanism for the formation of benzimidazole/benzoxazole and benzothiazole.*

The successful synthesis of benzimidazole prompted us to apply this strategy to the synthesis of aminobenzoxazoles. This class of compounds has great potential as drug candidates, and its use is currently under investigation in the treatment of a wide variety of disorders, such as HIV, neurogeneration, and inflammatory diseases. The general method used for the synthesis of aminobenzoxazoles is the cyclodesulfurization of *N*-substituted 2-hydroxyphenylthioureas. The cyclodesulfurization reagents include NiO, HgO, $AgNO_3$, KO_2, salts of transition metals, dicyclohexylcarbodiimide (DCC) and DIB. The strategy applied for the synthesis of 2-aminobenzimidazole was applied for the synthesis of aminobenzoxazoles. The *in situ* generated mono thioureas obtained from phenyl isothiocyanate (*Scheme III.1*) on treatment with EDPBT produced the desired aminobenzoxazole by a similar mechanism as proposed in *Scheme III.1.* Further, several aminobenzothiazoles and aminobenzoxazines have also been prepared using similar strategy.

A noteworthy aspect is that the unsymmetrical thiourea (**F**) generated from the 1-napthyl isothiocyanate and 2-aminophenol, when treated with EDPBT gave benzothiazole (**G**) as the major product rather than the expected benzoxazole (**H**) as shown in *Scheme III.2.* The predominant formation of benzothiazole (**G**) can be in part due to the intramolecular electrophilic substitution of the activated naphthyl ring, and poor

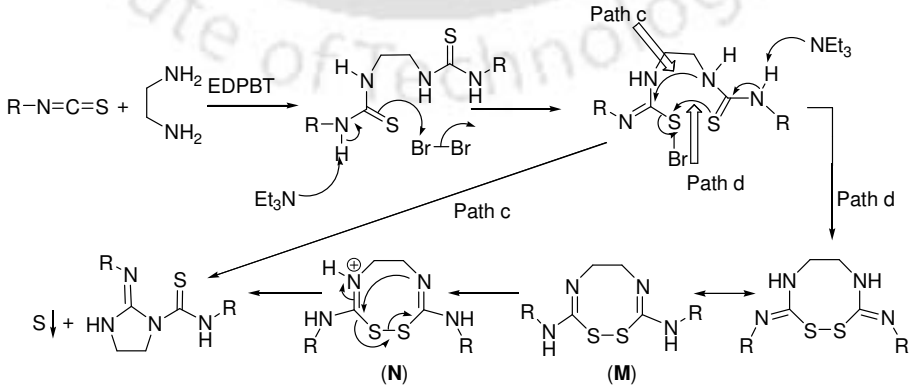
nucleophilicity of the −OH group. To ascertain the later effect, i.e nucleophilicity plays the role in the product formation; the −OH nucleophile was replaced with a $-NH_2$ nucleophile by designing corresponding substrate (**I**). Interestingly, the substrate having an amino group under an identical condition gave exclusively benzimidazole (**K**) without giving any traces of benzothiazole (**J**) thus supporting our assumption.



Scheme III.2. *Differential reactivity of naphthyl-phenyl thiourea (**F**) and (**I**).*

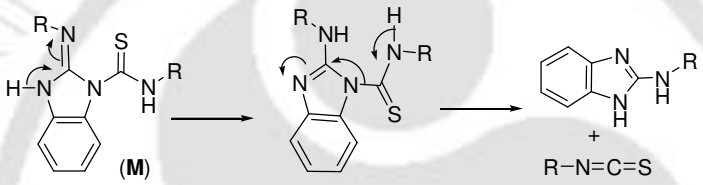
There exist several possibilities for *bis*-thiourea derived from arylisothiocyanate and 1,2-diamine when separated by two carbon spacer. As shown in *Scheme III.3*, the S−Br type species could be attacked by any one of the two nitrogen nucleophiles from the adjacent thiourea either giving a five or a seven membered ring. Alternatively, sulfur atom from the adjacent thiourea can attack to give a six membered ring or form an eight membered disulfide ring (**L**).

To scrutinize this, we treated the *bis*-thiourea resulted from phenyl isothiocyanate and ethylenediamine with EDPBT gave excellent yield of imidazolidinecarbothioamide (*Scheme III.3.*). These class of compounds are useful as insecticides, particularly for the control of *Epilachna varivestis*.



Scheme III.3. *Mechanism for the formation of 1-imidazolidinecarbothioamide.*

A plausible mechanism for the formation of imidazolidinecarbothioamide as shown in *Scheme III.3.* The bromine from EDPBT reacts with one side of the thiourea to give S-Br intermediate. The soft nuclephile from the other side of the thiourea would attack on the S-Br species to give the unstable eight memebered disulfide ring which inturn undergo an acid mediated rearrangement to give imidazolidinecarbothioamide. Interestingly, the *bis*-thiourea obtained by the treatment of *o*-phenylenediamine (*o*-PD) and aryl isothiocyanate gave benzimidazole and aryl isothiocyanate instead of the expected imidazolidinecarbothioamide. In this case the intermediate imidazolidinecarbothioamide (**M**) which is non-aromatic in character rapidly loses a molecule of isothiocyanate giving benzimidazole (*Scheme III.4.*).



Scheme III.4. *Reactivity of aromatic 1,2-bis-thiourea with EDPBT.*

In summary, EDPBT has been employed as a thiophilic / desulfurizing reagent for the efficient construction of five and six membered *N*, -*O*, -*S* heterocycles in one-pot. Regioselective products formation was observed for unsymmetrical thiourea having a napthyl moiety in one side and an *o*-amino or an *o*-hydroxyphenyl on the other side which is dependent on the nature of the nucleophiles (−OH or $-NH_2$). Another interesting aspect is the differential reactivity of *bis*-thioureas of aliphatic and aromatic 1,2-diamines, the former giving 1-imidazolidinecarbothioamide and the later benzimidazole and isothiocyanate.

Chapter IV. Arylthioureas with Bromine or its Equivalents Gives No 'Hugerschoff' Reaction Product

This chapter deals with the mechanistic investigation of *anti*-Hugerschoff reaction i.e. thioamidoguanidino moiety and competitive formation of benzothiazoles (Hugerschoff product) from aryl-*sec.*alkylthiourea using EDPBT (*Figure IV.1.*).

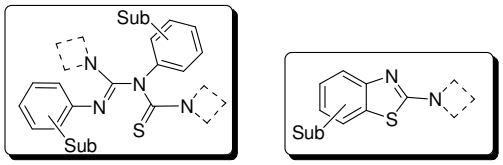
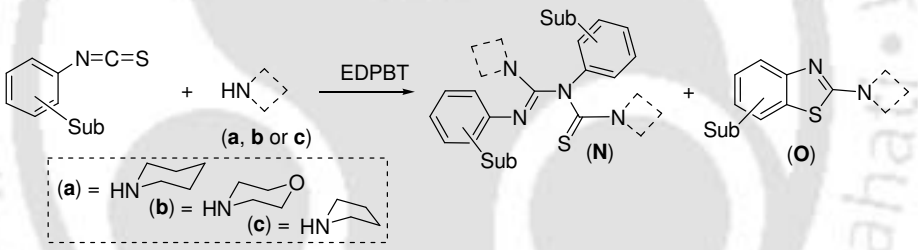


Figure IV.1. *Thioamidoguanidino moiety and benzothiazole.*

The reagent EDPBT is an excellent source of bromine capable of brominating varieties of organic substrates. Being a source of bromine we thought of utilize this for the synthesis of benzothiazole from aryl-*sec*.alkylthiourea following the reported procedure of Jordan (*J. Org. Chem.* **2003**, *68*, 8693) and Le *et. al* (*J. Heterocycl. Chem.* **2006**, *43*, 1123). When we treated phenyl isothiocyanate, (1 equiv.) and piperidine (1 equiv.) in CH_2Cl_2 to this was added bromine equivalent EDPBT and stirred for 1 h. The major product isolated (77%) was found to have a thioamido guanidino moiety (**N**) and the minor product (**O**) (~12%) was the expected 2-aminobenzothiazole as shown in *Scheme IV.1*.

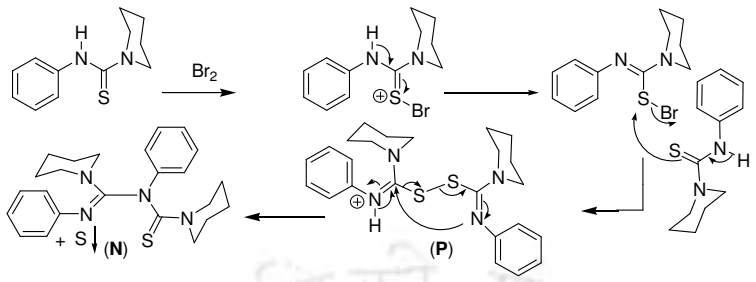


Scheme IV.1. *Reaction products of the in situ generated thiourea with EDPBT.*

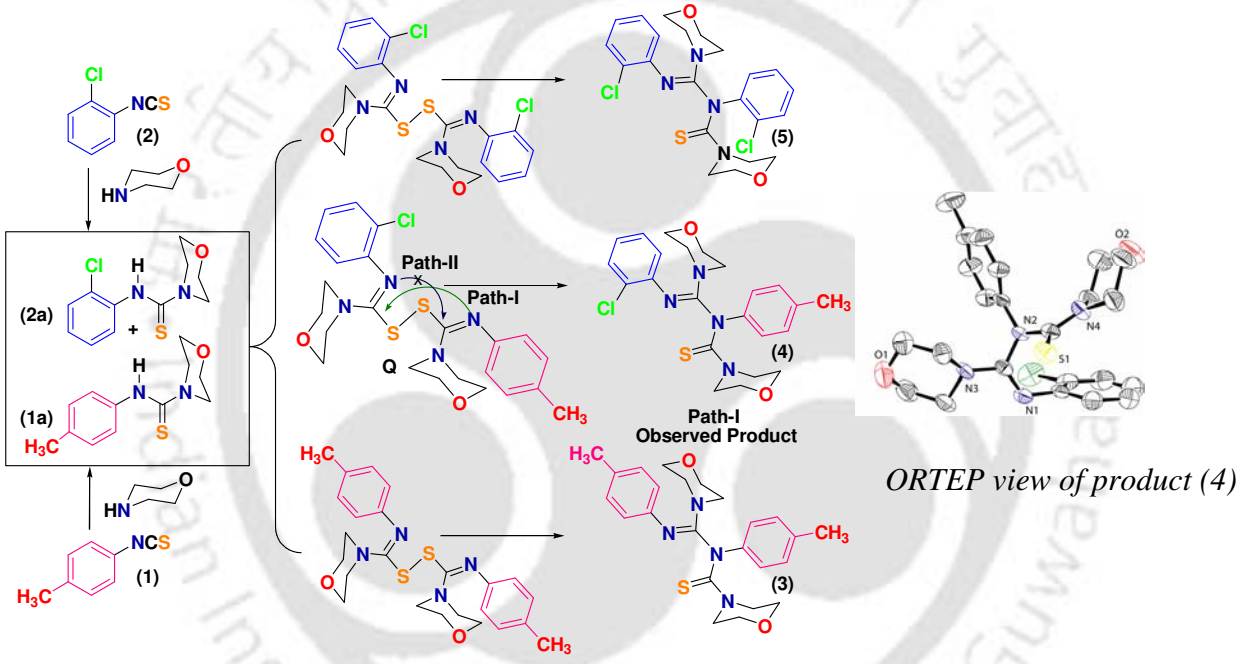
It may be mentioned here that in a classical Hugerschoff reaction the substrates employed are 1,3-diarylthioureas, where the arylamines are primary and not secondary in nature. These kinds of substrates invariably give Hugerschoff product, 2-aminobenzothiazoles irrespective of the nature of brominating reagents used. However the difference is noticed only when one side of the thiourea is having a primary aryl amine and the other side a secondary aliphatic amine.

A mechanism as shown in *Scheme IV.2* can be proposed to account for the formation of the product (**N**). This mechanism essentially involves the formation of a disulfide intermediate (**P**) followed by the attack of one of the iminium nitrogen on to the

adjacent iminium carbon with the concurrent expulsion of elemental sulfur to give the desired product (**N**) as shown in *Scheme IV.2*.



Scheme IV.2. *Proposed mechanism for the formation of (**N**).*



ORTEP view of product (4)

Scheme IV.3. *Crossover experiment and product distribution.*

In order to ascertain this mechanism, a crossover experiment as shown in *Scheme IV.3* was performed. The *in situ* generated thioureas from their corresponding isothiocyanates (**1** and **2**) and morpholine on treatment with EDPBT gave three products (**3**), (**4**) and (**5**) isolated in 8%, 78% and 11% yields respectively. The products (**3**) and (**5**) obtained from their thioureas (**1a**) and (**2a**). However, formation of the major product (**4**) can be explained if there is formation of a mixed disulfide (**Q**) as shown in *Scheme IV.3*. In principle, the intramolecular attack of the two different imino nitrogens on to the adjacent imino carbons of the mixed disulfide (**Q**) is expected to result in two isomeric products.

Interestingly, the formation of only one of the isomeric products was clearly observed. The structure of the product (**4**) has been unequivocally confirmed by X-ray crystallographic analysis.

The scope of this reaction has been demonstrated with various aliphatic secondary amines such as piperidine (**a**), morpholine (**b**), pyrrolidine (**c**) and di-*n*-butylamine to give major products thioamido guanidino moiety respectively. In all these cases, the Hugerschoff product 2-aminobenzothiazole was obtained as a minor products or not observed at all.

Aryl isothiocyanates substituted with moderately deactivated or strongly deactivated substituents are expected to be less susceptible towards intramolecular electrophilic substitution to give Hugerschoff product 2-aminobenzothiazole and are more likely to yield the intermolecular nucleophilic substitution product *i.e.* anti-Hugerschoff product and this is indeed the case.

In conclusion, we have demonstrated that some of the activated and all the deactivated aryl thioureas under the Hugerschoff reaction condition (bromine or its equivalents) gave a product having a thioamido guanidino moiety (*anti*-Hugerschoff product) as the major product. The formation of *anti*-Hugerschoff reaction goes via a disulfide intermediate which has been supported by a cross-over experiment. Further, we have observed that the generally expected Hugerschoff product is the major product only when the aryl ring is sufficiently activated.

CHAPTER V. Tandem Regioselective Synthesis of Tetrazoles and Related Heterocycles Using Iodine

In this chapter, tandem process for the synthesis of tetrazoles, thiamidoguanidino moiety and thiadiazole from the *in situ* generated thiourea have been discussed (*Figure V.1*).

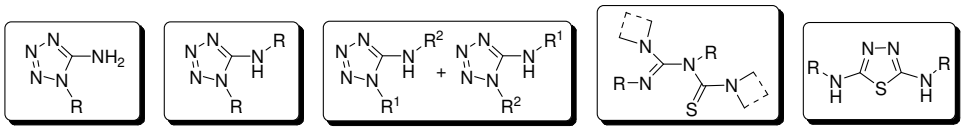


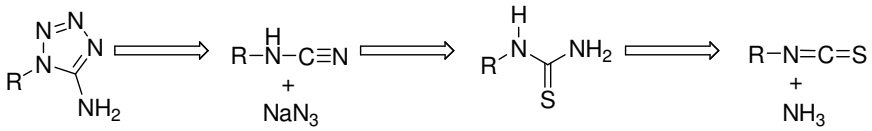
Figure V.1. *Various tetrazoles and the related heterocycles.*

Aminotetrazoles are an interesting class of heterocyclic compounds that have not been found in the nature so far. They are resistant to metabolic degradation as well as towards chemical oxidants, and have found application in propellants, explosives and as structural components of many biologically important molecules. For a drug to be effective, it should be sufficiently lipophilic in nature so as to pass through the cell membrane effectively. Hansch has shown that anionic tetrazoles are at least ten times more lipophilic than the corresponding carboxylates. Due to the tunable lipophilicity of various tetrazole derivatives; it is possible to use them as "isosteric substituents" of various functional groups. In particular, 5-substituted (alkyl/aryl) tetrazoles (RCN_4H) may serve as "non-classical isosteres" for the carboxylic acid moiety (RCO_2H) in biologically active molecules. Additionally, aminotetrazoles are found in compounds having antiallergic/antiasthmatic, antiviral, anti-inflammatory, antineoplastic, and cognition disorder activities.

A variety of methods are available in the literature for the synthesis amino tetrazoles such as (i) nucleophilic substitution by azide in α–chloroformamidines, and amino iminomethane sulfonic acids; (ii) desulfurization of thiourea in the presence of toxic mercury(Hg) or lead(Pb) salts followed by the treatment with NaN_3; (iii) diazotiazation of aminoguanidine with $NaNO_2$ followed by an electrocyclization; (iv) Reaction of cyanamides with NaN_3 or hydrazoic acid and the reaction of carbodiimide with sodium azide or hydrazoic acid and with trimethyl silyl azide; (v) reaction of cyanogen azide with primary amines followed by an intramolecular cyclization; (vi) nucleophilic substitution by amines in 5-chloro tetrazole.

Our interest in the thiophilic properties of hypervalent iodine and tribromide reagents led us to imagine the development of an efficient three step tandem process to construct the aminotetrazoles from isothiocyanates. The synthetic sequence for the proposed one-pot tandem process can be envisaged by treating the organic isothiocyanates with amines (ammonia, aryl or alkyl amine) to form thioureas. The *in situ* generated thioureas can give rise to cyanamides/carbodiimides in the medium which when reacted with molecular iodine in the presence of a base. Subsequent treatment of the

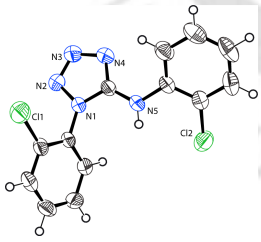
cyanamides/carbodiimides with sodium azide would generate tetrazoles. The retrosynthetic strategy for the proposed one-pot tandem process is shown in *Scheme V.I.*



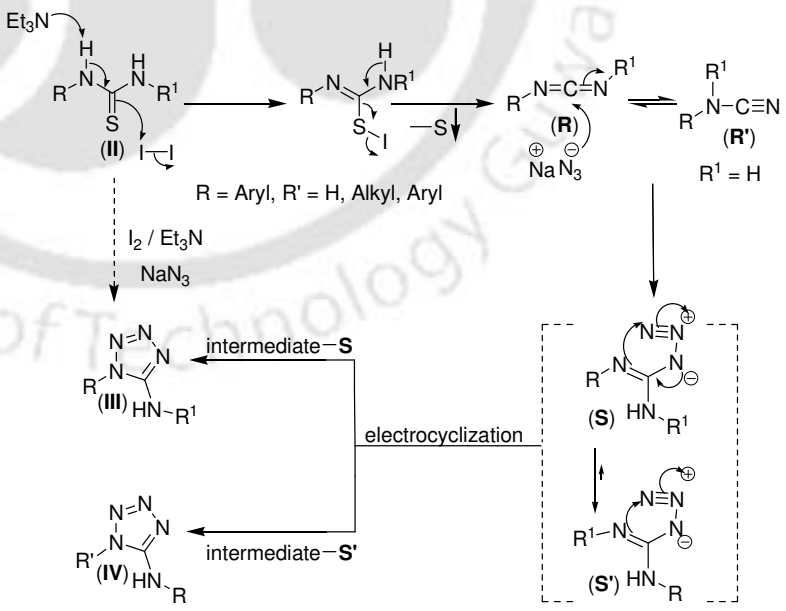
Scheme V.I. *Retrosynthetic strategy for the synthesis of aminotetrazoles.*

The use of molecular iodine in the present method overcomes the many of the drawbacks associated with reported methods. The *in situ* generated monosubstituted thiourea (**II**) (where R' = H) was admixed with DMF followed by the treatment of NaN_3 (3 equiv), I_2 (1.1 equiv) and triethylamine (3 equiv) at room temperature afforded 1-aryl-1*H*-tetrazole-5-amine (**III**) in good yield.

A plausible reaction mechanism for this transformation has been proposed as shown in *Scheme V.1.* The intermediate cyanamide (**R**), obtained from thiourea (where R' = H) (**II**) has been confirmed by its isolation and characterization. The intermediate cyanamide (**R'**) is attacked by the azide ion giving the intermediate guanyl azide **S** which then undergoes electrocyclization giving 1-phenyl-1*H*-tetrazole-5-amine.



ORTEP of 1,5-disubstituted tetrazole



Scheme V.1. *A plausible mechanism for formation of tetrazole.*

Employing this one-pot strategy, we have successfully prepared a series of 1-aryl-1*H*-tetrazole-5-amines from their corresponding isothiocyanates possessing electron withdrawing and electron donating substituents at *o*, *m* and *p*-positions. 1,5-Disubstituted tetrazoles were also obtained similarly starting from aryl isothiocyanates and aryl amines in which case the intermediate is a carbodiimide (where R = aryl, R' = aryl, alkyl) instead of a cyanamide. Regioselective tetrazole formation was observed for 1,3-disubstituted unsymmetrical thioureas which are depend on the p*Ka*'s of the amine attached to thiourea. It has been found that larger the difference between the p*Ka*'s of the precursor amines in thiourea greater the regioselectivity of tetrazole formation with amine having lower p*Ka* as part of heterocyclic nitrogen and amine having higher p*Ka* contributes to the exocyclic nitrogen. Further, aryl-*sec*-alkyl unsymmetrical thiourea under the present experimental condition gave *anti*-Hugerschoff product *i.e.* product having a thioamido guanidino moiety as discussed in previous section *(Chapter IV, Scheme IV.2.). Bis*-thioureas derived from aryl isothiocyanates and hydrazine gave exclusively thiadiazoles.

In conclusion, we have synthesized various tetrazoles from the *in situ* generated diverse mono and disubstituted symmetrical and unsymmetrical thiourea mediated by molecular iodine. For the first time, regioselective formation of tetrazoles has been studied for unsymmetrical thioureas which are depending on p*Ka* of the amines attached to the thioureas. Aryl-*sec*-alkyl thiourea under the present experimental condition gave thioamido guanidine and not the expected tetrazole. *Bis*-thiourea resulted from hydrazine and aryl isothiocyanate gave exclusively thiadiazole.

CHAPTER VI. Structural Correction and Synthesis of 2-Imino-4-thiazolidinone

This chapter deals with the structural correction of a heterocyclic compound which was wrongly interpreted as thiohydantoins in *Green. Chem.* **2001**, *3*, 278 but are actually 2-imino-4-thiazolidinones. Subsequently an efficient method for the synthesis of 2-imino-4-thiazolidinones was developed and regioselective product formation was investigated (*Figure VI.1.*).

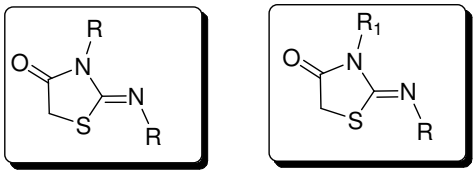
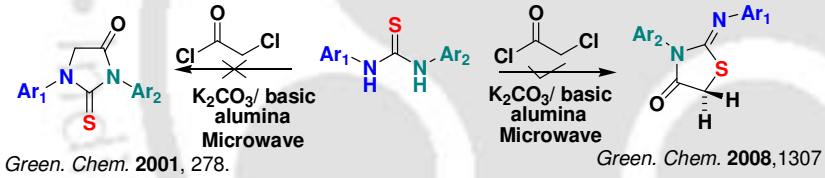


Figure VI.1. *2-Imino-4-thiazolidinone*

2-Imino-4-thiazolidinone was found to have applications in various biological activities such as hypnotic, hypotensive, antibacterial agent anticancer, and antimicrobial agent.

Having understood the reactivity of thioureas towards α-haloketones, we were interested to prepare the 2-imino-4-thiazolidinone using unsymmetrical thiourea and chloroacetylchloride. When 1,3-diphenylthiourea was treated with chloroacetylchloride in a basic condition following the reported procedure we found the structure to have a 2-imino-4-thiazolidinone skeleton and not the thiohydantoin as has been reported (*Green. Chem.* **2001**, *3*, 278).



Green. Chem. **2001**, 278.

Green. Chem. **2008**,1307

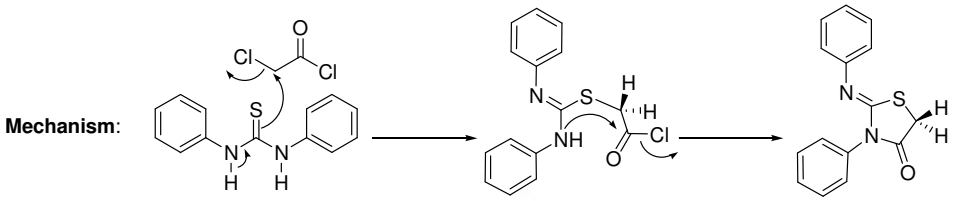
ORTEP view of 2-imino-4-thiazolidinone

Scheme V1.1. *Reaction product of thiourea with chloroacetylchloride.*

Our assumption is based on the fact that the sulfur atom (soft nucleophile) of the thiourea will preferentially attack on the α-haloketone (soft electrophile) and NH (hard nucleophile) will attack the carbonyl centre (hard electrophile). Thus we envisaged the following mechanism leading to the formation of 2-imino-4-thiazolidinone *Scheme V1.2.*

Proton NMR analysis of the product showed the presence of a doublet at δ = 3.97 (*J* = 3.6 Hz) corresponding to two protons. The appearence of the doublet may be due to the non equivalency of the two protons attached adjacent to a sulfur atom, an observation consistent with the literature. Its HRMS analysis corresponds to a product with molecular formula ($C_{15}H_{12}N_2OS$). Thus it was difficult to conclude whether the

product obtained was 2-imino-4-thiazolidinone as suggested by us or thiohydantoins as has been reported (*Green. Chem.* **2001**, *3*, 278).



Scheme VI.2. *Mechanism for the formation of 2-imino-4-thiazolidinone.*

Interestingly, the compound crystallized out from a mixture of chloroform and hexane (9:1). Crystal X-ray crystallography of the product unequivocally confirmed having the 2-imino-4-thiazolidinone skeleton as shown in *Scheme VI.1,* an assumption made by us at the very beginning. Having resolved the structural conflict, we further develop an efficient method for the preparation of various 2-imino-4-thiazolidinones. When 1,3-diphenylthiourea (1 mmol.) was reacted with chloroacetylchloride (1.5 mmol.) in the presence of two equivalents of triethylamine under a solvent free condition at room temperature, the desired product was obtained in 90% isolated yield. We wanted to see if the reaction can be performed in the absence of a base since chloroacetylchloride is quite reactive. It was surprising to note that when 1.5 equivalent of chloroacetylchloride was added to 1,3-diphenylthiourea, a sticky solid was obtained and it was again found to be identical (melting point, IR, ^{1}H and ^{13}C NMR). Thus the change in the reaction condition has no effect on the reaction path leading to the product formation.

In conclusion, we have unambiguously proved that the reaction of 1,3-disubstituted thioureas with chloroacetylchloride in the presence of basic alumina and K_2CO_3 are 2-imino-4-thiazolidinone derivatives and not thiohydantoins as reported earlier. This reaction can be performed at room temparature without using any base. Regioselective formation of 2-imino-4-thiazolidinones are observed for unsymmetrical thioureas which are depend on the p*Ka*'s of the amine attached to thiourea. We have also found a good correlation between the regioselective 2-imino-4-thiazolidinones formation and p*Ka*'s of the amines attached to the thiourea.

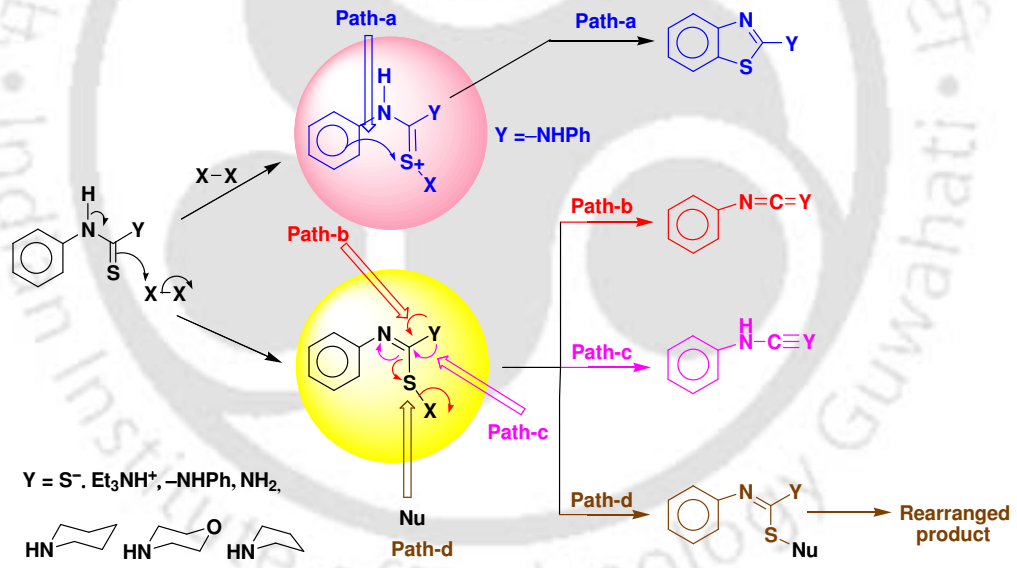
Contents

CHAPTER I

I. Introduction to Heterocumulenes and their Applications in Heterocyclic Synthesis

I.1. Thiophilic Reagents and its Applications

An electrophilic reagent which has affinity for sulfur atom and can form bond with it is termed a thiophilic reagent. Halogens such as bromine or its equivalent, iodine and hypervalent iodine are electrophilic in nature and they reacts with the sulphur nucleophiles easily. The sulphur nucleophiles can be part of dithiocarbamates, thioamides, monothioureas, or 1, 3-disubstituted thioureas (symmetrical and unsymmetrical) (*Scheme I.1.1*).



Scheme I.1.1. *Applications of thiophilic reagents in various organic transformations.*

I.2. Cumulenes and Heterocumulenes

Cumulenes are the substrates which have two or more *cumulative* (consecutive) double bonds, for instance propadiene (allene) as shown in *Figure I.2.1*. Unlike alkanes and most alkenes, cumulenes are more rigid and are deficient in hydrogens.

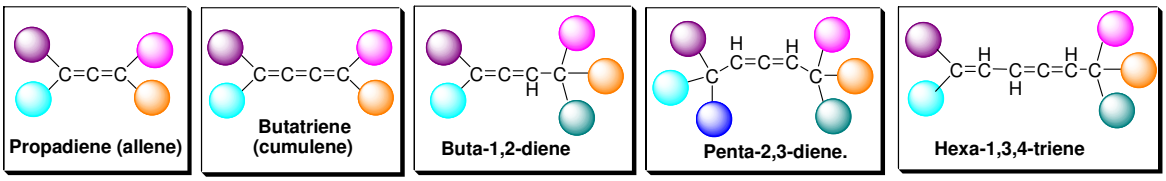


Figure I.2.1. *Examples of simple allenes and cumulenes.*

As shown in *Figure I.2.1*, from left to right, propadiene (allene), butatriene (cumulene), buta-1,2-diene, penta-2,3-diene all belong to the class of cumulene. Carbon suboxide is the one type of inorganic cumulene. An important class of organic cumulenes is ketenes, which are intermediate in character between CO_2 and allene.

The stringency of cumulenes generally arises from the internal carbon atoms carrying two double bonds, and their sp hybridization results in two bonds separated by 90°. Grippingly, cumulenes with (a) an even number of consecutive double bonds and (b) dissimilar substituents on either end can be chiral even though they lack a classical stereo center. For example, penta-2,3-diene and hexa-1,3,4-trienes are chiral as shown in *Figure I.2.1.* On the other hand odd numbers of double bonds in a cumulated system with proper substituents show geometrical isomerism.

The reactions of cumulene are similar to that of the isolated double bond. Although this molecule possesses two π-bonds in very close vicinity, in essence these act as isolated double bonds. This is because the two π-bonds on the central carbon atom are formed by the non-hybridized p-orbitals. As these orbitals are perpendicular towards each other and occupy each others nodal planes the two bonds are in essence isolated.

Heterocumulenes are obtained from the cumulenes by replacing one or more carbon atoms of the *cumulative* bond system by hetero atoms. In another words, a chemical compound having two or more *cumulative* or consecutive double bonds by replacing one or more carbon atoms by *N*, *O*, *S* are called as heterocumulenes. For example, isocyanate, isothiocyanate, cyanamides and carbodiimides all belong to the class of heterocumulenes (*Figure I.2.2*).

In general, heterocumulenes are very reactive in nature, because of high electrophilicty. Due to high reactivity associated with heterocumulene they are synthetically important precursors in the synthesis of many of the biologically important molecules.

Figure I.2.2. *Examples of heterocumulenes.*

I.2.1. Important Application of Heterocumulenes

The *cumulative* heteroatom sequence in isothiocyanate follows the order N, C and S (–N=C=S) obtained by replacing the oxygen atom in the isocyanate group with a sulphur atom.

Isothiocyanates (ITC) usually occur in a wide variety of plants, many of which are consumed by humans on a regular basis.[1] For example, mustard, garden cress, water cress, and broccoli (especially broccoli sprouts) are rich sources of allyl-ITC (**AITC**),[2a] benzyl-ITC (**BITC**),[2b,c] phenethyl-ITC (**PEITC**),[2d] and sulforaphane (**SF**),[2e,f] respectively as shown in *Figure I.2.1.1*. They are synthesized by glucosinolates as part of cruciferous plants defense mechanism.[2g]

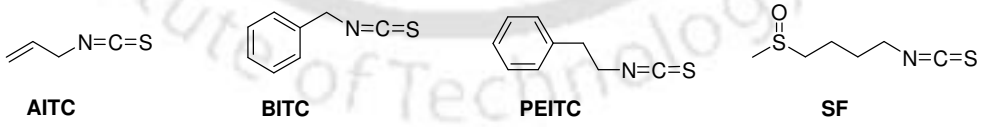


Figure I.2.1.1.

Isothiocyanate functionality (–NCS) is also encountered in many marine susquiterpenes.[3a,b]Additionally, synthetic isothiocyanates have been proved to have some biological activity, such as anti-proliferatives[3c] (*Figure I.2.1.2.*) and enzyme inhibitors for the HIV virus.[3d] Considering the antiproliferative activity found for ITCs,

these compounds could be considered potentially responsible for the reduction of colorectal cancer associated to diets rich in cruciferous vegetables.

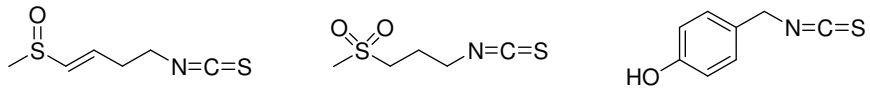


Figure I.2.1.2.

Isothiocyanates are also important synthetic intermediates for the preparation of both sulfur and nitrogen containing heterocycles such as thiohydantoins, thiopyrimidones, thioquinazolones, mercaptoimidazoles, thioamidazolones, and benzothiazines.[4] Furthermore, methyl 2-isothiocyanatobenzoate (**A**) (*Figure I.2.1.3.*), (ethy1thio)thiocarbonyl isothiocyanate (**B**) (*Figure I.2.1.3.*), 2-isothiocyanatobenzyl bromide (**C**) (*Figure I.2.1.3.*) and [*N*-aryl-*N*-(chloroacetyl)aminom]ethyl isothiocyanate (**D**) (*Figure I.2.1.4.*) are precursors of triazoloisoquinoline, 2-(ethylthio)-5,5-diphenyl-4-thioxo-5,6-dihydro-4H-1,3-thiazin, benzothiazine and thiadiazepines[4a] respectively.

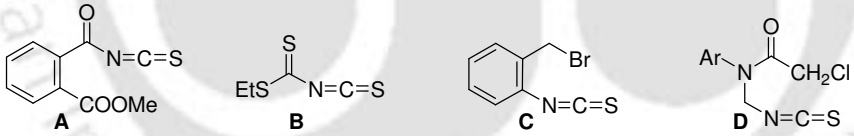


Figure I.2.1.3.

Beside these, they are also widely employed as chemoselective electrophiles in bioconjugate chemistry because of their tolerance towards aqueous reaction conditions.[5a] It has been proven to be the key reagent in Edman peptide sequencing and other biological assays of DNA and proteins.[5b-d]

Similar to isothiocyanates, due to its unique reactivity, cyanamides is an important functional group in synthetic organic chemistry.[6a-e] They have been employed in the synthesis of biologically active compounds, such as minoxidil,[6f] (*Figure I.2.1.4*) known for

its ability to reduce hair loss and promote hair re-growth, and herbicides[6g,h] (*Figure I.2.1.4.*). The *N*-cyanoamidines, Amitivir and Pinacidil, are isosteric to α-aminoacids, thus Amitivir show anti-viral activity and Pinacidil and similar compounds show anti-diabetes activity[6i] (*Figure I.2.1.4*). On the other hand, Cyanamides (RR'N–C≡N) are known as tumor inhibitors.[7]

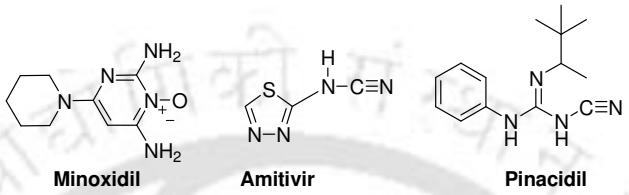


Figure I.2.1.4.

Cyanamides have both nucleophilic and electrophilic sites within the molecule, and hence they undergo various di, tri and polymerization reactions under acidic reaction conditions. Cyanamide dimerizes to give 2-cyanoguanidine (dicyandiamide) and its trimer is called melamine, an important precursors for thermosetting polymer. It exists in two tautomeric forms as shown in *Figure I.2.1.5.*

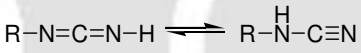
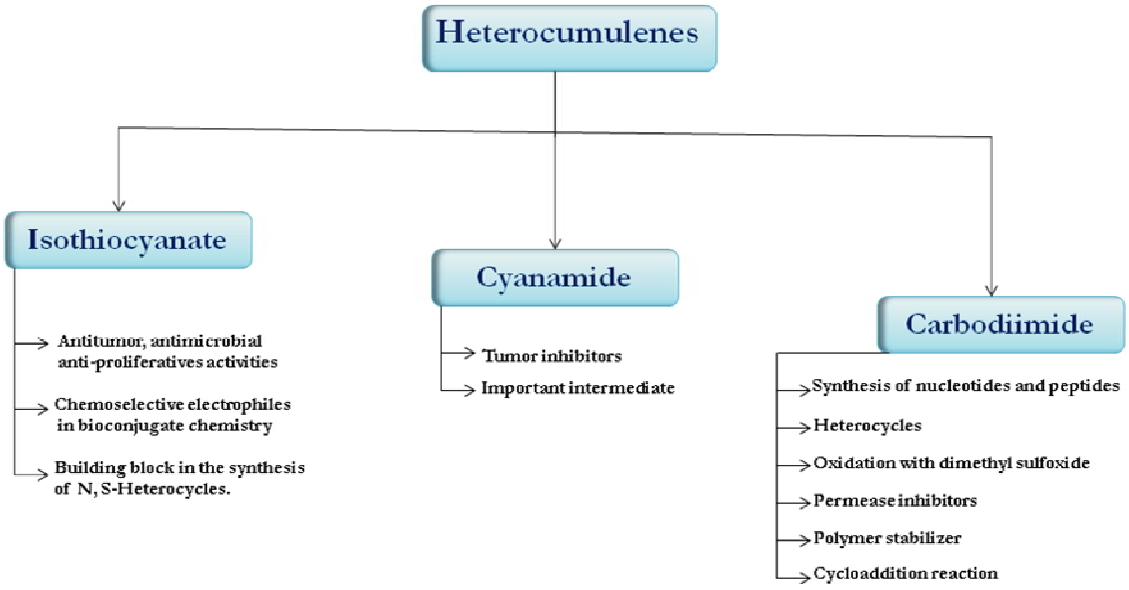


Figure I.2.1.5.

Carbodiimides are yet another class of the heterocumulene and have a functional group consisting of the formula R–N=C=N–R. They are one of most important class of reagent in synthetic organic chemistry, and valuable synthetic intermediates. They have also been found applications in the synthesis of nucleotides, peptides and heterocycles, oxidation with dimethyl sulfoxide, permease inhibitors, polymer stabilisers, cycloaddition reactions *etc*.[8] The wide spread use of some of the heterocumulenes are shown below.



I.3. Heterocycles in Drug Discovery

Heterocyclic compounds are those which contain a cyclic structure and at least two or more different kinds of atoms in the ring. They may also be composed of two or more than two fused rings, of which at least one must be a heterocyclic ring.

In general, pharmaceutical production is facing the challenge of increasing productivity and innovation. The major hurdles are the increasing costs of research and development and a simultaneous stagnating number of **new chemical entities** (**NCE**s). Inspite of the successful introduction of protein therapeutics and the promise of gene therapy, **major pharmaceutical companies** are still focused on the discovery and development of **low-molecular weight compounds**. Therefore, the brave is to select the most drugable targets and to find the corresponding drug-like molecules. It has been estimated that the number of possible molecules with a molecular weight of less than 500 Da is 10^{200}, of which only 10^{60} may possess drug-like properties. The proportion of these drugs-like molecules synthesized todate has been estimated as one part in 10^{57}, of roughly of the mass of one protan to mass of the sun! The issue is therefore the selection of new molecules from this vast universe that have the potential to be biological active.[9a]

Combinatorial chemistry has a revolutionary impact on drug discovery. **Tandem reactions** involving C–C, C–N, C–O, and C–S bond formation are one of the vital tools in

combinatorial chemistry for the construction of a library of small molecules. Generally, they involve numerous chemical transformations in one-pot, and the advantages associated with these reactions are minimal workup and minimization of waste generation.[9b-h] Another advantage is to create the molecular complexity and diversity from simple starting substrates, with simultaneous consideration of the economic and environmental aspects, great challenge in modern organic chemistry, both from academic and industrial point of view. The power of this new approach is now unquestioned, and drug discovery proceeds today in a radically different manner than earlier.

I.3.1. Classification and Nomenclature

Heterocyclic compounds are cyclic compounds with ring containing carbon and other elements, most commonly oxygen, nitrogen and sulphur. They have been 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. 2*H*-pyran, 4*H*-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 the trivial names. Some common five- and six-membered heterocycles that contain one oxygen, nitrogen or sulfur atom are shown in *Figure I.3.1.1.*

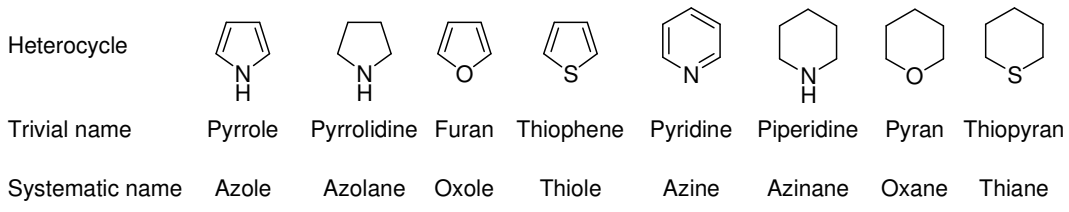


Figure I.3.1.1. *Trivial and systematic names of some common five and six membered heterocycles.*

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.[10] This nomenclature specifies the ring size, 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.3.1.1* and *I.3.1.2*).

Table I.3.1.1. *Prefixes for heteroatoms (in decreasing order of priority).*

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

Table I.3.1.2. *Stems for three to ten membered heterocycles.*

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

Figure I.3.1.2. *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.3.1.2.*). This system of nomenclature works reasonably well in many related cases and is widely used in the literature.[11] 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.3.1.2*). Monocyclic heterocyclic systems which are synthesized in this thesis are shown in *Figure I.3.1.3.*

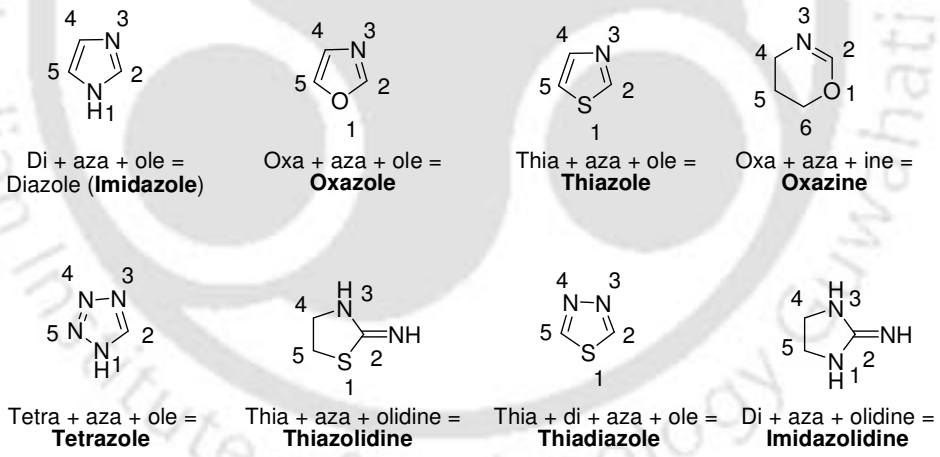


Figure I.3.1.3. *Monocyclic heterocycles and their nomenclature.*

I.3.1.1. Nomenclature of the Fused Ring System

As some of the chapters deal with the synthesis of bicyclic fused ring systems, its nomenclature is herewith shortly reviewed. The nomenclature follows the following rules:

(i) The individual components are named without any application of fused ring system.

(ii) The parent component is represented in the fusion name by citing it last in the name. The parent is the one with highest priority according to the following criteria:

a) a heterocyclic component containing the heteroatom occurring earliest in the order: N, F, Cl, Br, I, O, S, Se, Te, P, As, Sb, Bi, Si, Ge, Sn, Pb, B, Hg.

b) a component containing the larger ring.

c) a component containing the greater number of heteroatoms.

d) a component containing the greater variety of heteroatoms.

(iii) The attached component is then added as a prefix to the parent component. In the name of the prefix, the terminal 'e' is changed to 'o'.

(iv) The bonds of the parent component are indicated by a,b,c… starting with the bond normally occupying the 1,2 positions. The atoms of the attached components are numbered as usual, following the order of numbers in the original heterocycle.

(v) The numbering of the final condensed heterocycle is carried out independently, starting at an atom adjacent to a bridged-head atom, whereby heteroatoms receive the smallest possible number.

The method of naming and numbering of some of the fused ring systems which are related to thesis works are shown in *Figure I.3.1.1.1*.

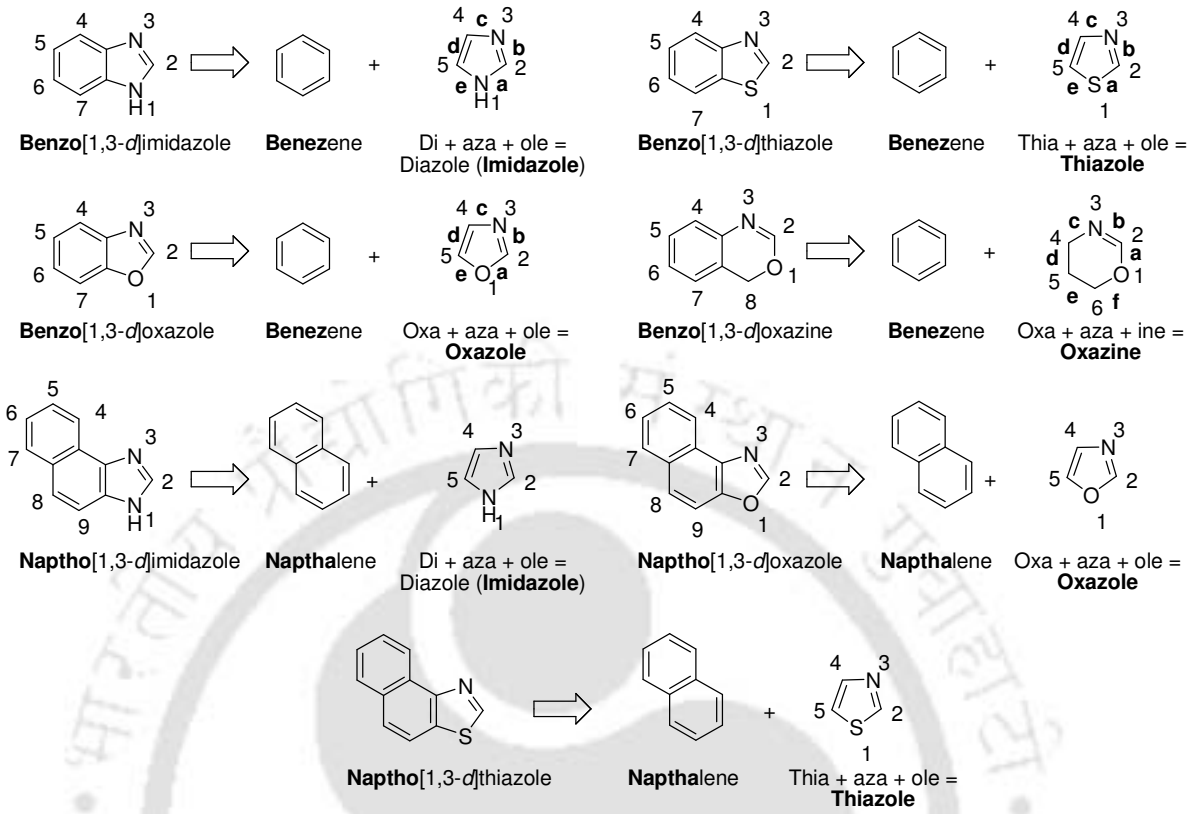
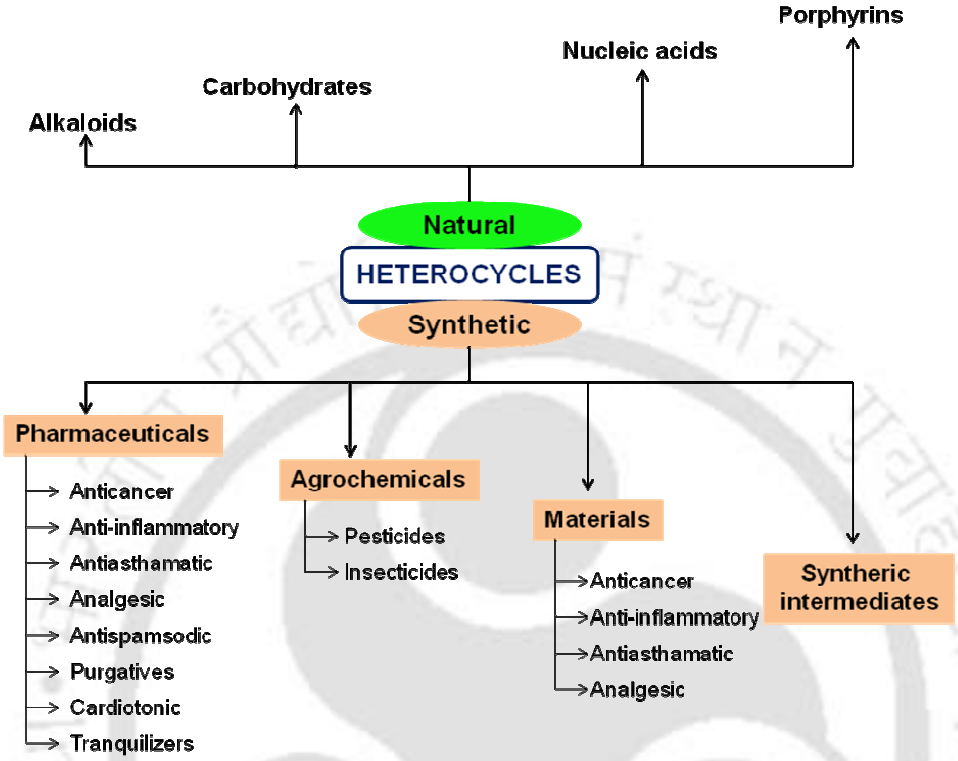


Figure I.3.1.1.1. *Nomenclature of fused heterocyclic ring system.*

I.3.2. Important Applications of Heterocycles

In general, there are two main sources of heterocyclic compounds. One source is that, most of the heterocyclic compounds are biosynthesized by plants and animals and possess various biological activities. The plant kingdom has an abundance of nitrogen compounds, most being heterocyclic, with some of great complexcity. Because they are weakly basic and form salts with mineral acids, meaning "alkali like," although the term has been extended to include those compounds of animal origin as well, especially those from the marine environment. Other source is the efficient procedures that have been developed in the laboratory for the synthesis of heterocyclic compounds. 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.3.2.1*). 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.3.2.1. *Various applications of heterocycles.*

One of the most important families of heterocyclic compounds is based on the porphyrin ring system. Porphyrins are common in living systems and are involved in various forms of biological activity. They are, for example, involved in the respiratory systems of both animals and plants. The two most well-known porphyrins are the Fe(II) complex **heme**, which when associated with protein globin is found in blood as the oxygen–carrying hemoglobin and **chlorophyll**, which is a Mg complex involved in photosynthesis. One of the vitamins (B_{12}, cyanocobalamine) also contains a modified porphyrin ring. 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.

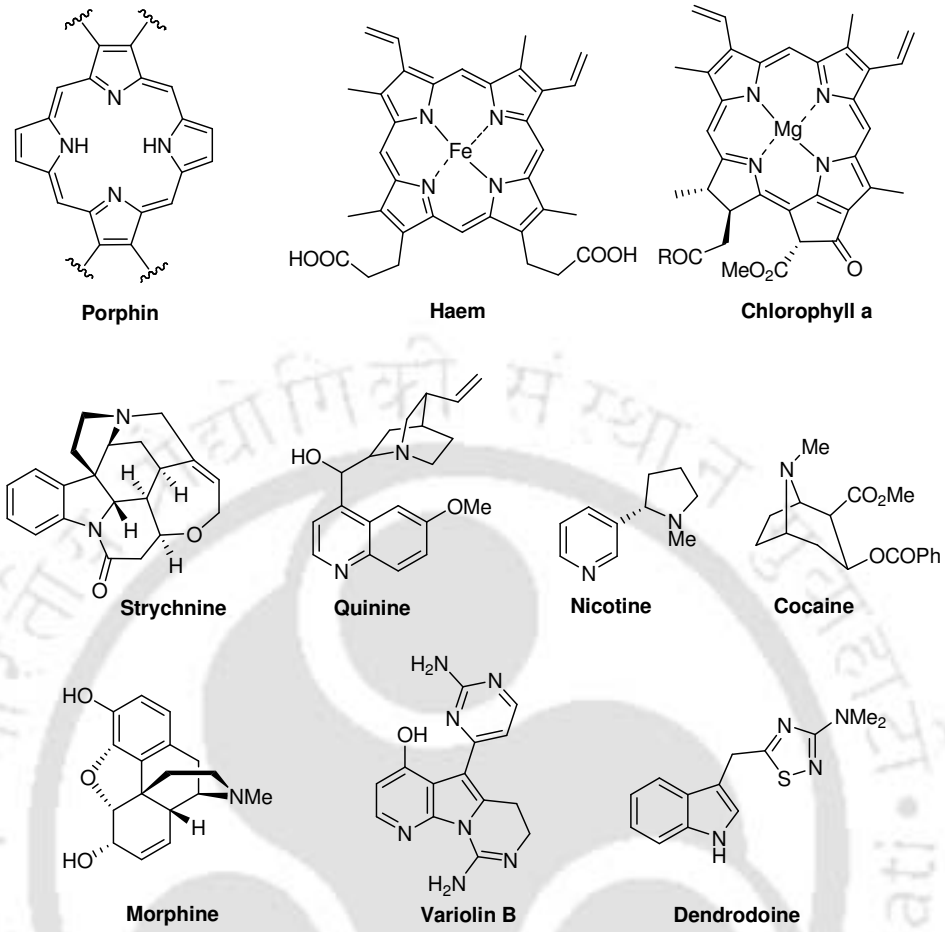


Figure I.3.2.1. *Examples of naturally occuring heterocycles.*

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 both for 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. **Nicotine** is another kind of alkaloid found in the nightshade family of plants which is an additive drug and acts as an insecticide. 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. Marine alkaloids

(also called as sea alkaloids) such as **variolin B** (sponge, *kirkpatrickia varialosa*) and **dendrodoine** (tunicate, *Dendroda grossular*) are example of multi-heteroatom compounds.

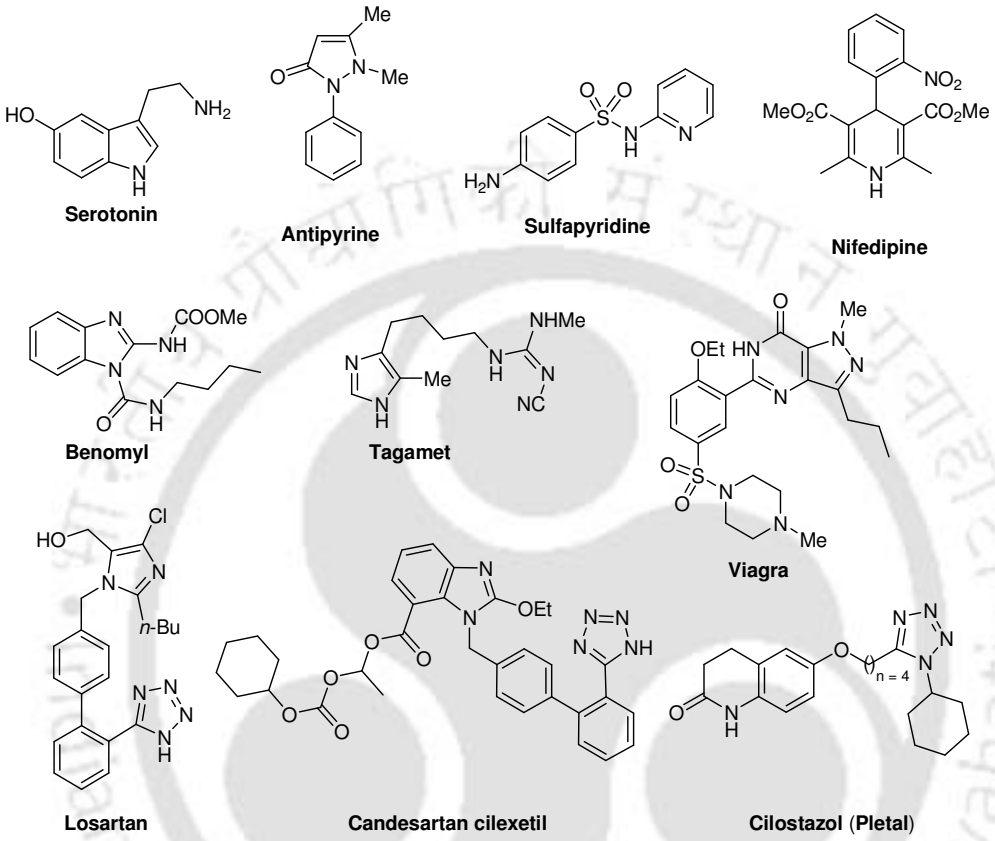


Figure I.3.2.2. *Examples of biologically active heterocycles.*

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. **Antipyrine** (1887) was the first synthetic drug used to reduce fever. Similarly, the first effective antibiotic was **sulfapyridine** (1938). **Nifedipine** is a cardiovascular drug and is a dihydropyridine calcium channel blocker. **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. 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.

Angiotension-II receptor antagonists can be used for the controlling the blood pressure and are generally derived from tetrazoles as replacements for carboxyl groups, resulting in increased potency. **Losartan** (cozaar) was a widely used angiotension-II antagonist, but more potent compounds such as candesartan cilexetil (Amias) (a complex-ester prodrug) are now more popular. **Cilostazol** (pletal), a selective inhibitor of PDE III, is used for the treatment of intermittent claudication, an occlusive disease of blood vessels in the legs, which is caused by walking. It acts as a vasodilator and inhibitor of platelet aggregation.

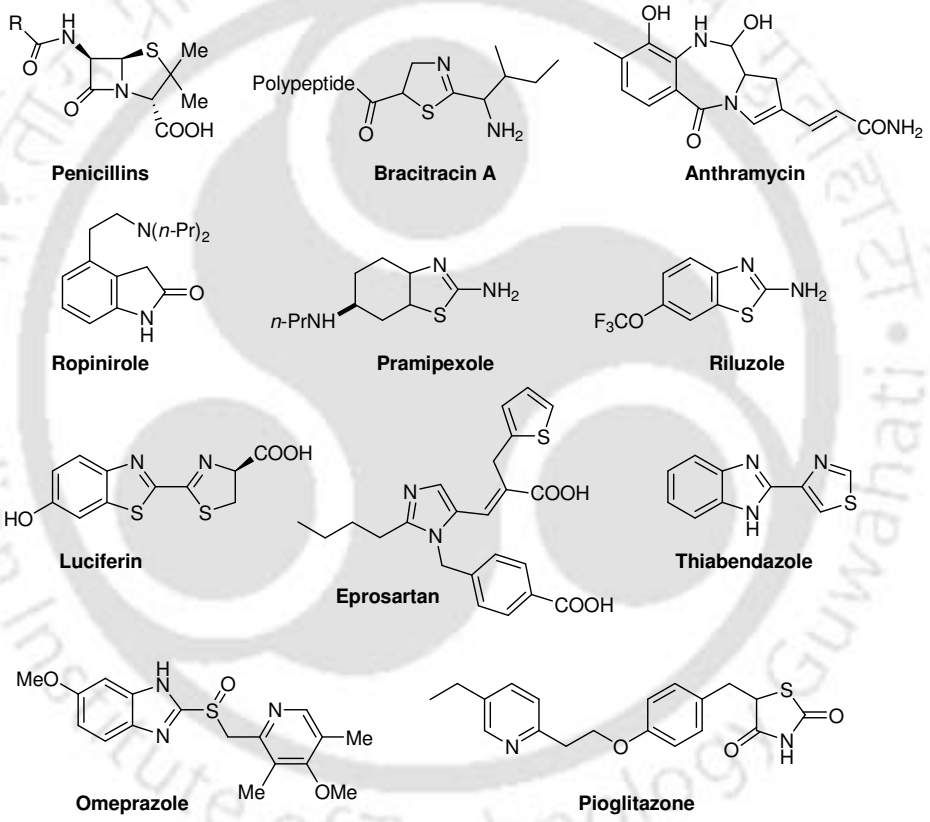


Figure I.3.2.3. *Examples of biologically active heterocycles.*

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 and the commercial antibiotic is **Bacitracin A** discovered in 1943. **Bacitracin A**, generally produced as a major one from the fermentation of *Bacillus subtlis* and having antitumor activity. Similary, **Anthramycin**

is an antibiotic with antitumor activity and is isolated from the growth of *Streptomyces refuineus*. Parkinson's disease is caused by a deficiency of dopamine. Dopamine agonists, such as **Ropinirole** (Requip) and **Pramipexole** (Mirapexin), are effective in alleviating some of the Parkinson's symptoms. **Riluzole** (Rilutek) is the only drug so far developed to have a significant effect in treatment of motorneurone disease. **Luciferin**, which occurs in fireflies and glow worms, upon enzymatic oxidation causes bioluminescence in these insects. **Eprosartan** is an angiotension II inhibitor and is 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. 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. **Pioglitazone** is a thiazolidinone compound that contains pyridine ring and is used for diabetes.

I.4. General Approaches for the Ring Construction of Aromatic Heterocycles

The following few general strategies are applied for the construction of heterocyclic ring of an aromatic heterocyclic compound from precursors that do not have that ring. Generally, it discusses principles and type of the reaction frequently used in constructing an aromatic heterocycle, and also the way in which appropriate functional groups are placed in the reactants, in order to achieve the desired ring synthesis.

(i) Ionic cyclizations in heterocyclic ring synthesis

(ii) Pericyclic reactions (electrocyclic process) in heterocyclic ring synthesis

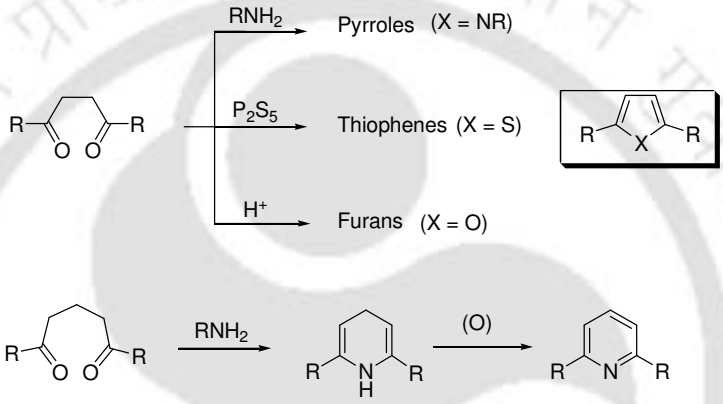
(iii) Modification of existing rings by electrophilic or nucleophilic aromatic substitution or by lithiation followed by reaction with electrophiles.

(iv) Typical heterocyclic ring synthesis involving C-heteroatom bond formation.

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

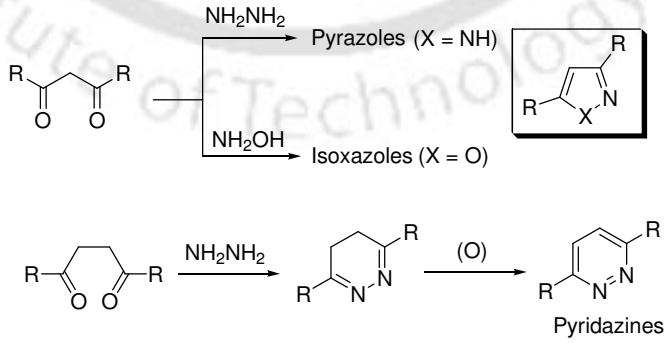
I.4.1. Ionic Cyclizations in Heterocyclic Ring Synthesis

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.4.1.1.* 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.



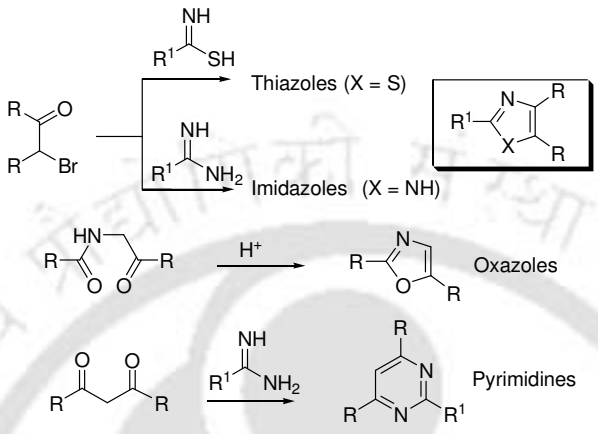
Scheme I.4.1.1. *Construction of five and six membered heterocycles with one heteroatom.*

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.4.1.2.*



Scheme I.4.1.2. *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.4.1.3.*

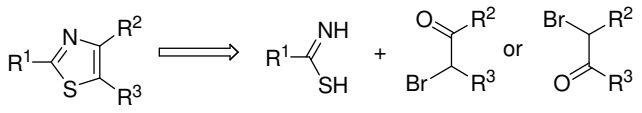


Scheme I.4.1.3. *Construction of five and six membered heterocycles with two nonadjacent heteroatoms.*

Ionic cyclizations using organic ammonium tribromides is one of the areas in heterocyclic synthesis, which is discussed in the forth coming section I.5. Their uses in heterocylic synthesis via oxidative and brominative cyclizations are reviewed.

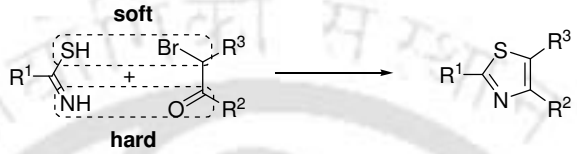
I.4.1.1. Selectivity of Unsymmetrical *bis*-Nucleophiles toward Unsymmetrical *bis*-Electrophiles

The synthesis of thiazoles from α-haloketones and thioamides is particularly interesting and challenging because of the major drawback with regioselectivity. When thioamides react with α-haloketones, there is a lack 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.4.1.1.1.*



Scheme I.4.1.1.1.

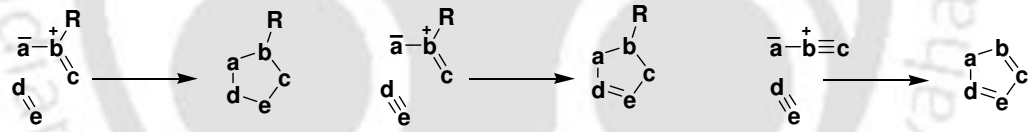
Carbonyl groups being '**hard**' electrophiles, their reactions are mainly under charge control and so they prefer to react with hard nucleophiles such as amines. Alkyl halides are '**soft**' electrophiles, so their reactions are mainly under frontier orbital control and they react best with large uncharged 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.4.1.1.2.*



Scheme I.4.1.1.2.

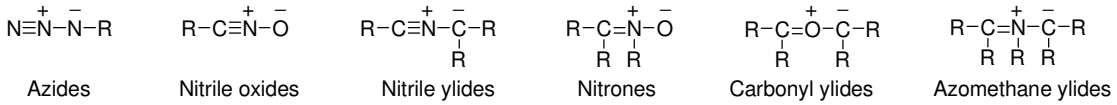
I.4.2. Pericyclic Reactions (Electrocyclic Process) in Heterocyclic Ring Synthesis

Electrocyclic reaction such as 1,3 dipolar cycloadditon is one of the powerful techniques to construct five-membered heterocycles (*Scheme I.4.2.1*).



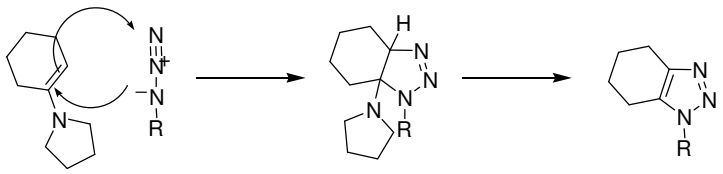
Scheme I.4.2.1.

In these reactions, dipoles generally contain the heteroatom as the central atom of the trio, either sp or sp^2 hybridized. Some of the important examples of the dipoles are as shown in *Scheme I.4.2.2.* In azides, nitrile oxides and nitrile ylides the central atom is sp-hybridized nitrogen where as in nitrones, carbonyl ylides and azomethane ylides the central atom is sp^2 hybridized.



Scheme I.4.2.2.

Enamines are dipolarophiles and interact with azides as a 1,3-dipole with subsequent elimination of the amine affording a 1,2,2-triazoles is shown in *Scheme I.4.2.3.*



Scheme I.4.2.3.

Chapter V in this thesis deals mainly with the construction of tetrazoles involving electrocyclizations.

I.5. Heterocyclic Synthesis Using Organic Ammonium Tribromides

Organic ammonium tribromides (OATBs) are attractive solid bromineless 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.5.1.*), which includes tetramethylammonium tribromide (TMATB), tetraethylammonium tribromide (TEATB), tetrabutylammonium tribromide (TBATB), cetyltrimethylammonium tribromide (CTMATB), phenyltrimethylammonium tribromide (PTATB), benzyl trimethylammonium tribromides (BTMATB), pyridine hydrobromide perbromide (PHPB), pentylpyridinium tribromide (PPTB), 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide, 1,8-diazabicyclo [5.4.0]-undec-7-ene hydrobromide perbromide ($DBUHBr_3$), 1-butyl-3-methylimidazoliumtribromide ([bmim] Br_3) and methylpyrrilidinone hydrobromide perbromide (MPHTB).

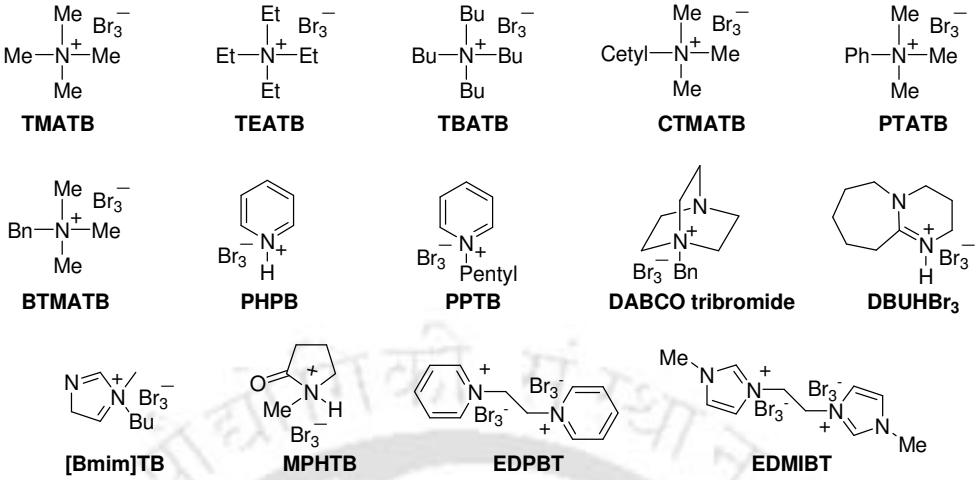
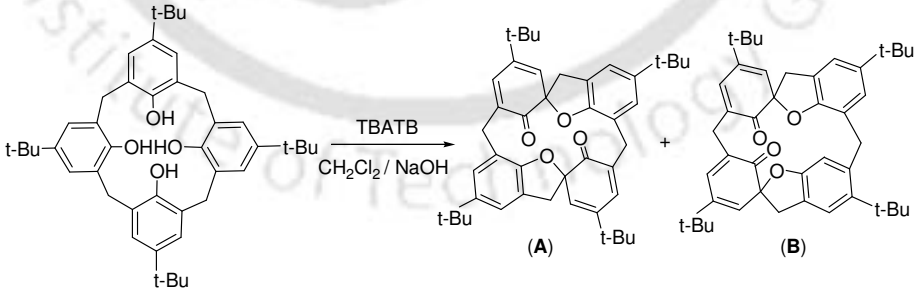


Figure I.5.1.

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.

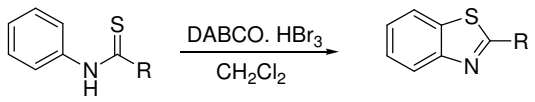
I.5.1. Tribromide Mediated Oxidative Cyclizations

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.5.1.1*).[12a,b]



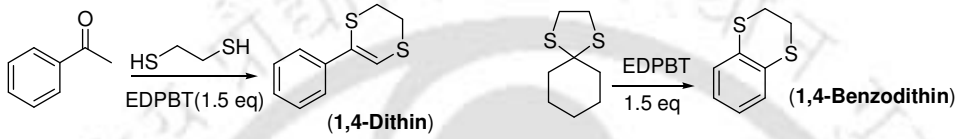
Scheme I.5.1.1.

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.5.1.2.*)[12c]



Scheme I.5.1.2.

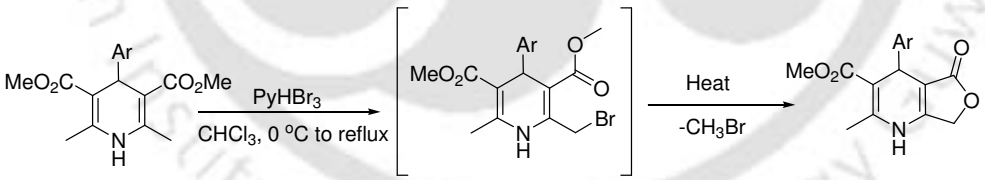
Recently, our group has developed a one-pot synthesis of 1,4-dithins and 1,4-benzodithins from ketones using 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (*Scheme I.5.1.3*).[12d]



Scheme I.5.1.3.

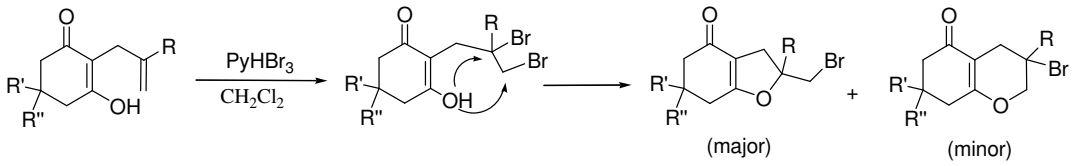
I.5.2. Brominative Cyclizations

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.5.2.1.* This reaction proceeds *via* bromination of methyl group of 1,4-dihydro pyrimidines, followed by cyclization with the ester moiety.[13a]



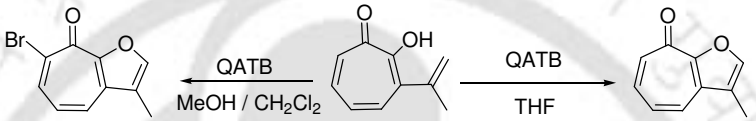
Scheme I.5.2.1.

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.5.2.2.*).[13b] This reaction proceeds through a 2-(2,3-dibromopropyl)-1,3-cyclohexanedione intermediate to form both the endo and exocyclic derivatives.



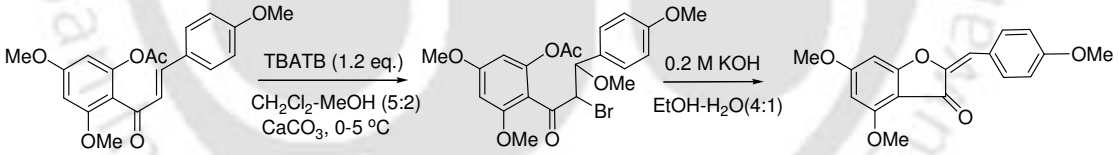
Scheme I.5.2.2.

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.5.2.3.*[13c]



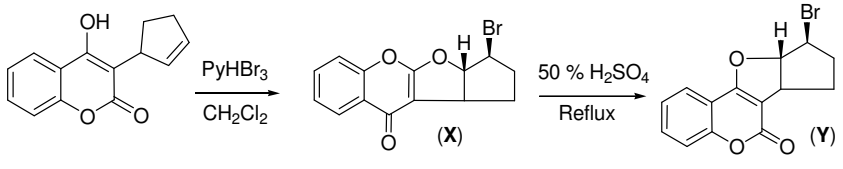
Scheme I.5.2.3.

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.5.2.4.*).[13d]



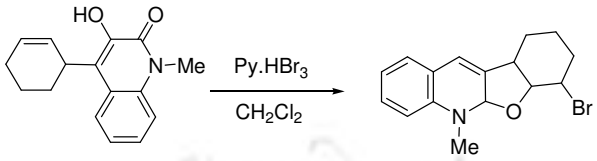
Scheme I.5.2.4.

