Exploration of Hypervalent Iodine(III) & Ditribromide (EDPBT) in Organic Synthesis

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Submitted by

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Dedicated to

My Parents

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Department of Chemistry

STATEMENT

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

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

May, 2010
IIT Guwahati

Harisadhan Ghosh

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CERTIFICATE

This is to certify that Harisadhan Ghosh has been working under my supervision since July, 2006 as a regular registered Ph. D. student. I am forwarding his thesis entitled "**Exploration of Hypervalent Iodine(III) & Ditribromide (EDPBT) in Organic Synthesis**" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

May, 2010.
IIT Guwahati

Prof. Bhisma K. Patel
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CERTIFICATE OF COURSE WORK

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

1) CH 603 : Supramolecules: Concepts & Application
2) CH 621 : New Reagents for Organic Synthesis
3) CH 611 : Bioinorganic Chemistry
4) CH 625 : Art in Organic Synthesis

Harisadhan Ghosh has successfully completed his Ph.D. qualifying examination in May 2007.

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Harisadhan Ghosh

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 different aspects of hypervalent iodine chemistry and the use of organic tribromides in the synthesis of various heterocycles. Chapter (II) describes the oxidation of aldoximes to *N*-acetoxy or *N*-hydroxy amides using two hypervalent iodine(III) reagents *viz.* (diacetoxyiodo)benzene (DIB) and Koser's reagent [hydroxy(tosyloxy)iodo]benzene (HTIB). Chapter (III) demonstrates the oxidative N-acylation of 1,3-disubstituted thioureas to *N*-acylureas using (diacetoxyiodo)benzene (DIB). Chapter (IV) illustrates synthesis of isothiocyanate and cyanamide through desulfurization of dithiocarbamic acid salt with hypervalent iodine(III) reagent. Chapter (V) and (VI) mainly focuses on the synthesis of various heterocycles using hypervalent iodine(III) reagents and ditribromide reagent 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). Each chapter constitutes of four sub sections, describing introduction, present work, experimental work and spectral data respectively.

CHAPTER I. Introduction to Hypervalent Iodine Chemistry and Use of Tribromides in Heterocyclic Synthesis

This chapter highlights the definition, bonding and nomenclature, methods of preparation, general reactivity and application in organic synthesis of various hypervalent iodine(III) compounds. It also includes a general description on the synthesis of various heterocycles using organic ammonium tribromides.

Since the early 1980s interest in hypervalent iodine compounds has experienced a renaissance. The upsurge in the use of hypervalent iodine reagent in recent years is due to its similarity in reactivity with metal based reagent such as Hg(II), Tl(III), Pb(IV) reagents. The useful mild oxidizing properties combined with their environmentally benign character and commercial availability has made the hypervalent iodine reagents as suitable alternatives to toxic heavy metal congeners.

The reactivity of the hypervalent iodine compound is mainly due to its hypervalent loose nature of the I-L (L = Electronegative element) ligands and by a distinct positive charge on the iodine atom. These structural features are responsible for the enhanced electrophilic properties of RIL_2 and explain typical pathways such as ligand exchange and reductive ligand transfer in their reaction with organic compounds. Hypervalent iodine(III) reagents have wide applications in oxidative functionalization reactions and synthesis of various heterocycles.

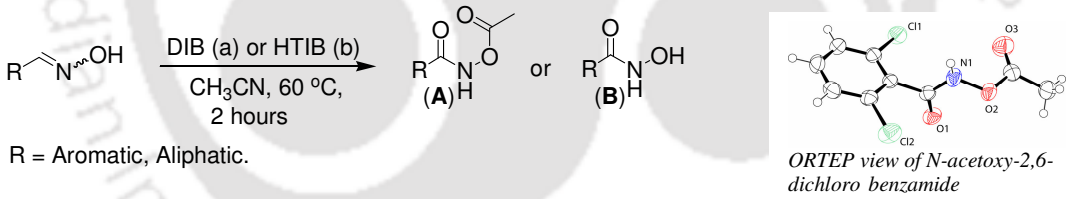
Organic ammonium tribromides are the attractive solid bromine less brominating agents. These crystalline stable solids are convenient source of bromine owing to the ease in maintenance of the desired stoichiometry and the ease in storage, transportation and handling. Apart from bromination, tribromides 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. This, in turn, can be utilized for various acid catalyzed organic transformations. We have synthesized a new ditribromide reagent, 1,1'-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT) which is superior to all known tribromides and has several advantages over molecular bromine and other tribromides. Our group is actively involved in the synthesis of various bioactive heterocycles possessing five or six membered ring systems bearing N, O, S atoms.

CHAPTER II. Oxidation of Aldoximes to *N*-Acetoxy or *N*-Hydroxy Amides

This chapter deals with the oxidation of various aldoximes with hypervalent iodine(III) reagents (diacetoxyiodo)benzene (DIB) or [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's Reagent) to *N*-acetoxy or *N*-hydroxy amides. The chemistry of nitrile oxide, *N*-acetoxy and *N*-hydroxy amide is attractive because of their immense biological and synthetic importance. Nitrile oxide is the main precursor for the compound, 5-aminoisoxazoles, which are of vast biological interest and display fungicidal, antihelmintic or bactericidal properties or are useful for the treatment of cerebrovascular disorders. *N*-

Acetoxy benzamides (*O*-acetyl hydroxamates) have insecticidal and herbicidal activity, thus they are important from biological point of view. On the other hand the hydroxamic acid functionality is present in a number of biologically active molecules. Nitrile oxides form an important class of reactive intermediates because of their ability to undergo l,3-dipolar cyclo-additions giving heterocyclic compounds, especially isoxazolines and isoxazoles. *N*-Acetoxy benzamides (*O*-acetyl hydroxamates) and *O*-tosyl hydroxamates are important candidates for classical Lossen rearrangements. Hydroxamic acids are important precursors for the preparation of acyl nitroso compounds, *O*-glycosylated hydroxamic acids *etc*.

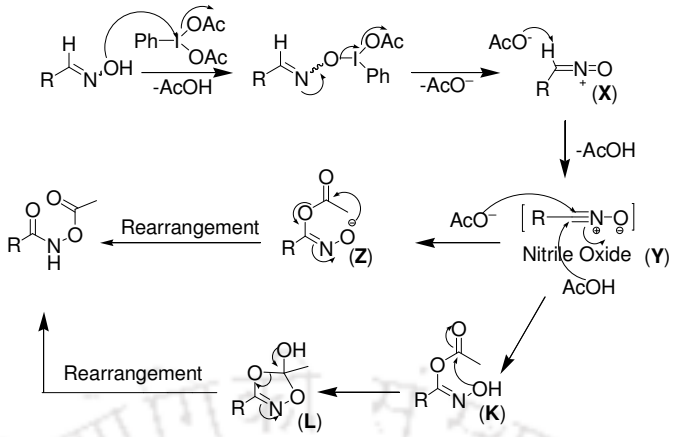
We have been interested in hypervalent iodine(III)-mediated oxidative desulfurization reactions. During the course of (diacetoxyiodo)benzene (DIB)-mediated oxidation of aromatic aldoximes, we observed the formation of *N*-acetoxy benzamide (**A**) (*Scheme II.1*). When the same reaction was performed using Koser's reagent [hydroxy(tosyloxy)iodo]benzene (HTIB), the product obtained was *N*-hydroxy benzamide (**B**) (*Scheme II.1*).



ORTEP view of N-acetoxy-2,6-dichloro benzamide

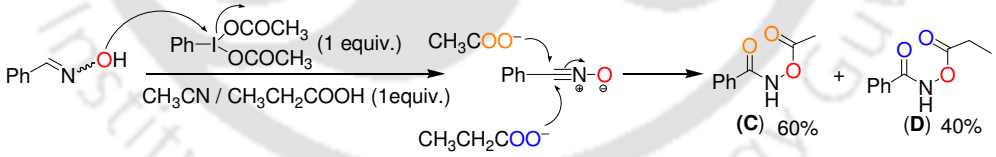
Scheme II.1. *Oxidation of aldoximes with hypervalent iodine(III) reagents*

When benzaldehyde oxime (1 equiv.) was reacted with (diacetoxyiodo)benzene (DIB) (1.1 equiv.) in acetonitrile at 60 ^{o}C, *N*-acetoxy benzamide was obtained in 78% isolated yield. The mechanism of the reaction is shown in *Scheme II.2*.



Scheme II.2. *Mechanism for the formation of N-acetoxy amides*

According to this mechanism, the first step is the nucleophilic displacement of one of the acetate groups of DIB by aldoxime oxygen. This is then followed by the formation of intermediate (**X**), which, upon deprotonation, gives nitrile oxide (**Y**) (*Scheme II.2*). Nitrile oxide (**Y**), which is reported to be the intermediate for this kind of reaction, is attacked by the *in situ* liberated acetate ion from DIB, giving acylated intermediate (**Z**). The intermediate (**Z**), upon intramolecular rearrangement, gave the expected *N*-acetoxy arylamide. Alternatively, attack of nitrile oxide (**Y**) by an acetic acid gives intermediate (**K**), which in turn generates a tetrahedral intermediate (**L**) leading to the expected *N*-acetoxy amide.



Scheme II.3. *Intermolecular nature of the mechanism*

When the reaction was carried out in the presence of one equivalent of propionic acid, *N*-acetoxy benzamide (**C**) along with *N*-propionyloxy benzamide (**D**) were obtained (*Scheme II.3*) in the ratio 60 : 40. The formation of *N*-propionyloxy benzamide (**D**) proves the intermolecular attack of acetate or propionate on benzonitrile oxide (*Scheme II.3*).

Due to the immense synthetic importance of *N*-acetoxy amides, we applied this strategy to various aldoximes for the construction of *N*-acetoxy amides. Both the aromatic

and aliphatic aldoximes were successfully converted to *N*-acetoxy amides with good yields.

When another hypervalent iodine(III) reagent [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's Reagent) was used as the oxidizing agent instead of DIB for the oxidation of benzaldehyde oxime, *N*-hydroxybenzamide (**B**) (*Scheme II.1*) was isolated as the sole product. Here, the –OH nucleophile (generated from the reagent, HTIB) attacks the intermediate benzonitrile oxide (*Scheme II.2*), forming *N*-hydroxy benzamide (**B**). This reaction works better in a chloroform medium compared to any other solvent.

Hydroxamic acids bearing various substituents on the aromatic ring can be efficiently prepared from the corresponding benzaldehyde oximes. Aliphatic aldoximes were successfully converted to their corresponding hydroxamic acids in a shorter time (30 min).

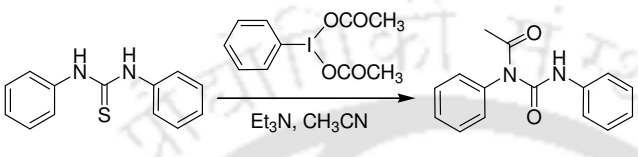
In conclusion, the oxidation of both aromatic and aliphatic aldoximes with hypervalent iodine(III) reagents DIB and HTIB gave the corresponding *N*-acetoxy and *N*-hydroxy amides in good yields, rather than the expected nitrile oxide dimerized products oxadiazole-*N*-oxides reported with other oxidizing agents. A plausible mechanism for this transformation involves acetate attack on the intermediate aryl/alkyl nitrile oxides, which, upon rearrangement, gave the expected *N*-acetoxy amides. Thus, using this approach, various *N*-acetoxy and *N*-hydroxy amides can be prepared conveniently from their corresponding aldoximes.

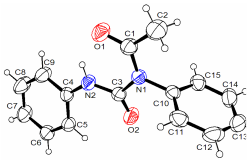
CHAPTER III. Oxidative N-Acylation of 1,3-Disubstituted Thioureas to *N*-Acylureas

In this chapter the oxidative N-acylation of 1,3-disubstituted thioureas to *N*-acylureas and the p*Ka* dependent regioselective nature of the N-acylation of thioureas mediated by hypervalent iodine(III) reagent (diacetoxyiodo)benzene (DIB) have been discussed.

Ureas and thioureas are useful synthons for the construction of heterocyclic compounds. *N*-Acylureas have found important applications in agrochemicals and pharmaceuticals.

The reported methods for the synthesis of *N*-acyl urea are by the reaction of substituted ureas with acyl chlorides or acids at elevated temperature and reaction of amides with isocyanates or carbodiimides. A similar N-acylation of thioureas using $Mn(OAc)_3$ was disclosed recently by Mu *et al.* We have demonstrated an unprecedented regioseletive N-acetylation of disubstituted thioureas leading to *N*-acetyl ureas using (diacetoxyiodo)benzene (DIB), as shown in *Scheme III.1*.

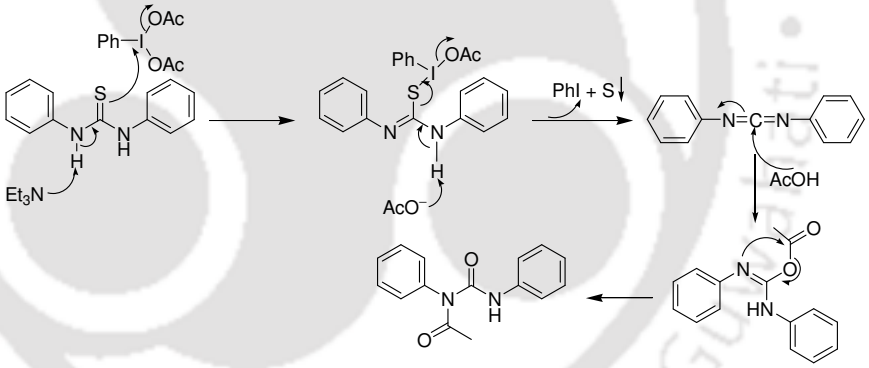




ORTEP view of 1-Acetyl-1,3-diphenylurea

Scheme III.1. *N-Acylated urea from thiourea*

The following intermolecular mechanism involving a carbodiimide intermediate has been proposed for this transformation (*Scheme III.2.*).



Scheme III.2. *Proposed mechanism of formation of N-acylurea (intermolecular)*

This has been proved by carrying out the reaction in the presence of one equivalent of propionic acid and an additional equivalent of triethylamine and it gave *N*-acetylated product along with the formation of propionylated product in the ratio 58 **:** 42.

Reaction of asymmetrical 1,3-disubstituted thioureas with (diacetoxyiodo)benzene (DIB) produces regioselectively *N*-acetylurea. We have prepared a series of *N*-acylated ureas starting from corresponding 1,3-disubstituted thioureas. We have also found a good correlation between regioselective N-acylation of unsymmetrical thiourea and p*Ka*'s of the

corresponding amines. It has been found that larger the difference between the p*Ka*'s of the precursor amines in thiourea greater the regioselectivity of N-acylation with preferential acylation taking place towards the amine having lower p*Ka*.

In conclusion, we have developed an efficient method for the synthesis of *N*-acylated ureas from 1,3-disubstituted thioureas using environmentally benign reagent (diacetoxyiodo)benzene (DIB). For the first time, DIB has been employed as an acylating agent. We have also found the correlation between the regioselectivity and the p*Ka* of the amine.

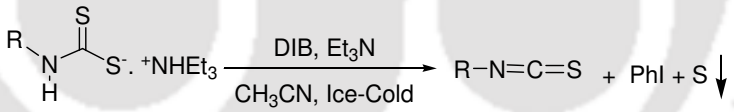
CHAPTER IV. Desulfurization of Dithiocarbamic Acid Salt with Hypervalent Iodine (III): A Facile One-Pot Access to Isothiocyanate and Cyanamide

In continuation to our interest in the chemistry of hypervalent iodine(III) mediated oxidation reactions, the oxidative desulfurization ability of (diacetoxyiodo)benzene (DIB) has been explored in the preparation of isothiocyanates and cyanamides from the corresponding dithiocarbamic acid salts.

In synthetic organic chemistry, isothiocyanates are an important class of molecule that are frequently encountered in many natural products and are key intermediates in the preparation of both sulfur- and nitrogen-containing organic compounds, especially for heterocycles. They are prepared conventionally by treating amines with thiophosgene. Owing to difficulties in handling thiophosgene, its equivalents have been prepared and employed for this purpose. The reactions of amines with "thiocarbonyl transfer" reagents afford the corresponding isothiocyanates. An alternative approach relies on the decomposition of dithiocarbamic acid salts into isothiocyanates promoted by various reagents. The drawbacks of this reported process mainly result from the use of environmentally unsafe halogenated solvents, longer reaction times, and hazardous and toxic reagents.

On the other hand, due to its unique reactivity, cyanamide is an important functional group in synthetic organic chemistry. Cyanamides are useful precursors in the synthesis of pharmaceutically important heterocycles and *N*-alkyl or *N*-aryl imides. Due to

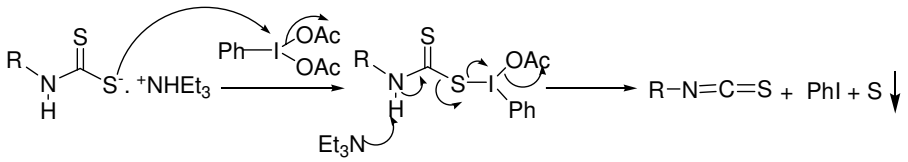
the easy removal of the cyano group from cyanamide, they often serve as a useful protecting group in the synthesis of secondary and tertiary amines containing heterocycles. Cyanamides are also important intermediates for the synthesis of many biologically active compounds, such as minoxidil and herbicides. The most frequently adopted method for the synthesis of cyanamides is the cyanation of amine using cyanogen halides, or its synthon (CN^+). In an alternative approach, cyanamides are obtained from ureas and thioureas. The other less commonly adopted method is the Tiemann rearrangement of amidoximes. Recently, they were prepared from organic isocyanides and trimethylsilyl azide via a Si–N bond cleavage catalyzed by $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$, and in one pot by reacting isocyanate or isothiocyanate with sodium bis(trimethylsilyl) amide as deoxygenating or desulfurizing agent in THF at room temperature. Most of the reported methods use cyano cation (CN^+) directly from highly toxic cyanogen bromide or indirectly from (CN^+) synthons which, in turn, are prepared from toxic cyanogen halides. Another reported method uses extremely alkaline conditions, toxic and expensive reagents, high reaction temperatures giving low yields, and involving tedious purification procedures.



Scheme IV.1. *Preparation of isothiocyanate from the dithiocarbamate salt*

The use of (diacetoxyiodo)benzene (DIB) overcomes many of the problems associated with the preparation of isothiocyanates. When the dithiocarbamate salt (1 equiv.) was treated with DIB (1 equiv.) in the presence of triethylamine (1.5 equiv.) in acetonitrile, isothiocyanate was obtained in excellent yield (*Scheme IV.1*).

The proposed mechanism is shown in *Scheme IV.2*. The formation of phenyl iodide and the precipitation of elemental sulfur from the reaction mixture support the mechanism.



Scheme IV.2. *Mechanism of the formation of isothiocyanate from the dithiocarbamate salt*

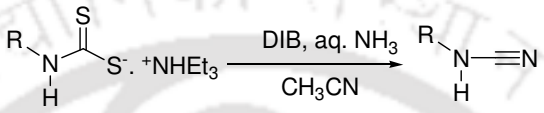
Several isothiocyanates were successfully prepared in good to excellent yields by utilizing this protocol. Aromatic substrates containing *ortho*, *meta,* and *para* substituents all gave isothiocyanates in good yields. Recently, we found that regioselective N-acylation of unsymmetrical 1,3-disubstituted thiourea is dependent on the p*Ka* of the amine attached to the thioureas. Based on this observation and the mechanism proposed in *Scheme IV.2*, we have reason to believe that an amine with a lower p*Ka* should yield the isothiocyanate faster because of its easy deprotonation. Triethylamine, the base employed for this purpose is sufficiently basic (p*Ka* = 10.78) compared with the aromatic amines used (p*Ka* = 2.46 – 5.63). The p*Ka* of the NH proton upon formation of the dithiocarbamate salt is expected to decrease further. Hence all the aromatic dithiocarbamic acid salts gave the corresponding aromatic isothiocyanates in excellent yields when triethylamine was used as the base along with DIB.

Alkylamines such as *n*-butyl- (p*Ka* = 10.77), cyclohexyl- (p*Ka* = 10.66), and benzylamine- (p*Ka* = 9.33), which have comparable basicity to that of triethylamine (p*Ka* = 10.78), yielded isothiocyanates in good yields in shorter reaction times. The attachment of hypervalent iodine to sulfur makes it a much better leaving group and is probably the rate-limiting step in this reaction (*Scheme IV.2*). Further, the NH protons of the alkylamines are expected to become more acidic due to the presence of a C=S moiety leading to facile deprotonation by the base triethylamine.

After successfully synthesizing various isothiocyanates, we focused our attention on the synthesis of cyanamides in one-pot. We observed that isothiocyanate can be obtained from dithiocarbamic acid salt and DIB in the presence of aqueous ammonia without using triethylamine. The *in situ* generated isothiocyanate will react further with ammonia giving alkyl or aryl thiourea, which, on oxidative desulfurization with DIB and ammonia, would form organic cyanamide. All these processess can be performed in one pot. Herein, we report a high yielding 'one-pot' preparation of cyanamides from

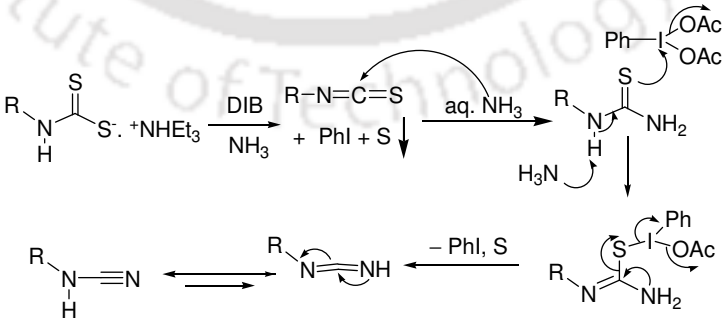
dithiocarbamate salts using the non-metallic, non-toxic, eco-friendly hypervalent iodine(III) reagent (diacetoxyiodo)benzene(DIB).

Various dithiocarbamate salts can be prepared easily in high yields from amines following the literature procedure. When a freshly prepared salt of dithiocarbamate salt (2 equiv.) in acetonitrile (5 mL) was treated with aqueous ammonia (25%) (2 mL) and DIB (2 equiv.) under an ice-cooled conditions, 1-phenylthiourea was obtained in good yield (*Scheme IV.3*).



Scheme IV.3. *Preparation of cyanamide from the dithiocarbamate salt*

When DIB (2 equiv.) was added to this reaction mixture, phenylcyanamide was isolated in 85% yield. A plausible mechanism for the transformation of dithiocarbamic acid salt to cyanamide is shown in *Scheme IV.4*. The mechanism for the formation of isothiocyanate is expected to be similar to the one proposed above for the isothiocyanate formation (*Scheme IV.2*). The *in situ* generated isothiocyanate on reaction with NH_3 would give 1-phenylthiourea. The 1-phenylthiourea on oxidative desulfurization leads to the formation of a carbodiimide type intermediate which is converted to its stable cyanamide analogue (*Scheme IV.4*).



Scheme IV.4. *Proposed mechanism for the formation of cyanamide*

The precipitation of elemental sulfur supports the mechanism proposed. The formation of isothiocyanate has been confirmed by recording the IR spectra of the crude reaction mixture, which shows a strong peak at 2063 cm^{-1} characteristic of isothiocyanate. Further, when isolated 1-phenylthiourea in acetonitrile was treated with DIB in an aqueous ammonia, it gave cyanamide confirming the intermediacy of phenylisothiocyanate and 1-phenylthiourea in the reaction mixture. It may be mentioned here that the reaction of 1-phenylthiourea with DIB in the absence of any base is reported to give 1,2,4-thiadiazole.

Irrespective of the mechanism involved, the success of the method depends on the strong thiophilic nature of the DIB. Employing this one pot strategy, we have successfully prepared a series of cyanamides from both aromatic and aliphatic amines. Aromatic amines containing various electron withdrawing as well as electron donating substituents in the phenyl ring gave corresponding cyanamides in good yields. Benzylic and aliphatic amines gave a satisfactory yield of corresponding cyanamides. The versatility of this method was demonstrated by synthesizing cyanamides containing functional groups such as $–NO_2$, –OH, and –COR. The stability of other functional groups containing substrates such as alkenes and esters was also found to be compatible in the second stage of the reaction giving the product in good yield.

In an attempt to synthesize cyanamide of secondary amines such as pyrrolidine, no traces of cyanamide could be detected; rather, it underwent oxidative dimerization. This is possible because of the inability of the secondary amine to form isothiocyanate, thereby further supporting our mechanism.

In conclusion, hypervalent iodine reagent DIB serves as an efficient desulfurizing agent for the conversion of dithiocarbamic acid salts to isothiocyanates and cyanamides. Organic isothiocyanate and cyanamide in the past were prepared by arduous method involving toxic and expensive reagents. It has been demonstrated here that the reactions can be carried out under mild conditions by using the hypervalent iodine reagent DIB.

CHAPTER V. Hypervalent Iodine(III) Mediated Desulfurization: A Novel Strategy for the Construction of Heterocycles

In this chapter, we have discussed the synthesis of four types of heterocycles *viz.* 2-aminobenzimidazole, aminobenzoxazole, benzoxazine and 1-imidazolidinecarbothioamide (*Figure V.1*) by hypervalent iodine(III) reagent, (diacetoxyiodo)benzene (DIB) mediated desulfurizaton strategy.

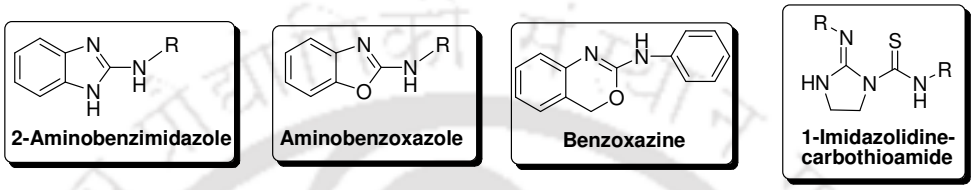
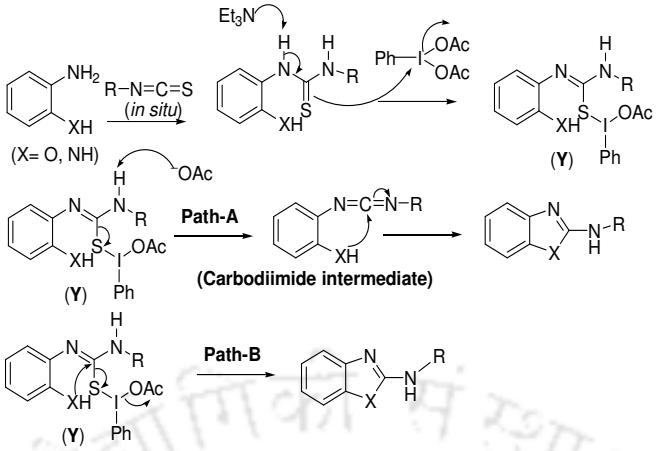


Figure V.1. *Various heterocycles*

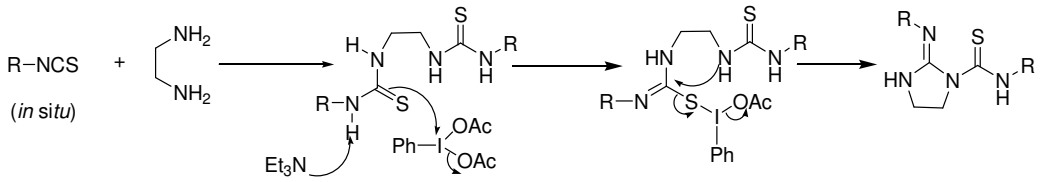
After successfully synthesizing various isothiocyanates using hypervalent iodine(III) reagent DIB, through the desulfurization strategy of dithiocarbamate salt, we focused our attention on the synthesis of 2-aminobenzimidazole. Benzimidazoles are widely used structural motifs in drug discovery and can be found in a number of biologically active molecules. The most commonly adopted method for the synthesis involves the cyclodesulfurization of preformed monothioureas. The reported desulfurization agents include carbodiimides, tosyl chloride, methyl iodide, mercury(II) oxide, mercury(II) chloride, and copper(I) salts. Because isothiocyanate can be generated from a dithiocarbamate salt by using DIB, which also has desulfurization ability, we decided to develop a one-pot procedure for the synthesis of 2-aminobenzimidazole by treating *o*-phenylenediamine with the in situ generated isothiocyanates (*Scheme V.1*). The formation of benzimidazole can be explained through the intermediacy of carbodiimide (path-A) or direct intramolecular cyclization at the immenium carbon (path B) (*Scheme V.1*).



Scheme V.1. *Mechanism for the formation of benzimidazole / benzoxazole*

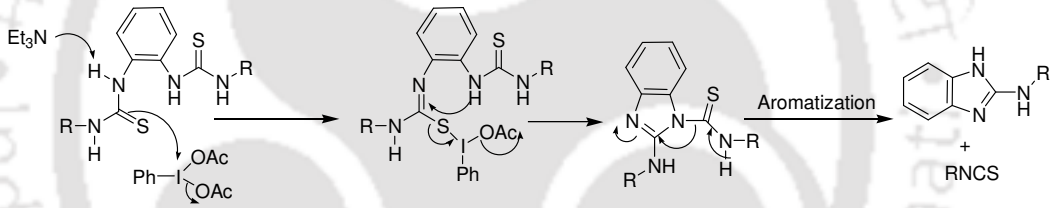
The successful synthesis of benzimidazole prompted us to apply this strategy to the synthesis of aminobenzoxazoles. This class of compounds has great potential as drug candidates, and its use is currently under investigation in the treatment of a wide variety of disorders, such as HIV, neurogeneration, 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, and dicyclohexylcarbodiimide (DCC). The strategy applied for the synthesis of 2-aminobenzimidazole was also applied for the synthesis of aminobenzoxazoles. The *in situ* generated isothiocyanate (*Scheme V.1*) was reacted with *o*-amino phenol to yield the monothiourea. The resultant monothiourea on treatment with another equivalent of DIB produced the desired aminobenzoxazoles. The proposed mechanism is expected to be similar to the one proposed in *Scheme V.1*.

The most interesting aspect of this investigation is the synthesis of 1-imidazolidinecarbothioamides. These compounds are useful as insecticides, particularly for the control of *Epilachna varivestis*. The *in situ* generated isothiocyanate (2 equiv.), when treated with ethylenediamine (1 equiv.), gave bis(thiourea), which, on reaction with DIB, gave an excellent yield of imidazolidinecarbothioamide (*Scheme V.2*). The mechanism for the formation of imidazolidinecarbothioamide is shown in *Scheme V.2*.



SchemeV.2. *Mechanism for the formation of 1-imidazolidinecarbothioamide*

When the flexible ethylenediamine was replaced by a rigid aromatic system such as *o*-phenylenediamine, the reactivity changed completely to give benzimidazole and isothiocyanate instead of imidazolidinecarbothioamide. The driving force for this reaction is the gain in the aromatic character of the product benzimidazole due to loss of isothiocyanate (*Scheme V.3*), which was not observed with aliphatic analogue ethylenediamine bis(thioureas) (*Scheme V.2*).



Scheme V.3. *Reaction of aromatic 1,2-bis(thiourea) with DIB*

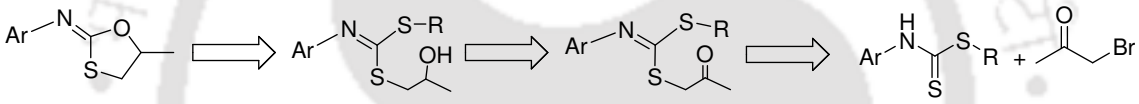
In conclusion we have demonstrated the multifaceted use of (diacetoxyiodo)benzene for various synthetically useful organic transformations. An interesting difference in reactivity was observed for the bis(thioureas) of aliphatic and aromatic 1,2-diamines, the former giving 1-imidazolidinecarbothioamide and the latter benzimidazole and isothiocyanate.

CHAPTER VI. A New Facile Synthetic Method for the Construction of 1,3-Oxathiolan-2-ylidenes

1,3-oxathiolan-2-ylidenes having an exocyclic imine group can be used in organic synthesis for the preparation of biologically active compounds. These heterocycles were

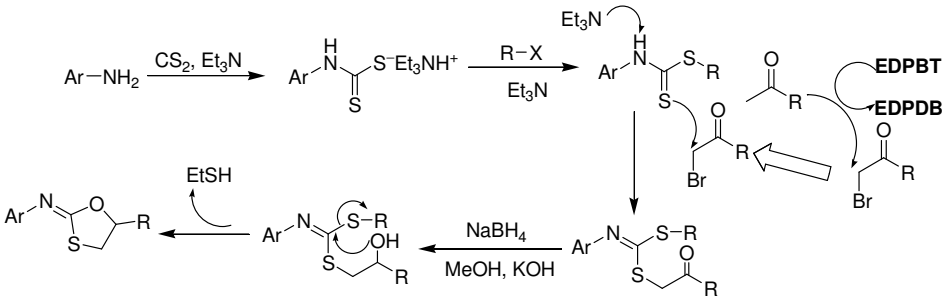
initially prepared by the reaction of alkylthiocyanates or acetyl and benzoyl isothiocyanates with epoxides and subsequently by the 1,3-cycloaddition of heterocumulenes, such as isothiocyanates with oxiranes under various reaction conditions. The drawbacks of the existing strategies are the requirement of expensive and specially designed substrates, reagents and catalysts and elevated temperatures. The use of polar solvents is accompanied by undesirable reactions such as trimerization of the isocyanate.

During the formation of thiazolidine-2-imine, the sulfur atom of the thiourea attacks the bromomethyl carbon of the α-bromoketone. Taking cues from the reactivity of thioureas, the leaving ability of a thiol attached to an imine functionality and the α-brominating ability of ketones using 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) we envisaged a synthetic scheme (*Scheme VI.1*) for the construction of 1,3-oxathiolan-2-ylidenes.



Scheme VI.1. *Synthetic scheme for the construction of 1,3-oxathiolan-2-ylidenes*

As expected the dithiocarbamic acid ester of aniline, (*Scheme VI.2*) reacted with the α-bromoketone formed by the reaction of acetone with EDPBT in the presence of triethylamine to give the adduct containing a carbonyl functionality within 0.5 h at room temperature. Carbonyl group of dithiocarbamate acid ester adduct was reduced selectively using sodium borohydride without affecting the imine functionality. Then the reduced product slowly cyclized to give the 1,3-oxathiolan-2-ylidenes with the liberation of smelly mercaptoethanol at room temperature. However, by performing the reduction of dithiocarbamate acid ester adduct in methanolic KOH, the carbonyl reduction was faster and complete cyclization was achieved by heating the reaction at 60 ^{o}C (*Scheme VI.2*).

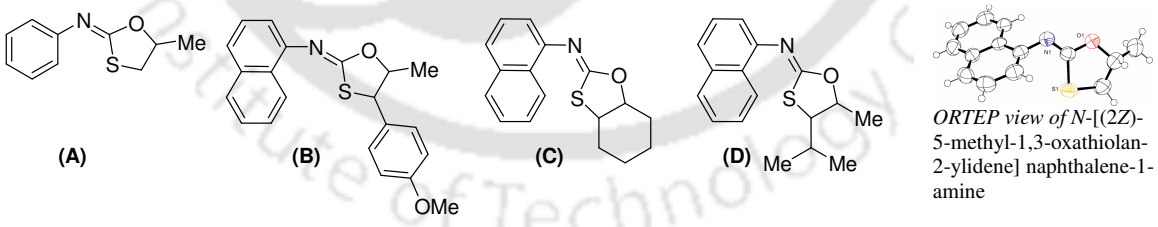


***Scheme VI.2**. Syntheses of 1,3-oxathiolane-2-ylidene*

Similarly, various other 1,3-oxathiolan-2-ylidenes of different dithiocarbamic acid esters were prepared employing this strategy in good yields. The nature of the leaving group was changed from -SEt to -SMe and -SCH_2Ph and the rate of the reaction and yield was found to be similar.

The versatility of this methodology has been demonstrated successfully using ketones other than acetone giving the corresponding 1,3-oxathiolan-2-ylidenes (**A**)-(**D**) (*FigureVI.1*). The presence of the 1,3-oxathiolan-2-ylidene skeleton is shown in the single crystal X-ray structure of *N*-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene] naphthalene-1-amine (*Figure VI.1*).

As bromoketone precursor, when bromoacetone or bromoaetophenone were used, products were obtained as racemic mixtures (**A**) whereas for other bromoketones products (**B**), (**C**) and (D) were obtained as diastereomeric mixtures.



ORTEP view of N-[(2Z)-5-methyl-1,3-oxathiolan-2-ylidene] naphthalene-1-amine

***Figure VI.1.** Various 1,3-oxathiolan-2-ylidenes prepared*

In conclusion, we reported an efficient method for the *S*-alkylation of dithiocarbamic acid esters with α-bromoketones under basic conditions. Subsequently we developed an efficient synthetic method for the construction of 1,3-oxathiolan-2-ylidenes by reduction of the addition product of dithiocarbamic acid esters with α-bromoketones. This method is convenient in terms of simplicity and general applicability.

Contents

Chapter I. Introduction to Hypervalent Iodine Chemistry and Use of Tribromides in Heterocyclic Synthesis **01**

I.1. Elemental Iodine and Organoiodine Compounds 01
I.2. Hypervalent Bonding 02
I.3. Classification and Nomenclature of Hypervalent Iodine Compounds 04
I.4. Preparative Methods for Hypervalent Iodine Reagents 06
I.5. General Reactivity of Hypervalent Iodine Reagents 09
I.6. Various Transformations Mediated by (Diacetoxyiodo)benzene (DIB) 12
I.6.1. Oxidative Functionalization with DIB 12
I.6.2. Reaction of DIB with carbonyl compounds 15
I.6.3. Oxidation of Phenols with DIB 16
I.6.4. Oxidation of Nitrogen Compounds with DIB 18
I.6.5. Oxidation of Sulfur Compounds 20
I.7. Various Transformations Mediated by [Hydroxy(tosyloxy)iodo]benzene 21
I.8.1. Hypervalent Iodine(III) in the Synthesis of Heterocycles and Total Synthesis 22
I.8.2. Future Scope and New Directions of Hypervalent Iodine Reagents 24
I.9. Heterocyclic Synthesis Using Organic Ammonium Tribromides 24
I.9.1. Tribromide Mediated Oxidative Cyclizations 25
I.9.2. Brominative Cyclizations 27
I.10. References 29

Chapter II. Oxidation of Aldoximes to *N*-Acetoxy or *N*-Hydroxy Amides **34**

II.1. Importance and Applications 34
II.2.1. Applications in Organic Synthesis 34
II.2. Available Synthetic Methods 38
II.3. Present Work 42

II.4. Experimental Section 48
II.4.1. Instrumentation and Characterization 48
II.4.2. General Procedures 49
II.5. References 50
II.6. Spectral Data 53
II.7. Selected Spectra 60

Chapter III. Oxidative *N*-Acylation of 1,3-Disubstituted Thioureas to *N*-Acylureas 63

III.1. Importance and Applications 63
III.1.1. Applications in Organic Synthesis 63
III.2. Available Synthetic Methods 65
III.3. Present Work 70
III.3.1. Hypervalent Iodine(III) Mediated Regioselective *N*-Acylation of 1,3-Disubstituted Thioureas 70
III.4. Experimental Section 80
III.4.1. Instrumentation and Characterization 80
III.4.2. General Procedures 80
III.5. References 81
III.6. Spectral Data 83
III.7. Selected Spectra 91

Chapter IV. Desulfurization of Dithiocarbamic Acid Salt with Hypervalent Iodine(III): A Facile One-Pot Access to Isothiocyanate and Cyanamide 94

IV.1. Importance and Applications 94
IV.1.1. Applications in Organic Synthesis 95
IV.2. Available Synthetic Methods 100
IV.3. Present Work 104

IV.4. Experimental Section 111
IV.4.1. Instrumentation and Characterization 111
IV.4.2. General Procedures 111
IV.5. References 112
IV.6. Spectral Data 116
IV.7. Selected Spectra 123

Chapter V. Hypervalent Iodine(III) Mediated Desulfurization: A Novel Strategy for the Construction of Heterocycles 126

V.1. Importance and Applications 126
V.2. Available Synthetic Methods 127
V.3. Present Work 130
V.4. Experimental Section 138
V.6.1. Instrumentation and Characterization 138
V.6.2. General Procedures 138
V.5. References 140
V.6. Spectral Data 143
V.7. Selected Spectra 152

Chapter VI. A New Facile Synthetic Method for the Construction of 1,3-Oxathiolan-2-ylidenes 155

VI.1. Importance and Applications 155
VI.2. Available Synthetic Methods 155
VI.3. Present Work 158
VI.4. Experimental Section 164
V.4.1. Instrumentation and Characterization 164
V.4.2. General Procedures 164
VI.5. References 165
VI.6. Spectral Data 167
VI.7. Selected Spectra 176

CHAPTER I

I. Introduction to Hypervalent Iodine Chemistry and Use of Tribromides in Heterocyclic Synthesis

I.1. Elemental Iodine and Organoiodine Compounds

Iodine, having atomic number 53, atomic weight 126.90, which comes in the 5th period, under Group VIIA, is a halogen element of the periodic table. Iodine was first extracted by a French industrial chemist Bernard Courtois in 1811 from the ash of a sea wood and it was subsequently named by J. L. Gay Lussac in 1813. The name **Iodine** is derived from the Greek word *"iodes"* meaning 'violet-colour' reflecting the characteristic lustrous, deep purple color of a resublimed crystalline iodine and also the color of its vapor. Elemental iodine is soluble in chloroform and carbon tetrachloride. Naturally, iodine occurs in seawater and soil as a dissolved iodide ion and other iodine derivatives.[1a] Iodine is commercially produced from the caliche, found in Chile and the iodine containing brines of natural gas and oil fields, especially in Japan and in the United States. Chile (59%) and Japan (32%) are the world's chief producers of iodine.

Iodine is an essential trace element for life. It is well-known that potassium iodide was used as a remedy for goiter, an enlargement of the thyroid gland, as early as 1819. The thyroid is responsible for the production of thyroxine (*Figure I.1.1*), a metabolism-regulating hormone. Elemental iodine is used as a disinfectant in various forms such as Tincture of iodine which is an alcoholic solution of iodine and potassium iodide. Iodine is a very common general stain used in thin-layer chromatography (TLC).

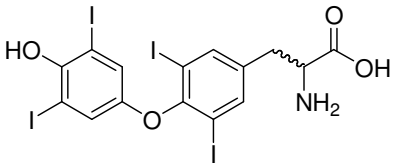


Figure I.1.1.

In organic synthesis, the organoiodine compounds are important intermediates, because of the easy formation and cleavage of the C-I bond (the bond dissociation energy, of a typical C-I bond being about 55 kcal/mol). So, these compounds have been used in some classical reactions such as Hofmann's alkylation of amines, the Williamson ether synthesis, and the Wurtz coupling reactions since early 1800s.[1b] Some industrially significant organoiodine compounds, often used as disinfectants or pesticides, are iodoform (CHI_3), methylene iodide (CH_2I_2), and methyl iodide (CH_3I).

I.2. Hypervalent Bonding

According to Lewis-Langmuir's theory, compounds should have either 2, 8, or 18 electrons in their valence shell. So, hypervalent compounds are those which contain a main group element with more than an octet of electrons in its valence shell.[2a] As iodine is the largest, most polarizable, and most electropositive member in the halogen family, it can extend its valency more than eight to form a series of stable polycoordinate, multivalent compounds. All these "polycoordinated iodine compounds" are now familiarly term as "hypervalent iodine compounds".

Although, the bonding characteristic of trihalide and pentaiodide anion was described by Pimentel[2b] and Rundle[2c] respectively in early 1951, these compounds were first described as hypervalent by Musher[2d] in 1969 and later were employed on hypervalent halogen and sulfur compounds by Martin[2e] in 1983.

In the hypervalent model, the participation of *d*-orbital is not considered in bonding purpose and that is the main difference from transition metal complexes in which *d*-orbital hybridization is considered to describe the bonding beyond the stable octet. Here, only non-hybridized *5p* orbitals of iodine are involved in bonding. The general feature of these compounds is described by the polarized linear three-center-four-electron (*3c-4e*) bond, in which the central atom bears a distinct positive charge and two electronegative monovalent ligands share the corresponding negative charge. Such 'hypervalent' bonds are weaker and have longer bond length than normal covalent bonds.

There are two types of hypervalent iodine compounds, IL_3 (I = iodine, L = ligands attached to iodine) or iodane and IL_5 or periodane. In the IL_3 type iodanes, the less

electronegative group- usually a phenyl ring is bound to iodine by a normal covalent bond, lying in the equatorial position of a trigonal bipyramid. The other two electronegative ligands are at axial positions, attached, one to each lobe, to one doubly occupied 5p orbital of iodine. This arrangement results in a linear three-centre four-electron (*3c-4e*) bond system. In this way, a single orbital of iodine participates to two *3c-4e* bonds, called usually hypervalent which are longer and weaker than the covalent bond. Molecules of this kind are T-shaped; the electronic formula for a typical member, (dichloroiodo)benzene, is depicted in *Fig. 1.2.1.*

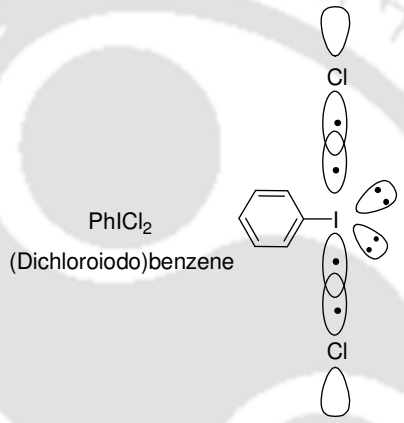


Figure I.2.1.

This concept of hypervalent bonding was later theoretically studied by Kutzelnigg[2f] in 1984 and Reed[2g] in 1990. A simplified hypervalent apical bond model of IF_3 is shown in *Figure I.2.2.*[2d]

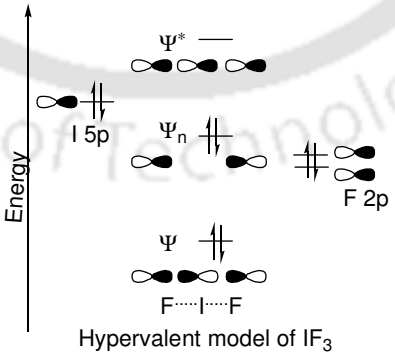


Figure I.2.2.

A 5p orbital of iodine overlaps with a 2p orbital of each fluorine to give a bonding orbital (ψ), a nonbonding orbital (ψ^n), and an antibonding orbital (ψ*) (*Figure I.2.2*). In the HOMO, the electron density is localized on the fluorine atoms so that central iodine atom bears a distinct positive charge.

I.3. Classification and Nomenclature of Hypervalent Iodine Compounds

There are three most acceptable methods to classify the hypervalent iodine compounds- on the basis of valency of the ligands, the λ- method and N-X-L method.

Depending on the valency of the ligand, hypervalent iodine compounds may be classified in to two categories. In the first category compounds such as RIX_2 or RIX_4 [where X is an electronegative ligand (atom or group)], where the ligands used are monovalent in nature and form one or two linear three centre-four electron (*3c-4e*) X-I-X bonds. In the second category of compounds such as RIZ or $RIZX_2$ or RIZ_2 the central iodine atom is bound with bivalent ligands (Z) forming "double" bonds which are actually polar two centre-four electron (*2c-4e*) bonds denoted as RI^+-Z^- [where Z is oxygen or an organic electronegative group linked to iodine with carbon or nitrogen].

According to IUPAC designation, a non-standard bond is denoted as λ notation and on the other hand hydrogen iodide (HI) is widely known as iodane. Thus, H_3I is denoted as λ^3-iodane and H_5I as λ^5-iodane. So, the most common hypervalent iodine reagents $ArIL_2$, represented as aryl-λ^3-iodane (L = heteroatom) and $ArIL_4$ as aryl-λ^5-iodane.

Martin-Arduengo N-X-L designation,[3] (*Figure I.3.1.),* which consider the number of valence electrons (N) surrounding the central atom (X), the number of ligands (L) and their chemical nature, in the classification of various polyvalent iodine species is very important for organic chemistry.

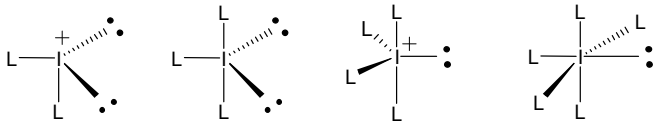
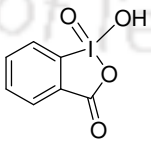
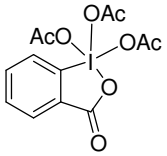


Figure I.3.1.

There are four structural types of polyvalent iodine species (**1-4**) (*Figure I.3.1.),* among which the first two species, 8-I-2 (**1**) and 10-I-3 (**2**), called iodanes, are conventionally considered as derivatives of trivalent iodine, and the last two, 10-I-4 (**3**) and 12-I-5 (**4**) periodanes, represent the most common structural types of pentavalent iodine. The most important classes of hypervalent iodine and some of their parent members are shown in *Table I.3.1.*

Table I.3.1. *Hypervalent iodine compounds*

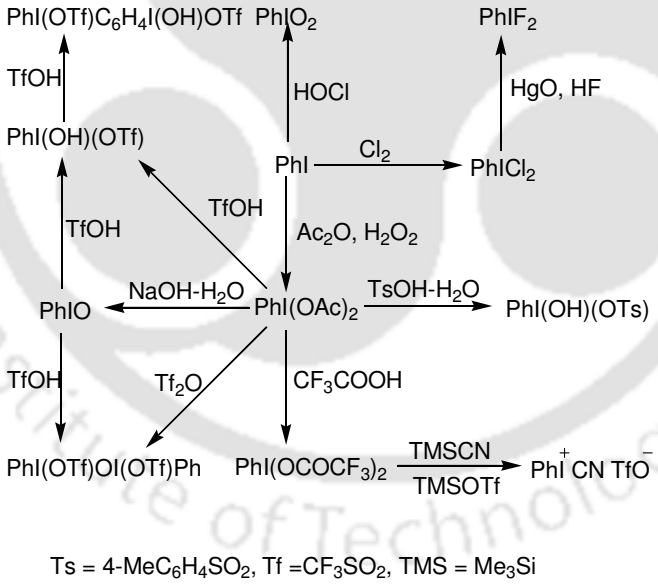
N-X-L	Example	Common name
10-I-3	$PhICl_2$	(Dichloroiodo)benzene
10-I-3	$PhI(OAc)_2$	(Diacetoxyoiodo)benzene
10-I-3	$PhI(OCOCF_3)_2$	[Bis(trifluoroacetoxy)iodo]benzene
10-I-3	PhI(OH)(OTs)	[Hidroxy(tosyloxy)iodo]benzene
8-I-2	Ph_2I^+	Diphenyliodonium
8-I-2	PhI^+Rf	Perfluoroalkyl phenyliodonium
8-I-2	$PhI^+CH{=}CH_2$	Alkenyl phenyliodonium
8-I-2	$Ph{-}I^+{-}C{\equiv}CH$	Alkenyl phenyliodonium
10-I-2	PhI=O	Iodosylbenzene
10-I-2	PhI=CXY	Phenyliodonium methylides
10-I-2	$PhI{=}NSO_2Ph$	(Phenylsulfonyliminoiodo)benzene
12-I-3	$PhIO_2$	Iodylbenzene
12-I-4		2-Iodoxy-benzoic acid (IBX)
12-I-5		Dess-Martin reagent

I.4. Preparative Methods for Hypervalent Iodine Reagents

German chemist Willgerodt introduced the first member, $PhICl_2$ a λ^3-iodane in hypervalent iodine chemistry in the year 1886.[4a] Subsequently, a number of hypervalent iodine compounds such as $PhI(OAc)_2$[4b] and the first iodonium salt,[4c] $Ar_2I^+HSO_4^-$, were prepared. Within the first report on polyvalent organoiodine species in 1914 by Willgerodt,[4d] there were nearly 500 hypervalent iodine compounds known.

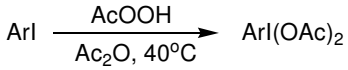
Most hypervalent iodine reagents can be prepared from readily available iodobenzene (PhI) and for ring substituted hypervalent iodine analogues; 2-iodobenzoic acid is the starting material. The *Scheme I.4.1* illustrates the main preparative approaches for iodobenzene derivatives. Preparation of some of them, such as $PhICl_2$, PhIO, $PhIO_2$, and $PhI(OAc)_2$ has appeared in the *Organic Syntheses* volumes. Interconversions among them occur readily and in several instances they offer improved procedures (*Scheme I.4.1*).

An exhaustive presentation of preparative ways for many individual compounds appeared in 1992 and 1997.[4e,f]



Scheme I.4.1.

Generally, two approaches are used for the preparation of [bis(acyloxy)iodo]arenes: (i) the oxidation of iodoarenes in the presence of a carboxylic acid and (ii) a ligand exchange reaction of the readily available DIB with suitable carboxylic acids.



Scheme I.4.2.

The most familiar and practically important representative of [bis(acyloxy)iodo]arenes, DIB, is usually prepared by the oxidation of iodobenzene with peracetic acid in acetic acid (*Scheme I.4.2*).[5a] This method is highly preferable; but it requires great care in maintaining temperature at exactly 40 °C. At a lower temperature, the reaction fails completely whereas at a higher temperature, overoxidation occurs. For the preparation of other varieties of [bis(acyloxy)iodo]arenes, different peracid oxidation of substituted iodobenzenes can be used.

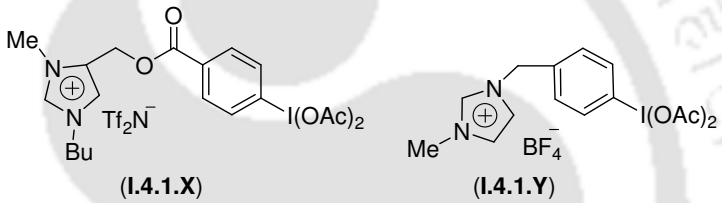
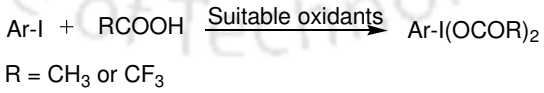


Figure I.4.1.

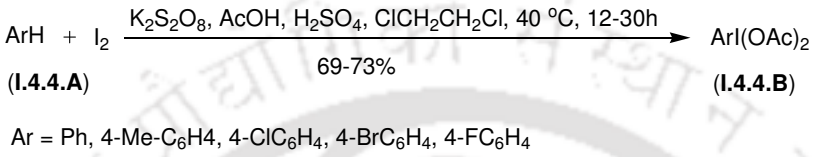
In particular, the polymer-supported analogues of DIB have been prepared by the treatment of poly(iodostyrene) or aminomethylated poly(iodostyrene) with peracetic acid.[5b-e] On the other hand, the ion-supported [bis(acyloxy) iodo]arenes, imidazolium derivatives (**I.4.1.X**) and (**I.4.1.Y**), (*Figure I.4.1*), have been prepared by the peracetic oxidation of the appropriate aryliodides.[5f,g]



Scheme I.4.3.

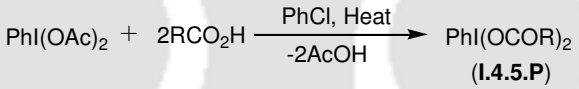
In a modified method (*Scheme I.4.3*), the oxidative diacetoxylation of iodoarenes in acetic or trifluoroacetic acid, in presence of suitable oxidants such as periodates,[6a-c] sodium percarbonate,[6d] *m*-chloroperoxybenzoic acid,[6e-i] potassium peroxodisulfate,[6j,k] H_2O_2-urea,[6l]

Selectfluor,[6m] and sodium perborate,[6n-p] are used. The oxidation of iodoarenes with sodium perborate in acetic acid at 40°C is the most simple and general procedure that has been used for a small scale preparation of numerous (diacetoxyiodo)-substituted arenes and heteroarenes.[7] This method can be improved by performing the perborate oxidation in the presence of trifluoromethanesulfonic acid.[7a]



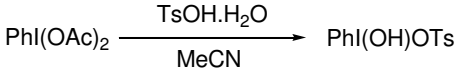
Scheme I.4.4.

An advance modification of this approach employs the interaction of arenes (**I.4.4.A**) with iodine and potassium peroxodisulfate in acetic acid (*Scheme I.4.4*).[7b] The mechanism of this reaction probably includes the oxidative iodination of arenes, followed by diacetoxylation of ArI *in situ*, leading to (diacetoxyiodo)arenas (**I.4.4.B**).



Scheme I.4.5.

The second general approach to [bis(acyloxy)iodo]arenes is based on the ligand exchange reaction of a (diacetoxyiodo) arene (usually DIB) with an appropriate carboxylic acid. A typical procedure consists of heating DIB with a nonvolatile carboxylic acid RCO_2H in the presence of a high boiling solvent, such as chlorobenzene (*Scheme I.4.5*).[8]



Scheme I.4.6.

The standard method for the preparation of [hydroxy(tosyloxy)iodo]benzene (HTIB) or Koser's Reagent is the reaction of (diacetoxyiodo)benzene (DIB) with *p*-toluenesulphonic acid hydrate (*Scheme I.4.6*) was first reported in 1970 by Neiland and Karele.[9a] Wirth *et.al.* described solvent-free reactions for the synthesis of Koser's Reagent and their use in solid-state reactions with improved yields and higher purities of the products.[9b]

I.5. General Reactivity of Hypervalent Iodine Reagents

All hypervalent iodine reagents are solids-amorphous or crystalline-colorless and odorless. They are fairly stable at room temperature and insensitive to atmospheric oxygen and moisture. The usual precaution required upon storage is simply light-protection and sometimes refrigeration.

For several decades, iodanes were more of chemical curiosities with no synthetic utility. However, the situation has changed and presently, many individual compounds as well as number of classes have proven to be promising new valuable reagents in organic synthesis; among them are several heterocycles, the chemistry of which is often of special interest. There are several books[4f,10] and review articles[10] for detailed discussions. A book by Varvoglis deals also specifically with synthetic applications.[11] Since the early 1980s, interest in hypervalent iodine compounds has experienced a renaissance. The upsurge in the use of hypervalent iodine reagent in recent years is due to the several reasons such as– (i) chemical properties and reactivity is similar to the heavy metal reagents such as Hg(II), Tl(III), Pb(IV) but without the toxicity and environmental issues; (ii) similarities (reductive elimination, ligand exchange, etc.) between organic transition metal complexes and polyvalent main group compounds such as organoiodine species; (iii) mild reaction condition and easy handling of hypervalent iodine compounds; (iv) commercial availability of key precursor such as $PhI(OAc)_2$; (v) the timely publication of a number of key reviews and surveys in the early 1980s.

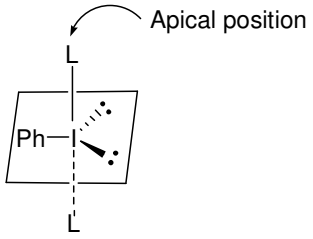
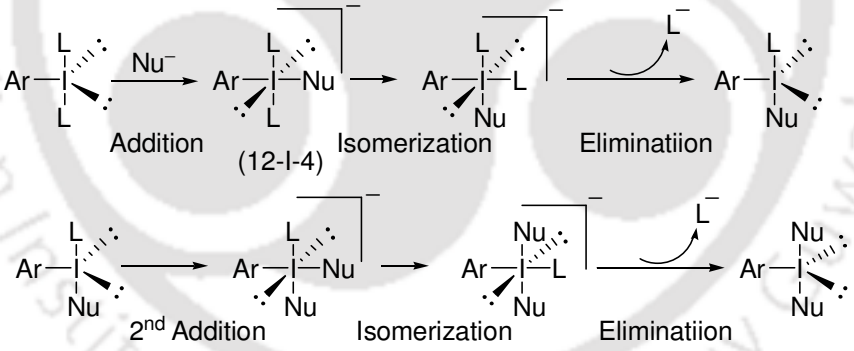


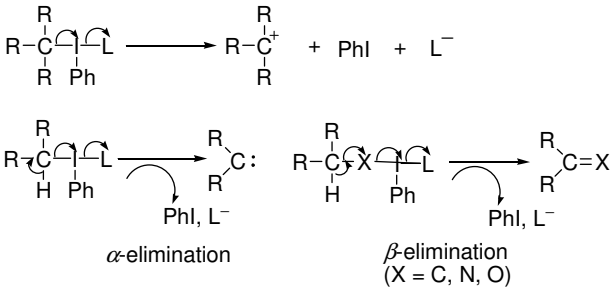
Figure I.5.1.