Treatment of 4-hydroxy[1]benzopyran-2-one with pyridine hydrobromide perbromide ($PyHBr_3$) gave fused furochromone (X) in 90% yield (*Scheme I.5.2.5.*). These heterocycles undergoes rearrangement to furnish fused furocoumarin (Y) in 87% yield.[13e]



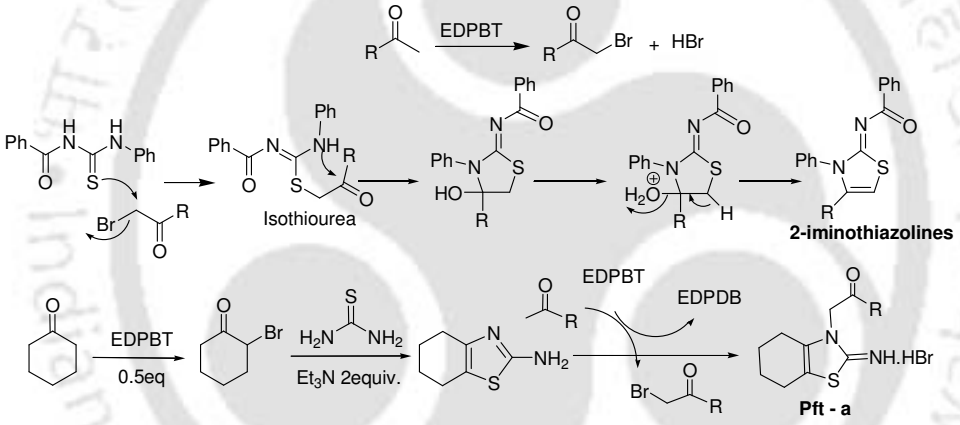
Scheme I.5.2.5.

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.5.2.6.*).[13e]



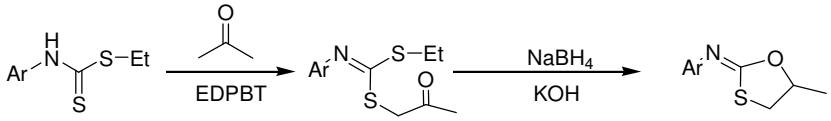
Scheme I.5.2.6.

Very recently, our group reported EDPBT mediated synthesis of 2-iminothiazolines, and that was further extended to the preparation of pifithrin analogues (*Scheme I.5.2.7*).[13g,h]



Scheme I.5.2.7.

A new, convenient and efficient synthetic technology for the construction of 2-oxathiolanimines has been devised. These are obtained by sodium borohydride reduction of the addition product of dithiocarbamic acid esters with α-bromoacetone under a basic condition. This method is general and applicable to a range of systems and hence superior to existing methods. (*Scheme I.5.2.8*). [13i]



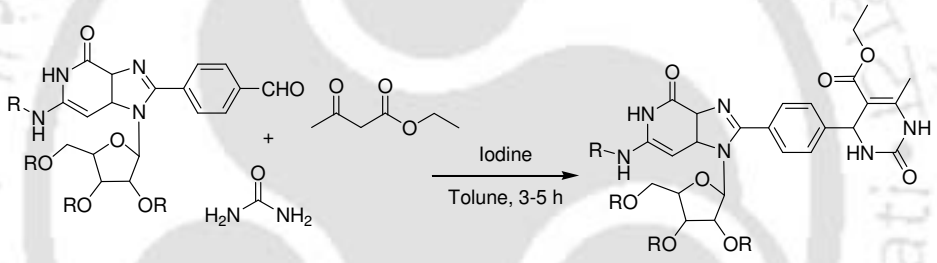
Scheme I.5.2.8.

I.6. Heterocyclic Synthesis Using Molecular Iodine

Recently, molecular iodine has received considerable attention in organic synthesis because of its low cost, non-toxicity and ready availability. The mild Lewis acidity associated with iodine has enhanced its use in organic synthesis to perform several organic transformations using stoichiometric[14a] to catalytic amounts.

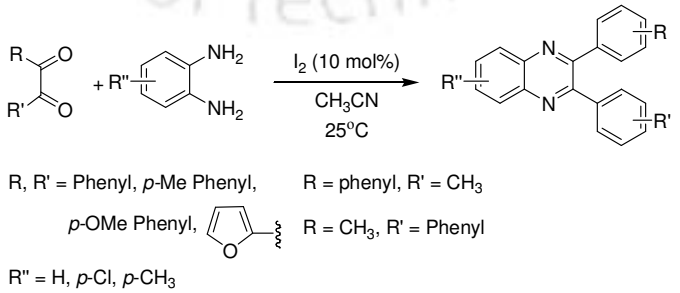
Owing to advantages associated with this eco-friendly reagent, molecular iodine has been explored as a powerful reagent[14b-d] and catalyst[15] for various organic transformations.

An efficient, high yield protocol for the one-pot synthesis of dihydropyrimidin-2(1*H*)-ones was achieved by iodine (*Scheme I.6.1.*).[16a]



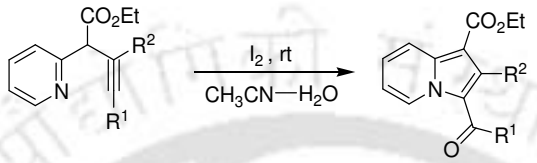
Scheme I.6.1.

Quinoxaline derivatives were synthesized by More *et al*. using inexpensive and nontoxic iodine in catalytic amount (10 mol%). Several aromatic as well as aliphatic 1,2-diketones and aromatic 1,2-diamines, such as substituted phenylenediamines, tetraamines were further subjected to afford the corresponding products in excellent yields[16b] (*Scheme I.6.2.*).



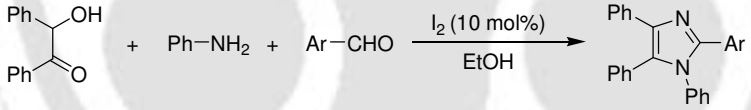
Scheme I.6.2.

Kim *et al.* have described a new synthetic route for the preparation of 3-acylated indolizine structures *via* iodine-mediated hydrative cyclization at room temperature. The mechanism for this transformation involves a 5-*exo-dig* iodocyclization, deprotonation, incorporation of another iodo group, deprotonation, and subsequent replacement of the diiodo group by H_2O.[16c] (*Scheme I.6.3.*).



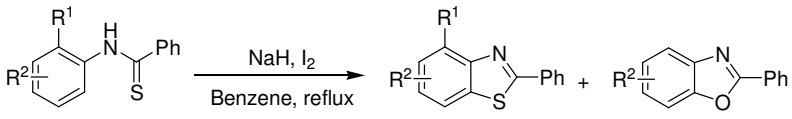
Scheme I.6.3.

Kidwai *et al*. synthesized 1,2,4,5-tetraarylimidazoles from benzoin, an aromatic aldehyde and an amine in the presence of ammonium acetate reported using molecular iodine as catalyst in one pot sequence. The advantage of this method is the direct use of benzoin, which is transformed into benzyl *in situ* and condenses further to generate the imidazole[16d] (*Scheme I.6.4.*).



Scheme I.6.4.

Jackson *et al.* reported for synthesis of benzothiazoles by the reaction of iodine with thiobenzamides, which lack an *ortho* alkoxy or ester group. Unlikely, benoxazoles obtained from the reaction of 2-alkoxythiobenzamides with iodine under an identical reaction condition.[17a] (*Scheme I.6.5.*).

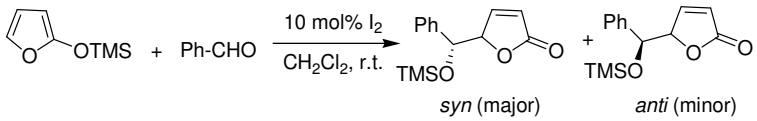


R^1 = H, OMe, OEt, O-*i*-Pr, OTs

R2 = H, Br, OMe

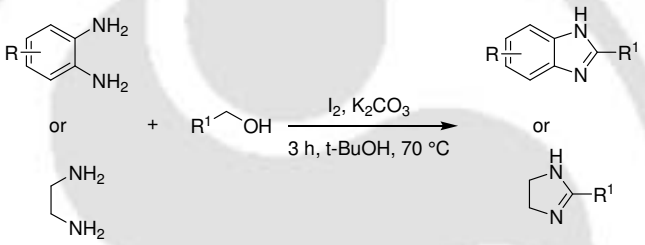
Scheme I.6.5.

Iodine was reported as a mild and efficient catalyst for the diastereoselective synthesis of δ-silyloxy-γ-lactones [17b] (*Scheme I.6.6.*).



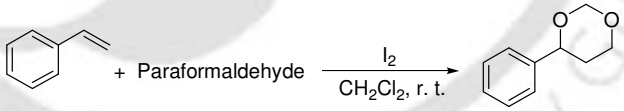
Scheme I.6.6.

Ren *et al*. developed an iodine-mediated synthesis of benzimidazoles and imidazolines by heterocyclization of *o*-phenylenediamine or ethylenediamine with primary alcohols. In this approach, iodine serves as both to activate the alcohols for attack by the diamine as well as to bring the products to their final oxidation state[17c] (*Scheme I.6.7.*).



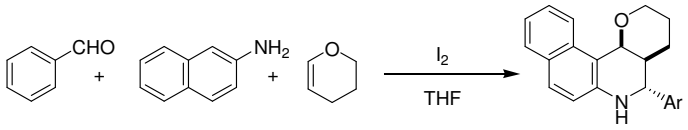
Scheme I.6.7.

Molecular iodine was used as a reagent for the synthesis of 1,3 dioxane by Prins reaction (*Scheme I.6.8.*).[17d]



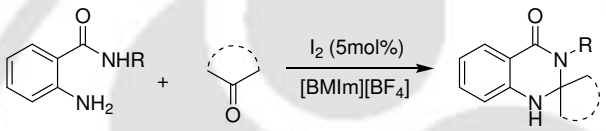
Scheme I.6.8.

Wang *et al*. described iodine catalyzed a mild, efficient, and highly selective method for the synthesis of pyranoquinoline and furoquinoline derivatives *via* a three-component reaction using aromatic aldehyde, naphthalen-2-amine or anthracen-2-amine and 2,3-dihydro furan, or 3,4-dihydro-2*H* pyran. Interesting aspect of the method is the exclusive formation of exo-isomer with high selectivity[17e] (*Scheme I.6.9.*).



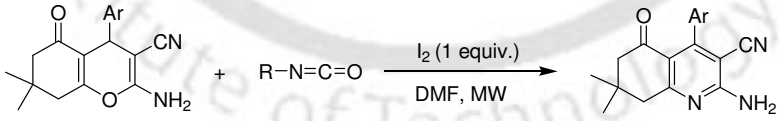
Scheme I.6.9.

Combinatorial strategy has been developed for the synthesis of quinazolin-4-(1*H*)-one derivatives, containing simple 2,2-disubstituted quinazolin-4-(1*H*)-ones, spirocyclicquinazolin-4-(1*H*)-ones, spiro-heterocyclic quinazolin-4-(1*H*)-ones, and dispirocyclicquinazolin-4-(1*H*)-ones in high yields using ionic liquids as green media. This method involves the reaction of 2-amino benzamides with various ketones catalyzed by iodine[17f] (*Scheme I.6.10.*).



Scheme I.6.10.

A new iodine-promoted domino reaction of 2-aminochromene-3-carbonitriles with various isocyanates is described and a set of poly functionalized *N*-substituted 2-aminoquinoline-3-carbonitriles with high regioselectivity were successfully synthesized under microwave heating. In this reaction, the ring-opening / recyclization process occurs unexpectedly at the ring of 4*H*-pyran with different isocyanates. [17g] (*Scheme I.6.11.*).



Scheme I.6.11.

I.7. Objective of the Thesis

Our interest was mainly in the synthesis of **mono** and **bicyclic heterocycles** using thiophilic reagents such as bromine equiv. 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (**EDPBT**) and **iodine**. Some of the compounds synthesized in the thesis are not frequently

used (thioamido guanidino moieties), and are therefore, totally absent in the literature. This prompted us to elaborate this type of chemistry and to synthesize five and six membered *N*, *O*, *S* and related heterocyclic scaffolds.

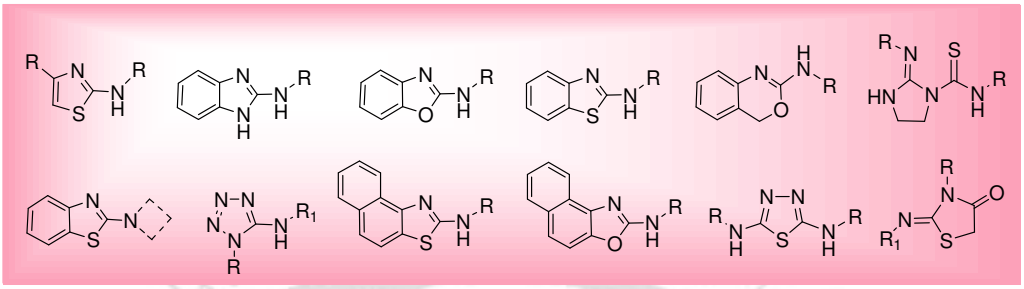


Figure I.7.1. *Structures of synthesized N, O, S heterocyclic scaffolds in this thesis.*

Combinatorial and parallel chemistry are powerful tools for medicinal chemistry in drug discovery. It has encouraged chemists to work out synthetic strategies and approaches that can be used for the construction of libraries of compounds. Combinatorial chemistry can be done on a solid support or in solution. Although solid-phase chemistry definitively has come advantages (mainly related to purification), however, we opted for the solution-phase approach to construct the libraries of compounds synthesized in this thesis.

I.8. References

1 (a) Fenwick, G. R.; Heaney, R. K.; Mullin, W. J. *Crit. Rev. Food Sci. Nutr,* **1983**, *18*, 123; (b) Fahey, J. W.; Zalcmann, A. T.; Talalay, P. *Phytochemistry* **2001**, *56*, 5.

2 (a) Ioannou, Y. M.; Burka, L. T. H.; Matthews, B. *Toxicol. Appl. Pharmacol.* **1984**, *75*, 173; (b) Gorler, K.; Krumbiegel, G.; Mennicke, W. H.; Siehl, H. U. *Xenobiotica* **1982**, *12*. 535; (c) Xiao, D.; Vogel, V.; Singh, S. V. *Mol. Cancer Ther.* **2006**, *5*, 2931; (d) Chung, F. L.; Morse, M. A.; Eklind, K. I.; Lewis, J. *Cancer Epidemiol., Biomarkers & Prev.*, **1992**, *1*, 383; (e) Zhang, Y.; Talalay, P.; Cho, C. G.; Posner, G. H. *Proc. Natl. Acad. Sci*., USA, **1992**, *89*, 2399; (f) Fahey, J. W.; Zhang, Y.; Talalay, P. *Proc. Natl. Acad. Sci*., USA, **1997**, *94*, 10367; (g) Bones, M.; Rossiter, J. T. *Physiol. Plant.* **1996**, *96*, 194.

3 (a) Kuhnert, N.; Williamson, G.; Holst, B. *J. Labl. Comp. Radiopharm.* **2001**. *44*, 347; (b) Kuhnert, N.; Lu, Y. *J. Labl. Comp. Radiopharm.* **2004**. *47*, 501; (c) Nastruzzi, C.; Cotesi, R.;

Eaposito, E.; Menegatti, E.; Leoni, O.; Iori, R.; Palmier, S. *J. Agric. Food. Chem.* **2000**, *48*, 3572; (d) Xu, K.; Thornalley, P. *J. Biochem. Pharmacol.* **2000**, *6*, 221.

4 (a) Mukerjee, A. K.; Ashare, R. *Chem. Rev.* **1991**, *91*, 1 and references therein; (b) Dobosz, M.; Wujec, M. *Heterocycles* **2002**, *57*, 1135.

5 (a) Ferna´ndez, J. M. G.; Mellet, C. O.; Blanco, J. L. J.; Mota, J. F.; Gadelle, A.; Coste Sarguet, A.; Defaye, J. *Carbohydr. Res.* **1995**, *268*, 57; (b) Edman, P. *Arch. Biochem.* **1949**, *22*, 475; (c) Cabantchik, Z. I.; Rothstein, A. *J. Membr. Biol.* **1974**, *15*, 227; (d) Podhradsky, D.; Oravec, P.; Antalik, M.; Kristian, P. *Collect. Czech. Chem. Commun.* **1994**, *59*, 213.

6 (a) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*, Academic, New York, **1972**, *3*, 286; (b) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*, Academic, New York, **1972**, *2*, 174; (c) Miyasaka, H.; Clerac, R.; Campos-Fernadez, C. S.; Dubner, K. R. *Inorg. Chem.* **2001**, *40*, 1663; (d) Hollebone, B. R.; Nyholm, R. S. *J. Chem. Soc. A* **1971**, 332; (e) Pombeiro, A. J. L. *Inorg. Chim. Acta* **1992**, *198*, 179; (f) McCall, J. M.; Tenbrink, R. E.; Ursprung, J. J. *J. Org.Chem.* **1975**, *40*, 3304; (g) Hu, L. Y.; Guo, J.; Magar, S.; Fischer, J. B.; Burkehowie, K. J.; Durant, G. J. *J. Med. Chem.* **1997**, *40*, 4281; (h) Robinson, J. R.; Brown, W. H. *Can. J. Chem.* **1951**, *29*, 1069; (i) Domling, A.; Herdtweckb, E.; Heck, S. *Tetrahedron Lett.* **2006**, *47*, 1745.

7 (a) Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad, F. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th ed.; Pergamon Press: New York, 1990, 899; (b) Saneyoshi, M.; Tokuzen, R.; Maeda, M.; Fukuoka, F. *Chem. Pharm. Bull.* **1968**, *16*, 505.

8 (a) Khorana, H. G. *Chem. Rev.* **1953**, *53*, 145; (b) Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* **1967**, *67*, 107; (c) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589; (d) Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron*, **1981**, *32*, 233.

9 (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; (b) Parsons, P. J.; Penkett, C. S.; Shell. A. J. *Chem. Rev*. **1996**, *96*, 195; (c) Rejzek, M.; Stockman, R. A.; van Maarseveen, J. H.; Hughes, D. L. *Chem. Commun*. **2005**, 4661; (d) Posner, G. H. *Chem. Rev*. **1986**, *86*, 831; (e) Ho, T.-L. *Tandem Organic Reactions*; Wiley-Interscience: New York, 1992; (f) Hall, N. *Science* **1994**, *266*, 32; (g) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (h) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.

10 (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry,* 4th edn., Blackwell Science, Oxford, 2000. (b) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*, Pergamon Press, Oxford, 1985.

11 Panico, R.; Powell, W. H.; Richer, J.-C. (eds.), *A Guide to IUPAC Nomenclature of Organic Compounds (Recommendations 1993)*, Blackwell Science, Oxford, 1993.

12 (a) Litwak, A. M.; Biali, S. E. *J. Org. Chem.* **1992**, *57*, 1943; (b) Georghiou, P. E.; Ashram, M.; Clase, H. J.; Bridson, J. N. *J. Org. Chem.* **1998**, *63*, 1819; (c) Moghaddam, F. M.; Boeini, H. Z. *Synlett* **2005**, 1612; (d) Murru, S.; Kavala, V.; Singh, C. B.; Patel, B. K. *Tetrahedron Lett.* **2007**, *48*, 1007.

13 (a) Young, S. D. *Synthesis* **1984**, 617; (b) Mphahlele, M. J.; Moekwa, T. B. *Org. Biomol. Chem.* **2005**, 3, 2469; (c) Matsunaga, Y.; Imafuku, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 295; (d) Bose, G.; Mondal, E.; Khan, A. T.; Bordoloi, M. J. *Tetrahedron Lett.* **2001**, *42*, 8907; (e) Majumdar, K. C.; Choudhury, P. K.; Biswas, P. *Ind. J. Chem. B* **1998**, *37B*, 1197; (f) Majumdar, K. C.; Kundu, A. K. *Synth. Commun*. **1996**, *26*, 4023; (g) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397; (h) Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. *Tetrahedron* **2008**, *64*, 1931; (i) Ghosh, H.; Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Tetrahedron Lett.* **2008**, *49*, 2602.

14 (a) Yadav, J. S.; Subba Reddy, B. V.; Narasimhulu, G.; Sivasankar Reddy, N.; Janardhan Reddy, P. *Tetrahedron Lett.* **2009**, *50*, 3760 and references therein; (b) Yadav, J. S.; Reddy, B. V. S.; Hara Gopal, A. V.; Narayana Kumar, G. G. K. S.; Madavi, C.; Kunwar, A. C. *Tetrahedron Lett.* **2008**, *49*, 4420; (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S.; Krishna, A. D. *Tetrahedron Lett.* **2007**, *48*, 5243; (d) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758.

15 (a) Yadav, J. S.; Reddy, B. V. S.; Jain, R.; Reddy, U. V. S. *J. Mol. Catal. A*: *Chemical* **2007**, *278*, 38; (b) Lin, X.-F.; Cui, S.-L.; Wang, Y.-G. *Tetrahedron Lett*. **2006**, *47* 4509; (c) Chen, W.-Y.; Lu, J. *Synlett* **2005**, 1337; (d) Royer, L.; De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 4595.

16 (a) Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wangb, T.; Zubaidhaa, P. K. *Tetrahedron Lett.* **2004**, *45*, 9111; (b) More, S. V.; Sastry, M. N. V.; Wang, C. C.; Yao, C. F. *Tetrahedron Lett*. **2005**, *46*, 6345; (c) Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron Lett*. **2007**, *48*, 8976; (d) Kidwai, M.; Mothsra, P. *Tetrahedron Lett*. **2006**, *47*, 5029.

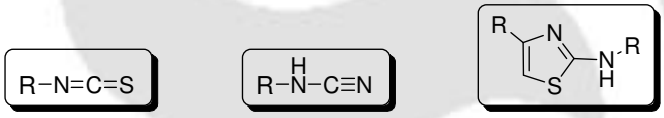
17 (a) Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2007**, *63*, 10276; (b) Yadav, J. S.; Reddy, B. V. S.; Narasimhulu, G.; Satheesh. G. *Tetrahedron Lett.* **2008**, *49*, 5683; (c) Ren, Y-M.; Cai, C. *Org. Prep. Proced. Int*. **2008**, *40*, 101; (d) Yadav, J. S.; Reddy, B. V. S.; Hara Gopal, A. V.; Narayana Kumar, G. G. K. S.; Madavi, C.; Kunwar, A. C. *Tetrahedron Lett.* **2008**, 49, 4420; (e) Wang, X. S.; Zhou, J.; Yin, M. Y.; Yang, K.; Tu, S. J. *J. Comb. Chem*. **2010**, *12*, 266. (f) Wang, X. S.; Yang, K.; Zhou, J.; Tu, S. J. *J. Comb. Chem.* **2010**, *12*, 417; (g) Jiang, B.; Li, C.; Tu, S. J.; Shi F. *J. Comb. Chem*. **2010**, *12*, 482.

CHAPTER II

II. One-Pot Synthesis of Isothiocyanates, Cyanamides and Thiazoles from Dithiocarbamic Acid Salts Using EDPBT

II.1. Structure and Nomenclature

Detailed discussion about heterocumulenes and nomenclature of thiazoles were discussed in CHAPTER I, Section I.2, Figure I.2.2, in page 1-6 and Section I.3.1, Figure I.3.1.3 in page 8-9. This chapter deals with the following two types of heterocumulenes namely, isothiocyanates and cyanamides. Further the scope of this strategy was extended to the synthesis of thiazoles in one-pot.



Isothiocyanates **Cyanamides** **Thiazoles**

II.2. Importance and Applications

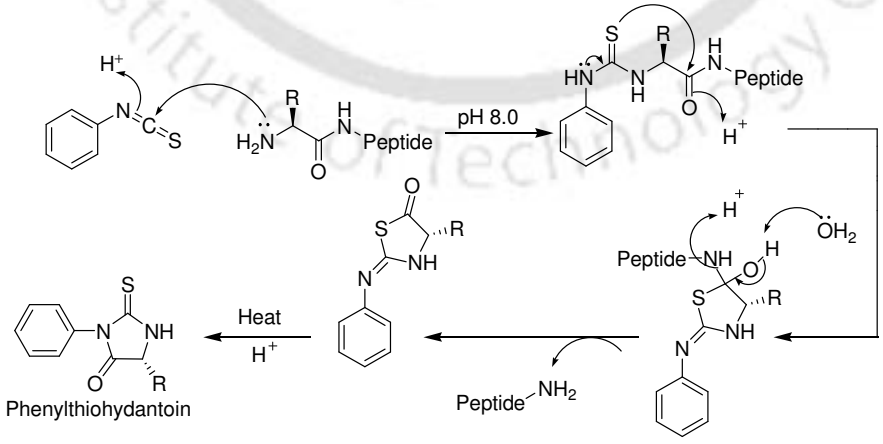
There is a great deal of interest in the chemistry of heterocumulenes because of their applications in synthetic organic chemistry and medicinal chemistry.[1] Isothiocyanates are one of the important class of heterocumulenes available from the plants, produced by enzymatic conversion of metabolites called glucosinolates. They are also important precursors for the construction of pharmaceutically important heterocycles and are frequently encountered in many natural products.[2,3] Some of the natural isothiocyanates, for instance allyl isothiocyanate are found in mustard oils and serves as a defence against herbivorous. The synthetic isothiocyanate, phenylisothiocyanate, is used for amino acid sequencing in the Edman peptide degradation. Due to their unique reactivity towards –OH and $-NH_2$ nucleophiles, present in nucleic acids and proteins, they serve as chemoselective electrophiles in bioconjugate and neoglycoconjugate chemistry, particularly for biological

assays.[4,5] Another important class of heterocumulenes is cyanamide which is widely used in agriculture, as precursors for the synthesis of pharmaceutically important heterocycles[6a-i] and *N*-alkyl or *N*-aryl imides.[6j] They have been used as an alcohol deterrent drug in Canada, Europe and Japan. They also serve as a protecting group during the synthesis of secondary and tertiary amine containing heterocycles.[7] Synthesis of biologically active compounds, such as minoxidil and herbicides[8] goes *via* cyanamide intermediates.

Thiazoles skeleton is present in several naturally occurring compounds such as penicillin, vitamin B1 (thiamin). Of late, thiazoles derivatives have attracted interest due to their biological activities. Among these, 2-aminothiazole ring system is a useful structural motif in medicinal chemistry having application in drug development for the treatment of allergies,[9] hypertension,[10] inflammation,[11] schizophrenia,[12] bacterial infections,[13] and HIV.[14] These are also known to be ligands for estrogen receptors,[15a] adenosine receptor antagonists[15b] and neuropeptide Y5 receptor.[15c]

II.2.1. Applications of Isothiocyanates in Organic Synthesis

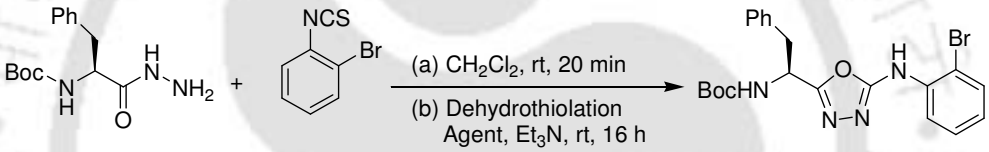
Isothiocyanates are important intermediates especially for the synthesis of *N*, *S*-containing heterocycles.[16] The use of isothiocyanates in the preparation of various heterocycles has been extensively discussed by Muhkerjee *et al.*[16a] Some recent literature reports on the use of isothiocyanates in the preparation of a wide range of heterocyclic compounds are depicted in this section.



Scheme II.2.1.1.

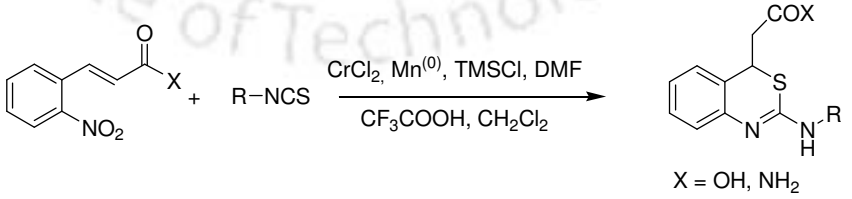
Phenylisothiocyanate is employed for amino acid sequencing in the Edman degradation,[17a-c] it proceeds from the *N*-terminus end of the protein and able to accurately sequence up to 30 amino acids with modern machines capable of over 99% efficiency per amino acid (*Scheme II.2.1.1.*).

Batey group have developed a synthetic route to peptidomimetic 2-arylamino 5-substituted 1,3,4-oxadiazoles by reacting Boc-protected amino acid hydrazides with arylisothiocyanates in the presence of either Hg(II) chloride, Mukaiyama's reagent (2-chloro-*N*-methylpyridinium iodide) or polymer supported Mukaiyama's reagent, with triethylamine in dichloromethane at ambient temperature in one-pot (*Scheme II.2.1.2.*). The reactions proceed *via* initial formation of thiosemicarbazides, followed by dehydrothiolative cyclization to the 1,3,4-oxadiazoles.[17d]



Scheme II.2.1.2.

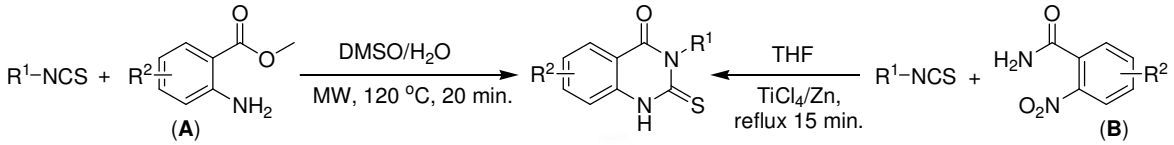
In addition to these, it has been used in the synthesis of spiro(imidazolidine-2,3'-benzo[b]thiophene),[18a] 3-alkyl 2-thiohydantoins,[18b] N,6-disubstituted-1,3,5-triazine-2,4-diamines,[18c] 1,2,4-thiadiazolidine-3,5-diones[18d] *etc*. They are the key component for the synthesis of both symmetrical and unsymmetrical 1,3-disubstituted thioureas which are again versatile building blocks for the preparation of various heterocycles.[18e]



Scheme II.2.1.3.

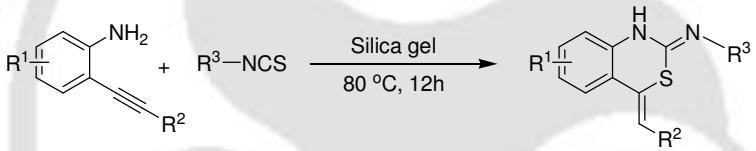
Miller and his co-workers have used isothiocyanates for the preparation of unexplored benzothiazines which are of synthetic and biological important. In this

approach, arylthioureas prepared on solid phase followed by triflouroacetic acid catalyzed conjugate addition afforded the desired benzothiazines (*Scheme II.2.1.3.*).[19a]



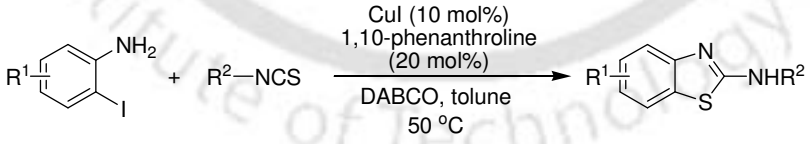
Scheme II.2.1.4.

Isothiocyanates was reacted with substituted methyl anthranilate (**A**) DMSO/H_2O under microwave irradiation to afford 2-thioxoquinazolinones.[19b] In yet another strategy, 2-thioxoquinazolinones have been prepared by the reaction of nitro-compounds (**B**) with isothiocyanates induced by low-valent titanium reagent ($TiCl_4$/Zn)[19c] (*Scheme IV.2.1.4.*).



Scheme II.2.1.5.

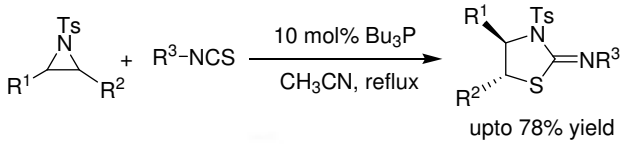
Very recently, Ding *et al.* developed a tandem addition-cyclization reactions of 2-alkynylbenzenamines with isothiocyanates promoted by silica gel to afford the 2,4-dihydro-1*H*-benzo[*d*]-[1,3]thiazines (*Scheme I1.2.1.5.*).[19d]



Scheme II.2.1.6.

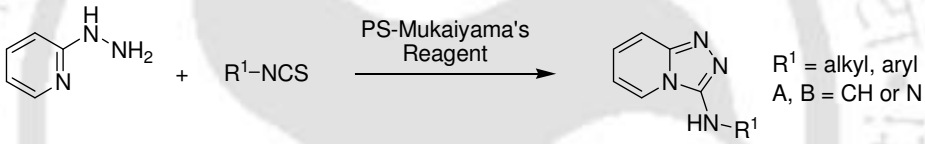
In another report, Wu *et al.* described a copper(I)-catalyzed tandem reactions of 2-iodobenzenamines with isothiocyanates which afforded 2-aminobenzothiazole (*Scheme II.2.1.6.*). The advantages of the method were demanded as the high efficiency, good substrate generality, mild reaction conditions, and experimental ease.[19e]

Thiazolidinone derivatives have been prepared by organophosphine-catalyzed ring-opening reaction of aziridines with isothiocyanates (*Scheme II.2.1.7.*).[19f]



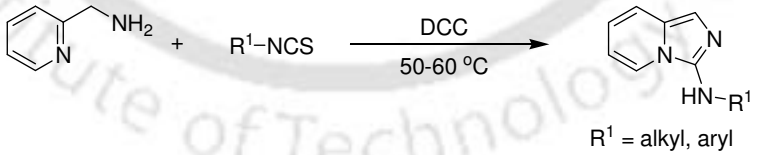
Scheme II.2.1.7.

The reaction of hydrazinopyridine with isothiocyanate affords the corresponding thiosemicarbazide, which upon desulfurization *in situ*, using polymer-supported Mukaiyama's reagent, gives the final cyclization product 3-amino-[1,2,4]triazolo[4,3-a]pyridine (*Scheme II.2.1.8.*) in one-pot.[19g]



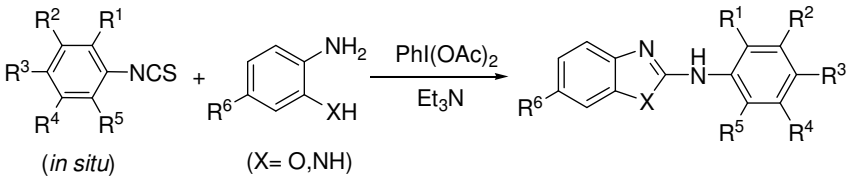
Scheme II.2.1.8.

A series of 3-substituted aminoimidazo-[1,5-α]pyridine derivatives have been synthesized by cyclodesulfurization of a variety of *N'*-substituted *N*-(2-pyridylmethyl)thioureas with dicyclohexylcarbodiimide (DCC) (*Scheme II.2.1.9.*).[19h]



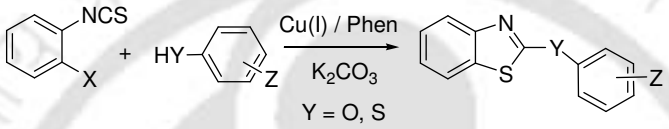
Scheme II.2.1.9.

Recently, our group has demonstrated the thiophilic nature of hypervalent iodine reagent diacetoxyiodobenzene (DIB) in the synthesis of heterocycles from the isothiocyanate and *o-phenylenediamine* (*o*-PD), and *o*-amino phenol (*Scheme II.2.1.10.*).[20a]



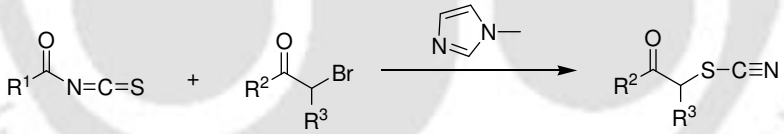
Scheme II.2.1.10.

In yet another report, our group disclosed a method to prepare 2-substituted benzothiazoles directly from 2-haloaryl isothiocyanates and phenols and thiophenols by a Cu-catalyzed, cascade intramolecular C–S bond formation (*Scheme II.2.1.11.*).[20b]



Scheme II.2.1.11.

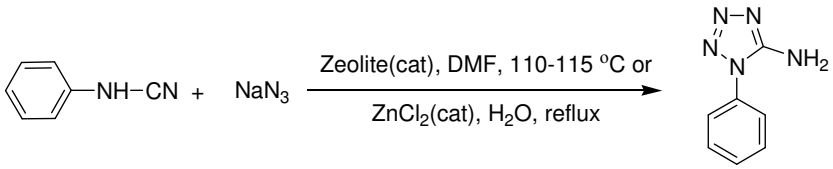
Another class of isothiocyanate is aroyl/acyl isothiocyanate used in the unprecedented transformation where the transfer of an isothiocyanate to alkyl/benzyl bromide is observed in the presence of a tertiary amine (*Scheme II.2.1.12.*).[20c]



Scheme II.2.1.12.

II.2.2. Applications of Cyanamides in Organic Synthesis

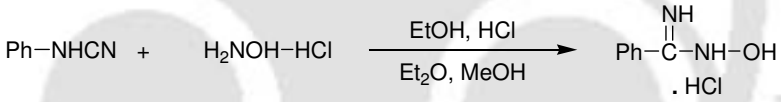
Due to its unique reactivity, cyanamide is an important functional group in synthetic organic chemistry and are useful precursors in the synthesis of pharmaceutically important heterocycles.[6a-i] Synthetic utility of cyanamides are discussed below.



Scheme II.2.2.1.

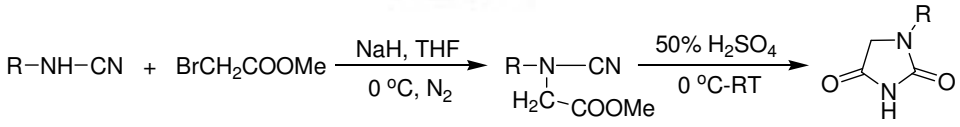
Nasrollahzadeh *et al*. employed the aryl cyanamides in the preparation of 5-amino tetrazoles using zeolite as catalyst at an elevated temperature. Further, they have modified the procedure by replacing the zeolite with $ZnCl_2$ in an aqueous medium under reflux condition. Additionally, they observed regioselective tetrazole formation which is dependent on the nature of the substituents attached to the arylcyanamide (*Scheme II.2.2.1.*).[21a,b]

The products *N*-aryl *N′*-hydroxyguanidines, a new class of NO-donors were obtained by treating phenyl cyanamide with hydroxyl amine hydrochloride in the presence of HCl in EtOH (*Scheme II.2.2.2*).[21c]



Scheme II.2.2.2.

Monoalkyl/aryl cyanamides on treatment with methyl bromoacetate in the presence of sodium hydride in tetrahydrofuran affords methyl *N*-cyano-*N*-alkyl/arylaminoacetate, which undergoes hydrolysis and cyclization in the presence of 50% H_2SO_4 to afford *N*-1 substituted hydantoins in good to excellent yields (*Scheme II.2.2.3.*).[21d]



Scheme II.2.2.3.

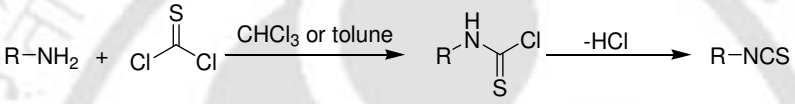
Aromatic cyanamides are used as popular ligands for binding with various metals, such as, octaethylporphyrin iron(III) complexes containing cyanamide derivatives as axial

ligand,[21e] Rh^{III} polypyridine complexes with phenyl cyanamide derivative ligands,[21f] tetraphenylporphyrin manganese(III) complexes of phenylcyanamide ligands,[21g] *cis*-bis(bipyridine) cobalt(III) complexes of phenyl cyanamide ligands[21h] *etc*.

II.3. Available Synthetic Methods

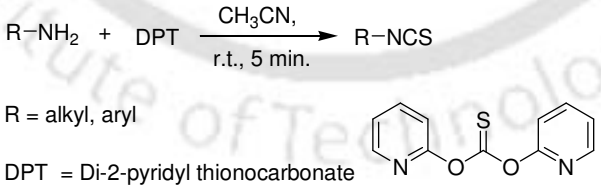
II.3.1 Known Methods for the Synthesis of Isothiocyanates

Isothiocyanates are prepared conventionally by treating amines with thiophosgene. Primary amines react with thiophosgene to give unstable thiocarbamoyl chlorides which in turn furnished isothiocyanates (*Scheme II.3.1.1.*).[22a,b]



Scheme II.3.1.1.

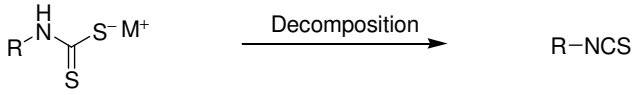
Owing to difficulties in handling thiophosgene, its equivalents have been prepared and employed for this purpose. This method was modified over the years and diethylthiocarbamoyl chloride,[22c] bis(diethylthiocarbamoyl) sulfide or disulfide,[22d] di-2-pyridyl thiocarbonate,[22e-f] 1,1'-(thiocarbonyldioxy)dibenzotriazole,[22g,h] and 1,1'-thiocarbonyl-2,2'-dipyridone,[22i] bis(trichloromethy1) pentathiodiperoxycarbonate[22j] were introduced as substitutes of the highly toxic thiophosgene (*Scheme II.3.1.2.*).



Scheme II.3.1.2.

The reactions of amines with "thiocarbonyl transfer" reagents like di-2-pyridyl thionocarbonate afford the corresponding isothiocyanates.[22k-m]

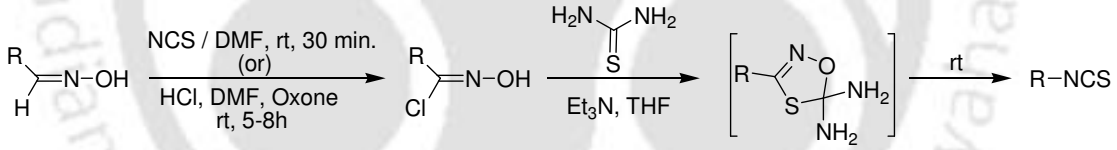
An alternative approach relies on the decomposition of dithiocarbamic acid salts into isothiocyanates promoted by various reagents (*Scheme II.3.1.3.*).



Scheme II.3.1.3.

The reagents used are uronium- and phosphonium based coupling agents,[23a-d] tosyl chloride,[23e] di-*tert*-butyl dicarbonate,[23f] hydrogen peroxide,[23g] ethyl chlorocarbonate,[23h] bis(trichloromethyl)carbonate (BTC) and trichloromethyl chloroformate (TCF),[23i] Claycop,[23j] and 2-chloro-1-methylpyridinium salt.[23k]

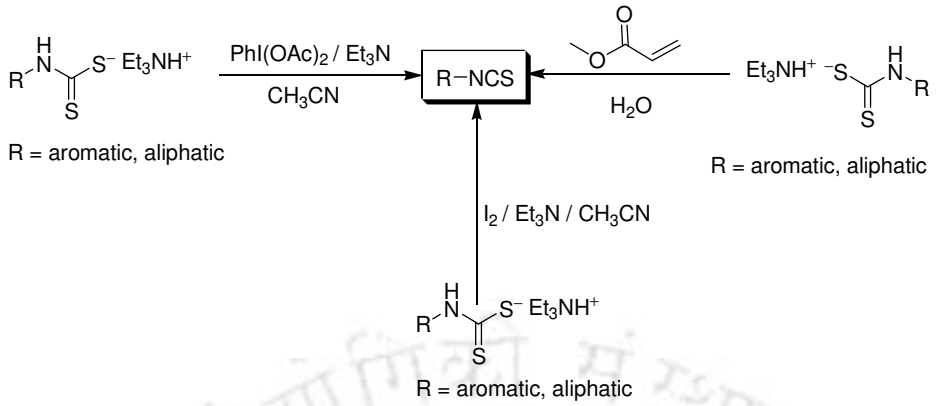
Isothiocyanates were prepared in a one-pot reaction from aldoxime derivatives by successive treatment of aldoxime with *N*-chlorosuccinimide (NCS), thiourea, and triethylamine (*Scheme II.3.1.4.*). The use of HC1/DMF/Oxone system in the reaction instead of NCS was equally effective (*Scheme II.3.1.4.*).[24a]



Scheme II.3.1.4.

Another method of preparation of isothiocyanate, with limited substrate scope, is by the treatment of 1,3-disubstituted thiourea with strong acids e.g. H_2SO_4 under a refluxed condition.[24b]

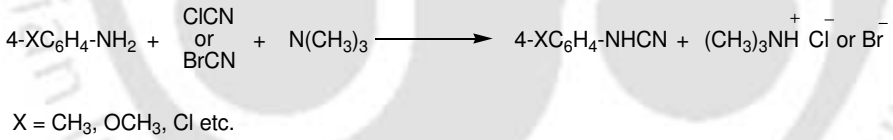
Very recently, our group has demonstrated a high yielding protocol for the preparation of isothiocyanate by the decomposition of dithiocarbamate salt with hypervalent iodine *i.e* diacetoxyiodobenzene (DIB).[24c] Further, we have demonstrated that molecular iodine,[24d] is equally effective for the decomposition of dithiocarbamate to isothiocyanates. In another approach, isothiocyanate can be prepared by treating dithiocarbamate salt with a Michael acceptor (methylacrylate) in an aqueous medium[24e] (*Scheme II.3.1.5.*).



Scheme II.3.1.5.

II.3.2. Known Methods for the Synthesis of Cyanamides and Thiazoles

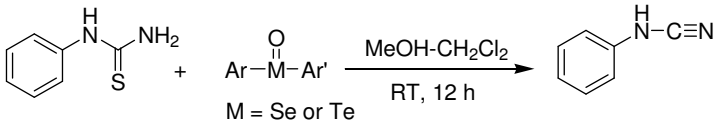
The wide applications of cyanamides have resulted in the development of several methods for their synthesis over the years. The most frequently adopted method for the synthesis of cyanamides is the cyanation of amine using cyanogen halides or its synthon (CN^+) (*Scheme II.3.2.1.*).[25a]



Scheme II.3.2.1.

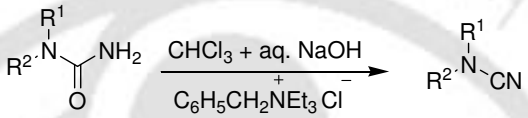
To avoid the use of toxic cyanogen halides, some electrophilic cyanating reagent that can serve as a cyano cation (CN^+) equivalent, have been prepared. The reagents capable of delivering electrophilic cyanogens (CN^+) are 2-chlorobenzyl thiocyanate,[25b] 1-cyanoimidazole,[25c] 2-cyanopyridazin-3-(2*H*)-ones,[25d] 1-cyanobenzotriazole and metal cyanide,[25e] tosylcyanide,[25f,g] thiocyanogen,[25h] and cyanogens azide.[25i]

Cyanamides are obtained from 1-phenylthioureas using various methods, such as, polymer supported diaryl solenoid or telluroxide mediated dehydrosulfurization,[26a] (*Scheme II.3.2.2.*) treatment with superoxide (KO_2) in pyridine at 60 ^oC under N_2 for 2 h,[26b] methylation[26c] followed by a basic work-up *etc.*



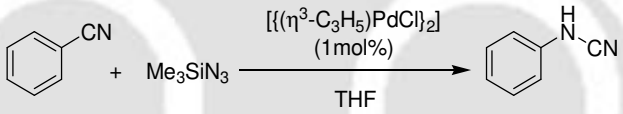
Scheme II.3.2.2.

In an alternative method, cyanamides are obtained from ureas through dehydration method using chloform and NaOH mixture (*Scheme II.3.2.3.*)[26d] or trichloromethyl chloroformate.[26e]



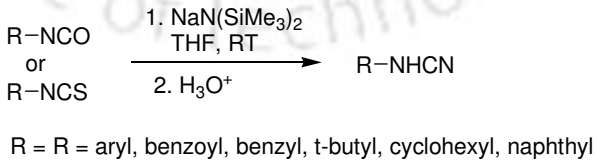
Scheme II.3.2.3.

The other less commonly adopted method is the Tiemann rearrangement of amidoximes.[26f]



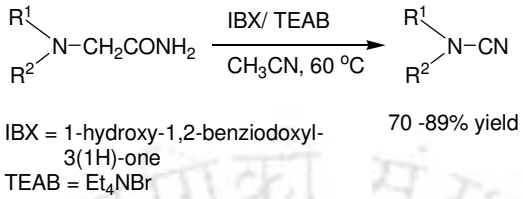
Scheme II.3.2.4.

Recently, Yamamto *et al.* they have prepared various organic cyanamide from organic isocyanides and trimethylsilyl azide *via* a Si-N bond cleavage catalyzed by [{(η^3-C_3H_5)PdCl}$_2$] (*Scheme II.3.2.4.*).[27a]



Scheme II.3.2.5.

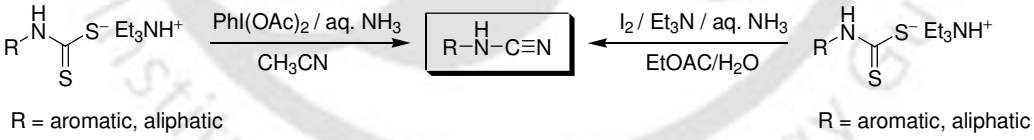
Cyanamides have been prepared in one-pot by reacting isocyanate or isothiocyanate with sodium bis(trimethylsilyl)amide as deoxygenating or desulfurizing agents in THF at room temperature (*Scheme II.3.2.5.*).[27b,c]



Scheme II.3.2.6.

In yet another method, cyanamides are prepared from *N.N'*-disubstituted glycylamide using a pentavalent iodine reagent in the presence of tetraethyl ammonium bromide at ambient temperature through a one-carbon dehomologation of primary carboxamides (*Scheme II.3.2.6.*).[27d]

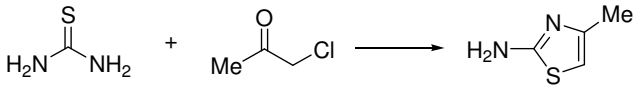
Very recently our group has disclosed a high yielding; environmentally benign method for the preparation of cyanamide from dithiocarbamate salt using diacetoxyiodobenzene (DIB).[27e] Due to high cost associated with DIB, the method cannot be applied to large scale reaction. To overcome this, expensive DIB was replaced by molecular iodine using green solvent ethyl acetate (*Scheme II.3.2.7.*).[27f]



Scheme II.3.2.7.

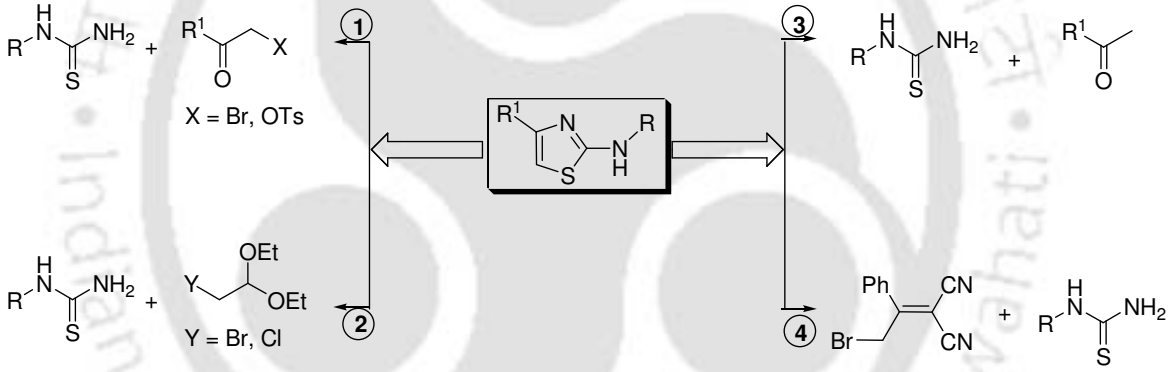
Thus inspite of a plethors of methods available for the synthesis of isothiocyanates and cyanamides due to the immense importance of these heterocumulines there is always scope for newer and milder strategy for their synthesis.

The basic moiety 2-aminothiazole was first synthesized (*Scheme II.3.2.8.*) by Hantzsch condensation reaction involving thiourea and α-haloketone.[28a]



Scheme II.3.2.8.

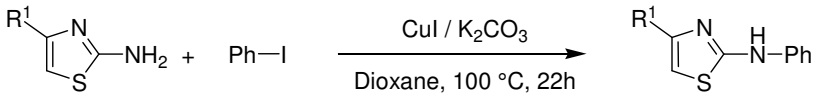
This approach was subsequently adopted for the synthesis of *N*-alkylated amino-thiazolines by replacing thioureas with mono-*N*-substituted thioureas. The condensation of α-haloketones with mono-*N*-substituted thioureas in greener solvent PEG,[28b] I_2 catalyzed condensation,[28c] led to the formation of 2-(*N*-substituted amino)thiazoles (*Method 1*, *Scheme II.3.2.9.*). Recently, a highly efficient method has been described for the synthesis of substituted 2-aminothiazoles in water without any catalyst or co-organic solvent (*Method 1*, *Scheme II.3.2.9.*).[28d] Alternatively, 2-amino thiazoles are prepared by the cyclocondensation of α-tosyloxyketones with thiourea (*Method **1**, Scheme II.3.2.9.*).[28e]



Scheme II.3.2.9.

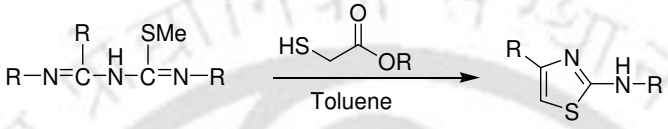
In continuation, Suzuki, and Anderson *et al*. have developed a general methods for the condensation of bromo or chloro derivative of dimethoxyethane with thioureas to afford the aminothiazoles (*Method **2***, *Scheme II.3.2.9.*).[29a,b]

Further, one-pot synthesis of 2-aminothiazoles was carried out in PEG-400 as a greener medium at room temp.[29c] This method avoids the use of lachrymatic α-bromoketones as well as the volatile, toxic organic solvents (*Method **3***, *Scheme II.3.2.9.*). 2-amino thiazoline also prepared from the treatment of phenyl amino acetonitrile with thiourea (*Method **4***, *Scheme II.3.2.9.*).[29d]



Scheme II.3.2.10.

Simple and inexpensive copper-mediated *N*-arylation of heteroarylamines was achieved using *N*,*N*′-dimethylethylenediamine (DMEDA) as a ligand and K_2CO_3 as a base in dioxane at 100°C (*Scheme II.3.2.10.*).[29e]



Scheme II.3.2.11.

A convenient one-pot synthesis of 2-aminothiazole derivatives involving reactions of 1,3-diazabuta-1,3-dienes with thioglycolic acid and ethyl bromoacetate are reported (*Scheme II.3.2.11.*).[29f]

II.4. Present Work

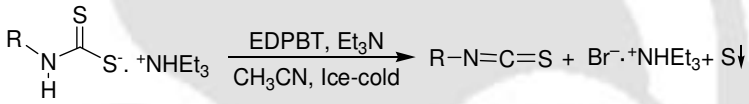
II.4.1. One-Pot Synthesis of Isothiocyanates, Cyanamides and Thiazoles from Dithiocarbamic Acid Salts Using EDPBT

In continuation to our ongoing research work on heterocyclic synthesis using tribromides, we have explored first time thiophophilic/desulfurization property of ditribromide in the preparation of heterocumulenes namely isothiocyanate and cyanamide because of their wide spread applications in medicinal chemistry, and synthetic organic chemistry as discussed above. We have been utilizing tetrabutylammonium tribromide (TBATB) for bromination[30a,b] and for various other organic transformations.[30c-i] Recently we have synthesized a new ditribromide reagent 1,2-dipyridiniumditribromide-ethane or 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) which is superior to all known tribromides and have several advantages over molecular bromine and other tribromides.[31a,b] This reagent has been utilized as catalyst/reagent for acylation of

alcohols,[31c] regioselective enolate addition of 9-phenyl-9H-xanthene-9-ol,[31d,e] synthesis of thiazolidene-2-imines,[31f-h] synthesis of 1,4-dithiins and 1,4-benzodithiins,[31i] construction of 1,3-oxathiolan-2-ylidenes[31j] and urazole to triazonediones.[31k]

In spite of the several methods available in the literature, some of the procedures suffer from extremely arduous reaction conditions, deadly toxic and expensive reagents and high reaction temperatures giving low yields and involving tedious purification procedures. Taking cues from thiophilic/desulfurizing ability of hypervalent iodine[24c,d] and molecular iodine, we envisaged if the same can be achieved with other halogens specially bromine or its equivalent (EDPBT).

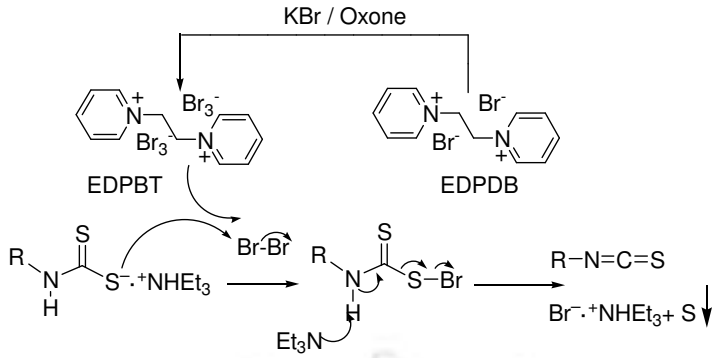
When dithiocarbamate "**1**" (1 mmol.) was treated with EDPBT (0.5 mmol.) in the presence of triethylamine (2 mmol.) in acetonitrile, isothiocyanate **1a** was obtained in nearly quantitative yields (96% after purification) (*Scheme IV.4.1.1.*).



Scheme II.4.1.1. *Preparation of isothiocyanate from the dithiocarbamate salt.*

Triethylamine is sufficiently basic (p*Ka* 10.78) compared to aromatic amines **1–10** (p*Ka* 2.46–5.63) (*Table II.4.1.1*), aliphatic and benzylic amines **11–17** (p*Ka* 9.33–10.77) (*Table II.4.1*) and the acidity of the dithiocarbamates bound NH proton is expected to increase upon salt formation. The proposed reaction mechanism for the formation of isothiocyanate is shown in *Scheme II.4.1.2.* The formation of elemental sulfur supports the proposed mechanism.

In these reactions, the most crucial aspect is the preparation of the dithiocarbamic acid salts,[32] and once the dithiocarbamate salts are obtained, EDPBT proved to be an effective reagent for their decomposition to the desired isothiocyanates in excellent yields.



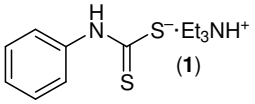
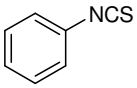
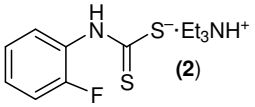
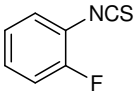
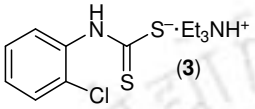
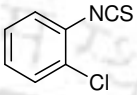
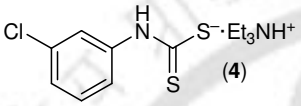
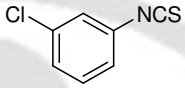
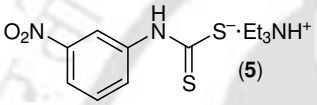
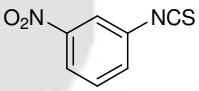
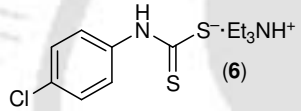
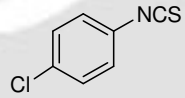
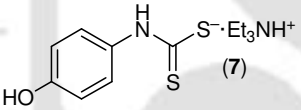
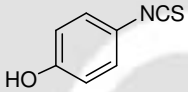
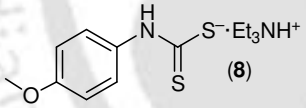
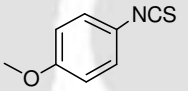
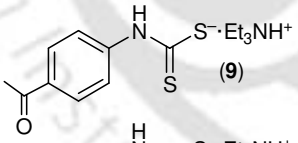
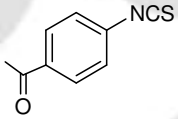
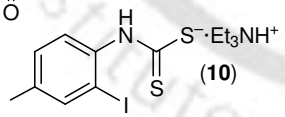
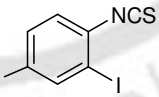
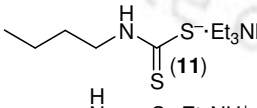
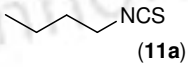
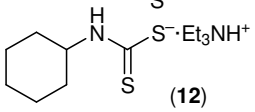
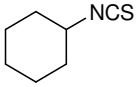
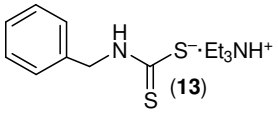
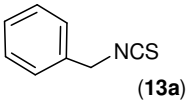
Scheme II.4.1.2. *Proposed reaction mechanism of formation of isothiocyanate.*

The consumed reagent 1,1'-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB) quantitatively precipitated out from the reaction medium (CH_3CN solvent), leaving the products and other byproducts soluble in acetonitrile. Quantitative recovery of the spent reagent can be achieved by filtration. The isolated spent reagent can be recycled by the addition of requisite amount of KBr and Oxone®.[31a,b] The mother liquor containing isothiocyanate was evaporated, admixed with water and desired isothiocyanate was extracted with hexane. Further purification was achieved by passing it through a short column of silica gel.

The scope of this transformation with different substituted aryl dithiocarbamates were evaluated as shown in *Table II.4.1.1.* In general, all the reactions were very clean and the isothiocyanates were obtained in high yields under the optimized reaction conditions.

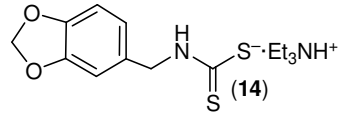
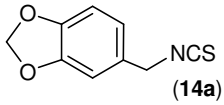
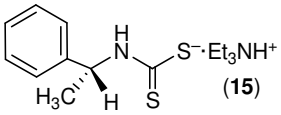
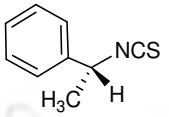
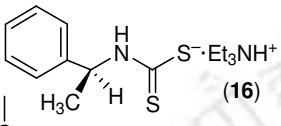
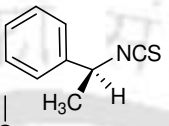
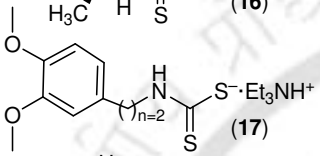
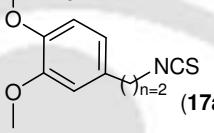
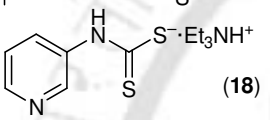
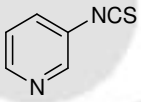
Substrate containing fluoro, chloro (**2–4**) and (**6**) substituents gave their corresponding isothiocyanates **2a–4a** and **6a** respectively, in excellent yields. Deactivating substrate having nitro functionality (**5**) efficiently yielded corresponding isothiocyanate **5a**. Activated substrates **7** and **8** are usually prone to ring bromination with EDPBT.[31a,b] However, in these cases, its thiophilicity seems to be predominating over its brominating ability as demonstrated by the isolation of exclusive isothiocyanates **7a** and **8a** without giving any traces of brominated products. Deactivating substrate having carbonyl functionality (**9**) furnished its isothiocyanate (**9a**) without undergoing α–bromination. Hindered and disubstituted dithiocarbamate (**10**) efficiently gave isothiocyanate (**10a**) in excellent yields. *o*-Iodoisothiocyanates (**10a**) are useful precursors for the construction of various heterocycles.[33]

Table II.4.1.1. *Preparation of isothiocyanates from dithiocarbamates and EDPBT.*[a]

Substrate	Product[b]	Yield (%)[c]
 (**1**)	 (**1a**)	96%
 (**2**)	 (**2a**)	85%
 (**3**)	 (**3a**)	95%
 (**4**)	 (**4a**)	96%
 (**5**)	 (**5a**)	95%
 (**6**)	 (**6a**)	92%
 (**7**)	 (**7a**)	91%
 (**8**)	 (**8a**)	94%
 (**9**)	 (**9a**)	88%
 (**10**)	 (**10a**)	95%
 (**11**)	 (**11a**)	60%
 (**12**)	 (**12a**)	72%
 (**13**)	 (**13a**)	73%

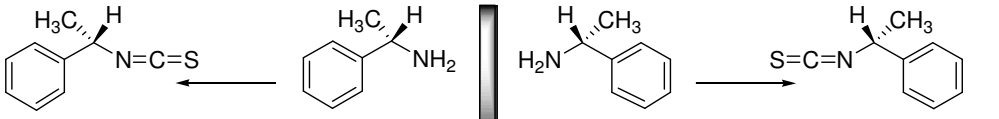
[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR. [c] Isolated yield.

Table II.4.1.1. Continued…

Substrate	Product[b]	Yield (%)[c]
 (**14**)	 (**14a**)	93%
 (**15**)	 (**15a**)	92%
 (**16**)	 (**16a**)	93%
 (**17**)	 (**17a**)	75%
 (**18**)	 (**18a**)	83%

[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR. [c] Isolated yield.

As shown in *Table II.4.1.1*, dithiocarbamates of aliphatic amines (**11** and **12**) and benzylic amines (**13–14**) gave their isothiocyanates in good yields shown in *Table II.4.1.1.* Dithiocarbamate salts derived from chiral amines (**15** and **16**) resulted in their isothiocyanates **15a** and **16a** in excellent yields with retention of optical activity as shown in *Scheme II.4.1.3.* The dextrorotatory R-(+)-α-methylbezylamine (**15**) gave levorotatory R-(-)-α-methylbenzylisothiocyanate (**15a**), where as the levorotatory S-(-)-α-methylbenzylamine (**16**) gave dextrorotatory S-(+)-α-methylbenzylisothiocyanate (**16a**). As expected the specific rotation for R-(-)-α-methylbenzylisothiocyanate (**15a**) is equal and opposite of its enantiomer S-(+)-α-methylbenzylisothiocyanate (**16a**) (*Scheme II.4.1.3.*).



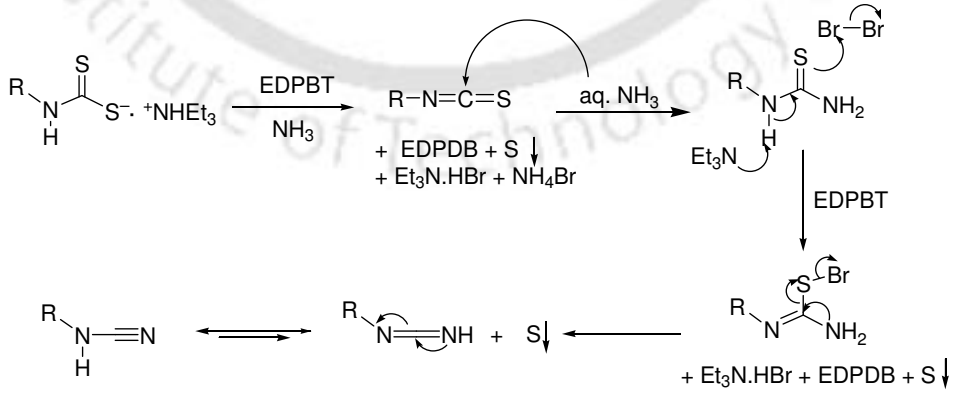
Scheme II.4.1.3. *Specific rotations of chiral amines and their isothiocyanates.*

Isothiocyanate of homoveratrylamine (**17a**) was obtained successfully in good yield from its dithiocarbamate salt (**17**). 4-Pyridyl isothiocyanate was found to be too unstable to be isolate by this method, an observation consistent with others.[33d] However, 3-pyridyl isothiocyanate (**18a**) could be synthesized in excellent yields from its dithiocarbamate salt (**18**).

In summary, for the first time this bromine less brominating reagent has been used as a thiophilic reagent for sustainable preparation of both alky and aryl isothiocyanates from dithiocarbamate salts. The ease of preparation of this reagent, facile isolation of products and recyclability of spent reagent make these methods environmentally acceptable.

Preparation of Cyanamide

After successfully synthesizing various isothiocyanates, we focused our attention on the synthesis of cyanamides in one-pot. Taking cues from the above work, we have reasoned that isothiocyanate can be obtained from dithiocarbamic acid salt and EDPBT in the presence of Et_3N. In this strategy, alkyl/aryl thioureas were prepared directly from dithiocrabamate salts and EDPBT followed by the treatment with aqueous ammonia (*Scheme II.4.1.4.*). The use of aqueous ammonia serves the dual purpose, as a base in the first step to generate isothiocyanate from dithiocarbamate salt, and as a nucleophile to form alkyl/aryl thioureas from the *in situ* generated isothiocyanates



Scheme II.4.1.4. *One-pot preparation of cyanamide from dithiocarbamate.*

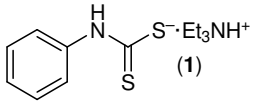
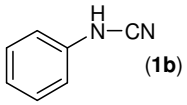
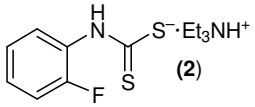
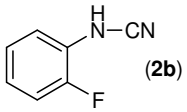
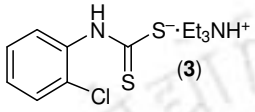
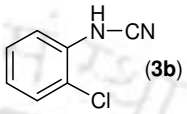
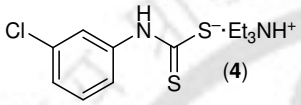
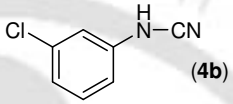
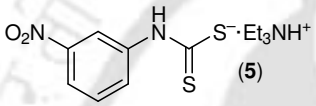
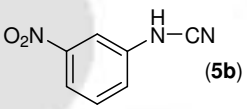
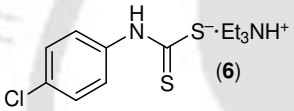
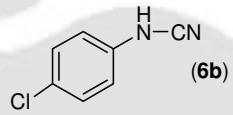
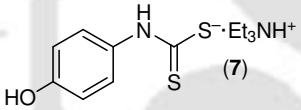
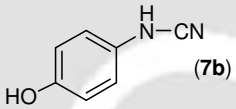
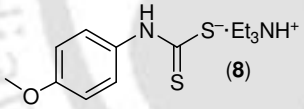
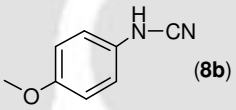
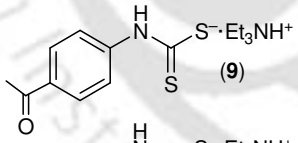
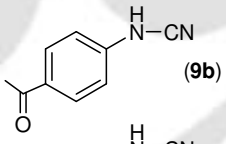
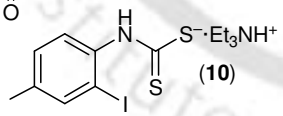
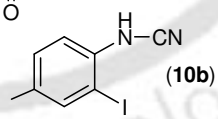
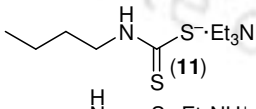
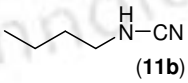
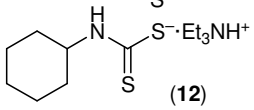
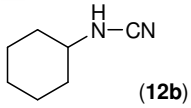
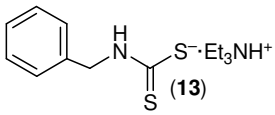
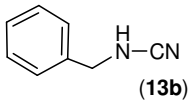
However, when EDPBT was used instead of hypervalent iodine *i.e* diacetoxyiodobenzene (DIB)[27e] ammonia was not that effective as a base in the second step and had to be replaced with a relatively stronger base triethylamine. This may be, in part, due to the lesser thiophilicity of bromine as compared to the DIB. Further, the relative acidity of NH proton of dithiocarbamate salt is higher compared to NH protons of alkyl/aryl thiourea, hence, a stronger base is required for the later.

After completion of the reaction, precipitated spent reagent was filtered and washed with acetonitrile. Acetonitrile was removed and admixed with water (10 mL) and product extracted with ethyl acetate and purified over a short column of silica gel. The aqueous layer containing the spent reagent EDPDB, along with the $Et_3N.HBr$ and NH_4Br, were combined with the precipitated spent reagent obtained by filtration and the EDPBT was regenerated using appropriate amount of KBr and Oxone®.[31a,b]

Employing this one-pot strategy several aromatic cyanamides (**1b–10b**) could be successfully prepared from their dithiocarbamate salts (**1–10**) as shown in *Table II.4.1.2*. As can be seen from *Table II.4.1.2*, this strategy was successful even when an electron withdrawing substituent such as $-NO_2$ group (**5**) was attached to the aromatic ring. Substrates amenable to ring bromination (**7–8**) and α-bromination (**9**) gave their corresponding cyanamides without undergoing bromination. This method also worked well for the preparation of hindered and disubstituted substrate (**10b**) starting from corresponding dithiocarbamate (**10**).

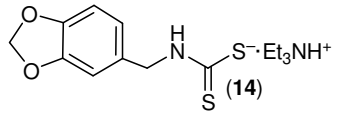
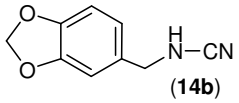
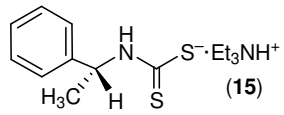
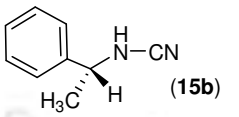
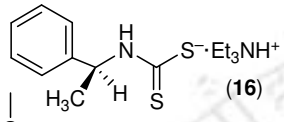
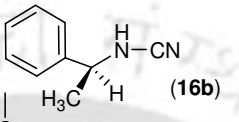
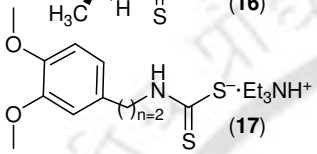
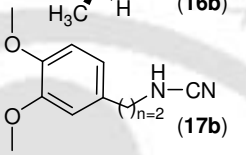
Cyanamides of aliphatic amines (**11** and **12**) and benzylic amines (**13** and **14**) were obtained from their dithiocarbamate salts (*Table II.4.1.2.*) in one-pot. Dithiocarbamate salts derived form chiral amines (**15** and **16**) yielded their cyanamides **15b** and **16b** respectively, in excellent yields with retention of optical activity as shown in *Scheme II.4.1.5*. Surprisingly, the magnitude of the specific rotation of both amines and cyanamides were found to be identical. Finally, cyanamide of homoveratrylamine (**17b**) was obtained successfully in good yield from its dithiocarbamate salt (**17**).

Table II.4.1.2. *Preparation of cyanamides from dithiocarbamates and EDPBT.*[a]

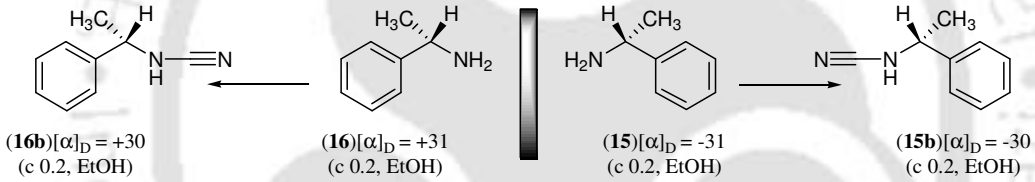
Substrate	Product[b]	Yield (%)[c]
 (**1**)	 (**1b**)	74%
 (**2**)	 (**2b**)	65%
 (**3**)	 (**3b**)	68%
 (**4**)	 (**4b**)	70%
 (**5**)	 (**5b**)	63%
 (**6**)	 (**6b**)	60%
 (**7**)	 (**7b**)	70%
 (**8**)	 (**8b**)	72%
 (**9**)	 (**9b**)	75%
 (**10**)	 (**10b**)	63%
 (**11**)	 (**11b**)	60%
 (**12**)	 (**12b**)	72%
 (**13**)	 (**13b**)	73%

[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR. [c] Isolated yield.

Table II.4.1.2. Continued…

Substrate	Product[b]	Yield (%) [c]
 (**14**)	 (**14b**)	74%
 (**15**)	 (**15b**)	69%
 (**16**)	 (**16b**)	69%
 (**17**)	 (**17b**)	65%

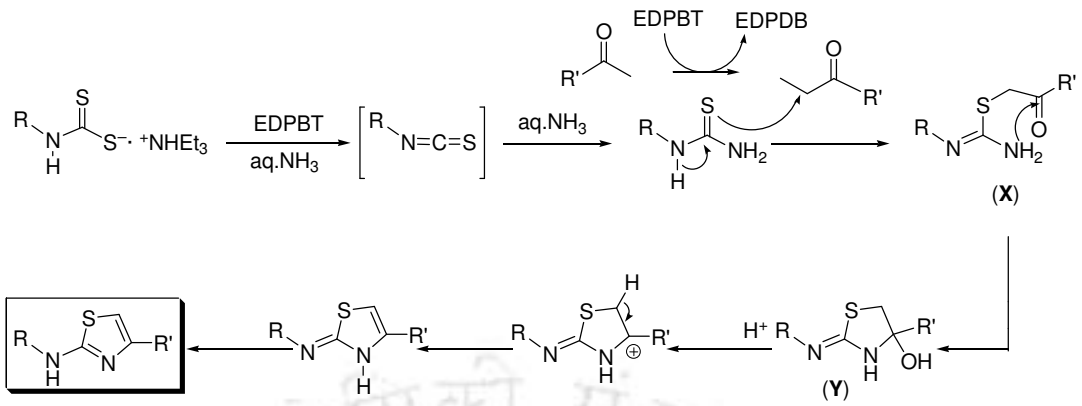
[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR. [c] Isolated yield.



Scheme II.4.1.5. *Specific rotations of chiral amines and their cyanamides.*

After successfully preparing a series of cyanamides we thought of exploiting the *in situ* generated 1-arylthiourea for the construction of substituted thiazoles by treating it with the *in situ* generated α-haloketones. In our strategy, both these precursors can be synthesized from readily available substrates using single recyclable reagent, EDPBT which in turn can be prepared from commercially available starting materials. The reaction at ambient temperature and the use of aqueous medium associated with the one-pot procedure adds to the synthetic potential of this method.

When phenyldithiocarbamate salt (**1**) was treated with EDPBT in the presence of aqueous ammonia, 1-phenylthiourea (**18**) was obtained directly. While EDPBT acts as a desulfurizing agent,[34a] the aqueous ammonia as a base in the formation of the intermediate isothiocyanate and as a nucleophile in the formation of 1-phenylthiourea (*Scheme II.4.1.6.*).