The stability and reactivity of hypervalent iodine compounds exhibit a greater dependence on the character of hypervalent bonds in the apical position (*Figure I.5.1*). The hypervalent bonds in the apical position are easily cleaved, and the cleavage causes trivalent iodine with 10 electrons to be reduced to monovalent iodine of a more stable octet structure. For this reason it exhibits good elimination and oxidation rates and finds application in organic synthesis.[12]



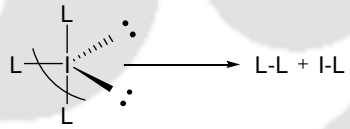
Scheme I.5.1.

Hypervalent iodine compounds participate in three main types of reaction: *ligand exchange*, *reductive elimination*, and *ligand coupling*. Ligand exchange of λ^3-iodanes is believed to occur by an associative pathway in which a nucleophile first adds to the electrophilic iodine centre, followed by isomerization and elimination, as shown in *Scheme I.5.1*.[13]



Scheme I.5.2.

Most important mode of reactions of hypervalent λ^3-iodanes is their reductive transformation to univalent iodide. This process is very facile and energetically favorable, and often proceeds without the assistance of the added reagent. Aryl-λ^3-iodanes are called as *hypernucleofuges,* because of their high dissociation rates when compared to leaving groups such as triflate. In the dissociation process of aryl-λ^3-iodanes, the iodane is eliminated from the substrate with concomitant reduction to univalent iodine, as shown in *Scheme I.5.2*. This process is called *reductive elimination*. Reductive elimination can yield carbocations, carbenes (α-elimination) or unsaturated bond (β-elimination).



L: Carbon and heteroatom ligands

Scheme I.5.3.

The term ligand coupling is introduced by Oae to describe an intramolecular coupling of two ligands bonded to a hypervalent atom, as shown in *Scheme I.5.3*.[14] The mechanism of ligand coupling in hypervalent iodine compounds currently is not well understood.

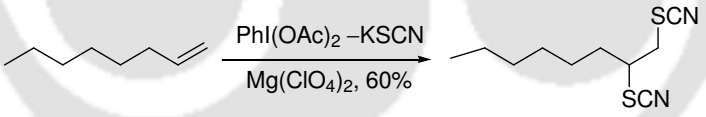
I.6. Various Transformations Mediated by (Diacetoxyiodo)benzene (DIB)

[Bis(acyloxy)iodo]arenes, $ArI(O_2CR)_2$, are practically useful derivatives of iodine(III) that have been used since 1939 in acetoxylations of ethylenic double bonds.[15] (Diacetoxyiodo)benzene, commonly abbreviated as DIB, PID (phenyliodo diacetate), PIDA (phenyliodine diacetate), IBD, or IBDA (iodosobenzene diacetate), is commercially available and extensively used oxidizing reagents. In our entire discussion, we shall use the most widely used abbreviations DIB, originally suggested by Varvoglis.[10a] Besides oxidations, DIB, is useful in other transformations such as α-functionalization of carbonyl compounds, carbon-carbon bond forming reactions, rearrangements, cyclizations etc.

I.6.1. Oxidative Functionalization with DIB

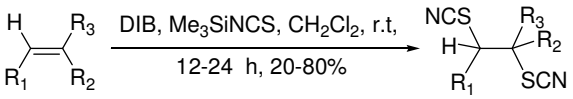
I.6.1.1. Thiocyanation

Thiocyanation of electron-rich olefins by $PhI(OAc)_2$ and KSCN in acetonitrile, *via* a radical process resulted in the formation of 1:1 mixtures of *cis*-and *trans*-adducts.[16a]



Scheme I.6.1.1.1.

Olefins such as 1-octene and cyclohexene gave no reaction; however, in the presence of $Mg(ClO_4)_2$ or the stable free radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), good yields of the appropriate adducts were obtained (*Scheme I.6.1.1.1*).



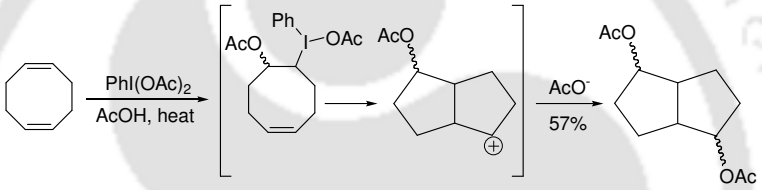
R_1, R_2 and R_3 = H, alkyl, aryl, cycloalkyl, etc.

Scheme I.6.1.1.2.

In a similar reaction, DIB was mixed with trimethylsilyl isothiocyanate and alkenes in dichloromethane to afford 1,2-dithiocyanates in modest yields (*Scheme I.6.1.1.2*). Cyclic alkenes, such as cyclohexene and 1-methylcyclohexene, react with this combined reagent system stereoselectively with the formation of the respective *trans*-adduct.[16b,c]

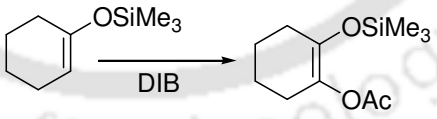
I.6.1.2. Acetoxylation with DIB

Moriarty *et. al.* described the preparative method of 2,6-diacetoxybicyclo[3.3.0]octane through acetoxylation followed by an intramolecular cyclization of 1,5-cyclooctadiene (*Scheme I.6.1.2.1*).[17]



Scheme I.6.1.2.1.

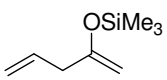
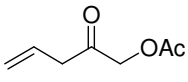
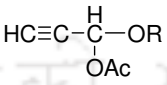
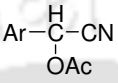
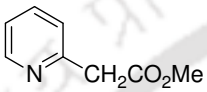
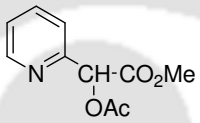
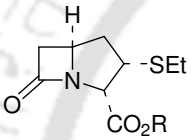
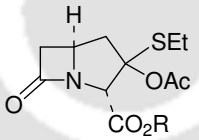
Various ketones, such as acetophenones, aliphatic and cyclic ketones were acetoxylated by DIB in acetic acid-acetic anhydride mixture, in the presence of sulphuric acid, in their α–position, while β–diketones were acetoxylated at the methylene carbon.



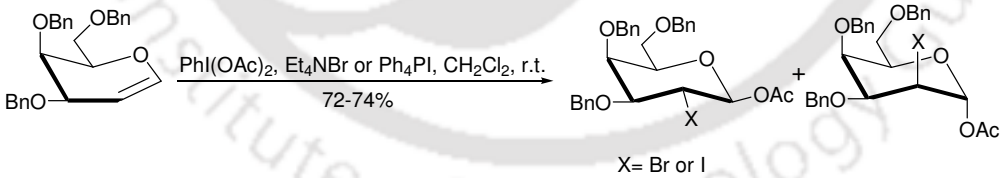
Scheme I.6.1.2.2.

The reactive trimethylsilyl ethers reacted with DIB at room temperature, with retention of their silyl group; the products came either from substitution of the vinylic hydrogen or from bis acetoxylation of the double bond (*Scheme I.6.1.2.2*).[18a] Some acetoxylations of various substrates using DIB are listed in *Table I.6.1.2.1.*[18a-f]

Table I.6.1.2.1. *Acetoxylations of various substrates*

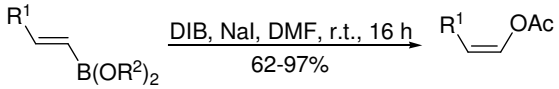
Substrate	Product	Yield (%)	Reference[18a-f]
		78	(18a)
p-$ClC_6H_4COCH_3$	*p*-$ClC_6H_4COCH_2OAc$	56	(18b)
$H_2C{=}C{=}CHOR$		63-68	(18c)
$ArCH_2CN$		79-87	(18d)
		90	(18e)
		60	(18f)

Kirschning and co-workers developed a mild method for the stereoselective bromoacetoxylation or iodoacetoxylation of alkenes by the reaction with DIB in the presence of the appropriate tetraalkylammonium or tetraphenylphosphonium salts.[19a,b]



Scheme I.6.1.2.3.

This method, for example, can be applied to the synthesis of R-glycosyl acetates from carbohydrate derived enol ether (*Scheme I.6.1.2.3*). The actual reacting electrophilic species in these reactions are the *in situ* generated diacetylhalogen(I) anions, $(AcO)_2I^-$ and $(AcO)_2Br^-$.



R^1 = Bu, *t*-Bu, Ph, C_6H_{13}, $MeCO(CH_2)_2$, $NC(CH_2)_2$; R^2 = H, *i* -Pr

Scheme I.6.1.2.4.

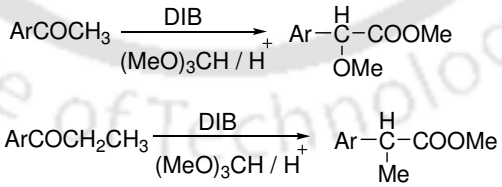
Masuda and co-workers reported the preparation of enol acetates starting from alkenylboronates when treated with DIB in the presence of sodium iodide (*Scheme I.6.1.2.4*). (*Z*)-Alkenylboronates under these conditions give stereochemically pure (*E*)-enol acetates in reasonable yields.[19c]

I.6.2. Reaction of DIB with Carbonyl Compounds

Carbonyl compounds undergo a variety of transformations with DIB in combination with alkali and methanol or trimethyl orthoformate. For these reactions, the outcome depends on the nature of the substrates. These are discussed below.

I.6.2.1. Reaction of Ketones with DIB in Acidic Medium

Acetophenones react with DIB in methanol-sulphuric acid affording a mixture of α-methoxyacetophenones (minor products) and rearranged esters.



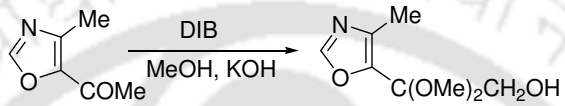
Scheme I.6.2.1.1.

A change in solvent from methanol to trimethyl orthoformate combined with the use of two equivalents of DIB resulted in an efficient double transformation to rearranged

methyl α-methoxyarylacetates (*Scheme I.6.2.1.1*).[20a] When the system was changed from acetophenones to propiophenones, the behaviour was different (*Scheme I.6.2.1.1*).[20b]

I.6.2.2. Reaction of Ketones with DIB in Methanolic KOH Medium

Enolizable ketones were converted directly into their α-hydroxy dimethyl acetals upon reaction with DIB and methanolic potassium hydroxide at room temperature.[21a-d]



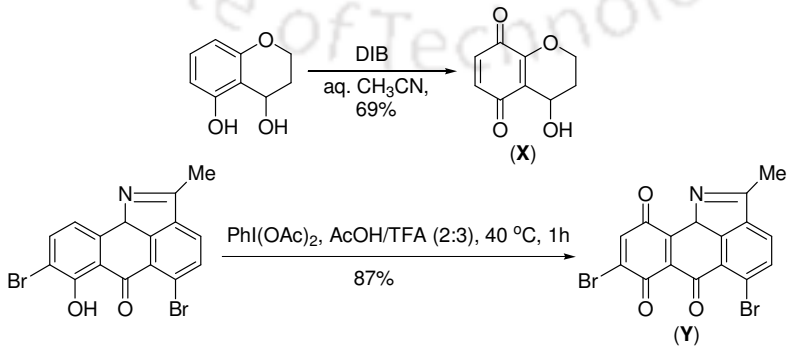
Scheme I.6.2.2.1.

This conversion for an acetyl-oxazole served for the preparation of pyrimidine derivatives (*Scheme I.6.2.2.1*).[21e]

I.6.3. Oxidation of Phenols with DIB

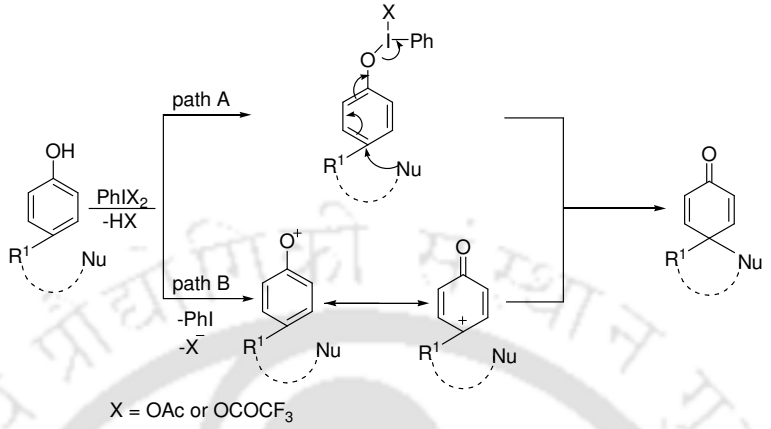
The oxidation of phenolic compounds with hypervalent iodine reagents may result mainly dehydrogenation and oxygenation, but also oxidative addition with carbon-carbon or carbon-oxygen bond formation inter- or intramolecularly.

Several complexes of phenols were converted by DIB into *p*-benzoquinones (**X**) (*Scheme I.6.3.1*).[22a]



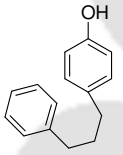
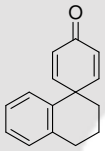
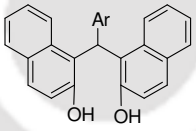
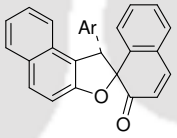
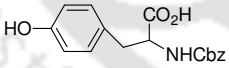
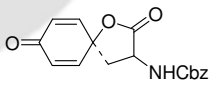
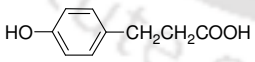
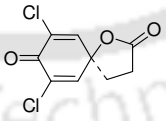
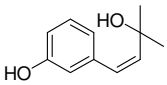
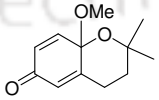
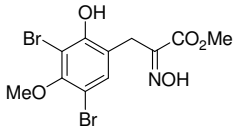
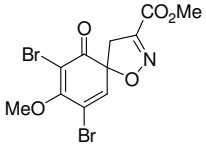
Scheme I.6.3.1.

The oxidation of phenol with DIB was recently used for the preparation of key intermediates in the synthesis of a novel class of antitumor agents (**Y**) (*Scheme I.6.3.1*).[22b]



Scheme I.6.3.2.

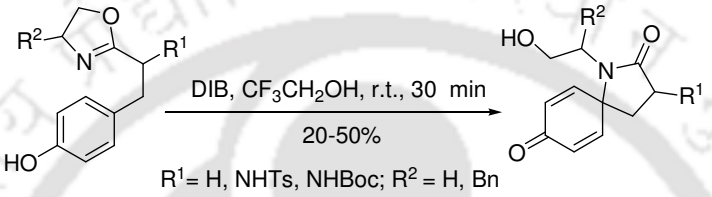
Table I.6.3.1. *Oxidation of phenols*[24a-f]

Substrate	Product	Yield (%)	Reference[24a-f]
		30	(24a)
		80	(24b)
		68	(24c)
		49[x]	(24d)
		95[y]	(24e)
		70	(24f)

x = with three equivalent of DIB, in the presence of NaCl, y = in methanol

The oxidation of *p*-substituted phenols in the presence of an appropriate external or internal nucleophile (Nu) leading to the respective spiro dienones, providing a powerful tool for the construction of various practically important polycyclic systems (*Scheme I.6.3.2*).

It is believed that this reaction proceeds via a concerted addition-elimination in the intermediate product or via a phenoxenium ion (*Scheme I.6.3.2*).[23] Some examples of DIB-induced intramolecular cyclization of phenolic compounds are tabulated above (*Table I.6.3.1).*[24]

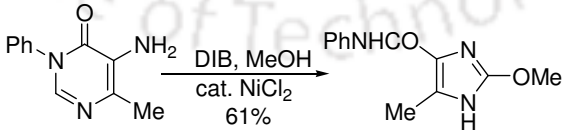


Scheme I.6.3.3.

The oxidative spirocyclizaton of phenolic substrates containing an internal nitrogen nucleophile provides a useful tool for the construction of nitrogen heterocycles. Ciufolini and co-workers reported the oxidative cyclization of phenolic oxazolines affording synthetically useful spirolactams (*Scheme I.6.3.3*).[25]

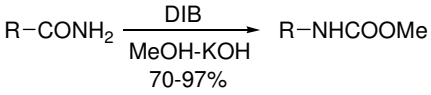
I.6.4. Oxidation of Nitrogen Compounds with DIB

Majority of the nitrogen-containing organic compounds are prone to oxidation on reaction with DIB through *N-H* dehydrogenations.



Scheme I.6.4.1.

Matsuura and co-workers reported an unexpected rearrangement of 1-phenyl-4-methyl-5-aminopyrimidinone to an imidazole derivative with DIB in the presence of catalytic amounts of nickel dichloride (*Scheme I.6.4.1*).[26a]

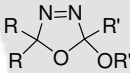
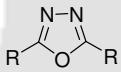
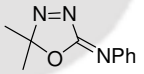
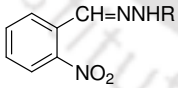
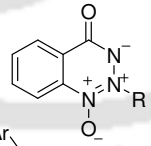
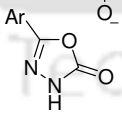
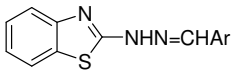
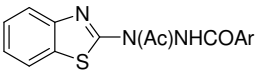
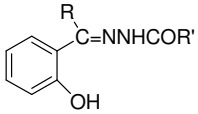
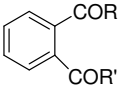
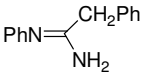
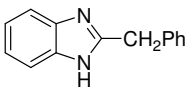


Scheme I.6.4.2.

Moriarty *et. al.* demonstrated the preparation of methyl carbamates in good to excellent yields by treating primary alkyl-and arylcarboxamides with DIB in KOH-MeOH at 5-10 ^{o}C temperature (*Scheme I.6.4.2*).[26b]

DIB mediated oxidation of nitrogen-containing derivatives of carbonyl compounds is very facile. Under the proper conditions, a great diversity of substrates afforded different types of products, as illustrated in *Table I.6.4.1.*

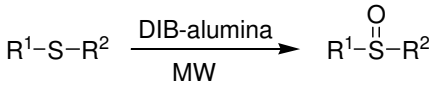
Table I.6.4.1. *Transformations of N-containing derivatives of carbonyl compounds mediated by DIB*[27]

Substrate	Product	Yield (%)	Reference[27a-l]
R_2C=NOH	R_2C=O	60-85	(27a)
R_2C=NNH_2	R_2CN_2	80	(27b)
R_2C=NNHTs	R_2C=O	87-93	(27c)
R_2C=NNH$CONH_2$	R_2C=O	70-82	(27d)
ArCH=NN=CHAr	$ArCH(OR)_2$	50-95	(27e)
R_2C=NNHCOR'		73-99[x]	(27f)
RCH=NNHCOR		48-70	(27g)
Me_2C=NNHCONHCOPh		93	(27g)
		75-82	(27h)
ArCH=NNHCO_2Bu^t		47-67	(27i)
		65-86	(27j)
		60-97	(27k)
		82	(27l)

X = In alcohol (R''OH)

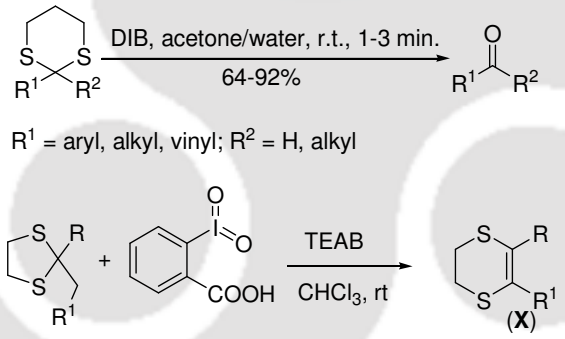
I.6.5. Oxidation of Sulfur Compounds

For the oxidation of various organosulfur compounds, the reagents, [bis(acyloxy)iodo]arenes (DIB) have been extensively used.



Scheme I.6.5.1.

Varma *et. al.* described the selective oxidation of organic sulfides to sulfoxides by the alumina supported DIB reagent system (*Scheme I.6.5.1*).[28a] Poly-[styrene(iodosodiacetate)] mediated oxidation of organic sulfides to a mixture of sulfoxides and sulfones is also reported.[28b-d]

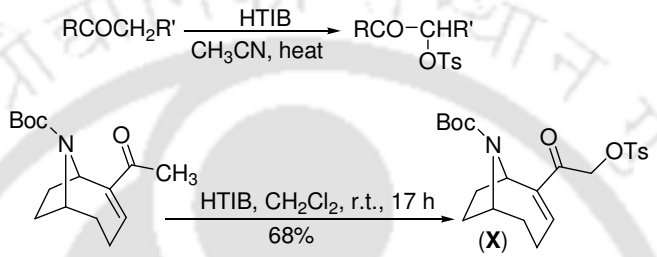


Scheme I.6.5.2.

The oxidation of dithianes with DIB leads to the formation of carbonyl compounds (*Scheme I.6.5.2*). This reaction is synthetically useful for the removal of the dithiane protecting group from aldehydes and ketones[28e] Akamanchi *et. al.* have developed a new method for the ring expansion of 1,3-dithiolanes and 1,3-dithines to dihydro-1,4-dithins (**X**, *Scheme I.6.5.2*) and dihydro-1,4-dithiepines respectively, using hypervalent iodine reagent *o*-iodoxybenzoic acid (IBX) in combination with tetraethylammonium bromide (TEAB) *Scheme I.6.5.2.*[28f]

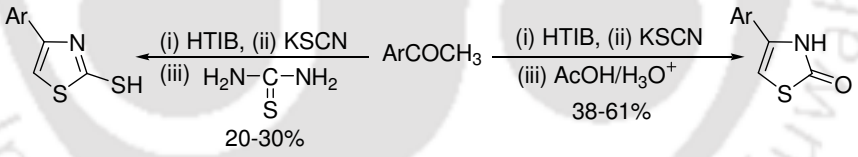
I.7. Various Transformations Mediated by [Hydroxy(tosyloxy)iodo] benzene (HTIB)

[Hydroxy(tosyloxy)iodo]benzene, PhI(OH)OTs (abbreviated as HTIB), is also known as Koser's reagent. The most typical reaction of HTIB is the functionalization of carbonyl compounds at α-carbon.[29] Koser *et. al.* reported the α-tosyloxylations of enolizable ketones and related keto compounds by HTIB (*Scheme I.7.1*).[30a]



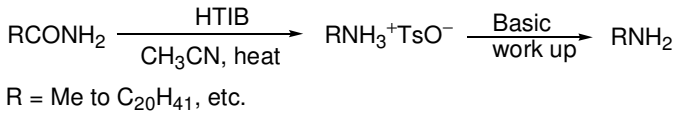
Scheme I.7.1.

HTIB has been used recently for the functionalization of the azabicyclic alkaloid anatoxin-a, a potent nicotinic antagonists (**X**) (*Scheme I.7.1*).[30b]



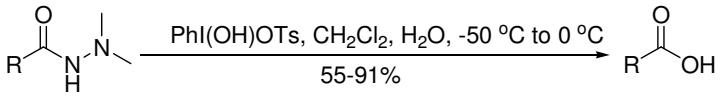
Scheme I.7.2.

Several heterocyclic systems in *one-pot* have been synthesized by the α-tosyloxylations method (*Scheme I.7.2*).[10c,31]



Scheme I.7.3.

Koser *et. al.* described a Hofmann-type preparation of amines for long-chain aliphatic amides which are unsuccessful under the normal Hofmann conditions (*Scheme I.7.3*).[32a]



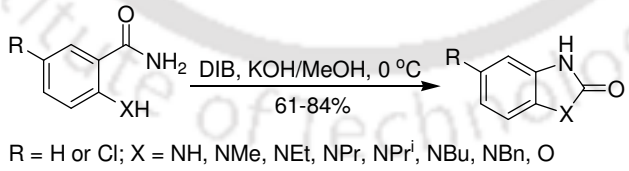
Scheme I.7.4.

Wuts and his co-workers demonstrated the cleavage of *N*,*N*-dimethylhydrazides to the corresponding acids by using HTIB in water or aqueous dichloromethane (*Scheme I.7.4*).[32b]

I.8.1. Hypervalent Iodine(III) in the Synthesis of Heterocycles and Total Synthesis

Synthesis of various heterocyclic systems is one of the most important achievements in hypervalent iodine mediated oxidation reactions.[10c] Syntheses of some heterocyclic compounds have already been discussed in the previous sections (*I.6.3*, *I.6.4*, *I.6.5*, *I.7*). Here, we will discuss the preparation of some nitrogen containing heterocycles.

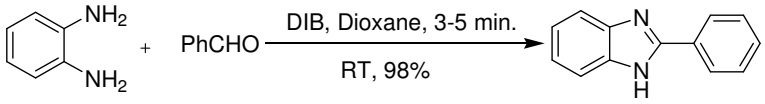
Moriarty *et. al.* developed Hofmann-type degradation and oxidative rearrangement of anthranilamides or salicylamides to the respective heterocycles (*Scheme I.8.1*).[33a]



Scheme I.8.1.1.

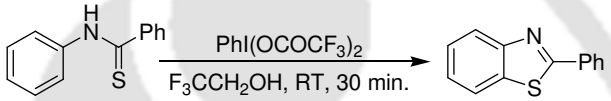
Du and his co-workers demonstrated the preparation of various 2-arylbenzimidazoles from phenylenediamines and aldehydes via a one-step process using hypervalent iodine(III) reagent DIB as the oxidant (*Scheme I.8.1.2*). The salient features of

the reported method include mild conditions, short reaction times, high yields, and operational simplicity.[33b]



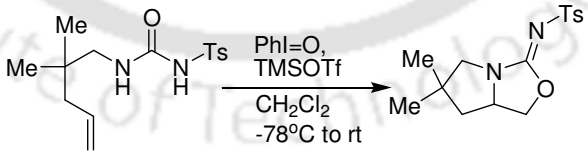
Scheme I.8.1.2.

Jackson *et. al*. reported the intramolecular cyclization of thiobenzamides to benzothiazoles via aryl radical cations as reactive intermediates utilizing phenyliodine(III) bis(trifluoroacetate) (PIFA) in trifluoroethanol at room temperature (*Scheme I.8.1.3*).[33c]



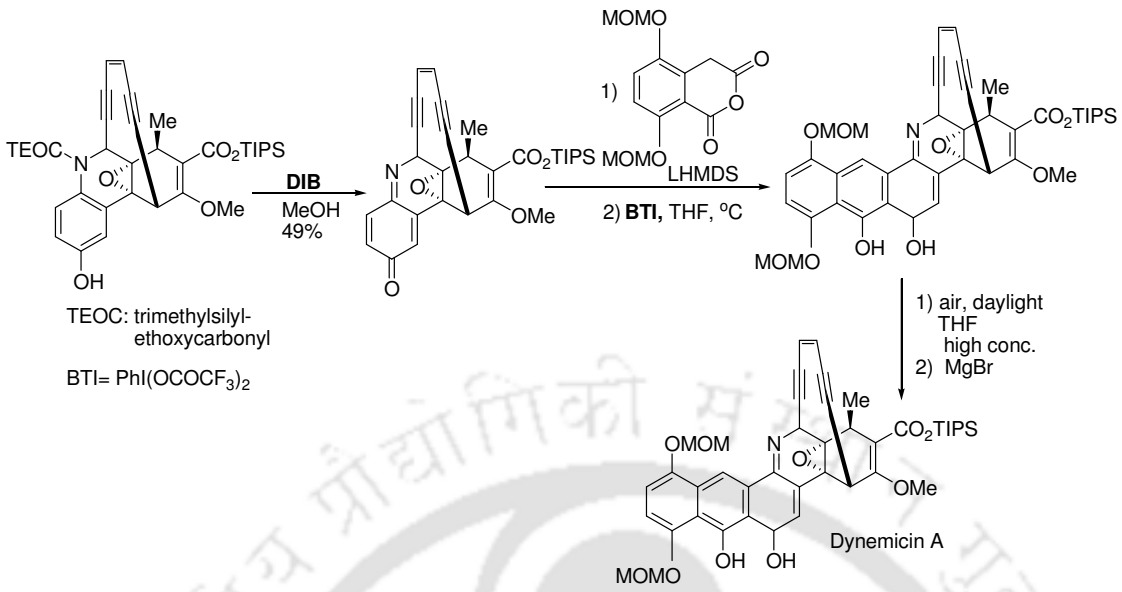
Scheme I.8.1.3.

Michael and his co-worker described a metal-free intramolecular oxidative cyclization of ureas onto an unactivated alkenes using iodosylbenzene in an acidic medium promoter (*Scheme I.8.1.4*). The products isolated were predominantly bicyclic isoureas resulting from an intramolecular oxyamination reaction. It was also reported that the nature of acid and urea substitution have a strong effect on the product formation.[33d]



Scheme I.8.1.4.

Danishefsky and co-workers demonstrated the use of hypervalent iodine towards their total synthesis of Dynemicin A (*Scheme I.8.1.5*).[33e]



Scheme I.8.1.1.5.

I.8.2. Future Scope and New Directions of Hypervalent Iodine Reagents

Hypervalent iodine reagents have wide advantages which are undeniably impressive, mild reaction conditions, operational simplicity, selectivity, efficiency and diversity, reasonable cost, non-toxicity, recyclability and possibility of use in catalytic amount (along with some suitable co-oxidant).[33f] Furthermore, new entries of solid-supported hypervalent iodine reagents have added numerous advantages. So, nowadays, iodanes are the reagents of choice for a plethora of useful transformations. Versatility of hypervalent iodine reagent is such that sometimes their reactions may lead to unexpected products which otherwise might not be easily available. Owing to these properties, one may expect a wide range of future research scope.