***Scheme II.4.1.6**. Proposed mechanism for the formation of thiazole.*

Since EDPBT used here is 0.5 equivalent (being a ditribromide reagent the bromine content is 1 equivalent) the reaction stops at the thiourea stage and do not lead to cyanamide. In another flask α-bromoketone was prepared using EDPBT according to our recently reported procedure[31h] which was then added to the above flask after getting rid of the excess ammonia. The thiourea being a *S*-based nucleophile particularly towards softer electrophiles attacks on the bromomethyl carbon forming S-alkylated product (**X**). Intramolecular attack of the NH_2 group of the intermediate on the carbonyl group would give the intermediate tertiary alcohol (**Y**) which undergo acid catalyzed E1-elimination in water medium as has been proved by us.[31h] Thus the removal of the excess ammonia is essential in the previous step to facilitate an acid mediated E1 process. Starting from 1-phenyl thiourea (**18**) several thiazoles derivatives (**18a–c**) were prepared successfully as shown in *Table II.4.1.3*. The presence of thiazole skeleton has been confirmed by X-ray crystallography as shown in *Figure II.4.1.1*.

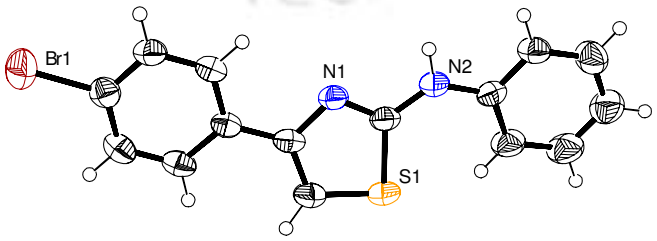
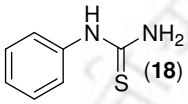
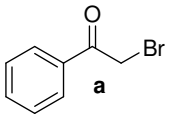
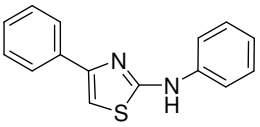
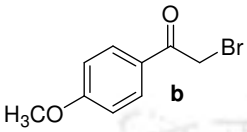
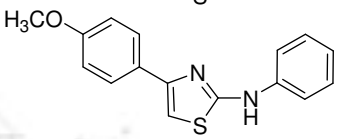
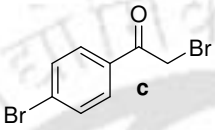
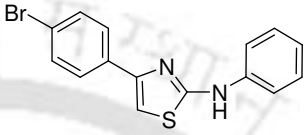
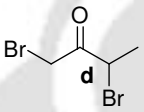
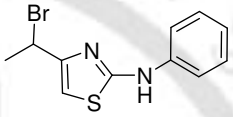
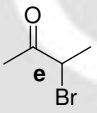
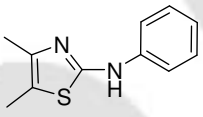
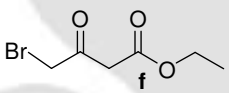
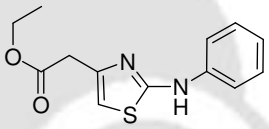
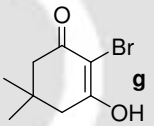
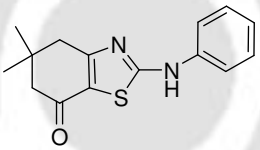
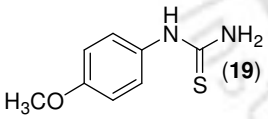
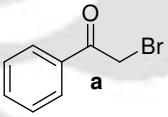
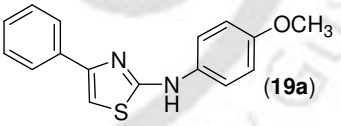
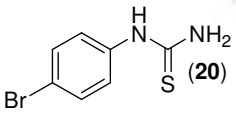
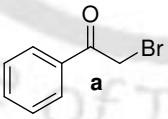
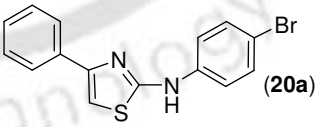


***Figure II.4.1.1.** ORTEP view of **18c** with the atomic numbering scheme.*

Table II.4.1.3. *One-pot preparation of 2-aminothiazoles.*[a]

Substrate	α-Bromoketone	Product[b]	Yield (%)[c]
 (**18**)	 **a**	 (**18a**)	72
	 **b**	 (**18b**)	76
	 **c**	 (**18c**)	73
	 **d**	 (**18d**)	55
	 **e**	 (**18e**)	55
	 **f**	 (**18f**)	60
	 **g**	 (**18g**)	61
 (**19**)	 **a**	 (**19a**)	69
 (**20**)	 **a**	 (**20a**)	65

[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR. [c] Isolated yield.

Unsymmetrical ketones such as ethyl methyl ketone (**d**) gave two different products (**18d** and **18e**) depending on the reaction condition. This is because when bromination is allowed to continue for a longer period of time dibrominated product (**d**) is obtained giving the major thiazole product (**18d**). However kinetically controlled bromination of

ethylmethylketone gave brominated product (**e**) leading to the thiazole (**18e**). Similarly, thermodynamically stable brominated product (**f**)[34b] of ethylacetoacetate gave exclusively thiazole derivative (**18f**). This type of isomerisation or formation of thermodynamic stable brominated product is well documented in the literature.[34b] Cyclic diketone gave exclusively brominated product flanked by two carbonyl group *i.e.* kinetically stable product and exist in the enol form,[34c] which led to the formation of product (**18g**). Other *in situ* generated thioureas such as (**19**) and (**20**) reacted with phenacyl bromide (**a**) giving thiazole derivatives (**19a**) and (**20a**) respectively in modest yield. The presence of thiazole skeleton and the structure of (**20a**) have been further confirmed by X-ray crystallography as shown in *Figure II.4.1.2.*

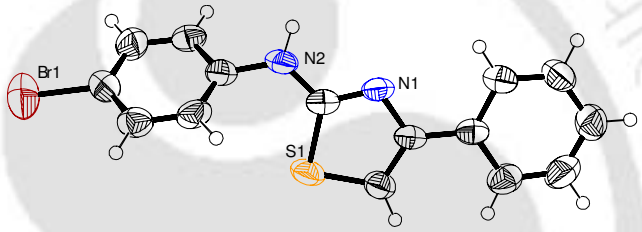


Figure II.4.1.2. *ORTEP view of* ***20a*** *with the atomic numbering scheme.*

In summary, EDPBT has been used as a thiophilic reagent for the preparation of alkyl and aryl cyanamides from their dithiocarbamates in one-pot. Subsequently, 2-amino thiazoles were synthesized by the condensation of the *in situ* generated bromoketones and thioureas from their dithiocarbamates. Although at a first glance the product yields seem to be moderate but the fact that these are actually three step reactions in one-pot hence the yield can be considered as very good.

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.

Chromatography was performed using Merck silica gel (60–120) mesh size with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Reaction progress was monitored by TLC using Merck silica gel 60 F_{254} (0.25 mm) with detection by UV or iodine.

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 flow gas. Gas-liquid chromatography was performed using a cross-linked methyl silicon gum capillary column (30 m x 0.32 mm x 0.25 µm) fitted with a FID. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian FT-400 MHz instrument using TMS as an internal standard. Data are presented as follows: chemical shift (ppm), multiplicity [s = singlet, d = doublet, t = triplet, m = multiplet, b = broad, br s = broad singlet, br *m* = broad multiplet, coupling constant *J* (Hz)]. Mass data were obtained with a WATERS MS system, Q-tof premier and data analyzed using Mass Lynx4.1. 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 Procedures

II.5.2.1. Preparation of Phenyl Isothiocyanate (1a) from Dithiocarbamate Salt (1)

To a stirred suspension of dithiocarbamate salt **1** (0.542g, 2 mmol) in acetonitrile (8 mL) containing triethylamine (0.556 µL, 4 mmol) was added EDPBT (0.666g, 1 mmol) pinch wise over a period of 10 min under ice cold condition. After completion of the reaction, as judged from TLC, the reaction mixture was allowed to stand and the precipitated spent reagent was filtered, washed with acetonitrile (2 x 1 mL) and kept aside for recycling. Acetonitrile was evaporated and admixed with water (10 mL) and the product extracted with hexane (2 x 10 mL). The hexane layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a short column of silica gel (100 % hexane) to give 96% of the product **1a**.

II.5.2.2. Preparation of Phenyl Cyanamide (1b) from Dithiocarbamate Salt (1)

Ice cooled aqueous ammonia (25%, 2 mL) was added to a stirred and ice cold solution of dithiocarbamate salt **1** (0.542g, 2 mmol) in acetonitrile (8 mL). To this was then added EDPBT (0.666g, 1 mmol) pinch wise over a period of 10 min. The reaction mixture was stirred at room temperature for 30-40 min and complete conversion to corresponding 1-phenyl thiourea was observed as judged from TLC. Excess amount of ammonia was removed by heating the reaction mixture on a hot water bath (60 ^oC) for 10 min. To this was added triethylamine (1.1 mL, 8 mmol) followed by pinch wise addition of EDPBT (0.666g, 1 mmol) at room temperature over a period of 10 min. The conversion of intermediate 1-phenylthiourea to corresponding cyanamide (**1b**) was observed within 10 min of complete addition of EDPBT. After completion of the reaction, some of the spent reagent was filtered washed with acetonitrile. Acetonitrile was evaporated, admixed with water (10 mL) and the product was extracted with ethyl acetate (2 x 10 mL) which was then dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a short column of silica gel (hexane : ethyl acetate, 8:2) to give 74% of the product **1b**.

II.5.2.3. Preparation of Thiazole (18a) from Dithiocarbamate Salt (1)

Ice cooled aqueous ammonia (25 %, 2 mL) was added to a stirred and an ice cold suspension of dithiocarbamate **1** (540 mg, 2 mmol) in water (6 mL), was added EDPBT (666 mg, 1 mmol) in CH_3CN (4 mL) drop wise over a period of 15 min. After complete addition of EDPBT, reaction mixture was allowed to stir at room temperature for 30–40

min and complete conversion to corresponding 1-phenyl thiourea was observed as judged from TLC. Excess amount of ammonia was removed by rotary a rotary evaporator during which CH_3CN also gets evaporated, leaving behind some aqueous layer.

To a solution of 1,1-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (666 mg, 1 mmol) in acetonitrile (4 mL) was added acetophenone (0.264 g, 2.2 mmol) and stirring continued for 45 mins. During this period, the bromination of acetophenone (**a**) was complete as judged from the disappearance of the orange color of EDPBT. The supernatant containing the bromoketone was then directly filtered into a solution of the *in situ* generated 1-phenyl thiourea **1** in water (obtained above) and kept stirring at room temperature. The reaction was completed within 1 h as can be judged from TLC. After completion of the reaction, solvent (CH_3CN) was evaporated and extracted with ethyl acetate (2 x 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 (hexane:EtOAc, 9:1) to give 74% of the product **18a**.

II.6. References

1. For a general review on isothiocyanates and thioureas see: The chemistry of cyanates and their thioderivatives; Patai, S., Ed.; Wiley: Chi chester, 1977; Applications of isothiocyanates as useful intermediates in bioconjugate chemistry, see for example, Fernaandez, J. M. G.; Mellet, C. O.; Blanco, J. L. J.; Mota, J. F.; Gadelle, A.; Coste-Sarguet, A.; Defaye, J. *Carbohydr. Res*. **1995**, *268*, 57.
2. (a) Xiao, D.; Powolny, A. A; Singh, S. V. *J. Biol. Chem.* **2008**, *283*, 30151; (b) Cuddihy, S. L.; Brown, K. K.; Thomson, S. J.; Hampton, M. B. *Cancer Lett.* **2008**, *271*, 215; (c) Wang, L. G.; Liu, X. M.; Fang, Y.; Dai, W.; Chiao, F. B.; Puccio, G. M.; Feng, J.; Liu, D.; Chiao, J. W. *Int. J. Oncol.* **2008**, *33*, 375; (d) Stoner, G. D.; Dombkowski, A. A.; Reen, R. K.; Cukovic, D.; Salagrama, S.; Wang, L.-S.; Lechner, J. F. *Cancer Res.* **2008**, *68*, 6460; (e) Bones, A. M.; Rossiter, J. T. *Physiol. Plant.* **1996**, *97*, 194; (f) Zhang, Y.; Tang, L.; Gonzalez, V. *Mol. Cancer Ther.* **2003**, *2*, 1045; (g) Xiao, D.; Vogel, V.; Singh, S. V. *Mol. Cancer Ther.* **2006**, *5*, 2931.
3. (a) Xu, K.; Thornalley, P. J. *Biochem. Pharmacol.* **2000**, *60*, 221; (b) Mukherjee, A. K.; *Chem. Rev.* **1991**, *91*, 1; (c) Stephensen, H.; Zaragosa, F. *J. Org. Chem.* **1997**, *62*, 6096; (d) Al-Hourani; B. J.; Banert, K.; Gomaa, N.; Vrobel, K. *Tetrahedron* **2008**, *64*, 5590; (e) Fajkusova, D.; Pazdera, P. *Synthesis* **2008**, 1297; (f) Wu, Y.-J.; Zhang, Y. *Tetrahedron Lett.* **2008**, *49*,

2869; (g) Thiel, O. R.; Bernard, C.; King, T.; Dilmeghani-Serna, M.; Bostick, T.; Larson, R. D.; Faul, M. M. *J. Org. Chem.* **2008**, *73*, 3508.

4. (a) Heckl, S.; Sturzu, A.; Regenbogen, M.; Beck, A.; Feil, G.; Gharabaghi, A.; Echner, H. A. *Med. Chem.* **2008**, *4*, 348; (b) Meng, F.; Manjula, B. N.; Smith, P. K.; Acharya, S. A. *Bioconjug. Chem.* **2008**, *19*, 1352; (c) Ladden, M. J. W.; Ling, X. Y.; Gang, T.; Bula, W. P.; Gardeniers, H. J. G. E.; Reinhoudt, D. N.; Huskens, J. *Chem. Eur. J.* **2008**, *14,* 136; (d) Vishwanath, V. A.; Nclntosh, J. M. *Bioconjug. Chem.* **2006**, *17*, 1612.
5. (a) Guo, X.; Meyerhoff, M. E. *Appl. Biochem. Biotech.* **1997**, *68*, 41; (b) Lerchen, H.-G.; Baumgarten, J.; Piel, N.; Kolb-Bachofen, V. *Angew Chem. Int. Edn.* **1999**, *38*, 3680; (c) Laulia, P.; Chan-park, M. B.; Yan, Y.; Wang, S. Q.; Li, C. M.; Lam, Y. C. *Small* **2008**, *4*, 69; (d) Dong, S.; Roman, M. *J. Am. Chem. Soc.* **2007**, *129*, 13810; (e) Schubert, W.; Bonnekoh, B.; Pommer, A. J.; Philipsen, L.; Boeckelmann, R.; Malykh, Y.; Gollnick, H.; Friedenberger, M.; Bode, M.; Dress, A. W. M. *Nat. Biotechnol.* **2006**, *24*, 1270.
6. (a) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*, Vol 3; Academic: New York, 1972, 286; (b) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*, Vol 2; Academic: New York, 1972, 174; (c) Nickon, A.; Fieser, L. F. *J. Am. Chem. Soc.* **1952**, *74*, 5566; (d) Jia, Q.; Cai, T.; Haung, M.; Li, H.; Xian, M.; Poulos, T. L.; Wang, P. G. *J. Med. Chem.* **2003**, *46*, 2271; (e) Cai, T.; Xian, M.; Wang, P. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1507; (f) Kumar, L. V.; Kaushik, M. P.; Mazumdar, A. *Eur. J. Org. Chem.* **2008**, 1910; (g) Saneyoshi, M.; Tokuzen, R.; Maeda, M.; Fukuoka, F. *Chem. Pharm. Bull.* **1968**, *16*, 505; (h) Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad, F. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th Ed.; Pergmon Press: New York, 1990, 899; (i) La Mattina, J. L. *J. Heterocycl. Chem.* **1983**, *20*, 533; (j) Stephens, R. W.; Domeier, L. A.; Todd, M. G.; Nelson, V. A. *Tetrahedron Lett.* **1992**, *33*, 733.
7. (a) Donetti, A.; Omodei-Sale, A.; Mantegani, A. *Tetrahedron Lett.* **1969**, *39*, 3327; (b) Pala, G.; Mantegani, A.; Zugna, E. *Tetrahedron* **1970**, *26*, 1275; (c) Currie, A. C.; Newbold, G. T.; Spring, F. S. *J. Chem. Soc.* **1961**, 4693.
8. (a) McCall, J. M.; Tenbrink, R. E.; Ursprung, J. J. *J. Org. Chem.* **1975**, *40*, 3304; (b) Hu, L. Y.; Guo, J.; Magar, S. S; Fischer, J. B.; Burke-Howie, K. J.; Durant, G. J. *J. Med. Chem.* **1997**, *40*, 4281; (c) Robinson, J. R.; Brown, W. H. *Can. J. Chem.* **1951**, *29*, 1069.
9. Hargrave, K. D.; Hess, F. K. *J. Med. Chem*. **1983**, *26*, 1158.
10. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. *J. Med. Chem.* **1992**, *35*, 2562.

11. (a) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719; (b) Clemence, F.; Le Martret, O.; Delevallee, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Deraedt, R. *J. Med. Chem.* **1988**, *31*, 1453.
12. Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem*. **1990**, *33*, 311.
13. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 1601.
14. Bell, F. W.; Cantrell, A. S.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M.; Noreen, R.; Öberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.X. *J. Med. Chem*. **1995**, *38*, 4929.
15. (a) Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. *Chem. Biol*. **1999**, *6*, 205; (b) van Muijlwijk-Koezen, J. E.; Timmerman, H.; Vollinga, R. C.; von Drabbe Kunzel, F. J.; de Groote, M.; Visser, S.; Ijzerman, A. P. *J. Med. Chem*. **2001**, *44*, 749; (c) Nettekoven, M.; Guba, W.; Neidhart, W.; Mattei, P.; Pflieger, P.; Plancher, J.; Taylor, S. *Chem Med Chem* **2006**, *1,* 45.
16. (a) Muhkerjee, A. K.; Ashare, R. *Chem. Rev*. **1991**, *91*, 1; (b) Stephensen, H.; Zaragosa, F. *J. Org. Chem.* **1997**, *62*, 6096; (c) Al-Hourani, B. J.; Banert, K.; Gomaa, N.; Vrobel, K. *Tetrahedron* **2008**, *64*, 5590; (d) Fajkusova, D.; Pazdera, P. *Synthesis* **2008**, 1297; (e) Wu, Y.-J.; Zhang, Y. *Tetrahedron Lett.* **2008**, *49*, 2869; (f) Thiel, O. R.; Bernard, C.; King, T.; Dilmeghani-Serna, M.; Bostick, T.; Larson, R. D.; Faul, M. M. *J. Org. Chem.* **2008**, *73*, 3508.
17. (a) Edman, P. *Arch. Biochem.* **1949**, *22*, 475; (b) Cabantchik, Z. I.; Rothstein, A. *J. Membr. Biol*. **1974**, *15*, 227; (c) Podhradsky, D.; Oravec, P.; Antalik, M.; Kristian, P. *Collect. Czech. Chem. Commun*. **1994**, *59*, 213; (d) Gavrilyuk, J. I.; Lough, A. J.; Batey, R. A. *Tetrahedron Lett*. **2008**, *49*, 4746.
18. (a) Xue, J.; Yang, Y.; Huang, X. *Synlett* **2007**, 1533; (b) Wolfe, D. M.; Schreiner, P. R. *Synthesis* **2007**, 2002; (c) Liu, C.; Lin, J.; Leftheris, K. *Tetrahedron Lett*. **2007**, *48*, 435; (d) Nasim, S.; Crooks, P. A. *Tetrahedron Lett*. **2009**, *50*, 257; (e) Ghosh, H. *Synlett* **2009**, 2882.
19. (a) Hari, A.; Miller, B. L. *Org. Lett*. **2002**, *2*, 3667; (b) Li, Z.; Huang, H.; Sun, H.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2008**, *10,* 484; (c) Dou, G.; Wang, M.; Shi, D. *J. Comb. Chem.* **2009**, *11,* 151; (d) Ding, Q.; Cao, B.; Zong, Z.; Peng, Y. *J. Comb. Chem.* **2010**, *12*, 370; (e) Ding, Q.; He, X.; Wu, J. *J. Comb. Chem.* **2009**, *11,* 587; (f) Wu, J.-Y.; Luo, Z.-B.; Dai, L.-X.; Hou, X.-L. *J. Org. Chem.* **2008**, *73*, 9137; (g) Comas, H.; Bernardinelli, G.; Swinnen, D. *J. Org. Chem.* **2009**, *74*, 5553; (h) Bourdais, J.; Omar, A.-M. M. E. *J. Heterocyclic. Chem.* **1980**, *17*, 555.

20. (a) Ghosh, H.; Yella, R.; Nath, J.; Patel, B. K. *Eur. J. Org. Chem.* **2008**, 6189; (b) Murru, S.; Mandal, P.; Yella, R.; Patel, B. K. *Eur. J. Org. Chem.* **2009**, 5406; (c) Palsuledesai, C.; Murru, S.; Sahoo, S. K.; Patel, B .K. *Org. Lett.* **2009**, *11*, 3382.

21. (a) Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. *Tetrahedron* **2009**, *65*, 10715; (b) Habibi, D.; Nasrollahzadeh, M.; Faragi, A. R.; Bayat, Y. *Tetrahedron* **2010**, *66*, 3866; (c) Renodon-Corniere, A.; Dijols, S.; Perollier, C.; Lefevre-Groboillot, D.; Boucher, J-L.; Attias, R.; Sari, M-A.; Stuehr, D.; Mansuy, D. *J. Med. Chem.* **2002**, *45*, 944; (d) Kumar, V.; Kaushik, M. P.; Mazumdar, A. *Eur. J. Org. Chem.* **2008**, 1910; (e) Khorasani-Motlagh, M.; Safari, N.; Noroozifar, M.; Shahroosvand, H.; Patrick B. O. *Inorg. Chim. Acta.* **2009**, *362*, 1260; (f) Hadadzadeh, H.; Rezvani, A. R.; Belanger-Gariepy, F. *J. Mol. Struct.* **2005**, *740*, 165; (g) Safari, N.; Notash, B.; Nezhad, J. M.; Chiniforoshan, H.; Hadadzadeh, H.; Rezvani, A. R. *Inorg. Chim. Acta* **2005**, *358*, 2967; (h) Rezvani, A. R.; Hadadzadeh, H.; Patrick, B. *Inorg. Chim. Acta* **2002**, *336*, 125.

22. (a) Dyer, E.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54*, 777; (b) Sharma, S. *Sulfur Reports* **1989**, *8*, 327; (c) Sayigh, A. A**.** R.; Ulrich, H.; Potts, J. S. *J. Org. Chem.* **1965**, *30,* 2465; (d) Marquardt, F. M. *Helv. Chim. Acta* **1966**, *49*, 1716; (e) Kim, S.; Yi, K. Y. *Tetrahedron Lett.* **1985**, *26*, 1661; (f) Kim, S.; Yi, K. Y. *Bull. Korean Chem. Soc.* **1987**, *8*, 446; (g) Chang, H.; Kim, S. *Bull. Korean Chem. Soc.* **1986**, *7*, 407; (h) *Chem. Abstr.* **1987**, *107*, 58940a; (i) Kim, S.; Yi, K. Y. *J. Org. Chem.* **1986**, *51*, 2613; (j) Gottfried, R. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 963; (k) Larsen, C.; Stelliou, K.; Harpp, D. N. *J. Org. Chem.* **1978**, *43*, 337; (l) Larsen, C.; Harpp, D. N. *J. Org. Chem.* **1981**, *46*, 2465; (m) Kim, S.; Yi, K. Y. *Tetrahedron Lett.* **1985**, *26*, 1661.

23. (a) Boas, U.; Jakobsen, M. H. *J. Chem. Soc.* **1995**, 1995; (b) Boas, U.; Pedersen, B.; Christensen, J. B. *Synth. Commun.* **1998**, *28*, 1223; (c) Boas, U.; Pedersen, H. G.; Christensen, J. B.; Heegaard, P. M. H. *Tetrahedron Lett.* **2004**, *45*, 269; (d) Molina, P.; Alajarin, N.; Tamiaki, H. *Synthesis* **1982**, 596; (e) Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72*, 3969; (f) Munch, H.; Hansen, J. S.; Pittelkow, M.; Christensen, J. B.; Boas, U. *Tetrahedron Lett.* **2008**, *49*, 3117; (g) Li, G.; Tajima, H.; Ohtani, T. *J. Org. Chem.* **1997**, *62*, 4539; (h) Hodgkins, J. E.; Reeves, W. P. *J. Org. Chem.* **1964**, *29*, 3098; (i) Bian, G.; Shan, W.; Su, W. *J. Chem. Res.* **2005**, 585; (j) Mesheram, H. M.; Dale, S.; Yadav, J. S. *Tetrahedron Lett.* **1997**, *38*, 8743; (k) Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 573.

24. (a) Kim, J. N.; Jung, K. S.; Lee, J. H.; Son, J. S. *Tetrahedron Lett.* **1997**, *38*, 1597; (b) Vogel, A. I.; Tatchell, A. R.; Furnis, B. S.; Hannaford, A. J.; Smith, P. W. G. *Vogel's Textbook of Practical Organic Chemistry*; Pearson: Prentice Hall, **2005**, 5th Ed., 966; (c) Ghosh, H.; Yella,

R.; Nath, J.; Patel, B. K. *Eur. J. Org. Chem.* **2008**, 6189; (d) Nath, J.; Ghosh, H.; Yella, R.; Patel B. K. *Eur. J. Org. Chem.* **2009**, 1849; (e) Jamir, L.; Ali, A. R.; Ghosh, H.; Chipem, F. A. S.; Patel, B. K. *Org. Biomol. Chem*. **2010**, *8*, 1674.

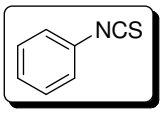
25. (a) Van Barun, J. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 1468; (b) Kaupp, G.; Schmeyers, J.; Boy, J. *Chem. Eur. J.* **1998**, *4*, 2467; (b) Wheland, R. C.; Martin, E. L. *J. Org. Chem.* **1975**, *40*, 3101; (c) Wu, Y.-Q.; Limburg, D. C.; Wilkinson, D. E.; Hamilton, G. S. *Org. Lett.* **2000**, *2*, 795; (d) Kim, J.-J.; Kweon, D.-H.; Cho, S.-D.; Kim, H.-K.; Jung, E.-Y.; Lee, S.-G.; Falck, J. R.; Yoon, Y.-J. *Tetrahedron* **2005**, *61*, 5889; (e) Hughes, T. V.; Hammond, S. D.; Cava, M. P. *J. Org. Chem.* **1998**, *63*, 401; (f) Davis, W. A.; Cava, M. P. *J. Org. Chem.* **1983**, *48*, 2774; (g) Kahne, D.; Collum, D. *Tetrahedron Lett.* **1981**, *22*, 5011; (h) Boltz, K. H.; Dell, H. D. *Justus Liebigs Ann. Chem.* **1967**, *709*, 63; (i) Hermes, M. E.; Marsh, F. D. *J. Org. Chem.* **1972**, *37*, 2969.
26. (a) Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 879; (b) Crank, G.; Makin, M. I. H. *J. Chem. Soc., Chem. Commun.* **1984**, 53; (c) Brand, H.; Mayer, P.; Schulz, A.; Soller, T.; Villinger, A. *Chem-Asian J.* **2008**, *3*, 1050; (d) Sarale, T.; Ishlguro, T.; Kawashima, K.; Morita, K. *Tetrahedron Lett.* **1973**, *23*, 2121; (e) Mai, K.; Patil, G. *Synth. Commun.* **1986**, *16*, 1823; (f) Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. *Synthesis* **2000**, 1148.
27. (a) Kamijo, S.; Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1780; (b) Wong, F. F.; Chen, C-Y.; Yeh, M-Y. *Synlett* **2006**, 559; (c) Chen, C-Y.; Wong, F. F.; Huang, J-J.; Lin, S-K.; Yeh, M-Y. *Tetrahedron Lett.* **2008**, *49*, 6505; (d) Chaudhuri, K. H.; Mahajan, U. S.; Bhalerao, D. S.; Akamanchi, K. G. *Synlett* **2007**, 2815; (e) Ghosh, H.; Yella, R.; Sahoo, S. K.; Patel B. K. *Tetrahedron Lett.* **2009**, 50, 2407; (f) Nath, J.; Patel, B. K.; Jamir, L.; Bora Sinha, U.; Satyanarayana, K. V. V. V. *Green Chem* **2009**, *11*, 1503.
28. (a) Hantzsch, A.; Weber, J. H. *Ber*. **1887**, *20*, 3118; (b) Traumann, V. *Liebigs Ann. Chem.* **1888**, 31; (b) Zhu, D.; Chen, J.; Xiao, H.; Liu, M.; Ding, J.; Wu, H. *Synth. Commun*. **2009**, *39*, 2895; (c) Kidwai, M.; Bhatnagar, D.; Mothsra, P.; Singh, A. K.; Dey, S. *J. Sulfur Chem*. **2009**, *30*, 29; (d) Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V. *Tetrahedron* **2008**, *64*, 5019; (e) Lin, P-Y.; Hou, R-S; Wang, H-M; Kang, I-J.; Chen, L-C. *J. Chin. Chem. Soc-TAIP*. **2009**, *56*, 455.
29. (a) Suzuki, T.; Igari, S.; Hirasawa, A.; Hata, M.; Ishiguro, M.; Fujieda, H.; Itoh, Y.; Hirano, T.; Nakagawa, H.; Ogura, M.; Makishima, M.; Tsujimoto, G.; Miyata, N. *J. Med. Chem.* **2008**, *51*, 7640; (b) Andersen, C. B.; Wan, Y.; Chang, J. W.; Riggs, B.; Lee, C.; Liu, Y; Sessa, F.; Villa, F.; Kwiatkowski, N.; Suzuki, M.; Nallan, L.; Heald, R.; Musacchio, A.; Gray, N. S. *ACS Chem. Biol.* **2008**, *3*, 180; (c) Jawale, D. V.; Lingampalle, D. L.; Pratap, U. R.; Mane, R. A. *Chinese Chem. Lett.* **2010**, *21*, 412; (d) Liebscher, J.; Mitzner, E. Sekt. *Tetrahedron Lett*. **1985**, *26*,

1835; (e) Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, 36, 6084; (f) Dey, P. D.; Sharma, A. K.; Jayakumar, S.; Mahajan, M. P. *Indian J. Chem. B*: **2002**, *41B*, 1286.

30. (a) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163; (b) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247; (c) Roy, R. K.; Bagaria, P.; Naik, S.; Kavala, V.; Patel, B. K. *J. Phys. Chem. A.* **2006**, *110*, 2181; (d) Roy, R. K.; Usha, V.; Patel, B. K.; Hairo, K. *J. Comp. Chem.* **2006**, 773; (e) Kavala, V.; Patel, B. K. *Eur. J. Org. Chem.* **2005**, 441; (f) Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. *Arkivoc* **2006**, 119; (g) Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. *Org. Biomol. Chem.* **2004**, 1670; (f) Gopinath, R.; Haque, Sk. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842; (h) Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, *42*, 7679; (i) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177.
31. (a) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267; (b) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 6556; (c) Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. *Arkivoc* **2006**, *11*, 21; (d) Kavala, V.; Murru, S.; Das, G.; Patel, B. K. *Tetrahedron* **2008**, *64*, 3960; (e) Kavala, V.; Murru, S.; Patel, B. K.; Das, G. *J. Chem. Crystallogr.* **2007**, *37*, 527; (f) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397; (g) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *J. Chem. Res.* **2007**, 136; (h) Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. *Tetrahedron* **2008**, *64*, 1931; (i) Murru, S.; Kavala, V.; Singh, C. B.; Patel, B. K. *Tetrahedron Lett.* **2007**, *48*, 1007; (j) Ghosh, H.; Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Tetrahedron Lett.* **2008**, *49*, 2602; (k) Zolfigol, M. A.; Chehardoli, G.; Ghaemi, E.; Madrakian, E.; Zare, R.; Azadbakht, T.; Niknam, K.; Mallakpour, S. *Monatsh. Chem.* **2008**, *139*, 261.
32. (a) Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72*, 3969; (b) Li, G.; Tajima, H.; Ohtani, T. *J. Org. Chem.* **1997**, *62*, 4539; (c) Emami, S.; Foroumadi, A. *Chinese J. Chem.* **2006**, *24*, 791; (d) Sattigeri, V. J.; Soni, A.; Singhal, S.; Khan, S.; Pandya, M.; Bhteja, P.; Mathur, T.; Rattan, A.; Khanna, J. M.; Mehta, A. *Arkivoc* **2005**, *ii*, 46.
33. (a) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802; (b) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133; (c) Murru, S.; Patel, B. K.; Bras, J. L.; Muzart, J. *J. Org. Chem.* **2009**, *74*, 2217; (d) Le Count, D. J.; Dewsbury, D. J.; Grundy, W. *Synthesis* **1977**, 582.
34. (a) Yella, R.; Ghosh, H.; Murru, S.; Sahoo, S. K.; Patek. B. K. *Synth. Commun.* **2010**, *40*, 2083; (b) Choi, H. Y.; Chi, D. Y. *Org. Lett.* **2003**, *5*, 411; (c) Khan, A. T.; Parvin, T.; Choudhury, L. H. *J. Org. Chem.* **2008**, *73*, 8398.

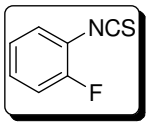
II.7. Spectral Data

1-Isothiocyanatobenzene (1a):



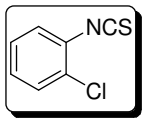
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.8, 127.4, 129.6, 131.3, 135.3. IR (KBr): 3064, 2164, 2063, 1591, 1489, 1474, 1451, 1070, 927, 905, 749, 684 cm^{-1}.

1-Fluoro-2-isothiocyanatobenzene (2a):



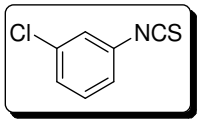
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08–7.26 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.5 (d, *J* = 19.1 Hz, 1C), 124.8 (d, *J* = 3.8 Hz, 1C), 126.5, 128.5 (d, *J* = 6.8 Hz, 1C), 140.9, 157.3, 159.9. IR (KBr): 3407, 3069, 2927, 2104, 2036, 1587, 1496, 1458, 1265, 1212, 1104, 941, 808, 752 cm^{-1}.

1-Chloro-2-isothiocyanatobenzene (3a):



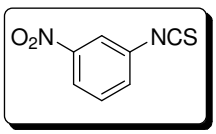
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 3H), 7.39 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.9, 126.4, 126.6, 127.6, 128.0, 130.1, 131.7. IR (KBr): 3066.4, 2562, 2126, 2053, 1582, 1472, 1442, 1068, 937, 750, 723, 660 cm^{-1}.

1-Chloro-3-isothiocyanatobenzene (4a):



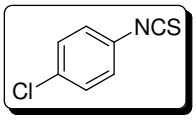
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09–7.12 (m, 1H), 7.21–7.28 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.8, 125.7, 127.4, 130.3, 132.4, 134.9, 137.5. IR (KBr): 3060, 2560, 2230, 2197, 2071, 1931, 1585, 1572, 1470, 1423, 1070, 1089, 960, 864, 776, 751, 672, 532 cm^{-1}.

1- Isothiocyanato 3- nitrobenzene (5a):



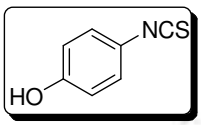
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 2H), 8.06 (s, 1H), 8.11–8.14 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.7, 121.9, 130.6, 131.6, 133.3, 139.6, 148.8. IR (KBr): 3091, 3074, 2227, 2161, 2106, 1526, 1470, 1348, 1302, 892, 809, 736, 665 cm^{-1}.

1-Chloro-4-isothiocyanatobenzene (6a):



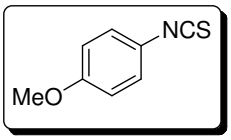
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.0, 129.8, 130.0, 133.0, 136.8. IR (KBr): 3082, 2928, 2175, 2126, 2086, 1482, 1089, 928, 824, 495 cm^{-1}.

1-Isothiocyanato-4-hydroxybenzene (7a):



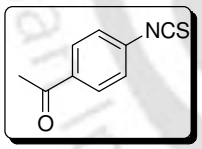
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.05 (br s, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.5, 123.8, 127.4, 133.7, 154.6. IR (KBr): 3373, 2923, 2117, 1607, 1504, 1352, 1269, 1094, 831 cm^{-1}.

1-Isothiocyanato-4-methoxybenzene (8a):



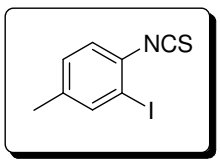
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 114.6, 123.2, 126.8, 133.7, 158.4. IR (KBr): 3000, 2956, 2835, 2170, 2098, 1580, 1599, 1503, 1459, 1440, 1292, 1251, 1179, 1166, 1028, 927, 824, 614, 513 cm^{-1}.

1-(4-Isothiocyanato-phenyl)ethanone (9a):



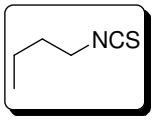
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 126.0, 129.9, 135.5, 135.8, 138.0, 196.6. IR (KBr): 3070, 2925, 2190, 2124, 1682, 1589, 1409, 1354, 1254, 1107, 961, 927, 843 cm^{-1}. C_9H_7NOS (177.22): calcd C 61.00, H 3.98, N 7.90, S 18.09; found C 61.12, H 4.07, N 7.84, S 17.98. MS (ESI): 177 [M^+].

2-Iodo-1-isothiocyanato-4-methylbenzene (10a):



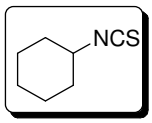
M.p. 62–65 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 7.13 (m, 2H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 94.2, 126.7, 130.1, 132.3, 136.1, 139.1, 139.9. IR (KBr): 2916, 2134, 1633, 1474, 1042, 929, 811 cm^{-1}. C_8H_6INS (275.11): calcd. C 34.92, H 2.20, N 5.09, S 11.65; found C 35.02, H 2.29, N 4.98, S 11.59. MS (ESI): 275 [M^+].

1-Isothiocyanatobutane (11a):



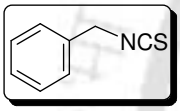
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.47–1.37 (m, 2H), 1.69-1.61 (m, 2H), 3.42 (t, *J* = 6.6 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 19.7, 31.9, 44.7, 129.4. IR (KBr): 2925, 2087 1597, 1401, 1218.1, 116, 753 cm^{-1}.

Isothiocyanatocyclohexane (12a):



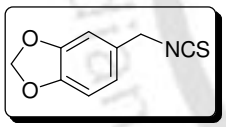
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28–1.96 (m, 10H), 3.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 24.9, 33.0, 34.4, 55.2, 129.6. IR (KBr): 2937, 2858, 2175, 2102, 2060, 1450, 1361, 1320, 986, 891, 720, 702 cm^{-1}.

1-Isothiocyanatomethylbenzene (13a):



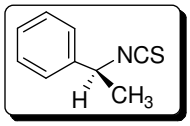
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (s, 2H), 7.31–7.41 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 126.7, 128.2, 128.8, 131.8, 134.1. IR (KBr): 3033, 2925, 2175, 2094, 1454, 1347, 1028, 700, 574 cm^{-1}.

5-(Isothiocyanatomethyl)benzo[*d*][1,3]dioxole (14a):



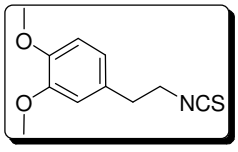
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59 (s, 2H), 5.98 (s, 2H), 6.74–6.80 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.7, 101.5, 107.7, 108.6, 120.7, 128.0, 132.1, 147.8, 148.2. IR (KBr): 2895, 2087, 1503, 1445, 1369, 1322, 1251, 1101, 1028, 924 cm^{-1}. MS (ESI): 194 [MH^+].

R-(-)-(1-Isothiocyanato-ethyl)benzene (15a):



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (d, *J* = 6.8 Hz, 3H), 4.89 (q, *J* = 6.8 Hz, 1H), 7.29–7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 57.1, 125.5, 128.3, 129.0, 132.2, 140.2. IR (KBr): 3373, 2984, 2090, 1635, 1454, 1308, 1097, 1021, 946 cm^{-1}.

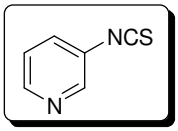
4-(2-Isothiocyanato-ethyl)-1,2-dimethoxybenzene (17a):



Oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (t, *J* = 6.6 Hz, 2H), 3.68 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 6.79 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.0, 46.6, 55.85, 55.87, 111.3, 111.9,

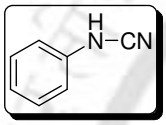
120.8, 129.5, 130.3, 148.0, 148.9. IR (KBr): 3000, 2935, 2835, 2181, 2100, 1592, 1515, 1455, 1347, 1263, 1142, 1028, 909 cm^{-1}.

3-Isothiocyanatopyridine (18a):



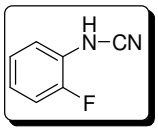
Oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 1H), 7.52 (m, 1H), 8.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.9, 129.4, 132.4, 139.0, 146.9, 147.5. IR (KBr): 3052, 2561, 2046, 1574, 1475, 1417, 1263, 1188, 1119, 1097, 1023, 929, 801 cm^{-1}.

Phenylcyanamide (1b):



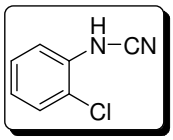
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02–7.07 (m, 3H), 7.28–7.33 (m, 2H), 7.64 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.2, 115.5, 123.6, 129.8, 137.4. IR (KBr): 3175, 2919, 2227, 1600, 1501, 1249, 748, 689 cm^{-1}.

2- Fluoro-phenylcyanamide (2b):



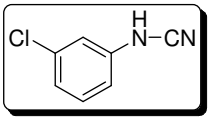
M.p. 95 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (br s, 1H), 6.90-7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.9, 115.7, 115.9, 116.8, 124.1, 124.1 125.09, 125.12, 125.6, 125.8, 150.1, 152.5. IR (KBr): 3068, 2037, 1606, 1587, 1495, 1265, 1212, 1104, 941, 808, 752 cm^{-1}.

2-Chloro-phenylcyanamide (3b):



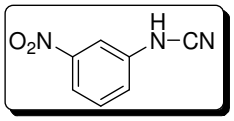
M.p. 101–103 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (br s,1H), 7.05 (m, 1H), 7.31 (m, 2H), 7.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.0, 116.2, 120.4, 124.5, 128.6, 129.9, 134.3. IR (KBr): 3163, 2921, 2243, 1598, 1500, 1426, 1295, 1049 cm^{-1}.

3-Chloro-phenylcyanamide (4b):



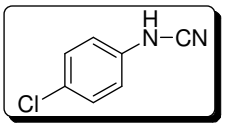
M.p. 93–95 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (m, 1H), 7.03 (m, 2H), 7.26 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.1, 113.8, 115.9, 124.0, 130.9, 135.7, 138.7. IR (KBr): 3154, 2910, 2237, 1602, 1513, 1423, 1256 cm^{-1}. MS (ESI): 152 [M^{+}].

3-Nitro-phenylcyanamide (5b):



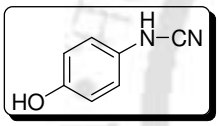
M.p. 133–135 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 7.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 109.6, 110.7, 116.8, 120.8, 130.1, 139.9, 148.4. IR (KBr): 3147, 2919, 2241, 1621, 1531, 1354, 1260, 1071, 937, 871cm^{-1}. MS (ESI): 163 [M^+].

4-Chloro-phenylcyanamide (6b):



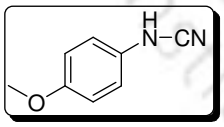
M.p. 95 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.4, 116.9, 128.9, 129.9, 136.2. IR (KBr): 3166, 2954, 2234, 1600, 1494, 1251, 1091 cm^{-1}.

4-Hydroxy-phenylcyanamide (7b):



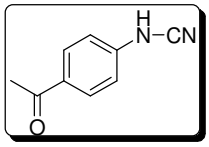
M.p. 259–261 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO): δ 5.67 (br s, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 8.98 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO): δ 112.8, 115.6, 115.8, 129.5, 152.2. IR (KBr): 3213, 2992, 2230, 1613, 1519, 1444, 1258, 1224 cm^{-1}. $C_7H_6N_2O$ (134.14): calcd C 62.68, H 4.51, N 20.88; found C 62.72, H 4.55, N 20.83.

4-Methoxy-phenylcyanamide (8b):



M.p. 86–89 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 112.8, 115.2, 117.0, 130.6, 156.1. IR (KBr): 3180, 2926, 2218, 1456, 1295, 1238, 1105, 1037, 826 cm^{-1}. $C_8H_8N_2O$ (148.17): calcd C 64.85, H 5.44, N 18.91; found C 64.91, H 5.40, N 18.93.

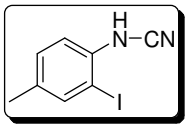
4-Acetyl-phenylcyanamide (9b):



M.p. 153–157 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.56 (s, 3H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 25.9, 110.9, 114.5, 129.8, 131.2, 142.9, 196.2. IR (KBr): 3188, 2966, 2228, 1666, 1599, 1585, 1411, 1362,

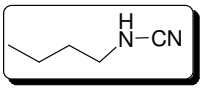
1278, 1176, 962 cm^{-1}. $C_9H_8N_2O$ (160.18): calcd C 67.49, H 5.03, N 17.48; found C 67.53, H 5.08, N 17.44. MS (ESI): 160 [M^+].

2-Iodo-4-methyl-phenylcyanamide (10b):



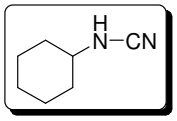
M.p. 144 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 6.17 (br s, 1H), 7.17 (m, 2H), 7.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 84.2, 110.7, 115.4, 130.9, 135.4, 139.6. IR (KBr): 3229, 2919, 2217, 1603, 1573, 1502, 1420, 1383, 1283, 1032, 866, 805 cm^{-1}.

***n*-Butylcyanamide (11b):**



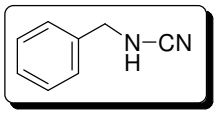
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.6 Hz, 3H), 1.40 (m, 2H), 1.58 (m, 2H), 3.06 (m, 2H), 4.61 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 19.5, 31.7, 45.7, 117.2. IR (KBr): 3207, 2961, 2875, 2221, 1614, 1463, 1373, 1171 cm^{-1}.

Cyclohexylcyanamide (12b):



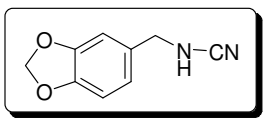
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (m, 5H), 1.61 (m, 1H), 1.78 (m, 2H), 1.95 (m, 2H), 3.09 (m, 1H), 3.91 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 25.1, 32.6, 54.3, 115.9. IR (KBr): 3196, 2933, 2857, 2217, 1453, 1367, 1167 cm^{-1}.

Benzylcyanamide (13b):



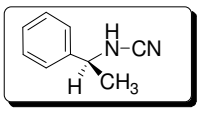
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (d, *J* = 5.2 Hz, 2H), 4.66 (br s, 1H), 7.27–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.9, 116.7, 127.9, 128.4, 128.9, 136.4. IR (KBr): 3207, 2925, 2220, 1455, 1359, 1155, 1014 cm^{-1}.

Benzo[1,3]dioxol-5-ylmethylcyanamide (14b):



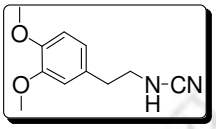
M.p. 82–84 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05 (d, *J* = 5.2 Hz, 2H), 4.57 (br s, 1H), 5.94 (s, 2H), 6.77 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.9, 101.4, 108.46, 108.54, 116.5, 121.7, 130.1, 147.8, 148.2. IR (KBr): 3233, 2952, 2897, 2220, 1500, 1445, 1038, 925, 809 cm^{-1}.

_R_(+)-1-Phenylethylcyanamide (15b):



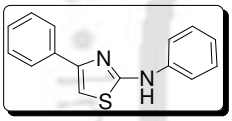
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, *J* = 6.8 Hz, 3H), 4.31 (q, *J* = 6.8 Hz, 1H), 4.86 (br s, 1H), 7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 55.4, 115.8, 126.2, 128.2, 128.9, 141.6. IR (KBr): 3202, 2924, 2217, 1454, 1378, 1275, 1209, 1159, 1028, 763 cm^{-1}.

3,4-Dimethoxyphenylethylcyanamide (17b):



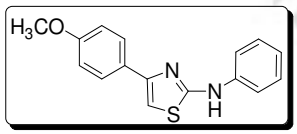
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (t, *J* = 7.2 Hz, 2H), 3.28 (t, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.37 (br s, 1H), 6.76 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.5, 47.5, 55.92, 55.95, 111.4, 111.9, 116.5, 120.9, 130.0, 147.8, 148.9. IR (KBr): 3274, 2937, 2219, 1592, 1517, 1464, 1262, 1236, 1156, 1142, 1026, 913 cm^{-1}.

Phenyl-(4-phenyl-thiazol-2-yl)-amine (18a):



M.p. 138–140 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 1H), 7.07 (t, *J* = 6.8 Hz, 1H), 7.29–7.42 (m, 7H), 7.56 (br s, 2H), 7.85 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.9, 118.5, 123.1, 126.3, 128.1, 128.8, 129.6, 134.7, 140.5, 151.4, 165.1. IR (KBr): 3447, 3226, 3185, 3049, 2929, 1600, 1567, 1499, 1459, 1425, 1314, 1212, 1072, 918, 751, 701 cm^{-1}. $C_{15}H_{12}N_2S$ (252.33): calcd C 71.40, H 4.79, N 11.10, S 12.71; found C 71.47, H 4.82, N 11.01, S, 12.73.

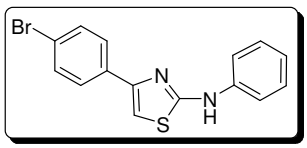
4-(4-Methoxyphenyl)-_N_-phenylthiazol-2-amine (18b):



M.p. 135–137 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), 6.68, (s, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.05 (t, *J* = 6.6 Hz, 1H), 7.27–7.36 (m, 4H), 7.77 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 100.1, 114.1, 118.4, 123.0, 127.6, 129.5, 140.6, 151.1, 159.6, 167.3. IR (KBr): 3379, 2937, 1601, 1543, 1485, 1287, 1245, 1206, 1109, 1029, 834, 747, 734 cm^{-1}.

4-(4-Bromophenyl)-_N_-phenylthiazol-2-amine (18c):

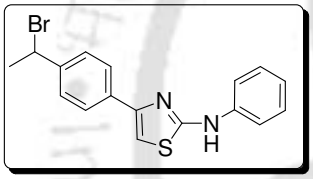
M.p. 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81, (s, 1H), 7.08 (m, 1H), 7.36 (m, 4H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz,



2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.4, 118.6, 121.9, 123.4, 127.9, 129.7, 131.9, 133.6, 140.4, 150.4, 165.2. IR (KBr): 3382, 3113, 1601, 1594, 1556, 1497, 1471, 1458, 1406, 1397, 1341, 1311, 1270, 1194, 1103, 1070, 1052, 1007, 914, 849, 829, 746, 726 cm^{-1}. HRMS (ESI): Calcd for $C_{15}H_{11}BrN_2S$ [MH^+] 330.9905, found 330.9901.

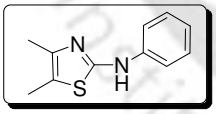
Crystaldata for 18c: Crystal dimensions (mm): 0.48 x 0.28 x 0.19; $C_{15}H_{11}BrN_2S$, M_r = 331.23; orthorhombic, space group *Pbca*; a = 14.7566(9) Å, b = 5.7446(4) Å, c = 31.925(2) Å; $\alpha = \beta = \gamma =$ 90°, V = 2706.3(3) Å^3; Z = 8; ρ_{cal} = 1.626 mg/m^3; μ (mm^{-1}) = 3.178; F(000) = 1328; reflection collected / unique = 4573 / 2353; refinement method = full-matrix least-squares on F^2; final R indices [I > 2σ_I] R_1 = 0.0431, wR_2 = 0.1312, R indices (all data) R_1 = 0.1126, wR_2 = 0.1700; goodness of fit = 0.975. CCDC # 739036.

[4-(1-Bromo-ethyl)-thiazol-2-yl]-phenyl-amine (18d):



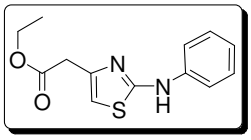
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 3H), 4.83 (q, J = 6.4 Hz, 1H), 6.40 (s, 1H), 7.05 (m, 1H), 7.24–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 66.3, 101.5, 118.6, 123.4, 129.7, 140.4, 156.2, 166.1. IR (KBr): 3274, 3130, 2975, 1602, 1542, 1498, 1459, 1312, 1260, 1139, 1095, 1027, 964, 885, 749 cm^{-1}.

4,5-Dimethyl-N-phenylthiazol-2-amine (18e):



M.p. 112–114 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18, (s, 3H), 2.32, (s, 3H), 7.02 (t, J = 6.8 Hz, 1H), 7.25–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2, 14.7, 114.3, 118.3, 122.6, 129.5, 141.1, 142.9, 161.8. IR (KBr): 3241, 3194, 3138, 3068, 2916, 1605, 1569, 1499, 1458, 1424, 1376, 1328, 1297, 1222, 1195, 991, 874, 846, 746, 713, 685 cm^{-1}.

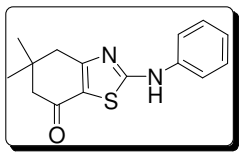
Ethyl-2-(2-(phenylamino)thiazol-4-yl)acetate (18f):



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H), 3.64 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 6.44 (s, 1H), 7.04 (m, 1H), 7.79-7.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 37.4, 61.2, 104.6, 118.6, 123.2, 129.6, 140.5, 144.7, 165.4, 170.7. IR (KBr): 3337, 3064, 2981,

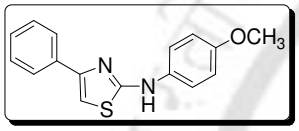
1731, 1603, 1526, 1497, 1459, 1445, 1370, 1311, 1246, 1178, 1030, 994, 939, 851, 751 cm^{-1}.

5,6-Dihydro-5,5-dimethyl-2-(phenylamino)benzo[*d*]thiazol-7(4H)-one (18g):



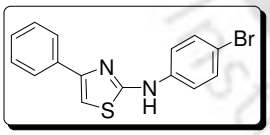
^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H), 2.41 (s, 2H), 2.68 (s, 2H), 7.19 (m, 1H), 7.41 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 35.1, 41.3, 51.5, 118.8, 120.5, 125.3, 129.9, 139.1, 165.3, 171.8, 191.0. IR (KBr): 3293, 3058, 2959, 1594, 1492, 1406, 1387, 1351, 1319, 1169, 913, 735 cm^{-1}.

4-Methoxy-phenyl-(4-phenyl-thiazol-2-yl)-amine (19a):



M.p. 163–165 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.73, (s, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 7.25–7.29 (m, 3H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.7, 101.4, 114.9, 122.3, 126.3, 127.9, 128.8, 133.8, 134.8, 151.6, 156.6, 167.3. IR (KBr): 3381, 3110, 3052, 2957, 2837, 1594, 1566, 1511, 1480, 1385, 1325, 1298, 1276, 1244, 1105, 1070, 1055, 1031, 913, 827, 819, 768, 705 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{14}N_2OS$ [MH^+] 283.0905, found 283.0917.

4-Bromo-phenyl-(4-phenyl-thiazol-2-yl)-amine (20a):

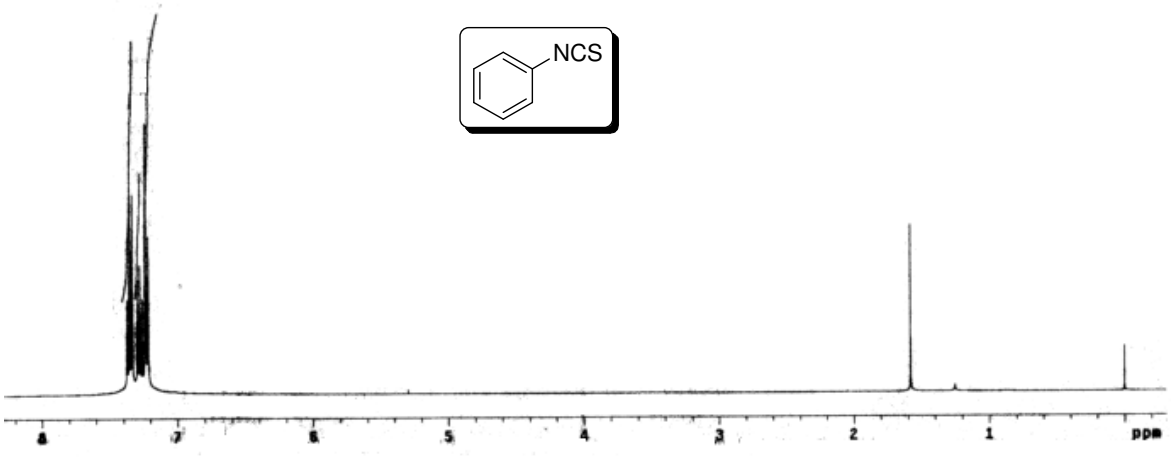


M.p. 147–148 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.83, (s, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.30 (m, 1H), 7.38 (m, 4H), 7.82 (d, *J* = 8.0 Hz, 2H), 8.00 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.3, 115.3, 119.8, 126.4, 128.2, 128.9, 132.4, 134.6, 139.6, 151.7, 164.3. IR (KBr): 3378, 3110, 2925, 1584, 1557, 1481, 1442, 1416, 1382, 1325, 1295, 1277, 1213, 1071, 1055, 1009, 915, 817, 770, 707 cm^{-1}.

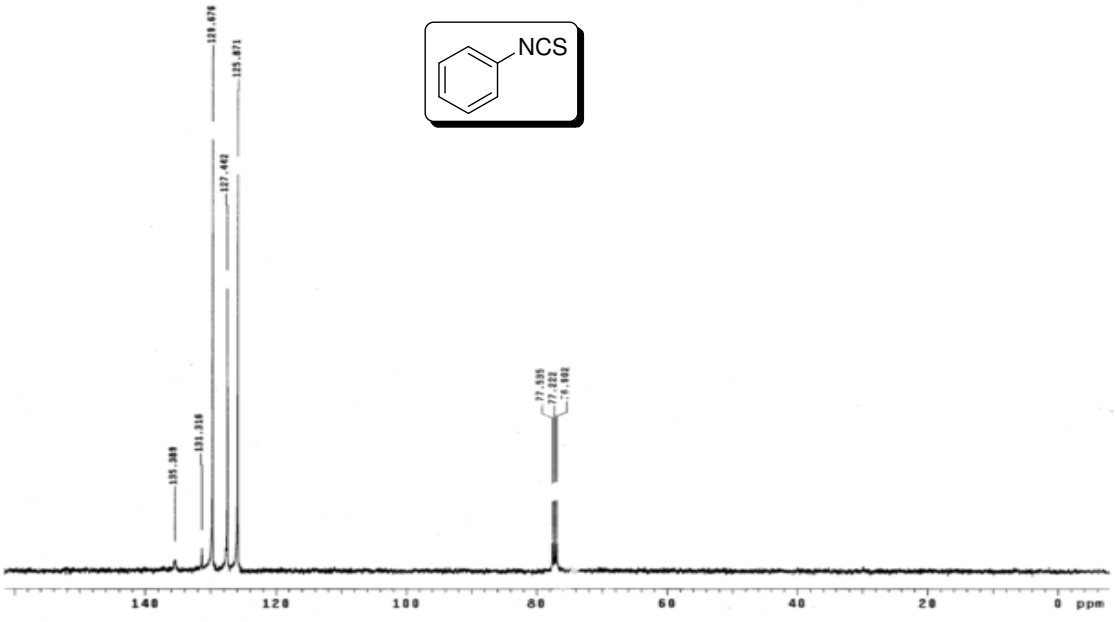
Crystal data for 20a: Crystal dimensions (mm): 0.45 x 0.28 x 0.23; $C_{15}H_{11}BrN_2S$, M_r = 331.23; triclinic, space group P-1; *a* = 5.7775(5) Å, *b* = 14.8715(12) Å, *c* = 16.3074(12) Å; α = 92.837(4)°, β = 100.20°, γ = 90.01°; *V* = 1377.23(19) (A^3); *Z* = 4; ρ_{cal} = 1.597 mg/m^3; μ (mm^{-1}) = 3.127; *F*(000) = 664; reflection collected / unique = 4279 / 2540; refinement method = full-matrix least-squares on F^2; final *R* indices [$I > 2\sigma_I$] R_1 = 0.1261, wR_2 = 0.3114, *R* indices (all data) R_1 = 0.1604, wR_2 = 0.3183; goodness of fit = 1.842. CCDC # 739035.

II.8. Selected Spectra

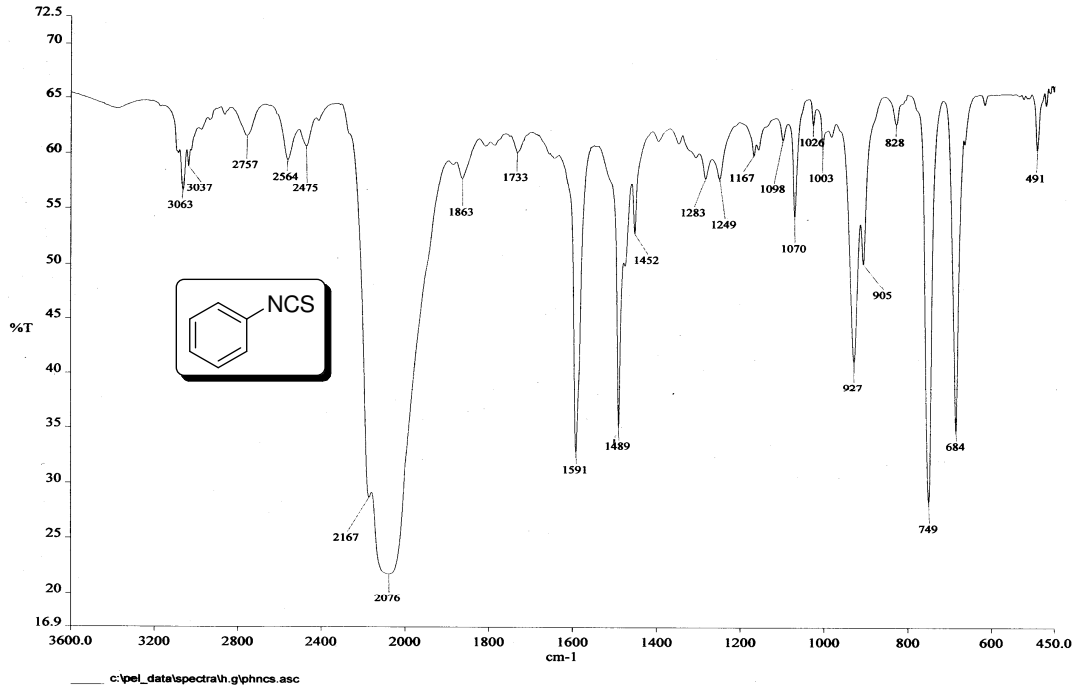
1-Isothiocyanatobenzene (1a): ^{1}H NMR (400 MHz, $CDCl_3$):



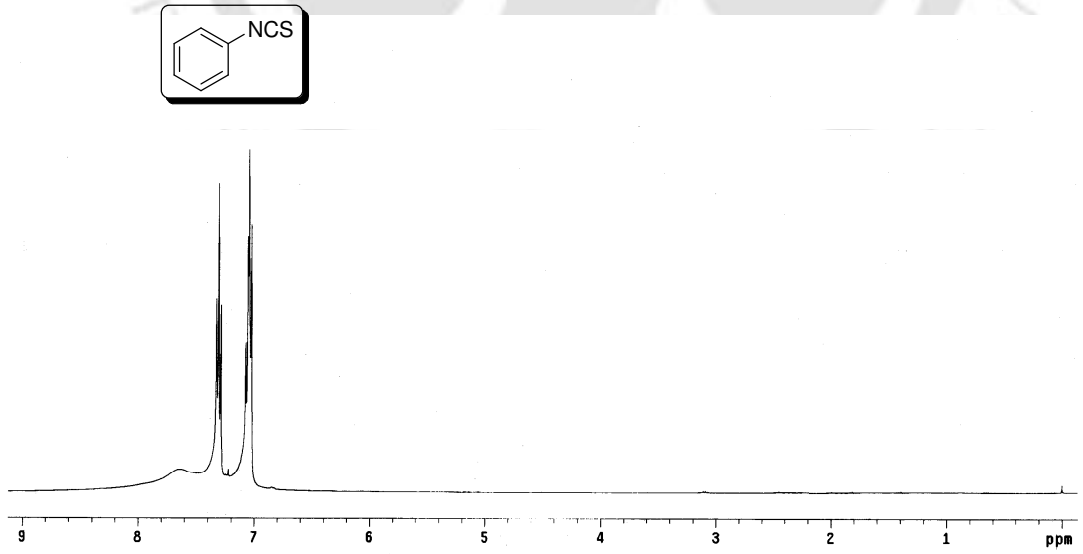
1-Isothiocyanatobenzene (1a): ^{13}C NMR (100 MHz, $CDCl_3$):



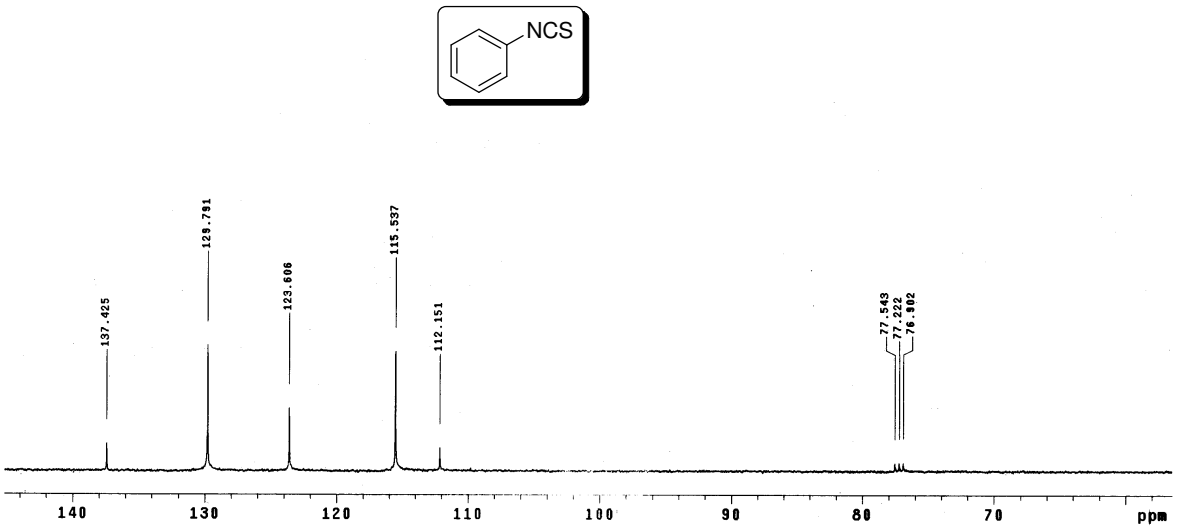
1-Isothiocyanatobenzene (1a): IR(KBr):



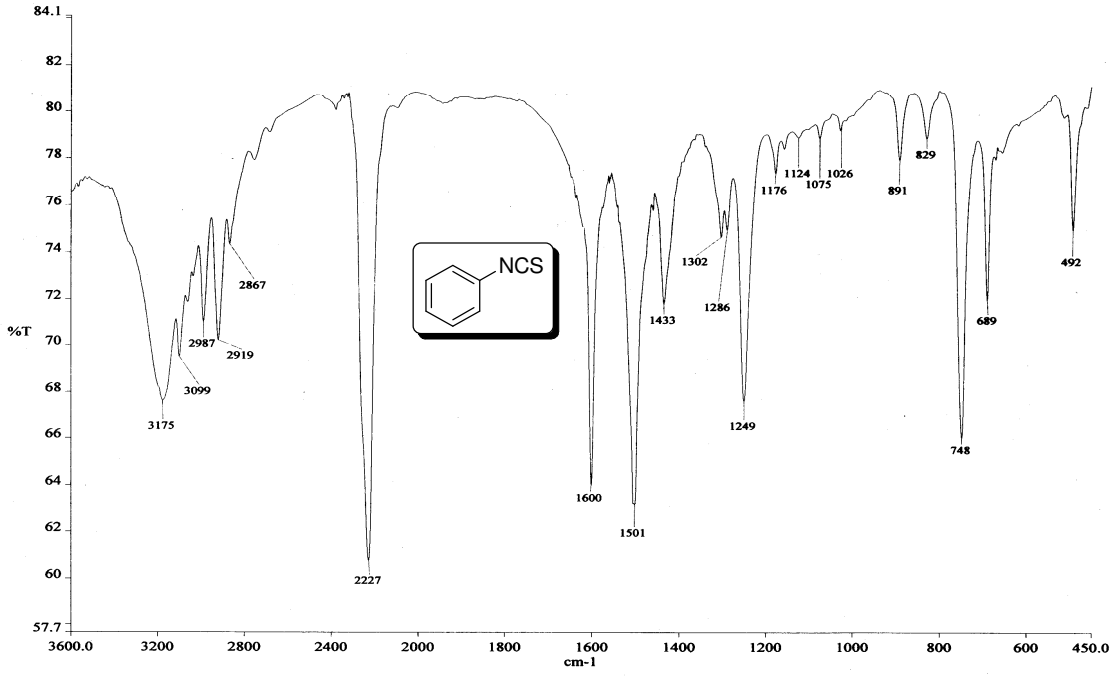
Phenylcyanamide (1b): ^{1}H NMR (400 MHz, $CDCl_3$):



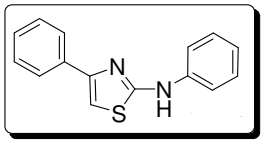
Phenylcyanamide (1b): ^{13}C NMR (100 MHz, $CDCl_3$):

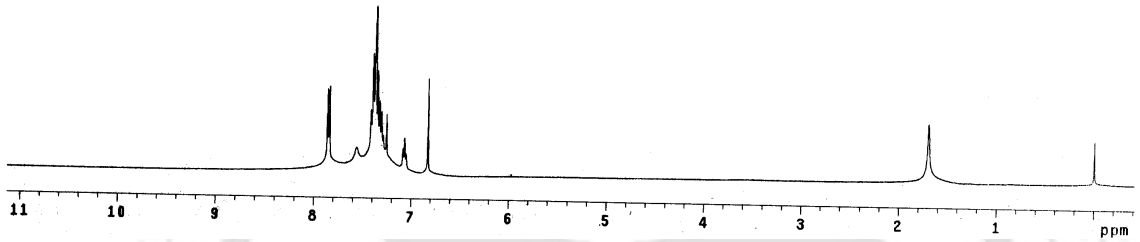


Phenylcyanamide (1b): IR(KBr):

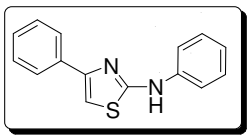


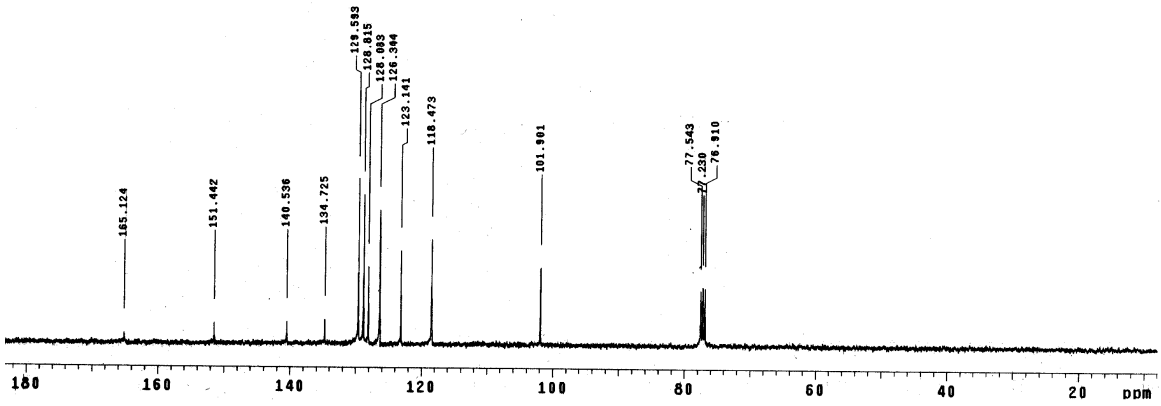
Phenyl-(4-phenyl-thiazol-2-yl)-amine (18a): ^{1}H NMR (400 MHz, $CDCl_3$):



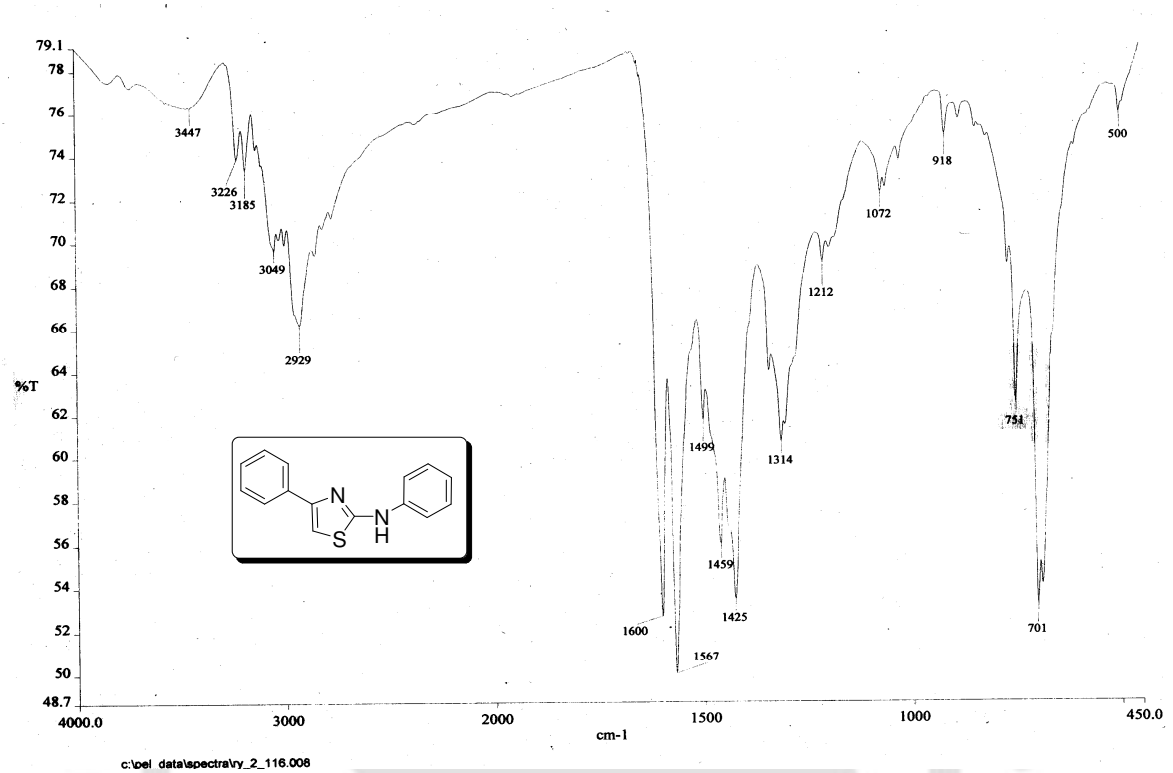


Phenyl-(4-phenyl-thiazol-2-yl)-amine (18a): ^{13}C NMR (100 MHz, $CDCl_3$):





Phenyl-(4-phenyl-thiazol-2-yl)-amine (18a): IR (KBr):

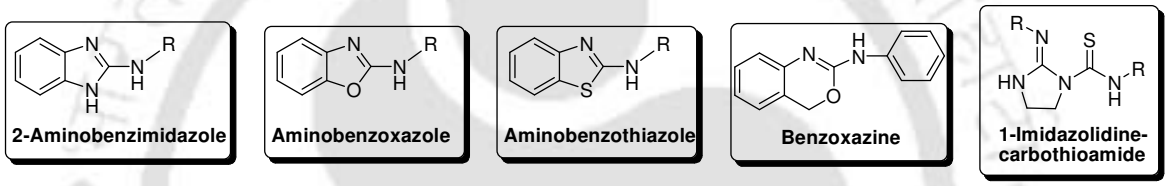


CHAPTER III

III. Synthesis of Five and Six Membered *N*, *O*, *S*- Heterocycles Using a Ditribromide Reagent

III.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I, Section I.3.1, Figure I.3.1.3, and Figure I.3.1.1.1, in page 8-11. This chapter deals with the following five types of heterocycles *viz.* 2-aminobenzimidazole, aminobenzoxazole, aminobenzothiazole, benzoxazine and 1-imidazolidinecarbothioamide.



III.2. Importance and Applications

Benzimidazoles are important structural motifs in medicinal chemistry, which involves nearly one-quarter of the top-100 selling drugs. Specifically, 2-amino benzimidazoles can be found in a number of biologically active molecules.[1] several compounds from this class have been used as anticancer,[2a] antihistamine,[2b]and antiviral agents.[2c-e] Some examples of pharmaceutically interesting benzimidazoles are shown in (*Figure III.2.1.*).

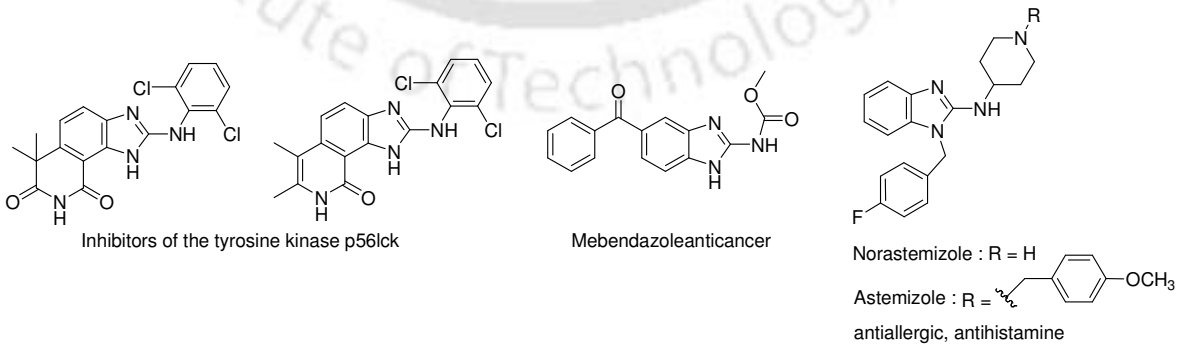
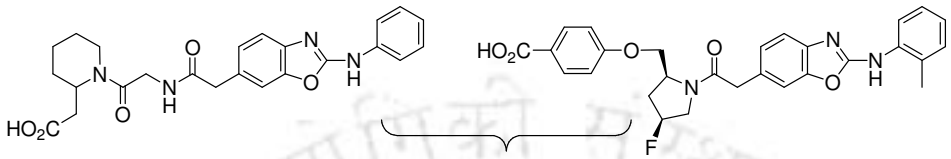


Figure III.2.1.

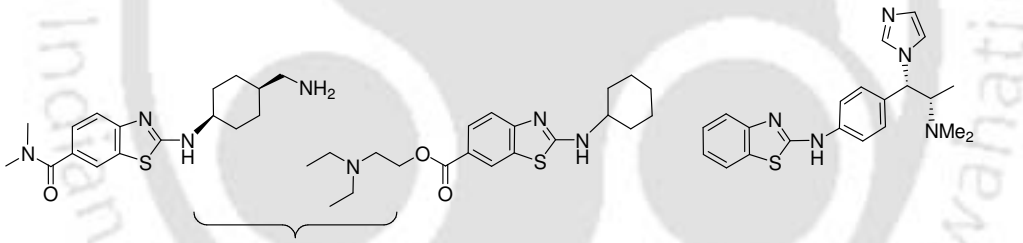
The 2-aminobenzoxazole moiety is a popular building block for the construction of pharmaceutically important[3a] compounds for instance, as shown in *Figure III.2.2*. These classes of compounds are vital as drug candidates, and their use is currently explored for the treatment of diseases such as HIV, neurodegeneration, and inflammation.[3b-e]



Potent VLA-4 (Very Late Antigen-4) antagonist

Figure III.2.2.

The 2-aminobenzothiazoles are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development for the treatment of diabetes,[4a] epilepsy,[4b-d] inflammation,[4e] amyotrophic lateral sclerosis,[4f] analgesia,[4g] tuberculosis,[4h] and viral infections.[4i] Some of representative examples of biologically important aminobenzothiazoles are shown in *Figure III.2.3*.[5,6]



***N*-Myristoyltransferase (Nmt) inhibitor** **Neurotransmission blocker**

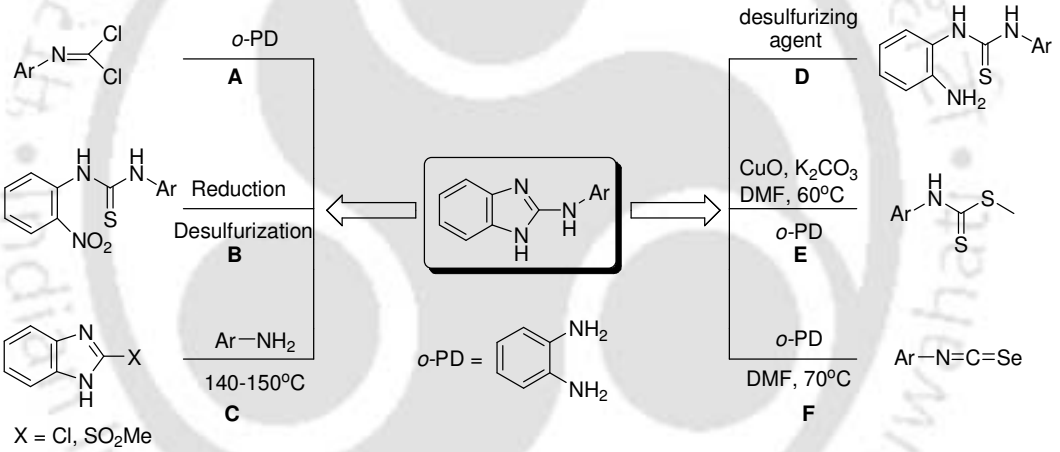
Figure III.2.3.

The oxazine analogous are of interest because it can be used as a masked carboxylic acid function,[7a] a chiral ligand for asymmetric synthesis,[7b] a versatile synthetic intermediates[7c] and as therapeutic agents.[7d] The heterocycle 1-imidazolidinecarbothioamides are known to be valuable insecticides, usually for the control of *Epilachna varivestis*.[7e]

III.3. Available Synthetic Methods

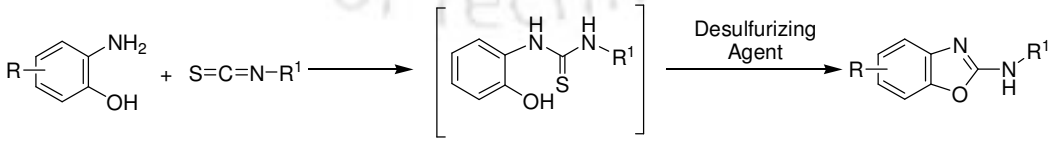
2-Aminobenzimidazoles are obtained by the reaction of arylcarbonimidoyl dichlorides which inturn are prepared by the chlorination of aryl isothiocyanate, with *o*-phenylenediamines in a suitable solvent **A** (*Scheme III.3.1*),[8a] reductive cyclization of *o*-

nitrothioureas **B** (*Scheme III.3.1*),[8b] S_NAr reaction of chlorobenzimidazole or methylsulfonyl benzimidazole with an amine nucleophiles **C** (*Scheme III.3.1*)[8c,d] under solvent-free conditions. The most commonly adopted method for the synthesis of 2-aminobenzimidazole involves the cyclodesulfurization of a preformed or *in situ* generated monothioureas **D** (*Scheme III.3.1*). The reported desulfurizing agents include carbodiimides,[9a,b] tosylchloride,[9c] methyl iodide,[9d] mercury(II) oxide,[9e] mercury(II) chloride,[9f] and diacetoxyiodobenzene (DIB).[9g] In addition to this, copper(I)/(II) salts have also been employed for the condensation of dithiocarbamate **E** (*Scheme III.3.1*) with *o*-phenylenediamine (*o*-PD) at high temparature.[10a,b] Very recently, Xie *et al*. reported the synthesis of benzimidazoles from a toxic isoselenocyanates in dimethylformamide (DMF) at high temperature **F** (*Scheme III.3.1*)[10c].



Scheme III.3.1.

The most commonly adopted method for the synthesis of 2-aminobenzoxazoles is the cyclodesulfurization of *N*-substituted 2-hydroxyphenylthioureas (*Scheme III.3.2.*).

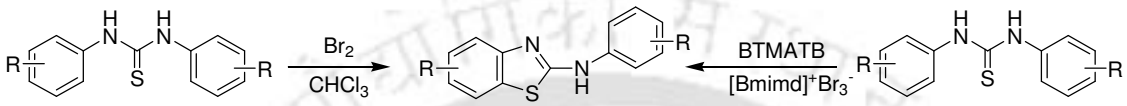


Scheme III.3.2.

The reported cyclodesulfurization agents includes, NiO,[11a] HgO,[11b-d] $AgNO_3$,[11e,f] KO_2[12a,b] salts of transition metals,[12c] and dicyclohexylcarbodiimide (DCC),[12d] aq. H_2O_2,[12e]

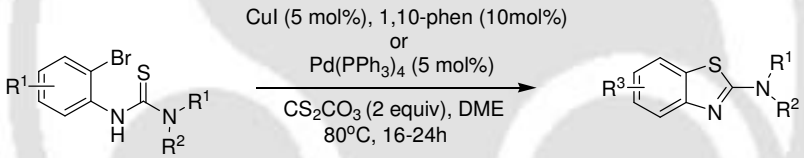
DIB.[9g] More recently it has been prepared by the direct amination of benzoxazoles using Cu-catalyst.[12f]

The Hugherschoff reaction is known to produce 2-aminobenzothiazole from 1,3-diaryl thiourea and liquid bromine in chloroform.[13a-c] Further, the toxic liquid bromine was replaced with solid brominating reagents *viz.* BTMATB,[13d] $[Bmim]^+Br_3^-$[13e] to give Hugerschoff product (*Scheme III.3.3.*).



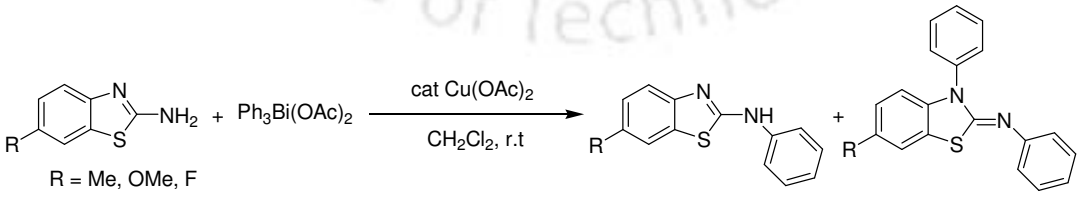
Scheme III.3.3.

Copper and palladium catalyzed intramolecular ligand assisted C–S bond formation between arylhalide and thiourea functionality has been employed for the synthesis of aminobenzothiazole (*Scheme III.3.4.*).[14a]



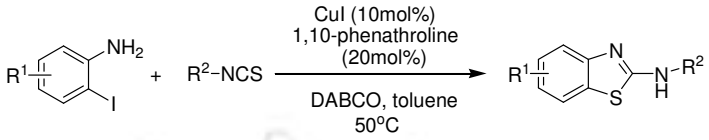
Scheme III.3.4.

Boyer *et al.* have developed copper diacetate catalyzed reaction of triphenylbismuth diacetate with 2-amino thiazoles or 6-amino benzothiazole to obtain a mixture of monophenylated and diphenylated products 2-aminophenyl thiazole and 2-(*N*-phenylamino)-3-*N*′-phenylthiazole derivatives, respectively, with diphenylated product being the predominant one (*Scheme III.3.5*).[14b]



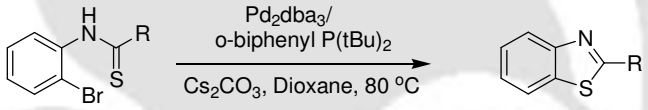
Scheme III.3.5.

Wu group have developed copper(I) catalyzed tandem strategy for the efficient and practical synthesis of 2-aminobenzothiazole by reacting 2-iodobenzenamine with isothiocyanates under a mild reaction condition (*Scheme III.3.6.*).[14c]



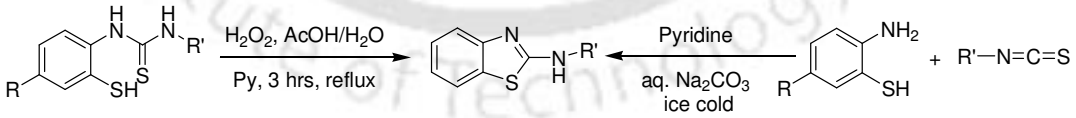
Scheme III.3.6.

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 III.3.7.*).[14d]



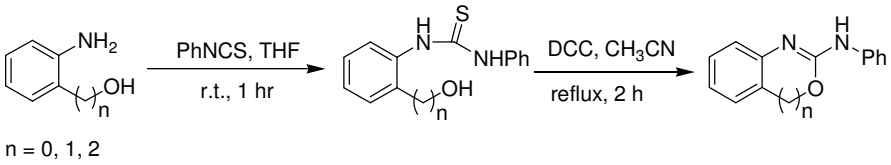
Scheme III.3.7.

So far only two methods have been reported for the preparation of aminobenzothiazoles using desulfurization strategy involving the oxidative cyclization in the presence of H_2O_2, acetic acid and water using pyridine as the co-solvent at higher temperature (*Scheme III.3.8.*).[15a,b]



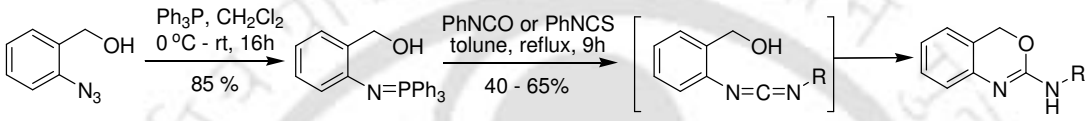
Scheme III.3.8.

Benzoxazines are yet another member of the heterocycle family which has been synthesized from thioureas by an analogous desulfurization strategy using expensive DCC[12d] and DIB[9g] as the desulfurizing agent (*Scheme III.3.9.*).



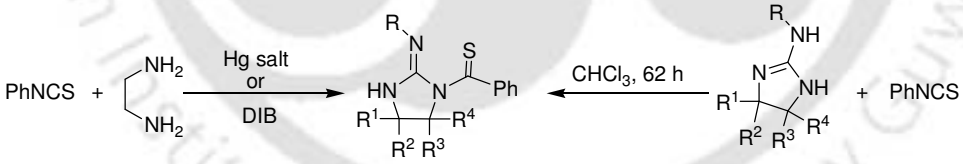
Scheme III.3.9.

Another literature method for the preparation of benzoxazines involves arduous tandem *aza*-Wittig/heterocumulene-mediated annulation strategy (*Scheme III.3.10*).[15c]



Scheme III.3.10.

Only three methods have been reported for the synthesis of 1-imidazolidinecarbothioamides. The first is the desulfurization strategy of *bis*-thioureas using toxic mercury salt[16a] or expensive hypervalent iodine (DIB)[9g] and the other involves the treatment of 2-methylamino-2-imidazoline[16b] with isothiocyanate (*Scheme III.3.11.*).



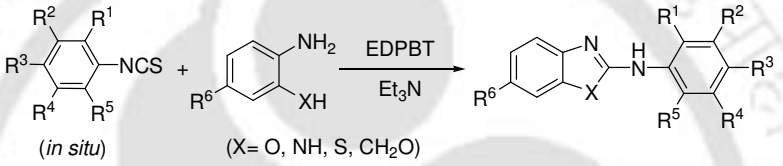
Scheme III.3.11.

As a part of our interest in the chemistry of heterocyclic compounds, we herein disclose the thiophilicity/desulfurizing ability of EDPBT in the synthesis of a spectrum of biologically active benzofused *N*, *O*, *S* heterocycles and study the regioselectivity of its formation.

III.4. Present Work

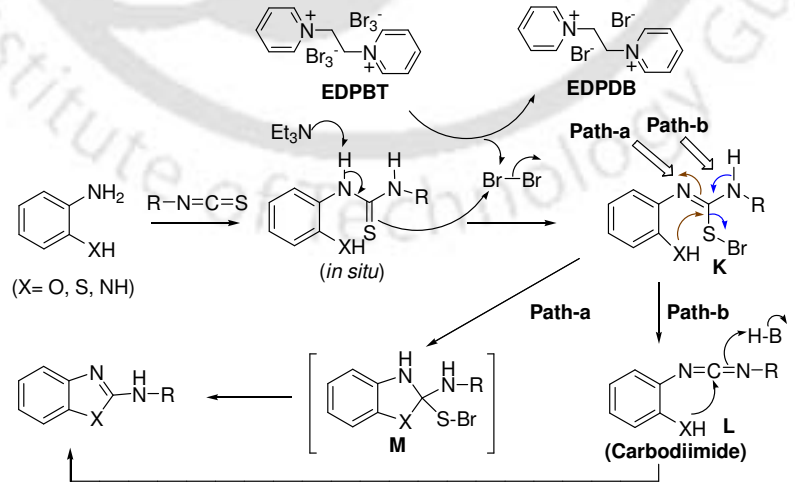
III.4.1 Synthesis of Five and Six Membered *N, O, S*- Heterocycles Using a Ditribromide Reagent

After successfully synthesizing heterocumulenes namely isothiocyanates,[17a] cyanamides[17b] from dithiocarbamates using 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) as discussed in the previous sections, we were further interested to explore the thiophilicity/desulfurizing ability of EDPBT in the synthesis of a series of biologically active benzofused *N*, *O*, *S* heterocycles (*Scheme III.4.1.1.*) starting from various isothiocyanates.



Scheme III.4.1.1. *Synthesis of benzofused N, O, S heterocycles.*

The *in situ* generated thiourea, obtained by treating phenyl isothiocyanate **1**[17a] (1 equiv) with *o-phenylenediamine* (1 equiv), followed by the addition of Et_3N (3 equiv) and subsequent treatment with EDPBT (0.5 equiv) in THF afforded the product 2-aminobenzimidazole **1b** in 81% yield. A mechanism as shown in *Scheme III.4.1.2* can be proposed to account for the formation of the product **1b**.

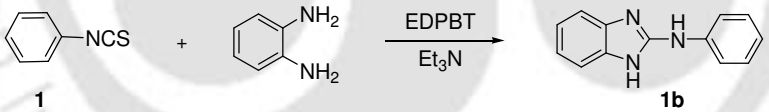


Scheme III.4.1.2. *Mechanism for the formation of benzimidazole/ benzoxazole / benzothiazole.*

The soft sulfur atom of the *in situ* generated thiourea first attacks on the thiophilic bromine forming a S–Br type of species **K** (*Scheme III.4.1.2*).[18a] An intramolecular attack of the amino nucleophile (where X = NH) as shown in path-a (*Scheme III.4.1.2.*) should yield the intermediate **M** which on elimination would give the desired benzimidazole **1b**. Alternatively, a reductive elimination as shown in path-b to form the intermediate carbodiimide **L** cannot be ruled out. Subsequent intramolecular attack of the *o*-amino group onto carbodiimide would generate the intermediate (**M**) as shown in *Scheme III.4.1.2.* This would subsequently form the desired product **1b**.

Among the various solvents tested such as CH_2Cl_2, dioxane, tetrahydrofuran (THF), CH_3CN, MeOH, *N*,*N*-dimethylformamide (DMF), and dimethylsulfoxide (DMSO), solvents CH_2Cl_2 and CH_3CN were found equally effective in giving good yields (86%, 90%) in short reaction time but for convenience CH_3CN was chosen for all other reactions. Further, the efficacy of the reagent/method was compared with some known tribromides including molecular bromine (*Table III.4.1.1*, entries **3–8**) using Et_3N as the base and CH_3CN as the solvent.

Table III.4.1.1. *Screening of different bromine equivalents using CH_3CN solvent.*



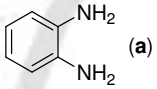
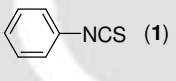
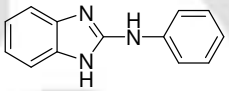
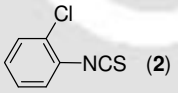
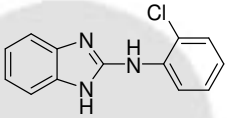
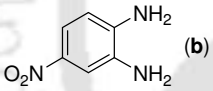
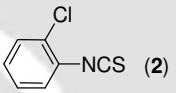
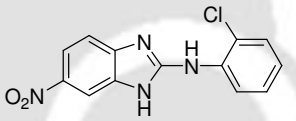
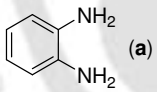
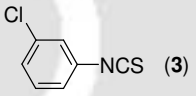
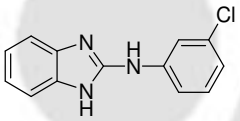
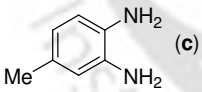
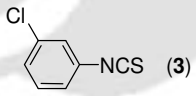
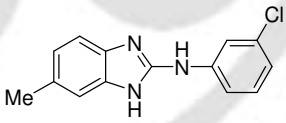
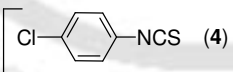
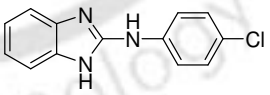
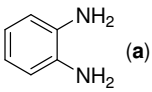
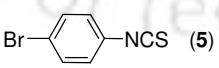
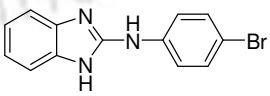
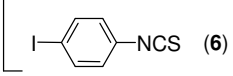
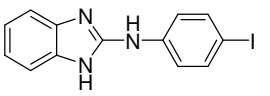
1 **1b**

Entry	Brominating Reagent/Time(h)	Yield (%)[a]
1	EDPBT[b]/0.5 h	67
2	EDPBT[c]/0.5 h	90
3	[Bmim[d]]$^+Br_3^-$/0.5 h	79
4	$Bu_4N^+Br_3^-$/0.5 h	84
5	$PhCH_2N^+Me_3Br_3^-$/0.5 h	81
6	$CH_3(CH_2)_{15}N^+Me_3Br_3^-$/0.5 h	86
7	$CH_3CH_2Ph_3PBr_3^-$/0.5 h	83
8	Br_2/1 h	75

[a] All the reactions performed in 1 mmol scale. Isolated yields. [b] 2 equiv Et_3N used. [b,c] Because it is a ditribromide reagent, 0.5 equiv of the reagent was used (all other casess entry 3-8 equiv of the reagents were used). [d] Bmim = 1-butyl-3-methylimidazolium.

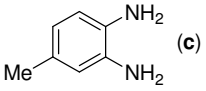
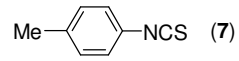
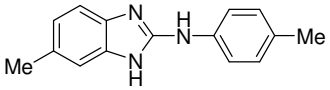
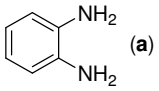
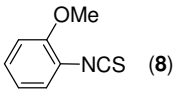
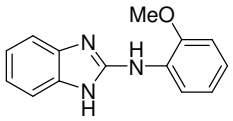
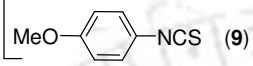
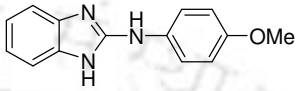
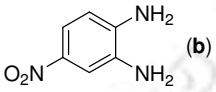
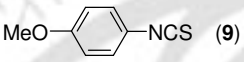
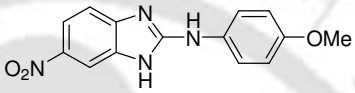
As can be seen from *Table III.4.1.1*, irrespective of the brominating reagents used, the formation of the 2-aminobenzimidazole **1b** is the exclusive product. On the basis of the overall isolated yield (*Table III.4.1.1.*), EDPBT was found to be the best among the various reagents assessed. In addition to this, the reagent is a stable crystalline solid, easy to prepare, handle, and maintain the desired stoichiometry. Further, the advantage of storage, transport and recyclability of the spent reagent makes this reagent superior to toxic, fuming liquid bromine and other reported tribromides, thus, and further supporting our argument about the superiority of the reagent.[18b]

Table III.4.1.2. *Reaction of o-phenylenediamine with isothiocyanates using EDPBT.*[a]

1,2-Diamine	Substrate	Product[b]	Yield (%)[c]
 (**a**)	 (**1**)		(**1b**) 90%
	 (**2**)		(**2b**) 88%
 (**b**)	 (**2**)		(**3b**) 76%
 (**a**)	 (**3**)		(**4b**) 76%
 (**c**)	 (**3**)		(**5b**) 80%
	 (**4**)		(**6b**) 83%
 (**a**)	 (**5**)		(**7b**) 79%
	 (**6**)		(**8b**) 82%

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

Table III.4.1.2. Continued….

1,2-Diamine	Substrate	Product[b]	Yield (%)[c]
 (**c**)	 (**7**)	 (**9b**)	84%
 (**a**)	 (**8**)	 (**10b**)	77%
	 (**9**)	 (**11b**)	75%
 (**b**)	 (**9**)	 (**12b**)	79%

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

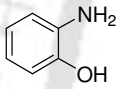
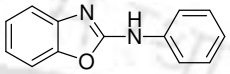
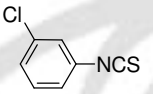
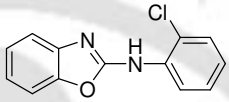
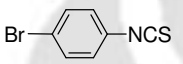
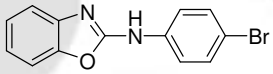
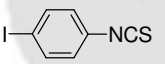
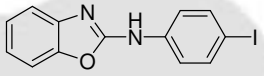
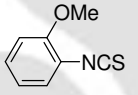
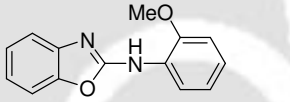
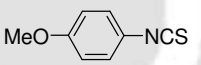
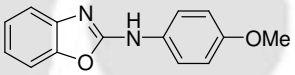
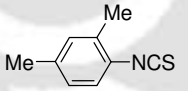
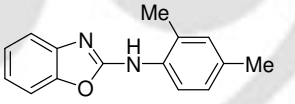
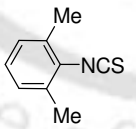
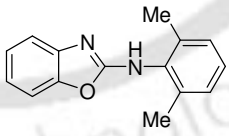
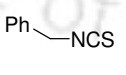
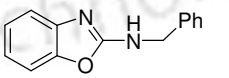
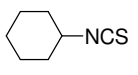
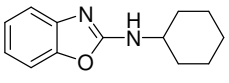
As shown in *Table III.4.1.2*, libraries of benzimidazoles (**1b–12b**) were synthesized in good yields following this protocol. It was observed that aryl isothiocyanates having moderately electron withdrawing groups (such as halide groups) (*Table III.4.1.2*, entries **2–6**) as well as electron donating groups (such as alkyl groups) (*Table III.4.1.2*, entries **7–9**) reacts efficiently with various aromatic 1,2-diamines possessing electron withdrawing substituents (–NO_2) **b** or electron donating (Me) **c** giving corresponding benzimidazoles **3b**, **5b**, **9b** and **12b** in good yields as shown in *Table III.4.1.2*.

The successful synthesis of benzimidazoles prompted us to synthesize another interesting class of compound, namely, benzoxazoles. The *in situ* generated monothiourea resulted from aryl isothiocyanate (*Scheme III.4.1.2.*) and *o*-amino phenol when treated with 0.5 equiv of EDPBT gave the desired *N*-2-phenyl-1,3-benzoxazol-2-amines **1c** in excellent yield. The mechanism is expected to be similar to the above (*Scheme III.4.1.2.*) proposed mechanism.

Several aminobenzoxazole derivatives (**2c–10c**) have been successfully prepared from the isothiocyanates substituted with electron-poor (*Table III.4.1.3*, entries **3**, **5**, **6**) and rich substituents (*Table III.4.1.3*, entries **8–11**) in excellent yields in shorter reaction times as shown in *Table III.4.1.3*. The structure of the *N*-2-(2,6-dimethylphenyl)-1,3-benzoxazol-

2-amine **8c** has been further confirmed by X-ray crystallography (*Figure III.4.1.1.*). In addition to aryl isothiocyanates, reactions of alkyl isothiocyanates for instance, benzyl isothiocyanate **12**, and cyclohexyl isothiocyanate **13** also proceeded smoothly to give rise to their corresponding aminobenzoxazoles **9c** and **10c** in good yields.

Table III.4.1.3. *Reaction of o-aminophenol with isothiocyanates using EDPBT.*[a]

Substrate	Product[b]	Yield (%)[c]
	 **1c**	82%
	 **2c**	85%
	 **3c**	87%
	 **4c**	81%
	 **5c**	79%
	 **6c**	78%
	 **7c**	80%
	 **8c**	82%
	 **9c**	69%
	 **10c**	67%

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

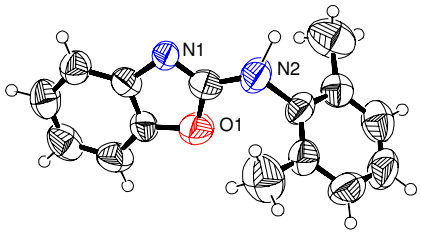
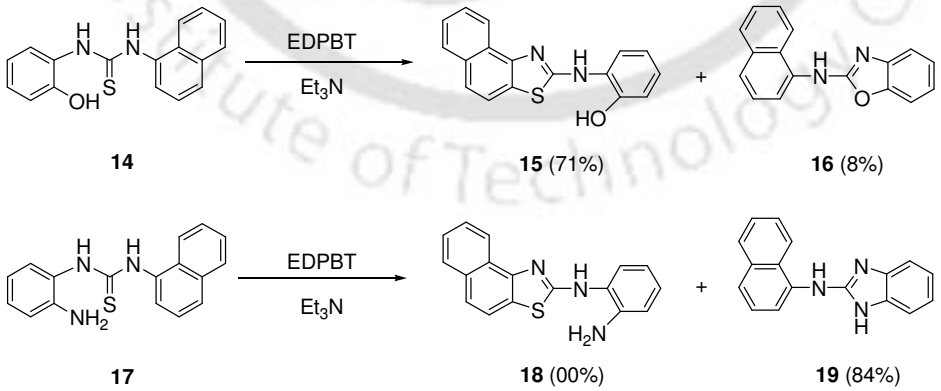


Figure III.4.1.1. *ORTEP view with the atomic numbering scheme of* ***8c****.*

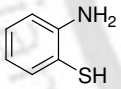
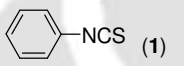
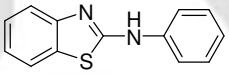
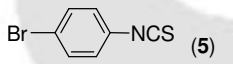
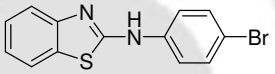
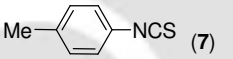
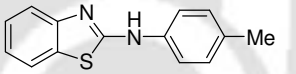
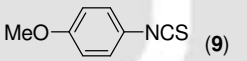
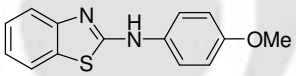
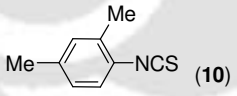
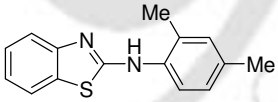
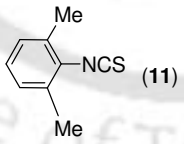
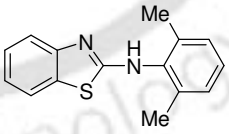
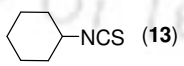
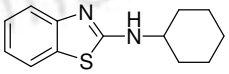
A noteworthy aspect is that the unsymmetrical naphthyl-hydroxyphenylthiourea **14** generated from the 1-napthyl isothiocyanate and 2-aminophenol, when treated with EDPBT gave the 2-(naphtho[1,2-*d*]thiazol-2-ylamino)phenol **15** as the major product rather than the expected *N*-(naphthalen-1-yl)benzo[*d*]oxazol-2-amine **16** (*Scheme III.4.1.3.*). The predominate formation of benzothiazole **15** can be in part due to the intramolecular electrophilic substitution of the activated naphthyl ring, and poor nucleophilicity of –OH group. This observation is analogous to Hugerschoff reaction known since 1901.[13a,b] To ascertain the later effect, that is, role of nucleophllicity in the product formation, the –OH nucleophile was replaced with a $-NH_2$ nucleophile by designing the substrate **17**. Interestingly, the substrate **17** having an amino group under an identical condition gave exclusively *N*-(naphthalen-1-yl)-1*H*-benzo[*d*]imidazol-2-amine **19** without giving any traces of benzothiazole **18** which is further confirmed by its mass spectra,[9a] thus supporting our assumption that nucleophilicity is equally important in deciding the course of the reaction (*Scheme III.4.1.3.*).



Scheme III.4.1.3. *Differential reactivity of naphthyl-phenyl thiourea* ***14*** *and* ***17****.*

The scope of this strategy was applied to the synthesis of benzothiazoles. The Hugherschoff reaction is known to produce 2-aminobenzothiazole from 1,3-diaryl thiourea and liquid bromine in chloroform.[13a,b] This reaction works well for symmetrical thioureas giving exclusively one product.[13d] But when the same reaction is performed using unsymmetrical 1,3-diaryl thioureas there is always uncertainty as to on which aryl ring the intramolecular electrophilic substitution would take place to give aminobenzothiazole. Therefore, we extended the synthesis of aminobenzimidazole, aminobenzoxazole strategy for the synthesis of aminobenzothiazoles.

Table III.4.1.4. *Reaction of o-aminothiophenol with isothiocyanates using EDPBT.*[a]

	Substrate	Product[b]		Yield (%)[c]
	 (**1**)		**1d**	81%
	 (**5**)		**2d**	84%
	 (**7**)		**3d**	80%
	 (**9**)		**4d**	74%
	 (**10**)		**5d**	72%
	 (**11**)		**6d**	74%
	 (**13**)		**7d**	68%

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

The *in situ* generated monothiourea from aryl isothiocyanate and *o*-aminothiophenol (*Scheme III.4.1.2.*), when treated with 0.5 equiv of EDPBT, afforded the desired aminobenzothazole **1d** in good yield. The proposed mechanism is similar to that of

benzimidazole and benzoxazole as shown in *Scheme III.4.1.2*. Various benzothiazoles **2d–7d** were obtained under our standard experimental conditions, irrespective of the nature of the substituents attached to the isothiocyanates (*Table III.4.1.4*, entry **5**, **7**, **9**, **10–11**, and **13**). Further, the structure of **4d** was confirmed by X-ray crystallography (*Figure III.4.1.2.*). In addition to aryl isothiocyanates, alkyl isothiocyanate such as cyclohexyl isothiocyanate **1m** (*Table III.4.1.4.*) also proceeded smoothly to give product **7d**.

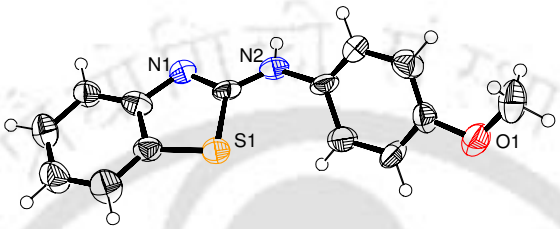
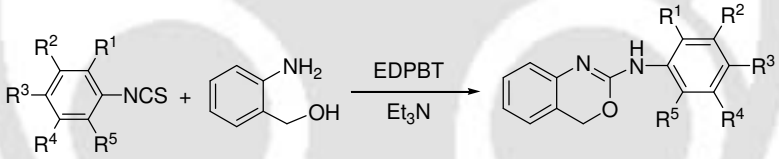


Figure III.4.1.2. *ORTEP view with the atomic numbering scheme of* ***4d.***

Benzoxazines are yet another member of the heterocycle family which has been synthesized using EDPBT in one-pot strategy (*Scheme III.4.1.4.*).



Scheme III.4.1.4. *Synthesis of benzoxazine*

A series of heterocycles **1e–6e** were prepared under our optimized experimental conditions as shown in *Table III.4.1.5*. The structure of the product **6e** has been confirmed by X-ray crystallography (*Figure III.4.1.3.*).

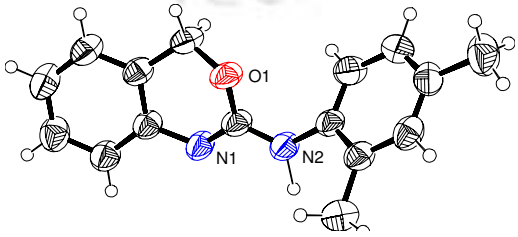
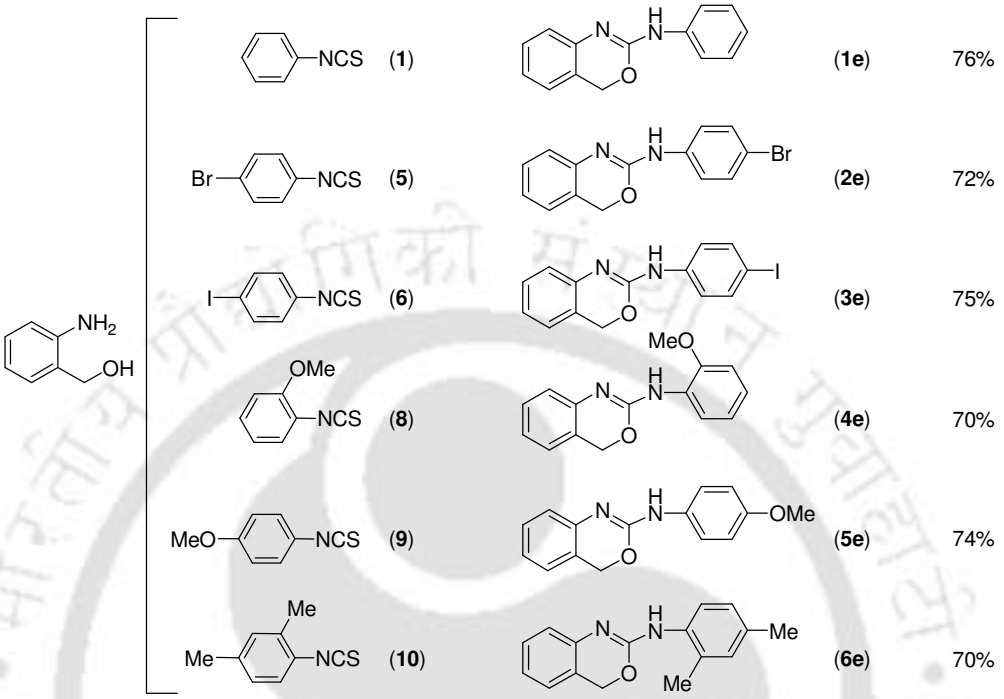
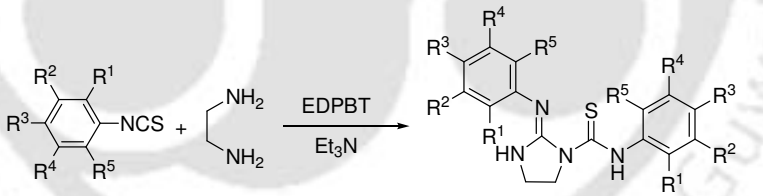


Figure III.4.1.3. *ORTEP view with the atomic numbering scheme of* ***6e****.*

Table III.4.1.5. *Reaction of o-aminobenzyl alcohol with isothiocyanates using EDPBT.*[a]

Substrate	Product[b]	Yield (%)[c]
		
(1)	(**1e**)	76%
(5)	(**2e**)	72%
(6)	(**3e**)	75%
(8)	(**4e**)	70%
(9)	(**5e**)	74%
(10)	(**6e**)	70%

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield

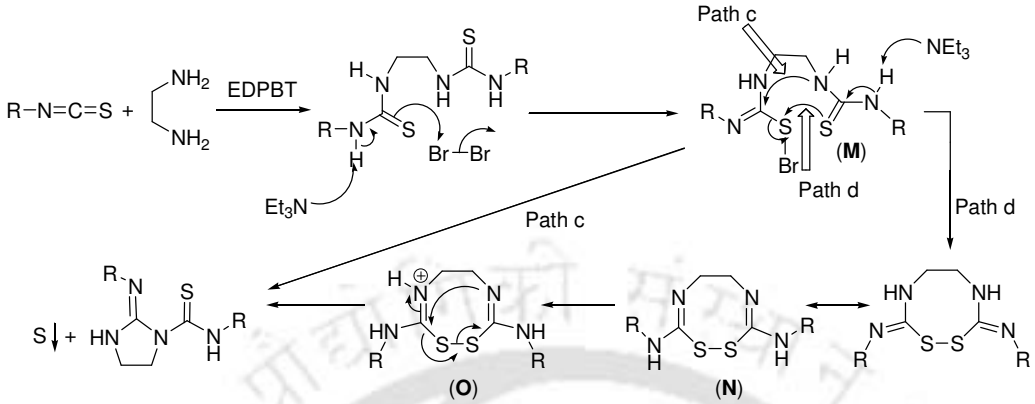


Scheme III.4.1.5. *Preparation of 1-imidazolidinecarbothioamide.*

There exist several possibilities for *bis*-thiourea when separated by two carbon spacer. The S−Br form on one side could be attacked by any one of the two nitrogen nucleophiles from the adjacent thiourea either giving a five membered or a seven membered ring. Alternatively, sulfur atom from the adjacent thiourea can attack to give a six membered ring or form an eight membered disulfide ring.

To scrutinize this, we treated the *bis*-thiourea resulted from phenyl isothiocyanate (2 equiv) and ethylenediamine (1 equiv) with EDPBT to get excellent yield of

imidazolidinecarbothioamide (*Scheme III.4.1.5.*). This class of compounds is useful as insecticides, particularly for the control of *Epilachna varivestis*.



Scheme III.4.1.6. *Mechanism for the formation of imidazolidinecarbothioamide.*

A plausible mechanism for the formation of imidazolidinecarbothioamide is shown in *Scheme III.4.6.* Bromine from EDPBT reacts with one side of the thiourea to give an S–Br intermediate (**M**). The soft nucleophile from the other side of the thiourea would attack on the S–Br species to give the unstable eight memebered disulfide ring (**N**) or (**O**) which inturn undergo an acid mediated rearrangement to give imidazolidine carbothioamide.

After successfully synthesizing imidazolidinecarbothioamide, the strategy was applied to electron poor (*Table III.4.1.6.*, **2**, **3**, **5**, and **6**) and electron rich (*Table III.4.1.6.*, **8–10**) isothiocyanates giving the products **2f–8f** in good to excellent yields, as shown in *Table III.4.6.* The structure of **6f** was confirmed by X-ray crystallography (*Figure III.4.1.4.*).

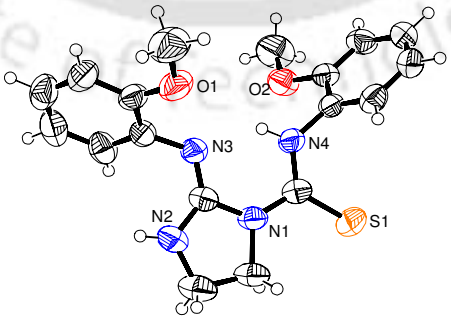
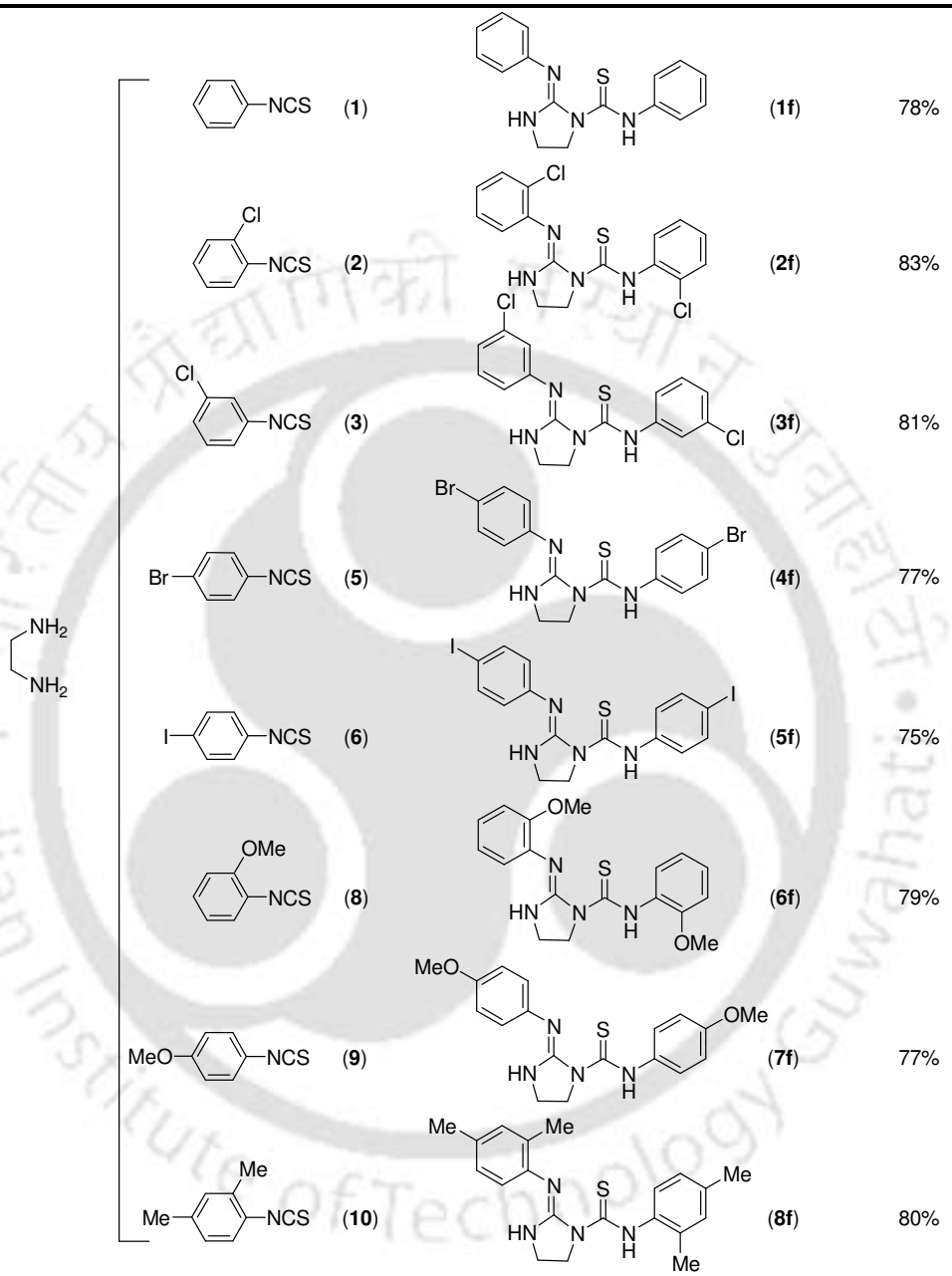


Figure III.4.1.4. *The ORTEP view with the atomic numbering scheme of* ***6f****.*

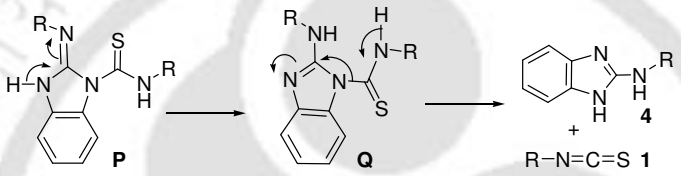
Table III.4.1.6. *Synthesis of imidazolidenecarbothioamides.*[a]

Substrate	Product[b]	Yield (%)[c]
		
(**1**)	(**1f**)	78%
(**2**)	(**2f**)	83%
(**3**)	(**3f**)	81%
(**5**)	(**4f**)	77%
(**6**)	(**5f**)	75%
(**8**)	(**6f**)	79%
(**9**)	(**7f**)	77%
(**10**)	(**8f**)	80%

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

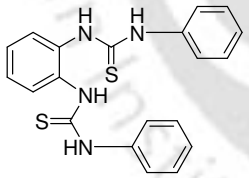
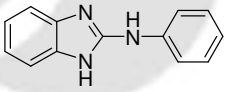
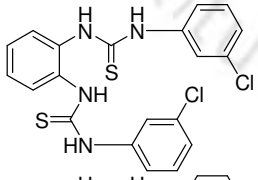
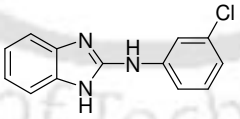
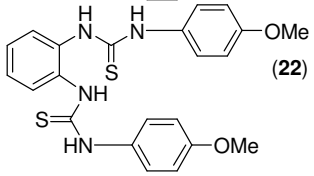
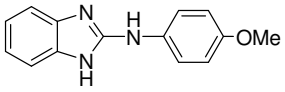
We were further interested to see if an aromatic 1,2-diamine such as *o*-phenylenediamine (*o*-PD) behaves similar to the aliphatic 1,2-diamine. Interestingly, the *bis*-thiourea obtained by the treatment of *o*-phenylenediamine (*o*-PD) and aryl

isothiocyanate gave benzimidazole and aryl isothiocyanate instead of the expected imidazolidinecarbothioamide. Various *bis*-thioureas (*Table III.4.1.7*, entry **20–22**) were reacted under the present experimental condition and in each case a benzimidazole (*Table III.4.1.7*, **1b**, **4b**, and **11b**) and an aryl isothiocyanate (*Table III.4.1.7*, **1**, **3**, and **9**) were isolated. In this case the intermediate imidazolidinecarbothioamide (**P**) (*Scheme III.4.1.6.*) which is non-aromatic in character rapidly loses a molecule of isothiocyanate giving benzimidazole. The driving force for this reaction seems to be the gain in the aromatic character of the product benzimidazole because of loss of an isothiocyanate from the intermediate (**Q**) (*Scheme III.4.1.7.*).



Scheme III.4.1.7. *Reactivity of aromatic 1,2-bis-thiourea with EDPBT.*

Table III.4.1.7. *Synthesis of imidazolidenecarbothioamides and benzimidazole.*[a]

Substrate	Product[b]		Yield (%)[c]
 (**20**)		**1b**	91%
 (**21**)		**4b**	90%
 (**22**)		**11b**	92%

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}CNMR. [c] Isolated yield.

In summary, bromineless brominating reagent EDPBT has been employed as a thiophilic/desulfurizing reagent for the efficient construction of a library of five and six membered *N*, -*O*, -*S* heterocycles in one-pot. So far, most of the reported methods were performed in multisteps using toxic heavy metals or using expensive reagents. The most interesting aspect of the present report is the regioselective product formation for unsymmetrical thiourea having a napthyl moiety in one side and an *o*-amino or an *o*-hydroxyphenyl on the other side which is dependent on the nature of the nucleophiles (OH or NH_2). Another interesting aspect is the differential reactivity of *bis*-thioureas of aliphatic and aromatic 1,2-diamines, the former giving 1-imidazolidinecarbothioamide and the later benzimidazole and isothiocyanate. In addition, the ease of preparation of this reagent, facile isolation of products, and recyclability of the spent reagent makes this method more practical over the existing methods in the literature.

III.5. Experimental Section

III.5.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1, Page number 56-57.

III.5.2. General Procedures

III.5.2.1. General Procedure for the Preparation of *N*-Phenyl-1*H*-benzo[*d*]imidazol-2-amine (1b)

To a solution of phenyl isothiocyanate **1** (270 mg, 2 mmol) in CH_3CN (6 mL) was added *o*-phenylenediamine **a** (216 mg, 2 mmol), at room temperature. Formation of monothiourea was observed within 30 min as judged from thin layer chromatography (TLC). To this reaction mixture was added triethylamine (835 μL, 6 mmol) followed by portion wise addition of EDPBT (666 mg, 1 mmol) over a period of 10–15 min The reaction was kept at room temperature for stirring, and complete conversion to benzimidazole **1b** was observed within 30 min with concomitant precipitation of sulfur as can be judged from TLC and disappearance of orange color of EDPBT. After completion of the reaction, the solvent was evaporated and the reaction mixture was admixed with

ethyl acetate (15 mL) and water (8 mL). The water layer containing the spent reagent 1,1'-(ethane-1,2-diyl)dipyridinium ditribromide (EDPDB) was collected separately for recycling. The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product was isolated by silica gel column (1:4 ethyl acetate/hexane) to give 90% the product **1b**.

III.5.2.2. General Procedure for the Preparation of *N*-2-Phenyl-1,3-benzoxazol-2-amine (1c)

To a solution of phenyl isothiocyanate **1** (270 mg, 2 mmol) in CH_3CN (6 mL) was added *o*-aminophenol (218 mg, 2 mmol), at room temperature. Formation of monothiourea was observed within 30 min as judged from TLC. To this reaction mixture was added triethylamine (835 µL, 6 mmol) followed by portion wise addition of EDPBT (666 mg, 1 mmol) over a period of 10-15 min. The reaction was kept for stirring at room temperature and complete conversion to benzoxazole was observed within 30 min with concomitant precipitation of sulfur as can be judged from TLC and disappearance of orange color of EDPBT. After completion of the reaction, solvent was evaporated and the reaction mixture was admixed with ethyl acetate (15 mL) and water (8 mL). The water layer containing the spent reagent 1,1'-(ethane-1,2-diyl)dipyridinium ditribromide (EDPDB) was collected separately for recycling.The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product was isolated by silica gel column (1:9 ethyl acetate/hexane) to give 82% of the product **1c**.

III.5.2.3. General Procedure for the Preparation Benzothiazol-2-yl-phenyl-amine (1d)

Similar to General Procedure III.5.2.2, except *o*-amino-thiophenol was used instead of *o*-aminophenol to give 81% of the product **1d**.

III.5.2.4. General Procedure for the Preparation *N*-(phenyl)-4H-benzo[*d*] [3,1]oxazin-2-amine (1e)

Similar to general procedure III.5.2.3, except 2-amino-bezyl alcohol was used instead of *o*-aminothiophenol to 76% of the give product **1e.**

III.5.2.5. General Procedure for the Preparation of *N*-Phenyl-2-(phenylimino)imidazolidine-1-Carbothioamides (1f)

To a solution of phenyl isothiocyanate **1** (270 mg, 2 mmol.) in CH_3CN (6 mL) was added ethylenediamine (1 mmol, 68 µL) at room temperature. Formation of *bis*-thiourea was observed within 30 min as judged from TLC. To this reaction mixture was added triethylamine (278 µL, 2 mmol) followed by portion wise addition of EDPBT (333mg, 0.5 mmol) over a period of 10-15 min. The reaction was kept for stirring at room temperature and complete conversion to *N*-phenyl-2-(phenylimino)imidazolidine-1-carbothioamide **1f** was observed with concomitant precipitation of sulfur (within 5 min) as can be judged from TLC and disappearance of orange color of EDPBT. After completion of the reaction, solvent was evaporated and the reaction mixture was admixed with ethyl acetate (15 mL) and water (8 mL). The water layer containing the spent reagent 1,1'-(ethane-1,2-diyl)dipyridinium ditribromide (EDPDB) was collected separately for recycling. The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product was isolated by silica gel column (1:9 ethyl acetate/hexane) to give 78% of the product **1f**

III.5.2.6. Regeneration of 1,1'-(Ethane-1,2-diyl)dipyridinium Bistribromide (EDPBT) from 1,1'-(Ethane-1,2-diyl)dipyridinium Ditribromide (EDPDB)

The spent reagent recovered from five consequitive reactions were combined which was concentrated to ~ 25 mL after keeping for few. The aqueous layer having approximately 5 mmol of 1,1'-(ethane-1,2-diyl)dipyridinium ditribromide (EDPDB) was added KBr 1.5g (12.5 mmol). To the above aqueous reaction mixture was cooled in an ice bath and Oxone® 6.75g (11 mmol) was added pinch wise over a period of 15 min. The precipitate orange solid was filtered, washed with water (2 x 5 mL), dried in a vacuum dessicator to yield 2.93 g (88%) of the 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). The recovered reagent was identical in all respects to that of the parent reagent with similar desulfurizing ability.

III.6. References

1. (a) Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N.; Rao, M. V. *Mini-Rev. Med. Chem.* **2006**, *6*, 71; (b) Boiani, M.; Gonzalez, M. *Min-Rev. Med. Chem.* **2005**, *5*, 409; (c) Sondhi, S. M.; Singhal, N.; Johar, M.; Reddy, B. S. N.; Lown, J. W. *Curr. Med. Chem.* **2002**, *9*, 1045; (d) McArthur, K. E.; Jensen, R. T.; Gardner, J. D. *Annu. Rev. Med.* **1986**, *37*, 97.
2. (a) Mukhopadhyay, T.; Sasaki, J.; Ramesh, R.; Roth, J. A. *Clin. Cancer Res.* **2002**, *8*, 2963; (b) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1925; (c) Navarrete-Vazquez, G.; Cedillo, R.; Hernandez-Campos, A.; Yepez, L.; Hernandez-Luis, F.; Valdez, J.; Morales, R.; Cortes, R.; Hernandez, M.; Castillo, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 187; (d) Palmer, B. D.; Kraker, A. J.; Hartl, B. G.; Panopoulos, A. D.; Panek, R. L.; Batley, B. L.; Lu, G. H.; Trumpp-Kallmeyer, S.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1999**, *42*, 2373; (e) Madsen, P.; Knudsen, L. B.; Wiberg, F. C.; Carr, R. D. *J. Med. Chem.* **1998**, *41*, 5150.
3. (a) Muro, F.; Iimura, S.; Yoneda, Y.; Chiba, J.; Watanabe, T.; Setoguchi, M.; Takayama, G.; Yokoyama, M.; Takashi, T.; Nakayama, A.; Machinaga, N. *Bio. Med. Chem.* **2009**, *17*, 1232; (b) Harris, N. V.; Fenton, G. World Pat. 2002098426, **2002**; (c) Surleraux, D. L. N. G.; Vendeville, S. M. H.; Verschueren, W. G.; De Bethune, M.-P. T. M. M. G.; De Kock, H. A.; Tahre, A. World Pat. 2002092595, **2002**; (d) Fenton, G.; McCarthy, C.; Mackenzie, R. E.; Morley, A. D. World Pat. 2001064659, **2001**; (e) Brittain, D. R.; Johnstone, C.; Davies, G**.** M.; Large, M. S. World Pat. 200005223, **2000**.
4. (a) Suter, H.; Zutter, H. *Helv. Chim. Acta* **1967**, *50*, 1084; (b) Hays, S. J.; Rice, M. J.; Ortwine, D. F.; Johnson, G.; Schwartz, R. D.; Boyd, D. K.; Copeland, L. F.; Vartanian, M. G.; Boxer, P. A. *J. Pharm. Sci.* **1994**, *83*, 1425; (c) Jimonet, P.; Audiau, F.; Barreau, M.; Blanchard, J.-C.; Boireau, A.; Bour, Y.; Coleno, M.-A.; Doble, A.; Doerflinger, G.; Do Huu, C.; Donat, M.-H.; Duchesne, J. M.; Ganil, P.; Gueremy, C.; Honore, E.; Just, B.; Kerphirique, R.; Gontier, S.; Hubert, P.; Laduron, P. M.; Le Blevec, J.; Meunier, M.; Miquet, J.-M.; Nemecek, C.; Pasquet, M.; Piot, O.; Pratt, J.; Rataud, J.; Reibaud, M.; Stutzmann, J.-M.; Mignani, S. *J. Med. Chem.* **1999**, *42*, 2828; (d) He, Y.; Benz, A.; Fu, T.; Wang, M.; Covey, D. F.; Zorumski, C. F.; Mennick, S. *Neuropharmacology* **2002**, *42*, 199; (e) Sawhney, S. N.; Arora, S. K.; Singh, J. V.; Bansal, O. P.; Singh, S. P. *Indian J. Chem.* **1978**, *16B*, 605; (f) Bensimon, G.; Lacomblez, L.; Meininger, V. *New Engl. J. Med.* **1994**, *330*, 585; (g) Foscolos, G.; Tsatsas, G.; Champagnac, A.; Pommier, M. *Ann. Pharm. Fr.* **1977**, *35*, 295; (h) Shirke, V. G.; Bobade, A. S; Bhamaria, R.

P.; Khadse, B. G.; Sengupta, S. R. *Indian Drugs* **1990**, *27*, 350; (i) Paget, C. J.; Kisner, K.; Stone, R. L.; Delong, D. C. *J. Med. Chem.* **1969**, *12*, 1016.

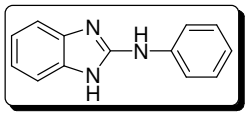
5. (a) Ohtsuka, T.; Aoki, Y. *Drugs Future* **2003**, *28*, 143 and references cited therein; (b) Armour, D. R.; Bell, A. S.; Kemp, M. I.; Edwards, M. P.; Wood, A. *Abstracts of Papers*, *221st national meeting of the American Chemical Society, San Diego, CA*; American Chemical Society: Washington, DC, 2001; Abstract MEDI-349; (c) Bell, A. S.; Armour, D. R.; Edwards, M. P.; Kemp, M. I.; Wood, A. *Abstracts of papers, 22[1st] national meeting of the American Chemical Society*, *San Diego*, *CA*; American Chemical Society: Washington, DC, 2001, Abstract MEDI-350; (d) Yamazaki, K.; Kaneko, Y.; Suwa, K.; Ebara, S.; Nakazawa, K.; Yasuno, K. *Bioorg. Med. Chem.* **2005**, *13*, 2509.
6. For neurotransmission see the reference: Benavides, J.; Camelin, J. C.; Mitrani, N.; Flamand, F.; Uzan, A.; Legrand, J. J.; Gue´re´my, C.; Le Fur, G. *Neuropharmacology* **1985**, *24*, 555
7. (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed.; John Wiley & Sons Inc.: 1991; pp 265-266 and 433; (b) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460; (c) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807; (d) Panek, J. S.; Masse, C. E. *J. Org. Chem.* **1998**, *63*, 2382; (e) William, B. T. *UK Pat. Appl.* GB 2010816, **1979**.
8. (a) Murphy, D. B. *J. Org. Chem.* **1963**, *29*, 1613; (b) Charton, J.; Girault-Mizzi, S.; Debreu-Fontaine, M.-A.; Foufelle, F.; Hainault, I.; Bizot-Espiard, J.-G.; Caignard, D.-H.; Sergheraert, C. *Bioorg. Med. Chem.* **2006**, *14*, 4490; (c) Carpenter, R. D.; De Bredt, P. B.; Lam, K. S.; Kurth, M. J. *J. Comb. Chem.* **2006**, *8*, 907; (d) Lan, P.; Romero, F. A.; Malcolm, T. S.; Stevens, B. D.; Wodka, D.; Makara, G. M. *Tetrahedron Lett.* **2008**, *49*, 1910.
9. (a) Cee, V. J.; Downing, N. S. *Tetrahedron Lett.* **2006**, *47*, 3747; (b) Omar, A.-M. M. E.; Habib, N. S.; Aboulwafa, O. M. *Synthesis* **1974**, 864; (c) Heinelt, U.; Schultheis, D.; Jager, S.; Lindenmaier, M.; Pollex, A.; Beckmann, H. S. G. *Tetrahedron* **2004**, *60*, 9883; (d) Omar, A.-M. M. E. *Synthesis* **1974**, 41; (e) Perkins, J. J.; Zartman, A. E.; Meissner, R. S. *Tetrahedron Lett.* **1999**, *40*, 1103; (f) Omar, A.-M. M. E.; Ragab, M. S.; Farghaly, A. M.; Barghash, A. M. *Pharmazie* **1976**, *31*, 348; (g) Ghosh, H.; Yella, R.; Nath, J.; Patel, B. K. *Eur. J. Org. Chem.* **2008**, 6189.
10. (a) Wang, X.-J.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Tetrahedron Lett.* **2004**, *45*, 7167; (b) Das, P.; Kumar, C. K.; Kumar, K. N.; Innus, M. D.; Iqbal. J.; Srinivas, N. *Tetrahedron Lett.* **2008**, *49*, 992; (c) Xie, Y.; Zhang, F.; Li, J.; Shi, X. *Synlett* **2010**, 901.
11. (a) Ogura, H.; Mineo, S.; Nakagawa, K. *Chem. Pharm. Bull.* **1981**, *29*, 1518; (b) Janssens, F. E.; van Offenwert, T. T.; Stokbroekx, R. A.; Boar, B. R. *Eur. Pat. Appl.* EP 199400, **1986**; (c)

Stokbroekx, R. A.; Luyckx, M. G. M.; Janssens, F. E. *Eur. Pat. Appl*. EP 184257, **1986**; (d) Qian, X. H.; Song, G.-H.; Li, Z.-B. *Gangkai Shuomingshu*, 1294126, **2001**; X. Qian,; Z. Li, G. Song, Z. Li, *J. Chem. Res. (S)* **2001**, 138; (e) Simov, D.; Davidkov, K. *Chem. Heterocycl. Compd.* **1976**, *12*, 151; (f) Simov, D.; Davidkov, K. *Chem. Heterocycl. Compd.* **1981**, *17*, 437.

12. (a) Chang, H.-S.; Yon, G.-H.; Kim, Y.-H. *Chem. Lett*. **1986**, 1291; (b) Mellor, D. P. *Chem. Ind*. (London) **1965**, 723; (c) Wishart, N.; Rudolph, A.; Ritter, K. *U.S. Pat Appl*. 20030109714, **2003**; (d) You, S.-W.; Lee, K.-J. *Bull. Korean Chem. Soc*. **2001**, *22*, 1270; (e) Tian, Z.; Plata, D. J.; Wittenberger, S. J.; Bhatia, A. V. *Tetrahedron Lett.* **2005**, *46*, 8341; (f) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6901.
13. (a) Hugerschoff, H. *Chem. Ber.* **1901**, *34*, 3130; (b) Hugerschoff, H. *Chem. Ber.* **1903**, *36*, 3121; (c) Sprague, J. M.; Land, A. H. In *Heterocyclic Compounds,* Elderfield, R. C.; Ed.; J. Wiley: New York, 1957; Vol.5, Chapter 8, pp 484-721; (d) Jordan, A. D.; Luo, C.; Reitz, A. B. *J. Org. Chem.* **2003**, *68*, 8693; (e) Le, Z.-G.; Xu, J.-P.; Rao. H.-Y.; Ying, M. *J. Heterocyclic Chem.* **2006**, *43*, 1123.
14. (a) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun*. **2004**, 446; (b) Miloudi, A.; El-Abed, D.; Boyer, G.; Finet, J. P.; Galy, J. P.; Siri, D. *Eur. J. Org. Chem*. **2004**, 1509; (c) Ding, Q.; He, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 587; (d) Benedı, C.; Bravo, F.; Uriz, P.; Ferna´ndez, E.; Claverb, C.; Castillon, S. *Tetrahedron Lett.* **2003**, *44*, 6073.
15. (a) Kandeel, M. M. *Bull. Pol. Acad. Sci-Chem.* **2002**, *50,* 309; (b) Fajkusova, D.; Pazdera, P. *Synthesis* **2008**, 1297; (c) Molina, P.; Arques, A.; Molina, A. *Synthesis* **1991**, 21.
16. (a) Walter, R.; Ruediger, O. *Chem. Ber*. **1973**, *106*, 484; (b) Wilfried, D.; Peter, B.; Joachim, S. H.; Klaus, L.; Schmidt, R. R. *EU Pat.* Appl. No. EP 451651, **1991**.
17. (a) Yella, R.; Ghosh, H.; Murru, S.; Sahoo, S. K.; Patel, B. K. *Synth. Commun.* **2010**, *40*, 2083; (b) Yella, R.; Kavala, V.; Patel, B. K. *Synth. Commun.* **2011**, LSYC 464774.
18. (a) Murru, S.; Singh, C. B.; Kavala, V.; Patel. B. K. *Tetrahedron* **2008**, *64*, 1931; (b) Highlighted on the web as best reagent. To see please use this link. http://www.organic-chemistry.org/Highlights/2006/18September.shtm.

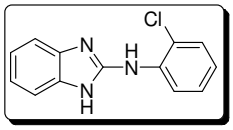
III.7. Spectral Data

_N_-Phenyl-1_H_-benzo[_d_]imidazol-2-amine (1b):



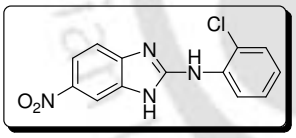
M.p. 150–152 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.29 (br s, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 7.04 (m, 2H), 7.23 (m, 2H), 7.30 (m, 2H), 7.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.7, 118.4, 120.7, 122.0, 129.1, 137.4, 140.0, 151.4. IR (KBr): 3053, 2917, 1635, 1603, 1573, 1531, 1498, 1456, 1270, 1233, 1184, 1045, 898, 754, 743 cm^{-1}.

_N_-(2-Chlorophenyl)-1_H_-benzo[_d_]imidazol-2-amine (2b):



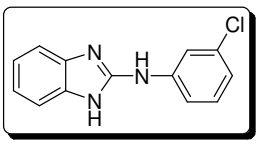
M.p. 152–154 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.70 (brs, 1H), 6.89 (t, *J* = 7.2 Hz, 1H), 7.07 (m, 2H), 7.25–7.38 (m, 4H), 8.66 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, + DMSO-d_6): δ 112.6, 118.9, 120.5, 121.6, 127.5, 128.8, 136.4, 150.2. IR (KBr): 3056, 2926, 1625, 1600, 1557, 1461, 1448, 1319, 1267, 1233, 1034, 738, 617 cm^{-1}.

_N_-(2-Chlorophenyl)-4-nitro-1_H_-benzo[_d_]imidazol-2-amine (3b):



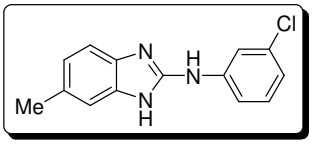
M.p. 213–215 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.58 (s, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 2H), 8.02 (m, 1H), 8.25 (s, 1H), 8.63 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 108.0, 111.8, 116.6, 119.4, 121.2, 122.3, 127.1, 128.5, 135.3, 141.0, 153.2. IR (KBr): 3374, 3312, 2924, 1609, 1567, 1532, 1468, 1450, 1362, 1324, 1124, 1070, 1026, 869, 820, 737 cm^{-1}.

_N_-(3-Chlorophenyl)-1_H_-benzo[_d_]imidazol-2-amine (4b):



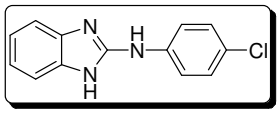
M.p. 183–185 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.68 (br s, 1H), 6.91 (m, 1H), 7.07 (m, 2H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.36 (m, 2H), 7.51 (m, 1H), 7.75 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.8, 115.6, 117.2, 117.7, 120.7, 121.1, 129.9, 130.4, 141.6, 150.4. IR (KBr): 3394, 2923, 1591, 1559, 1459, 1241, 1193, 776, 747 cm^{-1}.

_N_-(3-Chlorophenyl)-6-methyl-1_H_-benzo[_d_]imidazol-2-amine (5b):



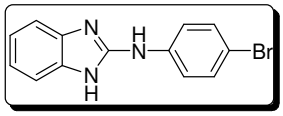
M.p. 95–97 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.41 (s, 3H), 4.62 (br s, 1H), 6.92 (t, *J* = 8.0 Hz, 2H), 7.21 (m, 3H), 7.44 (m, 1H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 21.6, 112.5, 112.8, 116.4, 118.0, 121.8, 122.4, 130.2, 130.9, 134.4, 134.6, 136.1, 141.2, 150.1. IR (KBr): 2921, 1648, 1594, 1558, 1478, 1275, 1094, 912, 856, 798, 770, 678, 594 cm^{-1}. $C_{14}H_{12}ClN_3$ (257.72): calcd C 65.25, H 4.69, N 16.30; found C 65.21, H 4.73, N 16.22.

_N_-(4-Chlorophenyl)-1_H_-benzo[_d_]imidazol-2-amine (6b):



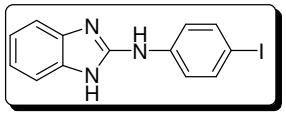
M.p. 178–180 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.40 (br s, 1H), 7.06 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 2H) 7.34 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.5, 118.9, 120.5, 125.7, 128.6, 136.9, 138.7, 150.4. IR (KBr): 3048, 2916, 1646, 1593, 1567, 1517, 1488, 1461, 1426, 1384, 1266, 1251, 1089, 1009, 841, 819, 742, 701 cm^{-1}. $C_{13}H_{10}ClN_3$ (243.69): calcd C 64.07, H 4.14, N 17.24; found C 64.10, H 4.12, N 17.27.

_N_-(4-Bromophenyl)-1_H_-benzo[_d_]imidazol-2-amine (7b):



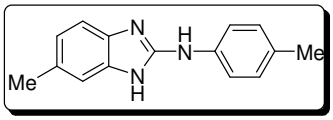
M.p. 213–215 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.80 (br s, 1H), 7.03 (m, 2H), 7.34 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.1, 112.3, 118.7, 120.0, 131.0, 136.6, 139.0, 149.9. IR (KBr): 3154, 3048, 2921, 1644, 1604, 1587, 1567, 1511, 1487, 1461, 1428, 1384, 1266, 1252, 1071, 1005, 817, 759, 740, 700, 661, 499, 475 cm^{-1}.

_N_-(4-Iodophenyl)-1_H_-benzo[_d_]imidazol-2-amine (8b):



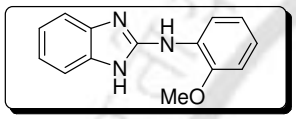
M.p. 108–110 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.52 (br s, 2H), 7.03 (m, 2H), 7.33 (m, 2H), 7.56 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 82.8, 112.7, 119.69, 119.7, 120.5, 137.4, 140.4, 150.2. IR (KBr): 3380, 3052, 2954, 1605, 1586, 1556, 1485, 1461, 1415,1266, 1240, 1042, 1005, 810, 739 cm^{-1}. HRMS (ESI): Calcd for $C_{13}H_{10}IN_3$ [MH^+] 335.9953, found 335.9981.

_N_-(_p_-Methylphenyl)-6-methyl-1_H_-benzo[_d_]imidazol-2-amine (9b):



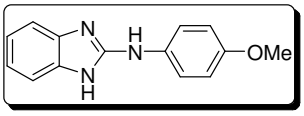
M.p. 191–194 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.27 (s, 3H), 2.37 (s, 3H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 9.06 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 19.1, 20.0, 110.8, 111.2, 116.1, 119.8, 127.7, 127.9, 128.4, 136.8, 149.4. IR (KBr): 3387, 3135, 3030, 2916, 2858, 1602, 1567, 1539, 1514, 1487, 1378, 1274, 1238, 1218, 1185, 1037, 809 cm^{-1}. $C_{15}H_{15}N_3$ (237.30): calcd C 75.92, H 6.37, N 17.71; found C 75.95, H 6.34, N 17.75.

_N_-(2-Methoxyphenyl)-1_H_-benzo[_d_]imidazol-2-amine (10b):



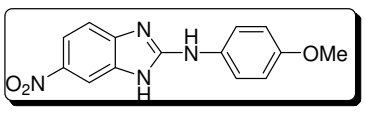
M.p. 175–177 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.93 (s, 3H), 4.60 (br s, 1H), 6.92 (m, 2H), 6.98–7.05 (m, 3H), 7.35 (m, 2H), 8.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6): δ 55.0, 109.1, 109.4, 116.5, 119.6, 120.2, 120.4, 121.6, 128.9, 146.5, 150.3. IR (KBr): 3412, 3053, 2958, 2927, 1606, 1567, 1530, 1459, 1421, 1357, 1251, 1177, 1121, 1029, 748 cm^{-1}.

_N_-(4-Methoxyphenyl)-1_H_-benzo[_d_]imidazol-2-amine (11b):



M.p. 180 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.76 (s, 3H), 4.12 (br s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.01 (m, 2H), 7.30 (m, 2H), 7.50 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 55.1, 109.5, 112.1, 114.0, 120.0, 133.1, 137.2, 151.6, 154.5. IR (KBr): 2921, 2832, 1623, 1605, 1574, 1514, 1461, 1393, 1314, 1274, 1175, 1026, 915, 806, 741, 593 cm^{-1}.

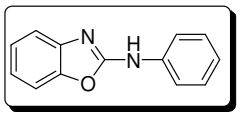
_N_-(4-Methoxyphenyl)-6-nitro-1_H_-benzo[_d_]imidazol-2-amine (12b):



M.p. 203–205 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.76 (s, 3H), 4.75 (br s, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 1H), 8.14 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 55.7, 107.9, 112.7, 114.2, 114.6, 117.5, 120.9, 121.0, 132.9, 141.4, 155.5. IR (KBr): 3415, 2926, 1676, 1614, 1586, 1510, 1471, 1316, 1285, 1244, 1071, 1031, 946, 823 cm^{-1}.

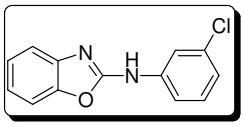
$C_{14}H_{12}N_4O_3$ (284.27): calcd C 59.15, H 4.25, N 19.71; found: C 59.17, H 4.29, N 19.65.

***N*-2-Phenyl-1,3-benzoxazol-2-amine (1c):**



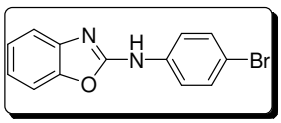
M.p. 172–174 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (m, 2H), 7.25 (t, *J* = 8.6 Hz, 1H), 7.39 (m, 3H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 9.18 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.4, 117.1, 118.8, 121.9, 123.6, 124.5, 129.6, 138.1, 142.2, 148.1, 158.9. IR (KBr): 3164, 3049, 2925, 1659, 1601, 1575, 1503, 1459, 1375, 1250, 1225, 1004, 973, 819 cm^{-1}.

***N*-2-(3-Chloro-phenyl)-1,3-benzoxazol-2-amine (2c):**



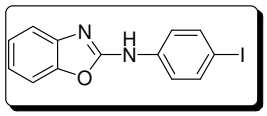
M.p. 184–186 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.99 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.92 (s, 1H), 10.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 108.2, 115.5, 116.4, 117.0, 121.2, 121.4, 123.4, 129.4, 133.6, 139.6, 141.8, 146.8, 157.3. IR (KBr) 3022, 2920, 1687, 1600, 1579, 1461, 1483, 1350, 1246, 1170, 1080, 882, 776, 737, 676 cm^{-1}. $C_{13}H_9ClN_2O$ (244.68): calcd C 63.81, H 3.71, N 11.45; found C 63.85, H 3.76, N 11.49.

***N*-2-(4-Bromophenyl)-1,3-benzoxazol-2-amine (3c):**



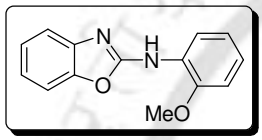
M.p. 219–221 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.10 (t, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.42–7.48 (m, 3H), 7.69 (d, *J* = 8.8 Hz, 2H), 10.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 108.5, 114.1, 116.7, 119.4, 121.4, 123.7, 131.4, 137.8, 142.3, 147.2, 157.8. IR (KBr): 3160, 3029, 1667, 1643, 1592, 1574, 1490, 1459, 1366, 1219, 1232, 1168, 1005, 822, 752, 737, 499 cm^{-1}. $C_{13}H_9BrN_2O$ (289.13): calcd C 54.00, H 3.14, N 9.69; found C 53.97, H 3.18, N 9.74.

_N_-2-(4-Iodophenyl)-1,3-benzoxazol-2-amine (4c):



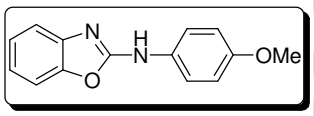
M.p. 227 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.11 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.59 (m, 4H), 10.21 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 84.5, 108.5, 116.8, 119.9, 121.5, 123.7, 137.5, 138.5, 142.4, 147.3, 157.9. IR (KBr): 3433, 3158, 2921, 1661, 1591, 1561, 1488, 1458, 1363, 1247, 1230, 1002, 978, 817, 752, 736 cm^{-1}. HRMS (ESI): Calcd for $C_{13}H_9IN_2O$ [MH^+] 336.9839, found 336.9857.

_N_-2-(2-Methoxyphenyl)-1,3-benzoxazol-2-amine (5c):



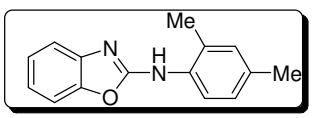
M.p. 106 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.00–7.13 (m, 3H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H,), 7.66 (br s, 1H), 8.41 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9, 109.1, 110.2, 117.6, 121.5, 122.5, 123.7, 124.3, 127.6, 142.9, 147.5, 147.9, 157.9. IR (KBr): 3388, 2926, 1638, 1606, 1578, 1528, 1456, 1346, 1254, 1242, 1213, 1165, 1115, 982, 740 cm^{-1}. $C_{14}H_{12}N_2O_2$ (240.26): calcd. C 69.99, H 5.03, N 11.66; found C 70.08, H 5.09, N 11.57.