I.9. 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.9.1*), which includes tetramethylammonium tribromide (TMATB), tetrabutylammonium tribromide (TBATB), cetyltrimethylammonium- tribromide (CTMATB), pyridine hydrobromide perbromide (PHPB), 1,8-diazabicyclo [5.4.0]-undec-7-ene hydrobromide perbromide ($DBUHBr_3$), pentylpyridinium tribromide (PPTB), 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide and 1-butyl-3-methylimidazoliumtribromide ([bmim] Br_3).

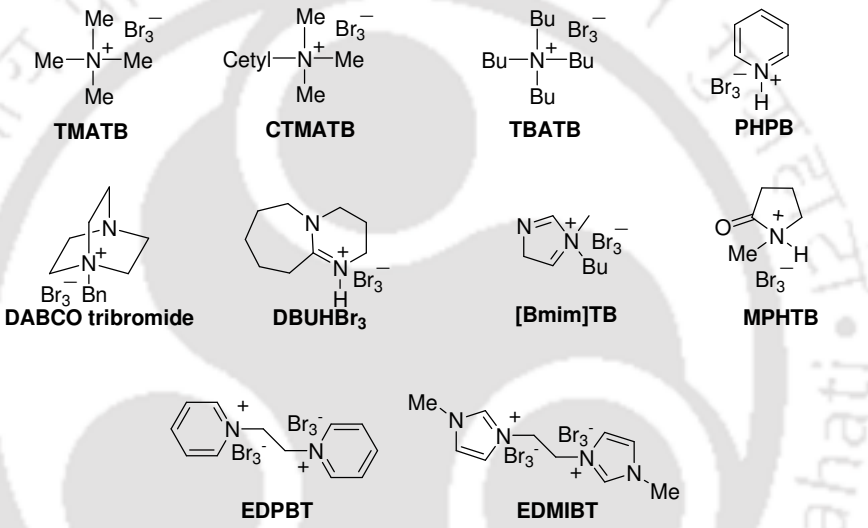
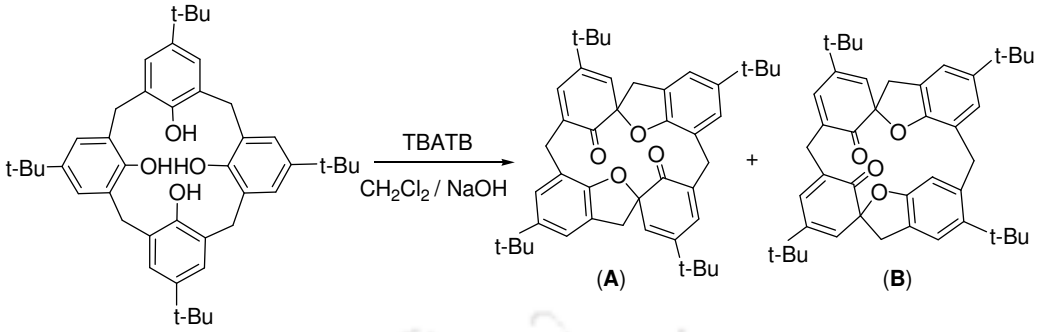


Figure I.9.1.

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.

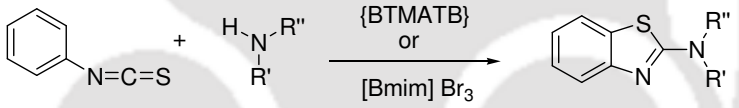
I.9.1. Tribromide Mediated Oxidative Cyclizations

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 (*Scheme I.9.1.1*).[34a,b]



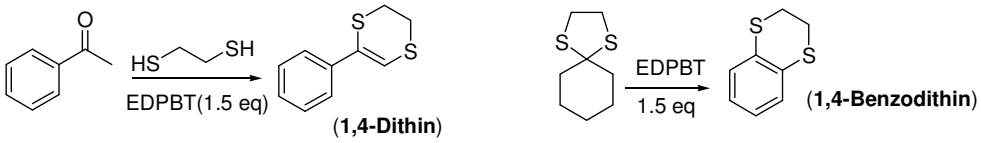
Scheme I.9.1.1.

Jordan and his coworkers have used benzyltrimethylammonium tribromide (BTMATB) for the oxidative cyclization of thioureas, generated *in situ* by reacting corresponding isothiocyanates and amines.[34c] The same synthesis was achieved by Le *et al.* using 1-butyl-3-methylimidazolium tribromide ([Bmim]Br_3) (*Scheme I.9.1.2*).[34d]



Scheme I.9.1.2.

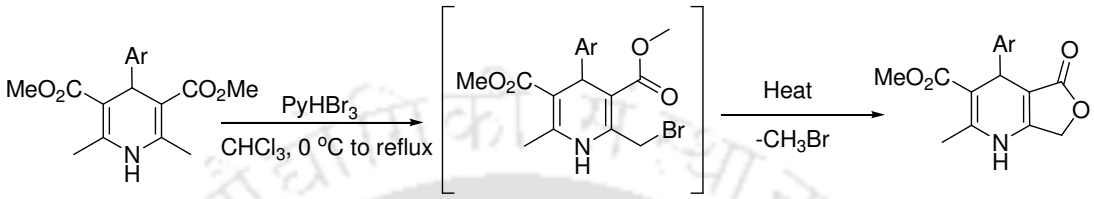
Recently, our group has developed a one-pot synthesis of 1,4-dithins and 1,4-benzodithins from ketones using 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (*Scheme I.9.1.3*).[34e]



Scheme I.9.1.3.

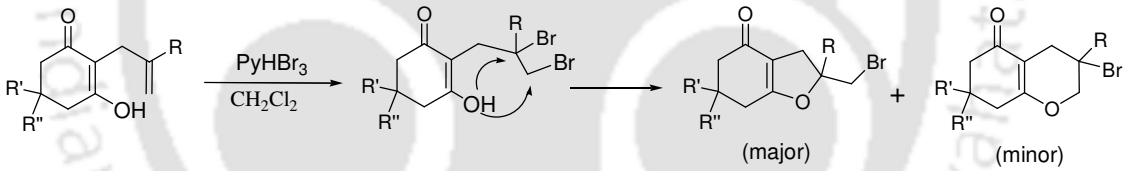
I.9.2. Brominative Cyclizations

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.9.2.1*.[35a]



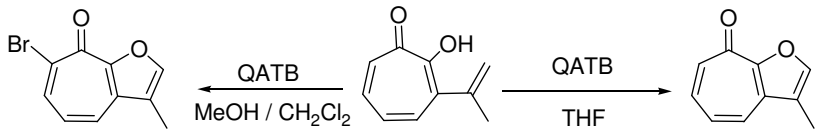
Scheme I.9.2.1.

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.9.2.2*).[35b]



Scheme I.9.2.2.

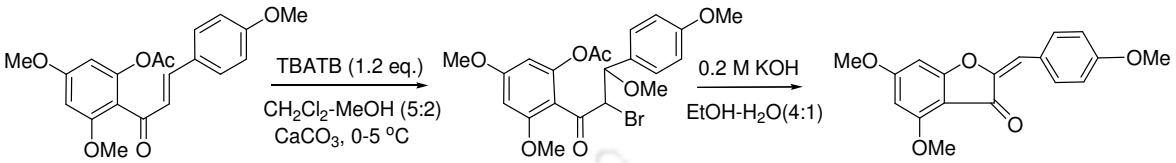
Treatment of 3-isopropenyltropolone with different quaternary ammonium tribromides (QATB) in THF afforded 3-methyl-8H-cyclohepta[b]furan-8-one. The same reaction in MeOH-CH_2Cl_2 gave 7-bromo-3-methyl-8H-cyclohepta[b]furan-8-one as shown in *Scheme I.9.2.3*.[35c]



Scheme I.9.2.3.

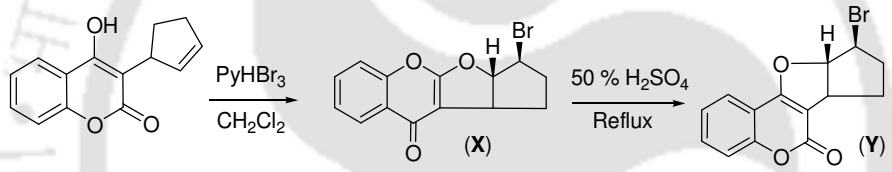
An environmentally benign synthesis of aurones and flavones from 2'-

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.9.2.4*).[35d]



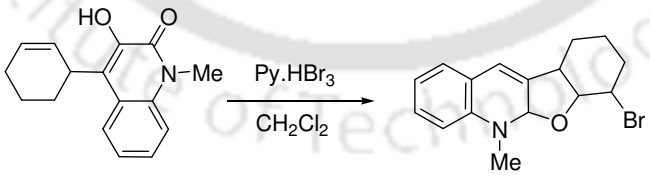
Scheme I.9.2.4.

Treatment of 4-hydroxy[1]benzopyran-2-one with pyridine hydrobromide perbromide ($PyHBr_3$) gave fused furochromone (**X**) in 90% yield (*Scheme I.9.2.5*). These heterocycles undergoes rearrangement to furnish fused furocoumarin (**Y**) in 87% yield.[35e]



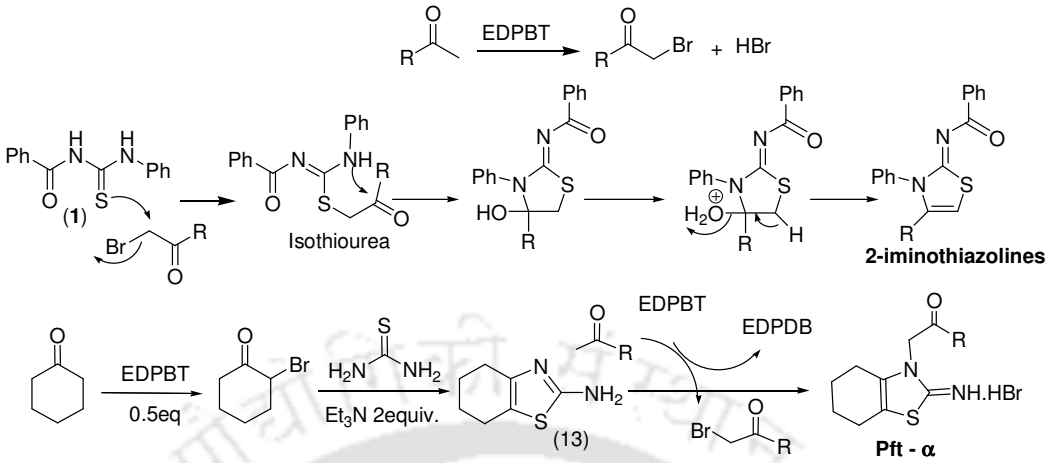
Scheme I.9.2.5.

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 °C afforded benzofluorene product in excellent yield (*Scheme I.9.2.6*).[35f]



Scheme I.9.2.6.

Very recently, our group reported EDPBT mediated synthesis of 2-iminothiazolines, and that was further extended to the preparation of pifithrin analogues (*Scheme I.9.2.7*).[35g,h]



Scheme I.9.2.7.

I.10. References

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Chapter II

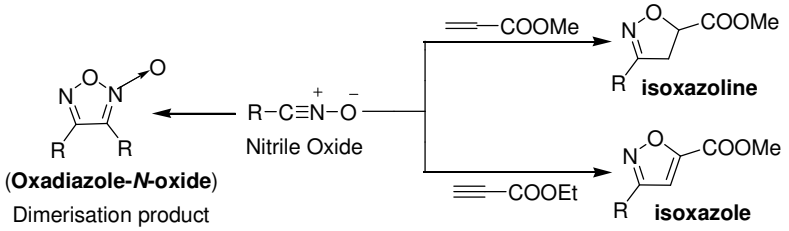
II. Oxidation of Aldoximes to *N*-Acetoxy or *N*-Hydroxy Amides

II.1. Importance and Applications

Nitrile oxide is the main precursor for the synthesis of 5-aminoisoxazoles, which display fungicidal, antihelmintic, bactericidal properties and are useful for the treatment of cerebrovascular disorders.[1a] *N*-Acetoxy benzamides (*O*-acetyl hydroxamates) have insecticidal and herbicidal activities and are therefore important from a biological point of view.[1b] On the other hand the hydroxamic acid functionality is present in a number of biologically active molecules with antibacterial, antifungal, anti-inflammatory, anti-asthmatic, and anticancer properties.[1c,d] Hydroxamic acid derivatives are reported to possess anti-melanogenic activity.[1e] They are well known as metal ion chelators, particularly as zinc coordinators, that have been widely used as zinc protease inhibitors.[1f,g] Over the past decade, hydroxamic acid-containing derivatives have emerged as a class of compounds of great therapeutical interest especially with respect to inhibition of histone deacetylases[1h] (HDACs) and matrix metalloproteases (MMPs).[1i] Thus, the chemistry of nitrile oxide, *N*-acetoxy and *N*-hydroxy amide has gain importance in recent years because of their immense biological and synthetic importance.

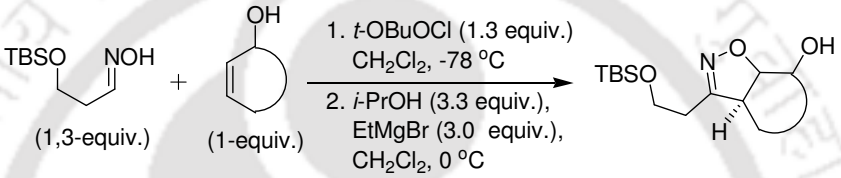
II.1.1. Applications in Organic Synthesis

Nitrile oxides form an important class of reactive intermediates because of their ability to undergo l,3-dipolar additions giving heterocyclic compounds, especially isoxazolines and isoxazoles. Functionalized nitrile oxides are useful for the syntheses of polyfunctionalized compounds. Most of the nitrile oxides are too reactive to be isolated and they undergo dimerization if not reacted *in situ* with appropriate substrates (*Scheme II.1.1*).[2]



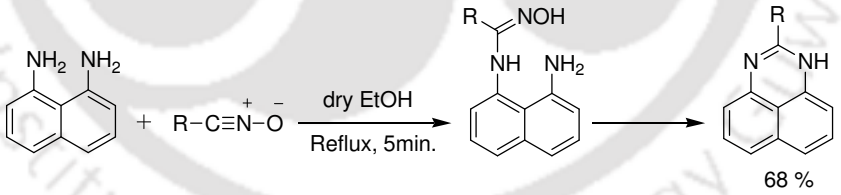
Scheme II.1.1.

Carreira and his co-workers reported the preparation of densely functionalized building blocks by diastereoselective cycloaddition reactions between a nitrile oxide and cyclic allylic alcohols (*Scheme II.1.2*).[3a]



Scheme II.1.2.

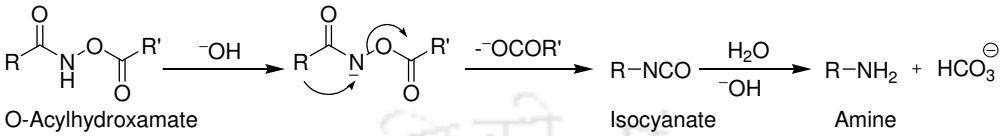
Paton *et. al.* demonstrated a new route to perimidines by reaction of a nitrile oxide with 1,8-diaminonaphthalene. In their report, formation of 2-phenylperimidine from benzonitrile oxide and 1,8-diaminonaphthalene is described (*Scheme II.1.3*).[3b]



Scheme II.1.3.

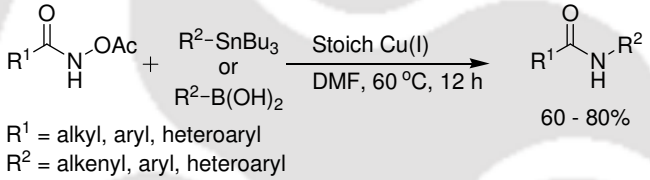
N-Acetoxy benzamides (*O*-acetyl hydroxamates) and *O*-tosyl hydroxamates are important candidates for classical Lossen rearrangements (*Scheme II.1.4*).[4] The Lossen rearrangements involves the abstraction of a proton from an *O*-acyl hydroxamates which is followed by the migration of an alkyl/aryl group with the concomitant departure of an acyl group giving an isocyanate. The resultant isocyanate undergoes hydrolysis followed by decarboxylation giving aryl/alkyl amine. The reaction also occurs with the hydroxamic acids themselves, but not as well as with their *O*-acyl derivatives as acyl group is a better

leaving group than $^{-}$OH. In Lossen rearrangement, the reaction is facilitated by electron-donating substituents in migrating group (*cf.* Hofmann), but also by electron-withdrawing substituents in leaving acyl group, i.e. both are involved in the rate-limiting step of the reaction (*Scheme II.1.4*).



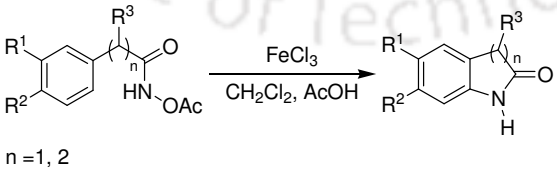
Scheme II.1.4.

Liebeskind and his co-workers disclosed a new non basic method for the preparation of *N*-substituted amides by the Cu-mediated cross-coupling of boronic acids and organostannanes, starting from *O*-acetyl hydroxamic acids (*Scheme II.1.5*).[5a]



Scheme II.1.5.

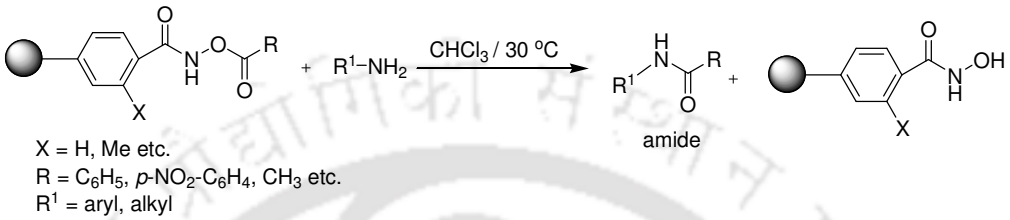
Cherest *et. al*. described the preparation of oxindoles and its analogues by treating *O*-acyl hydroxamates bearing an aromatic group with ferric chloride (*Scheme II.1.6*). The action of $FeC1_3$ on *O*-acetyl hydroxamates leads to an electron deficient species which react either intra or inter-molecularly with an aromatic ring to give oxindoles or its analogues.[5b]



Scheme II.1.6.

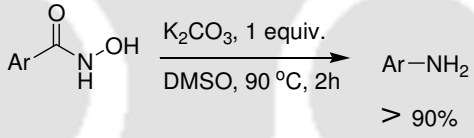
Sreekumar and his co-workers developed a polystyrenebound hydroxamic esters based solid phase reagent for the selective acylation of amines and amino acids to give the

corresponding amides (*Scheme II.1.7*). The cross-linking agents used were divinylbenzene (DVB) and ethyleneglycol dimethacrylate (EGDMA). Their experimental findings revealed that acyl transfer reagents derived from EGDMA-cross-linked polystyrene support was superior to those based on DVB-cross-linked polystyrene support in terms of functional group capacity and reactivity.[5c]



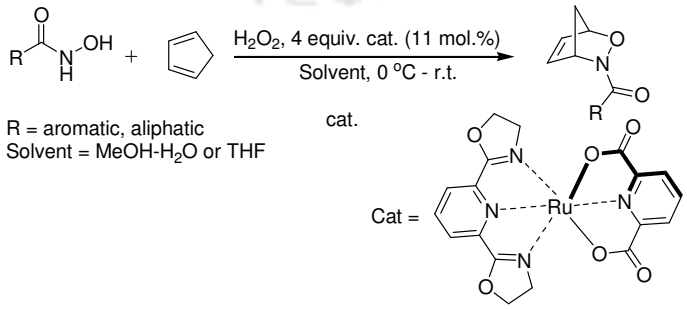
Scheme II.1.7.

Hoshino *et. al.* demonstrated a base (K_2CO_3) mediated rearrangement of a variety of aromatic hydroxamic acids to aromatic amines without using activating agents (*Scheme II.1.8*). Operational simplicity and efficiency, excellent yields in short reaction times are the attractive features of the reported method.[5d]



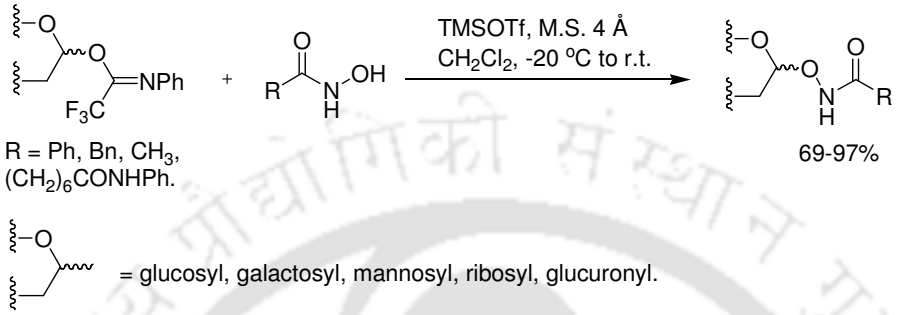
Scheme II.1.8.

Iwasa and co-workers have reported a ruthenium-catalyzed-H_2O_2 mediated oxidation of hydroxamic acid to nitroso intermediate *in situ,* and its subsequent hetero Diels–Alder reaction with cyclopentadiene to give acyl nitroso cycloadducts in 74–99% yield (*Scheme II.1.9*).[5e]



Scheme II.1.9.

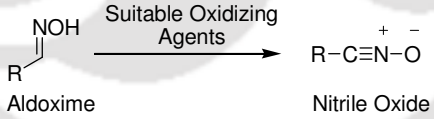
Papot *et. al.* described the preparation of *O*-glycosylated hydroxamic acids which have immense biological interest as prodrugs for selective cancer chemotherapy (*Scheme II.1.10*).[5f]



Scheme II.1.10.

II.2. Available Synthetic Methods

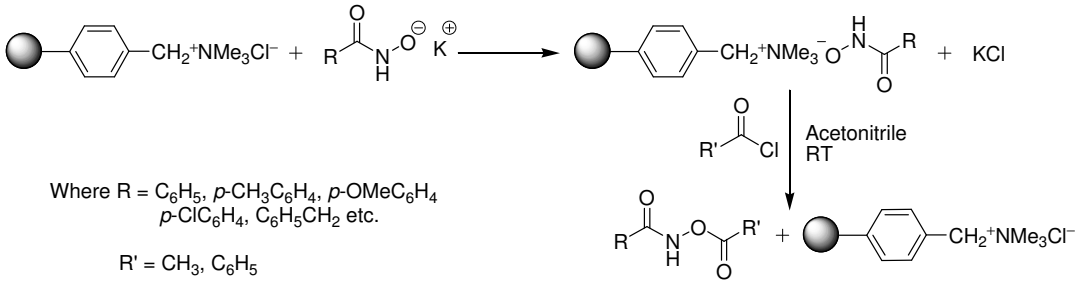
Aromatic aldoximes are invariably oxidized to aryl nitrile oxides with various oxidizing agents such as NaOCl,[6a] $Pb(OAc)_4$,[6b] NBS,[6c] 1-chlorobenzotriazole,[6d] Magtrieve^{TM} (CrO_2),[6e] chloramine-T,[6f] and $PhICl_2$[6g] (*Scheme II.2.1*).



Scheme II.2.1.

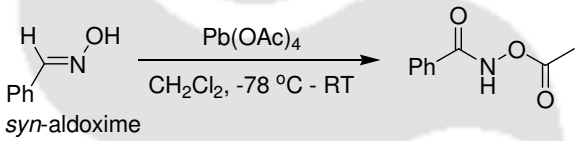
Generally, the *N*-acetoxy amides are prepared by the base catalyzed acylation of hydroxamic acids.[7a,b] The main drawback of these reported procedures is the formation of a mixture of *O*-acyl and *N*-acyl hydroxamate, resulting in a low yield of the desired *O*-acylated product.

Lately, Mane *et. al.* reported the preparation of *O*-acyl /*O*-benzoyl hydroxamates *via* a polymer supported reagent, which has a number of advantages (*Scheme II.2.2*).[7c]



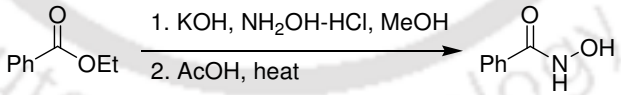
Scheme II.2.2.

Dahl *et. al.* demonstrated the formation of *N*-acetoxy-amides while treating *syn*-aldoximes with lead tetraacetate at low temperature (*Scheme II.2.3*). It is reported that aromatic *anti*-aldoximes afforded the arylaldazine-*bis*-*N*-oxides which decomposed on heating to nitrile oxides and aldoximes.[7d]



Scheme II.2.3.

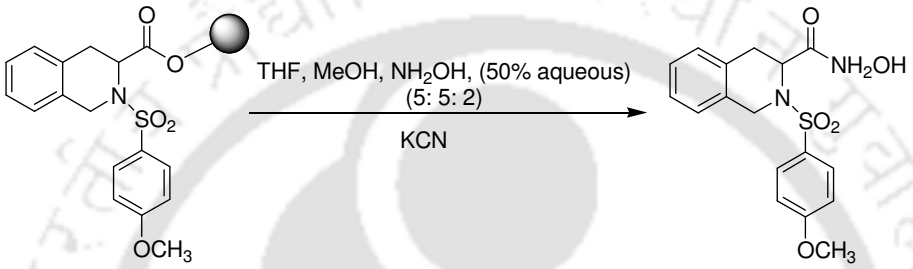
Several methods have been reported with varying degrees of success for the preparation of hydroxamic acids. The most widely used method is the amidation of esters using hydroxylamine by various techniques.



Scheme II.2.4.

The direct solution-phase hydroxyamination of esters is generally achieved by a two-step preparation of the potassium salt of hydroxylamine followed by the addition of the ester in an alcoholic medium (*Scheme II.2.4.*)[8a,b] or by the step-wise saponification of an ester to the acid followed by the activation of the acid as the acyl chloride or mixed anhydride and then quenching with an *O*-protected hydroxylamine analogue.[8c,d] In special cases, the hydroxyamination of ester substrates has been achieved via an enzymatic

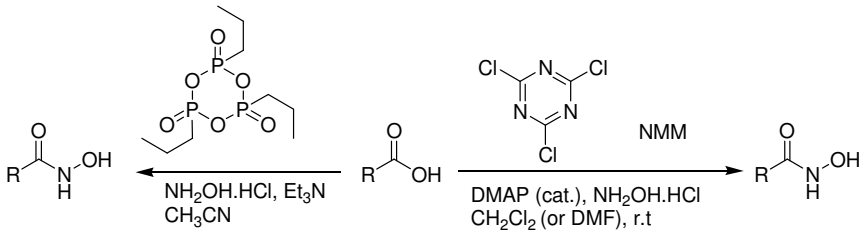
methods[8e] or, for more reactive esters, by treatment with excess hydroxylamine in an alcoholic medium.[8f] The solid-phase synthesis of hydroxamic acids via the direct *trans*-hydroxamination of an ester-linked substrate has been reported.[9a,b] Several activated resins have been designed to facilitate the direct *trans*-hydroxamination process.[9c-e] Another approach has been a step wise method, where the ester library was cleaved from the resin to give carboxylic acid intermediates that are subsequently reattached to a hydroxylamine resin by a peptide coupling agent then cleaved to the hydroxamic acids.[9f]



Scheme II.2.5.

Ho *et. al.* discovered that the addition of small amounts of solid KCN to both solution and solid-phase THF/MeOH/50% aqueous NH_2OH, accelerate the formation of hydroxamic acids from simple esters of alkyl, aryl, and amino acids (*Scheme II.2.5*).[9g] In other reports, a variety of specialized hydroxylamine resins have been used.[10] Martinelli and co-workers have developed a simple and high-yielding method for the synthesis of hydroxamic acids directly from the corresponding carboxylic esters using a continuous flow tubing reactor.[11a] The synthetic advantages of the developed method were identified as an increased reaction rate and higher product purity along with applicability to the multi-step preparation of suberoylanilide hydroxamic acid. The reaction of esters with *O*-benzyl hydroxylamine leads to various hydroxamate derivatives.[11b,c]

Another general method of preparation of hydroxamic acid is amidation of carboxylic acids with hydroxylamine using various coupling reagents. Giacomelli *et. al.* reported the synthesis of hydroxamic acids from carboxylic acids and *N*-protected amino acids that uses 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride, TCT) as a coupling agent (*Scheme II.2.6*).[11d,e].One similar method describes the coupling of aromatic and aliphatic acids with hydroxylamine in the presence of cyclic phosphonic anhydride (PPAA) (*Scheme II.2.6*).[11f]

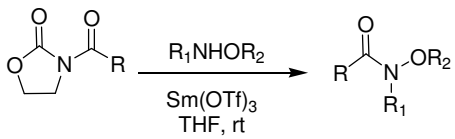


NMM = *N*-methylmorpholine, DMAP = dimethylamino pyridine

Scheme II.2.6.

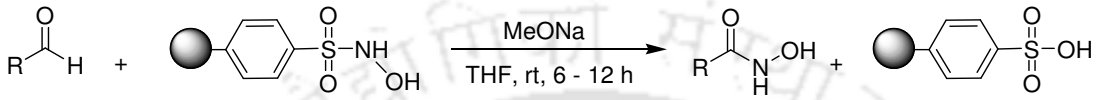
Several resins have reportedly been used for the syntheses of hydroxamic acids from various acids. Pang *et. al.* reported the use of the hydroxythiophenol (Marshall) resin to convert a library of discrete aliphatic and aromatic carboxylic acids including *N*-protected amino acids to their corresponding hydroxamic acids in good yields.[12a] Another method describes the preparation of hydroxamic acids by treating the organic acids with ethychloroformate in the presence of *N*-methylmorpholine followed by hydroxyl amine in diethylether medium.[12b] The coupling of different carboxylic acids and *N*-protected α-amino acids with *N*,*O*-dimethyl- or *O*-benzylhydroxylamine hydrochlorides was carried out using tetrafluoroborate and hexafluorophosphate thiouronium salts derived from 2-mercaptopyridone-1-oxide and tetramethylurea (TOTT and HOTT) or *N*,*N*-dimethylpropyleneurea (TODT and HODT) as coupling agents to prepare Weinreb amides and *N*-methoxy or *N*-benzoxyamides.[12c] Katritzky and co-workers demonstrated the conversion of carboxylic acids into unsubstituted, *N*-alkyl-, *O*-alkyl-, and *O*,*N*-dialkylhydroxamic acids via acylbenzotriazole intermediates. The ready availability of the reagents, mild conditions, and easy handling of the intermediates are advantageous over the reported methods.[12d]

Sibi *et.al.* demonstrated a simple and effective methodology for the conversion of *N*-acyloxazolidinones to hydroxamic acid derivatives through the amidation of *N*-acyloxazolidinones with hydroxylamines using samarium triflate as a Lewis acid at room temperature (*Scheme II.2.7*).[12e]



Scheme II.2.7.

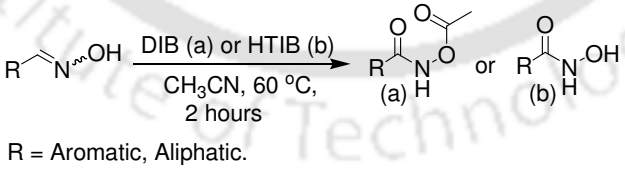
The classical **Angeli-Rimini reaction** describes the preparation of hydroxamic acids from aldehydes using *N*-hydroxybenzenesulfonamide in the presence of a strong base.[13a-f] Because of the separation difficulty of byproduct, benzenesulfinic acid, from the desired product; the Angeli-Rimini's reaction has been seldom used in organic synthesis. Porcheddu *et. al.* developed a modified route to Angeli-Rimini reaction by using solid-supported *N*-hydroxybenzenesulfonamide (*Scheme II.2.8*).[13g]



Scheme II.2.8.

II.3. Present Work

As a part of our ongoing programme on the synthetic utility of hypervalent iodine(III) reagents,[14a-c] we undertook the reaction of aldoximes with (diacetoxyiodo)benzene (DIB) and Koser's reagent [hydroxy(tosyloxy)iodo]benzene (HTIB). During the course of (DIB)-mediated oxidation of aromatic aldoximes, we observed the formation of *N*-acetoxy benzamide (**a**) (*Scheme II.3.1*). When the same reaction was performed using (HTIB), the product obtained was *N*-hydroxy benzamide (**b**) (*Scheme II.3.1*).

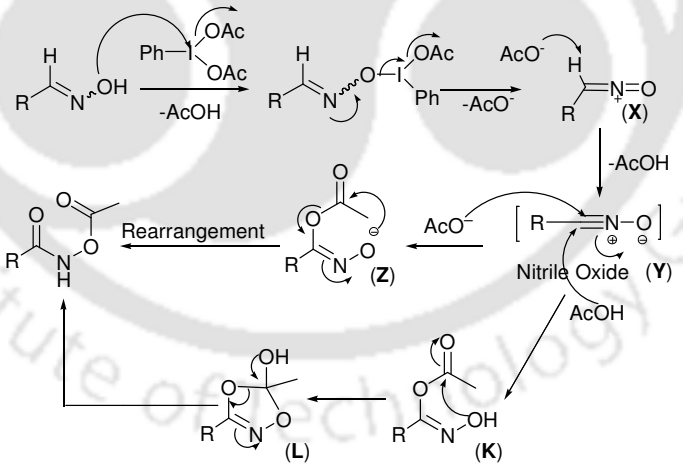


Scheme II.3.1. *Reaction of aldoximes with DIB or HTIB*

When benzaldehyde oxime (**1**) (1 equiv.) was reacted with (diacetoxyiodo)benzene (DIB) (1.1 equiv.) in acetonitrile at 60 °C, *N*-acetoxy benzamide (**1a**) was obtained in 78% isolated yield rather than the expected benzonitrile oxide or its dimerized product. This observation is in sharp contrast to the observation made by Das *et al.*,[14d] where in a CH_2Cl_2

medium and in the absence of any alkenes, the nitrile oxide dimerized product is speculated. The difference between Das *et al.*[14d] and ours is the use of different organic solvents. In order to ascertain the role of the solvent, the reaction was carried out in various organic solvents such as CH_3CN, $CHCl_3$, CH_2Cl_2, THF, MeOH, toluene and DMSO. The isolated yields of (**1a**) after 2 h were 78, 70, 58, 50, 51, 35 and ~7%, respectively. In the CH_2Cl_2 solvent, the product (**1a**) was obtained in 58% isolated yield along with a mixture of other side products. However, in THF, MeOH, toluene and DMSO, the reaction gave an unclean reaction mixture. Thus, CH_3CN was found to be the most suitable solvent giving good yield of *N*-acetoxy amide.

Although the starting aldoxime (**1**) was a diastereomeric (*syn*- and *anti*-) mixture, both gave the same product *N*-acetoxy benzamide (**1a**). Alkyl/aryl aldoxime, when treated with heavy metal oxidants such as $Pb(OAc)_4$,[6b] is reported to form nitrile oxide along with other products. In this oxidation, the *anti*-aldoxime proceeds *via* an iminoxy radical path, whereas the *syn*-aldoxime reacts in concerted path giving nitrile oxide.[6b] A (diacetoxyiodo)benzene (DIB)-mediated nitrile oxide formation from aldoxime has been proposed by Das *et al.*[14d]

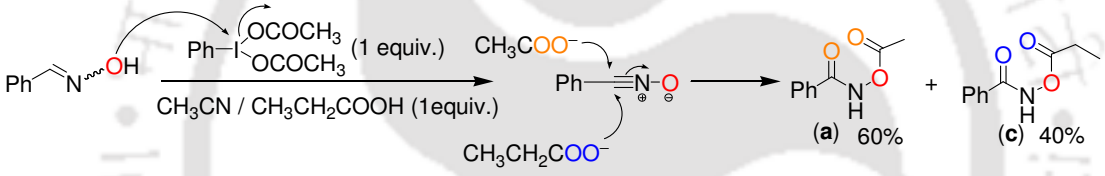


Scheme II.3.2. *Mechanism for the formation of N-acetoxy amides*

According to this mechanism, the first step is the nucleophilic displacement of one of the acetate groups of DIB by an aldoxime oxygen. This is then followed by the formation of intermediate (**X**), which, upon deprotonation, gives nitrile oxide (**Y**) (*Scheme*

II.3.2). Nitrile oxide (**Y**), which is reported to be the intermediate for this kind of reaction,[14d,e] is attacked by the *in situ* liberated acetate ion from DIB, giving acylated intermediate (**Z**). The intermediate (**Z**), upon intramolecular rearrangement, gave the expected *N*-acetoxy arylamide. Alternatively, attack of nitrile oxide (**Y**) by an acetic acid gives intermediate (**K**), which in turn generates a tetrahedral intermediate (**L**) leading to the expected *N*-acetoxy amide.

When the reaction was carried out in the presence of one equivalent of propionic acid, *N*-acetoxy benzamide (**1a**) along with *N*-propionyloxy benzamide (**1c**) were obtained in the ratio 60 : 40. The formation of *N*-propionyloxy benzamide (**1c**) proves the intermolecular attack of acetate or propionate on benzonitrile oxide (*Scheme II.3.3*), thus ruling out the possibility of a radical-type mechanism in this case as has been proposed for $Pb(OAc)_4$.mediated reaction.[6b]



Scheme II.3.3. *Intermolecular nature of the mechanism*

When the DIB-mediated oxidation of aromatic aldoxime was conducted in the presence of an activated alkene, methyl acrylate, in dicloromethane, there was no formation of *N*-acetoxy benzamide, but isoxazoline was isolated as the sole product an observation consistent with the literature.[14d] It is also reported that oxidation of aldoxime with iodosyl arene forms the dimerized product of nitrile oxide, oxadiazole-*N*-oxide, which has been isolated and well characterized.[14e] Therefore, it is clear that in the absence of an activated alkene the dimerization of the intermediate nitrile oxide solely depends on the presence or absence of external nucleophiles. In the presence of a suitable external nucleophiles, such as acetate or hydroxy, the intermediate nitrile oxides undergo oxidative rearrangement to produce the corresponding *N*-acetoxy amides or *N*-hydroxy-amides without forming any dimerized product.

Due to the immense synthetic importance of *N*-acetoxy amide, we applied this strategy to various aldoximes for the construction of *N*-acetoxy amide. Various aromatic

aldoximes containing electron donating groups (**2–3**) as well as electron withdrawing groups (**4–9**) all gave their corresponding *N*-acetoxy benzamide (**2a–9a**) in good yields (*Table II.3.1*) when reacted with DIB in acetonitrile at 60 ^{o}C within 2 h. The structure of *N*-acetoxy-2,6-dichloro benzamide (**9a**) has been confirmed by crystal X-ray crystallography (*Figure II.3.1*).

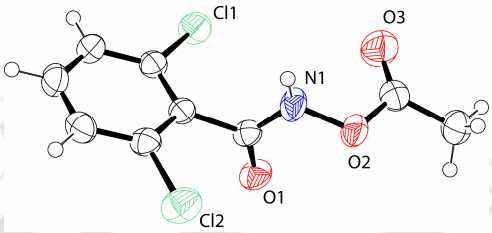
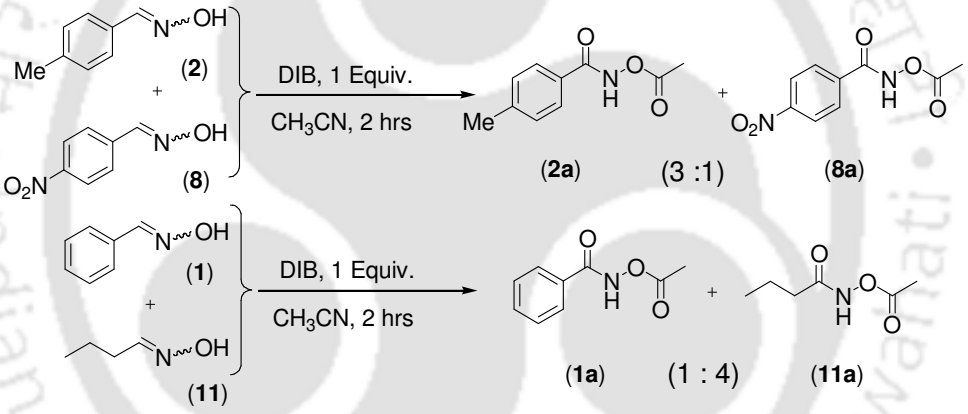


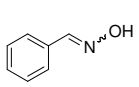
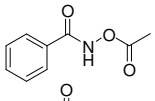
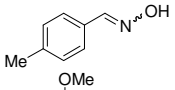
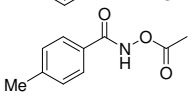
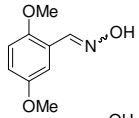
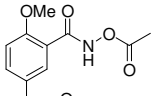
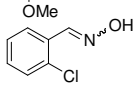
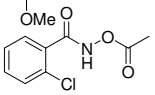
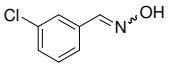
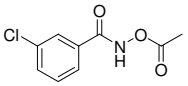
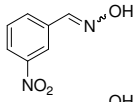
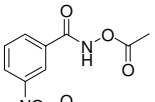
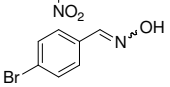
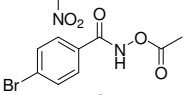
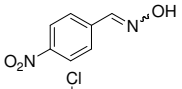
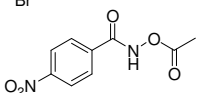
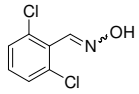
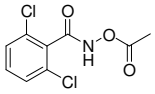
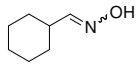
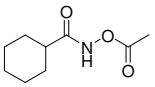
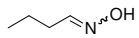
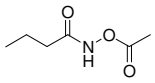
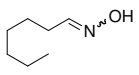
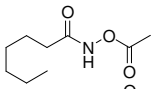
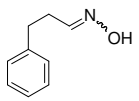
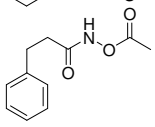
Figure II.3.1. *ORTEP view of (**9a**) with atom-numbering scheme*



Scheme II.3.4. *Competing reactions*

Furthermore, the method was successfully extended to the synthesis of a variety of aliphatic *N*-acetoxy amides (**10a–13a**) from their corresponding aliphatic aldoximes (**10–13**). It was observed that aliphatic aldoximes were more reactive than aromatic aldoximes. For aliphatic aldoximes (**10–13**), complete conversion took 30 min compared to 2 h for the aromatic aldoxime. Substrates containing both electron donating as well as electron withdrawing groups in the aromatic ring react efficiently (*Table II.3.1*). In a competing reaction, when an equimolar mixture of 4-methylbenzaldehyde oxime (**2**) and 4-nitrobenzaldehyde oxime (**8**) was reacted with 1 equiv. of DIB, the ratio of the acetoxy products (**2a**) and (**8a**) formed after 2 h was 3 : 1.

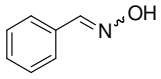
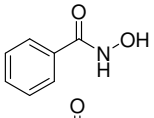
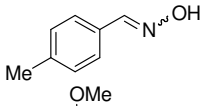
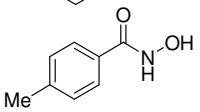
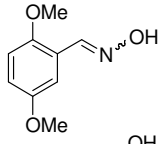
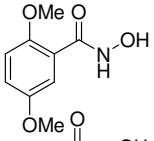
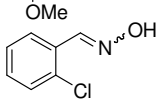
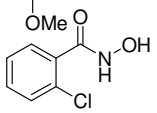
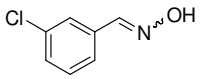
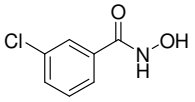
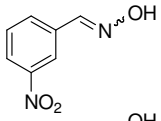
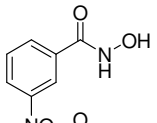
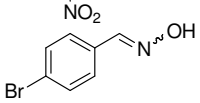
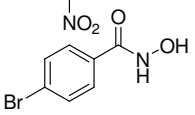
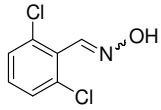
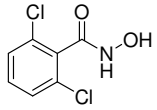
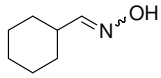
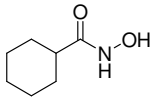
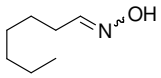
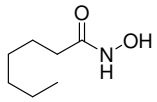
Table II.3.1. *Preparation of N-acetoxy amide*[a]

Entry	Substrate	Product[b]		Yield (%)[c]
(1)			(1a)	78
(2)			(2a)	83
(3)			(3a)	74
(4)			(4a)	77
(5)			(5a)	69
(6)			(6a)	76
(7)			(7a)	79
(8)			(8a)	86
(9)			(9a)	86
(10)			(10a)	75
(11)			(11a)	61
(12)			(12a)	66
(13)			(13a)	69

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

This demonstrates the faster reactivity for the substrates with an electron donating group compared to the substrates with an electron withdrawing group. In a similar competing reaction between an aliphatic aldoxime (**11**) and an aromatic aldoxime (**1**), the ratio of the acetoxy product (**11a**) and (**1a**) formed after 2 h was 4 : 1, (*Scheme II.3.4*), exhibiting the faster reactivity of the aliphatic aldoxime compared to the aromatic aldoxime.

Table II.3.2. *Preparation of N-hydroxy amide*[a]

Entry	Substrate	Product[b]		Yield (%)[c]
(**1**)			(**1b**)	76
(**2**)			(**2b**)	81
(**3**)			(**3b**)	73
(**4**)			(**4b**)	83
(**5**)			(**5b**)	74
(**6**)			(**6b**)	72
(**7**)			(**7b**)	70
(**9**)			(**9b**)	78
(**10**)			(**10b**)	62
(**12**)			(**12b**)	68

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

When hypervalent iodine (III) reagent hydroxy (tosyloxy) iodo benzene (HTIB, Koser's reagent) was used as the oxidizing agent instead of DIB for the oxidation of benzaldehyde oxime (**1**), *N*-hydroxybenzamide (**1b**) was isolated as the sole product. Here, the OH^- nucleophile (generated from the reagent, HTIB) attacks the intermediate benzonitrile oxide (*Scheme II.3.2*), forming *N*-hydroxy benzamide (**1b**). This reaction works better in a chloroform medium compared to an acetonitrile medium

Hydroxamic acids bearing various substituents on the aromatic ring (**1b–9b**) can be efficiently prepared from the corresponding benzaldehyde oximes (**1–9**), as shown in *Table II.3.2.* Here again, aliphatic aldoximes (**10**) and (**12**) were successfully converted to their corresponding hydroxamic acids (**10b**) and (**12b**) in a shorter time (30 min). Although quantitative conversions to hydroxamic acids for both aromatic and aliphatic compounds from the parent aldoximes were observed by GC/TLC, the isolated yields were modest. This is because of the difficulties in separating the water soluble product and byproduct *p*-toluenesulfonic acid (generated from reagent HTIB). Several extraction and chromatographic techniques were adopted but efficient separation could not be achieved. The yield in the table refers to the pure isolated product only. Similar purification difficulties were encountered by others and have been overcome by attaching the reagent on a solid support.[13g]

In conclusion, the oxidation of both aromatic and aliphatic aldoximes with hypervalent iodine(III) reagents DIB or HTIB gave the corresponding *N*-acetoxy and *N*-hydroxy amides in good yields, rather than the expected nitrile oxide dimerized products oxadiazole-*N*-oxides reported with other oxidizing agents. A plausible mechanism for this transformation involves acetate attack on the intermediate aryl/alkyl nitrile oxides, which, upon rearrangement, gave the expected *N*-acetoxy amides. Thus, using this approach, various *N*-acetoxy and *N*-hydroxy amides can be prepared conveniently from their aldoximes.

II.4. Experimental Section

II.4.1. 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, appt = apparent triplet, 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.4.2. General Procedures

II.4.2.1. General Procedure for Preparation of *N*-Acetoxy Benzamide (1a) from Benzaldehyde Oxime (1)

DIB (708 mg, 2.2 mmol) was added to a stirred solution of benzaldehyde oxime **1** (242 mg, 2 mmol) in acetonitrile at room temperature, portion wise over a period of 10 min. A white precipitate started to separate out during this period. After the complete

addition of DIB, the reaction mixture was heated at 60 ^{o}C for 2 h (30 min for aliphatic substrates), and conversion to the corresponding *N*-acetoxy benzamide **1a** was monitored by TLC. At the end of the reaction, the reaction mixture becomes a clear solution. The organic layer was concentrated and admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with water (5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified through a short column of silica gel to afford the pure product **1a**.

II.4.2.2. General Procedure for Preparation of *N*-Hydroxy Benzamide (1b) from Benzaldehyde Oxime (1)

HTIB (862 mg, 2.2 mmol) was added to a stirred solution of benzaldehyde oxime **1** (242 mg, 2 mmol) in chloroform at room temperature, in portion wise manner over a period of 10 min. After the complete addition of HTIB, the reaction mixture was heated at 60 ^{o}C for 2 h (30 min for aliphatic substrates), and conversion to the corresponding *N*-hydroxy benzamide **1b** was confirmed by TLC. The organic layer was concentrated and admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with 10% HCl water solution (5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified through a short column of silica gel to afford the pure product **1b**.

II.5. References

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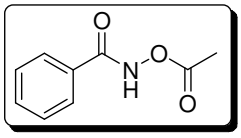
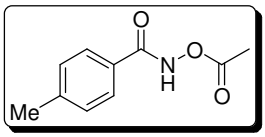
II.6. Spectral Data

_N_-Acetoxy benzamide (1a):



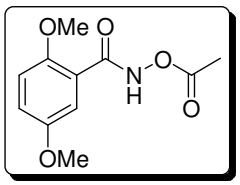
M.p. 126 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 2H), 9.63 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 127.7, 128.9, 130.7, 132.9, 166.5, 169.3. IR (KBr): 3151, 2961, 1793, 1650, 1531, 1366, 1198, 1021, 896, 695 cm^{-1}. MS (ESI): 180.07 (MH^+).

_N_-Acetoxy-4-methyl-benzamide (2a):



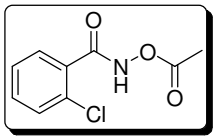
M.p. 133-135 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.41 (s, 3H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 9.64 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 21.7, 127.7, 127.9, 129.6, 143.6, 166.6, 169.4. IR (KBr): 3180, 2949, 2851, 1794, 1660, 1651, 1488, 1302, 1176, 1017, 906, 851, 753, 602 cm^{-1}. Elemental analysis: $C_{10}H_{11}NO_3$ (193.20): calcd C, 62.17; H, 5.74; N, 7.25. found: C, 62.15; H, 5.79; N, 7.24.

_N_-Acetoxy-2,5-dimethoxy-bemzamide (3a):



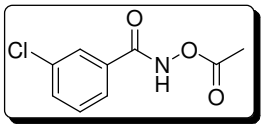
Gummy, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.74 (s, 3H), 3.89 (s, 3H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.98 (dd, J_1 = 3.2 Hz, J_2 = 3.6 Hz, 1H), 7.62 (d, *J* = 3.2 Hz, 1H), 11.18 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 55.9, 56.9, 113.1, 115.5, 119.2, 120.6, 151.6, 154.1, 163.1, 168.6. IR (KBr): 3307, 2946, 2839, 1790, 1668, 1496, 1464, 1283, 1217, 1185, 1042, 815, 736 cm^{-1}. Elemental analysis: $C_{11}H_{13}NO_5$ (239.23): calcd C, 55.23; H, 5.48; N, 5.85. found: C, 55.23; H, 5.46; N, 5.84.

_N_-Acetoxy-2-chloro-benzamide (4a):



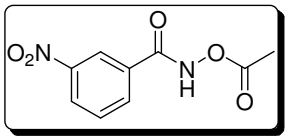
M.p. 99-101 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 7.36 (m, 1H), 7.44 (m, 2H), 7.71 (d, *J* = 7.2 Hz, 1H), 9.80 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 127.2, 130.5, 130.6, 131.2, 131.6, 132.5, 164.1, 168.6. IR (KBr): 3140, 2951, 2824, 1797, 1651, 1531, 1435, 1365, 1189, 1022, 901, 755, 638 cm^{-1}. Elemental analysis: $C_9H_8ClNO_3$ (213.62): calcd C, 50.60; H, 3.77; N, 6.56. found: C, 50.61; H, 3.77; N, 6.50.

_N_-Acetoxy-3-chloro-benzamide (5a):



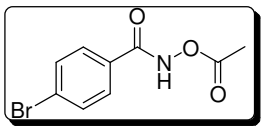
M.p. 100-102 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.80 (s, 1H), 9.90 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 125.7, 127.9, 130.3, 132.4, 132.9, 135.2, 165.2, 169.2. IR (KBr): 3147, 2955, 2824, 1798, 1651, 1533, 1188, 1027, 915, 751 cm^{-1}. Elemental analysis: $C_9H_8ClNO_3$ (213.62): calcd C, 50.60; H, 3.77; N, 6.56. found: C, 50.58; H, 3.79; N, 6.53.

_N_-Acetoxy-3-nitro-benzamide (6a):



M.p. 146-148 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.29 (s, 3H), 7.68 (t, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 7.2 Hz, 1H), 8.39 (d, *J* = 7.2 Hz, 1H), 8.81 (s, 1H), 12.29 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 18.4, 122.7, 126.6, 129.7, 132.7, 134.1, 147.9, 163.0, 168.7. IR (KBr): 3148, 2958, 1798, 1661, 1524, 1352, 1185, 1027, 857, 844, 737, 680 cm^{-1}. Elemental analysis: $C_9H_8N_2O_5$ (224.17): calcd C, 48.22; H, 3.60; N, 12.50. found: C, 48.22; H, 3.63; N, 12.45.

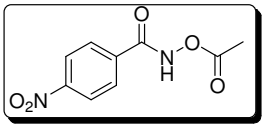
_N_-Acetoxy-4-bromo-benzamide (7a):



M.p. 126-128 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ .27 (s, 3H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 9.84 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 127.9, 129.2, 129.6, 132.3, 165.7, 169.3. IR (KBr): 3194, 2938, 1789, 1662, 1588, 1479, 1196, 1069, 1011, 909, 841, 750, 514 cm^{-1}. Elemental analysis:

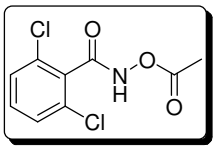
$C_9H_8BrNO_3$ (258.07): calcd C, 41.89; H, 3.12; N, 5.43. found: C, 41.92; H, 3.14; N, 5.40.

N-Acetoxy-4-nitro-benzamide (8a):



M.p. 189-191 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.29 (s, 3H), 8.09 (d, *J* = 8.4 Hz, 2H), 8.28 (d, *J* = 8.4 Hz, 2H), 12.11 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 18.4, 123.5, 129.2, 136.9, 149.9, 163.6, 168.7. IR (KBr): 3154, 2971, 1795, 1660, 1603, 1524, 1352, 1297, 1187, 1107, 1029, 1012, 850, 725, 588 cm^{-1}. Elemental analysis: $C_9H_8N_2O_5$ (224.17): requires C, 48.22; H, 3.60; N, 12.50. found: C, 48.25; H, 3.57; N, 12.47.

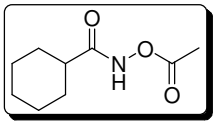
N-Acetoxy-2,6-dichloro-benzamide (9a):



M.p. 162-164 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.26 (s, 3H), 7.35 (m, 5H), 12.19 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 18.1, 127.7, 131.2, 132.6, 133.0, 160.5, 167.8. IR (KBr): 3149, 2995, 2809, 1798, 1661, 1524, 1434, 1191, 1026, 910, 792, 561 cm^{-1}. Elemental analysis: $C_9H_7Cl_2NO_3$ (248.06): requires C, 43.58, H, 2.84, N, 5.65. found: C, 43.59; H, 2.81; N, 5.63.

Crystal data for 9a: $C_9H_7Cl_2NO_3$ *M* = 248.06, Monoclinic, space group *P2(1)/c*, *a* = 9.8316(4), *b* = 12.1236(5), *c* = 8.8033(3)A°, α = 90.00, β = 92.170(2), γ = 90.00, *V* = 1048.55(7) A°^{3}, *T* = 298(2) K, Z = 4, μ–(Mo-Kα)=0.71073A°, colourless block, crystal dimensions 0.50 X 0.30 X 0.20 mm, crystal density 1.571. Full matrix least squares based on F^2 gave R1 = 0.0299 and *w*R2 = 0.0753 for 1655 ($I \geq 2\sigma(I)$), GOF = 1.046 for 141 parameters. CCDC # 744680.

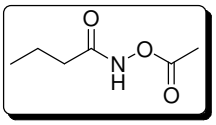
Cyclohexanecarboxylic acid acetoxy-amide (10a):



M.p. 85-87 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (m, 3H), 1.53 (m, 2H), 1.69 (m, 1H), 1.82 (m, 5H), 2.23 (s, 3H), 9.08 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 25.60, 25.63, 29.3, 42.3, 169.0, 174.6. IR (KBr): 3175, 2856, 1798, 1667, 1520, 1450, 1370, 1189, 1019, 961, 857, 761, 589 cm^{-1}. Elemental analysis:

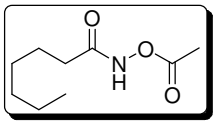
$C_9H_{15}NO_3$ (185.22): requires C, 58.36, H, 8.16, N, 7.56. found: C, 58.38; H, 8.11; N, 7.52.

_N_-Acetoxy-butyramide (11a):



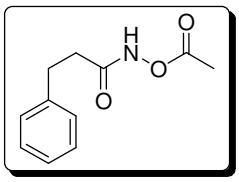
Oily, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, 3H, J = 7.6 Hz), 1.69 (m, 2H), 2.20 (s, 3H), 2.22 (m, 2H), 10.37 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 13.9, 18.2, 18.7, 34.5, 168.7, 171.5. IR (KBr): 3196, 2878, 1797, 1669, 1505, 1464, 1369, 1181, 1029, 853, 748 cm^{-1}. Elemental analysis: $C_6H_{11}NO_3$ (145.16): requires C, 49.65, H, 7.64, N, 9.65. found: C, 49.61; H, 7.63; N, 9.68.

Heptanoic acid acetoxy-amide (12a):



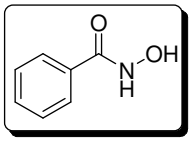
M.p. 80-82 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.4 Hz, 3H), 1.30 (m, 6H), 1.67 (m, 2H), 2.21 (s, 3H), 2.24 (m, 2H), 9.47 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8, 18.4, 22.6, 25.3, 28.9, 31.6, 32.9, 168.9, 171.5. IR (KBr): 3156, 2859, 1791, 1658, 1533, 1418, 1378, 1192, 1042, 852, 565 cm^{-1}. Elemental analysis: $C_9H_{17}NO_3$ (187.24): requires C, 57.73; H, 9.15; N, 7.48. found: C, 57.70; H, 9.18; N, 7.48.

_N_-Acetoxy-3-phenyl-propionamide (13a):



M.p. 64-66 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.25 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 7.21 (m, 3H), 7.28 (m, 2H), 9.20 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 31.2, 34.7, 126.7, 128.6, 128.8, 140.4, 168.9, 170.7. IR (KBr): 3148, 2961, 1790, 1667, 1497, 1453, 1368, 1176, 1063, 1017, 858, 747, 700, 560 cm^{-1}. Elemental analysis: $C_{11}H_{13}NO_3$ (207.23): requires C, 63.76; H, 6.32; N, 6.76. found: C, 63.75; H, 6.35; N, 6.71.

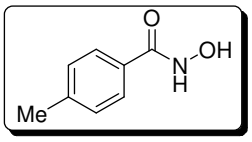
_N_-Hydroxy benzamide (1b):



M.p. 124 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.17 (m, 2H), 7.24 (t, J = 7.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 10.9 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 126.8, 128.1,

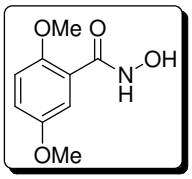
131.1, 131.8, 165.2. IR (KBr): 3300, 2753, 1645, 1613, 1563, 1453, 1435, 1163, 1022, 898, 690 cm^{-1}. MS (ESI): 138.06 (MH^+).