_N_-2-(4-Methoxyphenyl)-1,3-benzoxazol-2-amine (6c):



M.p. 136–138 °C, ^{1}H NMR: (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.80 (s, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 9.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 55.5, 108.7, 114.3, 116.6, 120.4, 121.2, 123.9, 131.6, 142.6, 147.7, 155.5, 159.2. IR (KBr): 3154, 3043, 2838, 1681, 1590, 1580, 1554, 1505, 1484, 1369, 1347, 1231, 1174, 1006, 1031, 967, 821, 742, 626, 600, 515 cm^{-1}.

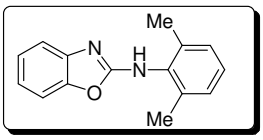
_N_-2-(2,4-Dimethylphenyl)-1,3-benzoxazol-2-amine (7c):



M.p. 131 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.32 (s, 3H), 7.00–7.10 (m, 3H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100

MHz, $CDCl_3$): δ 17.9, 21.0, 109.2, 117.1, 121.7, 124.3, 127.8, 131.6, 133.5, 134.6, 142.8, 148.3, 159.6. IR (KBr): 3131, 3016, 2912, 1673, 1577, 1459, 1349, 1278, 1240, 1215, 1166, 1004, 965, 872, 803, 735 cm^{-1}.

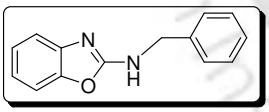
***N*-2-(2,6-Dimethylphenyl)-1,3-benzoxazol-2-amine (8c):**



M.p. 198 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 6H), 7.00 (m, 2H), 7.10–7.23 (m, 5H), 9.10 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 109.3, 116.3, 121.0, 124.2, 127.6, 128.7, 134.5, 136.3, 142.7, 148.7, 161.4. IR (KBr): 3137, 3021, 2901, 1659, 1580, 1459, 1349, 1336, 1245, 1212, 1163, 1100, 968, 842, 754 cm^{-1}.

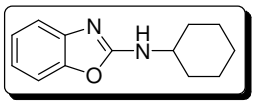
Crystal data for 8c: Crystal dimension (mm): 0.3 x 0.2 x 0.1; $C_{15}H_{14}N_2O$, M_r = 238.28; monoclinic, space group P21/n; a = 11.0031(4) Å, b = 17.0388(6) Å, c = 14.9909(5) Å; $\alpha = \gamma = 90.00^o$, β = 109.882(2)°; V = 2642.97(16) $Å^3$; Z = 8; ρ_{cal} = 1.198 mg/m^3; μ(mm^{-1}) = 0.077; F(000) = 1008; reflection collected / unique = 5913 / 5560; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] R_1 = 0.0786, wR_2 = 0.1842, R indices (all data) R_1 = 0.1749, wR_2 = 0.2169; goodness of fit = 1.062. CCDC # 769692.

***N*-2-(Benzyl)-1,3-benzoxazol-2-amine (9c):**



M.p. 122–124 °C, ^{1}H NMR: (400 MHz, $CDCl_3$): δ 4.67 (s, 2H), 6.58 (br s, 1H), 7.03 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 8.4 Hz, 2H), 7.28–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.1, 108.9, 116.4, 120.9, 124.1, 127.7, 127.9, 128.9, 137.9, 142.9, 148.6, 162.4. IR (KBr): 3439, 3027, 2912, 1665, 1585, 1456, 1371, 1341, 1245, 1179, 1111, 943, 738 cm^{-1}.

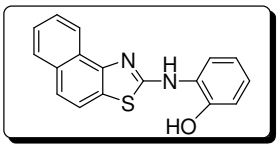
***N*-2-(Cyclohexyl)-1,3-benzoxazol-2-amine (10c):**



M.p. 108–110 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13–1.45 (m, 5H), 1.60–1.78 (m, 2H), 2.11 (m, 2H), 3.73 (br s, 1H), 6.09 (br s, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.0 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 25.6, 33.6, 52.2, 108.7, 115.9, 120.5, 123.9, 143.1, 148.4, 161.9. IR (KBr):

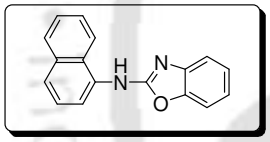
3395, 3203, 3021, 2934, 2857, 1643, 1580, 1374, 1352, 1281, 1176, 1146, 1108, 1004, 886, 836, 732 cm^{-1}.

2-(Naphtho[1,2-*d*]thiazol-2-ylamino)phenol (15):



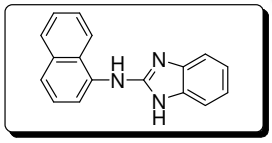
M.p. 216–218 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.92–6.99 (m, 3H), 7.50–7.65 (m, 3H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.90 (t, *J* = 7.0 Hz, 1H), 8.12 (d, *J* = 7.2 Hz, 1H), 8.52 (t, *J* = 7.2 Hz, 1H), 9.41 (br s, 1H), 10.2 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 115.6, 117.8, 118.8, 119.0, 121.4, 122.7, 122.8, 124.1, 124.5, 125.1, 125.4, 127.0, 127.9, 130.9, 146.1, 162.9. IR (KBr): 3418, 2255, 2128, 1649, 1542, 1456, 1393, 1368, 1048, 1025, 1002, 826, 764 cm^{-1}. HRMS (ESI): Calcd for $C_{17}H_{12}N_2OS$ [MH^+] 293.3691, found 293.3685.

***N*-(Naphthalen-1-yl)benzo[*d*]oxazol-2-amine (16):**



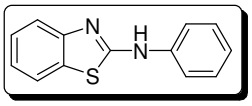
M.p. 165 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05–7.16 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.51–7.58 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.92 (m, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 8.15 (m, 1H), 9.22 (br s, 1H). ^{13}C NMR (100 MHz): δ 109.4, 117.1, 119.3 121.5, 121.8, 124.4, 125.5, 126.1, 126.5, 126.7, 127.4, 128.9, 133.3, 134.6, 142.3, 148.2, 160.2. IR (KBr): 2898, 1656, 1622, 1574, 1515, 1459, 1402, 1332, 1273, 1239, 1052, 1004, 961, 848 cm^{-1}. HRMS (ESI): Calcd for $C_{17}H_{12}N_2O$ [MH^+] 261.3031, found 261.3057.

***N*-(Naphthalen-1-yl)-1*H*-benzo[*d*]imidazol-2-amine (19):**



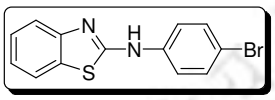
M.p. 245–248 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 5.37 (br s, 1H), 7.03 (m, 2H), 7.32 (m, 2H), 7.44–7.49 (m, 3H), 7.56 (m, 1H), 7.84 (m, 1H), 8.16–8.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.0, 115.8, 119.9, 120.9, 122.3, 125.0, 125.3, 125.6, 127.8, 133.6, 134.7, 151.4. IR (KBr): 3379, 3043, 2917, 1618, 1599, 1569, 1459, 1393, 1259, 1237, 1042, 776 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{13}N_3$ [MH^+] 260.1188, found 260.1327.

Benzothiazol-2-yl-phenyl-amines (1d):



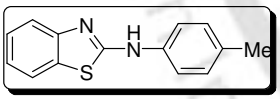
M.p. 156–158 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10–7.20 (m, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.40 (m, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 9.23 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.4, 120.7, 120.9, 121.0, 122.5, 124.7, 125.0, 126.3, 129.8, 140.1, 151.5. IR (KBr): 3189, 3053, 2932, 1625, 1603, 1571, 1497, 1466, 1446, 1272, 1248, 921 cm^{-1}.

Benzothiazol-2-yl-(4-bromo-phenyl)-amine (2d):



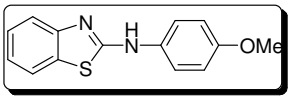
M.p. 217 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.15 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H,), 7.43 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 10.34 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 114.1, 119.9, 120.2, 120.9, 122.8, 129.1, 130.6, 131.8, 140.4, 152.5, 161.9. IR (KBr): 3174, 3069, 2956, 2899, 1619, 1584, 1562, 1454, 1448, 1445, 1311, 1298, 1270, 1246, 1226, 1076 cm^{-1}. $C_{13}H_9BrN_2S$ (305.19): calcd C 51.16, H 2.97, N 9.18, S 10.51; found C 51.20, H 2.94, N 9.21, S 10.57.

Benzothiazol-2-yl-p-tolyl-amine (3d):



M.p. 177–178 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.35–7.40 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 9.17 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 119.2, 121.0, 121.4, 122.3, 123.5, 126.3, 130.3, 134.8, 137.6, 151.6, 166.2. IR (KBr): 3183, 3029, 2914, 1624, 1572, 1514, 1447, 1404, 1330, 1271, 1247, 919 cm^{-1}.

Benzothiazol-2-yl-(4-methoxy-phenyl)-amine (4d):

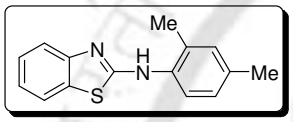


M.p. 160 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 3H), 7.56 (d, *J* = 8.0 Hz, 1H), 9.72 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.7, 115.0, 118.9, 121.0, 122.0, 124.6, 126.2,

129.8, 133.2, 151.8, 157.6; IR (KBr): 3181, 2835, 1619, 1572, 1511, 1444, 1414, 1241, 1037, 918 cm^{-1}.

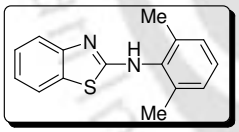
Crystal data for 4d: Crystal dimension (mm): 0.3 x 0.2 x 0.1; $C_{14}H_{12}N_2OS$, M_r = 256.33; triclinic, space group P1; a = 6.9368(2) Å, b = 8.9658(3) Å, c = 10.6643(4) Å; α = 78.187(2)°, β = 74.508(2)°, γ= 89.919(2)°; V = 624.62(4) $Å^3$; Z = 2; ρ_{cal} = 1.363 mg/m^3; $\mu(mm^{-1})$ = 0.247; $F(000)$ = 268; reflection collected/unique = 3074 / 2329; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] R_1 = 0.0380, wR_2 = 0.0981, R indices (all data) R_1 = 0.0500, wR_2 = 0.1057; goodness of fit = 1.063. CCDC # 769691.

Benzothiazol-2-yl-(2,4-dimethyl-phenyl)-amine (5d):



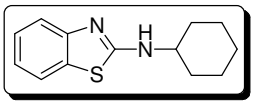
M.p. 135 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.37 (s, 3H), 7.10 (m, 3H), 7.26 (m, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 21.2, 118.9, 121.0, 122.0, 125.2, 126.2, 128.0, 132.2, 133.3, 135.9, 136.9, 152.0, 168.2. IR (KBr): 3063, 2851, 1618, 1607, 1568, 1449, 1268, 1217, 1126, 906 cm^{-1}.

Benzothiazol-2-yl-(2,6-dimethyl-phenyl)-amine (6d):



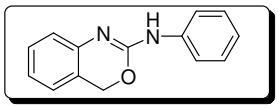
M.p. 224 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 6H), 7.01 (m, 1H), 7.22 (m, 5H), 7.48 (m, 1H), 10.20 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 118.3, 121.1, 121.5, 126.1, 128.4, 129.1, 130.4, 137.4, 137.5, 152.3, 170.2. IR (KBr): 3173, 3127, 3066, 2850, 1613, 1567, 1447, 1326, 1310, 1269, 1251, 1208, 1017, 912 cm^{-1}.

Benzothiazol-2-yl-cyclohexyl-amine (7d):



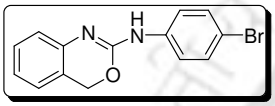
M.p. 107 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17–1.46 (m, 5H), 1.61–1.65 (m, 1H), 1.73–1.79 (m, 2H), 2.10 (m, 2H), 3.53 (s, 1H), 5.70 (br s, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.25–7.29 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 25.6, 25.63, 33.40, 33.45, 54.8, 118.8, 119.8, 120.9, 121.5, 123.4, 126.1, 129.2. IR (KBr): 3202, 3017, 2927, 2852, 1590, 1538, 1445, 1365, 1345, 1248, 1209, 1076, 885, 804, 746, 720 cm^{-1}.

_N_-(phenyl)-4_H_-benzo[_d_] [3,1]oxazin-2-amine (1e):



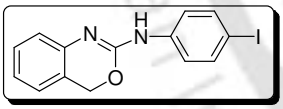
M.p. 140–142 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (s, 2H), 6.98–7.06 (m, 4H), 7.18–7.29 (m, 1H), 7.26–7.36 (m, 2H), 7.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.9, 120.7, 120.9, 121.1, 123.1, 123.2, 123.9, 129.1, 129.2, 139.8, 141.2, 152.3. IR (KBr): 3435, 2858, 1693, 1600, 1497, 1457, 1405, 1315, 1271, 1247, 1206, 1028, 899, 787, 747 cm^{-1}. HRMS (ESI): Calcd for $C_{14}H_{12}N_2O$ [MH^+] 225.1029, found 225.1028.

_N_-(4-Bromophenyl)-4_H_-benzo[_d_] [3,1]oxazin-2-amine (2e):



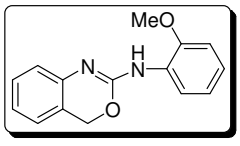
M.p. 182–184 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (s, 2H), 6.93 (d, J = 7.6 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 7.22 (m, 3H), 7.38 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.0, 115.8, 120.4, 120.7, 122.7, 123.3, 124.1, 129.4, 132.0, 139.7, 140.4, 151.7. IR (KBr): 2919, 1633, 1600, 1482, 1412, 1226, 1029, 824, 753 cm^{-1}. $C_{14}H_{12}N_2O$ (303.15): calcd C 74.98, H 5.39, N 12.49; found C 75.04, H 5.31, N 12.42.

_N_-(4-Iodophenyl)-4_H_-benzo[_d_] [3,1]oxazin-2-amine (3e):



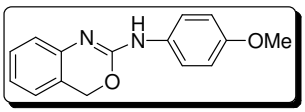
M.p. 148–150 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.23 (s, 2H), 6.97 (d, J = 8.0 Hz, 1H), 7.02 (m, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.23 (m, 1H), 7.58 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.1, 86.2, 120.8, 122.7, 123.5, 124.0, 129.4, 138.0, 151.4. IR (KBr): 3401, 2916, 1666, 1610, 1556, 1496, 1477, 1396, 1319, 1299, 1267, 1225, 1139, 1110, 1071, 909 cm^{-1}.

_N_-(2-Methoxyphenyl)-4_H_-benzo[_d_] [3,1]oxazin-2-amine (4e):



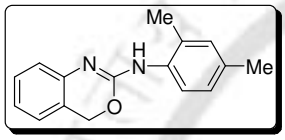
M.p. 92–94 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 5.22 (s, 2H), 6.85 (m, 1H), 6.95–7.02 (m, 5H), 7.11 (d, 1H, J = 8.4 Hz), 7.24 (m, 1H), 8.36 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 67.8, 110.1, 119.3, 121.2, 121.3, 121.9, 122.5, 122.6, 123.4, 123.8, 129.1, 148.1, 151.7. IR (KBr): 3411, 2927, 2853, 1590, 1581, 1538, 1485, 1461, 1435, 1371, 1292, 1248, 1211, 1175, 1116, 1028, 748 cm^{-1}.

_N_-(4-Methoxyphenyl)-4_H_-benzo[_d_] [3,1]oxazin-2-amine (5e):



M.p. 150–152 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.78 (s, 3H), 5.19 (s, 2H), 6.84 (d, J = 9.2 Hz, 2H), 6.98 (m, 3H), 7.20 (m, 1H), 7.40 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 55.4, 67.5, 114.0, 120.9, 121.0, 122.2, 122.5, 123.6, 128.9, 132.7, 141.5, 152.3, 155.5. IR (KBr): 3159, 3043, 2956, 2836, 1681, 1600, 1511, 1496, 1461, 1405, 1268, 1239, 1206, 1028, 885, 837, 755, 697, 594, 528 cm^{-1}.

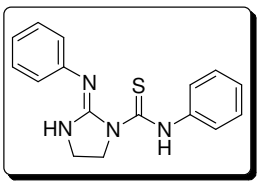
_N_-(2,4-dimethylphenyl)-4_H_-benzo[_d_] [3,1]oxazin-2-amine (6e):



M.p. 163–166 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.30 (s, 3H), 5.14 (s, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.92–6.99 (m, 4H), 7.15 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 21.0, 67.8, 120.1, 120.6, 122.5,123.8, 124.0, 127.2, 129.2, 130.9, 131.3, 134.1, 135.8, 141.2, 152.5. IR (KBr): 2976, 2917, 2865, 1680, 1650, 1598, 1484, 1457, 1402, 1305, 1268, 1251, 1206, 1251, 1206, 1123, 1031, 908, 831,756 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{16}N_2O$ [MH^+] 253.1342, found 253.1348.

Crystal data for 6e: Crystal dimension (mm): 0.3 x 0.2 x 0.1; $C_{16}H_{16}N_2O$, M_r = 252.31; monoclinic, space group P21/n; a = 5.9545(2) Å, b = 20.9440(8) Å, c = 10.9955(5) Å; $\alpha = \gamma = 90.00^o$, β = 98.408(3)^o, V = 1356.52(9) Å^3; Z = 4; ρ_{cal} = 1.235 mg/m^3; μ(mm^{-1}) = 0.078; F(000) = 536; reflection collected / unique = 3326 / 1584; refinement method = full-matrix least-squares on F^2; final R indices [I > 2σ_I] R_1 = 0.0559, wR_2 = 0.1338, R indices (all data) R_1 = 0.1308, wR_2 = 0.1618; goodness of fit = 0.982. CCDC # 769693.

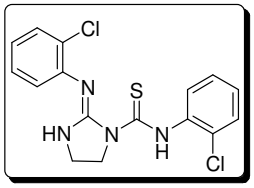
_N_-Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1f):



M.p. 190–192 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.46 (t, J = 7.9 Hz, 2H), 4.45 (t, J = 8.0 Hz, 2H), 5.39 (s, 1H), 7.02 (m, 2H), 7.08 (t, J = 6.4 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 7.35 (m, 4H), 7.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 38.4, 48.4, 122.6, 123.7, 124.4, 125.7, 128.6, 129.5, 139.1, 146.5, 151.9, 178.8. IR (KBr): 3290, 3061, 2900, 1662, 1620, 1574, 1591, 1480, 1426,

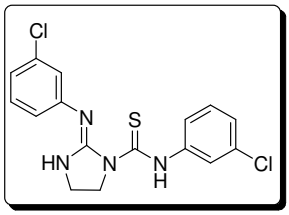
1404, 1378, 1323, 1289, 1212, 1129, 1069, 821, 785, 761, 731, 695 cm^{-1}.

2-(2-Chlorophenylimino)-N-(2-chlorophenyl)imidazolidine-1-carbothioamide (2f):



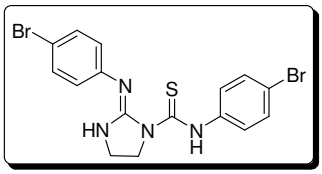
M.p. 147–149 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.48 (t, *J* = 8.0 Hz, 2H), 4.42 (t, *J* = 8.4 Hz, 2H), 6.24 (s, 1H), 7.02 (m, 1H), 7.15 (m, 2H), 7.21–7.30 (m, 2H), 7.39 (m, 2H), 8.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 38.1, 48.3, 123.6, 124.1, 126.2, 126.6, 127.3, 127.4, 127.8, 128.8, 129.1, 129.6, 136.3, 143.3, 151.2, 179.1. IR (KBr): 3230, 2889, 1689, 1600, 1581, 1556, 1470, 1415, 1395, 1364, 1322, 1294, 1123, 1067, 1048, 779, 742, 684 cm^{-1}.

2-(3-Chlorophenylimino)-N-(3-chlorophenyl)imidazolidine-1-carbothioamide (3f):



M.p. 138–140 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (t, *J* = 8.0 Hz, 2H), 4.44 (t, *J* = 8.0 Hz, 2H), 4.86 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H,), 7.27 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.73 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 38.5, 48.6, 121.1, 122.6, 123.0, 124.3, 124.4, 126.0, 129.7, 130.8, 134.3, 135.3, 140.3, 147.8, 152.1, 178.8. IR (KBr): 3417, 3104, 2894, 1667, 1586, 1562, 1474, 1425, 1403, 1376, 1322, 1294, 1133, 1078, 898, 829, 791, 679 cm^{-1}.

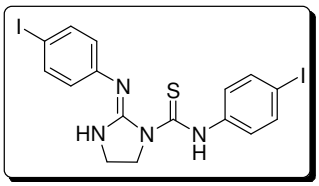
2-(4-Bromophenylimino)-N-(4-bromophenyl)imidazolidine-1-carbothioamide (4f):



M.p. 180–182 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.47 (t, *J* = 7.6 Hz, 2H), 4.44 (t, *J* = 8.4 Hz, 2H), 4.78 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.45 (m, 4H), 7.52 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 38.6, 48.7, 117.2, 119.0, 124.6, 126.1, 131.9, 132.9, 138.3, 145.6, 152.1, 178.9. IR (KBr): 3230, 2813, 1658, 1589, 1572, 1530, 1458, 1365, 1338, 1246, 1230, 1165, 1056, 1033, 1003, 970, 919, 836, 742, 710, 631 cm^{-1}.

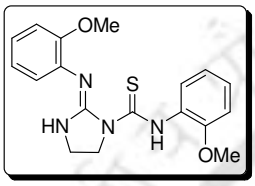
2-(4-Iodomophenylimino)-N-(4-Iodophenyl)imidazolidine-1-carbothioamide (5f):

M.p. 166–168 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (t, *J* = 7.6 Hz, 2H), 4.44 (t, *J* = 7.6 Hz, 2H), 4.80 (br s, 1H), 6.77 (d, *J* = 8.8 Hz, 2H),



7.41 (d, *J* = 8.8 Hz, 2H), 7.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.6, 48.7, 87.2, 90.0, 125.0, 126.3, 137.9, 138.6, 138.8, 146.2, 152.0, 178.7. IR (KBr): 3370, 2923, 1656, 1555, 1478, 1409, 1386, 1365, 1315, 1299, 1277, 1124, 1057, 1002, 814, 751 cm^{-1}. $C_{16}H_{14}I_2N_4S$ (548.18): calcd C 35.06, H 2.57, N 10.22, S 5.85; found C 35.10, H 2.54, N 10.18, S 5.81.

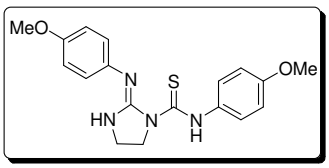
2-(2-Methoxyphenylimino)-*N*-(2-methoxyphenyl)imidazolidine-1-carbothioamide (6f):



M.p. 153 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (t, *J* = 7.6 Hz, 2H), 3.76 (s, 3H), 3.83 (s, 3H), 4.44 (t, *J* = 7.6 Hz, 2H), 4.71 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.98 (m, 3H), 7.04–7.15 (m, 3H), 8.47 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.6, 48.8, 55.9, 56.2, 111.0, 112.5, 120.1, 121.6, 124.5, 124.7, 124.8, 125.9, 128.8, 135.3, 151.3, 151.4, 151.9, 178.2. IR (KBr): 3403, 2938, 2898, 2835, 1669, 1607, 1564, 1495, 1475, 1398, 1371, 1323, 1295, 1247, 1108, 1046, 1026, 910, 748 cm^{-1}. $C_{18}H_{20}N_4O_2S$ (356.44): calcd C 60.65, H 5.66, N 15.72, S 9.00; found C 60.60, H 5.60, N 15.77, S 9.09.

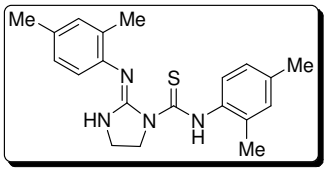
Crystal data for 6f: Crystal dimension (mm): 0.3 x 0.2 x 0.1; $C_{18}H_{20}N_4O_2S$, M_r = 356.44; monoclinic, space group C2/c; *a* = 22.8434(8) Å, *b* = 12.7023(5) Å, *c* = 15.6024(6) Å; $\alpha = \gamma = 90.00^o$, $\beta = 126.6390(10)^o$, *V* = 3632.7(2) Å^3; *Z* = 8; ρ_{cal} = 1.222 mg/m^3; μ(mm^{-1}) = 0 .164; *F*(000) = 872; reflection collected / unique = 3101 / 2424; refinement method = full-matrix least-squares on F^2; final *R* indices [I > 2σ$_I$] R_1 = 0.0398, *w*R_2 = 0.1449, *R* indices (all data) R_1 = 0.0519, *w*R_2 = 0.1604; goodness of fit = 1.015. CCDC # 769691.

2-(4-Methoxyphenylimino)-*N*-(4-methoxyphenyl)imidazolidine-1-carbothioamide (7f):



M.p. 126–128 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.44 (t, *J* = 7.6 Hz, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 4.42 (t, *J* = 8.0 Hz, 2H), 5.48 (s, 1H), 6.80–6.96 (m, 6H), 7.45 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 29.4, 38.3, 48.3, 55.3, 113.6, 114.5, 123.3, 126.0, 132.1, 139.5, 152.2, 155.7, 157.2, 179.0. IR (KBr): 2956, 2917, 2835, 1660, 1633, 1573, 1505, 1446, 1429, 1401, 1374, 1324, 1293, 1238, 1178, 1129, 1030, 827, 765, 712, 545, 519 cm^{-1}.

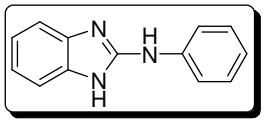
2-(2,4-Dimethylphenylimino)-*N*-(2,4-dimethylphenyl)imidazolidine-1-carbothioamide (8f):

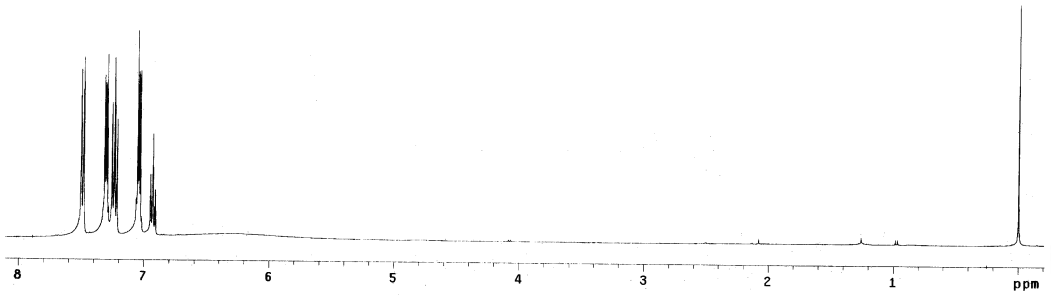


M.p. 162 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 2.28 (s, 3H), 2.29 (s, 3H), 2.32 (s, 3H), 3.46 (t, *J* = 8.0 Hz, 2H), 4.48 (t, *J* = 8.0 Hz, 2H), 4.58 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 10.4 Hz, 4H), 7.43 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 18.4, 20.9, 21.2, 38.7, 48.9, 121.7, 127.2, 127.6, 130.7, 131.4, 131.9, 133.6, 133.8, 135.5, 136.7, 142.7, 151.5, 180.2. IR (KBr): 3401, 2916, 1666, 1610, 1556, 1496, 1476, 1396, 1319, 1299, 1267, 1225, 1110, 1071, 910 cm^{-1}.

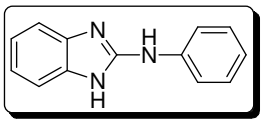
III.8. Selected Spectra

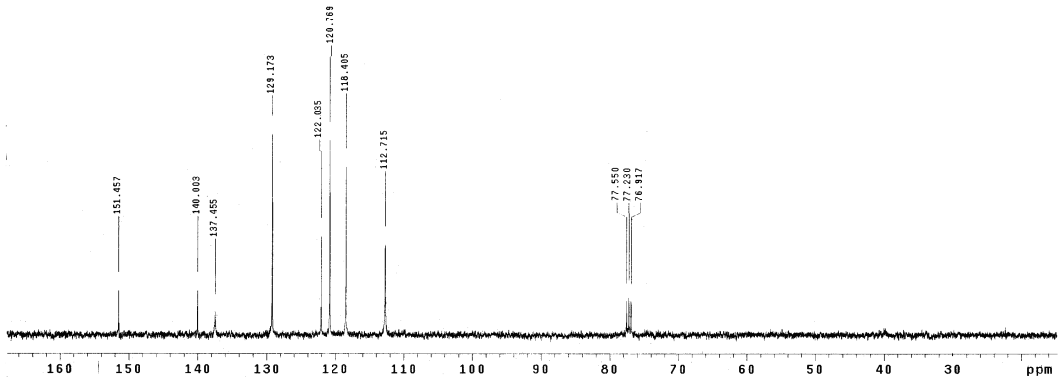
***N*-Phenyl-1*H*-benzo[*d*]imidazol-2-amine (1b): ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6):**



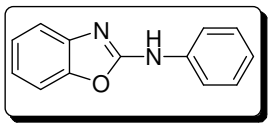


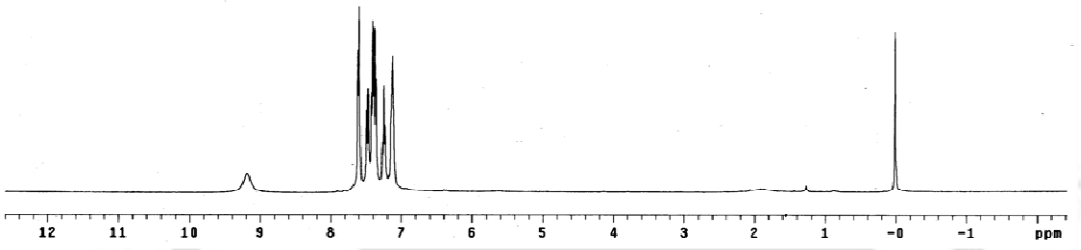
***N*-Phenyl-1*H*-benzo[*d*]imidazol-2-amine (1b): ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6):**



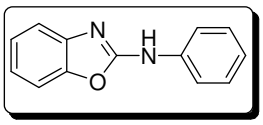


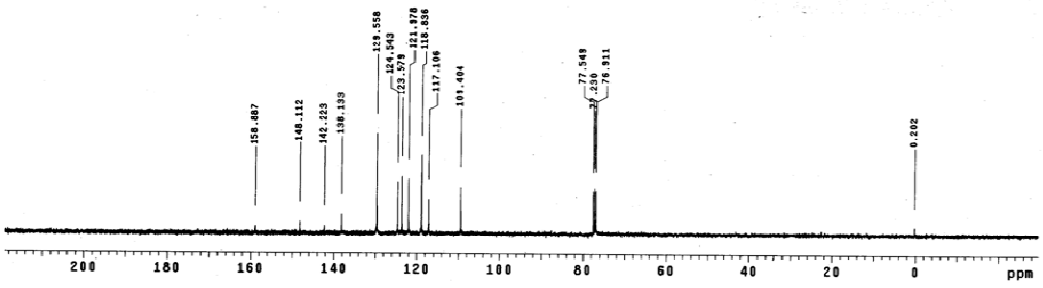
***N*-2-Phenyl-1,3-benzoxazol-2-amine (1c): ^{1}H NMR (400 MHz, $CDCl_3$):**



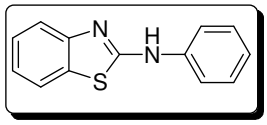


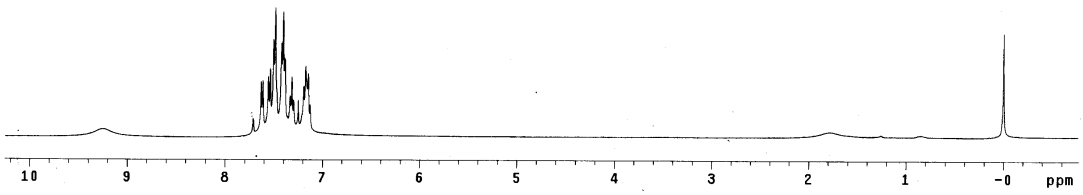
***N*-2-Phenyl-1,3-benzoxazol-2-amine (1c): ^{13}C NMR (100 MHz, $CDCl_3$):**



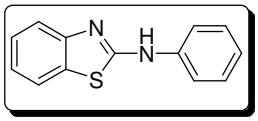


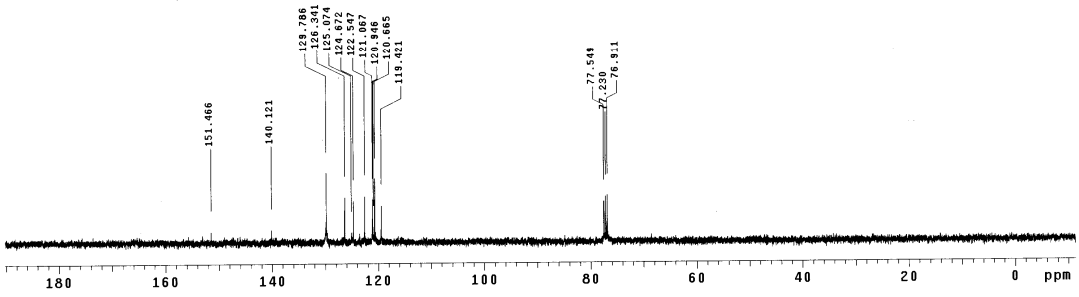
Benzothiazol-2-yl-phenyl-amine (1d): ^{1}H NMR (400 MHz, $CDCl_3$):



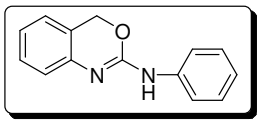


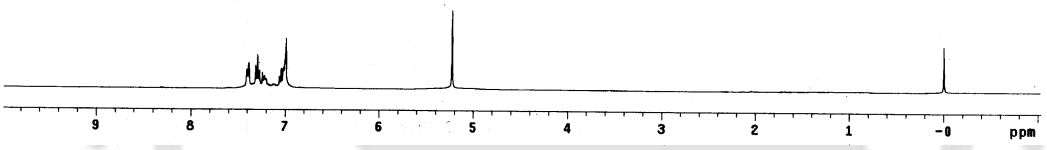
Benzothiazol-2-yl-phenyl-amine (1d): ^{13}C NMR (100 MHz, $CDCl_3$):



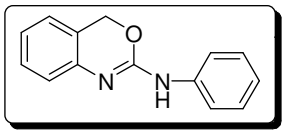


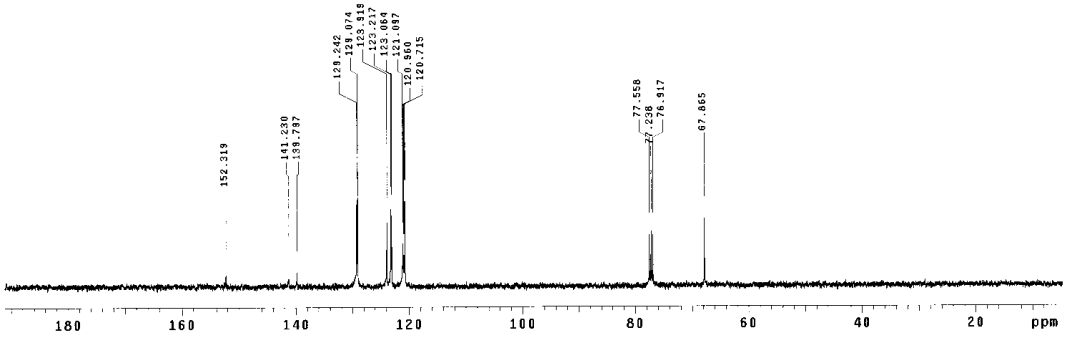
***N*-(phenyl)-4*H*-benzo[*d*] [3,1]oxazin-2-amine (1e): ^{1}H NMR (400 MHz, $CDCl_3$):**



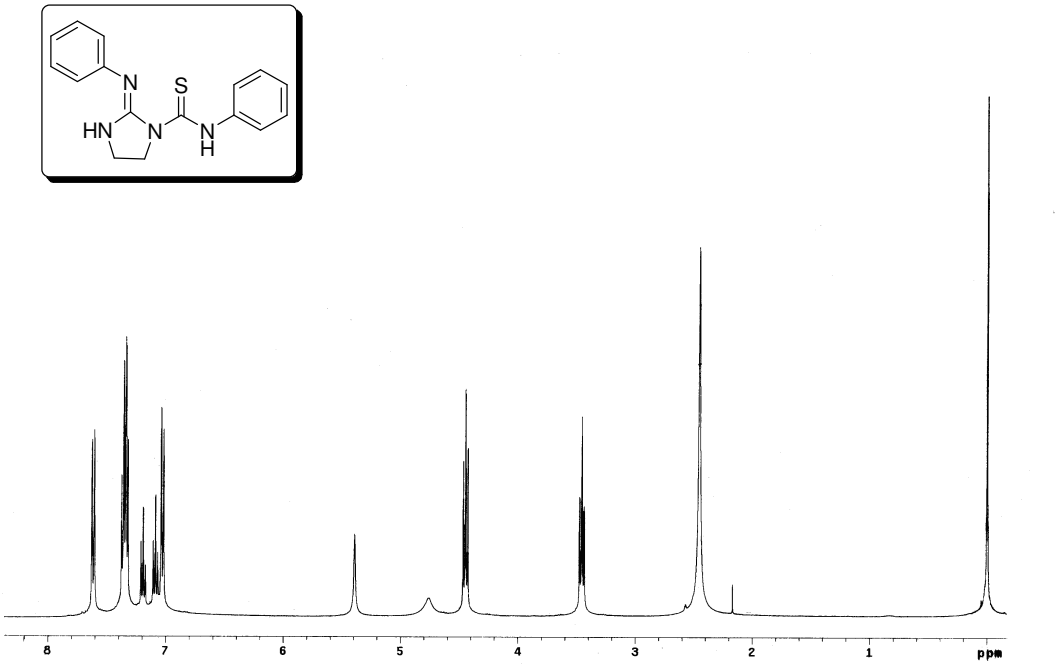


***N*-(phenyl)-4*H*-benzo[*d*] [3,1]oxazin-2-amine (1e): ^{13}C NMR (100 MHz, $CDCl_3$):**

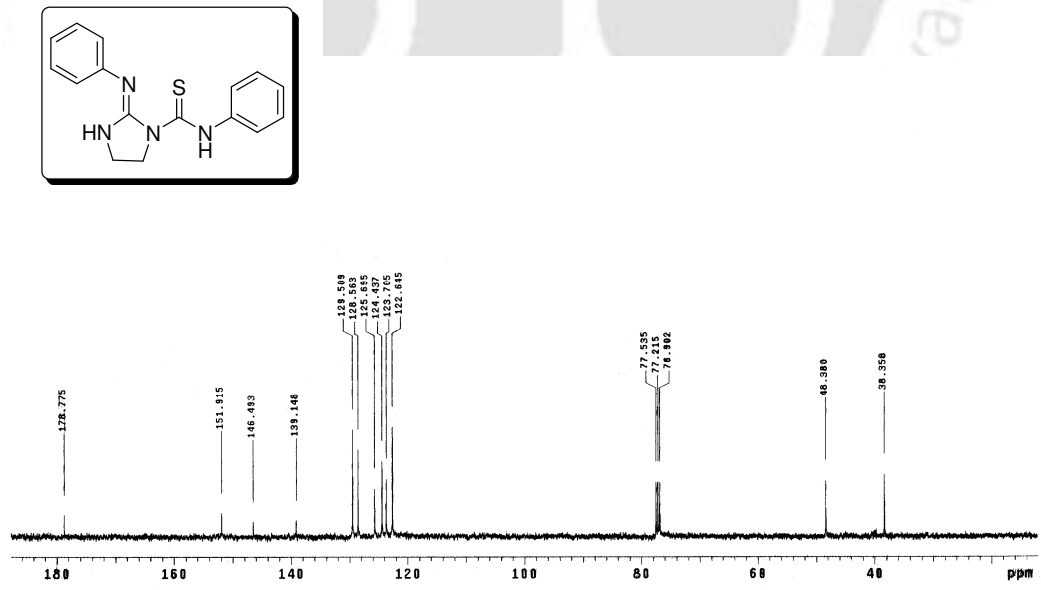




_N_-Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1f): ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6):



_N_-Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1f): ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6):

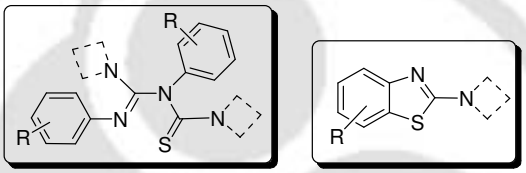


CHAPTER IV

IV. Arylthioureas with Bromine or its Equivalents Gives No 'Hugerschoff' Reaction Product

IV.1. Structure and Nomenclature

Details of nomenclature of benzothiazoles were discussed in CHAPTER I, Section I.3.1.1., Figure I.3.1.1.1. in page 10-11. This chapter deals with the following two types of molecules namely, thioamidoguanidino moiety and benzothiazole.



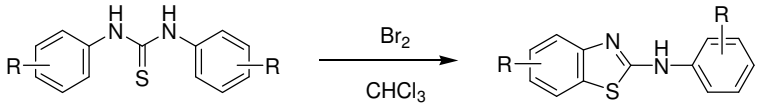
Thioamidoguanidino moiety **Benzothiazole**

IV.2. Importance and Applications

The 2-aminobenzothiazole scaffold is one of the 'privileged' structures in medicinal chemistry.[1] Indeed, various examples featuring this particular scaffold have been prepared, many exhibiting remarkable biological activities.[2] Given the importance of this particular chemical entity to the field of medicinal chemistry, the development of improved and alternative methods for the rapid construction of libraries of derivatives is desirable.

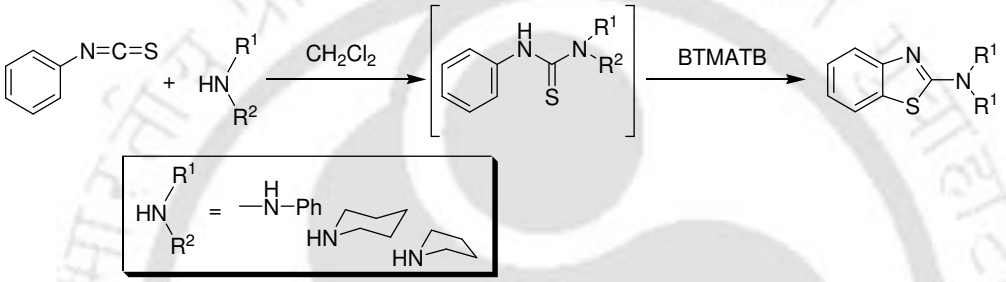
IV.3. Available Synthetic Methods

The classical Hugerschoff reaction known since 1901 involves the reaction of a 1,3-diaryl thiourea and liquid bromine in chloroform medium to produce 2-aminobenzothiazole.[3] This reaction essentially involves the intramolecular aromatic electrophilic substitution reaction of an aryl ring to the thiocarbonyl group of a thiourea and the process is facilitated by thiophilic bromine (*Scheme IV.3.1.*).



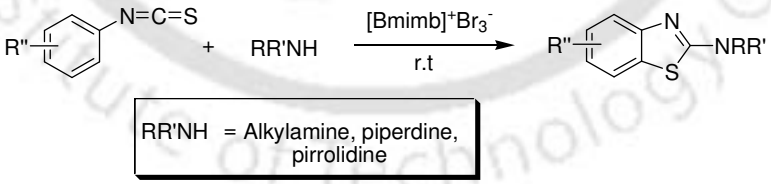
Scheme IV.3.1.

Jordan *et al*. have replaced the toxic molecular bromine with solid brominating reagent *i.e.* BTMATB (benzyltrimethylammonium tribromide) for the preparation of 2-aminobenzothiazoles from 1,3-diarylthioureas and aryl-*sec*-alkyl thioureas using CH_2Cl_2 as a solvent (*Scheme IV.3.2.*).[4a]



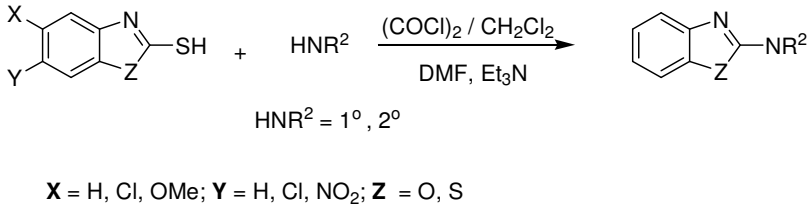
Scheme IV.3.2.

Further, Le *et al*. have employed other bromine equivalent *i.e.* 1-butyl-3-methylimidazolium $[Bmim]^+Br_3^-$ (1-butyl-3-methylimidazolium tribromide) in the preparation of 2-aminobenzothiazoles from 1,3-diarylthiourea and aryl-*sec*-alkyl thioureas at room temperature (*Scheme IV.3.3.*).[4b]



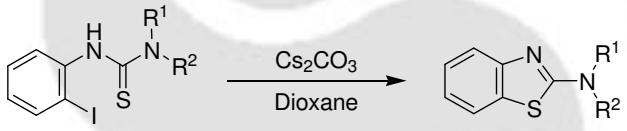
Scheme IV.3.3.

Stewart *et al*. described an efficient one-pot chlorination-amination procedure for the synthesis of 2-aminobenzoxazoles. Further, this methodology has been successfully extended towards the synthesis of 2-amino benzothiazoles[5] (*Scheme IV.3.4.*).



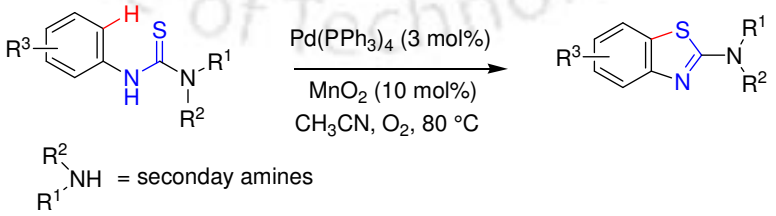
Scheme IV.3.4.

Feng *et al*. demonstrated the formation of 2-substituted (N, O, C) benzothiazoles from *N*'-substituted-*N*-(2-halophenyl)thioureas, *O'*-substituted-*N*-(2-halophenyl)carbamothioates, or *N*-(2-halophenyl)thioamides via a base-promoted cyclization in dioxane solvent without any transition metal. Transition-metal-free, mild reactive conditions, wide application scope, and shorter reaction times make this method superior to the reported methods for the synthesis of 2-substituted benzothiazoles and suitable for combinatorial format (*Scheme IV.3.5.*).[6a]



Scheme IV.3.5.

Batey *et al*. developed an intramolecular C–S bond formation/C–H functionalization for the preparation of 2-aminobenzothiazoles from *N*-arylthioureas utilizing an unusual co-catalytic system *i.e.* $Pd(PPh_3)_4/MnO_2$ under an oxygen atmosphere at 80 °C. This method eliminates the need of an ortho-halo substituted precursor, instead achieving direct functionalization of the ortho-aryl C–H bond[6b] (*Scheme IV.3.6.*).

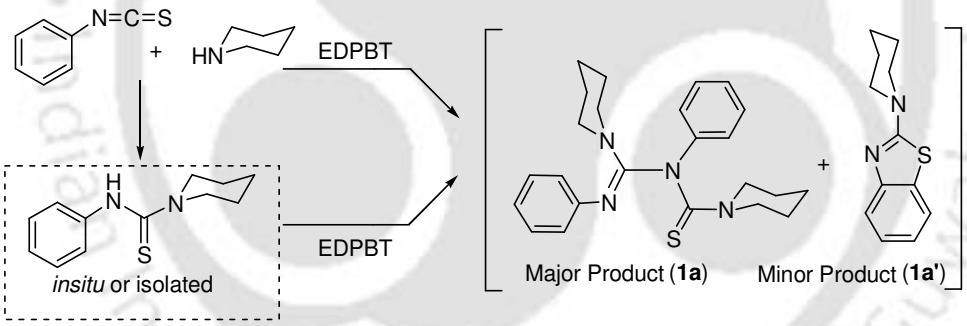


Scheme IV.3.6.

IV.4. Present Work

IV.4.1. Arylthioureas with Bromine or its Equivalents Gives No 'Hugerschoff' Reaction Product

After successful synthesis of various benzofused *N*, *O*, *S*-heterocycles as discussed in previous section (*Chapter III*), we were further interested to prepare the benzothiazoles from the aryl-alkyl thioureas generated from aryl isothiocyanates and secondary amines such as piperidine and pyrrolidine. In this context, we treated phenyl isothiocyanate **1** (1 equiv) and piperidine **a** (1 equiv) in CH_2Cl_2 to which was added bromine equivalent, 1,1'(ethane-1,2-diyl)dipyridinium bistribromide(EDPBT), and stirred for 1 h. The major product isolated (77%) was found to have a thioamido guanidino moiety (**1a**) and the minor product (~12%) was the expected 2-aminobenzothiazole (**1a'**) as shown in *Scheme IV.4.1.1*. This observation was consistent even when the reaction was carried out with an isolated thiourea as shown in *Scheme IV.4.1.1*.



Scheme IV.4.1.1. *Reaction products of the in situ generated thiourea with EDPBT.*

This result however, is in sharp contrast to the recent report by Jordan[4a] and Le[4b] *et al.* where 2-aminobenzothiazole (**1a'**) is reported to be the major product. The only difference between Jordan,[4a] Le[4b] *et al*. and ours is the selection of the brominating reagent. We have been working on various bromine equivalents such as tetrabutylammonium tribromide (TBATB),[7] and EDPBT[8] for last one decade. All these reagents are after all bromineless brominating reagent with similar reactivity hence we have never encountered any major change in their reactivity/selectivity. Thus, there is no

reason why the product obtained using different brominating reagents should be so much different. In order to ascertain this, the same reaction was performed in CH_2Cl_2 with different brominating reagents including bromine and the result is summarized in *Table IV.4.1.1.*

Table IV.4.1.1. *Reagent dependent reactivity of phenyl isothiocyanate and piperidine in CH_2Cl_2.*

Entry	Reagent/Time	Total yield of (**1a**)+(**1a'**)	Ratio[a] of (**1a**):(**1a'**)
1	EDPBT/0.5h	89	77:12
2	$Bu_4N^+Br_3^-$/0.5h	86	70:16
3	[Bmim[b]]$^+Br_3^-$/1h	78	48:30
4	$PhCH_2N^+Me_3Br_3^-$/1h	85	68:17
5	$CH_3(CH_2)_{15}N^+Me_3Br_3^-$/3h	80	73:7
6	Br_2/1h	75	40:35

[a] Isolated yields. [b] Bmim = 1-butyl-3-methylimidazolium.

As can be seen from *Table IV.4.1.1*, irrespective of the brominating reagent used, the formation of the product containing a thiomido guanidino moiety (**1a**) is always the dominant over the expected 2-aminobenzothiazole (**1a'**). The difference in distribution of two products with various brominating reagents listed in *Table IV.4.1.1* could possibly be due to the intrinsic acidity caused by these reagents in the reaction medium. Acidity is dependent on the nature of the reagent *i.e.* counter cation present in a given solvent. It may be mentioned here that in a classical Hugerschoff reaction the substrates employed are 1,3-diarylthioureas, where the aryl amines are primary and not secondary in nature. These kind of substrates invariably gives Hugerschoff product 2-aminobenzothiazole irrespective of the nature of brominating reagents used. However the difference is noticed only when one side of the thiourea is having a primary aryl amine and the other side a secondary aliphatic amine. Thus, in the latter case irrespective of the brominating reagent (*Table IV.4.1.1.*) used the *anti*-Hugerschoff *i.e* product containing a thiomido guanidino moiety (**1a**) is the major product (*Table IV.4.1.1.*). The results of Jordan,[4a] Le[4b] *et al.* even under their reported condition could not be reproduced in our hand. We always obtained a thiomido guanidino moiety (**1a**) as the major product and 2-aminobenzothiazole (**1a'**) as the minor

product, which is in contrast to the literature reports[4] where 2-aminobenzothiazole is always the major product.

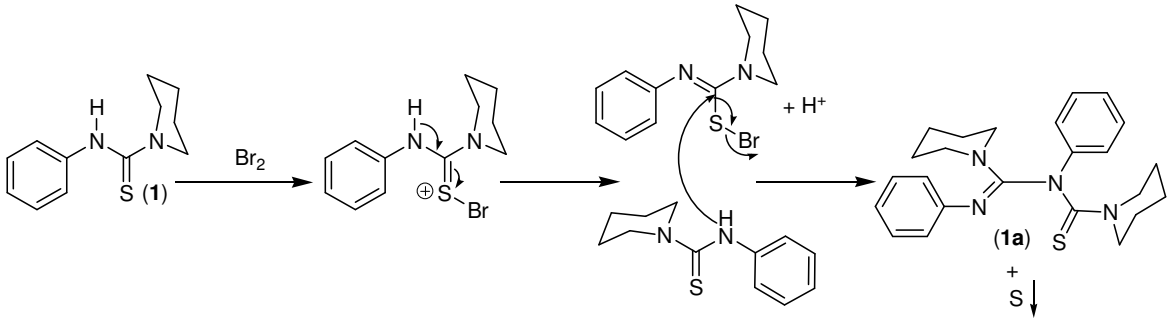
Next, we wished to investigate the effects of various solvents on the distribution of products (**1a**) and (**1a'**). The above reaction was performed in various organic solvents listed in *Table IV.4.1.2*, using EDPBT. From *Table IV.4.1.2*, it is evident that irrespective of the solvents used, the major product is having a thioamido guanidino moiety (**1a**). Better selectivity was obtained in THF compared to other solvents, possibly due to the controlled release of bromine from EDPBT due to its partial solubility (*Table IV.4.1.2*, entry 4).

Table IV.4.1.2. *Solvent dependency of Hugerschoff reaction with EDPBT.*

Entry	Solvent/Time	Total isolated yield of (**1a**)+(**1a'**)	Ratio[a] (**1a**):(**1a'**)
1	CH_2Cl_2/0.5h	89	77:12
2	CH_3CN/0.5h	82	68:14
3	Dioxane/1.5h[b]	75	60:15
4	THF/1.5h[b]	92	85:7
5	THF/1.5h [c]	94	94:0
6	MeOH/0.5h [d]	80	80:0
7	DMF/0.5h	78	78:0
8	AcOH/0.5h	77	55:22

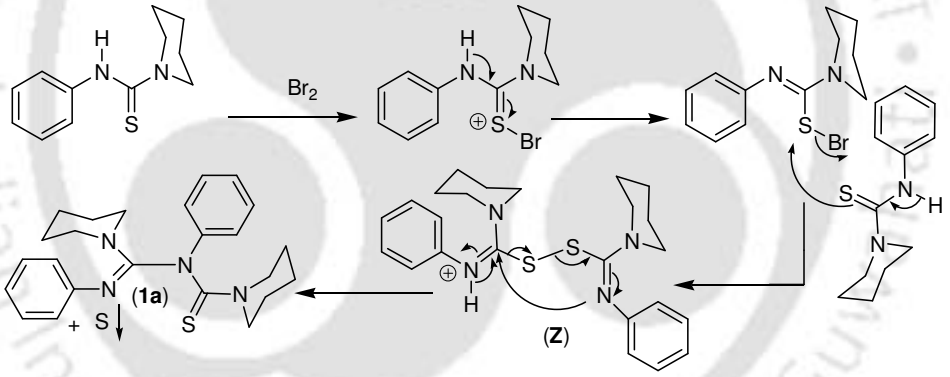
[a] Isolated yields. [b] Possibly due to lesser solubility of EDPBT reagent. [c] Reaction was performed with 0.25eq of EDPBT. [d] Some other minor side products were also obtained.

A mechanism as shown in *Scheme IV.4.1.2* can be envisaged for the formation of the product (**1a**). Although this mechanism accounts for the formation of product (**1a**), the attack of non-nucleophilic thioamidic nitrogen on to a hindered carbon atom is unlikely. Further, when this reaction was performed in the presence of an external aliphatic amine such as *n*-butyl amine, a guanidino moiety derived from *n*-butyl amine is expected to be the major product because of the better nucleophilicity of an amine over an amide. In this reaction, however, no traces of guanidine derivative were obtained thereby ruling out the possibility of the mechanism proposed in *Scheme IV.4.1.2*.



Scheme IV.4.1.2. *Proposed mechanism for the formation of* ***1a****.*

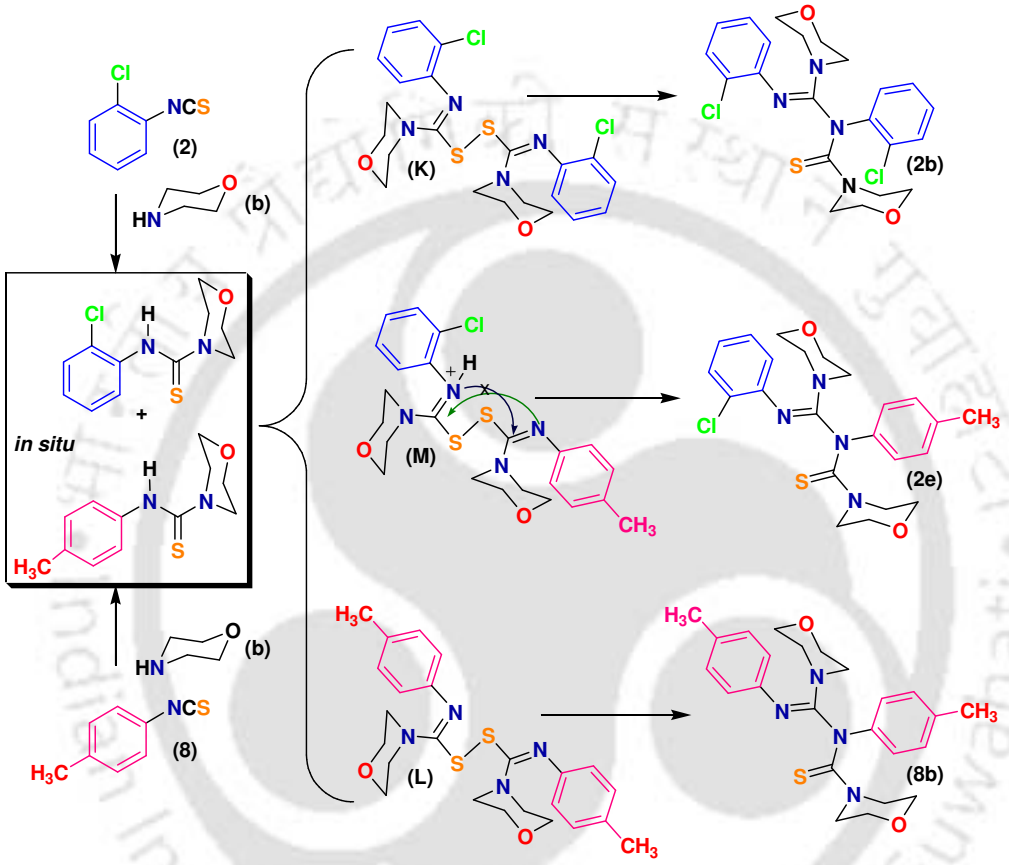
Alternatively, the following mechanism as shown in *Scheme IV.4.1.3* can be proposed to account for the formation of the product (**1a**). This mechanism essentially involves the formation of a disulfide intermediate (**Z**) followed by the attack of one of the iminium nitrogen on to the adjacent iminium carbon with the concurrent expulsion of elemental sulfur to give the desired product (**1a**) as shown in *Scheme IV.4.1.3.*



Scheme IV.4.1.3. *Proposed mechanism for the formation of* ***1a****.*

In order to ascertain this mechanism, a crossover experiment as shown in *Scheme IV.4.1.4*, was performed. The *in situ* generated thioureas from their corresponding isothiocyanates (**2** and **8**) and morpholine (**b**) on treatment with EDPBT gave three products **2b**, **2e** and **8b** isolated in 8%, 78% and 11% yields respectively. In this reaction, two symmetrical disulfides (**K**) and (**L**) and an unsymmetrical disulfide (**M**) (*Scheme IV.4.1.4.*) are expected to form in the medium. Products **2b** and **8b** can originate from their corresponding symmetrical disulfides (**K**) and (**L**) respectively. However, formation of the major product **2e** can be explained if there is formation of a mixed disulfide (**M**) as shown

in *Scheme IV.4.1.4.* In principle, the intramolecular attack of the two different imino nitrogens on to the adjacent imino carbons of the mixed disulfide (**M**) is expected to result in two isomeric products. Interestingly, the formation of only one of the isomeric products was clearly observed. The structure of the product (**2e**) has been unequivocally confirmed by X-ray crystallographic analysis as shown in *Figure IV.4.1.1.*



Scheme IV.4.1.4.*Crossover experiment and product distribution.*

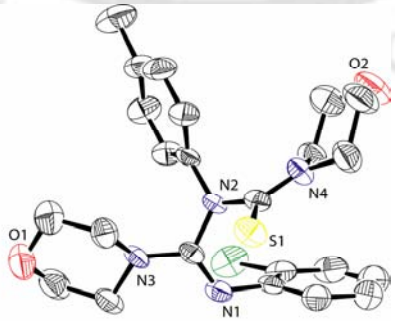
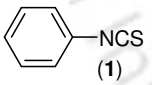
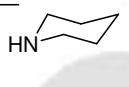
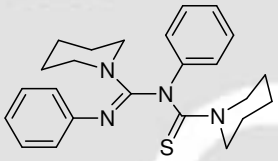
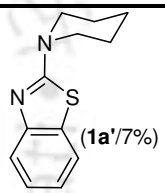
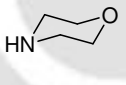
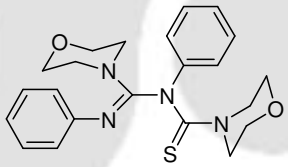
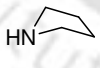
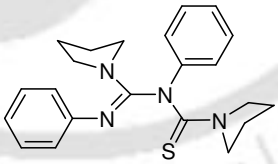
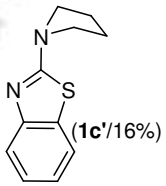
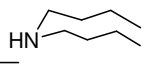
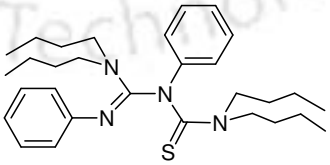


Figure IV.4.1.1*. ORTEP view with the atomic numbering scheme of* ***2e****.*

Previously, we have observed a good correlation between p*Ka*'s of the amines and the regioselective *N*-acylation of thioureas[9a] and also during the formation of 2-imino-4-thiazolidinones.[9b] Having the knowledge of p*Ka*'s of the amines and reactivity of the thioureas, [8f,g,9] one can account for the exclusive formation of the product (**2e**). Due to the higher p*Ka* of *p*-methyl aniline (p*Ka* = 5.08) compared to *o*-chloro aniline (p*Ka* = 2.65), the imine nitrogen of the former is expected to be more nucleophilic and hence preferentially attack in an intramolecular fashion as shown in *Scheme IV.4.1.3* and *Scheme IV.4.1.4* giving the major product (**2e**). Further, due to the lower p*Ka* of *o*-chloroaniline (p*Ka* = 2.65) its imine nitrogen preferentially gets protonated over the other imine of the intermediate (**M**) thereby enhancing the electrophilicity of the imine carbon of *o*-chloroaniline as shown in *Scheme IV.4.1.4.*

Table IV.4.1.3. *Reaction of phenyl isothiocyanates with secondary amines and EDPBT.*[a]

Isothiocyanate	Sec.amine/Time(h)		Product(s)[b]	Yield (%)[c]
 (**1**)	 (**a**)	1.5	 (**1a**/85%)	 (**1a'**/7%)
	 (**b**)	1	 (**1b**/88%)	nd[d]
	 (**c**)	1	 (**1c**/75%)	 (**1c'**/16%)
	 (**d**)	1	 (**1d**/73%)	nd[d]

[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR. [c] Isolated yield. [d] nd = not detected.

The scope of this reaction has been demonstrated with various aliphatic secondary amines such as piperidine (**a**), morpholine (**b**), pyrrolidine (**c**) and di-*n*-butylamine (**d**) to give major products (**1a**), (**1b**), (**1c**), and (**1d**) respectively, all possessing the thioamido guanidino moiety as shown in *Table IV.4.1.3.* Structure of the product **1a** has been confirmed by crystal X-ray crystallography as shown in *Figure IV.4.1.2.* In all these cases, the Hugerschoff product 2-aminobenzothiazole was obtained as a minor products (**1a'** or **1c'**) as shown in *Table IV.4.1.3*, or not observed at all.

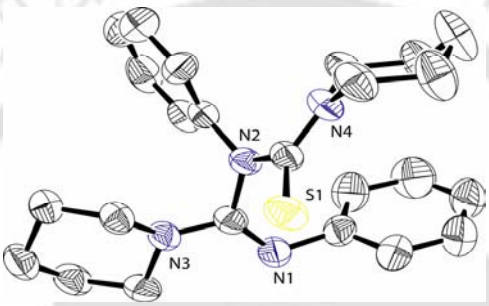


Figure IV.4.1.2. *ORTEP view with the atomic numbering scheme of* ***1a****.*

The success of this strategy was then applied to various other aryl isothiocyanates (*Table IV.4.1.4.*). Substrates (**2**) and (**3**) containing weakly deactivating substituents (Cl and Br) in the ortho position gave **2b**, **2c** and **3b** respectively, as the exclusive products. Aryl isothiocyanate having a strong electron withdrawing group (-NO_2) (**4**) in its meta position on reaction with piperidine (**a**), followed by treatment with EDPBT gave **4a** as the only isolated product. Further, weakly deactivating substituents (Cl and Br) when present in the para-position of an isothiocyanates (**5** and **6**), when reacted with aliphatic secondary amines such as morpholine (**b**) and piperidine (**a**) followed by treatment with EDPBT yielded the thioamido guanidino moiety containing products **5b**, **6a** and **6b**. The structure of the products **5b** and **6a** have been further confirmed by crystal X-ray crystallography as shown in *Figure IV.4.1.3 and Figure IV.4.1.4.*

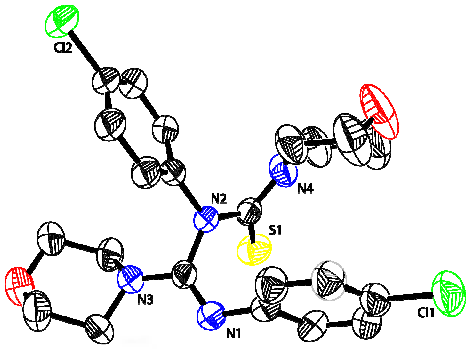
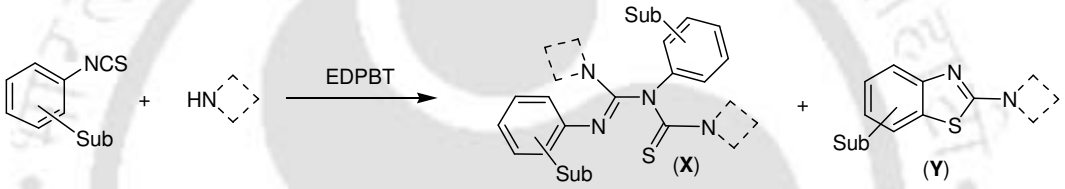
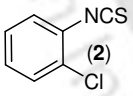
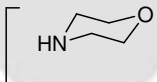
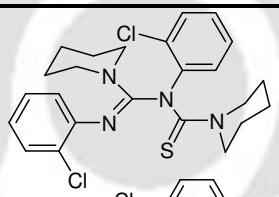
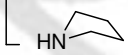
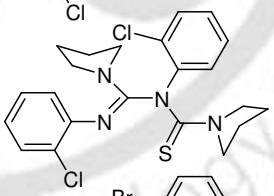
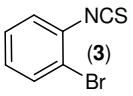
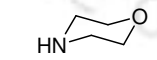
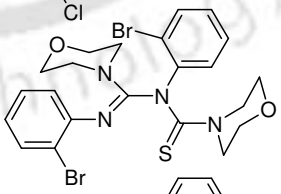
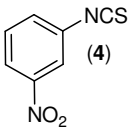
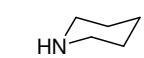
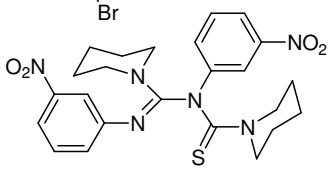


Figure IV.4.1.3. *ORTEP view with the atomic numbering scheme of* ***5b****.*

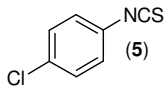
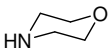
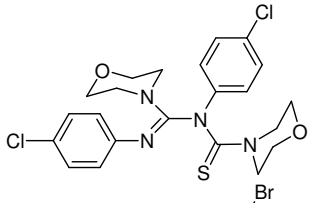
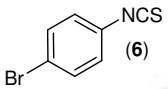
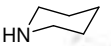
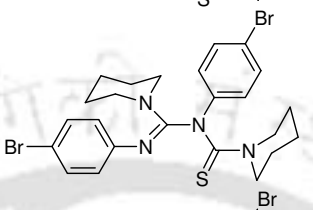
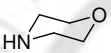
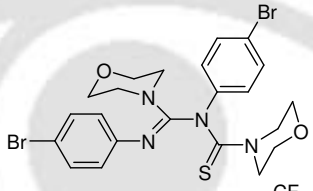
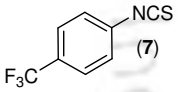
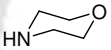
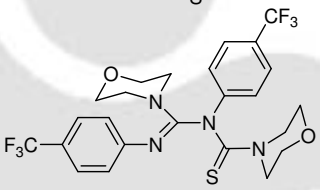
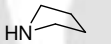
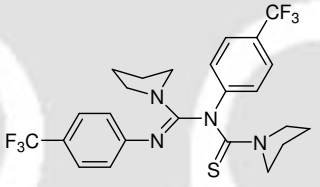
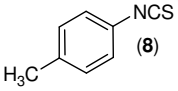
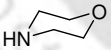
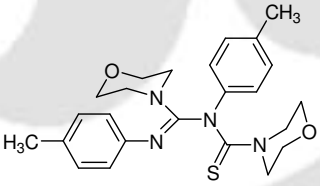
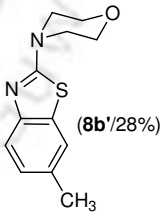
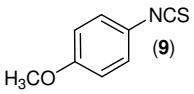
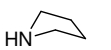
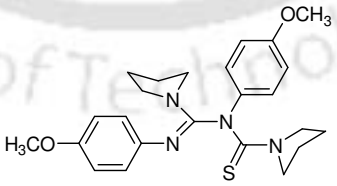
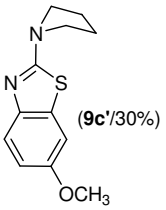
Table IV.4.1.4. *Reaction of aryl isothiocyanates with secondary amines and EDPBT.*[a]



Isothiocyanate	Sec.amine/Time(h)	Product(s)[b]	Yields[c]
	 (**b**) 2		(**2b**/86%)
	 (**c**) 2		(**2c**/89%)
	 (**b**) 2		(**3b**/85%)
	 (**a**) 2		(**4a**/84%)

[a] Reactions were perfomed with 0.5eq. EDPBT and monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. [c] Isolated yields.

Table IV.4.1.4. Continued…

Isothiocyanate	Sec.amine/Time(h)	Product(s)[b]	Yields[c]
 (**5**)	 (**b**) 2		(**5b**/88%) nd[d]
 (**6**)	 (**a**) 2		(**6a**/83%) nd[d]
	 (**b**) 2		(**6b**/86%) nd[d]
 (**7**)	 (**b**) 2.5		(**7b**/87%) nd[d]
	 (**c**) 2.5		(**7c**/86%) nd[d]
 (**8**)	 (**b**) 1		(**8b**/56%)  (**8b'**/28%)
 (**9**)	 (**c**) 1		(**9c**/58%)  (**9c'**/30%)

[a] Reactions were perfomed with 0.5eq. EDPBT and monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. [c] Isolated yields. [d] not detected.

Isothiocyanate (**7**) containing strongly deactivating substituent (-CF_3) in its para position gave single products **7b** and **7c** respectively, when reacted with a secondary

amines morpholine (**b**) and pyrrolidine (**c**) under the identical condition. Even isothiocyanates (**8** and **9**) having moderately activating groups (Me and OMe) in its para position gave no significant amount of benzothiazoles **8b'** and **9c'** and the dominant product was still the *anti*-Hugerschoff product **8b** and **9c** respectively.

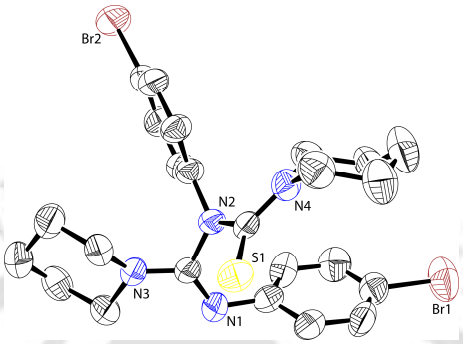


Figure IV.4.1.4. *ORTEP view with the atomic numbering scheme of* ***6a****.*

Except isothiocyanates (**8** and **9**), all other aryl isothiocyanates listed in *Table IV.4.1.4* are either moderately deactivated or strongly deactivated. Thus, they are expected to be less susceptible towards intramolecular electrophilic substitution to give Hugerschoff product 2-aminobenzothiazole and are more likely to yield the intermolecular nucleophilic substitution product *i.e. anti*-Hugerschoff product. In order to ascertain this effect, we selected some activated aryl isothiocyanates (**10**) and (**11**) as shown in *Table IV.4.1.5*.

Interestingly, morpholine thiourea of isothiocyanate (**10**) when reacted with EDPBT gave two inseparable regioisomeric benzothiazoles **10b'** and **10b''** in the ratio of 3:2. Surprisingly, when the secondary amine was changed to pyrrolidine (**c**), (**10c'**) was the lone isolated product. Further, structure of the **10c'** was confirmed by crystal X-ray crystallography as shown in *Figure IV.4.1.5*. 1-Isothiocyanato napthalene (**11**), an activated fused aromatic substrate, underwent intramolecular electrophilic substitution reaction giving exclusively napthothiazoles **11b'** and **11c'** respectively, in good yield.

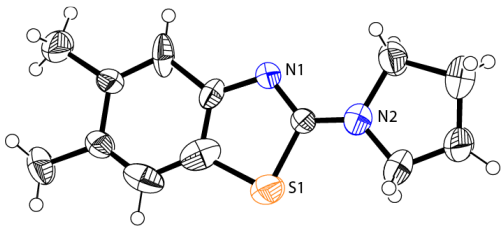
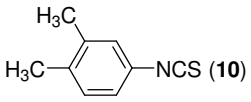
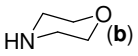
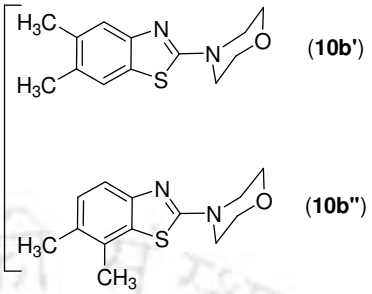
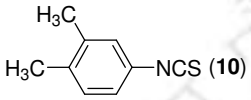
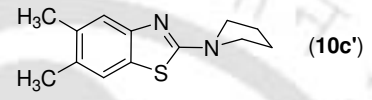
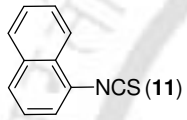
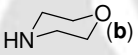
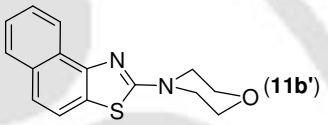
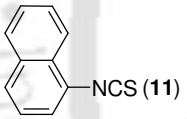
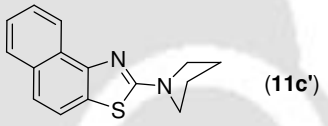


Figure IV.4.1.5 *ORTEP view with the atomic numbering scheme of* ***10c'****.*

Table IV.4.1.5. *Reaction of activated aryl isothiocyanates with secondary amine and EDPBT.*[a]

Isothiocyanate	Sec. amine	Product[b]	Yields[c,d]
			78% (3:2)
			76%
			80%
			75%

[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. [c] Isolated yields. [d] Complete conversion was observed with in 1 h

IV.5. Experimental Section

IV.5.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1, Page number 56-57.

IV.5.2. General Procedures

IV.5.2.1. General Procedure for the Preparation of Guanidine (1a) from Phenylisothio--cyanate and Piperidine (a)

To a solution of phenylisothiocyanate **1** (270 mg, 2 mmol) in THF (2 mL) was added drop wise piperidine **a** (197 μL, 2 mmol), dissolved in THF (2 mL) at room

temperature. Formation of thiourea was observed within 15 min as judged from TLC. To this was then added EDPBT (666 mg, 1 mmol) pinch wise over a period of 10 min. The reaction was kept for stirring at room temperature and complete conversion to anti-Hugerschoff product was observed within 1 h as can be judged from TLC and from the disappearance of the orange color of EDPBT. After completion of the reaction, solvent was evaporated and the reaction mixture was admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product was isolated by recrystallisation using ethyl acetate and hexane (8:2). Alternatively, the products can be purified by passing through a silica gel column (saturated with 1% triethylamine) and eluted with hexane/ethyl acetate (8:2) to give 85 % of the product **1a**.

IV.5.2.2. General Procedure for the Cross-over Experiment

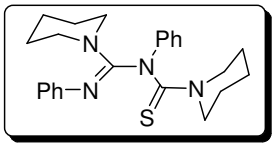
To a solution of *o*-chloro phenyl isothiocyanate **2** (338 mg, 2 mmol) and *p*-methyl phenylisothiocyanate **8** (298 mg, 2 mmol) in THF (2 mL) was added drop wise morpholine **b** (175 µL, 4 mmol), dissolved in THF (2 mL) at room temperature. Formation of corresponding thioureas was observed within 15 min as judged from TLC. To this was then added EDPBT (1332 mg, 2 mmol) pinch wise over a period of 10 min. The reaction was kept for stirring at room temperature and complete conversion to *anti*-Hugerschoff product was observed within 2 h as can be judged from TLC and from the disappearance of the orange color of EDPBT. After completion of the reaction, solvent was evaporated and the reaction mixture was admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The products were purified through a column of silica gel (saturated with 1% triethylamine) and eluted with (hexane/ethyl acetate 8:2) to give 8% of **2b**, 78% of **2e** and 11% of the product **8b**.