_N_-Hydroxy-4-methyl-benzamide (2b):



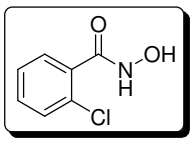
M.p. 145-147 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 2.37 (s, 3H), 7.21 (d, J = 7.6 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 8.72 (br s, 1H), 11.05 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 21.2, 127.2, 129.2, 141.8, 165.8. IR (KBr): 3296, 2760, 1648, 1565, 1508, 1374, 1309, 1161, 1037, 902, 839, 738, 538 cm^{-1}. Elemental analysis: $C_8H_9NO_2$ (151.16): calcd C, 63.57; H, 6.00; N, 9.27. found: C, 63.52; H, 6.10; N, 9.20.

_N_-Hydroxy-2,5-dimethoxy-benzamide (3b):



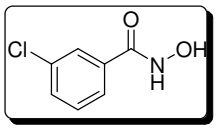
Gummy, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.80 (s, 3H), 3.92 (s, 3H), 6.90 (d, J = 9.2 Hz, 1H), 7.00 (dd, J_1 = 3.2 Hz, J_2 = 2.8 Hz, 1H), 7.70 (d, J = 3.2 Hz, 1H), 10.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 56.0, 56.6, 112.8, 115.2, 118.8, 119.8, 151.5, 154.0, 163.7. IR (KBr): 3305, 2944, 2837, 1645, 1607, 1495, 1282, 1218, 1179, 1043, 813, 735 cm^{-1}. Elemental analysis: $C_9H_{11}NO_4$ (197.19): calcd C, 54.82; H, 5.62; N, 7.10. found: C, 54.80; H, 5.57; N, 7.15.

2-Chloro-_N_-hydroxy-benzamide (4b):



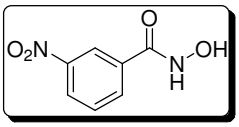
M.p. 150 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.28 (br s, 1H), 7.30 (m, 1H), 7.38 (m, 2H), 7.49 (m, 1H), 10.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 126.6, 129.5, 129.8, 131.1, 131.4, 133.1, 164.3. IR (KBr): 3228, 1632, 1594, 1543, 1474, 1321, 1172, 907, 750, 724, 649 cm^{-1}. Elemental analysis: $C_7H_6ClNO_2$ (171.58): calcd C, 49.00; H, 3.52; N, 8.16. found: C, 48.97; H, 3.51; N, 8.14.

3-Chloro-_N_-hydroxy-benzamide (5b):



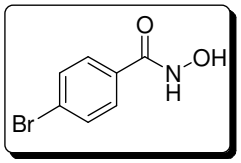
M.p. 169-171 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.46 (m, 2H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 124.4, 126.1, 129.1, 130.1, 132.7, 133.2, 162.6. IR (KBr): 3295, 2758, 1655, 1621, 1564, 1474, 1173, 1047, 796, 747, 726, 673, 530 cm^{-1}. Elemental analysis: $C_7H_6ClNO_2$ (171.58): calcd C, 49.00; H, 3.52; N, 8.16. found: C, 49.08; H, 3.50; N, 8.08.

_N_-Hydroxy-3-nitro-benzamide (6b):



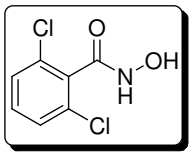
M.p. 142-144 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.64 (t, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.00 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.75 (s, 1H), 11.67 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 122.1, 125.6, 129.5, 133.2, 133.7, 147.9, 162.6. IR (KBr): 3375, 3178, 1670, 1656, 1619, 1521, 1350, 1172, 1035, 933, 715, 671 cm^{-1}. Elemental analysis: $C_7H_6N_2O_4$ (182.14): calcd C, 46.16; H, 3.32; N, 15.38. found: C, 46.18; H, 3.31; N, 15.27.

4-Bromo-_N_-hydroxy-benzamide (7b):



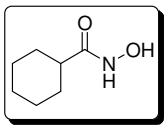
M.p. 184-186 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.10 (br s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 11.25 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 125.3, 128.5, 129.5, 131.1, 163.7. IR (KBr): 3294, 3065, 2754, 1646, 1614, 1591, 1483, 1433, 1329, 1075, 843, 742, 525 cm^{-1}. Elemental analysis: $C_7H_6BrNO_2$ (216.04): calcd C, 38.92; H, 2.80; N, 6.48. found: C, 38.85; H, 2.83; N, 6.46.

2,6-Dichloro-_N_-hydroxybenzamide (9b):



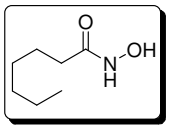
M.p. 165-167 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.30 (br s, 1H), 7.32 (m, 4H), 10.79 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 127.4, 130.5, 132.6, 133.4, 160.9. IR (KBr): 3227, 3031, 2905, 1630, 1580, 1524, 1433, 1310, 1194, 1098, 1025, 901, 804, 780, 467 cm^{-1}. Elemental analysis: $C_7H_5Cl_2NO_2$ (206.03): requires C, 40.81; H, 2.45; N, 6.80. found: C, 40.81; H, 2.41; N, 6.78.

_N_-hydroxycyclohexanecarboxamide (10b):



M.p. 120 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (m, 3H), 1.47 (m, 2H), 1.69 (m, 1H), 1.80 (m, 4H), 2.08 (m, 1H), 8.37 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 25.4, 28.6, 29.0, 41.7, 174.0. IR (KBr): 3296, 2852, 1632, 1541, 1449, 1142, 1060, 963, 808, 753, 663, 617 cm^{-1}. Elemental analysis: $C_7H_{13}NO_2$ (143.18): requires C, 58.72; H, 9.15; N, 9.78. found: C, 58.77; H, 9.18; N, 9.76.

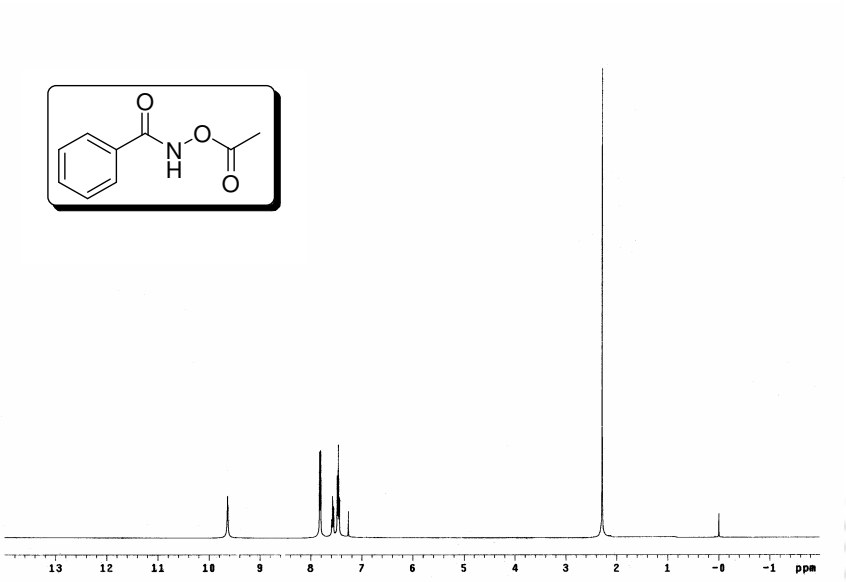
_N_-hydroxyheptanamide (12b):



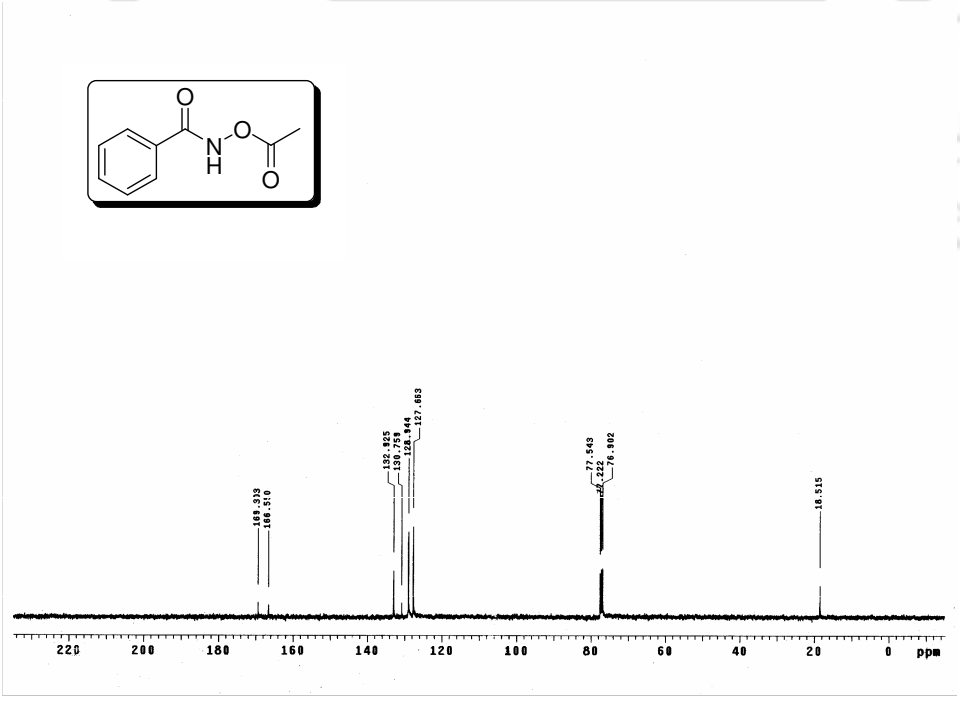
M.p. 72-74 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J = 6.0 Hz, 3H), 1.18 (m, 6H), 1.47 (m, 2H), 2.01 (m, 2H), 9.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 14.1, 22.7, 25.7, 29.3, 29.8, 31.7, 171.7. IR (KBr): 3250, 2857, 1644, 1467, 1401, 1176, 1125, 1037, 1011, 816, 690, 615, 570 cm^{-1}. Elemental analysis: $C_7H_{15}NO_2$ (145.20): requires C, 57.90; H, 10.41; N, 9.65. found: C, 57.93; H, 10.40; N, 9.61.

II.7. Selected Spectra

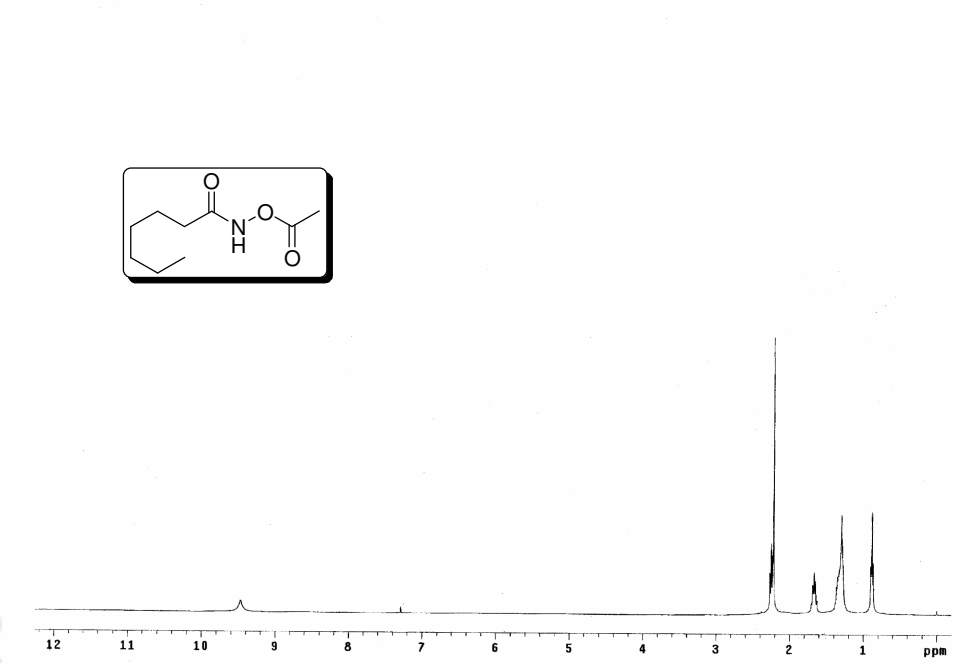
N-Acetoxy-benzamide (1a): ^{1}H NMR (400 MHz, $CDCl_3$):



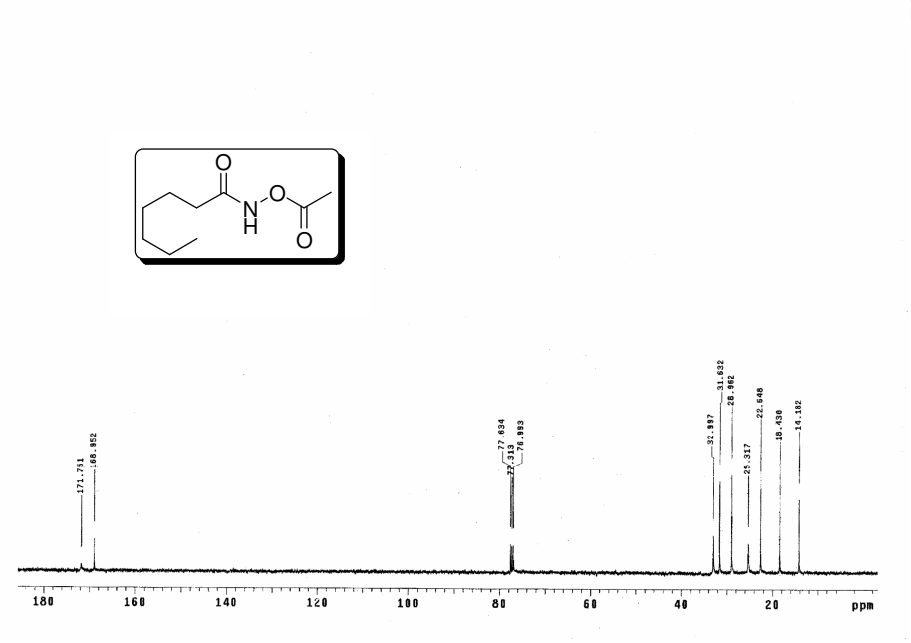
N-Acetoxy-benzamide (1a): ^{13}C NMR (100 MHz, $CDCl_3$):



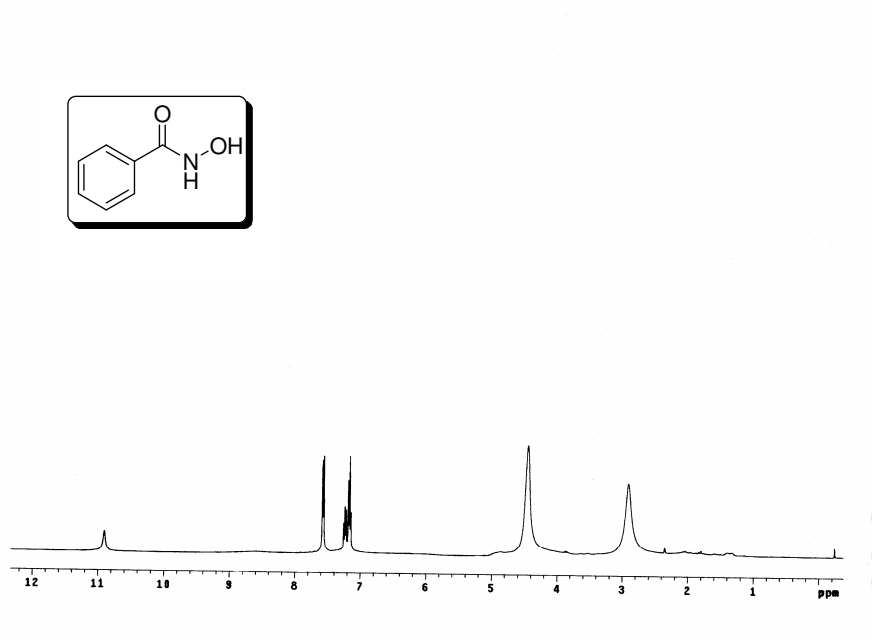
Heptanoic acid acetoxy-amide (12a): ^{1}H NMR (400 MHz, $CDCl_3$):



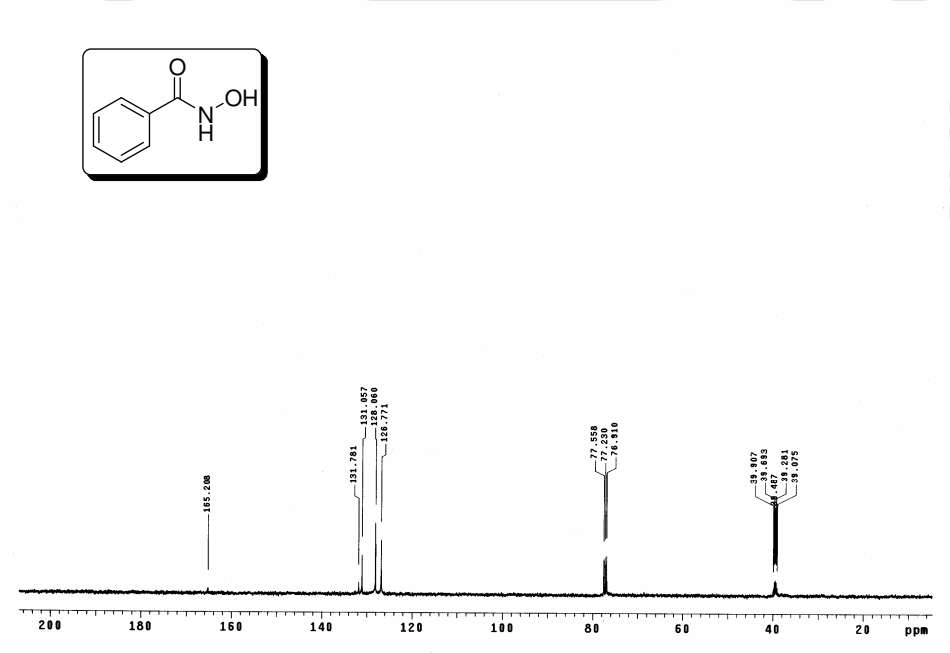
Heptanoic acid acetoxy-amide (12a): ^{13}C NMR (100 MHz, $CDCl_3$):



***N*-Hydroxy-benzamide (1b): ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6):**



***N*-Hydroxy-benzamide (1b): ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6):**



CHAPTER III

III. Oxidative *N*-Acylation of 1,3-Disubstituted Thioureas to *N*-Acylureas

III.1. Importance and Applications

There is a great deal of interest in the chemistry of 1,3-disubstituted thioureas, ureas and *N*-acetyl ureas owing to their wide applications in synthetic organic chemistry. Ureas and thioureas are useful synthons for the construction of heterocyclic compounds.[1] *N*-Acylureas have found important applications in agrochemicals and pharmaceuticals.[2a-c] Dopamine D2 agonist cabergoline (*Figure III.1.1*), having an *N*-acyl derivative is an anti-Parkinson agent.[2d]

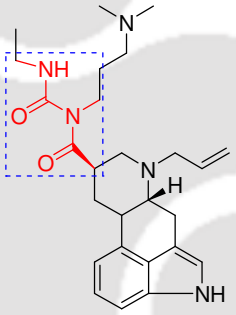
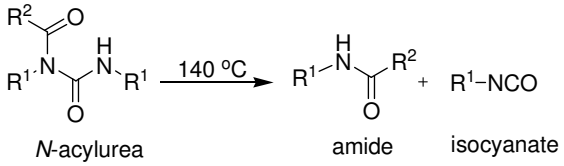


Figure III.1.1. *Cabergoline*

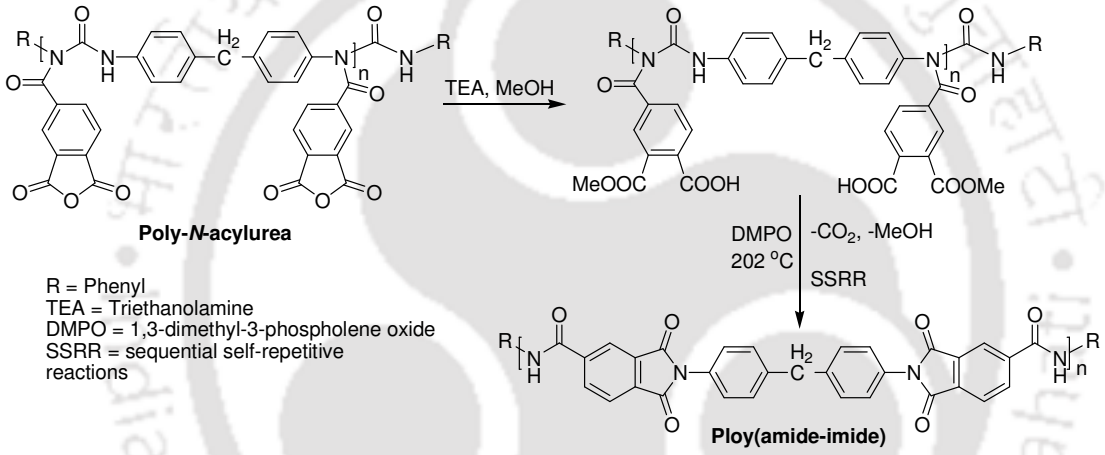
III.1.1. Applications in Organic Synthesis

N-Acylated urea is a well-known side product during the preparation of peptide bond[3a,b] and ester[3c] using carbodiimide as coupling reagent. *N*-Acylated urea products can be employed as interesting semi-crystalline materials and auxiliaries for the preparation of chiral cyclic carboxylic acids.[4] Derivatives of acyl urea have been used for the allylation of sulfoxides,[5a] Claisen rearrangement,[5b] Diels-Alder reaction,[5c,d] nucleophilic addition of TMSCN,[5e] Michael addition,[5f] and enantioselective Strecker and Mannich reactions.[5g-i] The *N*-acylurea is stable below 140 °C but decomposes at a higher temperature into fragments consisting of isocyanates and amides (*Scheme III.1.1.1*).



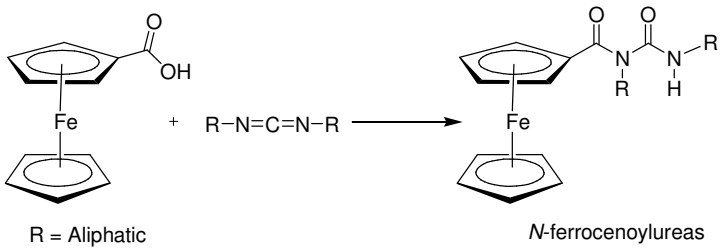
Scheme III.1.1.1.

The thermal conversion of an *N*-acylurea into an isocyanate and an amide is a well documented reaction in organic transformations.[6a-c] In a report, Dai *et. al* described the preparation of aryl *N*-acylureas in high yield, their consequential thermal reactions, and applications in a stepwise synthesis of aryl amides and polyamides (*Scheme III.1.1.2*).[6d]



Scheme III.1.1.2.

It is well-known that ferrocene unit acts as a redox active building block in larger molecular structures, or in new medicinal drugs, where it is often bound by amide linkers. Speiser and co-workers discovered a novel route to activate ferrocene carboxylic acids through the formation of *N*-ferrocenoylureas under mild conditions (*Scheme III.1.1.3*).[6e]

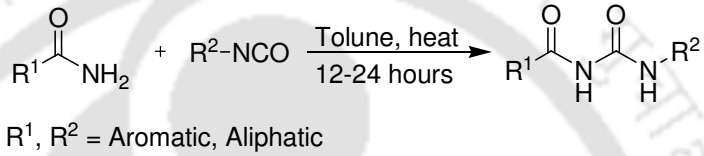


Scheme III.1.1.3.

III.2. Available Synthetic Methods

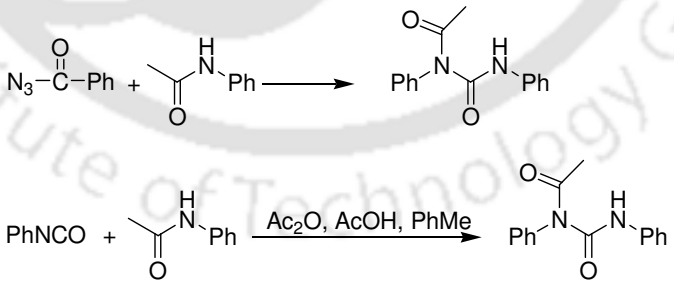
A careful scrutiny of the literature reports reveals that *N*-acylureas have been prepared mainly from isocyanates, 1,3-disubstituted ureas and carbodiimides, out of which the carbodiimide approach is the most frequently adopted method. Some of the synthetic methods reported in the literature are discussed below.

Wiley reported the preparation of *N*-acylurea by reacting unsubstituted amides and isocyanates (*Scheme III.2.1*).[7a]



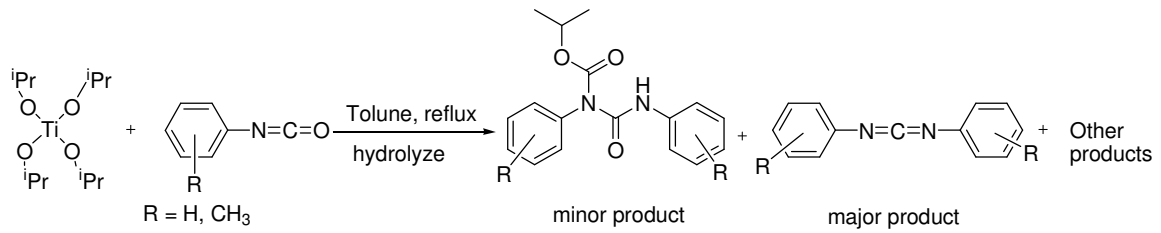
Scheme III.2.1.

Schweim reported the preparation of *N*-acylurea in 14-69.7% yield by the reaction of $RCONHR^1$ with R^2CON_3 (*Scheme III.2.2*). But it is also reported that treatment of PhNCO with Ac_2O, followed by $MeCONHR^1$ (R^1 = Ph, Me) gave poorer yields of $AcNR^1CONHPh$ than the other methods.[7b]



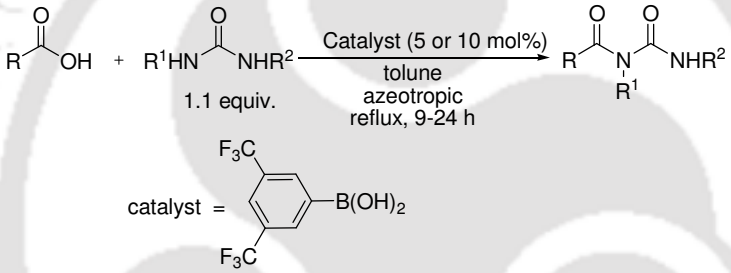
Scheme III.2.2.

Samuelson and co-workers reported the formation of trace amount of *N*-acylurea while investigating the insertion of isopropoxide ligand of titanium isopropoxide into aryl isocyanate (*Scheme III.2.3*).[7c]



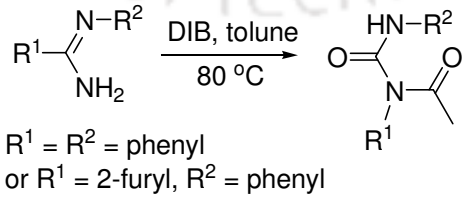
Scheme III.2.3.

Yamamoto and co-workers demonstrated that arylboronic acids bearing an electron-withdrawing substituents are efficient catalyst for the direct condensation of carboxylic acids with ureas (*Scheme III.2.4*). Using that catalytic condensation method, they have prepared a wide range of monoacylureas from their corresponding ureas.[7d]



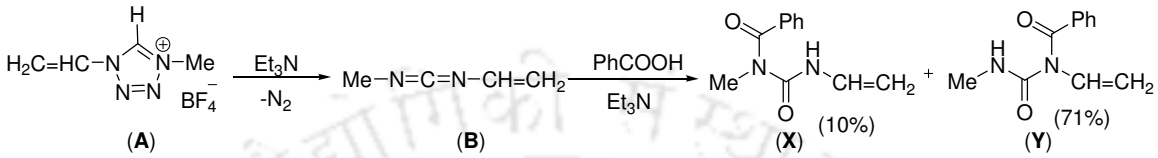
Scheme III.2.4.

Ramsden and his co-workers reported the hypervalent iodine(III) reagent (diacetoxyiodo)benzene (DIB) mediated oxidation of benzimidamide to *N*-acetylurea (*Scheme III.2.5*). The formation of carbodiimide intermediate and its concerted rearrangement upon attack with acetic acid (released from reagent DIB) to *N*-acetylurea have been discussed as the mechanism of the reaction.[7e]



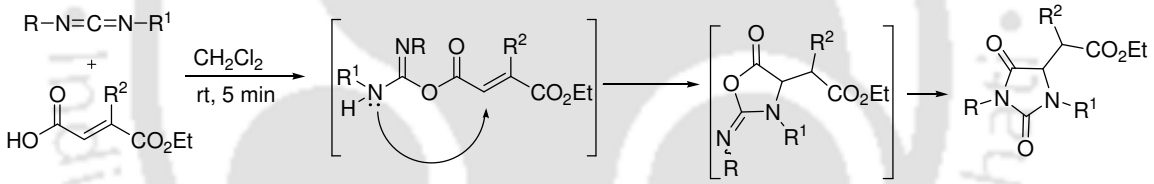
Scheme III.2.5.

Olofson and co-workers reported the formation of a mixture of *N*-acylated urea starting from 1-vinyltetrazole (**A**) (*Scheme III.2.6)*. 1-Vinyltetrazole upon treatment with Et_3N in several solvents liberates N_2 and forms the *N*-methyl-*N*-vinylcarbodiimide (**B**). The reaction of *N*-methyl-*N*-vinylcarbodiimide with benzoic acid in the presence of Et_3N afforded a mixture of two *N*-acylureas (**X**) and (**Y**) in the ratio 1:7 (*Scheme III.2.6*).[7f]



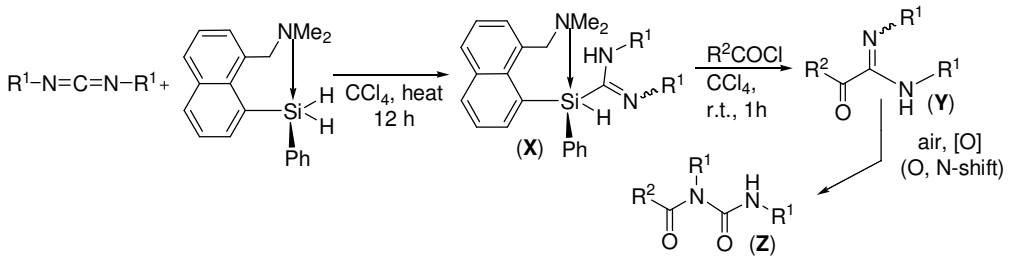
Scheme III.2.6.