IV.6. References

1. Evans, B. E.; Rittle, K. E.; Bock, M. G.; Di Pardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S. *J. Med. Chem.* **2002**, *31*, 2235.
2. (a) Jimonet, P.; Audiau, F.; Barreau, M.; Blanchard, J. C.; Boireau, A.; Bour, Y.; Coleno, M. A.; Doble, A.; Doerflinger, G.; Huu, C. D.; Donat, M. H.; Duchesne, J. M.; Ganil, P.; Gueremy, C.; Honor, E.; Just, B.; Kerphirique, R.; Gontier, S.; Hubert, P.; Laduron, P. M.; LeBlevec, J.; Meunier, M.; Miquet, J. M.; Nemecek, C.; Mignani, S. *J. Med. Chem.* **1999**, *42*, 2828; (b) Young, R. C.; Mitchell, R. C.; Brown, T. H.; Ganellin, C. R.; Griffiths, R.; Jones, M.; Rana, K. K.; Saunders, D.; Smith, I. R.; Sore, N. E. *J. Med. Chem.* **1988**, *31*, 656; (c) Piscitelli, F.; Ballatore, C.; Smith, A. B. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 644.
3. (a) Hugerschoff, H. *Chem. Ber.* **1901**, *34*, 3130; (b) Hugerschoff, H. *Chem. Ber.* **1903**, *36*, 3121; (c) Sprague J. M.; Land, A. H. In *Heterocyclic Compounds,* Elderfield, R. C. Ed.; J. Wiley: New York, 1957; Vol.5, Chapter 8, pp 484-721.
4. (a) Jordan, A. D.; Luo, C.; Reitz, A. B. *J. Org. Chem.* **2003**, *68*, 8693; (b) Le, Z-G.; Xu, J-P.; Rao, H-Y.; Ying, M. *J. Heterocyclic Chem.* **2006**, *43*, 1123.
5. Stewart, G. W.; Baxter, C. A.; Cleator, E.; Sheen, F. J. *J. Org. Chem.* **2009**, 74, 3229.
6. Feng, E.; Huang, H.; Zhou, Y.; Ye, D.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2010**, *12*, 422; (b) Joyce, L. L.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2792.
7. (a) Roy, R. K.; Pagaria, P.; Naik, S.; Kavala, V.; Patel, B. K. *J. Phys. Chem. A.* **2006**, *110*, 2181; (b) Roy, R. K.; Usha, V.; Patel, B. K.; Hairo, K. *J. Comp. Chem.* **2006**, 773; (c) Kavala, V.; Patel, B. K. *Eur. J. Org. Chem.* **2005**, 441; (d) Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. *Arkivoc*, **2006**, 119; (e) Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. *Org. Biomol. Chem.* **2004**, 1670; (g) Gopinath, R.; Haque, Sk. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842; (h) Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, *42*, 7679; (i) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177.
8. (a) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267 and 6556; (b) Naik, S.; Kavala, V.; Gopinath, R.; Patel. B. K. *Arkivoc* **2006** (xi), 21; (c) Kavala, V.; Murru, S.; Das, G.; Patel. B. K. *Tetrehedron* **2008**, *64*, 3960; (d) Murru, S.; Kavala, V.; Singh, C. B.; *Patel,* B. K. *Tetrahedron Lett.* **2007**, *48*, 1007; (e) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *J. Chem. Res.* **2007**, 136; (f) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397; (g) Murru, S.; Singh, C. B.; Kavala, V.; Patel. B. K. *Tetrehedron* **2008**, *64*, 1931.
9. (a) Singh, C. B.; Ghosh, H.; Murru, S.; Patel, B. K. *J. Org. Chem.* **2008**, *73*, 2924; (b) Yella, R.; Ghosh, H.; Patel, B. K. *Green. Chem.* **2008**, *10*, 1307.

IV.7. Spectral Data

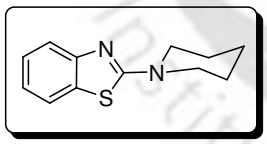
_N_-Phenyl-_N_-((_E_)-(phenylimino)(piperidin-1-yl)methyl)piperidine-1-carbothioamide (1a):



M.p. 186–188 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–1.67 (m, 12H), 2.63–3.82 (m, 8H), 6.90 (t, J = 7.6 Hz, 2H), 7.02–7.12 (m, 3H), 7.16 (t, J = 8.4 Hz, 2H), 7.26–7.40 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 24.5, 24.6, 24.9, 47.4, 51.4, 122.1, 122.3, 124.1, 128.4, 129.2, 143.7, 149.7, 150.0, 184.9. IR (KBr): 2936, 2854, 1632, 1588, 1481, 1454, 1416, 1295, 1261, 1240, 1207, 1028, 989, 903, 749 cm^{-1}. HRMS (ESI): Calcd for $C_{24}H_{30}NS$ [MH^+] 407.2269, found 407.2222.

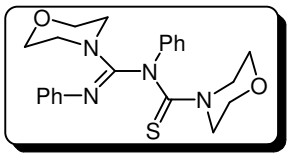
Crystal data for 1a: Crystal dimensions (mm): 0.29 x 0.21 x 0.17; $C_{24}H_{30}N_4S$, M_r = 406.58; monoclinic, space group $P2_1/c$; a = 9.5428(10) Å, b = 10.2273(11) Å, c = 22.766(2) Å; $\alpha = \gamma =$ 90.00°, β = 96.034(6)°, V = 2209.6(4) Å^3; Z = 4; ρ_{cal} = 1.222 mg/m^3; μ (mm^{-1}) = 0 .164; F(000) = 872; reflection collected / unique = 5335 / 3394; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] R_1 = 0.0676, wR_2 = 0.1946, R indices (all data) R_1 = 0.1001, wR_2 = 0.2551; goodness of fit = 1.060. CCDC # 754859.

2-(Piperidin-1-yl)benzo[_d_]thiazole (1a'):



M.p. 93 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 6H), 3.58 (s, 4H), 7.03 (t, J = 7.6 Hz,1H), 7.26 (t, J = 8.0 Hz,1H), 7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.5, 49.8, 118.9, 120.7, 121.2, 126.0, 130.8, 153.1, 169.0. IR (KBr): 2961, 2858, 1608, 1562, 1542, 1473, 1443, 1356, 1305, 1270, 1220, 1058, 1038, 868, 838 cm^{-1}.

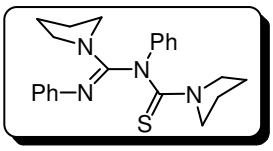
_N_-((_E_)-Morpholino(phenylimino)methyl)-_N_-phenylmorpholine-4-carbothioamide (1b):



M.p. 150 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62–3.80 (m, 16H), 6.81 (br m, 1H), 6.95–7.10 (m, 4H), 7.13 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 2H), 7.28–7.48 (br m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.8, 50.7, 65.5, 66.2, 120.4, 121.4, 122.2, 122.9, 124.8, 128.8, 129.8, 142.8, 149.3, 185.2. IR (KBr): 2979, 2904, 2894, 2856, 1634, 1586,

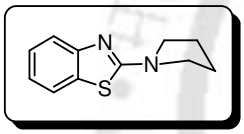
1485, 1453, 1351, 1301, 1277, 1239, 1206, 1157, 1109, 1062, 1022, 994, 937, 855, 765, 753 cm^{-1}. HRMS (ESI): Calcd for $C_{22}H_{26}N_4O_2S$ [MH^+] 411.1855, found 411.1858

_N_-Phenyl-_N_-((_E_)-(phenylimino)(pyrrolidin-1-yl)methyl)pyrrolidine-1-carbothioamide (1c):



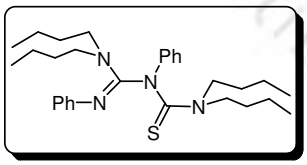
M.p. 152 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 1.05–2.50 (m, 12H), 3.37–3.90 (m, 4H), 6.82 (m, 1H), 6.89 (t, *J* = 7.2 Hz, 1H), 6.96 (m, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.15 (m, 2H), 7.19–7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 25.1, 25.8, 26.2, 47.2, 48.4, 51.9, 53.7, 120.9, 122.2, 123.2, 123.9, 128.4, 129.3, 129.8, 141.8, 150.0, 181.0. IR (KBr): 2962, 2863, 1587, 1488, 1438, 1415, 1330, 1288, 1260, 1233, 1175, 1149, 906, 859, 770, 761 cm^{-1}.

2-(Pyrrolidin-1-yl)benzo[_d_]thiazole (1c'):



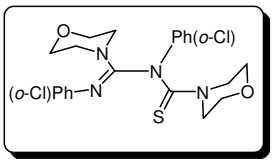
M.p. 101 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (m, 4H), 3.56 (m, 4H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7, 49.6, 118.7, 120.7, 120.8, 126.0, 130.8, 153.4, 165.5. IR (KBr): 2950, 2868, 1604, 1561, 1544, 1442, 1365, 1341, 1317, 1276, 1258, 1175, 1120, 1069, 859, 747, 720 cm^{-1}. $C_{11}H_{12}N_2S$ (204.29): calcd C 64.67, H 5.92, N 13.71, S 15.70; found: C 64.61, H 5.89, N 13.76, S 15.78.

_N_-Phenyl-_N_-((_E_)-(phenylimino)(dibutylamin-1-yl)methyl)dibutylamine-1-carbothioamide (1d):



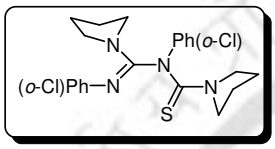
Gummy: ^1H NMR (400 MHz, $CDCl_3$): δ 0.07–1.13 (m, 15H), 1.14–1.40 (m, 7H), 1.63 (s, 6H), 2.90–3.10 (m, 4H), 3.36–3.70 (m, 4H), 6.88 (t, *J* = 7.2 Hz, 2H), 7.02 (d, *J* = 7.2 Hz, 2H), 7.08 (t, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 8.0 Hz, 2H), 7.20–7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 14.1, 14.2, 14.4, 20.3, 20.7, 21.2, 27.3, 28.6, 29.8, 48.1, 49.5, 51.2, 51.4, 121.9, 122.2, 122.6, 124.7, 128.6, 129.2, 144.4, 149.4, 150.4, 189.5. IR (KBr): 2958, 2932, 2872, 1626, 1591, 1488, 1462, 1417, 1375, 1314, 1283, 1223, 1139, 943, 913, 768, 751 cm^{-1}. HRMS (ESI): Calcd for $C_{30}H_{46}N_4S$ [MH^+] 495.3521, found 495.3546.

_N_-((_E_)-(2-Chlorophenylimino)(morpholino)methyl)-_N_-(2-chlorophenyl)morpholine-4-carbothioamide (2b):



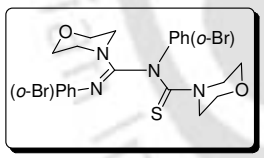
M.p. 157 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50–4.60 (m, 16H), 6.39–7.16 (m, 5H), 7.22–7.68 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.1, 47.5, 50.9, 66.1, 122.8, 123.9, 126.5, 127.3, 128.0, 129.1, 131.0, 139.7, 145.7, 148.6, 187.2. IR (KBr): 2950, 2894, 2849, 1632, 1580, 1470, 1427, 1401, 1363, 1303, 1272, 1237, 1219, 1206, 1159, 1150, 1119, 1109, 1051, 1031, 999, 953, 876, 757, 750 cm^{-1}.

***N*-((*E*)-(2-Chlorophenylimino)(pyrrolidin-1-yl)methyl)-*N*-(2-chlorophenyl)pyrrolidine-1-carbothioamide (2c):**



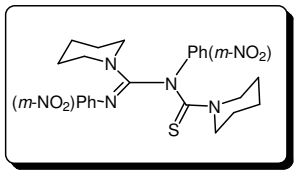
M.p. 154 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70–2.21 (m, 10H), 3.14–4.02 (m, 6H), 6.43–6.86 (m, 3H), 6.90–7.06 (m, 2H), 7.12–7.53 (m, 2H), 7.77 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.1, 26.1, 26.7, 46.9, 48.1, 51.6, 54.5, 122.3, 123.3, 123.8, 125.3, 126.3, 127.2, 127.5, 128.2, 128.9, 130.9, 138.6, 146.6, 183.2. IR (KBr): 2968, 2949, 2862, 1623, 1580, 1440, 1413, 1330, 1283, 1261, 1205, 1177, 1051, 947, 874, 756 cm^{-1}.

***N*-((*E*)-(2-Bromophenylimino)(morpholino)methyl)-*N*-(2-bromophenyl)morpholine-4-carbothioamide (3b):**



M.p. 180–182 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23–4.80 (m, 16H), 6.61–7.13 (m, 5H), 7.48–8.02 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.3, 51.2, 66.2, 117.8, 119.6, 123.1, 123.9, 127.3, 127.8, 128.1, 128.8, 132.5, 134.5, 141.3, 147.3, 187.6. IR (KBr): 2949, 2894, 2849, 1628, 1575, 1466, 1427, 1400, 1364, 1302, 1272, 1238, 1219, 1205, 1158, 1149, 1109, 1065, 1024, 998, 953, 874, 749 cm^{-1}.

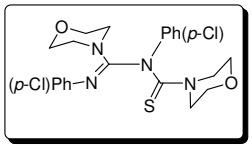
***N*-((*E*)-(3-Nitrophenylimino)(piperidin-1-yl)methyl)-*N*-(3-nitrophenyl)piperidine-1-carbothioamide (4a):**



M.p. 186 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91–1.92 (m, 12H), 3.35 (m, 8H), 7.14–7.41 (m, 3H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.63–7.86 (m, 3H), 7.93 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7, 24.3, 25.0, 47.9, 52.1, 116.8, 117.1, 119.3, 127.4, 129.3, 130.4, 144.4, 148.7, 148.9, 150.5, 184.1. IR (KBr): 2942, 2925, 2851, 1637, 1606,

1522, 1479, 1444, 1417, 1352, 1299, 1280, 1244, 1206, 1182, 1027, 901, 739 cm^{-1}.

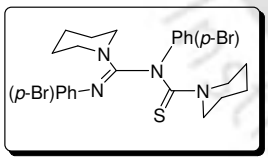
_N_-((_E_)-(4-Chlorophenylimino)(morpholino)methyl)-_N_-(4-chlorophenyl)morpholine-4-carbothioamide (5b):



M.p. 162–164 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.81–3.92 (m, 16H), 6.74 (m, 2H), 6.93 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 50.9, 65.6, 66.3, 122.3, 123.5, 128.3, 128.9, 130.1, 130.5, 141.2, 147.7, 149.5, 184.9. IR (KBr): 2963, 2889, 2845, 1637, 1584, 1487, 1461, 1416, 1360, 1297, 1273, 1258, 1232, 1207, 1159, 1112, 1094, 1074, 1010, 997, 825 cm^{-1}.

Crystal data for 5b: Crystal dimension (mm): 0.31 x 0.25 x 0.19; $C_{22}H_{24}Cl_2N_4O_2S$, M_r = 479.42; monoclinic, space group $P2_1/c$; a = 9.1161(6) Å, b = 11.1981(6) Å, c = 22.7023(13) Å; $\alpha = \gamma$ = 90°, β = 90.02 °, V = 2317.5(2) Å^3; Z = 4; ρ_{cal} = 1.374 mg/m^3; μ (mm^{-1}) = 0.397; F(000) = 1000; reflection collected / unique = 3718 / 2603; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] R_1 = 0.0396, wR_2 = 0.1186, R indices (all data) R_1 = 0.0587, wR_2 = 0.1319; goodness of fit = 0.842. CCDC # 754858.

_N_-((_E_)-(4-Bromophenylimino)(piperidin-1-yl)methyl)-_N_-(4-bromophenyl)piperidine-1-carbothioamide (6a):

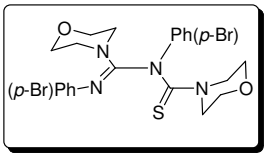


M.p. 177–179 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01–1.85 (m, 13H), 2.81–3.82 (m, 7H), 6.77 (m, 2H), 6.88 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 24.5, 24.9, 25.1, 47.7, 51.9, 115.2, 117.4, 123.1, 124.2, 131.5, 132.5, 142.8, 148.8, 150.1, 184.7. IR (KBr): 2936, 2917, 2851, 1630, 1578, 1483, 1423, 1362, 1297, 1270, 1240, 1205, 1185, 1066, 1051, 1026, 1005, 987, 891, 851, 822, 776 cm^{-1}.

Crystal data for 6a: Crystal dimensions (mm): 0.28 x 0.22 x 0.18; $C_{24}H_{28}Br_2N_4S$, M_r = 564.38; monoclinic, space group $P2_1/c$; a = 9.2041(17) Å, b = 11.356(2) Å, c = 23.799(5) Å; $\alpha = \gamma$ = 90.00°, β = 93.183(12)°, V = 2483.7(8) Å^3; Z = 4; ρ_{cal} = 1.509 mg/m^3; μ (mm^{-1}) = 0.367; F(000) = 1144; reflection collected / unique = 6128 / 2368; refinement method = full-matrix least-squares on

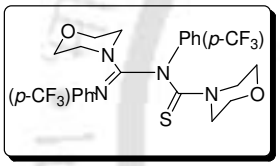
F^2; final *R* indices [I > 2σ_I] R_1 = 0.0638, *w*R_2 = 0.1170, *R* indices (all data) R_1 = 0.1539, *w*R_2 = 0.1398; goodness of fit = 0.899. CCDC # 754857.

***N*-((*E*)-(4-Bromophenylimino)(morpholino)methyl)-*N*-(4-bromophenyl)morpholine-4-carbothioamide (6b):**



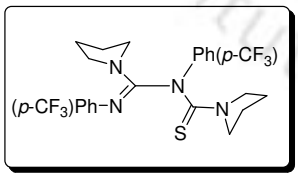
M.p. 173–175 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60–3.81 (m, 16H), 6.61–7.12 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.49 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 50.9, 65.5, 66.3, 115.8, 118.0, 121.9, 123.9, 131.8, 132.9, 141.7, 148.7, 148.3, 149.3, 184.8. IR (KBr): 2964, 2921, 2853, 1633, 1578, 1485, 1417, 1359, 1296, 1274, 1235, 1156, 1113, 1067, 999, 854, 831, 785 cm^{-1}.

***N*-((*E*)-(4-(Trifluoromethyl)phenylimino)(morpholino)methyl)-*N*-(4-(trifluoromethyl) phenyl)morpholine-4-carbothioamide (7b):**



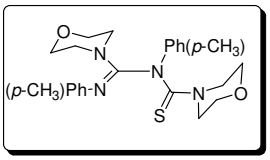
M.p. 147 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92–3.95 (m, 16H), 6.90 (br s, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.62 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 51.0, 65.4, 66.2, 120.5, 121.1, 122.3, 122.4, 124.9, 125.2, 125.3, 125.9, 126.1, 126.5, 126.8, 127.2, 145.4, 148.9, 152.5, 184.5. IR (KBr): 2965, 2920, 2857, 1640, 1602, 1514, 1475, 1424, 1324, 1292, 1261, 1235, 1159, 1113, 1064, 1035, 1013, 998, 942, 844 cm^{-1}.

***N*-((*E*)-(4-(Trifluoromethyl)phenylimino)(pyrrolidin-1-yl)methyl)-*N*-(4-(trifluoromethyl) phenyl)pyrrolidine-1-carbothioamide (7c):**



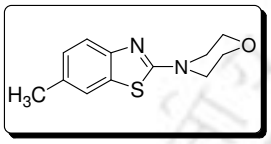
M.p. 148 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12–2.10 (m, 10H), 2.22–2.61 (m, 2H), 3.53–3.86 (m, 4H), 6.89–6.98 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 25.1, 26.1, 47.5, 48.8, 52.3, 54.1, 120.7, 123.3, 124.3, 124.6, 125.6, 126.2, 126.8, 127.1, 144.6, 147.5, 153.2, 180.4. IR (KBr): 2976, 2946, 2867, 1630, 1597, 1516, 1468, 1445, 1413, 1327, 1296, 1258, 1233, 1211, 1177, 1154, 1119, 1064, 1013, 938, 906, 860, 843 cm^{-1}.

***N*-((*E*)-(*p*-Tolylimino)(morpholino)methyl)-*N*-*p*-tolylmorpholine-4-carbothioamide (8b):**



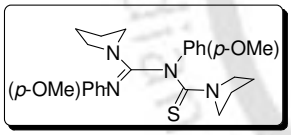
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.33 (s, 3H), 2.74–3.75 (m, 16H), 6.80 (br s, 1H), 6.85 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.08–7.27 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 20.9, 46.7, 50.6, 65.4, 66.2, 121.2, 121.9, 129.2, 130.2, 131.8, 134.4, 140.2, 146.7, 149.5, 185.2. IR (KBr): 2963, 2919, 2857, 1632, 1607, 1506, 1472, 1422, 1360, 1296, 1279, 1236, 1160, 1115, 1066, 1034, 1018, 999, 940, 911, 855, 829, 818, 732 cm^{-1}.

6-Methyl-2-morpholinobenzo[*d*]thiazole (8b'):



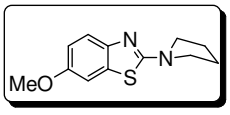
M.p. 133 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.60 (t, *J* = 5.2 Hz, 4H), 3.83 (t, *J* = 5.2 Hz, 4H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 48.7, 66.4, 119.1, 121.0, 127.5, 131.7, 150.5, 168.7. IR (KBr): 2964, 2911, 2857, 1604, 1577, 1466, 1439, 1379, 1352, 1282, 1271, 1237, 1113, 1070, 1027, 945, 914, 840, 812 cm^{-1}.

***N*-((*E*)-(4-Methoxyphenylimino)(pyrrolidin-1-yl)methyl)-*N*-(4-methoxyphenyl)pyrrolidine -1-carbothioamide (9c):**



M.p. 172–174 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–3.66 (br m, 16H), 3.71 (s, 3H), 3.76 (s, 3H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.80 (br s, 4H), 7.05 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.5, 26.3, 48.1, 52.0, 53.6, 55.5, 55.6, 113.7, 114.6, 114.7, 122.9, 123.9, 135.1, 143.3, 148.6, 155.1, 156.3, 181.4. IR (KBr): 2973, 2942, 2868, 1618, 1504, 1479, 1439, 1413, 1331, 1283, 1237, 1179, 1034, 944, 860, 834 cm^{-1}. $C_{24}H_{30}N_4O_2S$ (438.59): calcd C 65.72, H 6.89, N12.77, S 7.31; found: C 65.77, H 6.93, N 12.71, S 7.28.

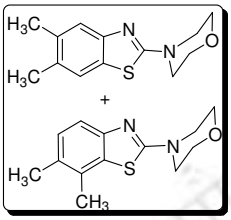
6-Methoxy-2-(pyrrolidin-1-yl)benzo[*d*]thiazole (9c'):



M.p. 110–111 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (t, *J* = 6.8 Hz, 4H), 3.55 (t, *J* = 6.8 Hz, 4H), 3.81 (s, 3H), 6.89 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 7.14 (d, *J* = 2.8 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 49.6, 56.1, 105.6, 109.9, 113.6, 119.1, 131.7, 147.7, 154.7. IR (KBr): 2951, 2865, 1604, 1573, 1545, 1455, 1434, 1366, 1305, 1272, 1218, 1065, 1039, 878, 848, 801 cm^{-1}.

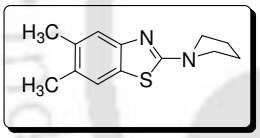
$C_{12}H_{14}N_2OS$ (234.32): calcd C 61.51, H 6.02, N 11.96, S 13.68; found C 61.56, H 5.98, N 11.99, S 13.72.

5,6-Dimethyl-2-morpholinobenzo[*d*]thiazole (10b') + 6,7-dimethyl-2-morpholino benzo[*d*] thiazole (10b''):



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.30 (s, 3H), 2.31 (s, 3H), 2.36 (s, 3H), 3.54–3.64 (m, 8H), 3.74–3.82 (m, 8H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 19.4, 19.8, 20.2, 48.5, 66.3, 116.6, 120.2, 121.1, 127.8, 128.1, 128.7, 129.3, 130.5, 131.9, 134.8, 150.5, 150.9, 168.2, 168.7. IR (KBr): 2965, 2855, 1532, 1443, 1373, 1339, 1283, 1262, 1227, 1114, 1071, 1042, 1020, 897, 858 cm^{-1}. $C_{13}H_{16}N_2OS$ (248.34): calcd C 62.87, H 6.49, N 11.28, S 12.91; found: C 62.84, H 6.53, N 11.33, S 12.87.

5,6-Dimethyl-2-(pyrrolidin-1-yl)benzo[*d*]thiazole (10c'):

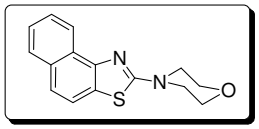


M.p. 176 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (t, *J* = 6.8 Hz, 4H), 2.28 (s, 3H), 2.30 (s, 3H), 3.55 (t, *J* = 6.8 Hz, 4H), 7.34 (s, 1H), 7.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 20.3, 25.7, 49.5, 119.6, 121.1, 127.9, 129.4, 134.6, 151.9, 165.1. IR (KBr): 2961, 2928, 2879, 2853, 1612, 1557, 1538, 1482, 1455, 1354, 1305, 1273, 1134, 989, 918, 859 cm^{-1}. HRMS (ESI): Calcd for $C_{13}H_{16}N_2S$ [MH^+] 233.1112, found 233.1110.

Crystal data for 10c': Crystal dimensions (mm): 0.27 x 0.21 x 0.17; $C_{39}H_{47}N_6S_3$, M_r = 696.01; monoclinic, space group P_{32}; *a* = 13.2914(10) Å, *b* = 13.2914(10) Å, *c* = 18.1404(13) Å; $\alpha = \beta =$ 90°, $\gamma =$ 120°, *V* = 2775.4(4) Å^3; *Z* = 3; ρ_{cal} = 1.249 mg/m^3; μ (mm^{-1}) = 0.237; *F*(000) = 1113; reflection collected / unique = 8763 / 4497; refinement method = full-matrix least-squares on F^2; final *R* indices [$I > 2\sigma_I$] R_1 = 0.1343, *w*R_2 = 0.3239, *R* indices (all data) R_1 = 0.2032, *w*R_2 = 0.3631; goodness of fit = 1.099. CCDC # 754861.

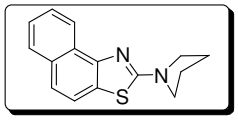
2-Morpholinonaphtho[1,2-*d*]thiazole (11b'):

M.p. 183–184 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (t, *J* = 5.2 Hz, 4H), 3.87 (t, *J* = 5.2 Hz, 4H), 7.59 (m, 3H), 7.98 (s, 1H), 8.23 (m, 1H), 8.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.7, 66.4, 114.9,



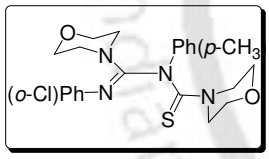
122.4, 124.7, 125.5, 126.8, 126.9, 127.5, 127.9, 130.5, 148.6, 169.7. IR (KBr): 2961, 2844, 1568, 1531, 1496, 1451, 1434, 1393, 1372, 1351, 1336, 1278, 1226, 1183, 1156, 1112, 1080, 1035, 931, 910, 841, 758 cm^{-1}.

2-(Pyrrolidin-1-yl)naphtho[1,2-*d*]thiazole (11c'):



M.p. 143–145 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (t, *J* = 6.8 Hz, 4H), 3.63 (t, *J* = 6.8 Hz, 4H), 7.43–7.55 (m, 3H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 49.7, 118.9, 120.8, 124.3, 125.3, 125.7, 126.9, 127.9, 132.4, 149.3, 166.1. IR (KBr): 2928, 2850, 1585, 1550, 1505, 1429, 1397, 1357, 1337, 1306, 1224, 1189, 1077, 936, 901, 799 cm^{-1}. $C_{15}H_{14}N_2S$ (254.35): calcd C, 70.83; H, 5.55; N, 11.01; S, 12.61. found: C, 70.88; H, 5.51; N, 11.07; S, 12.56.

***N*-((*E*)-(2-Chlorophenylimino)(morpholino)methyl)-*N*-*p*-tolylmorpholine-4-carbothioamide (2e):**

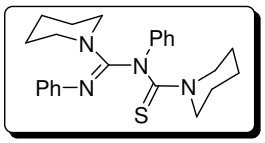


M.p. 133–134 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.64–3.90 (m, 16H), 6.61 (br s, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 47.1, 50.4, 65.4, 66.3, 120.2, 122.8, 123.5, 125.5, 126.4, 127.1, 129.5, 130.3, 134.8, 140.5, 146.2, 150.7, 186.2. IR (KBr): 2963, 2910, 2851, 1631, 1583, 1475, 1436, 1418, 1360, 1291, 1279, 1235, 1156, 1114, 1076, 1021, 998, 941, 851, 813, 754 cm^{-1}. $C_{23}H_{27}ClN_4O_2S$ (459.00): calcd C 60.18, H 5.93, N 12.21, S 6.99; found: C 60.14, H 5.98, N 12.14, S 7.93.

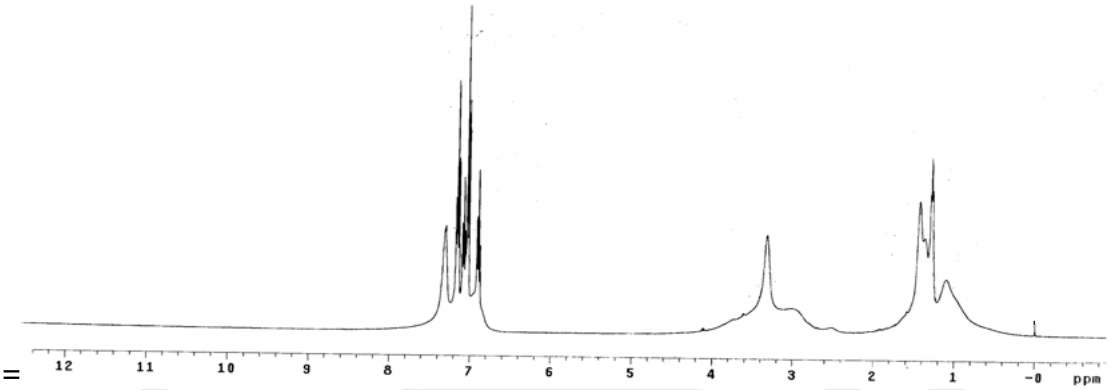
Crystal data for 2e: Crystal dimensions (mm): 0.30 x 0.23 x 0.18; $C_{23}H_{27}ClN_4O_2S$, M_r = 459.00; triclinic, space group *P-1*, *a* = 9.083(3) Å, *b* = 11.470(4) Å, *c* = 13.401(4) Å, α = 66.049(5)°, β = 83.186(5)°, γ = 67.231(5)°, *V* = 1175.2(6) $Å^3$; *Z* = 2; ρ_{cal} = 1.297 mg/m^3; μ (mm^{-1}) = 0.278; *F*(000) = 484, reflection collected / unique = 4785 / 2683; refinement method = full-matrix least-squares on F^2, final *R* indices [$I > 2\sigma_I$] R_1 = 0.0458, wR_2 = 0.1149, *R* indices (all data) R_1 = 0.0577, wR_2 = 0.1234; goodness of fit = 0.851. CCDC # 754860.

IV.7. Selected Spectra

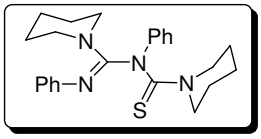
***N*-Phenyl-*N*-((*E*)-(phenylimino)(piperidin-1-yl)methyl)piperidine-1-carbothioamide (1a): ^{1}H NMR (400 MHz, $CDCl_3$):**

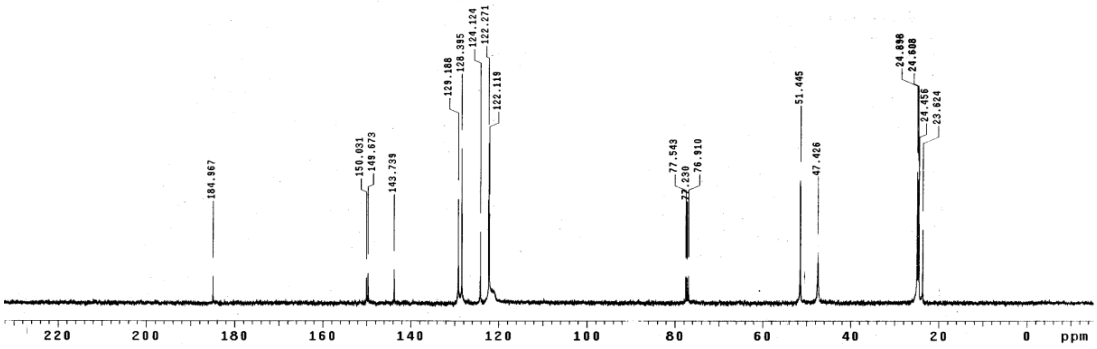


=

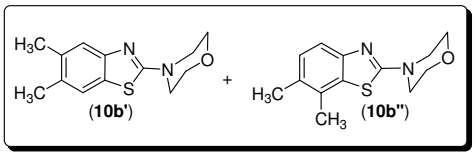


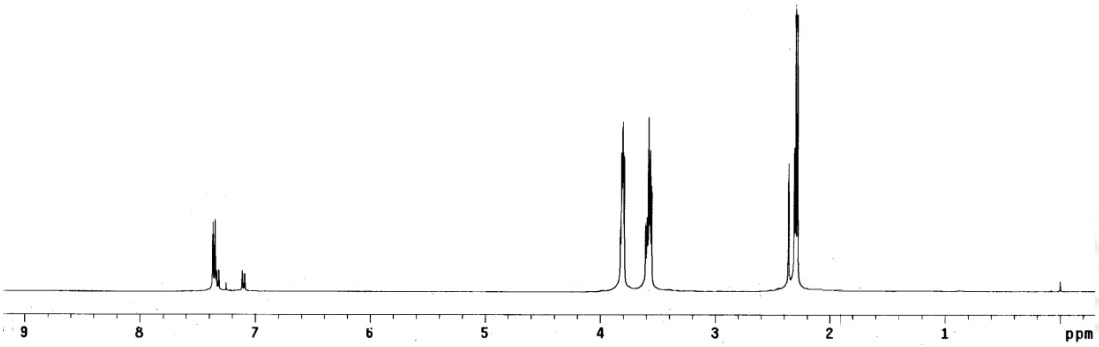
***N*-Phenyl-*N*-((*E*)-(phenylimino)(piperidin-1-yl)methyl)piperidine-1-carbothioamide (1a): ^{13}C NMR (100 MHz, $CDCl_3$):**



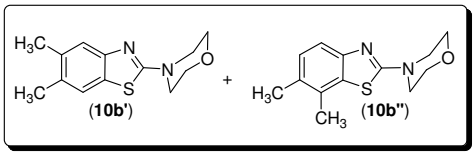


5,6-Dimethyl-2-morpholinobenzo[*d*]thiazole (10b') & 6,7-dimethyl-2-morpholinobenzo[*d*]--thiazole (10b"): ^{1}H NMR (400 MHz, $CDCl_3$):





5,6-Dimethyl-2-morpholinobenzo[*d*]thiazole (10b') and 6,7-dimethyl-2-morpholinobenzo[*d*]--thiazole (10b"): ^{13}C NMR (100 MHz, $CDCl_3$):

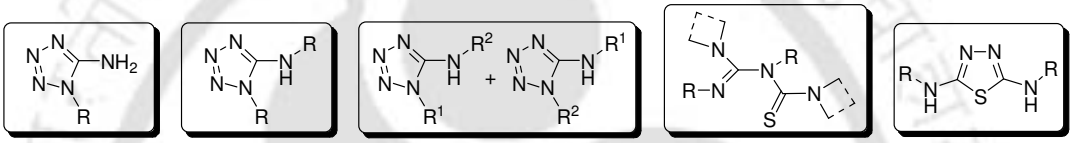


CHAPTER V

V. Tandem Regioselective Synthesis of Tetrazoles and Related Heterocycles Using Iodine

V.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I., Section I.3.1., Figure I.3.1.3., in pages 8 and 9. This chapter deals with the following two types of heterocycles namely tetrazoles, and thiadiazoles and a product having a thiamidoguanidino moiety.



V.2. Importance and Applications

Aminotetrazoles are an interesting class of heterocyclic compounds that have not been found in the nature so far. They are resistant to metabolic degradation as well as towards chemical oxidants,[1] and have been used in propellants,[2a] explosives[2b] and as structural components of many biologically important molecules.[3] For a drug to be effective, it should be sufficiently lipophilic in nature so as to pass through the cell membrane effectively. Hansch has shown that anionic tetrazoles are at least ten times more lipophilic than the corresponding carboxylates.[4] Due to the tunable lipophilicity of tetrazole derivatives; it is possible to use them as "isosteric substituents" of various functional groups. In particular, 5-substituted (alkyl/aryl) tetrazoles (RCN_4H) may serve as "non-classical isosteres" for the carboxylic acid moiety (RCO_2H) in biologically active molecules.[5,6]

Additionally, aminotetrazoles are found in compounds having antiallergic/antiasthmatic,[7a,b] antiviral,[7c] anti-inflammatory,[7c] antineoplastic,[7d,e] and cognition disorder activities.[7f] *Figure V.2.1*, illustrate the examples of some heterocycles having pharmacological activity,[8a]antiviral,[8b] and receptor modulator[8c,d] activities. They

are also used in high energy density materials (HEDM),[9] as ligands in coordination chemistry[10a-c] and in the preparation of imidoylazides.[10d]

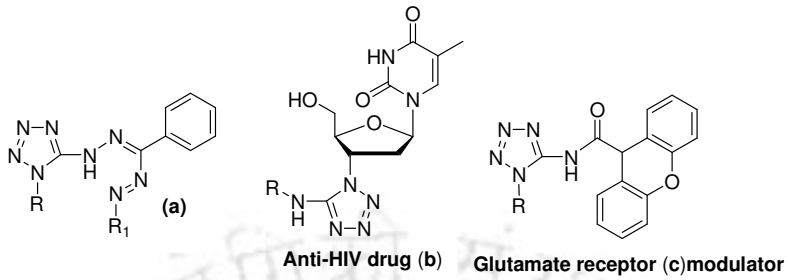
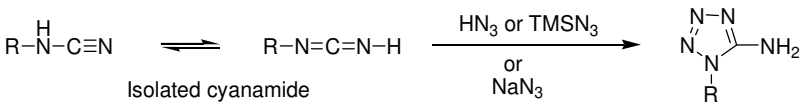


Figure V.2.1. *Some of the biologically important aminotetrazoles.*

Compound possessing 1,3,4-thiadiazole moiety shows diverse biological activities[11a] such as antibacterial similar to that of sulfonamide drugs,[11b,c] antimicrobial,[11d] antirrhythmic,[11e] anti-inflammatroy,[11f] antidepressant,[11g] anti-HIV[11h] and anticancer activity.[12] In addition to this, there has been an increase in interest towards the synthesis of heterocyclic moieties attached to the peptides and α-amino acids.[13a-d] Very recently, the thiadiazole moiety has been successfully incorporated into the peptides from the heterocyclization of novel *N*-(Cbz-aminoacyl) thiosemicarbazides.[13e]

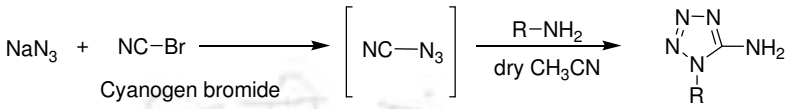
V.3. Available Synthetic Methods

The classical reaction for the preparation of 5-amino-1-aryl tetrazoles is the treatment of cyanamides with hydrazoic acid[14a] at higher temperature. In an alternative approach, hydrazoic acid has been replaced with NaN_3 to prepare 5-amino-1-aryl tetrazoles.[14b-g] Very recently; Habibi *et al.* synthesized aryl aminotetrazole derivatives efficiently by the action of arylcyanamides and sodium azide using $ZnCl_2$ as the catalyst under an aqueous medium at refluxed condition.[14h] Formation of the product depends on the nature of the substituent attached to the cyanamide (*Scheme V.3.1.*)



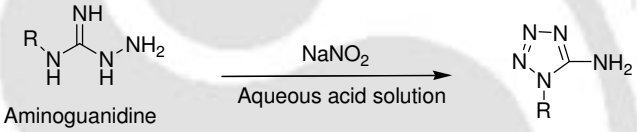
Scheme V.3.1.

1-Substituted 5-aminotetrazoles have been prepared from the *in situ* generated cyanogen azide with primary amines followed by an intramolecular cyclization.[15a] This method is also successful for the synthesis of bis- and tris (1-substituted 5-aminotetrazole) derivatives (*Scheme V.3.2.*).



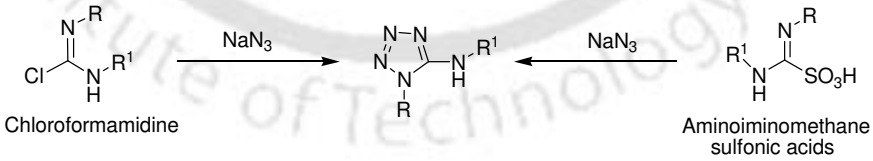
Scheme V.3.2.

Diazotization of amino guanidine with $NaNO_2$ followed by an electrocyclization in the presence of aqueous acidic solution gave corresponding tetrazoles in good yields (*Scheme V.3.3.*).[15b-d]



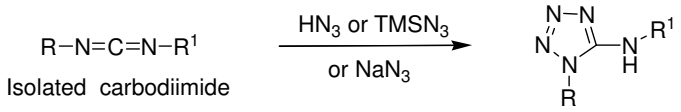
Scheme V.3.3.

Formation of tetrazoles has been observed by a nucleophilic substitution of an azide in α–chloroformamidines,[16a,b] at an elevated temperature. Following a similar strategy, Miller *et al*. have also synthesized tetrazoles from aminoiminomethanesulfonic acids using sodium azide[16c] (*Scheme V.3.4.*).



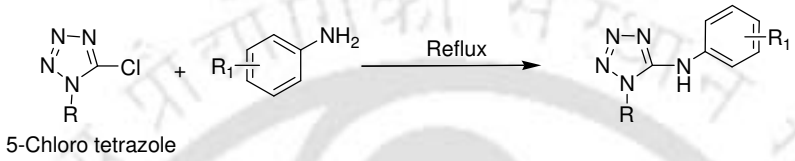
Scheme V.3.4.

Cycloaddition reaction of carbodiimides with hydrazoic acid in dry benzene, sodium azide or with trimethylsilyl azide (*Scheme V.3.5.*) is reported to give tetrazoles in good yield.[16d-h]



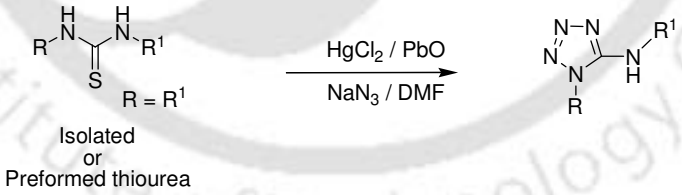
Scheme V.3.5.

Tetrazole derivatives are prepared by the nucleophilic substitution reaction of amines in 5-chloro tetrazole under heating condition[17a] (*Scheme V.3.6.*).



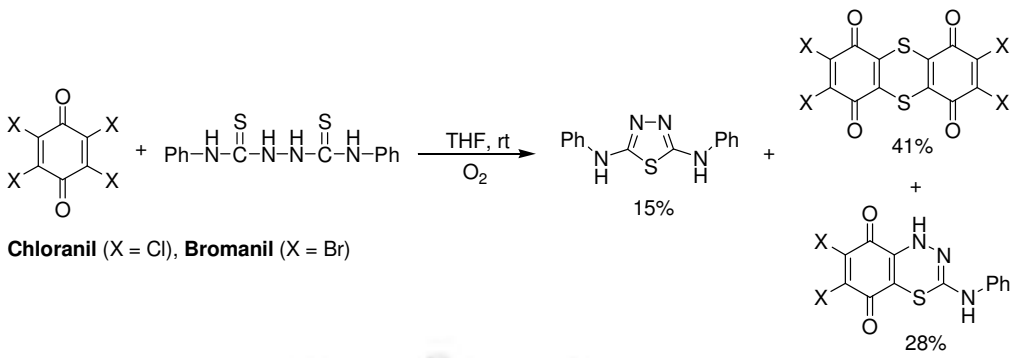
Scheme V.3.6.

Batey *et al.* developed a general method for the synthesis of 5-aminotetrazoles using Hg(II)-promoted attack of azide anion onto thiourea. This reaction proceeds *via* desulfurization of thiourea followed by the attack of azide ion giving a guanyl azide intermediate, which undergoes electrocyclization to form the tetrazole.[17b] This method is high yielding and provides access to mono-, di-, and tri substituted 5-aminotetrazoles, targets of potential interest for combinatorial library development. In yet another method, lead (Pb) salt[17c,d] has been employed as desulfurizing agent for the preparation of tetrazoles (*Scheme V.3.7.*).



Scheme V.3.7.

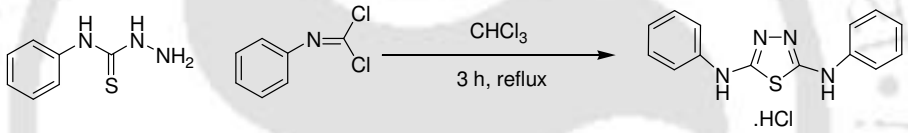
The reaction of *N*,*N*′-disubstituted hydrazinecarbothioamides with chloranil [3,5,6-tetrachloro-1,4-benzoquinone] or bromanil [2,3,5,6-tetrabromo-1,4-benzoquinone][18a,b] yielded the corresponding thiadiazoles, thiadiazines and tetraones (*Scheme V.3.8.*).



Chloranil (X = Cl), **Bromanil** (X = Br)

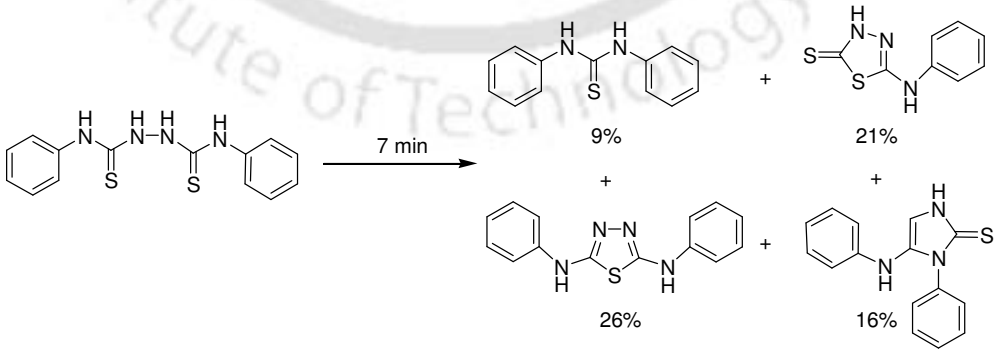
Scheme V.3.8.

The interaction of aryl/alkyl thiosemicarbazides and phenylcarbonimidic dichloride under refluxing condition using chloroform as solvent afforded 2-phenylimino-5-aryl/alkylimino-1,3,4-thiadiazolidines hydrochlorides which on basification with dilute ammonium hydroxide solution gave corresponding thiadiazole compounds (*Scheme V.3.9.*).[18c]



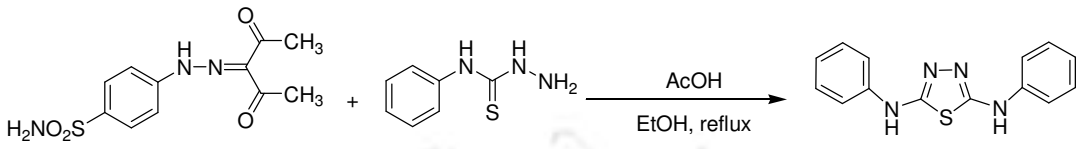
Scheme V.3.9.

Hassan *et al*. have reported both microwave and thermal heterocyclization of *N,N'*-disubstituted hydrazinecarbothioamides and substituted thioureidoethylthioureas as well as 1-phenyl-3[2-(3-phenylthioureido)phenyl]thiourea to form 1,3-diphenylthioureas and thiadiazoles (*Scheme V.3.10.*).[18d]



Scheme V.3.10.

Thiadiazoles were prepared in quantitative yields by the condensation of *p*-substituted phenyl sulfonamide with phenylthiosemicarbazide in the presence of AcOH using EtOH as a solvent under reflux condition[18e] (*Scheme V.3.11.*).



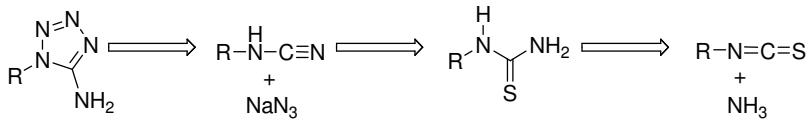
Scheme V.3.11.

V.4. Present Work

V.4.1. Tandem Regioselective Synthesis of Tetrazoles and Related Heterocycles Using Iodine

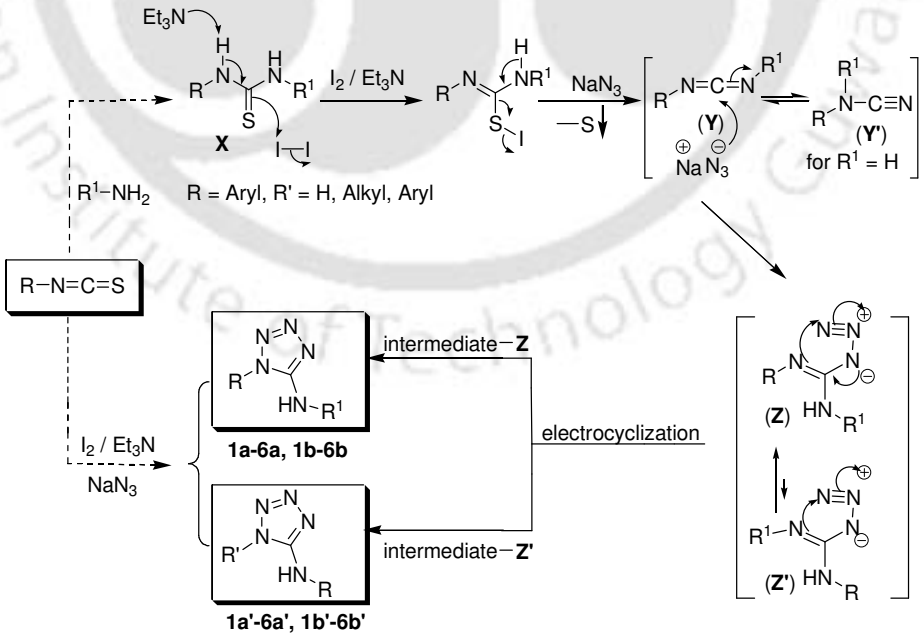
Our interest in the thiophilic properties of hypervalent iodine[19] and tribromide reagents[20] led us to imagine the development of an efficient three step tandem process to construct the aminotetrazoles from isothiocyanates.

The synthetic sequence for the proposed one-pot tandem process can be envisaged by treating the organic isothiocyanates with amines (ammonia, aryl or alkyl amine) to form thioureas. The *in situ* generated thioureas can give rise to cyanamides/carbodiimides in the medium which when reacted with molecular iodine in the presence of a base. Subsequent treatment of the cyanamides/carbodiimides with sodium azide would generate tetrazoles. The retro synthetic strategy for the proposed one-pot tandem process is shown in *Scheme V.4.1.1.*



Scheme V.4.1.1. *Retro synthetic strategy for the synthesis of aminotetrazoles.*

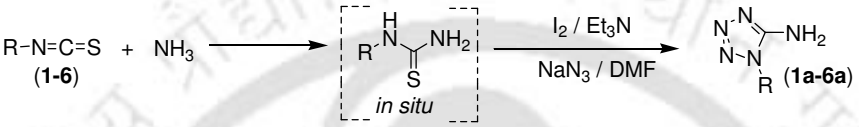
The development of three step tandem processes was carried out using freshly prepared phenyl isothiocyanate **1** [19b,20a] (1 equiv). To this was added aqueous ammonia (25%, 1 mL) in an ice-cold condition and the mixture was stirred for 20 min to give 1-phenylthiourea **X**. The excess of ammonia was removed in a rotary evaporator to prevent the formation of nitrogen triiodide NI_3.[21] Subsequently, DMSO (2 mL) was admixed to the 1-phenylthiourea **X**, and which was added sequentially, NaN_3 (2 equiv), I_2 (1 equiv) followed by a drop wise addition of triethylamine (2 equiv) at room temperature. During this time the reaction was exothermic. After complete addition of triethylamine the reaction mixture was stirred for 14 h to convert the *in situ* generated 1-phenylthiourea **X** (*Scheme V.4.1.2.*) to 1-phenyl-1*H*-tetrazole-5-amine in moderate yield (55%). Other organic solvents such as chloroform, tetrahydrofuran, toluene, acetonitrile, dioxane, ethanol *etc.* were not effective in converting the cyanamide into corresponding tetrazole **1a** even at higher temperature as sodium azide remains insoluble in these solvents. Additionally, the optimization of the reaction conditions e.g. increase in the quantity of I_2 from 1 to 1.1 equiv, Et_3N from 2 to 3 equiv and switching the solvent from DMSO to DMF reduced the time to 4 h and improved the yield (75%) at room temperature. Therefore, we continued to use our optimized reaction condition [arylthiourea (1 equiv.), Et_3N (3 equiv.), iodine (1.1 equiv.), DMF (2 mL)] for the synthesis of various mono substituted tetrazoles.

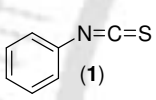
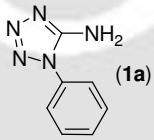
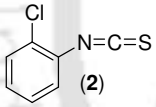
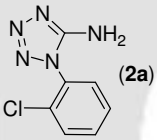
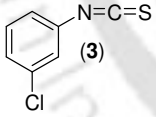
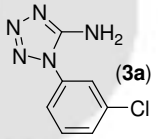
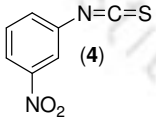
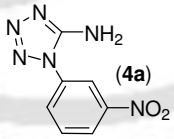
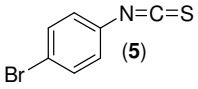
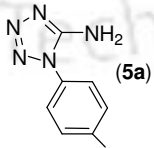
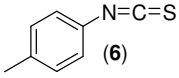
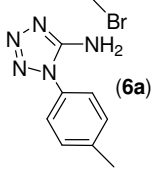


Scheme V.4.1.2. *Plausible mechanism for formation of 5-aminotetrazole.*

A plausible reaction mechanism for this transformation has been proposed as shown in *Scheme V.4.1.2*. The intermediate cyanamide **Y** or **Y'** obtained from thiourea **X** (where R^1 = H), has been confirmed by its isolation and characterization. The precipitation of elemental sulfur further supports our proposed mechanism. The intermediate cyanamide **Y** is attacked by the azide ion giving the intermediate guanyl azide **Z** which then undergoes electrocyclization giving 1-aryl-1*H*-tetrazole-5-amine **1a–6a**.

Table V.4.1.1. *Formation of 1-aryl-1H-tetrazole-5-amines from aryl isothiocyanates.*[a,b]



Isothiocyanate	Product[c]	Time/h	Yields (%)[d]
 (**1**)	 (**1a**)	4.0	75
 (**2**)	 (**2a**)	2.5	88
 (**3**)	 (**3a**)	3	79
 (**4**)	 (**4a**)	2.6	86
 (**5**)	 (**5a**)	3.5	85
 (**6**)	 (**6a**)	5	73

[a] Reactions were carried out at room temperature in DMF. [b] Reactions were monitored by TLC at an interval of 10 min. [c] Confirmed by IR, ^{1}H and ^{13}C NMR. [d] Isolated yield.

Employing this one-pot strategy, we have successfully prepared a series of 1-aryl-1*H*-tetrazole-5-amine **1a–6a** from their corresponding isothiocyanates **1–6** as shown in *Table V.4.1.1*. Aryl isothiocyanates containing weakly deactivating groups (-Cl, -Br) (*Table V.4.1.1*, entry **2**, **3** and **5**) in their ortho, meta or para positions reacted efficiently to afford the corresponding tetrazoles **2a**, **3a** and **5a** in good yields. Strongly deactivating group (-NO_2) (*Table V.4.1.1*, entry **4**) when present in the *m*-position yielded the corresponding tetrazole **4a** in good yield. Further, the structure of **2a** has been confirmed by X-ray crystallography as shown in *Figure V.4.1.1*.

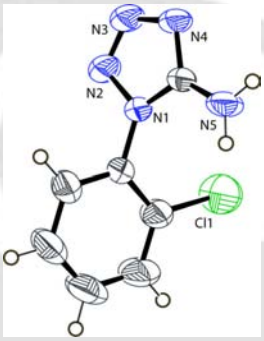


Figure V.4.1.1. *ORTEP view with the atomic numbering scheme of* ***2a****.*

Aryl isothiocyanate substituted with a weakly activating group (*p*-CH_3) (*Table V.4.1.1*, entry **6**) also resulted in the corresponding tetrazole **6a** in good yield, though it required longer reaction time compared to the substrates possessing electron withdrawing groups (*Table V.4.1.1*, entry **1–5**).

It may be mentioned here that formation of both the isomeric products *i.e.* 1-aryl-5-amino-1*H* tetrazole **1a–6a** and 5-arylamino-1*H*-tetrazole **1a'–6a'** (where R = Aryl, R' = H) from thiourea **X** have been observed as shown in *Scheme V.4.1.2*, using hydrazoic acid and aryl cyanamide under a thermal condition which is because of the thermal isomerization of the intermediates **Z** and **Z'**.[17d,e] Recently, exclusive formation of one of the isomer has been achieved using zeolite[14g] or $ZnCl_2$[14h] catalyst at an elevated temperature. This of course is dependent on the nature of the substituents attached to the aryl cyanamides. For substrates having electron donating substituents, the formation of 1-aryl-5-amino-1*H*-tetrazole **1a–6a** is favorable which goes *via* guanyl azide intermediate **Z** (*Scheme V.4.1.2*). As the electro

negativity of the substituent increases, the product is shifted towards the 5-arylamino-1*H*-tetrazole **1a'–6a'** which goes *via* guanyl azide intermediate **Z'** (*Scheme V.4.1.2*). Under the present experimental condition which is carried out at room temperature irrespective of the nature of the substituents present (*Table V.4.1.1*, entry **1**) in the aryl cyanamide, exclusive formation of the 1-aryl-5-amino-1*H* tetrazole **1a–6a** was observed.

1,5-Disubstituted tetrazoles **1b–6b** were obtained from the reaction of aryl isothiocyanates (*Table V.4.1.2*, entry **1–6**) and corresponding aryl amines by a similar mechanism as shown in *Scheme V.4.1.2*. Symmetrical thioureas containing moderately electron-withdrawing substituents such as *o*-Cl, *m*-Cl, or *p*-Br and strongly electron-withdrawing substituent *m*-NO_2, all gave their corresponding tetrazoles 2**b–5b** (*Table V.4.1.2.*) in good to excellent yields. The structure of one of the products **2b** has been confirmed by X-ray crystallography as shown in *Figure V.4.1.2.* This methodology was found to be equally efficient for the symmetrical thiourea having moderately electron-donating substituent *p*-Me (*Table V.4.1.2*, entry **6**) to give the corresponding product **6b**.

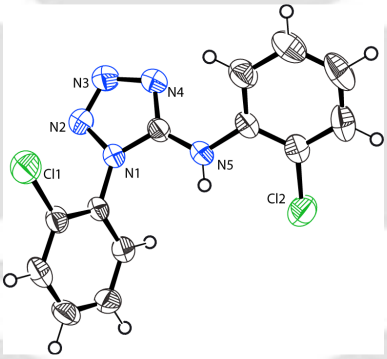
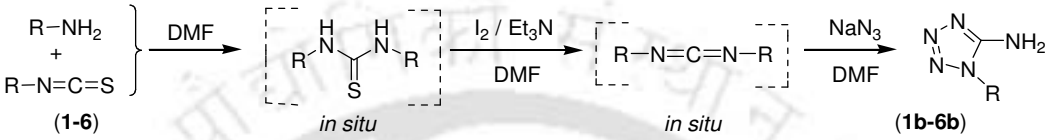


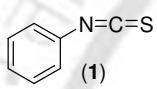
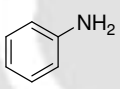
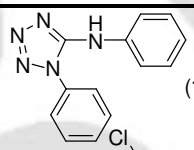
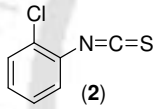
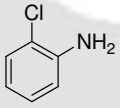
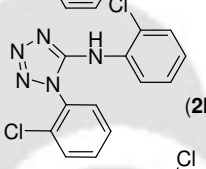
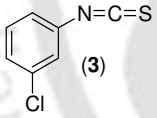
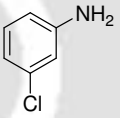
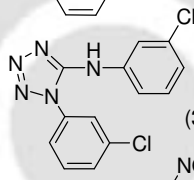
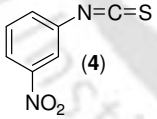
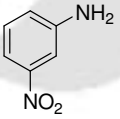
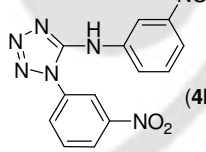
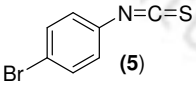
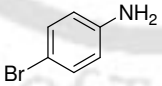
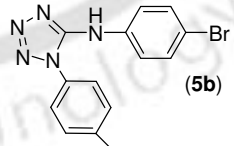
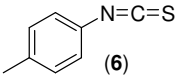
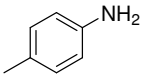
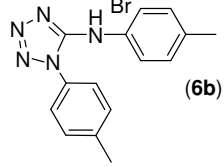
Figure V.4.1.2. *ORTEP view with the atomic numbering scheme of* ***2b****.*

A noteworthy aspect is that the parent amines attached to the *in situ* generated thioureas (*Scheme V.4.1.2*, X where R = aryl, R' = H, aryl) and having lower p*Ka*'s resulted in the formation of the intermediate cyanamide or carbodiimide faster because of the facile N-H deprotonation (*Scheme V.4.1.2.*) compared to the amine having higher p*Ka's*. Once the intermediate cyanamide/carbodiimide is build up the attack by the azide ion is possibly the rate determining step. The effect of electron withdrawing groups

facilitates this and hence faster formation of tetrazoles **2a–5a** and **2b–5b**. The p*Ka* of *o*-Cl, *m*-NO_2, *m*-Cl, *p*-Br, *p*-Me anilines and aniline are 2.65, 2.46, 3.46, 3.86, 5.08 and 4.63 respectively, which is clearly reflected in their reactivity order as can be seen from *Table V.4.1.1* and *Table V.4.1.2*, leading to the formation of heterocycles **1a–5a** and **1b–5b**.

Table V.4.1.2. *Formation of aryl-(1-aryl-1H-tetrazol-5-yl)-amine from the in situ generated 1,3-diarylthiourea.*[a,b]

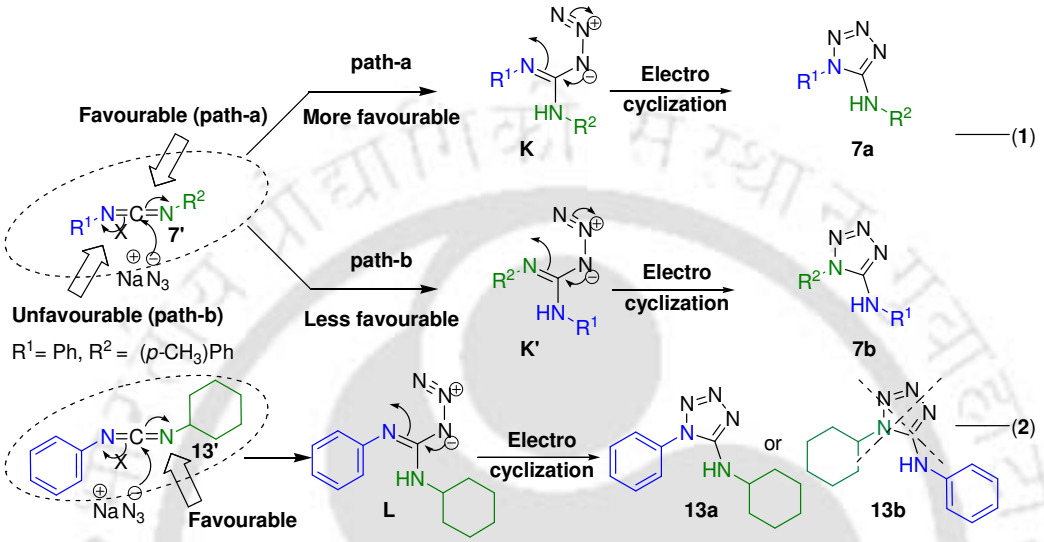


Isothiocyanate	Amine	Product[c]	Time/h	Yields (%)[d]
 (**1**)		 (**1b**)	4.5	70
 (**2**)		 (**2b**)	2.6	85
 (**3**)		 (**3b**)	3	80
 (**4**)		 (**4b**)	2.8	78
 (**5**)		 (**5b**)	3.6	78
 (**6**)		 (**6b**)	8	75

[a] Reactions carried out at room temperature in DMF solvent. [b] Reactions were monitored by TLC at an interval of 10 min. [c] Confirmed by IR and ^{1}H and ^{13}C NMR. [d] Isolated yield.

So far there are no literature reports on the regioselectivity in the formation of 1,5-disubstituted tetrazole from 1,3-disubstituted unsymmetrical thioureas **X** (where R = R').

We were interested to investigate the regioselectivity of tetrazole formation from unsymmetrical thioureas *i.e.* whether the amine having lower p*Ka* would be attached to the ring nitrogen or contribute to the exocyclic amino group giving product of the type **7a** or a reverse orientation giving product of the type **7b** as shown in *Scheme V.4.1.3, eq 1.*



Scheme V.4.1.3. *Regioselective product formation for unsymmetrical thiourea* ***7*** *and* ***13****.*

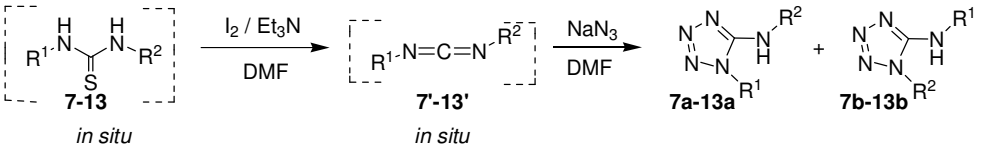
After the formation of an unsymmetrical carbodiimide **7'** (*Scheme V.4.1.3*, *eq 1*), the attack of an azide group to an unsymmetrical carbodiimide would led to the flow of electron (protonation) towards the amine having more basic nature (higher p*Ka*) hence path-a is more favorable (*Scheme V.4.1.3*, *eq 1*), without affecting the imine group on the other side. The resultant guanidyl intermediate **K**, *Scheme V.4.1.3*, *eq 1* undergoes electrocyclization giving product of the type **7a** where the amine having lower p*Ka* goes to the ring nitrogen and the other amine having higher p*Ka* is part of the exocyclic nitrogen. The flow of electron (protonation) towards the amine having less basic nature (lower p*Ka*) path-b is less favorable (*Scheme V.4.1.3*, *eq 1*) and hence unlikely to generate intermediate **K'** leading to the product type **7b**. This is illustrated using phenylcyclohexyl carbodiimide **13'** as a typical example as shown in *Scheme V.4.1.3*, *eq 2*. The measured p*Ka* of cyclohexyl amine and aniline are 10.66 and 4.63 respectively and hence product **13a** is expected to form exclusively as shown in *Scheme V.4.1.3*, *eq 2* and it is indeed the case.

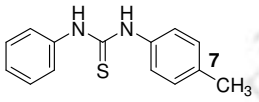
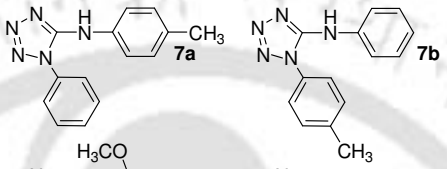
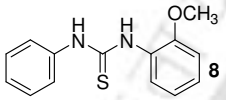
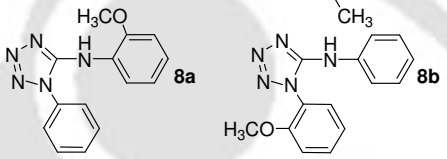
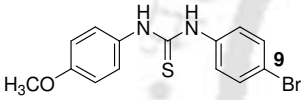
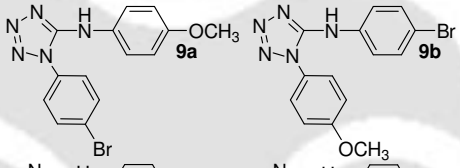
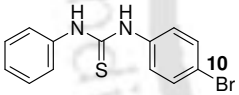
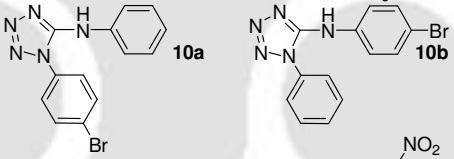
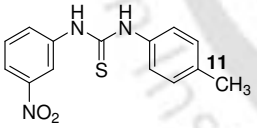
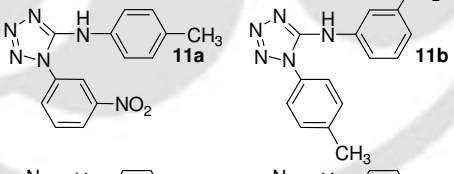
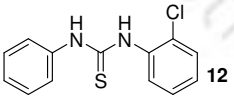
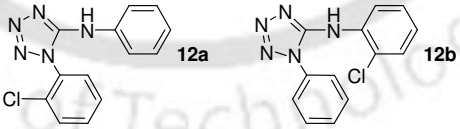
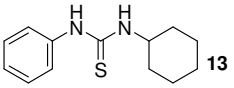
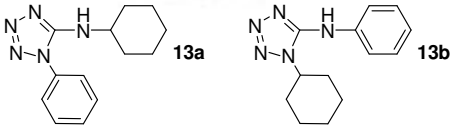
As can be seen from *Table V.4.1.3*, an unsymmetrical thiourea **7** containing an aniline and a *p*-methyl aniline group attached to the thiourea form the corresponding unsymmetrical carbodiimide **7'** *in situ*, which when reacted with sodium azide gave a mixture of tetrazoles **7a** and **7b** in the ratio of 77:23. The measured p*Ka* of aniline and *p*-methyl aniline are 4.63 and 5.08 respectively. Thus, as per the mechanism proposed, *Scheme V.4.1.3*, *eq 1*, in the major product, the amine having lower p*Ka* (aniline) is a part of the heterocyclic nitrogen and the other amine (*p*-methyl aniline) attached to the thiourea having a higher p*Ka* is part of the other exocyclic nitrogen in tetrazoles skeleton **7a** .

This assumption is again demonstrated for another unsymmetrical thiourea **8** having aniline and *o*-methoxyaniline. Earlier we have demonstrated that larger the difference between the p*Ka*'s of the amines attached to the thiourea, greater is the regioselectivity.[19a,22] In this case, the p*Ka* difference between the two amines, *o*-methoxyaniline (5.45) and aniline (4.63) is 0.82, hence, expected to give better selectivity. The ratio of the product **8a** and **8b** formed was (84:16) which can be explained based on the measured p*Ka*'s of the parent amines. The X-ray crystallographic analysis of the major product **8a** as shown in *Figure V.4.1.3* is clearly revealed the disposition of the phenyl group as part of the ring nitrogen and the *o*-methoxy phenyl group attached to the exocyclic nitrogen.

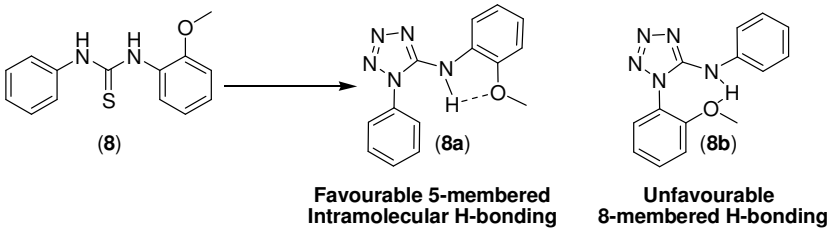
It may be mentioned here that the regioisomeric mixture **7a** and **7b** could not be resolved by thin layer chromatography (TLC) whereas the regioisomer **8a** and **8b** are well separated by TLC. One of the regioisomer **8a** forms intramolecular hydrogen bonding between exocyclic NH and the *o*-methoxy group thereby reducing its polar character. Similar intramolecular hydrogen bonding possibility does not exist in the other isomer **8b** as shown in *Scheme V.4.1.4*. The single crystal XRD structure of the product **8a** shows the intramolecular hydrogen bonding N5H$^{\cdots}$O with a bond length of 2.223 Å as shown in *Figure V.4.1.3.*

Table V.4.1.3. *Regioselective formation of aryl-(1-aryl-1H-tetrazol-5-yl)-amine from unsymmetrical 1,3-diarylthiourea.*[a,b]



Thiourea	Product(s)[c]	Time/h	Yields (%)[d,e]
 **7**	 **7a** **7b**	6	75 (77:23)
 **8**	 **8a** **8b**	3	84 (84:16)
 **9**	 **9a** **9b**	3	77 (57:43)
 **10**	 **10a** **10b**	6	80 (59:41)
 **11**	 **11a** **11b**	6	72 (61:39)
 **12**	 **12a** **12b**	3	88 (100:00)
 **13**	 **13a** **13b**	12	35 (100:00)

[a] Reactions carried out at room temperature in DMF solvent. [b] Reactions were monitored by TLC. [c] Confirmed by IR and ^{1}H and ^{13}C NMR. [d] Isolated yield. [e] Ratio of regioisomers determined by ^{1}H NMR.



Scheme V.4.1.4. *Intramolecular hydrogen bonding in regioisomers* ***8a*** *and* ***8b****.*

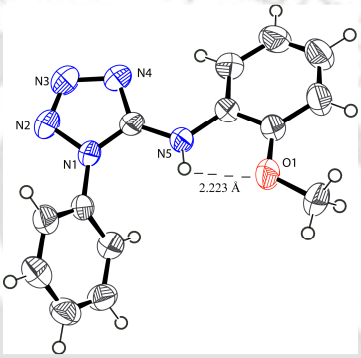
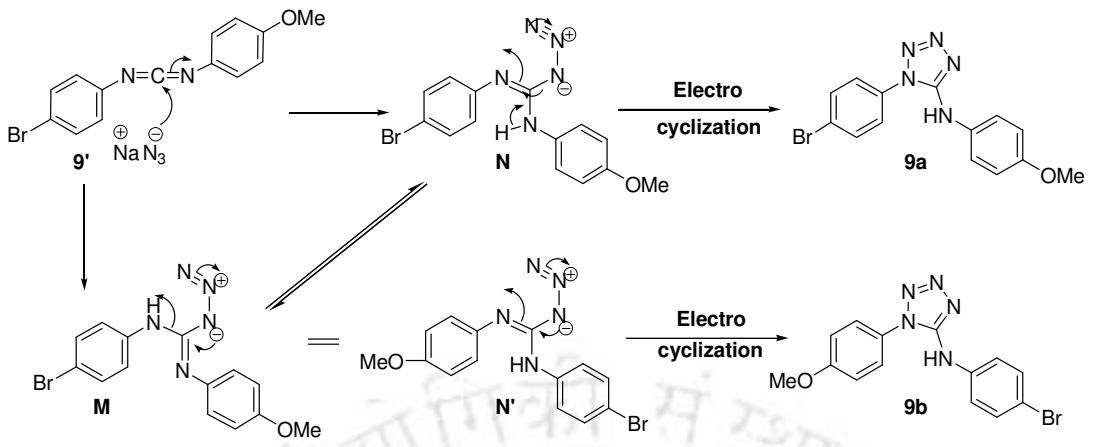


Figure V.4.1.3. *ORTEP view with the atomic numbering scheme of* ***8a****.*

An anomaly to the proposed regioselective mechanism was observed in the case of thiourea **9** where the measured p*Ka* of *p*-methoxyaniline and *p*-bromoaniline are 5.37 and 3.84 respectively, a difference of 1.53 units, thus expected to give a better regioselectivity compared to the thioureas **7** and **8**. However, the ratio of product **9a**:**9b** was found to be 57:43, less than expected. This could be possibly due to the possible interconversion of the two intermediates there by loss in the regioselectivity. This can be explained based on proposed mechanism as shown in *Scheme V.4.1.5*. Unsymmetrical carbodiimide **9'**, obtained from thiourea **9**, after the azide attack would result in the formation of intermediate **M** or **N** which on electrocyclization would give regioisomer **9a**. Alternatively, the intermediate **M** can also be converted to **N'** (*Scheme V.4.1.5*) or can be obtained directly giving the product **9b** thereby loss in the regioselectivity.