Zanda *et. al.* reported domino condensation/aza-Michael/O-N acyl migration of activated α,β-unsaturated carboxylic acids with carbodiimides, producing the cyclic *N*-acyl urea derivatives *N*,*N*-disubstituted hydantoins in good yields (*Scheme III.2.7*).[7g]



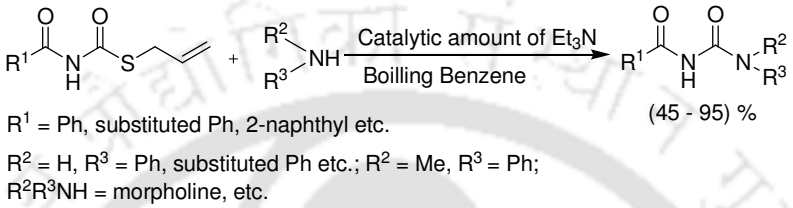
Scheme III.2.7.

Corriu *et. al.* described the hydrosilylation of diisopropylcarbodiimide and dicyclohexylcarbodiimide in refluxing carbon tetrachloride for 12 hours to form the C-silylated compounds (**X**) (*Scheme III.2.8*). The intermediate (**X**) upon treatment with acyl chloride undergoes Si-C bond cleavage to form *C*-acyl amidines (**Y**). In the presence of air, the C-acyl amidines are oxidized to *N*-acyl ureas (**Z**).[7h]



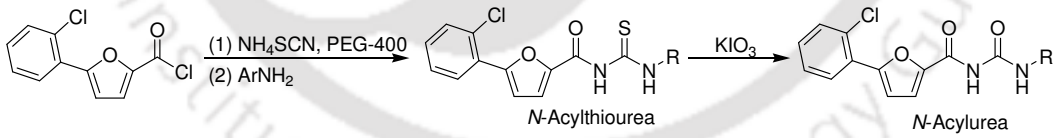
Scheme III.2.8.

Kutschy *et. al.* demonstrated that *S*-allyl *N*-acylmonothiocarbamates react in boiling benzene with primary and secondary amines in the presence of a catalytic amount of triethylamine to form *N*-acylurea in 45-95% yield (*Scheme III.2.9*). It is reported that the *S*-allyl group is replaced with the amino group affording the *N*-acylurea derivatives in 45-90% yields.[7i]



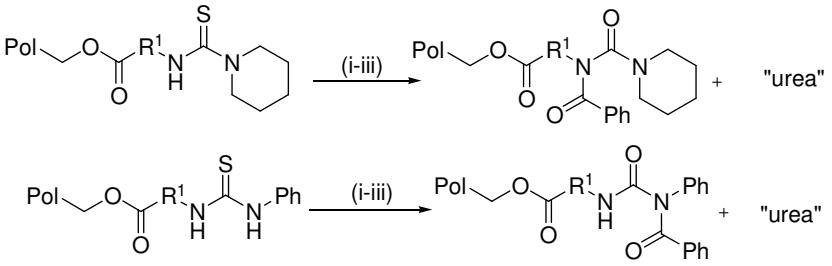
Scheme III.2.9.

Wang *et. al.* discovered a novel route to acyl urea. They reported that reaction of 5-(2-chlorophenyl)-2-furoyl chloride with ammonium thiocyanate, followed by reaction with arylamine under phase transfer catalysis gave N-[5-(2-chlorophenyl)-2-furoyl]-*N'*-arylthioureas, which on potassium iodate mediated oxidation under reflux resulted in the formation of *N*-[5-(2-Chlorophenyl)-2-furoyll-*N'*-arylureas (*Scheme III.2.10*).[7j]



Scheme III.2.10.

Lau *et. al.* developed a novel method for the synthesis of tri- and disubstituted *N*-acyl ureas utilizing resin-bound carbimidoyl chlorides and carbodiimide respectively (*Scheme III.2.11*). Carboxylic acids were added to a resin-bound carbimidoyl chloride affording *O*-acyl isourea which subsequently rearranged to the corresponding *N*-acyl urea.[8a]

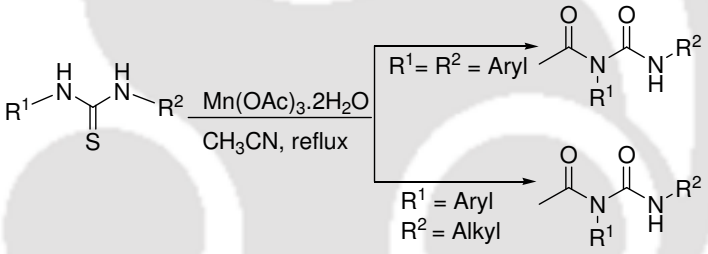


Where Pol = Wang PS, R^1 = 4-$CH_2(C_6H_4)CH_2$

Reagents and conditions: (i) C_2Cl_6, PPh_3, dry THF, 20 °C, 5 h; (ii) $PhCO_2H$, 1,4-dioxane, Et_3N, 20 °C, 16 h; (iii) TFA/DCM (1:1, v/v) 20 °C, 1 h.

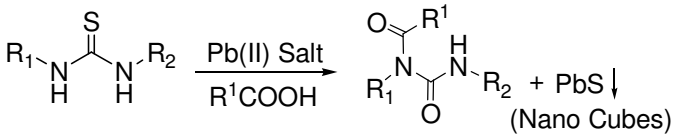
Scheme III.2.11.

Mu *et. al.* developed a method for the synthesis of *N*-acetylureas by manganese(III) acetate reaction of 1,3-disubstituted-thioureas (*Scheme III.2.12*). They have reported the formation of interesting regioselective *N*-acetylureas of asymmetrical 1,3-disubstituted-thioureas.[8b]



Scheme III.2.12.

Very recently our group has demonstrated a highly efficient method for the *N*-acylation of both symmetrical and unsymmetrical thioureas by the use of lead(II) salts and triethylamine (*Scheme III.2.13*). Investigation of p*Ka* dependent regioselectivity along with characterization of a side product, nano crystallite lead sulfide (nanocubes of 20 nm), which is important to material science, has been discussed.[8c]

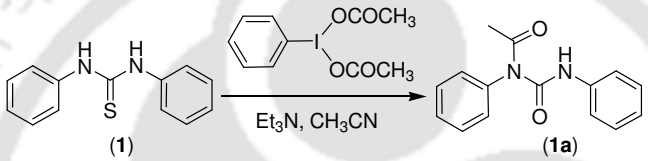


Scheme III.2.13.

III.3. Present Work

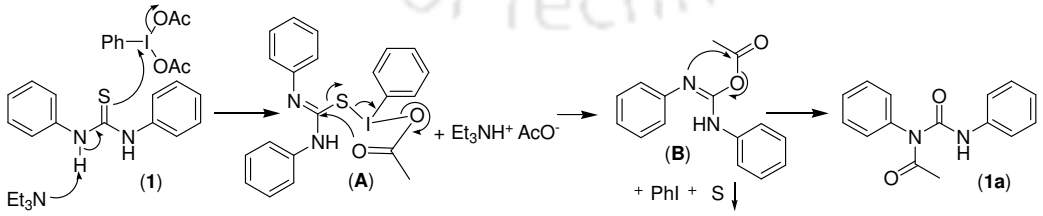
III.3.1. Hypervalent Iodine(III) Mediated Regioselective *N*-Acylation of 1,3-Disubstituted Thioureas

In continuation to our interest in the chemistry of hypervalent iodine(III) mediated oxidation reactions,[9] we have investigated the oxidation result of 1,3-disubstituted-thiourea with (diacetoxyiodo)benzene(DIB). We have demonstrated an unprecedented regioseletive *N*-acetylation of disubstituted thioureas leading to *N*-acetyl ureas using (diacetoxyiodo)benzene (DIB) as shown in *Scheme III.3.1*.



Scheme III.3.1. *N-Acylurea from thiourea*

In organic chemistry, $Mn(OAc)_3$ has been most commonly used in the generation of carbon centered radicals from various carbonyl compounds and their oxidative addition to alkenes.[10] However, significant drawbacks to the use of $Mn(OAc)_3$ are the harsh reaction condition and its poor solubility in organic solvents. On the other hand, (diacetoxyiodo)benzene in the presence of iodine or under photochemical condition generates radicals. This similarity between (diacetoxyiodo)benzene (DIB) with $Mn(OAc)_3$ and the *N*-acetylating ability[8b] of the later reagent prompted us to use metal free reagent (diacetoxyiodo)benzene for the preparation of *N*-acetyl urea.



Scheme III.3.2. *Proposed mechanism of formation of N-acylurea*

In a typical reaction, equimolar mixture of 1,3-diphenyl-thiourea **1**, triethylamine and (diacetoxyiodo)benzene (DIB) were mixed together in acetonitrile and the reaction mixture was stirred at room temperature. The reaction was completed within five minutes giving *N*-acetylated product **1a** in good yield. The proposed mechanism for the formation of *N*-acetylated product is shown in *Scheme III.3.2*.

The sulfur atom of the 1,3-disubstituted-thiourea attacks the thiophilic iodine of $PhI(OAc)_2$ displaying one of the acetate group giving the intermediate (**A**) which is then followed by an intra-molecular nucleophilic attack of the carbonyl group of the acetate on the imine carbon giving sulfur and phenyliodide as byproducts. Formation of elemental sulfur and phenyl iodide has actually been confirmed by their isolation and characterization. The resultant 2-acetyl-1,3-disubstituted-isourea (**B**) rearranges to 1-acetyl-1,3-disubstituted-urea **1a** as shown in *Scheme III.3.2*. The structure of *N*-acylated product **1a** has been confirmed by crystal X-ray crystallography (*Figure III.3.1*).

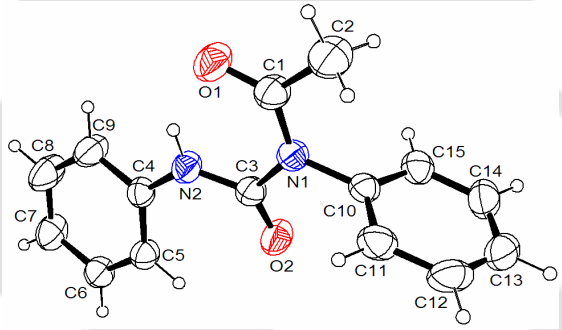
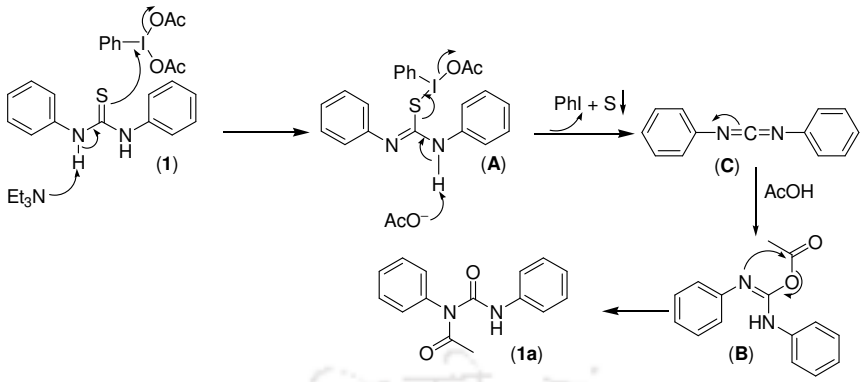


Figure III.3.1. *ORTEP view of (**1a**) with atom-numbering scheme*

However, when the reaction of **1** was carried out in the presence of one equivalent of propionic acid and an additional equivalent of triethylamine, it gave *N*-acetylated product **1a** along with the formation of propionylated product **1a'** in the ratio 58 : 42. In a second experiment, the reaction was carried out with a five fold excess of propionic acid and triethylamine wherein the products **1a** and **1a'** obtained were in the ratio 17 : 83. The formation of propionylated product **1a'** rules out any possibility of an intramolecular mechanism as proposed in *Scheme III.3.2*.



Scheme III.3.3. *Proposed mechanism of formation of N-acylurea*

In another experiment, a similar competitive reaction with dodecanoic acid gave the dodecanylated product (**1a''**) in good yield (64%). The structure of *N*-dodecanylated product (**1a''**) has been confirmed by crystal X-ray crystallography (*Figure III.3.2*).

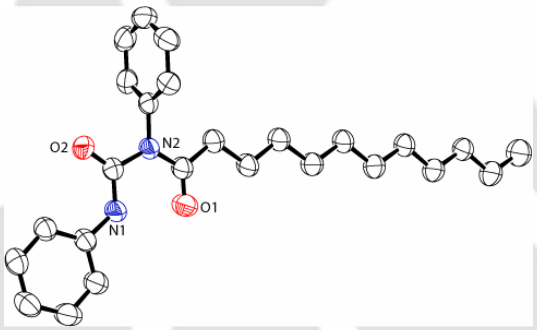


Figure III.3.2. *The ORTEP view with the atomic numbering scheme of (**1a''**)*

Based on the above two cross-over experiments, a mechanism involving the intermediacy of carbodiimide seems to be a reasonable proposition as shown in *Scheme III.3.3*. Reductive β-elimination of λ^3-iodane intermediate (**A**) with the expulsion of sulfur will produce carbodiimide (**C**) (*Scheme III.3.3*), which on reaction with acetic acid, liberated in the medium, would give 2-acetyl-1,3-disubstituted-isourea. Infrared spectral analysis of the reaction mixture showed a characteristic peak for carbodiimide group at 2138 cm^{-1}. Further, the isolation of stable carbodiimide **10a** (*Table III.3.1*) is testimony to this fact and support the mechanism proposed in *Scheme III.3.3*. However similar reactions were not successful for ureas, probably due to the lower acidity of the NH protons in urea and lesser affinity of oxygen towards iodine compared to sulfur present in thioureas.

Compound **1a''** is having a polar head, the urea moiety and a hydrophobic unit, the long alkyl chain. The phenyl ring attached to the acylated N (N2) is almost perpendicular to the long hydrocarbon chain and the other phenyl ring. The amide proton (H1), forms a strong 6-membered cyclic intramolecular H- bonding with the carbonyl oxygen O1 (N1-H1—O1 = 1.87 Å). It also forms weak C-H…π intermolecular H- bonding (C8-H8….centroid C1-C6 = 3.08 Å). Long hydrophobic chains are packed along a- axis and the overall crystal forms alternate disposition of hydrophobic chains along c- axis. The crystal is packed along bc plane in alternate layer of hydrophobic and hydrophilic part (*Figure III.3.3.*). This class of compound might find interesting applications as nonionic surfactant used in no tears shampoo.

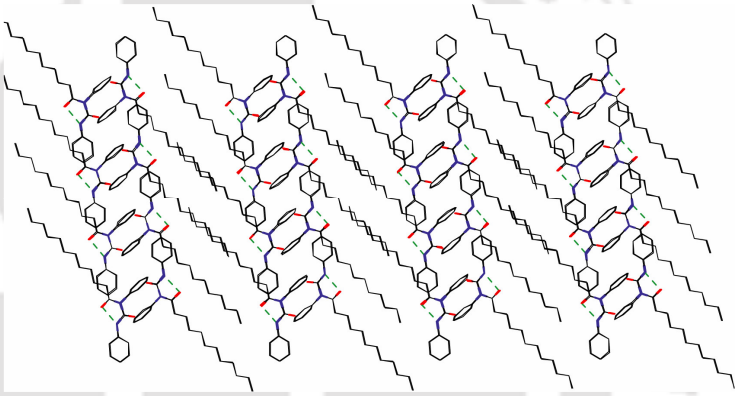


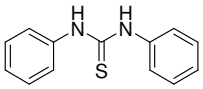
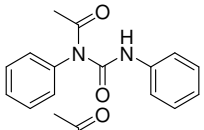
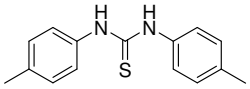
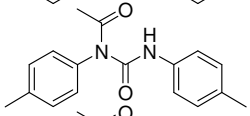
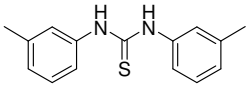
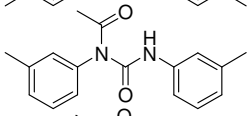
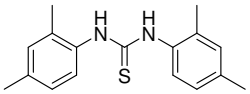
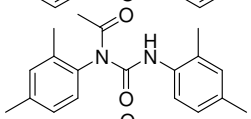
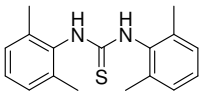
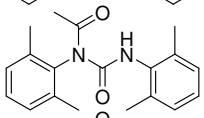
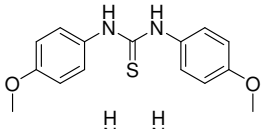
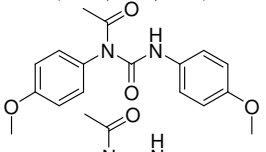
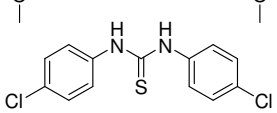
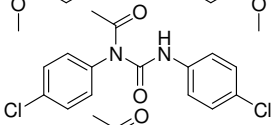
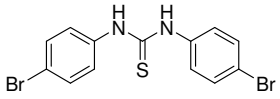
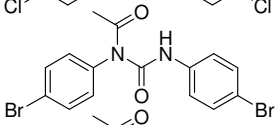
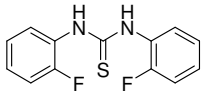
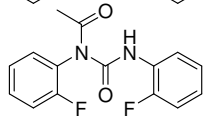
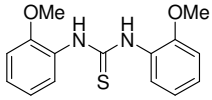
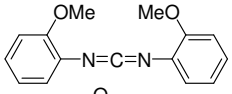
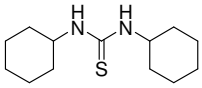
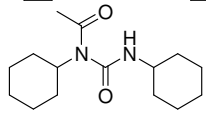
Figure III.3.3. *The lattice diagram of dodecanylated product (**1a''**)*

Several symmetrical thioureas **2**-**9** having various substituents in the phenyl ring gave their corresponding mono N-acylated ureas **2a**-**9a** within 5 minutes giving excellent yields of the products as shown in *Table III.3.1*, but for uniformity all the reactions were allowed to stirr for 15 minutes.

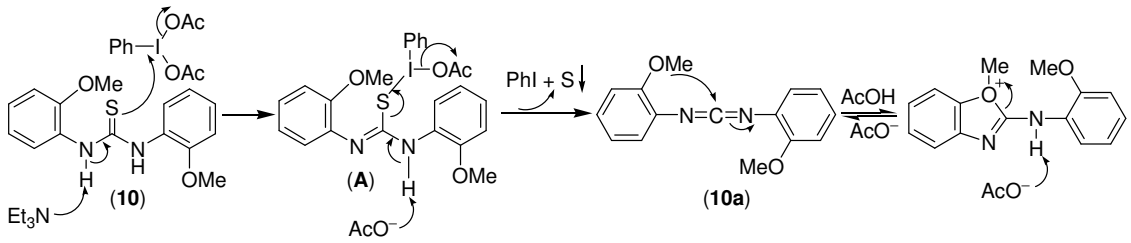
When the reaction was performed with 1,3-bis-(2-methoxy-phenyl)-thiourea **10**, no *N*-acetylated product was observed and the only isolated product obtained was found to have bis-(2-methoxy-phenyl)-carbodiimide **10a** moiety. The stability of carbodiimide **10a** can be explained by the neighboring group participation of *o*-methoxy group from the adjacent phenyl ring as shown in *Scheme III.3.4*. Aliphatic thiourea **11**, does not undergo *N*-acylation, this may be due to difficulty in deprotonating due to the substantial basic

character of cyclohexylamine (p*Ka* 10.66). This observation is consistent with the *N*-acylation using $Mn(OAc)_3$.[8b]

Table III.3.1. *N-Acylureas from thioureas*[a]

Entry	Substrate	Product[b]	Yield (%)[c]
(**1**)		 (**1a**)	92
(**2**)		 (**2a**)	95
(**3**)		 (**3a**)	96
(**4**)		 (**4a**)	91
(**5**)		 (**5a**)	72
(**6**)		 (**6a**)	96
(**7**)		 (**7a**)	70
(**8**)		 (**8a**)	72
(**9**)		 (**9a**)	65
(**10**)		 (**10a**)	90
(**11**)		 (**11a**)	00

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



Scheme III.3.4. *Proposed mechanism of formation of carbodiimide*

Having successfully synthesized a series of *N*-acylated ureas, we were interested in regioselective *N*-acylation of unsymmetrical thiourea. We have found that the larger the difference between the p*Ka*'s of the precursors amines in thiourea the greater the regioselectivity of *N*-acylation with preferential acylation taking place towards the amine having lower p*Ka*. Unsymmetrical thiourea **12** would form an unsymmetrical carbodiimide as the intermediate. The attack of acetic acid on unsymmetrical carbodiimide would lead to the protonation towards the amine having higher p*Ka* unaffecting the imine group on the other side. The resultant isourea on rearrangement would yield *N*-acylated product in regioselective manner. For 1-phenyl-3-*p*-tolyl thiourea (**12**), the phenyl side is acylated 60% compared to *p*-tolyl side (40%) as evident from the ^{1}H NMR. The measured p*Ka*'s of aniline and *p*-methyl aniline are 4.61 and 5.08 respectively supporting our arguments and the mechanism involving carbodimide intermediate (*Scheme III.3.4*). The structure of *N*-acylated product **12b** has been confirmed by crystal X-ray crystallography (*Figure III.3.4*).

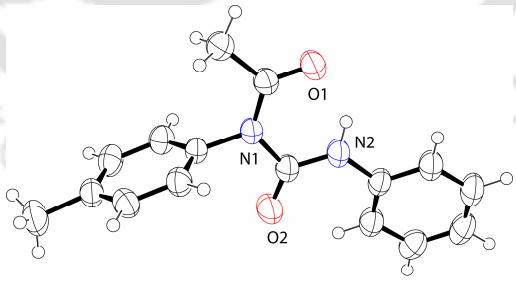


Figure III.3.4. *ORTEP view of (**12b**) with atom-numbering scheme*

The measured p*Ka*'s of both *p*-chloro (4.15) and *p*-bromo (3.86) anilines are lower than aniline (4.61), hence the preferential *N*-acylation towards the *p*-chloro and *p*-bromo aniline

side in substrates **13** and **14** giving **13b** and **14b** as the major product as shown in *Table III.3.2*. The measured p*Ka*'s of *o*-fluoro (p*Ka* 3.20), *o*-chloro (p*Ka* 2.65), *o*-iodo (p*Ka* 2.60) and *o*-methoxy (p*Ka* 4.52) anilines are lower than that of aniline (p*Ka* 4.63); thus, the preferential *N*-acylation took place toward the *o*-fluoro, *o*-chloro, *o*-iodo and *o*-methoxy aniline sides in substrates **15**, **16**, **17** and **18**, giving major products **15b**, **16b**, **17b**, and **18b**, respectively. The structure of *N*-acylated product **18b** has been confirmed by crystal X-ray crystallography (*Figure III.3.5*).

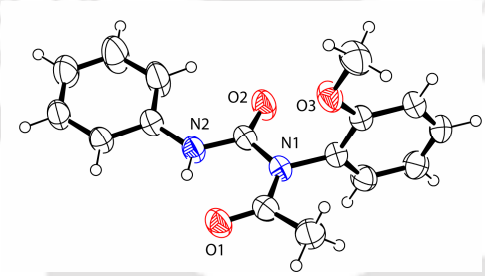


Figure III.3.5. *ORTEP view of (**18b**) with atom-numbering scheme*

In substrates **19** and **20** possessing *p*-methoxy and 2,4-dimethyl aniline, the measured p*Ka*'s of the parent amines are 5.34 and 4.88, respectively. These values are higher as compared to aniline; thus, preferential acylation took place toward the aniline side to afford regioselective products **19a** and **20a**, respectively. The product **19a** crystallized out preferentially and has been confirmed by crystal X-ray crystallography (*Figure III.3.6*).

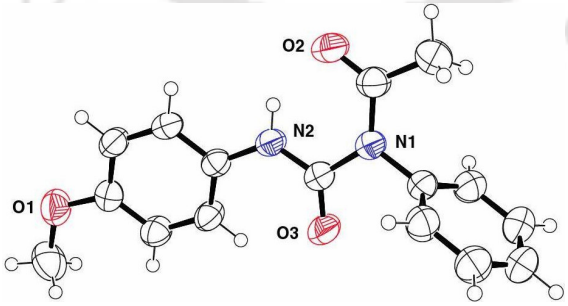
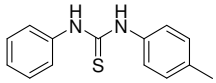
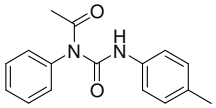
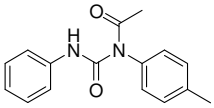
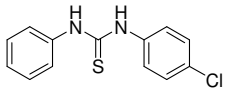
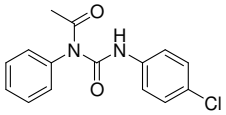
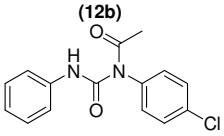
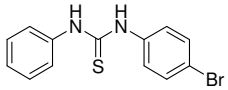
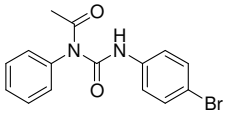
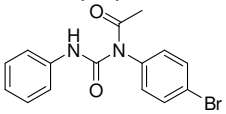
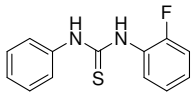
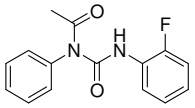
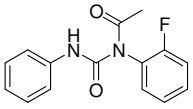
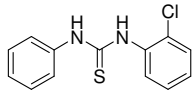
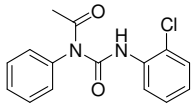
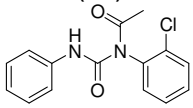
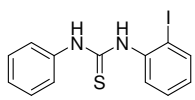
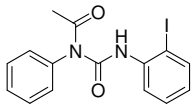
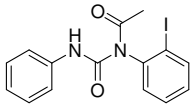
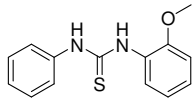
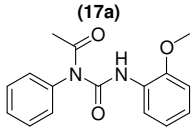
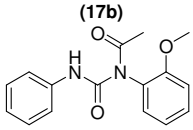
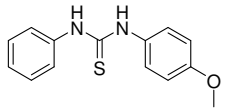
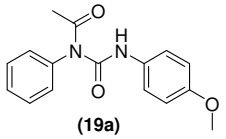
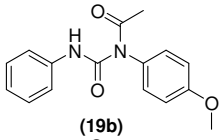
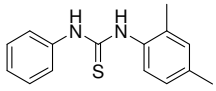
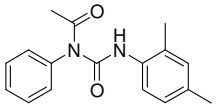
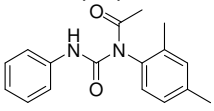


Figure III.3.6. *ORTEP view of (**19a**) with atom-numbering scheme*

Table III.3.2. *Regioselective N-acylation of thioureas to N-acylureas*[a]

Entry	Substrate	Product[b]	Yield (%)[c]
(12)		 (12a)  (12b)	86 (60 : 40)
(13)		 (13a)  (13b)	76 (40 : 60)
(14)		 (14a)  (14b)	85 (33: 67)
(15)		 (15a)  (15b)	87 (20 : 80)
(16)		 (16a)  (16b)	91 (19 : 81)
(17)		 (17a)  (17b)	81 (32 : 68)
(18)		 (18a)  (18b)	88 (43 : 57)
(19)		 (19a)  (19b)	86 (55 : 45)
(20)		 (20a)  (20b)	96 (73 : 27)

[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 the regioselectivity observed. The p*Ka* difference and the ratio of regioselectivity are tabulated in *Table III.3.3* and shown graphically in *Figure III.3.5*. The ratios of regioselectivities were calculated assuming the *N*-acylation toward the aniline

nitrogen side 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 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 III.3.3*). A direct correlation between the p*Ka* difference and regioselectivity should fall on a straight line. From the graph (*Figure III.3.5*), there seems to be few deviations in the cases of **15**, **16** and **17** having fluoro, iodo and methyl groups in the *o*-position. These deviations may be due to the steric factors of these substituents.