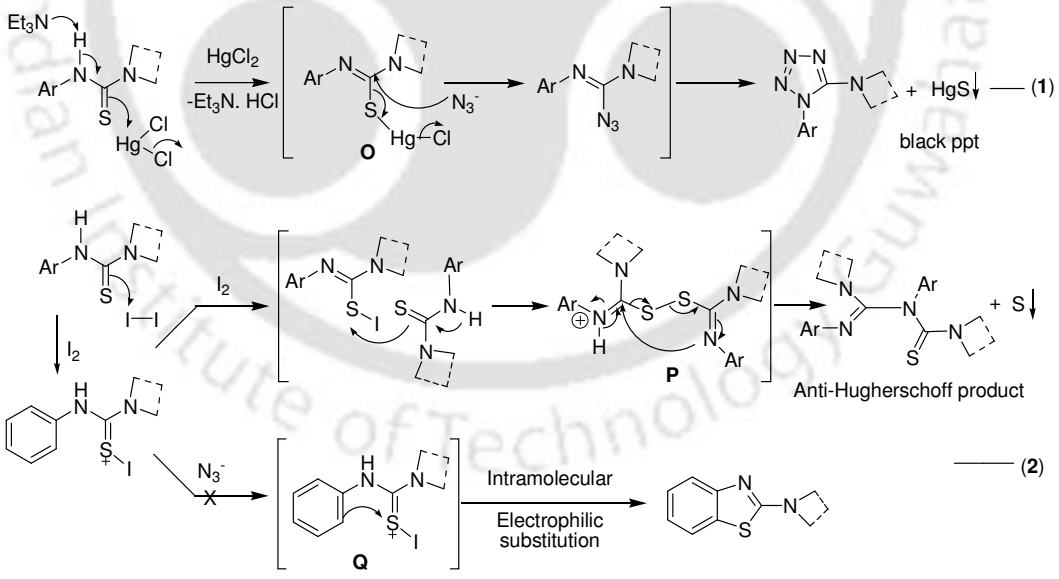
Scheme V.4.1.5. *Regioselective product formation for unsymmetrical thiourea* ***9****.*

In the case of thiourea **10**, the p*Ka* difference between the two amines, aniline (4.63) and *p*-bromoaniline (3.84) is 0.79. The ratio of the product **10a** and **10b** formed was 59:41 which can be again explained based on the measured p*Ka*'s of the amines. Unlike other regioisomers, the isomers **11a** and **11b** derived from thiourea **11** could be separated by column chromatography and the regioisomeric product ratios is in agreement with measured p*Ka*'s of the amine. However, when the p*Ka* difference between the amines attached to the thiourea is sufficiently large (<2 unit), only one of the regioisomer is obtained exclusively. This has been demonstrated with two other unsymmetrical thioureas **12** and **13**. In the case of thiourea **12**, the p*Ka*'s of the parent amines, aniline and *o*-chloroaniline are respectively 4.63 and 2.65, a difference of 1.98, which gave exclusively one of the regioisomer **12a**. As discussed above, in the thiourea **13**, the p*Ka*'s of the parent amines, aniline and cyclohexylamine are 4.63 and 10.66 respectively, a difference of 6.03, which gave exclusively one regioisomer **13a**. The yield obtained in the case of thiourea **13** was much less (35%) which is because of the inability of unsymmetrical thiourea **13** to efficiently form corresponding carbodiimide **13'** because of the presence of an aliphatic amine in one side, an observation consistent with our recent report on carbodiimide formation.[19c]

After the successful synthesis of various tetrazoles from mono substituted, symmetrical and unsymmetrical disubstituted thioureas, we were interested to apply this

strategy on thioureas generated from isothiocyanates and alkyl *sec*-amines. Previously, Batey *et al.* have successfully synthesized several tetrazoles using mercuric chloride ($HgCl_2$) as the desulfurizing agent.[17b]

To scrutinize this, phenyl isothiocyanate **1** (1 equiv) was treated with piperidine **k** (1 equiv) to form the corresponding unsymmetrical thiourea under our optimized reaction condition. To this was added NaN_3 (3 equiv), iodine (1.1 equiv) followed by a drop wise addition of triethylamine (3 equiv) over a period of 10 min. After the complete addition of triethylamine, the reaction mixture was allowed to stir for an additional 3 h. TLC showed complete disappearance of the intermediate thiourea and the formation of a new product. Further, ^{1}H NMR, ^{13}C NMR analysis of the product reveals the formation of a thioamido guanidine **1c** as the major product (87%) along with 2-aminobenzothiazole **1d** (10%) (*Table V.4.1.4.*). This observation is consistent with our recent report on the formation of thioamido guanidino moiety rather than the expected 2-aminobenzothiazole (Hugerschoff product)[23] when the *in situ* generated thiourea, aryl-*sec*-alkyl thiourea was treated with bromine or its equivalents.[20b]



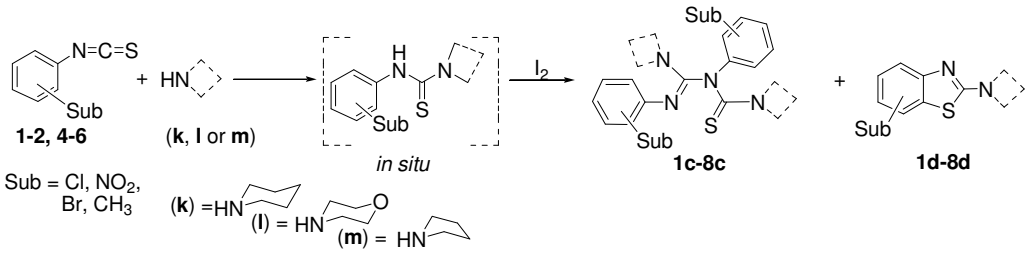
Scheme V.4.1.6. *Differential reactivity of aryl-sec-alkyl thiourea.*

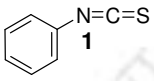
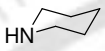
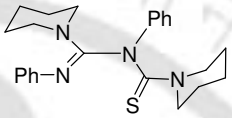
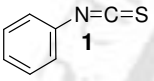
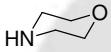
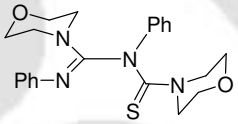
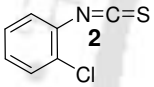
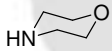
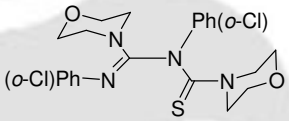
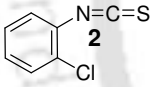
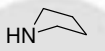
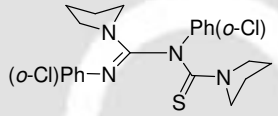
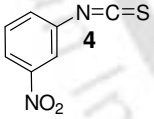
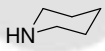
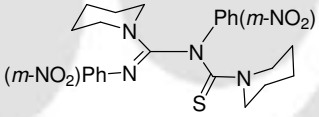
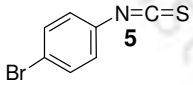
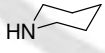
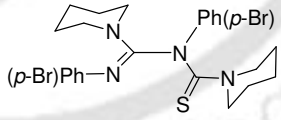
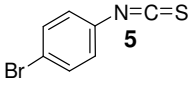
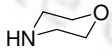
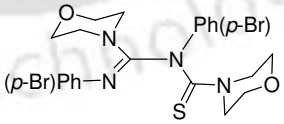
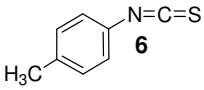
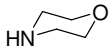
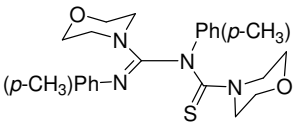
The difference in the desulfurizing ability of $HgCl_2$ and I_2 is quite evident. In the former, the intermediate imino S–HgCl **O** (*Scheme V.4.1.6, eq 1*) is attacked by an azide ion directly giving guanidyl azide intermediate[17b] whereas in the later case the imino S–I intermediate is attacked by a second molecule of the thiourea giving a disulfide intermediate **P** (*Scheme V.4.1.6, eq 2*) which rearrange to give the thioamido guinidino moiety (*Table V.4.1.4*).[20b] However when the aryl ring is sufficiently activated, it would prefer an intramolecular electrophilic substitution reaction **Q** (*Scheme V.4.1.6, eq 2*) to give Hugerschoff product *i.e*. aminobenzothiazole (*Table V.4.1.4*). It is pertinent to mention here that tetrazole formation is not possible from *N*,*N*-disubstituted thiourea using $HgCl_2$ possibly because of the formation of *bis*-thiomercury (II) complex.[17b,24]

As can be seen from *Table V.4.1.4*, a range of aryl isothiocyanates reacted with aliphatic secondary amines such as piperidine **k**, morpholine **l**, pyrrolidine **m** to give the major product having a thioamido guanidine skeleton in each case. Thiourea obtained by the reaction of phenyl isothiocyanate **1** and morpholine **l** gave product **2c** in excellent yield. Similarly, weakly deactivating substituents (Cl, Br) when present in the ortho-position or para-position (*Table V.4.1.4*, entry **2** and **5**) reacts with secondary amines piperidine **k**, morpholine **l** and pyrrolidine **m** to give products **3c**, **4c**, **6c** and **7c** in good yields as shown in *Table V.4.1.4*.

This method also worked equally effective for aryl isothiocyanate bearing a strong electron withdrawing group (-NO_2) (*Table V.4.1.4*, entry **4**) in its meta-position which on reaction with piperidine **k** followed by the treatment with iodine gave **5c** as the only isolated product. Substrates **2**, **4** and **5** are moderately deactivating in nature hence are less susceptible to intramolecular nucleophilic substitution to give Hugerschoff reaction product 2-aminobenzothiazole.[23]Aryl isothiocyanate **6** bearing moderately activating groups (Me) in its para position gave no significant amount (14%) of benzothiazole and the dominant product (60%) was still the thioamido guanidine product **8c**.

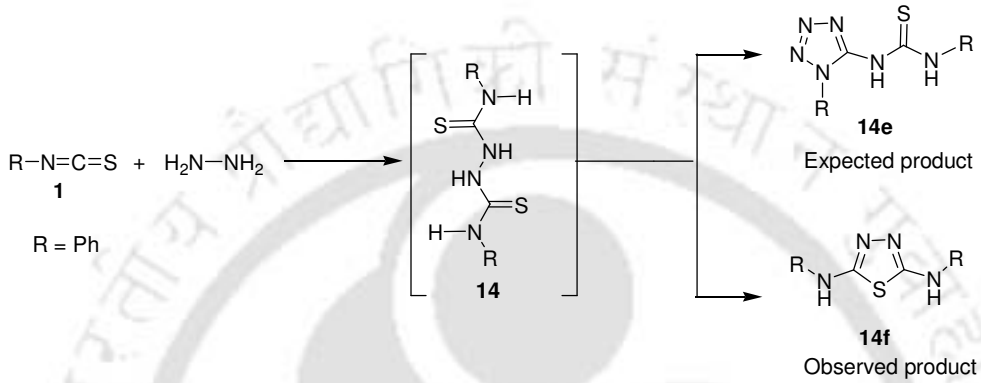
***Table V.4.1.4**. Reaction of aryl isothiocyanates with secondary amines and iodine.*[a,b]



Isothiocyanate	Sec.amine(s)	Product(s)[c]	Yields (%)[d]			
 **1**	 **k**		**1c**	87	**1d**	10
 **1**	 **l**		**2c**	93	**2d**	nd[e]
 **2**	 **l**		**3c**	94	**3d**	nd[e]
 **2**	 **m**		**4c**	91	**4d**	nd[e]
 **4**	 **k**		**5c**	88	**5d**	nd[e]
 **5**	 **k**		**6c**	86	**6d**	nd[e]
 **5**	 **l**		**7c**	89	**7d**	nd[e]
 **6**	 **l**		**8c**	60	**8d**	14

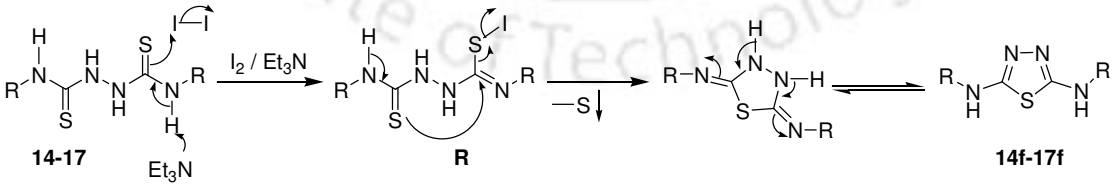
[a] Reactions carried out at room temperature in EtOH solvent. [b] Reactions were monitored by TLC. [c] Confirmed by IR and ^{1}H and ^{13}C NMR. [e] nd = not detected.

The success of this iodine mediated heterocyclization prompted us to apply this strategy to *bis*-diarylthiourea **14**, obtained by reacting hydrazine hydrate (1 equiv) with phenyl isothiocyanate **1** (2 equiv), to yield an aryl/alkyl tetrazoylthiourea of the type **14e** (*Scheme V.4.1.7.*). When the resultant *in situ* generated *bis*-diarylthiourea **14** was treated with iodine, the desired tetrazole derivative **14e** was not observed at all; rather thiadiazole **14f** was the sole isolated product as shown in *Scheme V.4.1.7.*



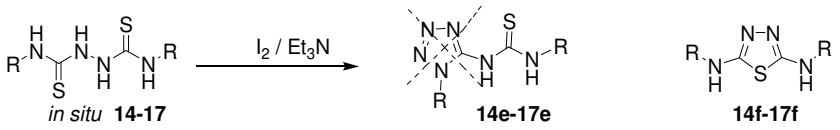
Scheme V.4.1.7. *Thiadiazole formation from bis-diarylthiourea.*

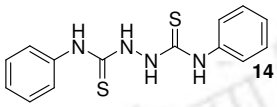
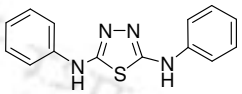
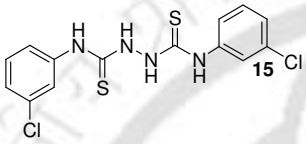
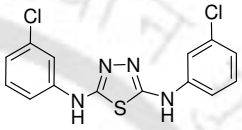
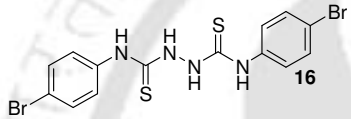
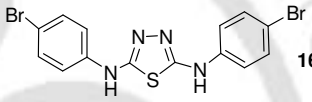
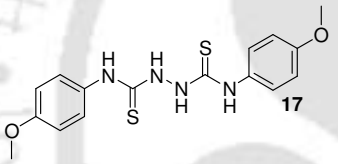
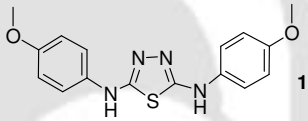
The proposed mechanism for the formation of thiadiazole **14f** can be explained as shown in *Scheme V.4.1.8.* The initial imino S–I intermediate **R** (*Scheme V.4.1.8*) obtained by the reaction of *bis*-diarylthiourea with iodine is attacked intramolecularly by the adjacent soft sulfur atom on the imino carbon rather than the attack by a hard nitrogen nucleophile and not by the weak azido nucleophile thus forming a five membered ring with the expulsion of sulfur. This is consistent with our recent proposed mechanisms[19a,20b,22] and as proposed by others.[25]



Scheme V.4.1.8. *Mechanism for the formation of N^2-N^5 disubstituted thiadiazole.*

Table V.4.1.5. *Formation of thiadiazoles from in situ generated bis-diarylthiourea.*[a,b]



Thiourea		Product[c]		Yields (%)[d]
	14	14e		14f	81
	15	15e		15f	79
	16	16e		16f	84
	17	17e		17f	87

[a] Reactions were carried out at room temperature in EtOH. [b] Reactions were monitored by TLC. [c] Confirmed by IR, ^{1}H and ^{13}C NMR. [d] Isolated yield.

Having a successful strategy in hand, we extend the present protocol toward the synthesis of various thiadiazoles as shown in *Table V.4.1.5*. Aryl ring having mild electron withdrawing group (*Table V.4.1.5*, entry **15** and **16**) as well as weakly activating group (*Table V.4.1.5*, entry **17**) all gave the desired products **15f–17f** in good yields. The structure of the **15f** has been further confirmed by X-ray crystallography (*Figure V.4.1.4.*).

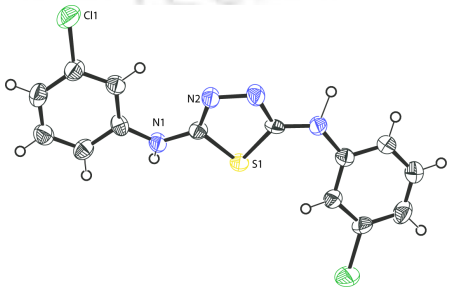


Figure V.4.1.4. *ORTEP view with the atomic numbering scheme of* ***15f****.*

V.5. Experimental Section

V.5.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1, Page number 56-57.

V.5.2. General Procedures

V.5.2.1. General Procedure for the Preparation of 1-Phenyl-1*H*-tetrazol-5-ylamine (1a)

Aqueous ammonia (25%, 2 mL) was added to phenyl isothiocyanate **1** (270 mg, 2 mmol) in an ice-cold condition and the reaction mixture was stirred for 20 min at room temperature. During this time complete formation of 1-phenyl thiourea was observed. Excess of ammonia was removed in a rotary evaporator and the reaction mixture was admixed with DMF (2 mL) followed by the sequential addition of NaN_3 (390 mg, 6 mmol), I_2 (559 mg, 2.2 mmol) and a drop wise addition of triethylamine (835 µL, 6 mmol) over a period of 5 min. During the addition of triethylamine the reaction was exothermic. After complete addition of triethylamine, the reaction mixture was stirred for an additional 3 h. complete conversion of the *in situ* generated 1-phenylthiourea to 1-phenyl-1*H*-tetrazol-5-ylamine **1a** was observed by thin layer chromatography (TLC). The reaction mixture was treated with a 5% hypo solution (5 mL) and the product was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate layer was washed with water (3 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified over a column of silica gel (saturated with 1% triethylamine) and eluted with (8:2 hexane/ethyl acetate) to give 75% of the product **1a**.

V.5.2.2. General Procedure for the Preparation of Phenyl-(1-phenyl-1*H*-tetrazol-5-yl)-amine (1b)

Aniline (186 mg, 2 mmol) was added to phenyl isothiocyanate **1** (270 mg, 2 mmol) in DMF (4 mL) and the reaction was stirred at room temperature for 20 min. During this time complete formation of 1,3-diphenylthiourea was observed. To this was added sequentially, NaN_3 (390 mg, 6 mmol), I_2 (559 mg, 2.2 mmol) and drop wise addition of triethylamine (835 µL, 6 mmol) over a period of 5 min. During the addition of

triethylamine reaction was exothermic. After complete addition of triethylamine, the reaction mixture was stirred for an additional 4.5 h. Complete conversion of the *in situ* generated 1,3-diphenylthiourea to phenyl-(1-phenyl-*1H*-tetrazol-5-yl)-amine **1b** was observed by thin layer chromatography (TLC). The reaction mixture was treated with a 5% hypo solution (5 mL) and the product was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate layer was washed with water (3 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified over a column of silica gel (saturated with 1% triethylamine) and eluted with (8:2 hexane:ethyl acetate) to give 70% of the product **1b**.

V.5.2.3. General Procedure for the Preparation of Phenyl-(1-*p*-tolyl-1*H*-tetrazol-5-yl)-amine / (1-Phenyl-1*H*-tetrazol-5-yl)-*p*-tolyl-amine (7a+7b)

Similar to general procedure described above, except *p*-methyl aniline (214 mg, 2 mmol) was used instead of aniline to give 75% of the product **7a+7b**.

V.5.2.4. General Procedure for the Preparation of Guanidine (1c)

To a solution of phenyl isothiocyanate **1** (270 mg, 2 mmol) in EtOH (2 mL) was added drop wise piperidine **k** (197 µL, 2 mmol), dissolved in EtOH (2 mL) at room temperature. Formation of thiourea was observed within 15 min as judged from thin layer chromatography (TLC). To this was then added I_2 (254 mg, 1 mmol) pinch wise over a period of 10 min. The reaction was kept for stirring at room temperature and complete conversion to *anti*-Hugerschoff product was observed within 30 min as can be judged from TLC. After completion of the reaction, solvent was evaporated, and the reaction mixture was quenched with 5% hypo solution (5 mL) and admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with water (2 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product was isolated by silica gel column (saturated with 1% triethylamine) (2:8 ethyl acetate and hexane) to give 87% of the product **1c**.

V.5.2.5. General Procedure for the Preparation of N^2, N^5-Diphenyl-1,3,4-thiadiazole-2,5-diamine (14f)

Hydrazine hydrate (50 mg, 1 mmol) was added to phenyl isothiocyanate **1** (270 mg, 2 mmol) in EtOH (2 mL) and the reaction was stirred at room temperature for 20 min. During this time complete formation of *bis*-thiourea was observed. To this was added triethylamine (2 equiv) followed by I_2 (0.5 equiv) pinch wise over a period of 5 min. The complete conversion of *bis*-thiourea **14** to N^2,N^5-diphenyl-1,3,4-thiadiazole-2,5-diamine **14f** was observed within 30 min. After completion, the reaction mixture was quenched with 5% hypo solution (5 mL), and product was extracted with ethyl acetate (2 x 10mL), dried over on anhydrous Na_2SO_4 and concentrated under reduced pressure. The pure product was isolated by silica gel column (1:9 ethyl acetate:hexane) to give 81% of the product **14f**.

V.6. References

1. Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Thieme: NewYork, 1995; p 212.
2. (a) Brown, M. U. S. Patent 3, 338, 915, **1967**; *Chem. Abstr.*, **1968**, 87299; (b) Tarver, C. M.; Goodale, T. C.; Shaw, R.; Cowperthwaite, M. Office of Naval Research (Technical Report), ACR (U.S.), ACR-221, Proc. Symp. Int. Detonation, 6th, 1967, pp231–249; *Chem. Abstr.*, **1980**, *92*, 8480
3. (a) Bradbury, R. H.; Allott, C. P.; Dennis, M.; Girdwood, J. A.; Kenny, P. W.; Major, J. S.; Oldham, A. A.; Ratcliffe, A. H.; Rivett, J. E.; Roberts, D. A. *J. Med. Chem.* **1993**, *36*, 1245; (b) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B.; Wells, G. J.; Wexler, R. R. *J. Med. Chem.* **1991**, *34*, 2525; (c) Koyama, M.; Ohtani, N.; Kai, F.; Moriguchi, F.; Inouye, M. *J. Med. Chem.* **1987**, *30*, 552; (d) Raman, K.; Parmar, S. S.; Singh, S. P. *J. Heterocycl. Chem.* **1980**, *17*, 1137.
4. Hansch, C.; Leo, L. Exploring QASR. *Fundamentals and Applications in Chemistry and Biology*; American Chemical Society: Washington, DC, 1995; Chapter 13.
5. (a) Butler, R. N. *In Comprehensive Heterocyclic Chem. II*, Vol. 4; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds.; Pergamon: Oxford, **1996**, 621; (b) Wittenberger, S. *J. Org. Prep. Proced. Int.* **1994**, *26*, 499; (c) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379; (d) Voitekhovich, S. V.; Gaponik, P. N.; Ivashkevich, O. A. *Russ. Chem. Rev.* **2002**, *71*, 721.

6. (a) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563; (b) Singh, H; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151; (c) Butler, R. N. *Adv. Het. Chem.* **1977**, *21*, 323; (d) Burger, A. *Prog. Drug. Res.* **1991**, *37*, 287; (e) Moderhack, D. *J. Prakt. Chem.* **1998**, *340*, 687; (f) Lipinski, C. A. *Annu. Rep. Med. Chem.* **1986**, *2721*, 283.
7. (a) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem.* **1986**, *29*, 538; (b) Peet, N. P.; Baugh, L. E.; Sundler, S.; Lewis, J. E.; Matthews, E. H.; Olberding, E. L.; Shah, D. N. *J. Med. Chem.* **1986**, *29*, 2403; (c) Girijavallabhan, V. M.; Pinto, P. A.; Genguly, A. K.; Versace, R. W. Eur. Patent EP 274867, 1988; *Chem. Abstr.* **1989**, *110*, 23890; (d) Akimoto, H.; Ootsu, K.; Itoh, F. Eur. Patent EP 530537, 1993; *Chem. Abstr.* **1993**, *119*, 2264; (e) Taveras, A. G.; Mallams, A. K.; Afonso, A. Int.patent WO 9811093, **1998**; *Chem. Abstr.* **1998**, *128*, 230253; (f) Mitch, C. H.; Quimby, S. J. Int patent WO 9851312, 1998; *Chem. Abstr.* **1998**, *130*, 13997.
8. (a) Yamazaki, K.; Hasegawa, H.; Umekawa, K.; Ueki, Y.; Ohashi, N.; Kanaoka, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1275; (b) Habich, D. *Synthesis*, **1992**, 358; (c) Vieira, E.; Huwyler, S.; Jolidon, S.; Knoflach, F.; Mutel, V.; Wichmann, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4628; (d) Harel, T.; Rozen, S. *J. Org. Chem.* **2010**, *75*, 3141.
9. (a) Singh, R. P.; Verma, R. D.; Meshri, D. T.; Shreeve, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3584; (b) Steinhauser, G.; Klapotke, T. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3330; (c) Singh, R. P.; Gao, H.; Meshri, D. T.; Shreeve, J. M. In *High Energy Density Materials*; Klapotke, T. M. Ed.; Springer: Berlin, Heidelberg, 2007; pp 35–83; (d) Klapotke, T. M. In *High Energy Density Materials*; Klapotke, T. M. Ed.; Springer: Berlin, Heidelberg, 2007; pp 85–122.
10. (a) Ek, F.; Wistrand, L.-G.; Frejd, T. *Tetrahedron* **2003**, *59*, 6759; (b) Flippin, L. A. *Tetrahedron Lett.* **1991**, *32*, 6857; (c) Rhonnstad, P.; Wensbo, D. *Tetrahedron Lett.* **2002**, *43*, 3137; (d) Modarresi-Alam, A. R.; Khamooshi, F.; Rostamizadeh, M.; Keykha, H.; Nasrollahzadeh, M.; Bijanzadeh, H. R.; Kleinpeter, E. *J. Mol. Struc.* **2007**, *841*, 61.
11. (a) Kurtzer, F.; Katritzky, A. R.; Boulton, A. J. in: *Advances in Heterocyclic Chemistry*, Academic Press, NewYork, 1965, pp.165–209 (5); (b) Swamy, S. N.; Basappa.; Priya, B. S.; Prabhuswamy, B.; Doreswamy, B. H.; Prasad, J. S.; Rangappa, K. S. *Eur. J. Med. Chem.* **2006**, *41*, 531; (c) Golgolab, H.; Lalezari, I.; Hosseini, L. *J. Heterocycl. Chem.* **1973**, *10*, 387; (d) Hussain, S.; Sharma, J.; Amir, M. *E. J. Chem.* **2008**, *5*, 963; (e) Abdel-Aziz, H. A.; Abdel-Wahab, B. F.; El-Sharief, M. A. M. S.; Abdulla, M. M. *Monatsh.Chem.* **2009**, *140*, 431; (f) Salgin-Goksen, U.; Gokhan-Kelekci, N.; Goktas, O.; Koysal, Y.; Kilic, E.; Isik, S.; Aktay, G.; Ozalp, M. *Bioorg. Med. Chem.* **2007**, *15*, 5738; (g) Clerici, F.; Pocar, D. *J. Med. Chem.* **2001**,

44, 931; (h) Akhtar, T.; Hameed, S.; Al-Masoudi, N. A.; Khan, K. M. *Heteroat. Chem.* **2007**, *18*, 316.

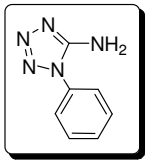
12. (a) Zheng, K. B.; He, J.; Zhang, J. *Chinese Chem. Lett.* **2008**, *19*, 1281; (b) Gujral, M. S.; Patnaik, P. M.; Kaul, R.; Parikh, H. K.; Conradt, C.; Tamhankar, C. P.; Daftary, G. V. *Cancer Chemother. Pharmacol.* **2001**, *47*, 23; (c) Stockler, M. R.; Wilcken, N. J. C.; Coates, A. *Breast Cancer Res. Treat.* **2003**, *81*, 49; (d) Wang, T.; Zhang, Y. H.; Yu, S.; Ji, H.; Lai, Y. S.; Peng, S. X. *Chin. Chem. Lett.* **2008**, *19*, 928; (e) Wei, M.-X.; Feng, L.; Li, X.-Q.; Zhou, X.-Z.; Shao, Z.-H. *Eur. J. Med. Chem.* **2009**, *44*, 3340.
13. (a) Gavrilyuk, J. I.; Lough, A. J.; Batey, R. A. *Tetrahedron Lett.* **2008**, *49*, 4746; (b) Severino, B.; Fiorino, F.; Perissutti, E.; Frecentese, F.; Cirino, G.; Roviezzo, F.; Santagada, V.; Caliendo, G. *Bioorg. Med. Chem.* **2008**, *16*, 6009; (c) Ursic, U.; Bevk, D.; Pirc, S.; Pezdirc, L.; Stanovnik, B.; Svete, J. *Synthesis* **2006**, 2376; (d) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans.1*, **2000**, 2311; (e) Katritzky, A. R.; El-Nachef, C.; Bajaj, K.; Kubik, J, Haase, D. N. *J. Org. Chem.* **2010**, *75*, 6009.
14. (a) Stolle.; Stark, H. *J. Prakt. Chem.* **1930**, *124*, 261; (b) Moderhack, D.; Goos, K.-H.; Preu, L. *Chem. Ber.* **1990**, *123*, 1575; (c) Garbrecht, W. L.; Herbst, R. M. *J. Org. Chem.* **1953**, *18*, 1014; (d) Herbst, R. M.; Roberts, C. W.; Harvill, E. *J. Org. Chem.* **1951**, *16*, 139; (e) Marchalin, M.; Martvon, A. *Collect. Czech. Chem. Commun.* **1980**, *45*, 2329; (f) Vorobiov, A. N.; Gaponik, P. N.; Petrov, P. T, Ivashkevich, O. A. *Synthesis* **2006**, 1307; (g) Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. *Tetrahedron* **2009**, *65*, 10715; (h) Habibi, D.; Nasrollahzadeh, M.; Faragi, A. R.; Bayat, Y. *Tetrahedron* **2010**, *66*, 3866.
15. (a) Joo, Y.-H; Shreeve, J. M. *Org. Lett.* **2008**, *10*, 4665; (b) Finnegan, W. G.; Henry, R. A.; Lieber, E. *J. Org. Chem.* **1953**, *18*, 779; (c) Jensen, K. A.; Holm, A.; Rachlin, S. *Acta Chem. Scand.* **1966**, *20*, 2795; (d) Percival, D. F.; Hebrst, R. M. *J .Org. Chem.* **1957**, *22*, 925.
16. (a) Reid, W.; Erle, H.-E. *Liebigs Ann. Chem.* **1982**, 201; (b) Quast, H.; Fuss, A.; Nahr, U. *Chem. Ber.* **1985**, *118*, 2164; (c) Miller, A. E.; Feeney, D. J.; Ma, Y.; Zarcone, L.; Aziz, M. A.; Magnuson, E. *Synth. Commun.* **1990**, *20*, 217; (d) Mironova, D. F.; Staninets, V. I. *Ukr. Khim. Zh.* (Russ Ed.), **1986**, *52*, 1269; (e) Herbst, R. M.; Roberts, C. W.; Harvill, E. J. *J. Org. Chem.* **1951**, *16*, 139; (f) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **2004**, *45*, 7787; (g) Tsuge, O.; Satoshi, U.; Oe, K. *J. Org. Chem.* **1980**, *45*, 5130; (h) Svetlik, J.; Martvon, A.; Lesko, J. *Chem. Zvesti* **1979**, *33*, 521.
17. (a) Brigas, A. F.; Clegg, W.; Dillon, C. J.; Fonseca, C. F. C.; Johnstone, R. A. W. *J. Chem. Soc., Perkin Trans. 2*, **2001**, 1315; (b) Batey, R. A.; Powell, D. A. *Org. Lett.* **2000**, *2*, 3237; (c) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **2004**, *45*, 7787; (d) Finnegan, W. G.;

Henry, R. A.; Lieber, E. *J. Org. Chem.* **1953**, *18*, 779. (e) Garbrecht, W. L.; Herbst, R. M. *J. Org. Chem.* **1953**, *18*, 1014.

18. (a) Hassan, A. A.; Mourad, A.-F. E.; El-Shaieb, K. M.; Abou-Zied, A. H. *Molecules*, **2005**, *10*, 82; (b) Hassan, A. A.; Mourad, A.-F. E.; El-Shaieb, K. M.; Abou-Zied, A. H. *J. Heterocyclic. Chem.* **2006**, *43*, 47; (c) Deshmukh, R. S.; Bhaskar, C. S.; Berad, B. N. *Asian J. Chem.* **2002**, *14*, 124; (d) Hassan, A. A.; Mourad, A.-F. E.; El-Shaieb, K. M.; Abou-Zied, A. H.; Doepp, D. *Heteroatom Chem.* **2003**, *14*, 535; (e) Shafik, R. M.; Hazzaa, A. A. B.; Soliman, F. S. G. *Pharmazie* **1978**, *33*, 23.
19. (a) Singh, C. B.; Ghosh, H.; Murru, S.; Patel, B. K. *J. Org. Chem.* **2008**, *73*, 2924; (b) Ghosh, H.; Yella, R.; Nath, J.; Patel, B. K. *Eur. J. Org. Chem.* **2008**, 6189; (c) Ghosh, H.; Yella, R.; Ali, A. R.; Sahoo, S. K.; Patel, B. K. *Tetraherdron Lett.* **2009**, *50*, 2407.
20. (a) Yella, R.; Ghosh, H.; Murru, S.; Sahoo, S. K.; Patel, B. K. *Synth. Commun.* **2010**, *40*, 2083; (b) Yella, R.; Murru, S.; Ali, A. R.; Patel, B. K. *Org. Bio. Chem.* **2010**, *8*, 3389; (c) Yella, R.; Patel, B. K. *J. Comb. Chem.* **2010**, *12*, 754. (d) Yella, R.; Kavala, V.; Patel, B. K. *Synth. Commun.* **2011**, LSYC. 46474.
21. (a) McAlpine, R. K.; *J. Am. Chem. Soc.* **1952**, *74*, 725.
22. (a) Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. *Tetraherdron* **2008**, *64,* 1931; (b) Yella, R.; Ghosh, H. Patel, B. K. *Green Chem.* **2008**, *10*, 1307.
23. (a) Jordan, A. D.; Luo, C.; Reitz, A. B. *J. Org. Chem.* **2003**, *68*, 8693; (b) Le, Z.-G.; Xu, J.-P.; Rao, H.-Y.; Ying, M. *J. Heterocycl. Chem.* **2006**, *43*, 1123.
24. Richter, R.; Seiler, J.; Beyer, L.; Lindqvist, O.; Anderson, L. *Z. Anorg. All. Chem.* **1985**, *522*, 171.
25. Shih, M.-H.; Wu, C.-L. *Tetrahedron* **2005**, *61*, 10917.

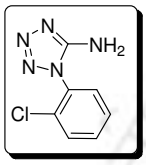
V.7. Spectral Data

1-Phenyl-1*H*-tetrazol-5-ylamine (1a):



M.p. 168 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.14 (br s, 2H), 7.48–7.61 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 123.6, 129.4, 129.8, 133.3, 154.2. IR (KBr): 3411, 3321, 3160, 1632, 1597, 1570, 1560, 1504, 1456, 1324, 1128, 1067, 1017, 770, 755 cm^{-1}.

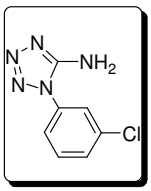
1-(2-Chloro-phenyl)-1*H*-tetrazol-5-ylamine (2a):



M.p. 183–185 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.35 (br s, 2H), 7.42–7.60 (m, 3H), 7.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 128.1, 129.2, 130.5, 131.5, 131.8, 155.4. IR (KBr): 3329, 3158, 2983, 1659, 1594, 1578, 1498, 1460, 1317, 1141, 1130, 1093, 1081, 1040, 760 cm^{-1}.

Crystal data for 2a: Crystal dimensions (mm): 0.45 x 0.35 x 0.25; $C_7H_6ClN_5$, M_r = 195.62; monoclinic, space group P21/c; a = 10.7905(4) Å, b = 7.4830(3) Å, c = 11.7242(4) Å; $\alpha = \gamma = 90^{o}$, $\beta = 108.708(2)^{o}$; V = 896.66(6) $Å^3$; Z = 4; ρ_{cal} = 1.449 mg/m^3; μ (mm^{-1}) = 0.384; $F(000)$ = 400; reflection collected / unique = 2232 / 1490; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] R_1 = 0.0547, wR_2 = 0.1932, R indices (all data) R_1 = 0.0726, wR_2 = 0.2112; goodness of fit = 1.022. CCDC # 787036.

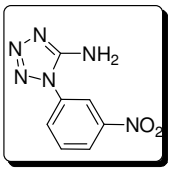
1-(3-Chloro-phenyl)-1*H*-tetrazol-5-ylamine (3a):



M.p. 177–179 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.65 (br s, 2H), 7.27–7.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 121.1, 122.9, 128.4, 130.3, 133.8, 134.1, 153.9. IR (KBr): 3355, 3151, 1651, 1593, 1489, 1458, 1422, 1322, 1140, 1102, 1080, 866, 791 cm^{-1}. $C_7H_6ClN_5$ (195.61): calcd C 42.98, H 3.09, N 35.80; found C 42.94, H 3.03, N 35.91.

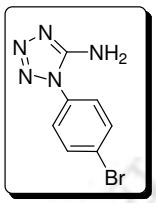
1-(3-Nitro-phenyl)-1*H*-tetrazol-5-ylamine (4a):

M.p. 161–163 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.92 (br s, 2H), 7.90 (t, J = 8.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.35 (d, J =



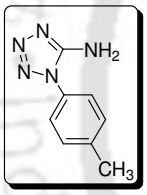
8.0 Hz, 1H), 8.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 117.9, 122.9, 128.8, 130.4, 133.9, 147.9, 154.2. IR (KBr): 3318, 3142, 3091, 1660, 1596, 1574, 1532, 1497, 1351, 1307, 1139, 1079, 909, 813, 780, 743 cm^{-1}. HRMS (ESI): Calcd for $C_7H_6N_6O_2$ [MH^+] 207.0630, found 207.0630.

1-(4-Bromo-phenyl)-1*H*-tetrazol-5-ylamine (5a):



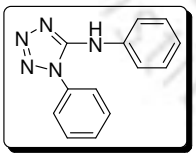
M.p. 240–242 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.81 (br s, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 121.3, 124.4, 131.3, 131.6, 153.5. IR (KBr): 3348, 3148, 2963, 2923, 1651, 1594, 1575, 1494, 1454, 1404, 1324, 1142, 1107, 1097, 1068, 1008, 836, 818 cm^{-1}. HRMS (ESI): Calcd for $C_7H_6BrN_5$ [MH^+] 239.9885, found 239.9884.

1-*p*-Tolyl-1*H*-tetrazol-5-ylamine (6a):



M.p. 188 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.46 (s, 3H), 5.27 (br s, 2H), 7.38–7.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 21.0, 123.5, 130.3, 130.6, 139.7, 154.4. IR (KBr): 3306, 3141, 2980, 1657, 1594, 1572, 1519, 1467, 1320, 1142, 1119, 1091, 1046, 1017, 839, 818, 765 cm^{-1}. HRMS (ESI): Calcd for $C_8H_9N_5$ [MH^+] 176.0936, found 176.0937.

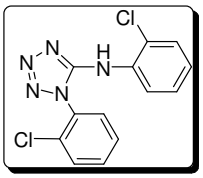
Phenyl-(1-phenyl-1*H*-tetrazol-5-yl)-amine (1b):



M.p. 159 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.54 (br s, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.34 (m, 1H), 7.52–7.71 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.4, 122.1, 123.6, 125.0, 129.5, 130.0, 132.8, 138.3, 151.8. IR (KBr): 3384, 3193, 3040, 2996, 2926, 1601, 1570, 1530, 1495, 1453, 1325, 1238, 1122, 1090, 764, 745 cm^{-1}. $C_{13}H_{11}N_5$ (237.26): calcd C 65.81, H 4.67, N 29.52; found C 65.86, H 4.71, N 29.42.

(2-Chloro-phenyl)-[1-(2-chloro-phenyl)-1*H*-tetrazol-5-yl]-amine (2b):

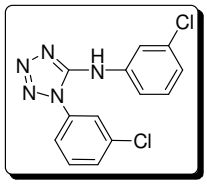
M.p. 106–108 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (br s, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.53–7.66 (m, 3H), 7.72



(d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.1, 121.7, 123.9, 128.2, 128.9, 129.1, 129.4, 129.6, 131.4, 130.0, 134.5, 151.8. IR (KBr): 3389, 1595, 1566, 1514, 1492, 1469, 1309, 1272, 1230, 1092, 1077, 1056, 1036, 766, 748 cm^{-1}. $C_{13}H_9Cl_2N_5$ (306.15): calcd C 51.00, H 2.96, N 22.88; found C 50.94, H 3.01, N 22.99.

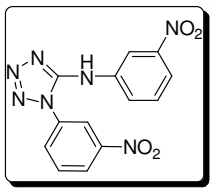
Crystal data for 2b: Crystal dimensions (mm): 0.21 x 0.15 x 0.12; $C_{13}H_9Cl_2N_5$, M_r = 306.15; triclinic, space group P-1; a = 7.3229(2) Å, b = 9.8303(3) Å, c = 10.1610(3) Å; α = 81.772(2)°, β = 70.996(2)°, γ = 76.860(2)°, V = 671.58(4) Å^3; Z = 2; ρ_{cal} = 1.514 mg/m^3; μ(mm^{-1}) = 0.479; F(000) = 312; reflection collected / unique = 3381 / 2756; refinement method = full-matrix least-squares on F^2; final R indices [I > $2\sigma_I$] R_1 = 0.0406, wR_2 = 0.1172, R indices (all data) R_1 = 0.0472, wR_2 = 0.1242; goodness of fit = 1.079. CCDC # 787037.

(3-Chloro-phenyl)-[1-(3-chloro-phenyl)-1*H*-tetrazol-5-yl]-amine (3b):



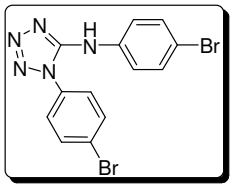
M.p. 143–145 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (br s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.46 (m, 2H), 7.55–7.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 116.6, 118.2, 122.1, 123.5, 125.2, 129.8, 130.9, 133.8, 134.7, 140.6, 151.8. IR (KBr): 3445, 2922, 2847, 1615, 1595, 1566, 1473, 1322, 1248, 1122, 1085, 834, 782 cm^{-1}. $C_{13}H_9Cl_2N_5$ (306.15): calcd C 51.00, H 2.96, N 22.88; found C 50.94, H 2.92, N 23.00.

(3-Nitro-phenyl)-[1-(3-nitro-phenyl)-1*H*-tetrazol-5-yl]-amine (4b):



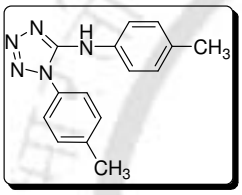
M.p. 188–190 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.56 (t, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.95 (t, *J* = 8.4 Hz, 1H), 8.05–8.13 (m, 2H), 8.47 (d, *J* = 8.0 Hz, 1H), 8.51 (s, 1H), 8.60 (s, 1H), 9.96 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.8, 116.6, 120.2, 123.8, 124.1, 129.4, 130.6, 131.0, 133.4, 140.2, 147.9, 148.2, 151.6. IR (KBr): 3444, 3258, 3089, 2925, 2857, 1622, 1574, 1524, 1393, 1353, 1245, 1119, 1081, 880, 803, 739 cm^{-1}. HRMS (ESI): Calcd for $C_{13}H_9N_7O_4$ [MH$^+$] 328.0794, found 328.0791.

4-Bromo-phenyl)-[1-(4-bromo-phenyl)-1*H*-tetrazol-5-yl]-amine (5b):



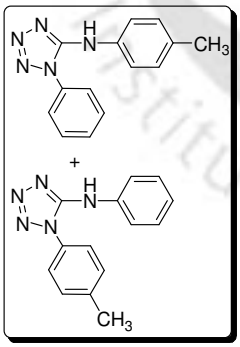
M.p. 191–193 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.40 (d, *J* = 9.2 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 9.2 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 9.20 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 113.9, 119.6, 123.0, 126.3, 130.9, 131.5, 132.3, 138.0, 151.5. IR (KBr): 3259, 3191, 3096, 1741, 1606, 1563, 1526, 1488, 1403, 1235, 1091, 1070, 1010, 823, 804, 718 cm^{-1}. $C_{13}H_9Br_2N_5$ (395.05): calcd C 39.52, H 2.30, N 17.73; found C 39.47, H 2.33, N 17.80.

***p*-Tolyl-(1-*p*-tolyl-1*H*-tetrazol-5-yl)-amine (6b):**



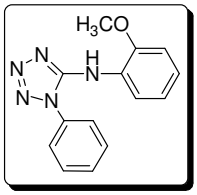
M.p. 206–208 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.29 (s, 3H), 2.50 (s, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.40–7.49 (m, 6H), 8.82 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6): δ 20.5, 21.1, 118.6, 122.9, 124.9, 129.2, 130.3, 131.6, 136.9, 139.9, 152.5. IR (KBr): 3226, 3178, 3018, 2922, 1605, 1562, 1506, 1387, 1231, 1123, 1079, 824, 808, 788 cm^{-1}. $C_{15}H_{15}N_5$ (265.31): calcd C 67.90, H 5.70, N 26.40; found C 67.94, H 5.65, N 26.31.

(1-Phenyl-1*H*-tetrazol-5-yl)-*p*-tolyl-amine / Phenyl-(1-*p*-tolyl-1*H*-tetrazol-5-yl)-amine (7a+7b):



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.46 (s, 3H), 6.58 (br s, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.30–7.43 (m, 10H), 7.44–7.60 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 21.5, 118.3, 118.7, 123.5, 124.9, 129.4, 129.9, 130.1, 130.5, 130.6, 131.2, 138.3, 141.1, 151.8. IR (KBr): 3239, 3193, 3056, 2924, 2853, 1607, 1569, 1560, 1531, 1514, 1498, 1457, 1401, 1230, 1178, 1121, 1078, 819, 745 cm^{-1}. $C_{14}H_{13}N_5$ (251.29): calcd C 66.92, H 5.21, N 27.87; found C 65.85, H 5.25, N 27.75.

(2-Methoxy-phenyl)-(1-phenyl-1*H*-tetrazol-5-yl)-amine (8a):

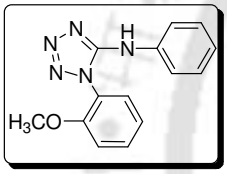


M.p. 128–130 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.88 (d, *J* = 7.4 Hz, 1H), 7.04 (m, 2H), 7.26 (s, 1H), 7.63 (m, 4H), 8.38 (m,

1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1, 110.1, 117.8, 121.7, 123.0, 124.4, 127.9, 130.5, 130.7, 133.2, 147.3, 151.4. IR (KBr) 3399, 3022, 2925, 1609, 1593, 1570, 1507, 1485, 1466, 1455, 1390, 1252, 1240, 1211, 1107, 1092, 1050, 1016, 765, 752 cm^{-1}.

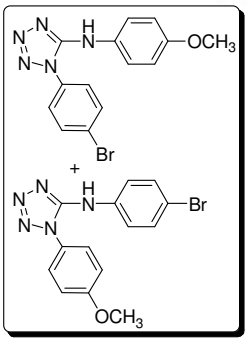
Crystal data for 8a: Crystal dimensions (mm): 0.32 x 0.24 x 0.16; $C_{14}H_{13}N_5O$, M_r = 267.29; monoclinic, space group P21/c; a = 10.8360(4) Å, b = 16.3772(6) Å, c = 7.6105(3) Å, $\alpha = \gamma = 90^o$, β = 107.280(2)^o, V = 1289.63(9) Å^3; Z = 4; ρ_{cal} = 1.377 mg/m^3; μ(mm^{-1}) = 0.093; F(000) = 560; reflection collected / unique = 3221 / 1965; refinement method = full-matrix least-squares on F^2; final R indices [I > $2\sigma_I$] R_1 = 0.0442, wR_2 = 0.1203, R indices (all data) R_1 = 0.0672, wR_2 = 0.1327; goodness of fit = 0.953. CCDC # 787038.

[1-(2-Methoxy-phenyl)-1*H*-tetrazol-5-yl]-phenyl-amine (8b):



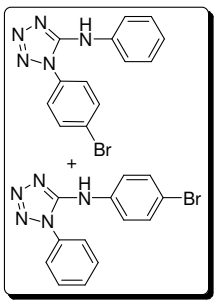
M.p. 178 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6): δ 3.87 (s, 3H), 7.02 (d, J = 6.0 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 6.0 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.54–7.65 (m, 3H), 8.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 55.7, 112.4, 118.1, 120.7, 122.1, 122.8, 128.2, 128.5, 131.7, 139.0, 152.7, 153.8. IR (KBr): 3250, 3200, 3168, 3115, 3088, 3052, 3012, 2971, 2926, 2842, 1614, 1574, 1532, 1499, 1471, 1406, 1384, 1318, 1305, 1280, 1260, 1240, 1185, 1163, 1113, 1087, 1043, 1020, 980, 785, 754 cm^{-1}

[1-(4-Bromo-phenyl)-1*H*-tetrazol-5-yl]-(4-methoxy-phenyl)-amine / (4-Bromo-phenyl)-[1-(4-methoxy-phenyl)-1*H*-tetrazol-5-yl]-amine (9a+9b):



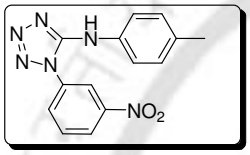
^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.78 (s, 3H), 3.88 (s, 3H), 6.83 (d, J = 8.0 Hz, 2H), 7.08 (m, 3H), 7.38 (d, J = 7.80 Hz, 2H), 7.45–7.50 (m, 5H), 7.57 (d, J = 7.80 Hz, 2H), 7.71 (d, J = 7.80 Hz, 2H), 8.64 (br s, 1H), 8.76 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 54.9, 55.9, 113.6, 114.2, 114.6, 119.7, 120.5, 123.0, 125.1, 126.3, 126.6, 131.2, 131.9, 132.5, 138.3, 151.9, 152.4, 155.1, 160.2. IR (KBr): 3253, 3190, 3090, 2960, 2927, 1613, 1573, 1537, 1514, 1489, 1462, 1441, 1313, 1301, 1256, 1180, 1170, 1121, 1099, 1072, 1030, 1007, 827 cm^{-1}. HRMS (ESI): Calcd for $C_{14}H_{12}BrN_5O$ [MH^+] 346.0303, found 346.0303.

1-(4-Bromophenyl)-*N*-phenyl-1*H*-tetrazol-5-amine / *N*-(4-bromophenyl)-1-phenyl-1*H*-tetrazol-5-amine (10a+10b):



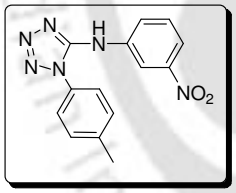
^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.03 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.60 (m, 8H), 7.75 (d, *J* = 8.4 Hz, 2H), 8.97 (br s, 1H), 9.09 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 114.8, 119.0, 120.7, 122.9, 123.8, 125.5, 127.4, 129.2, 130.3, 131.9, 132.7, 133.3, 139.3, 139.9, 152.5, 152.8. IR (KBr): 3189, 3030, 1600, 1574, 1314, 1238, 1179, 1126, 1095, 1069, 834, 823, 762, 747 cm^{-1}.

1-(3-Nitrophenyl)-*N*-*p*-tolyl-1*H*-tetrazol-5-amine (11a):



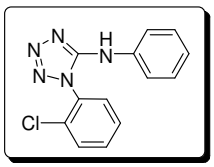
M.p. 203–205 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.50 (s, 3H), 7.40–7.55 (m, 3H), 7.83 (d, *J* = 8.0 Hz, 2H), 8.22 (d, *J* = 8.0 Hz, 2H), 8.53 (s, 1H), 9.34 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 20.5, 112.2, 115.8, 123.3, 124.6, 129.0, 129.7, 138.7, 140.3, 147.7, 151.2. IR (KBr): 3447, 2923, 2851, 1607, 1572, 1526, 1380, 1355, 1097, 1079, 834, 823, 733 cm^{-1}.

***N*-(3-Nitrophenyl)-1-*p*-tolyl-1*H*-tetrazol-5-amine (11b):**



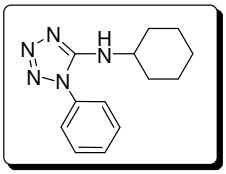
M.p. 173–175 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.43 (s, 3H), 6.21 (br s, 1H), 7.41–7.54 (m, 2H), 7.85 (d, *J* = 7.2 Hz, 2H), 8.28 (d, *J* = 7.2 Hz, 2H), 8.44 (s, 1H), 8.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 20.7, 112.5, 116.0, 123.4, 124.8, 128.5, 129.2, 129.9, 139.9, 140.6, 147.9, 151.5. IR (KBr): 3432, 2923, 2846, 1608, 1574, 1525, 1344, 1110, 1089, 823, 733 cm^{-1}. HRMS (ESI): Calcd for $C_{14}H_{12}N_6O_2$ [MH^+] 297.1100, found 297.1103.

[1-(2-Chloro-phenyl)-1*H*-tetrazol-5-yl]-phenyl-amine (12a):



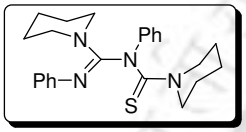
M.p. 132–134 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 5.93 (br s, 1H), 7.03 (d, *J* = 6.4 Hz, 1H), 7.30 (s, 2H), 7.53–7.66 (m, 5H), 8.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 118.4, 122.4, 123.9, 124.8, 128.1, 128.5, 129.6, 130.5, 132.0, 139.1, 152.9. IR (KBr): 3241, 3078, 3038, 2997, 2926, 1603, 1614, 1593, 1529, 1489, 1454, 1318, 1245, 1120, 1087, 1077, 1020, 756, 748 cm^{-1}. HRMS (ESI): Calcd for $C_{13}H_{10}ClN_5$ [MH^+] 272.0703, found 272.0702.

Cyclohexyl-(1-phenyl-1*H*-tetrazol-5-yl)-amine (13a):



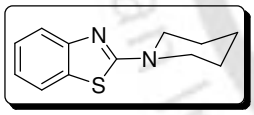
M.p. 128–130 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11–1.50 (m, 5H), 1.62–1.80 (m, 4H), 2.14 (d, *J* = 9.2 Hz, 1H), 3.77 (m, 1H), 4.17 (d, *J* = 7.2 Hz, 1H), 7.43–7.53 (m, 2H), 7.54 (m, 1H), 7.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 25.6, 33.5, 53.7, 124.2, 129.9, 130.5, 133.5, 154.1. IR (KBr): 3230, 2927, 2853, 1595, 1514, 1498, 1449, 1372, 1137, 1095, 1071, 1018, 765, 693 cm^{-1}. $C_{13}H_{17}N_5$ (243.31): calcd C 64.17, H 7.04, N 28.78; found C 64.22, H 6.99, N 28.71.

***N*-Phenyl-*N*-((*E*)-(phenylimino)(piperidin-1-yl)methyl)piperidine-1-carbothioamide (1c):**



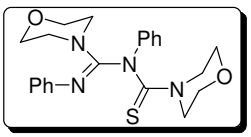
M.p. 186–188 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–1.67 (m, 12H), 2.63–3.82 (m, 8H), 6.90 (t, *J* = 7.6 Hz, 2H), 7.02–7.12 (m, 3H), 7.16 (t, *J* = 8.4 Hz, 2H), 7.26–7.40 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 24.5, 24.6, 24.9, 47.4, 51.4, 122.1, 122.3, 124.1, 128.4, 129.2, 143.7, 149.7, 150.0, 184.9. IR (KBr): 2936, 2854, 1632, 1588, 1481, 1454, 1416, 1295, 1261, 1240, 1207, 1028, 989, 903, 749 cm^{-1}. HRMS (ESI): Calcd for $C_{24}H_{30}N_4S$ [MH^+] 407.2269, found 407.2222.

2-(Piperidin-1-yl)benzo[*d*]thiazole (1d):



M.p. 93 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 6H), 3.58 (s, 4H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.5, 49.8, 118.9, 120.7, 121.2, 126.0, 130.8, 153.1, 169.0. IR (KBr): 2961, 2858, 1608, 1562, 1542, 1473, 1443, 1356, 1305, 1270, 1220, 1058, 1038, 868, 838 cm^{-1}. $C_{12}H_{14}N_2S$ (218.32): calcd C 66.02, H 6.46, N 12.83, S 14.69; found C 66.08, H 6.88, N 12.76, S 14.74.

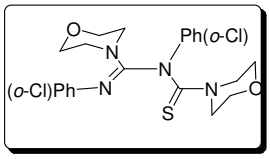
***N*-((*E*)-Morpholino(phenylimino)methyl)-*N*-phenylmorpholine-4-carbothioamide (2c):**



M.p. 150 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62–3.80 (m, 16H), 6.81 (br m, 1H), 6.95–7.10 (m, 4H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.28–7.48 (br m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.8, 50.7, 65.5, 66.2, 120.4, 121.4, 122.2, 122.9, 124.8, 128.8, 129.8, 142.8, 149.3, 185.2. IR (KBr): 2979, 2904, 2894, 2856, 1634, 1586,

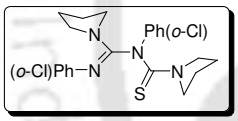
1485, 1453, 1351, 1301, 1277, 1239, 1206, 1157, 1109, 1062, 1022, 994, 937, 855, 765, 753 cm^{-1}.

_N_-((_E_)-(2-Chlorophenylimino)(morpholino)methyl)-_N_-(2-chlorophenyl)morpholine-4-carbothioamide (3c):



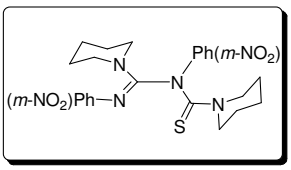
M.p. 157 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50–4.60 (m, 16H), 6.39–7.16 (m, 5H), 7.22–7.68 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.1, 47.5, 50.9, 66.1, 122.8, 123.9, 126.5, 127.3, 128.0, 129.1, 131.0, 139.7, 145.7, 148.6, 187.2. IR (KBr): 2950, 2894, 2849, 1632, 1580, 1470, 1427, 1401, 1363, 1303, 1272, 1237, 1219, 1206, 1159, 1150, 1119, 1109, 1051, 1031, 999, 953, 876, 757, 750 cm^{-1}. $C_{22}H_{24}Cl_2N_4O_2S$ (479.42): calcd C 55.12, H 5.05, N 11.69, S 6.69; found C 55.18, H 5.09, N 11.82, S 6.75.

_N_-((_E_)-(2-Chlorophenylimino)(pyrrolidin-1-yl)methyl)-_N_-(2-chlorophenyl)pyrrolidine-1-carbothioamide (4c):



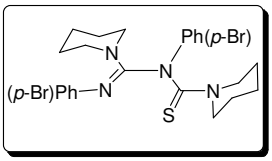
M.p. 154 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70–2.21 (m, 10H), 3.14–4.02 (m, 6H), 6.43–6.86 (m, 3H), 6.90–7.06 (m, 2H), 7.12–7.53 (m, 2H), 7.77 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.1, 26.1, 26.7, 46.9, 48.1, 51.6, 54.5, 122.3, 123.3, 123.8, 125.3, 126.3, 127.2, 127.5, 128.2, 128.9, 130.9, 138.6, 146.6, 183.2. IR (KBr): 2968, 2949, 2862, 1623, 1580, 1440, 1413, 1330, 1283, 1261, 1205, 1177, 1051, 947, 874, 756 cm^{-1}.

_N_-((_E_)-(3-Nitrophenylimino)(piperidin-1-yl)methyl)-_N_-(3-nitrophenyl)piperidine-1-carbothioamide (5c):



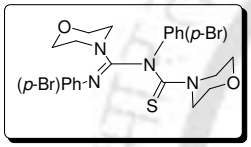
M.p. 186 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91–1.92 (m, 12H), 3.35 (m, 8H), 7.14–7.41 (m, 3H), 7.50 (t, J = 7.6 Hz, 1H), 7.63–7.86 (m, 3H), 7.93 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7, 24.3, 25.0, 47.9, 52.1, 116.8, 117.1, 119.3, 127.4, 129.3, 130.4, 144.4, 148.7, 148.9, 150.5, 184.1. IR (KBr): 2942, 2925, 2851, 1637, 1606, 1522, 1479, 1444, 1417, 1352, 1299, 1280, 1244, 1206, 1182, 1027, 901, 739 cm^{-1}.

***N*-((*E*)-(4-Bromophenylimino)(piperidin-1-yl)methyl)-*N*-(4-bromophenyl)piperidine-1-carbothioamide (6c):**



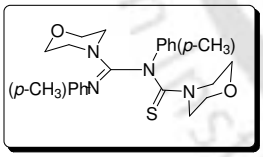
M.p. 177–179 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01–1.85 (m, 13H), 2.81–3.82 (m, 7H), 6.77 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 24.5, 24.9, 25.1, 47.7, 51.9, 115.2, 117.4, 123.1, 124.2, 131.5, 132.5, 142.8, 148.8, 150.1, 184.7. IR (KBr): 2936, 2917, 2851, 1630, 1578, 1483, 1423, 1362, 1297, 1270, 1240, 1205, 1185, 1066, 1051, 1026, 1005, 987, 891, 851, 822, 776 cm^{-1}.

***N*-((*E*)-(4-Bromophenylimino)(morpholino)methyl)-*N*-(4-bromophenyl)morpholine-4-carbothioamide (7c):**



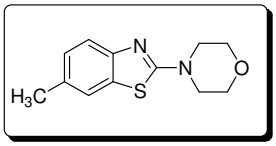
M.p. 173–175 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60–3.81 (m, 16H), 6.61–7.12 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.49 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 50.9, 65.5, 66.3, 115.8, 118.0, 121.9, 123.9, 131.8, 132.9, 141.7, 148.7, 148.3, 149.3, 184.8. IR (KBr): 2964, 2921, 2853, 1633, 1578, 1485, 1417, 1359, 1296, 1274, 1235, 1156, 1113, 1067, 999, 854, 831, 785 cm^{-1}.

***N*-((*E*)-(*p*-Tolylimino)(morpholino)methyl)-*N*-*p*-tolylmorpholine-4-carbothioamide (8c):**



Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.33 (s, 3H), 2.74–3.75 (m, 16H), 6.80 (br s, 1H), 6.85 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.08–7.27 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 20.9, 46.7, 50.6, 65.4, 66.2, 121.2, 121.9, 129.2, 130.2, 131.8, 134.4, 140.2, 146.7, 149.5, 185.2. IR (KBr): 2963, 2919, 2857, 1632, 1607, 1506, 1472, 1422, 1360, 1296, 1279, 1236, 1160, 1115, 1066, 1034, 1018, 999, 940, 911, 855, 829, 818, 732 cm^{-1}.

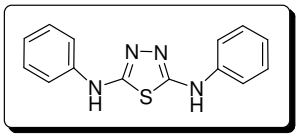
6-Methyl-2-morpholinobenzo[*d*]thiazole (8d):



M.p. 133 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.60 (t, *J* = 5.2 Hz, 4H), 3.83 (t, *J* = 5.2 Hz, 4H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 48.7, 66.4, 119.1, 121.0, 127.5, 131.7, 150.5, 168.7. IR (KBr): 2964,

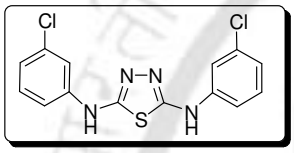
2911, 2857, 1604, 1577, 1466, 1439, 1379, 1352, 1282, 1271, 1237, 1113, 1070, 1027, 945, 914, 840, 812 cm^{-1}.

***N*²*, N*⁵-Diphenyl-1,3,4-thiadiazole-2,5-diamine (14f):**



M.p. 239–242 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 4H), 7.54 (d, *J* = 7.6 Hz, 4H), 9.38 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.8, 120.9, 128.5, 140.9, 156.3. IR (KBr): 3233, 3186, 2965, 2846, 1601, 1551, 1497, 1481, 1445, 1311, 1294, 1254, 1194, 1092, 896, 832, 746 cm^{-1}.

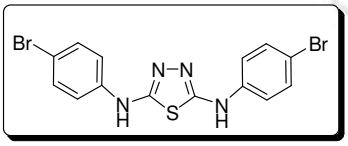
***N*²*, N*⁵-Bis(3-chlorophenyl)-1,3,4-thiadiazole-2,5-diamine (15f):**



M.p. 217–219 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (br s, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.74 (s, 2H), 9.69 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.7, 116.2, 120.3, 129.2, 133.5, 141.6, 155.6. IR (KBr): 3280, 3075, 1600, 1567, 1541, 1528, 1478, 1451, 1407, 1079, 773 cm^{-1}.

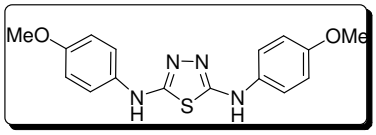
Crystal data for 15f: Crystal dimensions (mm): 0.30 x 0.25 x 0.20; $C_{14}H_{10}Cl_2N_4S$, M_r = 337.22; monoclinic, space group C 2/c'; *a* = 29.6523(10) Å, *b* = 17.5907(10) Å, *c* = 17.3440(7) Å; $\alpha = \gamma = 90^o$, $\beta = 108.649(3)^o$, *V* = 8571.7(7)) $Å^3$; *Z* = 4; ρ_{cal} = 1.568 mg/m^3; μ(mm^{-1}) = 0.093; *F*(000) = 560; reflection collected / unique = 9883 / 2429; refinement method = full-matrix least-squares on F^2; final *R* indices [$I > 2\sigma(I)$] R_1 = 0.0345, *w*R_2 = 0.1011, *R* indices (all data) R_1 = 0.1132, *w*R_2 = 0.1412; goodness of fit = 0.947. CCDC # 787035.

***N*²*, N*⁵-Bis(4-bromophenyl)-1,3,4-thiadiazole-2,5-diamine (16f):**



M.p. 244–246 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.35 (d, *J* = 8.8 Hz, 4H), 7.54 (d, *J* = 8.8 Hz, 4H), 9.76 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.0, 118.1, 130.6, 139.5, 155.4. IR (KBr): 3387, 2923, 1624, 1588, 1574, 1531, 1487, 1440, 1393, 1336, 1311, 1218, 1116, 1075, 1017, 827, 803 cm^{-1}.

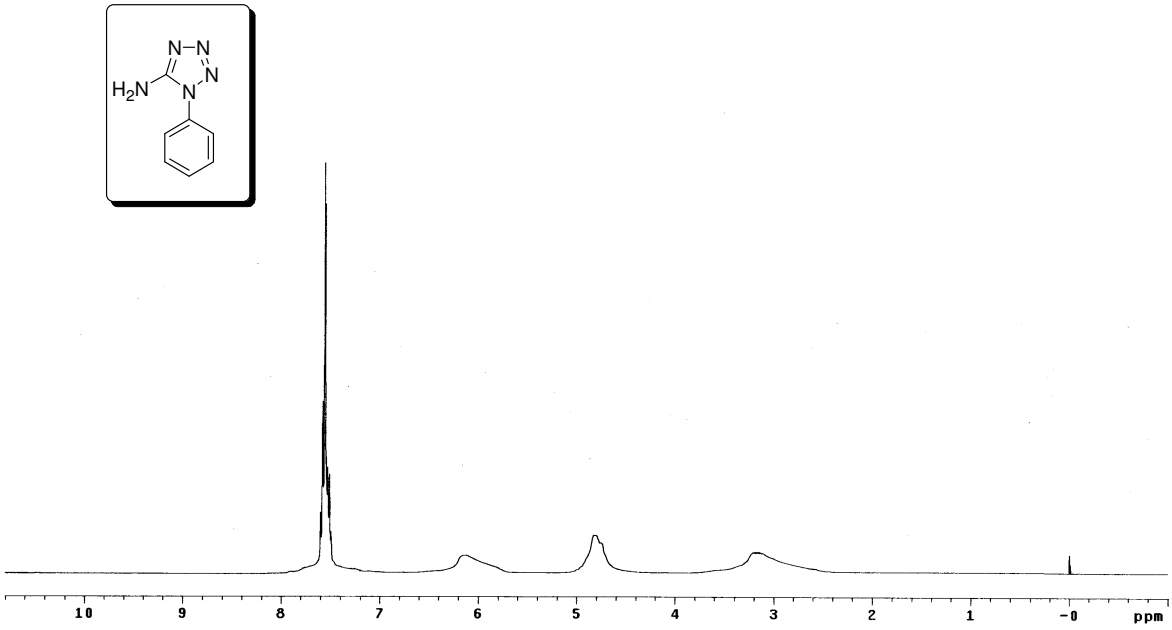
N^2, N^5-Bis(4-methoxyphenyl)-1,3,4-thiadiazole-2,5-diamine (17f):



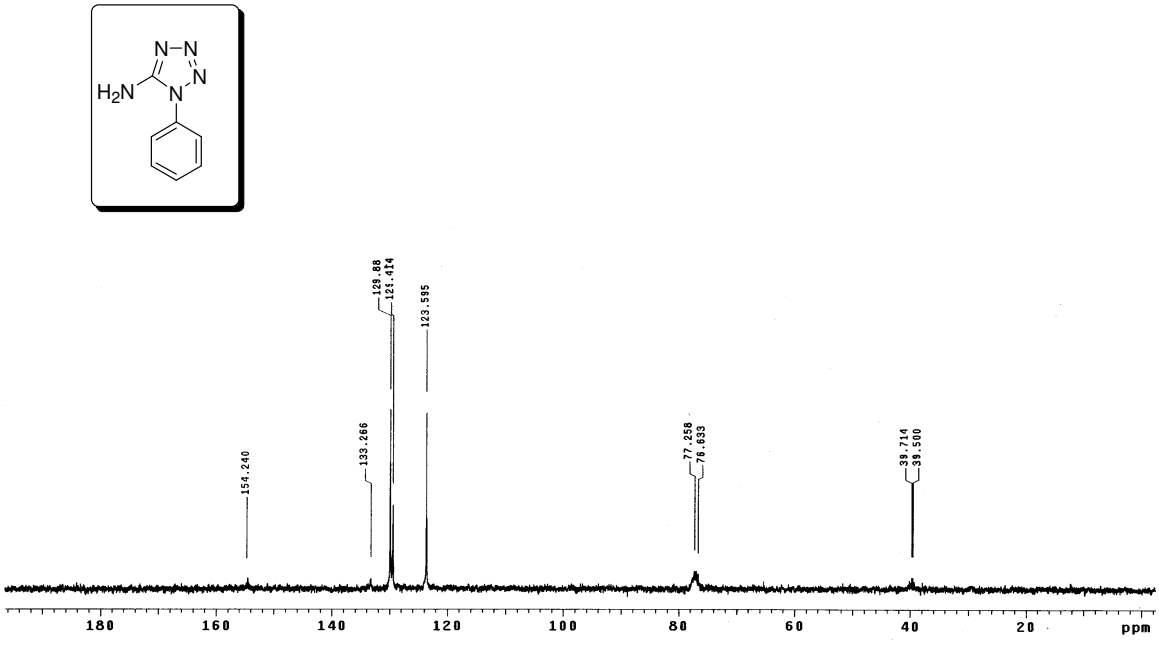
M.p. 235–237 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6): δ 3.80 (s, 6H), 6.82 (d, J = 9.2 Hz, 4H), 7.45 (d, J = 9.2 Hz, 4H), 9.07 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6): δ 54.9, 113.6, 118.7, 134.5, 153.9, 156.6. IR (KBr): 3393, 3293, 3186, 3126, 3005, 2923, 2857, 1599, 1531, 1509, 1434, 1298, 1243, 1229, 1177, 1111, 1083, 1026, 819, 770 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{16}N_4O_2S$ [MH^+] 329.1072, found 329.1072.

V.8. Selected Spectra

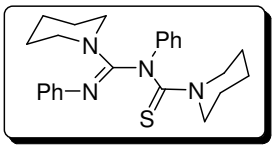
1-Phenyl-1*H*-tetrazol-5-ylamine (1a): ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6):

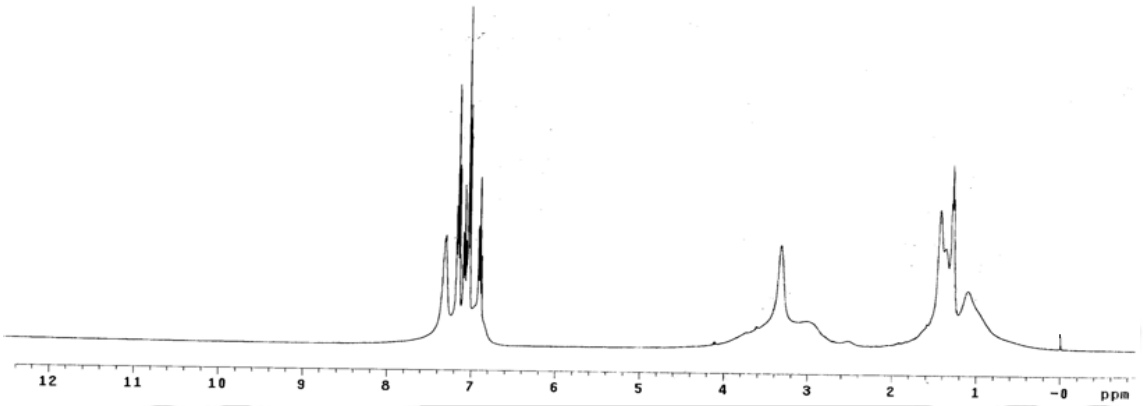


1-Phenyl-1*H*-tetrazol-5-ylamine (1a): ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6):

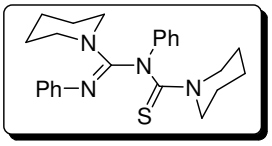


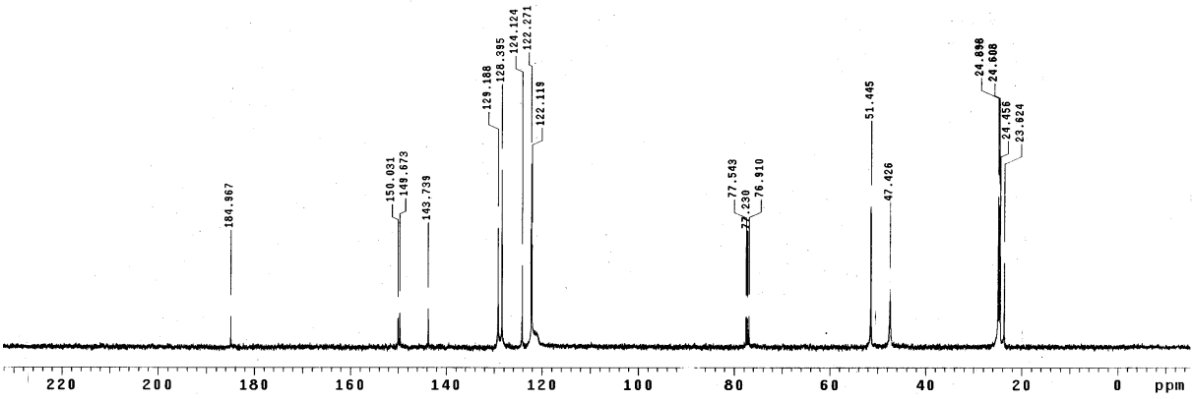
***N*-Phenyl-*N*-((*E*)-(phenylimino)(piperidin-1-yl)methyl)piperidine-1-carbothioamide (1c): ^{1}H NMR (400 MHz, $CDCl_3$):**



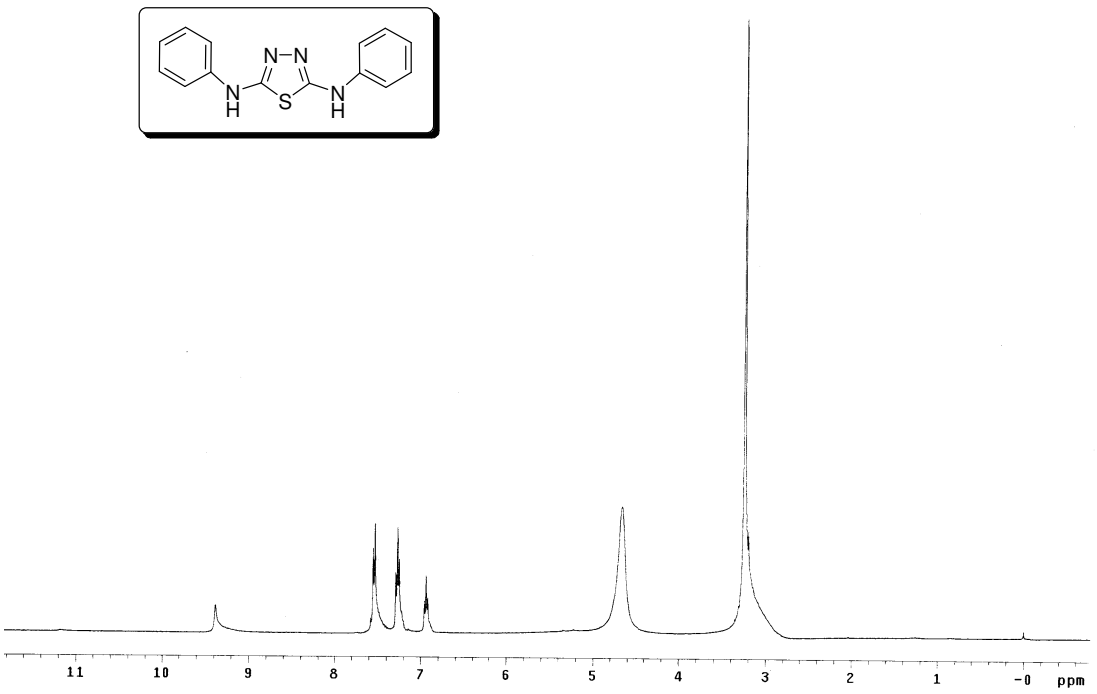


***N*-Phenyl-*N*-((*E*)-(phenylimino)(piperidin-1-yl)methyl)piperidine-1-carbothioamide (1c): ^{13}C NMR (100 MHz, $CDCl_3$):**

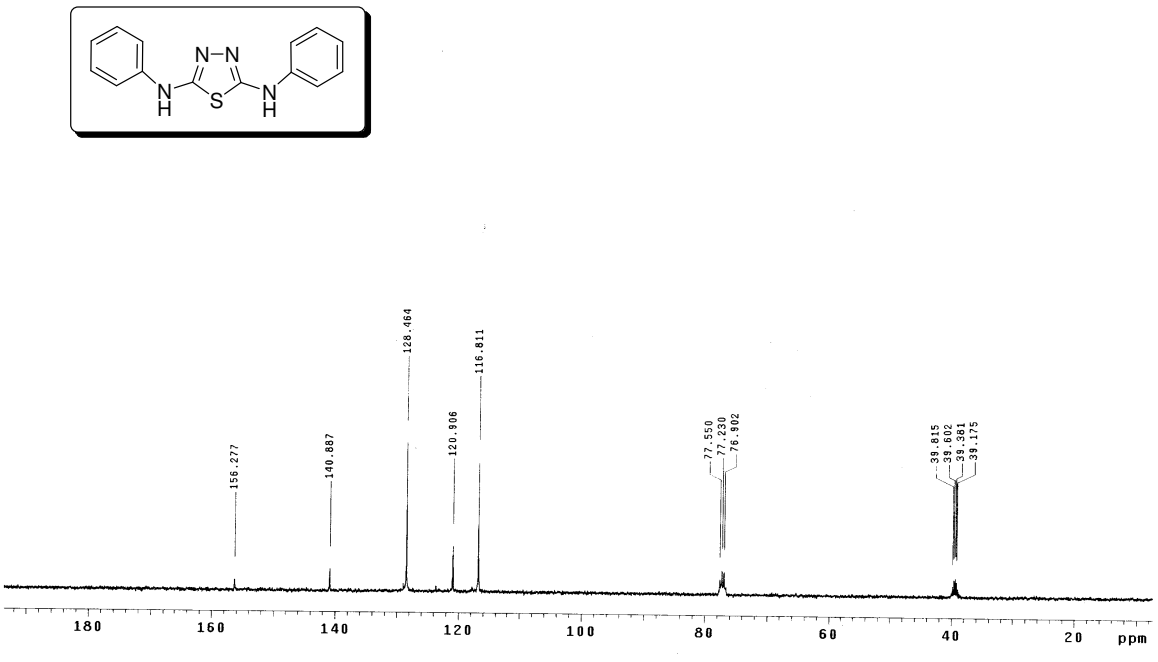




N^2, N^5-diphenyl-1,3,4-thiadiazole-2,5-diamine (14f): ^{1}H NMR (400 MHz, $CDCl_3$):



N^2, N^5-diphenyl-1,3,4-thiadiazole-2,5-diamine (14f): ^{13}C NMR (100 MHz, $CDCl_3$):

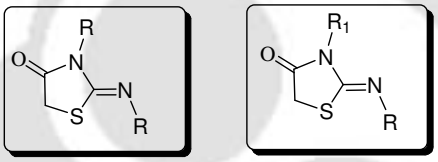


CHAPTER VI

VI. Structural Correction and Synthesis of 2-Imino-4-thiazolidinone

VI.1. Structure and Nomenclature

Details of nomenclature of heterocycles were discussed in CHAPTER I., Section I.3.1., Figure I.3.1.3., in pages 8 and 9. This chapter deals with the five membered heterocycle *i.e*. 2-imino-4-thiazolidinone.



2-Imino-4-thiazolidinones

VI.2. Importance and Applications

Thiazolidinones are the derivatives of thiazolidine which belong to an important class of heterocyclic compounds. Over the past two decades, thiazolidinones with a carbonyl group at 2, 4, or 5 positions (*Figure VI.2.1.*) have been extensively studied.[1] They have been widely employed in the investigation of pharmacologically active compounds,[1a] perhaps most notably as a common structural motif in the glitazone class of PPAR-γ agonists.[2] Furthermore, various biological activities such as bactericidal, pesticidal, fungicidal, insecticidal, anticonvulsant, tuberculostatic, anti-inflammatory and antithyroidal have been found to be associated with thiazolidinone derivatives.[1a]

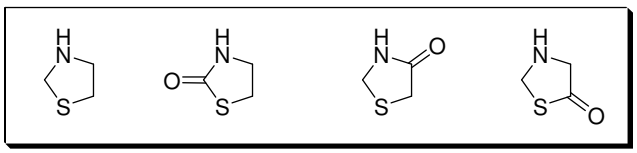


Figure VI.2.1. *Structures based on thiazolidinone.*

Thiazolidinone, in particular, 2-imino-4-thiazolidinone were found to have diverse biological activities such as hypnotic,[3a,b] hypotensive,[3c] antibacterial,[3d] anticancer[3e] and antimicrobial[3f,g] as shown in *Figure VI.2.2*.

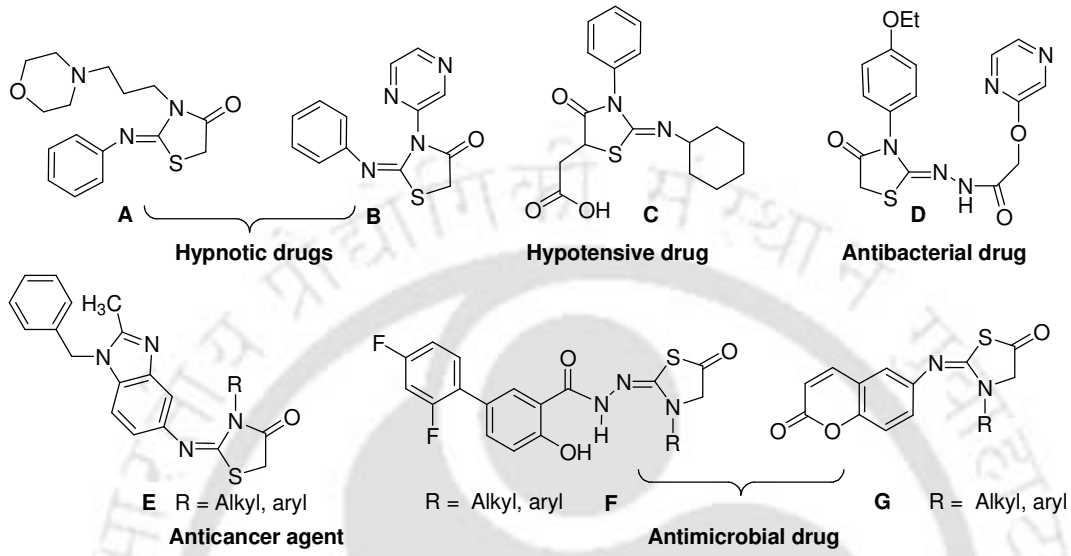


Figure VI.2.2. *Structures of pharmacologically important 2-imino-4-thiazolidinones.*

The synthetic methods available for the preparation of imino derivatives of thiazolidinones are less common. One reason might be the lack of efficient synthetic methods to introduce chemical diversity of thiazolidinone based pharmacophore, in particular with distinct substitution patterns on each of the nitrogen atoms. Hence, there are clear opportunities to introduce new synthetic methods that will explore the chemical diversity of unmapped regions of thiazolidinones (*Figure VI.2.3*.).

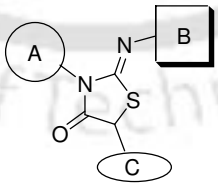
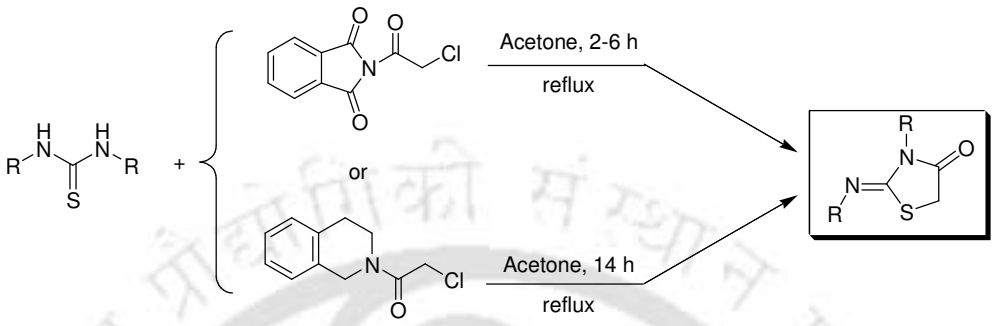


Figure VI.2.3. *Diversities in 2-imino-4-thiazolidinone ring system.*

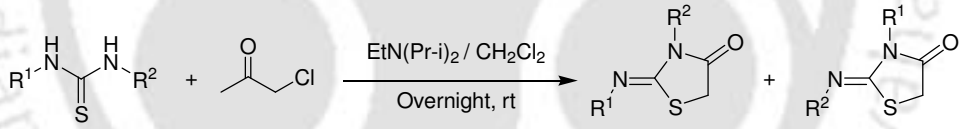
VI.3. Available Synthetic Methods

2-Aryl-4-thiazolidonone moiety has been synthesized by the reaction of *N*-chloroacetyl phthalimide or *N*-chloroacetyl-1,2,3,4-tetrahydroisoquinoline with substituted thioureas under reflux condition[4] (*Scheme VI.3.1.*).



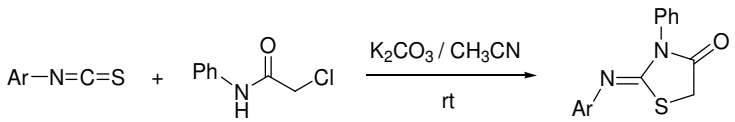
Scheme VI.3.1.

Another method involves the condensation of α-haloketones with 1,3-disubstituted thioureas in usual organic solvents led to the formation of 2-imino-4-thiazolidonone. However, this condensation involves the formation of both isomeric 2-imino-1,3-thiazolidinones[5a] as shown in *Scheme VI.3.2.*



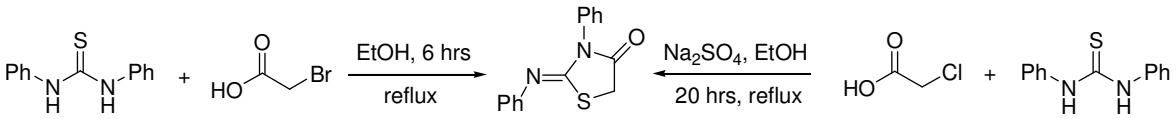
Scheme VI.3.2.

An efficient and simple route is presented for the synthesis of iminothiazolidinone derivatives. In this approach, α-chloro amide derivatives undergo condensation with isothiocyanate followed by an intramolecular nucleophilic substitution of chlorine by the sulfur atom of isothiocyanate in the presence of a mild base[5b] (*Scheme VI.3.3.*).



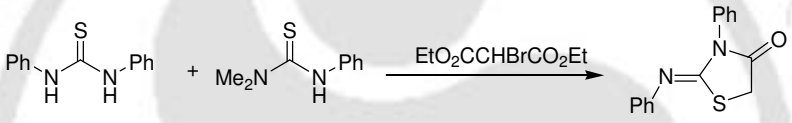
Scheme VI.3.3.

The condensation of bromo or chloro acetic acid with 1,3-disubstituted thiourea in a protic solvents *i.e.* ethanol under a reflux condition is reported to give imino thiazolidinones (*Scheme VI.3.4.*).[6]



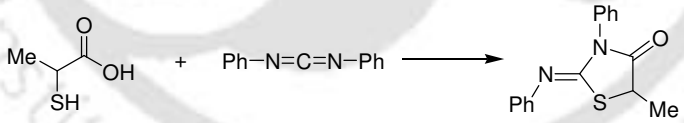
Scheme VI.3.4.

Treatment of 1,3-disubstituted thiourea with *N*,*N* dimethyl 1-phenylthiourea in the presence of triethylamine as a base in CH_2Cl_2 solvent afforded the corresponding 2-imino-4-thiazolidinone (*Scheme VI.3.5.*). The reaction mechanism for this transformation has been discussed.[7a]



Scheme VI.3.5.

Thiazolidinones were also prepared by the reaction of diaryl carbodiimides with 2-mercaptopropanoic acid at ambient temperature. However, this method reported to give lesser yields[7b] (*Scheme VI.3.6.*).



Scheme VI.3.6.

VI.4. Present Work

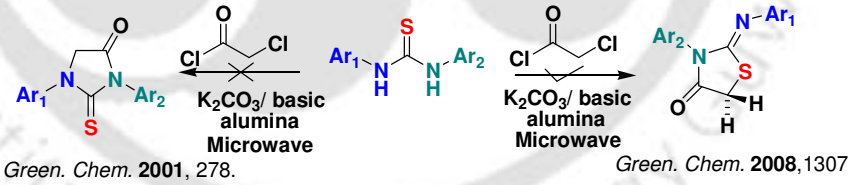
VI.4.1. Structural Correction of the Reaction Product of Thioureas with Chloroacetylchloride

Over the past few years, as a continuation of our research on "Diversity Amplification (DA)" of thiourea, we have synthesized successfully various heterocycles such as thiazol-2-imine,[8a-c] 2-mercapto benzimidazole.[8d] Further, we have explored the

thiophilic property of diacetoxyiodobenzene (DIB) for the regioselective *N*-acylation of thioureas,[9a,b] and for synthesis of heterocycles,[9c] and cyanamides.[9d] Very recently, ditribromide (EDPBT) reagent is employed as an alternative thiophilic reagent for the construction of five and sex membered benzofused *N*, *O*, *S* heterocycles.[10a] Apart from this, in yet another project we have unambiguously proved that aryl-*sec*-alkyl thiourea with bromine or its equivalent gives no Hugershoff reaction product and the Hugerschoff product 2-aminobenzothiazole as the minor product.[10b]

The mechanism of thiazole-2-imine formation has not been well understood leading to the proposal of incorrect structures for the products obtained by the reaction of thiourea analogues with α-haloketones by two independent research groups.[11] Recently, we have suggested a plausible reaction mechanism for the formation of thiazole-2-imine. Our mechanism is supported by isolating the reaction intermediate, confirming its structure and that of the products by X-ray crystallography.

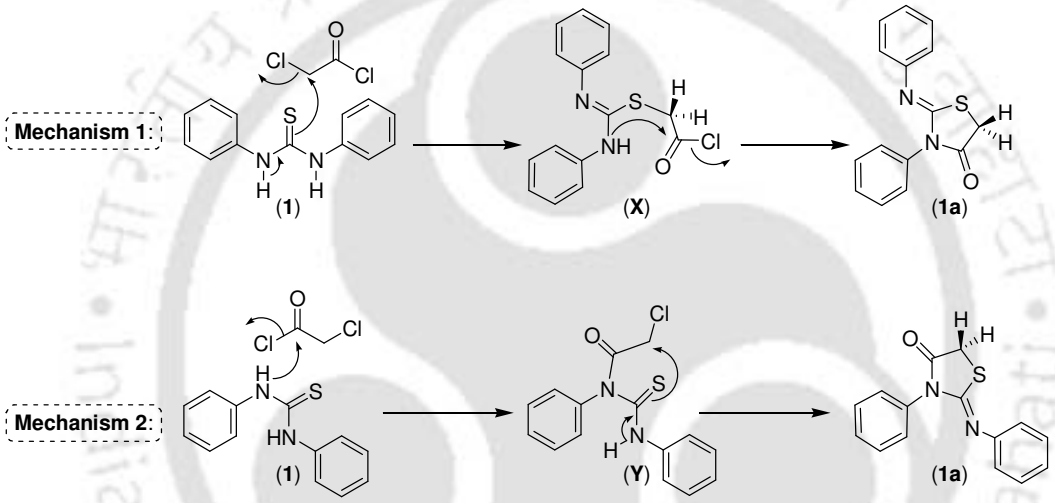
Having understood the reactivity of thioureas towards α-haloketones, we have reasoned that the products obtained by the reaction of thiourea with chloroacetylchloride under a basic medium should not be thiohydantoins as has been reported.[12a] Rather they are expected to have an isomeric 2-imino-4-thiazolidinone skeleton (*Scheme V1.4.1.1.*).[12b]



Scheme V1.4.1.1. *Reaction product of thiourea with chloroacetylchloride.*

Our assumption is based on the fact that the sulfur atom (soft nucleophile) of the thiourea will preferentially attack on the α-haloketone (soft electrophile) and NH (hard nucleophile) will attack the carbonyl centre (hard electrophile). Thus we envisaged the following mechanism (*Scheme V1.4.1.2.*) leading to the formation of 2-imino-4-thiazolidinone.

The soft nucleophile sulfur of thiourea attacks the soft electrophilic centre chloromethyl carbon giving intermediate **X** as proposed in mechanism 1, *Scheme V1.4.1.2*. Intramolecular attack of the second NH group of the intermediate **X**, a hard nucleophile will attack the carbonyl carbon of chloroacetylchloride leading to the formation of the expected product **1a**. Alternatively, a second mechanism can not be ruled out where the hard nucleophile NH will attack first at the hard electroplilic carbonyl carbon giving intermediate **Y** as shown in mechanism 2, *Scheme V1.4.1.2*. This is then followed by an intramolecular attack of sulfur on the chloromethyl group leading to the formation of the 2-imino-4-thiazolidinone derivative **1a**.



Scheme V1.4.1.2. *Mechanism for the formation of 2-imino-4-thiazolidinone.*

With this assumption, when 1,3-diphenylthiourea **1** was reacted with chloroacetylchloride under an identical condition as has been described by Kidwai *et al*. report[12a] a product was obtained in mere 45% isolated yield. Proton NMR analysis of the product showed the presence of a doublet at $\delta = 3.97$ ($J = 3.6$ Hz) corresponding to two protons. The appearence of the doublet may be due to the non equivalency of the two protons attached adjacent to a sulfur atom, an observation consistent with the literature.[6a] Its HRMS analysis corresponds to a product with molecular formula ($C_{15}H_{12}N_2OS$). Thus it was difficult to conclude whether the product obtained was 2-imino-4-thiazolidinone as suggested by us or thiohydantoins as has been reported.[12a]

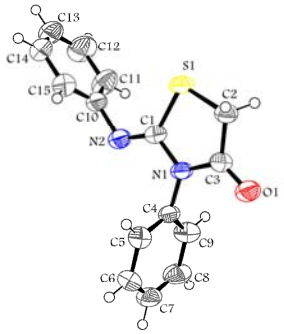


Figure V1.4.1.1. *ORTEP view with the atomic numbering scheme of* ***1a****.*

Interestingly, the compound crystallized out from a mixture of chloroform and hexane (9:1). Crystal X-ray crystallography of the product unequivocally confirmed having the 2-imino-4-thiazolidinone skeleton as shown in *Figure V1.4.1.1* an assumption made by us at the very beginning. The presence of an imino-thiazolidinone skeleton can be clearly seen from *Figure V1.4.1.1*. The imino group (C=N) C1–N2 (1.266 Å) having shorter bond distance compared to C1–N1 (1.403 Å) of the ring system. Furthermore, the C2–S1 (1.801 Å) and C1–S1 (1.768 Å) bond distances are characteristic of sp^3-S and sp^2-S bond distances. Melting point of the isolated compound **1a** was found to be 178 ^oC, which closely resembles the melting point of 172 ^oC and 175–176 ^oC reported by other groups.[6a,7a] Surprisingly the melting point reported is much less (96–97 ^oC) in Kidwai *et al*. report for the proposed structure.[12a] Had the structure been isomeric thiohydantoin as reported the melting point would have been 218–220 ^oC as has been reported in the literature.[13] Thus the melting point reported neither correspond to the proposed thiohydantoin structure nor 2-imino-4-thiazolidinone. We were also surprised with the choice of methanol as the solvent as it will react with chloroacetylchloride to form chloroacetic acid methylester which is expected to be less reactive.

In our hand, we obtained much lesser lower yield (45%) as compared to the literature method (80 %).[12a] Having resolved the structural conflict, we wished to develope an efficient method for the preparation of various 2-imino-4-thiazolidinones.

However, when 1,3-diphenylthiourea **1** (1 mmol) was reacted with chloroacetylchloride (1.5 mmol) in the presence of two equivalents of triethylamine

under a solvent free condition at room temperature, the desired product **1a** was obtained in 90% ioslated yield. This product was identical in all respects (melting point, IR, ^{1}H and ^{13}C NMR) to the product obtained by us using K_2CO_3-basic alumina under microwave-irrediation. We wanted to see if the reaction can be performed in the absence of a base since chloroacetlychloride is quite reactive. It was surprising to note that when 1.5 equivalent of chloroacetylchloride was added to 1,3-diphenylthiourea **1**, a sticky solid was obtained. To this was added acetinitrile (1 mL) to make the medium homogeneous and stirred for 5 min. Thin layer chromatography showed complete conversion to product **1a**. After usual workup, the product obtained was again found to be identical (melting point, IR, ^{1}H and ^{13}C NMR). Thus the change in the reaction condition has no effect on the reaction path leading to the product formation.

Symmetrical thioureas **2–9** gave their corresponding 2-imino-4-thiazolidinones **2a–9a** in excellent yields under the described reaction conditions as shown in *Table VI.4.1.1.* The formation of 2-imino-4-thiazolidinone skeleton has been further confirmed from the crystal X-ray crystallography of product **6a** (*Figure V1.4.1.2.*). Here again, the measured bond lengths C1–N2 (1.282 Å) for imino group is shorter compared to C1–N1 (1.428 Å) of the ring system and the C2–S1 (1.834 Å) and C1–S1 (1.778 Å) bond distances are characteristic of sp^3-S and sp^2-S bond distances.

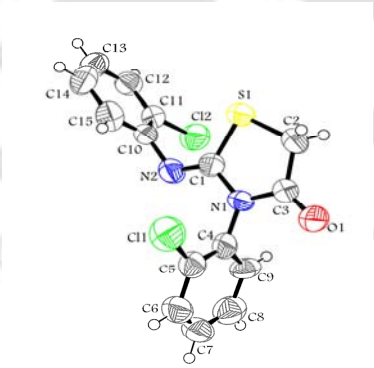
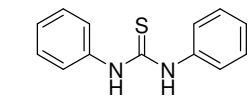
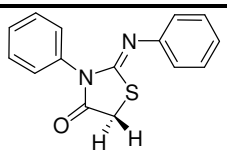
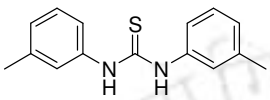
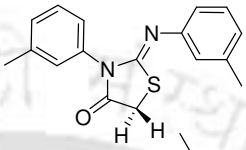
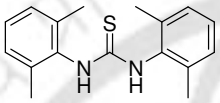
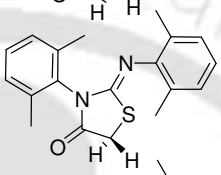
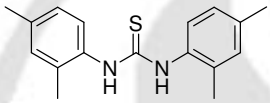
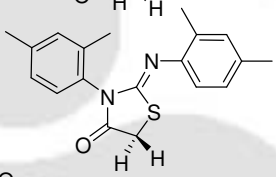
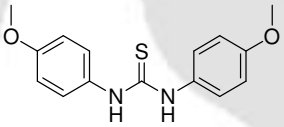
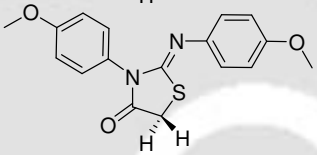
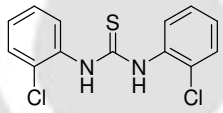
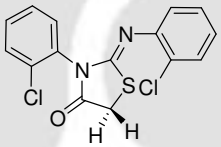
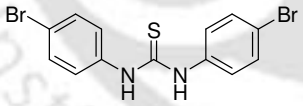
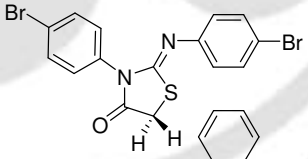
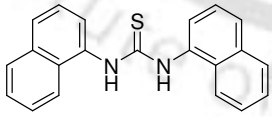
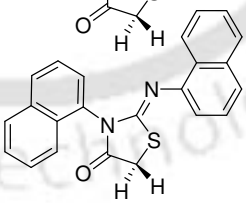
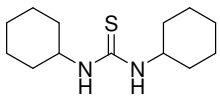
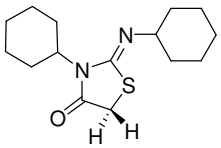


Figure V1.4.1.2. *ORTEP view with the atomic numbering scheme of* ***6a****.*

Table VI.4.1.1. *Formation of 2-imino-4-thiazolidinone from 1,3-disubstituted thiourea and chloroacetylchloride*[a]

Entry	Substrate	Product[b]		Yield (%)[c]
(**1**)			(**1a**)	92
(**2**)			(**2a**)	94
(**3**)			(**3a**)	95
(**4**)			(**4a**)	93
(**5**)			(**5a**)	92
(**6**)			(**6a**)	93
(**7**)			(**7a**)	95
(**8**)			(**8a**)	94
(**9**)			(**9a**)	85

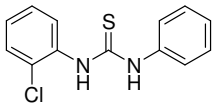
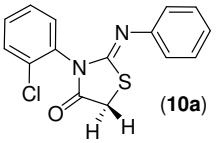
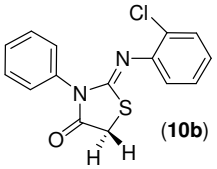
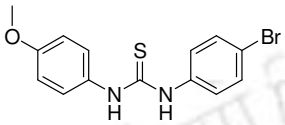
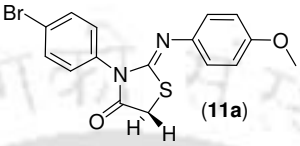
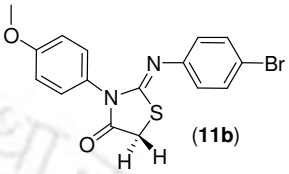
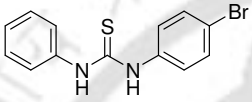
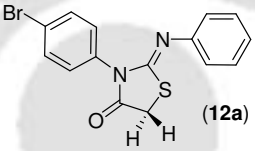
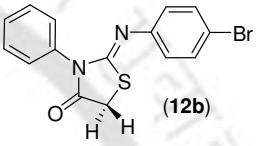
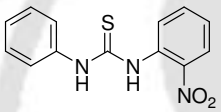
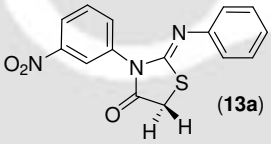
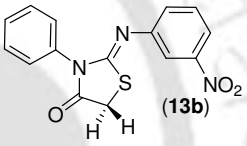
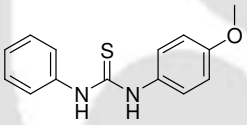
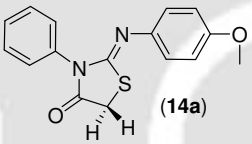
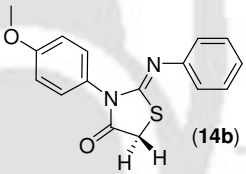
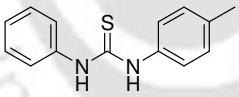
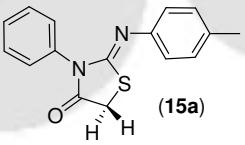
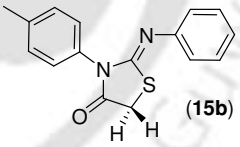
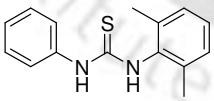
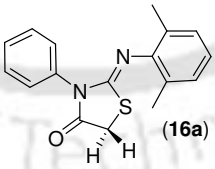
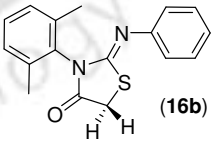
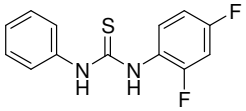
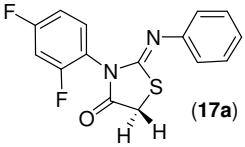
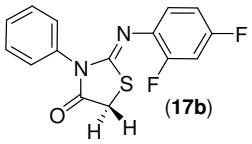
[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

Having successfully synthesized a series of 2-imino-4-thiazolidinones from symmetrical thioureas, we were interested to investigate the regioselectivity in the reaction for unsymmetrical thioureas. Recently we have found a good correlation between the regioselective *N*-acylation and the p*Ka*'s of the precursor amines attached to the thioureas.[9a,b] A similar observation was also observed during the synthesis of thiazole-2-imine or 2-iminothiazoline.[8a-c] The larger the difference between the p*Ka* of the precursor amines in thioureas, the higher is the regioselectivity of *N*-acylation with preferential acylation taking place towards the amine having lower p*Ka*.[9a,b] We wanted to see if this is applicable for the synthesis of 2-imino-4-thiazolidinones as well. When unsymmetrical thiourea **10** containing a phenyl and a *o*-chlorophenyl group attached to the thiourea reacted with chloroacetylchloride it gave a mixture of 2-imino-4-thiazolidinones **10a** and **10b** in the ratio of 36:64 as shown in *Table VI.4.1.2.* The measured p*Ka* of aniline and *o*-chloroaniline respectively are 4.63 and 2.65. Thus as per the mechanism 1, *Scheme VI.4.1.2*. the amine having lower p*Ka* will be a part of the imino component and the other amine attached to the thiourea having higher p*Ka* will contribute to the other heterocyclic nitrogen in 2-imino-4-thiazolidinone skeleton.

This assumption has been again demonstrated for thiourea **11**. The ratio (34:66) of the product **9a** and **9b** can be again explained based on the measured p*Ka*'s of *p*-methoxy aniline (5.34) and *p*-bromoaniline (3.86). In the case of thiourea **12**, the p*Ka* difference between the two amines, aniline (4.63) and *p*-bromoaniline (3.84) is 0.79. The ratio of the product **12a** and **12b** formed was 47:53 which can again be explained by a similar mechanism. In the thiourea **13**, the p*Ka*'s of the parent amines, aniline and *m*-NO_2 aniline are 4.63 and 2.46 respectively, a difference of 2.17, gave **13a** and **13b** in 30:70 ratio.

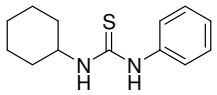
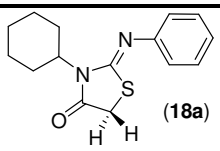
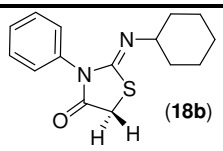
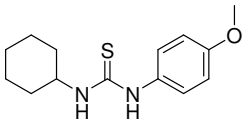
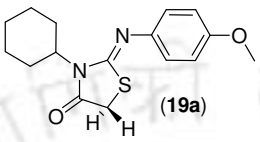
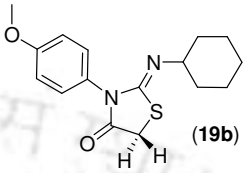
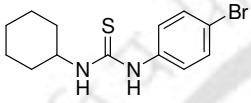
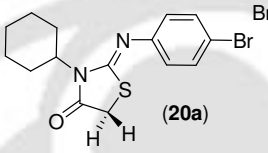
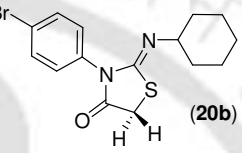
In this case of thiourea **14**, the p*Ka* difference between the two amines, aniline (4.63) and *p*-methoxyaniline (5.34) is 0.71, gave **14a** and **14b** in 49:51. Similarly, thiourea **15** and **16**, gave corresponding products in the ratio of 45:55 and 44:56. Finally, this assumption has been again demonstrated with thiourea **17**. The ratio (40:60) of the product **17a** and **17b** which can be again explained based on the measured p*Ka*'s of aniline (4.63) and 2,4-difluoroaniline (3.92).

Table VI.4.1.2. *Regioselecive formation of 2-imino-4-thiazolidinones.*[a]

Entry	Substrate	Product(s)[b]	Yield (%)[c] / Ratio
(**10**)		 (**10a**)  (**10b**)	90 (36 : 64)
(**11**)		 (**11a**)  (**11b**)	92 (34 : 66)
(**12**)		 (**12a**)  (**12b**)	93 (47 : 53)
(**13**)		 (**13a**)  (**13b**)	91 (30 : 70)
(**14**)		 (**14a**)  (**14b**)	92 (49 : 51)
(**15**)		 (**15a**)  (**15b**)	89 (45 : 55)
(**16**)		 (**16a**)  (**16b**)	90 (44 : 56)
(**17**)		 (**17a**)  (**17b**)	94 (40 : 60)

[a] Reactions were monitored by TLC. [b] Confirmed by IR and 1H and 13C NMR. [c] Isolated yield and ratio was determined by ^{1}HNMR.

Table VI.4.1.3. *Regioselecive formation of 2-imino-4-thiazolidinones.*[a]

Entry	Substrate	Product(s)[b]	Yield (%)[c] / Ratio
(**18**)		 (**18a**)  (**18b**)	93 (100 : 00)
(**19**)		 (**19a**)  (**19b**)	90 (100 : 00)
(**20**)		 (**20a**)  (**20b**)	91 (100 : 00)

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield and ratio was determined by $^{1}HNMR$.

We found that the larger the difference between the p*Ka*'s of the amine attached to the thiourea, the greater is the regioselectivity. The p*Ka* difference and the ratio of regioselectivity are tabulated in *Table VI.4.1.4* and shown graphically in *Figure V1.4.1.3.* The ratios of regioselectivities were calculated assuming th imino nitrogen component as unity and the other side as the ratio of it. A plot of p*Ka* difference of various substituted aromatic amines with respect to aniline in the *x*-axis and ratio of regioselectivity in the *y*-axis shows a linear relationship for most of the substrates examined.

A negative value of p*Ka* difference means the ratio of regioselectivity is less than one and positive value means more than one (*Table VI.4.1.4*). A direct correlation between the p*Ka* difference and regioselectivity should fall on a straight line. From the graph (*Figure V1.4.1.3.*), there seems to be a good correlation between the regioselectivity and p*Ka o*f the amine attached to the thiourea.

Table VI.4.1.4. *Regioselective 2-imino-4-thiazolidinone from unsymmetrical 1,3-disubstituted thiourea as a function of* p*Ka*

Thioureas	pKa_1-pKa_2[a]	Ratio of regioselectivity
(11)	(+) 1.50	2.13
(12)	(+) 0.77	1.13
(13)	(+) 2.16	2.33
(14)	(-) 0.71	1.03
(15)	(-) 0.45	1.23
(16)	(+) 0.19	1.20
(17)	(+) 0.70	1.52

Notes: [a] pKa_1= p*Ka* of aniline, pKa_2= p*Ka* of other amine attached to thiourea

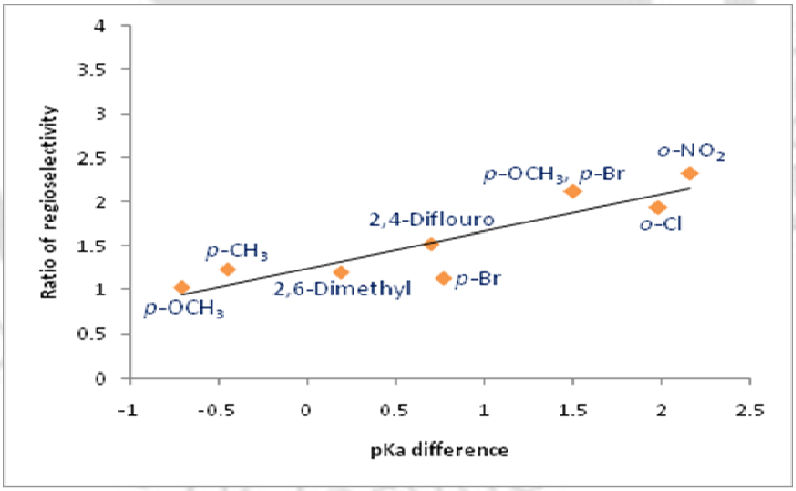


Figure V1.4.1.3. *Plot of* p*Ka dependent regioselectivity.*

In conclusion, we have unambiguously proved that the reaction of 1,3-disubstituted thioureas with chloroacetylchloride in the presence of basic alumina and K_2CO_3 are 2-imino-4-thiazolidinone derivatives and not thiohydantoins as reported earlier.[12a] This reaction can be performed at room temparature without using any base. Regioselective

formation of 2-imino-4-thiazolidinones are observed for unsymmetrical thioureas in which amine attached to the thiourea having lower p*Ka* is a part of the imino component and the amine having higher p*Ka* is the contributor to the other heterocyclic nitrogen.[12b] There is a linear correlation between the p*Ka* of the amine and regioselectivity.

VI.5. Experimental Section

VI.5.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1, Page number 56-57.

VI.5.2. General Procedure for the Preparation of 3-Phenyl-2-phenylimino-thiazolidin-4-one (1a)

To 1,3-diphenylhiourea **1** (457 mg, 2 mmol) in 2 mL round bottom flask was added chloroacetylchloride (233 µl, 3 mmol) drop wise. After complete addition of chloroacetyl chloride acetonitrile (1 mL) was added to the reaction mixture and stirred for 10 min. Acetonitrile was evaporated and admixed with ethyl acetate (25 mL). Ethyl acetate layer was washed subsequently washed with saturated sodium bicarbonate solution (2 x 5 mL), water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and crystallized from a mixture of chloroform:hexane (8:2) to give 92% of the product **1a.**

VI.6. References

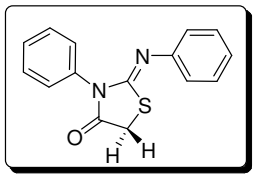
1. (a) Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev*. **1981**, *81*, 175; (b) Barreca, M. L. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1793; (c) Barreca, M. L.; De Clercq, E. *J. Med. Chem*. **2002**, *45*, 5410; (d) Goel, B.; Kumar, A. *Eur. J. Med. Chem*. **1999**, *34*, 265; (e) Allen, S. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1619; (f) Verma, A.; Saraf, S. K. *Eur. J. Med. Chem*. **2008**, *43*, 897.
2. (a) Van Gaal, L.; Scheen, A. J. *Diabetes/Metabolism Res. Rev*. **2002**, *18*(Suppl.2), S1–S4; (b) Hulin, B.; McCarthy, P. A.; Gibbs, E. M. *Curr. Pharm. Design* **1996**, *2*, 85.
3. (a) Chaudhary, S. K.; Verma, M.; Chaturvedi, A. K.; Parmar, S. S. *J. Pharm. Sci. 64*, **1974**, 614; (b) Chaudhary, M.; Parmar, S. S.; Chaudhary, S. K.; Chaturvedi, A. K.; Ramasastry, B. V. *J. Pharm. Sci. 64*, **1976**, 443; (c) Nagar, S.; Singh, H. H.; Sinha, J. N.; Parmar, S. S. *J. Med.*

Chem. **1973**, *16*, 178; (d) Bonde, C. G.; Gaikwad, N. J. *Bioorg*. *Med*. *Chem*. **2004**, *12*, 2151; (e) Ramla, M. M.; Omar, M. A.; Tokuda, H.; El-Diwani, H. I. *Bioorg*. *Med*. *Chem*. **2007**, *15*, 6489 and references are cited therein; (f) Kücükgüzel, G.; Kocatepe. A.; Clercq, E. D.; Sahin, F.; Güllüce, M. *Eur*. *J*. *Med*. *Chem*. **2006**, *41*, 353; (g) Amin, K. M.; Abdel Rahman, D. E.; Al-Eryani, Y. A. *Bioorg*. *Med* .*Chem.* **2008**, *16*, 5377.

4. (a) Hua, W.; Xu, Y.; Zhang, D. *Faming Zhuanli Shenqing Gongkai Shuomingshu*, 1556107, 2004; (b) Zhang, D.; Xiang, H.; Xu, Y.; Hua, W. *Yaoxue Xuebao* **2006**, *41*, 825.
5. (a) Kline, T.; Felise, H. B.; Barry, K. C.; Jackson, S. R.; Nguyen, H. V.; Miller, S. I. *J*. *Med*. *Chem*. **2008**, *51*, 7065; (b) Moghaddam, F. M.; Hojabri, L. *J*. *Heterocycl. Chem*. **2007**, *44*, 35.
6. (a) Erol, S.; Dogan, I. *J*. *Org*. *Chem*. **2007**, *72*, 2494; (b) Shen, J.; Jiang, H.; Shen, X.; Li, S.; Huang, W.; Gui, C.; Chen, J.; Sun, T.; Ye, F. *Faming Zhuanli Shenqing Gongkai Shuomingshu*, 1699354, 2005.
7. (a) Singh, H.; Ahuja, A. S.; Malhotra, N. *J*. *Chem. Soc*., *Perkin Trans.1,* **1982**, 653; (b) Monforte, P.; Fenech, G.; Basile, M.; Ficarra, P.; Silvestro, A. *J*. *Heterocycl*. *Chem*. **1979**, *16*, 341.
8. (a) Singh, C.B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397; (b) Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. *Tetrahedron* **2008**, *64*, 1931; (c) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *J. Chem. Res.* **2007**, *64*, 136; (d) Murru, S.; Patel, B. K.; Bras, J. L.; Muzart, J. *J. Org*. *Chem*. **2009**, *74*, 2217.
9. (a) Singh, C. B.; Ghosh, H.; Murru, S.; Patel, B. K. *J. Org. Chem.* **2008**, *73*, 2924; (b) Ghosh, H.; Sarkar, S.; Ali, A. R.; Patel, B. K. *J*. *Sulfur Chem*. **2010**, *31*, 1; (c) Ghosh, H.; Yella, R.; Nath, J.; Patel, B. K. *Eur. J. Org. Chem.* **2008**, 6189; (d) Ghosh, H.; Yella, R.; Sahoo, S. K.; Patel B. K. *Tetrahedron Lett.* **2009**, 50, 2407.
10. (a) Yella, R.; Patel, B. K. *J*. *Comb*. *Chem*. **2010**, *12*, 754; (b) Yella, R.; Murru, S.; Ali, A.R.; Patel, B. K. *Org*. *Bio*. *Chem*. **2010**, *8*, 3389.
11. (a) Zeng, R.-S.; Zou, J.-P.; Zhi, S.-J.; Chen, J.; Shen, Q. *Org. Lett.* **2003**, *5*, 1657; (b) Wang, X.-C.; Wang, F.; Quan, Z. J.; Wang, M.-G.; Li, Z. *J. Chem. Res.* **2005**, 689.
12. (a) Kidwai, M.; Venkataraman, R.; Dave, B. *Green. Chem.* **2001**, *3*, 278; (b) Yella, R.; Ghosh, H.; Patel, B. K. *Green. Chem.* **2008**, *10*, 1307.
13. Wolfe, D. M.; Schreiner, P. R. *Eur. J. Org. Chem.* **2007**, 2825.

VI.7. Spectral Data

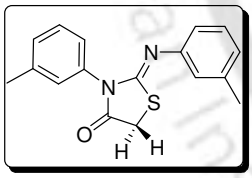
3-Phenyl-2-phenylimino-thiazolidin-4-one (1a):



M.p. 178 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (d, *J* = 0.8 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.25–7.54 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.8, 120.8, 124.6, 127.9, 128.9, 129.1, 129.3, 134.7, 148.0, 154.9, 171.4. IR (KBr): 3049, 1722, 1634, 1591, 1493 , 1374, 1270, 1195, 1154, 897, 868, 693, 552 cm^{-1}. HRMS (ESI): Calcd for $C_{15}H_{12}N_2OS$ [MH^+] 269.3467, found 269.0564.

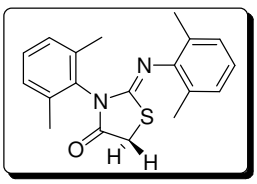
Crystal data for 1a: Crystal dimensions (mm): 0.20 x 0.10 x 0.10; $C_{15}H_{12}N_2OS$, M_r = 268.33; orthorhombic, space group Pbca; *a* = 10.9047(2) Å, *b* = 10.0696(2) Å, *c* = 24.2827(6) Å; $\alpha = \beta = \gamma = 90.00^o$; *V* = 2666.39(10) Å^3; *Z* = 8; ρ_{cal} = 1.337 mg/m^3; μ (mm^{-1}) = 0.235; *F*(000) = 1120; reflection collected / unique = 3281 / 2215; refinement method = full-matrix least-squares on F^2; final *R* indices [$I > 2\sigma_I$] R_1 = 0.346, wR_2 = 0.0859, *R* indices (all data) R_1 = 0.0569, wR_2 = 0.0928; goodness of fit = 0.949. CCDC # 686655.

3-*m*-Tolyl-2-*m*-tolylimino-thiazolidin-4-one (2a):



M.p. 158 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.40 (s, 3H), 3.95 (s, 2H), 6.73 (m, 2H), 6.93 (d, *J* = 7.6 Hz, 1H), 7.17–7.24 (m, 4H), 7.39 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 33.1, 117.9, 121.8, 125.2, 125.6, 128.7, 129.1, 129.4, 130.1, 134.9, 139.2, 139.6, 148.3, 154.9, 171.7. IR (KBr): 2919, 1720, 1638, 1599, 1581, 1487, 1370, 1284, 1203, 1132, 936, 800, 691 cm^{-1}. HRMS (ESI): Calcd for $C_{17}H_{16}N_2OS$ [MH^+] 297.4003, found 297.0800.

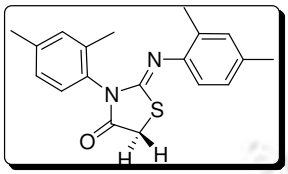
3-(2,6-Dimethyl-phenyl)-2-(2,6-dimethyl-phenylimino)-thiazolidin-4-one (3a):



M.p. 188 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 6H), 2.29 (s, 6H), 3.98 (d, *J* = 2.4 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 18.3, 33.0, 124.4, 128.2, 128.4, 129.0, 129.9,

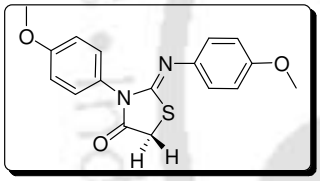
133.2, 136.2, 145.9, 154.0, 171.0. IR (KBr): 2947, 1718, 1644, 1589, 1473, 1363, 1275, 1247, 1184, 1156, 1086, 873, 764. HRMS (ESI): Calcd for [MH^+] 325.4539, found 325.1300.

3-(2,4-Dimethyl-phenyl)-2-(2,4-dimethyl-phenylimino)-thiazolidin-4-one (4a):



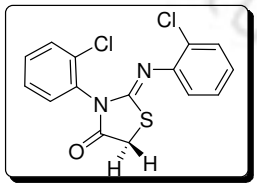
M.p. 114 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.23 (s, 3H), 2.25 (s, 3H), 2.32 (s, 3H), 3.89 (d, *J* = 1.2 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.89–6.94 (m, 2H), 7.09–7.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 17.9, 21.2, 21.5, 33.2, 119.9, 127.3, 128.3, 128.5, 129.4, 131.6, 131.7, 132.3, 134.3, 135.9, 139.9, 144.7, 154.3, 171.6. IR (KBr): 2920, 1728, 1633, 1496, 1367, 1270, 1239, 1199, 1178, 1119 cm^{-1}. HRMS (ESI): Calcd for $C_{19}H_{20}N_2OS$ [MH^+] 324.4480, found 325.0700.

3-(4-Methoxy-phenyl)-2-(4-methoxy-phenylimino)-thiazolidin-4-one (5a):



M.p. 135 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.79 (s, 3H), 3.92 (s, 2H), 6.82 (s, 4H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.9, 55.5, 55.6, 114.4, 114.8, 122.1, 127.5, 129.2, 141.4, 155.2, 156.8, 159.8, 171.8. IR (KBr): 2947, 1725, 1631, 1504, 1370, 1247, 1193, 1031, 832 cm^{-1}. HRMS (ESI): Calcd for $C_{17}H_{16}N_2O_3S$ [MH^+] 329.3983, found 329.0800.

3-(2-Chloro-phenyl)-2-(2-chloro-phenylimino)-thiazolidin-4-one (6a):

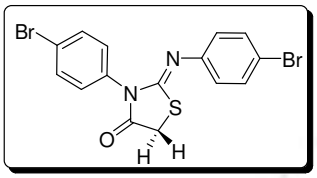


M.p. 175 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 7.06 (m, 1H), 7.22 (m, 1H), 7.35–7.48 (m, 4H), 7.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.3, 122.0, 125.8, 126.3, 127.6, 128.2, 130.2, 130.7, 131.1, 132.6, 133.0, 145.2, 155.8, 170.6. IR (KBr): 2942, 1731, 1632, 1583, 1478, 1374, 1286, 1201, 1171, 1065, 881 cm^{-1}. HRMS (ESI): Calcd for $C_{15}H_{10}Cl_2N_2OS$ [M^+] 337.2290, found 337.0000.

Crystal data: for 6a: Crystal dimensions (mm): 0.40 x 0.30 x 0.30; $C_{15}H_{10}Cl_2N_2OS$, M_r = 337.21, orthorhombic, space group Pbca, *a* = 12.900(4) Å, *b* = 10.035(4) Å, *c* = 24.251(8) Å; α = *β* = *γ* =

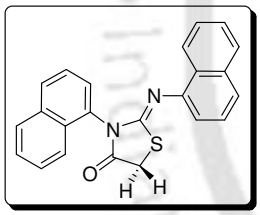
90.00°, V = 3139.2(18) Å^3; Z = 8, ρ_{cal} = 1.427 mg/m^3; μ (mm^{-1}) = 0.545; F(000) = 1376; reflection collected / unique = 3513 / 1684; refinement method = full-matrix least-squares on F^2; final R indices [I > 2σ_I] R_1 = 0.0576, wR_2 = 0.1633, R indices (all data) R_1 = 0.1194, wR_2 = 0.1954; goodness of fit = 0.970. CCDC # 692011.

3-(4-Bromo-phenyl)-2-(4-bromo-phenylimino)-thiazolidin-4-one (7a):



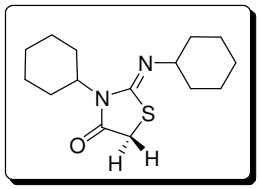
M.p. 124 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 2H), 6.79 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0, 118.0, 122.8, 123.3, 129.8, 132.5, 132.8, 133.6, 146.9, 155.3, 171.1. IR (KBr): 2930, 1718, 1634, 1580, 1487, 1360, 1260, 1190, 1144, 1072, 1012, 869, 830 cm^{-1}. HRMS (ESI): Calcd for $C_{15}H_{10}Br_2N_2OS$ [M$^+$] 426.1310, found 426.0100.

3-(Naphthlen-1-yl-2(napthlen-2-ylimino)-thiazolidin-4-one (8a):



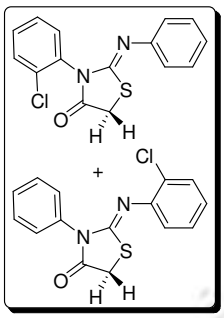
M.p. 176–178 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01–4.12 (d, J = 1.4 Hz, 2H), 7.01 (d, J = 7.6 Hz, 2H), 7.30 (m, 1H), 7.34–7.43 (m, 2H), 7.54–7.65 (m, 5H), 7.75 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.1, 114.9, 122.0, 123.3, 124.8, 125.5, 125.7, 126.2, 126.6, 126.9, 127.3, 127.7, 128.8, 129.6, 130.2, 131.8, 134.2, 134.6, 144.2, 155.0, 171.6. IR (KBr): 3050, 1720, 1630, 1506, 1394, 1361, 1249, 1195, 1151, 1072, 1039, 1015, 886 cm^{-1}. HRMS (ESI): Calcd for $C_{23}H_{16}N_2OS$ [MH$^+$] 368.4600, found 369.1000.

3-Cyclohexyl-2-cyclohexylimino-thiazolidin-4-one (9a):



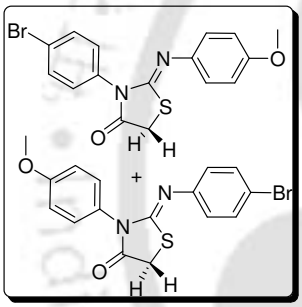
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08–1.45 (m, 8H), 1.49–1.76 (m, 10H), 2.30 (m, 2H), 3.02 (m, 1H), 3.66 (d, J = 2.0 Hz, 2H), 4.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 25.4, 25.9, 26.2, 28.0, 32.4, 33.5, 55.6, 61.3, 148.3, 171.9. IR (KBr): 2929, 2854, 1716, 1645, 1450, 1400, 1358, 1337, 1257, 1204, 1138, 1078, 969, 896 cm^{-1}. HRMS (ESI): Calcd for $C_{15}H_{24}N_2OS$ [MH$^+$] 281.4415, found 281.1700.

3-(2-Chloro-phenyl)-2-phenylimino-thiazolidin-4-one (10a) + 2-(2-chloro-phenylimino)-3-phenyl-thiazolidin-4-one (10b):



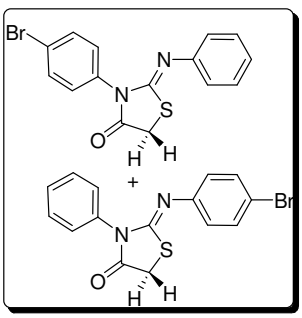
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (m, 4H), 6.90 (m, 3H), 7.01 (m, 1H), 7.08 (m, 1H), 7.16 (m, 1H), 7.30 (m, 3H), 7.32–7.46 (m, 6H), 7.46–7.60 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.9, 33.1, 120.9, 121.8, 124.8, 125.6, 127.5, 128.01, 128.03, 128.9, 129.1, 129.2, 129.4, 130.1, 130.5, 130.6, 130.8, 132.78, 132.81, 134.5, 145.2, 147.9, 153.6, 156.8, 170.6. 171.2. IR (KBr): 2986, 1729, 1634, 1592, 1584, 1480, 1373, 1272, 1198, 1158, 1066, 1026, 903, 874 cm^{-1}.

3-(4-Bromo-phenyl)-2-(4-methoxy-phenylimino)-thiazolidin-4-one (11a) + 2-(4-bromo-phenylimino)-3-(4-methoxy-phenyl)-thiazolidin-4-one (11b):



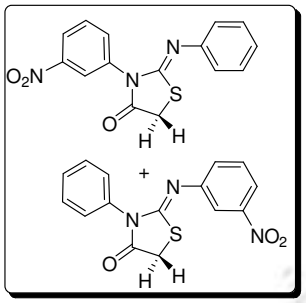
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (d, *J* = 0.8 Hz, 4H), 3.82 (s 3H), 3.96 (s, 3H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 4H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 4H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0, 55.6 114.6, 114.9, 117.8, 122.1, 122.9, 123.1, 127.2, 129.2, 129.8, 132.3 132.7, 133.9, 141.0, 147.3, 154.4, 157.0, 159.9, 171.3, 171.6. IR (KBr): 2930, 2834, 1728, 1632, 1504, 1487, 1364, 1244, 1190 1150, 1029, 1013, 875, 830 cm^{-1}. $C_{16}H_{13}BrN_2O_2S$ (377.26): calcd. C 50.94, H 3.47, N 7.43, S 8.50; found C 50.99, H 3.54, N 7.39, S 8.46.

3-(4-Bromophenyl)-2-(phenylimino)thiazolidin-4-one (12a) + 2-(4-bromophenylimino)-3-phenylthiazolidin-4-one (12b):



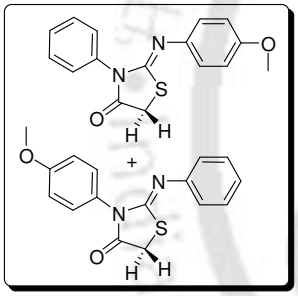
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 2H), 3.93 (s, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.22–7.35 (m, 6H), 7.39–7.43 (m, 3H), 7.47–7.51 (m, 2H), 7.60–7.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.9, 33.0, 117.8, 120.9, 122.9, 123.0, 124.9, 128.0, 129.2, 129.3, 129.5, 129.7, 132.3, 132.6, 133.7, 134.7, 147.1, 147.8, 154.6, 155.7, 171.2, 171.3. IR (KBr): 2931, 1726, 1634, 1487, 1366, 1267, 1221, 1190, 1151, 1069, 1013 cm^{-1}.

3-(3-Nitrophenyl)-2-(phenylimino)thiazolidin-4-one (13a) + 2-(3-nitrophenylimino)-3-phenylthiazolidin-4-one (13b):



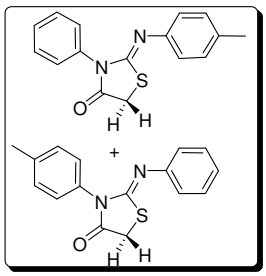
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (s, 2H), 4.03 (s, 2H), 6.92 (d, *J* = 7.2 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.31–7.40 (m, 5H), 7.45–7.56 (m, 4H), 7.70 (t, *J* = 8.4 Hz, 1H), 7.77–7.81 (m, 2H), 7.95–7.98 (m, 1H), 8.30–8.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0, 33.1, 116.4, 119.6, 120.9, 123.9, 125.2, 127.6, 128.1, 129.5, 129.7, 130.16, 130.18, 134.5, 134.54, 135.5, 147.5, 148.8, 149.0, 149.2, 154.2, 157.3, 171.0, 171.2. IR (KBr): 1731, 1633, 1525, 1350, 1261, 1193, 1156, 1087 cm^{-1}.

2-(4-methoxyphenylimino)-3-phenylthiazolidin-4-one (14a) + 3-(4-Methoxyphenyl)-2-(phenylimino)thiazolidin-4-one (14b):



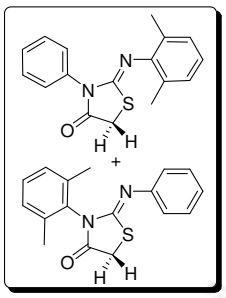
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.82 (s, 3H), 3.93 (d, *J* = 2.0 Hz, 2H), 3.95 (d, *J* = 2.4 Hz, 2H), 6.88 (s, 4H), 6.93 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 9.2 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.30–7.35 (m, 4H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.9, 32.94, 55.5, 55.55, 114.4, 114.8, 121.0, 122.0, 124.7, 127.3, 128.1, 129.0, 129.2, 129.4, 134.9, 141.3, 148.3, 154.9, 156.8, 159.8, 171.6, 171.7. IR (KBr): 2971, 1726, 1626, 1591, 1507, 1365, 1252, 1191, 1151, 1031, 872, 830 cm^{-1}. $C_{16}H_{14}N_2O_2S$ (298.36): calcd C 68.41, H 4.73, N 9.39, S 10.75; found C 68.54, H 4.69, N 9.34, S 10.84.

2-(*p*-Tolylimino)-3-phenylthiazolidin-4-one (15a) + 2-(phenylimino)-3-*p*-tolylthiazolidin-4-one (15b):



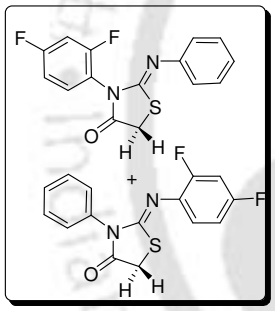
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.38 (s, 3H), 3.93 (m, 4H), 6.79–6.82 (m, 2H), 6.89–6.91 (m, 2H), 7.07–7.12 (m, 2H), 7.22–7.32 (m, 4H), 7.35–7.43 (m, 4H), 7.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.4, 32.9, 120.8, 121.0, 124.7, 127.8, 128.1, 129.0, 129.3, 129.5, 129.9, 130.2, 132.2, 134.3, 134.9, 139.2, 145.6, 148.3, 171.7. IR (KBr): 2924, 1722, 1633, 1592, 1505, 1370, 1271, 1193, 1153 cm^{-1}.

2-(2,6-dimethylphenylimino)-3-phenylthiazolidin-4-one (16a) + 3-(2,6-dimethylphenyl)-2-(phenylimino)thiazolidin-4-one (16b):



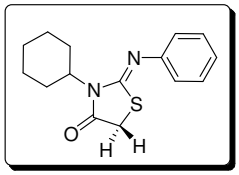
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 6H), 2.29 (s, 6H), 3.96 (d. *J* = 3.6Hz, 2H), 4.00 (d, *J* = 2.4 Hz, 2H), 6.94 (m, 3H), 7.04 (m, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.25–7.35 (m, 3H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 17.9, 32.9, 33.2, 121.0, 124.3, 124.7, 128.0, 128.1, 128.2, 128.8, 129.2, 129.6, 129.7, 133.2, 132.5, 134.9, 136.0, 145.6, 148.3, 153.7, 170.9. 171.6. IR (KBr): 2921, 1719, 1635, 1590, 1474, 1362, 1274, 1189, 1151, 1090, 872 cm^{-1}.

3-(2,4-difluorophenyl)-2-(phenylimino)thiazolidin-4-one (17a) + 2-(2,4-difluorophenylimino)-3-phenylthiazolidin-4-one (17b):



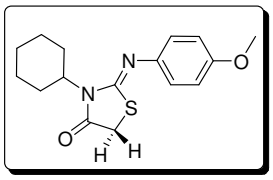
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 2H), 4.00 (s, 2H), 6.79–6.93 (m, 5H), 7.02 (m, 2H), 7.13 (m, 2H), 7.29–7.35 (m, 2H), 7.40–7.47 (m, 5H), 7.50–7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0, 33.2, 104.6, 104.9, 105.1, 111.3, 111.5, 111.6, 120.9, 121.0, 123.4, 123.5, 124.8, 124.8, 125.0, 128.1, 129.1, 129.3, 129.5, 129.6, 130.1, 130.2, 134.5, 134.9, 146.7, 148.2, 152.0, 154.2, 158.3, 158.5, 160.7, 171.4, 171.6. IR (KBr): 2923, 1731, 1633, 1497, 1368, 1154, 748, 692 cm^{-1}. $C_{15}H_{10}F_2N_2O_2S$ (304.31): calcd C 59.20, H 3.31, N 9.21, S 10.54; found C 59.28, H 3.27, N 9.15, S 10.58.

3-Cyclohexyl-2-phenylimino-thiazolidin-4-one (18a):



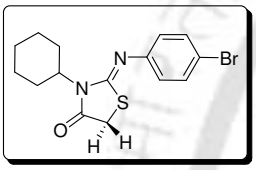
M.p. 155 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.34 (m, 4H), 1.57–1.68 (m, 6H), 3.13 (m, 1H), 3.92 (d, *J* = 0.8 Hz, 2H), 7.20–7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 25.5, 32.5, 33.1, 61.5, 127.9, 128.3, 128.8, 135.3, 149.1, 171.4. IR (KBr): 2927, 2853, 1724, 1626, 1591, 1496, 1452, 1365, 1233, 1164, 1071, 892, 854 cm^{-1}. HRMS (ESI): Calcd for $C_{15}H_{18}N_2OS$ [MH^+] 275.3941, found 275.3948

3-Cyclohexyl-2-(4-methoxy-phenylimino)-thiazolidin-4-one (19a):



M.p. 140 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–1.35 (m, 4H), 1.56–1.71 (m, 6H), 3.14 (m, 1H), 3.81 (s, 3H), 3.94 (d, *J* = 0.8 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.5, 32.4, 33.2, 55.4, 61.6, 114.2, 127.9, 129.0, 149.4, 159.2, 171.6. IR (KBr): 2927, 2852, 1724, 1638, 1514, 1369, 1253, 1234, 1164, 1070, 1025 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{20}N_2O_2S$ [MH^+] 305.4199, found 305.1100.

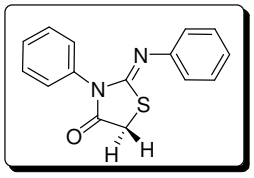
2-(4-Bromo-phenylimino)-3-cyclohexyl-thiazolidin-4-one (20a):

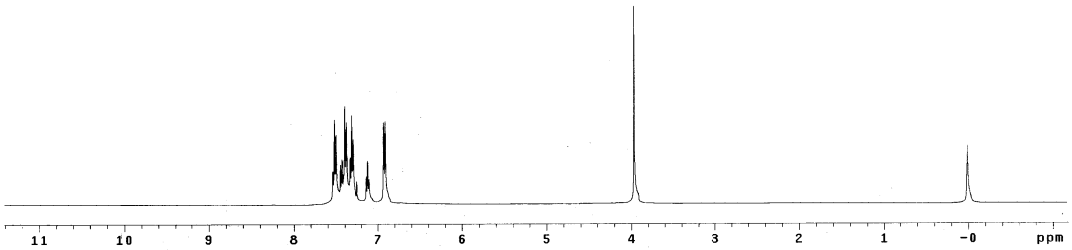


M.p. 149 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.35 (m, 4H), 1.54–1.69 (m, 6H), 3.12 (m, 1H), 3.93 (s, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 25.7, 32.7, 33.3, 61.7, 122.4, 129.8, 132.3, 134.3, 148.9, 171.3. IR (KBr): 2929, 2853, 1723, 1645, 1489, 1365, 1228, 1069, 816 cm^{-1}. HRMS (ESI): Calcd for $C_{15}H_{17}BrN_2OS$ [MH^+] 353.2823, found 353.0100.

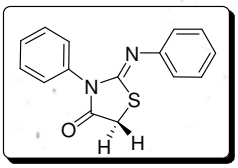
VI.8. Selected Spectra

3-Phenyl-2-phenylimino-thiazolidin-4-one (1a): ^{1}H NMR (400 MHz, $CDCl_3$):

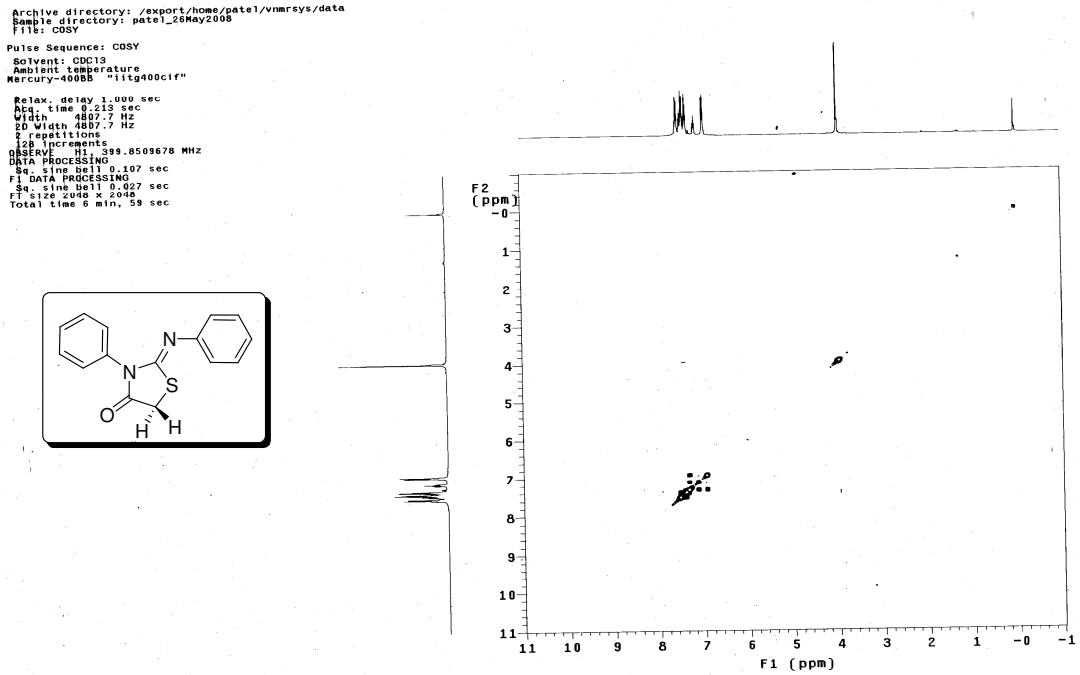




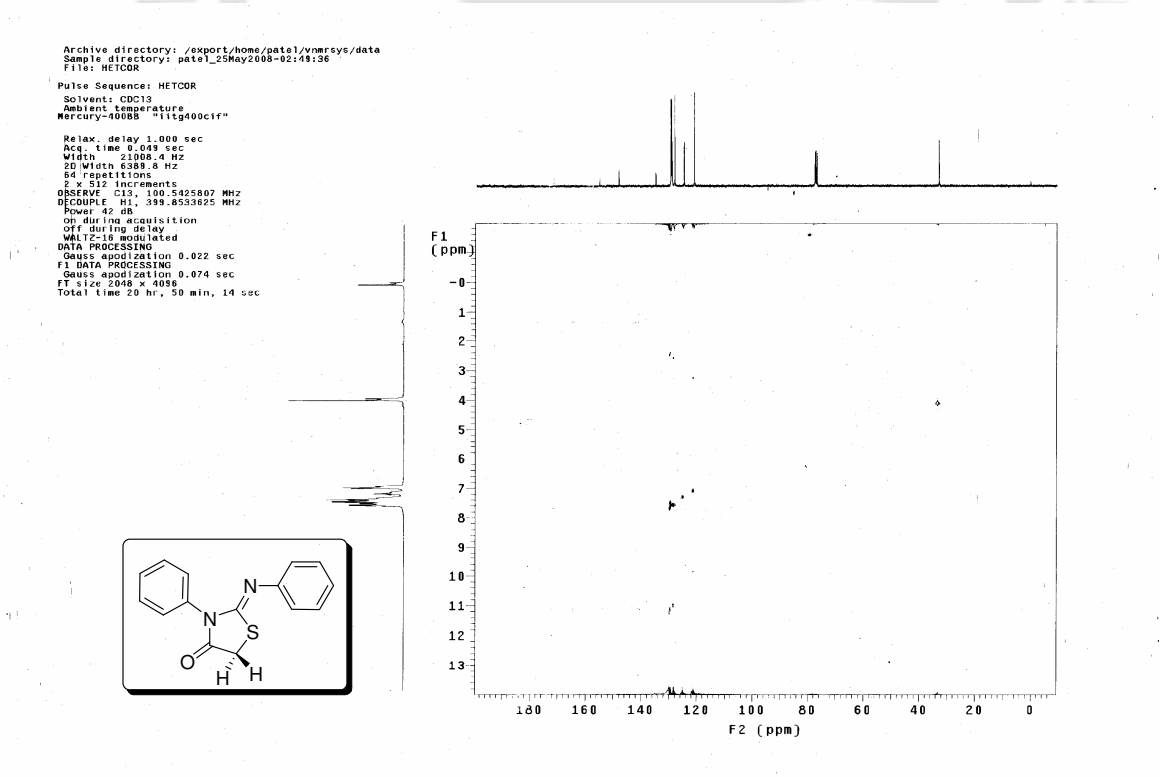
3-Phenyl-2-phenylimino-thiazolidin-4-one (1a): ^{13}C NMR (100 MHz, $CDCl_3$):



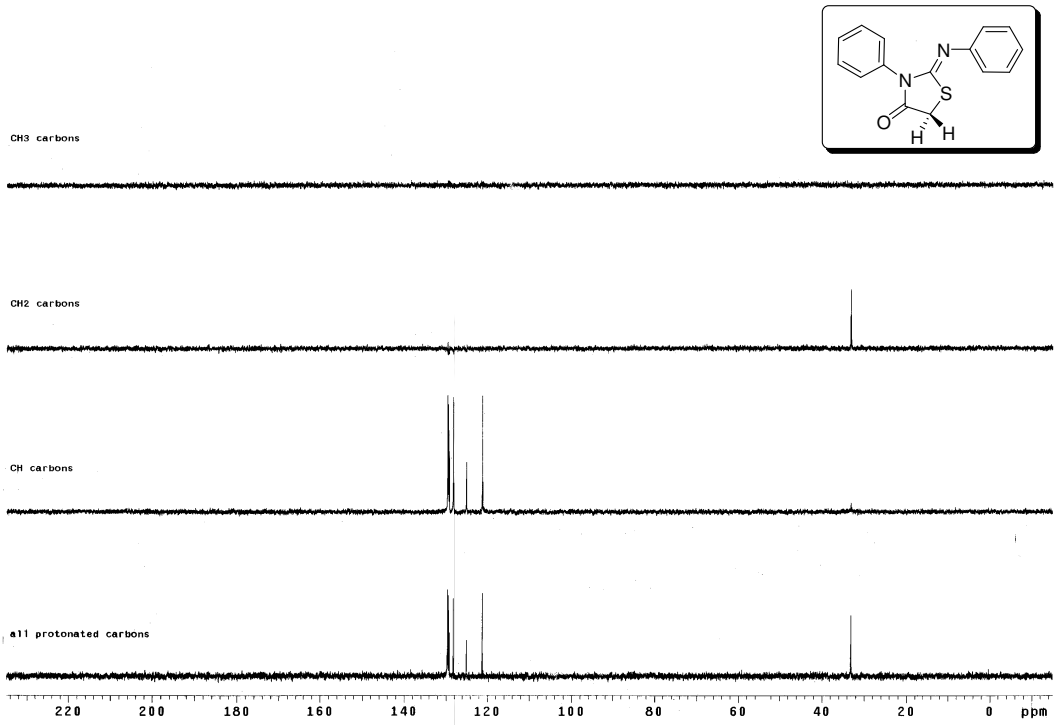
3-Phenyl-2-phenylimino-thiazolidin-4-one (1a): ^{1}H NMR (400 MHz, $CDCl_3$): COSY



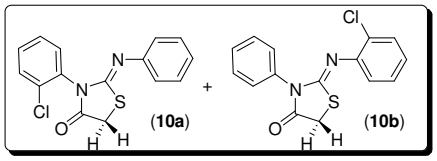
3-Phenyl-2-phenylimino-thiazolidin-4-one (1a): HETCOR

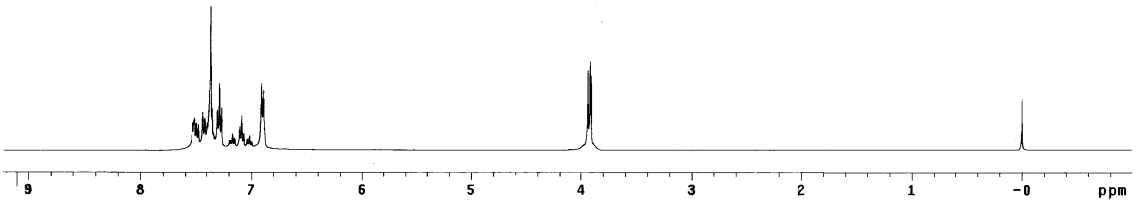


3-Phenyl-2-phenylimino-thiazolidin-4-one (1a): ^{13}C NMR (100 MHz, $CDCl_3$): HETCOSY

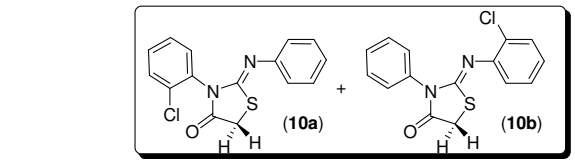


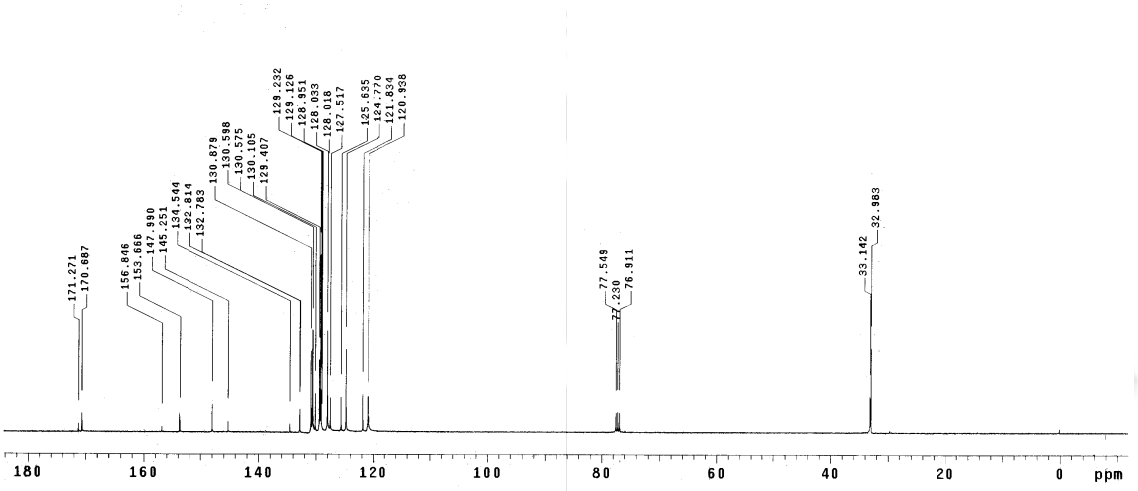
3-(2-Chloro-phenyl)-2-phenylimino-thiazolidin-4-one (10a) + 2-(2-chloro-phenyl imino)-3-phenyl-thiazolidin-4-one (10b): ^1H NMR (400 MHz, $CDCl_3$):





3-(2-Chloro-phenyl)-2-phenylimino-thiazolidin-4-one (10a) + 2-(2-chloro-phenyl imino)-3-phenyl-thiazolidin-4-one (10b): ^{13}C NMR (100 MHz, $CDCl_3$):





LIST OF PUBLICATIONS

1. "Tandem Regioselective Synthesis of Tetrazoles and Related Heterocycles Using Iodine." **Ramesh Yella,** Nilufa Khatun, Saroj Kumar Rout, Bhisma K Patel.***** *Org. Biomol. Chem.* **2011**, (*Under revision*).
2. "Bromineless Bromine as an Efficient Desulfurizing Agent for the Preparation of Cyanamides and 2-Aminothiazoles from Dithiocarbamate salts." **Ramesh Yella,** Veerababurao Kavala, Bhisma K. Patel* *Synth. Commun*. **2011**, LYSC 464774.
3. "One-Pot Synthesis of Five and Six Membered *N*, *O*, *S*-Heterocycles Using a Ditribromide Reagent." **Ramesh Yella,** Bhisma K. Patel.* *J. Comb. Chem.* **2010**, *12*, 754.
4. "An Efficient Preparation of Isothiocyanates from Dithiocarbamates Using Bromineless Brominating Reagent." **Ramesh Yella,** Harisadhan Ghosh, Siva Murru, Santosh K. Sahoo, Bhisma K. Patel.* *Synth. Commun*. **2010**, *40*, 2083.
5. "Chloroacetylchloride: A Versatile Reagent in Heterocyclic Synthesis." **Ramesh Yella,** *Synlett Spotlight*, **2010**, 835**.**
6. "Arylthioureas with Bromine or Its Equivalents Gives No 'Hugherschoff' Reaction Product." **Ramesh Yella,** Siva Murru, Abdur Rezzak Ali, Bhisma K. Patel.* *Org. Biomol. Chem.* **2010**, *8*, 3389.
7. "An Efficient Synthesis of Cyanamide from Amine Promoted by a Hypervalent Iodine(III) Reagent." Harisadhan Ghosh, **Ramesh Yella,** Abdur Rezzak Ali, Santosh K. Sahoo, Bhisma K. Patel* *Tetrahedron Lett.* **2009**, *50*, 2407.
8. "Molecular Iodine Mediated Preparation of Isothiocyanates from Dithiocarbamic Acid Salts." Jayashree Nath, Harisadhan Ghosh, **Ramesh Yella,** Bhisma K. Patel* *Eur. J. Org. Chem.* **2009**, 1849.
9. "Copper(I) Catalyzed Cascade Synthesis of 2-Substituted Benzothiazoles: An Easy Access to Benzothiazolones." Siva Murru, Pravat Mondal, **Ramesh Yella,** Bhisma K. Patel.* *Eur. J. Org. Chem.* **2009**, 5406.
10. "Efficient One-Pot Preparation of *Bis*-alkyl Xanthogen Disulfides from Alcohols." Latonglila Jamir, **Ramesh Yella,** Bhisma K. Patel.* *J. Sulfur. Chem.* **2009**, *30*, 128.
11. "Desulfurization Mediated by Hypervalent Iodine (III): A Novel Strategy for the Construction of Heterocycles." Harisadhan Ghosh, **Ramesh Yella,** Jayashree Nath, Bhisma K. Patel.* *Eur. J. Org. Chem.* **2008**, 6189.
12. "It is '2-imino-4-thiazolidinones' and Not Thiohydantoins as the Reaction Product of 1,3-Disubstituted Thioureas and Chloroacetylchloride." **Ramesh Yella,** Harisadhan Ghosh, Bhisma K. Patel* *Green Chem.* **2008**, *10*, 1307.