Table III.3.3. *Regioselective N-acylation of thioureas to N-acylureas as a function of* p*Ka*

Thioureas	pKa_1-pKa_2[a]	Ratio of regioselectivity
(12)	(-) 0.45	1 : 0.66
(13)	(+) 0.48	1 : 1.15
(14)	(+) 0.77	1 : 2.03
(15)	(+) 1.43	1 : 4.00
(16)	(+) 1.98	1 : 4.26
(17)	(+) 2.03	1 : 2.13
(18)	(+) 0.11	1 : 1.32
(19)	(-) 0.71	1 : 0.81
(20)	(-) 0.25	1 : 0.36

Notes: [a] pKa_1= p*Ka* of aniline, pKa_2= p*Ka* of other amine attached to thiourea

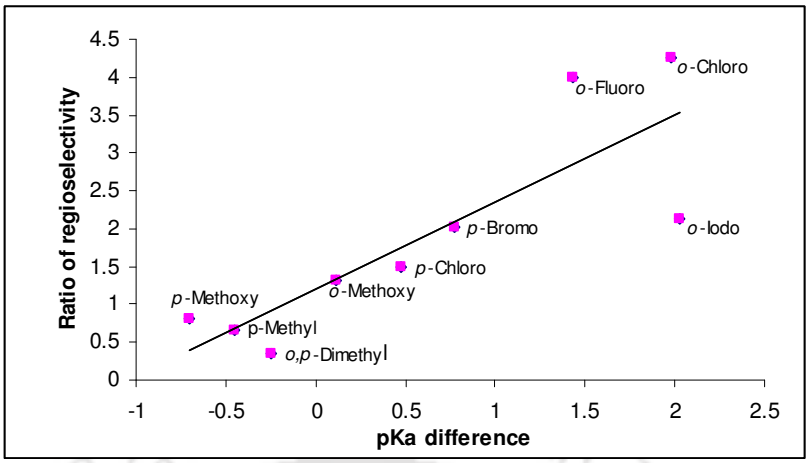
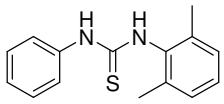
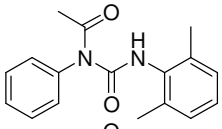
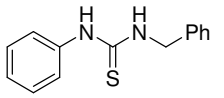
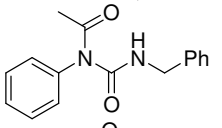
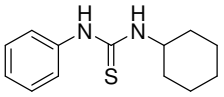
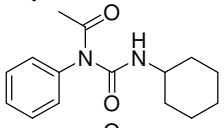
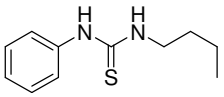
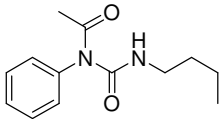


Figure III.3.7. *Plot of* p*Ka dependent regioselectivity*

Although the p*Ka* difference between the 2,6-dimethyl aniline (p*Ka* 4.74) and aniline (p*K*a 4.61) in substrate **21** is small, it gave exclusively regioselective product **21a** instead of a mixture of products *(Table III.3.4)*. This is presumably due to the steric factor imparted by the two *o*-substituted methyl groups. Again, the higher acidic character of the aromatic amine aniline compared to aliphatic amines such as benzylamine (p*Ka* 9.41), cyclohexylamine (p*Ka* 10.66) and *n*-butylamine (p*Ka* 10.77) indicates that the acylation is towards the aniline side of the urea as shown for substrates **22**, **23** and **24** giving regioselective products **22a**, **23a** and **24a** respectively *(Table III.3.4)*.

Table III.3.4. *N-Acylureas from thioureas*

Entry	Substrate	Product[b]	Yield (%)[c]
(**21**)		 (**21a**)	82
(**22**)		 (**22a**)	65
(**23**)		 (**23a**)	70
(**24**)		 (**24a**)	50

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

In conclusion, we have reported an efficient method for the synthesis of *N*-acylated ureas from 1,3-disubstituted-thioureas using environmentally benign reagent (diacetoxyiodo)benzene (DIB). For the first time, DIB has been employed as an acylating agent. We have also found the correlation between the regioselectivity and the p*Ka* of the amine. Compared to the existing arduous methods of synthesis this methodology is superior in terms of environmental acceptability, simplicity, convenience and general applicability.

III.4. Experimental Section

III.4.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1, page 48-49.

III.4.2. General Procedures

III.4.2.1. General Procedure for the Preparation of *N*-Acylated Urea (1a) from Thiourea (1)

To a stirred solution of diphenylthiourea **1** (456 mg, 2 mmol) and triethylamine (276 µL, 2 mmol) in acetonitrile (10 mL) was added DIB (644 mg, 2 mmol) at room temperature and the mixture was allowed to stir for 15 minutes. Precipitation of sulfur was observed during this period. After completion of the reaction, solvent was evaporated and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed subsequently with saturated solution of $NaHCO_3$ (5 mL) and 5 % solution of sodium thiosulphate (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure and purified over a silica gel column (Hexane / EtOAc, 9:1) to give (419 mg, 92 %) of the product **1a**. Compound **1a** was recrystallized from a mixture of EtOAc : hexane (8 : 2) to give colorless crystal.

III.4.2.2. Preparation of *N*-Propionylated Urea (1a') from Thiourea (1)

To a stirred solution of diphenylthiourea **1** (456 mg, 2 mmol), triethylamine (982 µL, 7 mmol) and propionic acid (374 µL, 5 mmol) in acetonitrile (10 mL) was added DIB (644 mg, 2 mmol) at room temperature and the mixture was allowed to stir for 15 minutes. Precipitation of sulfur was observed during this period. After completion of the reaction, solvent was evaporated and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed subsequently with saturated solution of $NaHCO_3$ (5 mL) and 5 % solution of sodium thiosulphate (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. ^{1}H NMR analysis of the crude reaction mixture shows the formation of 1,3-diphenyl-1-propionyl-urea **1a'** and 1-acetyl-1,3-diphenyl urea **1a** in the ratio 83 : 17. Compound **1a'** was and purified over a silica gel column (Hexane / EtOAc, 9:1) to give (376 mg, 70 %) of the product 1,3-diphenyl-1-propionyl-urea **1a'**. Compound **1a'** was recrystallized from a mixture of EtOAc : hexane (8 : 2) to give a colorless needle crystal.

III.5. References

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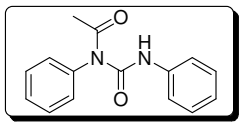
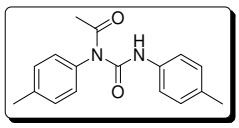
III.6. Spectral Data

1-Acetyl-1,3-diphenylurea (1a):



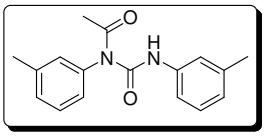
M.p. 100-102 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 7.08 (t, 1H, *J* = 7.2 Hz), 7.28 (m, 4H), 7.48 (m, 5H), 11.44 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 26.8, 120.3, 124.3, 129.1, 129.2, 129.3, 129.9, 137.8, 139.0, 152.1, 175.2. IR (KBr): 3230, 2928, 2857, 1722, 1668, 1602, 1544, 1492, 1445, 1166, 1050, 823, 751, 699 cm^{-1}. HRMS (ESI): MH^+, found 255.2946, $C_{15}H_{15}N_2O_2$ requires 255.2957.

1-Acetyl-1,3-di-*p*-tolylurea (2a):



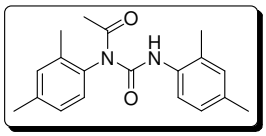
M.p. 138-140 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 7.10 (d, 2H, *J* = 8.0 Hz), 7.14 (d, 2H, *J* = 8.4 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 8.0 Hz), 11.35 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 20.9, 21.3, 26.7, 120.2, 128.8, 129.6, 130.5, 133.6, 135.3, 136.4, 139.1, 152.1, 175.2. IR (KBr): 3176, 3053, 2920, 2872, 1712, 1688, 1597, 1523, 1452, 1310, 1165, 813 cm^{-1}. HRMS (ESI): MH^+, found 283.3488, $C_{17}H_{19}N_2O_2$ requires 283.3493.

1-Acetyl-1,3-di-(*m*-methylphenyl)urea (3a):



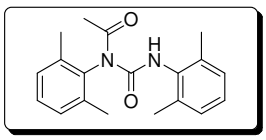
M.p. 82-84 °C, ^{1}H NMR (400 MHz $CDCl_3$): δ 2.00 (s, 3H), 2.31 (s, 3H), 2.40 (s, 3H), 6.90 (d, 1H, *J* = 7.2 Hz), 7.07 (d, 1H, *J* = 7.2 Hz), 7.08 (s, 1H), 7.17 (t, 1H, *J* = 7.6 Hz), 7.25 (d, 1H, *J* = 7.6 Hz), 7.29 (d, 1H, *J* = 8 Hz), 7.37 (t, 1H, *J* = 7.6 Hz), 7.46 (s, 1H), 11.40 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 21.3, 21.5, 26.5, 117.2, 120.8, 124.8, 125.9, 128.8, 129.5, 129.8, 137.7, 138.8, 139.8, 152.0, 175.0. IR (KBr): 3230, 3176, 1727, 1667, 1609, 1548, 1488, 1367, 1322, 1268, 1192, 1177, 1057, 794, 704, 690, 631 cm^{-1}. HRMS (ESI): MH^+, found 283.3490, $C_{17}H_{19}N_2O_2$ requires 283.3493.

1-Acetyl-1,3-di-(*o,p*-dimethylphenyl)urea (4a):



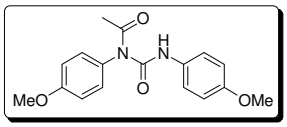
M.p. 137-139 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.20 (s, 3H), 2.28 (s, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 6.99 (m, 2H), 7.10 (m, 3H), 7.91 (d, 1H, *J* = 8 Hz), 11.27 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 17.7, 18.4, 21.1, 21.4, 26.3, 121.5, 127.4, 128.0, 128.4, 128.9, 131.2, 132.3, 133.8, 134.1, 135.6, 136.0, 139.5, 151.7, 175.6. IR (KBr): 3180, 2916, 1711, 1671, 1595, 1547, 1498, 1444, 1317, 1253, 1180, 1050, 965, 824, 725, 627, 506 cm^{-1}. HRMS (ESI): MH^+, found 311.4021, $C_{19}H_{23}N_2O_2$ requires 311.4029.

1-Acetyl-1,3-di-(*o,o*-dimethylphenyl)urea (5a):



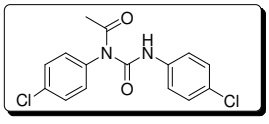
M.p. 109-111 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.26 (s, 6H), 2.31 (s, 6H), 7.05-7.26 (m, 6H), 10.67 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 18.0, 18.9, 25.3, 127.2, 128.3, 129.1, 129.2, 134.1, 135.4, 136.2, 137.3, 151.5, 175.4. IR (KBr): 3246, 2916, 1710, 1668, 1494, 1371, 1313, 1260, 1238, 1165, 1033, 777 cm^{-1}. HRMS (ESI): MH^+, HRMS (ESI): MH^+, found 311.4018, $C_{19}H_{23}N_2O_2$ requires 311.4029.

1-Acetyl-1,3-di-(*p*-methoxyphenyl)urea (6a):



M.p. 140-142 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 6.84 (d, 2H, *J* = 8.4 Hz), 6.98 (d, 2H, *J* = 8.4 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.4), 11.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 55.6, 55.7, 114.3, 115.1, 121.8, 130.1, 131.0, 131.7, 152.4, 156.4, 159.9, 175.5. IR (KBr): 3180, 3076, 2934, 2835, 1718, 1607, 1593, 1544, 1511, 1295, 1246, 1168, 1029, 834, 746, 550 cm^{-1}. HRMS (ESI): MH^+, found 315.3470, $C_{17}H_{19}N_2O_4$ requires 315.3481.

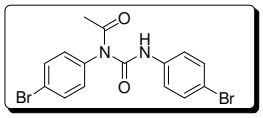
1-Acetyl-1,3-di-(*p*-chlorophenyl)urea (7a):



M.p. 144-145 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3H), 7.21 (d, 2H, *J* = 8 Hz), 7.26 (d, 2H, *J* = 8 Hz), 7.46 (d, 2H, *J* = 8 Hz), 7.47 (d, 2H, *J* = 6.8 Hz), 11.41 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 26.7, 121.6, 129.2, 129.5, 130.3, 130.6, 135.5, 136.3, 137.3, 151.8, 174.9.

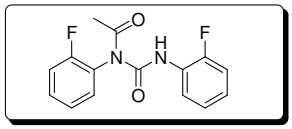
IR (KBr): 3157, 3098, 1718, 1673, 1590, 1537, 1494, 1369, 1311, 1264, 1230, 1159, 1086, 828, 717, 621 cm^{-1}. HRMS (ESI): MH^+, found 324.1847, $C_{15}H_{13}Cl_2N_2O_2$ requires 324.1859.

1-Acetyl-1,3-di-(*p*-bromophenyl)urea (8a):



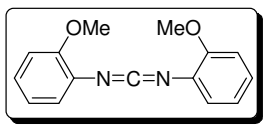
M.p. 152-154 ^oC, ^1H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 7.16 (d, 2H, *J* = 8 Hz), 7.43 (s, 4H), 7.64 (d, 2H, *J* = 8 Hz), 11.42 (s, 1H). $^{13}CNMR$ (100 MHz, $CDCl_3$): δ 26.8, 117.0, 121.9, 123.9, 130.9, 132.2, 133.3, 136.8, 137.8, 151.7, 174.8. IR (KBr): 3171, 2992, 2753, 1697, 1591, 1398, 1303, 1074, 1008 cm^{-1}. HRMS (ESI): MH^+, found 413.0876, $C_{15}H_{13}Br_2N_2O_2$ requires 413.0889.

1-Acetyl-1,3-di-(*o*-fluorophenyl)lurea (9a):



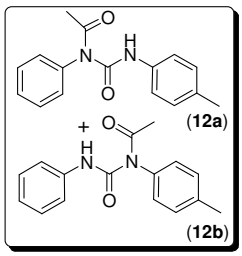
M.p. 99-101 ^oC, ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 7.00-7.15 (m, 3H), 7.24-7.36 (m, 3H), 7.45-7.51 (m, 1H), 8.18 (m, 1H), 11.64 (s, 1H). $^{13}CNMR$ (100 MHz, $CDCl_3$): δ 25.9, 115.1, 115.2, 117.0, 117.2, 121.9, 124.5, 124.6, 124.7, 125.3, 125.4, 131.1, 131.5, 131.6, 151.2, 151.9, 154.3, 159.7, 160.0, 174.9. IR (KBr): 3377, 3136, 1724, 1683, 1543, 1496, 1456, 1249, 1163, 1107, 567 cm^{-1}. HRMS (ESI): MH^+, found 291.2759, $C_{15}H_{13}F_2N_2O_2$ requires 291.2767.

Bis-(2-methoxy-phenyl)-carbodiimide (10a):



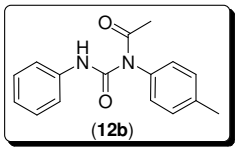
M. p. 75-76 ^oC, ^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.90 (m, 4H), 7.13 (m, 4H). $^{13}CNMR$ (100 MHz, $CDCl_3$): δ 56.2, 111.5, 121.1, 125.1, 126.1, 128.0, 137.6, 154.1. IR (KBr): 2966, 2938, 2837, 2104, 1586, 1491, 1453, 1310, 1257, 1207, 1112, 1024, 754, 609 cm^{-1}. HRMS (ESI): MH^+, found 255.2929, $C_{15}H_{15}N_2O_2$ requires 255.2957.

1-Acetyl-1-phenyl-3-*p*-tolylurea (12a) + 1-Acetyl-1-*p*-tolyl -3-phenylurea (12b) (60 : 40):



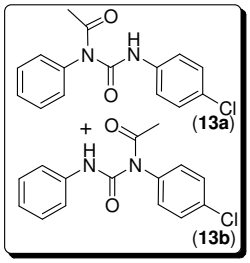
^1H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 6H), 2.30 (s, 3H), 2.40 (s, 3H), 7.06-7.56 (m, 18H), 11.34 (s, 1H), 11.43 (s, 1H). $^{13}CNMR$ (100 MHz, $CDCl_3$): δ 20.9, 21.3, 26.6, 120.2, 124.1, 128.8, 129.0, 129.5, 129.8, 130.5, 133.6, 136.3, 137.9, 139.2, 152.1, 175.3. IR (KBr): 3169, 3028, 2922, 1716, 1670, 1593, 1533, 1317, 1165, 1037, 750 cm^{-1}.

1-Acetyl-1-phenyl-3-p-tolylurea (12b):



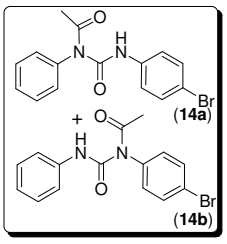
White solid, M.p. 120-122 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.41 (s, 3H), 7.09 (t, 1H, *J* = 7.6 Hz), 7.16 (d, 2H, *J* = 7.6 Hz), 7.30 (m, 4H), 7.55 (d, 2H, *J* = 8.2 Hz), 11.45 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 21.4, 26.8, 120.4, 124.3, 128.9, 129.2, 130.7, 136.5, 138.0, 139.4, 152.3, 175.4. IR (KBr): 3131, 3060, 1714, 1666, 1590, 1546, 1509, 1057, 744, 630, 512 cm^{-1}.

1-Acetyl-3-(*p*-chlorophenyl)-1-phenylurea (13a) + 1-Acetyl-1-(*p*-chlorophenyl)-3-phenylurea (13b): (40 : 60):



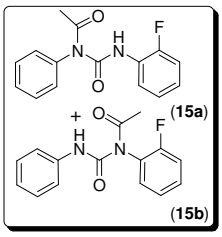
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.023 (s, 3H), 2.033 (s, 3H), 7.10-7.56 (18H), 11.40 (s, 1H), 11.53 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 26.7, 120.3, 121.5, 124.4, 129.1, 129.2, 129.3, 130.2, 130.6, 135.3, 137.5, 137.6, 151.8, 174.7. IR(KBr): 3156, 3098, 1718, 1673, 1590, 1537, 1494, 1401, 1369, 1311, 1264, 1230, 1174, 1159, 1102, 1086, 828, 621, 512 cm^{-1}.

1-Acetyl-1-phenyl-3-(*p*-bromophenyl)urea (14a) + 1-Acetyl-1-(*p*-bromophenyl)-3-phenylurea (14b): (33 : 67):



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (2 × 3H), 7.09-7.64 (m, 18H), 11.36 (s, 1H), 11.42 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 26.8, 120.4, 121.9, 123.4, 124.5, 129.2, 130.8, 130.9, 132.1, 133.2, 133.3, 137.6, 138.0, 151.8, 174.7. IR (KBr): 3220, 3175, 2928, 1705, 1670, 1586, 1529, 1489, 1367, 1320, 1262, 1225, 1165, 1070, 824, 696 cm^{-1}.

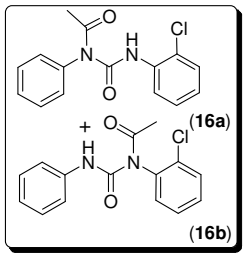
1-Acetyl-3-(*o*-fluorophenyl)-3-phenylurea (15a) + 1-Acetyl-1-(*o*-fluorophenyl)-3-phenylurea (15b) (20 : 80):



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.04 (s, 3H), 7.00-7.55 (m, 18H), 11.35 (s, 1H), 11.71 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 25.9, 26.6, 115.0, 115.1, 116.9, 117.1, 120.5, 121.9, 124.3, 124.4, 124.6, 125.2, 125.3, 126.6, 126.8, 129.2, 129.4, 129.9, 130.0, 131.1, 131.4, 131.5, 137.7, 138.9, 151.2, 152.0, 154.4, 157.3, 159.8, 174.8,

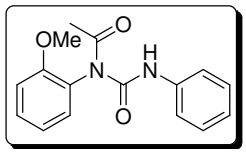
175.2. IR(KBr): 3179, 1718, 1681, 1593, 1538, 1499, 1373, 1278, 1171, 1059, 859, 827, 790 cm^{-1}.

1-Acetyl-3-(*o*-chlorophenyl)-1-phenylurea (16a) + 1-Acetyl-1-(*o*-chlorophenyl)-3-phenylurea (16b) (19: 81):



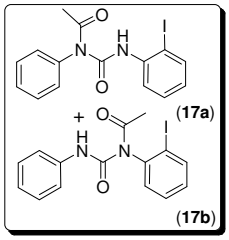
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.02 (s, 3H), 6.99-7.56 (m, 18H), 11.37 (s, 1H), 11.93 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 25.8, 26.6, 120.4, 121.9, 124.4, 124.6, 127.6, 128.4, 129.1, 129.4, 130.0, 130.7, 130.8, 131.1, 133.8, 136.6, 137.7, 151.1, 174.7. IR(KBr): 3376, 3236, 1719, 1679, 1598, 1541, 1479, 1446, 1370, 1277, 1230, 1174, 1069, 755, 628 cm^{-1}.

1-Acetyl-1-(*o*-methoxyphenyl)-3-phenylurea (16b):



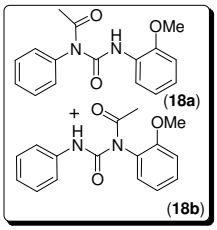
White solid, M.p. 107-109 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 3.85 (s, 3H), 7.06 (m, 3H), 7.28 (m, 4H), 7.56 (d, 2H, *J* = 8.4 Hz), 11.48 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 25.7, 55.9, 112.1, 120.2, 121.3, 124.0, 127.6, 129.0, 130.4, 130.8, 138.1, 151.7, 155.4, 175.7. IR (KBr): 3179, 3001, 2841, 1714, 1670, 1602, 1552, 1499, 1450, 1319, 1247, 1171, 1023, 757, 629, 507 cm^{-1}.

1-Acetyl-3-(*o*-iodophenyl)-1-phenylurea (17a) + 1-Acetyl-1-(*o*-iodophenyl)-3-phenylurea (17b) (32 : 68):



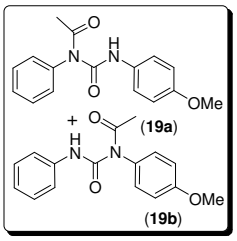
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (s, 3H), 2.05 (s, 3H), 6.81-8.14 (m, 18H), 11.39 (s, 1H), 11.56 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 26.3, 26.5, 100.8, 120.1, 122.6, 124.1, 125.8, 128.6, 128.7, 128.9, 129.0, 129.7, 129.8, 130.0, 130.5, 137.5, 138.6, 138.7, 139.2, 139.3, 139.9, 141.2, 150.7, 152.1, 174.3, 174.7. IR(KBr): 3057, 1722, 1681, 1598, 1551, 1464, 1445, 1313, 1273, 1173, 1056, 752, 714, 626 cm^{-1}.

1-Acetyl-3-(*o*-methoxyphenyl)-1-phenylurea (18a) + 1-Acetyl-1-(*o*-methoxyphenyl)-3-phenylurea (18b) (43 : 57):



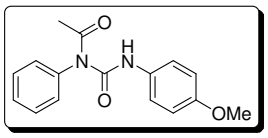
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.01 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 6.90-7.57 (m, 17H), 8.23 (d, 1H, *J* = 8.4 Hz), 11.48 (s, 1H), 11.74 (s, 1H). IR (KBr): 3178, 3073, 2841, 1714, 1670, 1549, 1318, 1270, 1118, 1023, 755, 701, 629, 546, 506 cm^{-1}.

1-Acetyl-3-(*p*-methoxyphenyl)-1-phenylurea (19a) + 1-Acetyl-1-(*p*-methoxyphenyl)-3-phenylurea (19b) (55 : 45):



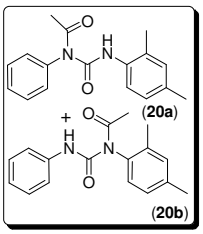
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.02 (s, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 6.80-7.56 (m, 18H), 11.29 (s, 1H), 11.45 (s, 1H).

1-Acetyl-3-(*p*-methoxyphenyl)-1-phenylurea (19a):



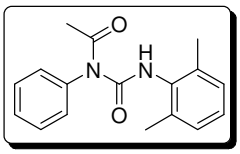
M.p. 127-129 ^oC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 3.84 (s, 3H), 6.99 (d, 2H, *J* = 8.8 Hz), 7.09 (t, 1H, *J* = 7.6 Hz), 7.18 (d, 2H, *J* = 8.8 Hz), 7.30 (t, 2H, *J* = 8.4 Hz), 7.54 (d, 2H, *J* = 7.6 Hz), 11.42 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 26.8, 55.7, 115.1, 120.3, 124.2, 129.2, 130.2, 131.6, 138.0, 152.3, 160.0, 175.7. IR (KBr): 3167, 3061, 2836, 1710, 1660, 1595, 1545, 1442, 1369, 1170, 1031, 827, 736, 630 cm^{-1}. HRMS (ESI): MH^+, found 285.3206 $C_{16}H_{17}N_2O_3$ requires 285.3219.

1-Acetyl-3-(*o,p*-dimethylphenyl)-1-phenylurea (20a) + 1-Acetyl-1-(*o,p*-dimethylphenyl)-3-phenylurea (20b) (73 :27):



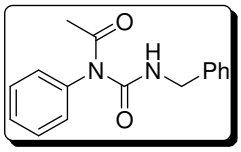
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (s, 3H), 1.99 (s, 3H), 2.19 (s, 3H), 2.27 (s, 3H), 2.34 (s, 3H), 2.35 (s, 3H), 6.96-7.57 (m, 16H), 11.29 (s, 1H), 11.49 (s, 1H). IR (KBr): 3185, 3035, 2921, 1719, 1670, 1595, 1551, 1500, 1446, 1369, 1317, 1269, 1225, 1173, 1055, 1033, 756, 694, 629, 507 cm^{-1}.

1-Acetyl-3-(*o,o*-dimethylphenyl)-1-phenylurea (21a):



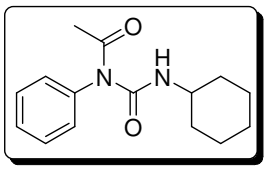
M.p 74-76 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3H), 2.26 (s, 6H), 2.31 (s, 6H), 7.08-7.60 (m, 8H), 11.52 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 17.7, 25.0, 120.0, 123.9, 128.9, 129.0, 135.9, 136.8, 137.7, 150.6, 175.0. IR (KBr): 3136, 3084, 2920, 1720, 1664, 1599, 1566, 1483, 1444, 1315, 1222, 1170, 759 cm^{-1}. HRMS (ESI): MH$^+$, found 283.3474, $C_{17}H_{19}N_2O_2$ requires 283.3493.

1-Acetyl-3-benzyl-1-phenylurea (22a):



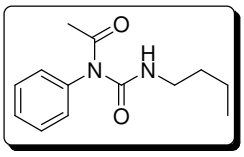
Gummy compound, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 4.52 (d, 2H, *J* = 5.6 Hz), 7.23-7.49 (m, 10H), 9.51 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 26.3, 44.3, 127.3, 127.7, 128.5, 128.7, 128.9, 129.5, 138.2, 139.1, 154.6, 174.4. IR (KBr): 3289, 3060, 3032, 2933, 1711, 1670, 1596, 1517, 1371, 1316, 1262, 1178, 1029, 758, 698, 527 cm^{-1}. HRMS (ESI): MH$^+$, found 269.3239, $C_{17}H_{17}N_2O_2$ requires 269.3225.

1-Acetyl-3-cyclohexyl-1-phenylurea (23a):



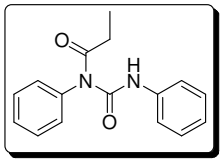
M.p. 82-84 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00-2.00 (m, 13H), 3.68 (m, 1H), 7.10-7.45 (m, 5H), 9.05 (d, 1H, *J* = 3.6 Hz). ^{13}CNMR (100 MHz, $CDCl_3$): δ 24.8, 25.8, 26.7, 33.0, 49.5, 128.9, 129.2, 129.7, 139.6, 153.9, 174.6. IR (KBr): 3273, 3054, 2938, 2858, 1706, 1662, 1518, 1491, 1370, 1321, 1256, 1173, 1060, 973, 703, 629 cm^{-1}. HRMS (ESI): MH$^+$, found 261.3419, $C_{15}H_{21}N_2O_2$ requires 261.3431.

1-Acetyl-3-(*n*-butyl)-1-phenylurea (24a):



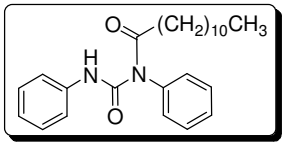
Oily liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 7.2 Hz), 1.35 (m, 2H), 1.52 (m, 2H), 1.90 (s, 3H), 3.27 (m, 2H), 7.16 (m, 2H), 7.30-7.45 (m, 3H), 9.08 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 13.7, 20.1, 26.4, 31.5, 40.1, 128.7, 129.0, 129.5, 139.4, 154.6, 174.4. IR (KBr): 3298, 3065, 2959, 2873, 1725, 1673, 1597, 1525, 1370, 1320, 1263, 1182, 1053, 759, 699, 619 cm^{-1}. HRMS (ESI): MH$^+$, found 235.3044., $C_{13}H_{19}N_2O_2$ requires 235.3053.

1,3-Diphenyl-1-propionyl- urea (1a'):



White solid, M.p. 114-115 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, 3H, *J* = 7.2 Hz), 2.18 (q, 2H, *J* = 7.2 Hz), 7.07-7.56 (m, 10H), 11.55 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 8.94, 31.6, 120.3, 124.2, 129.1, 129.2, 129.4, 129.9, 137.9, 138.3, 152.23, 178.4. IR (KBr): 3310, 2029, 1704, 1615, 1540, 1395, 1215, 1174, 1078, 899, 810, 753, 712 cm^{-1}. HRMS (ESI): MH^+, found 269.3235, $C_{15}H_{15}N_2O_2$ requires 269.3229.

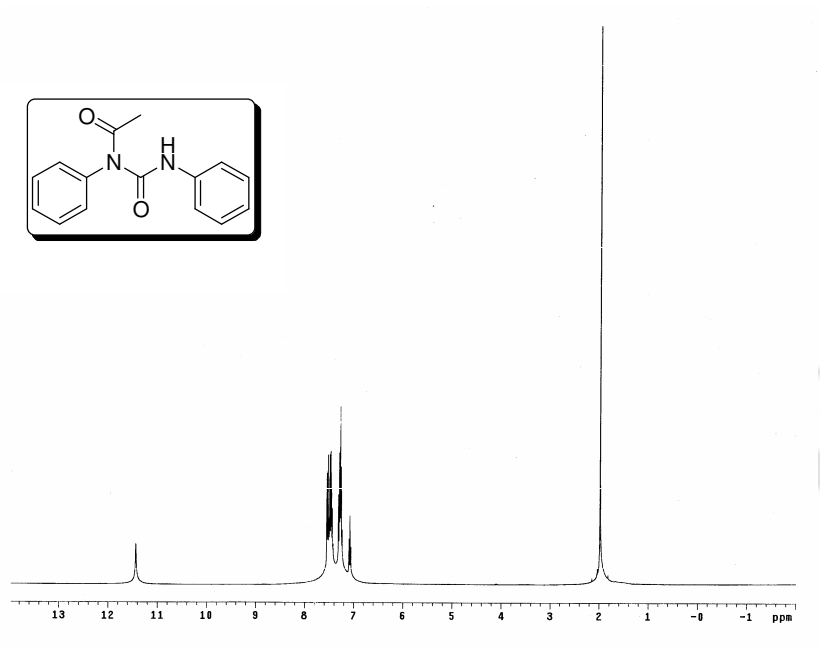
1-Dodecanyl-1,3-diphenylurea (1a"):



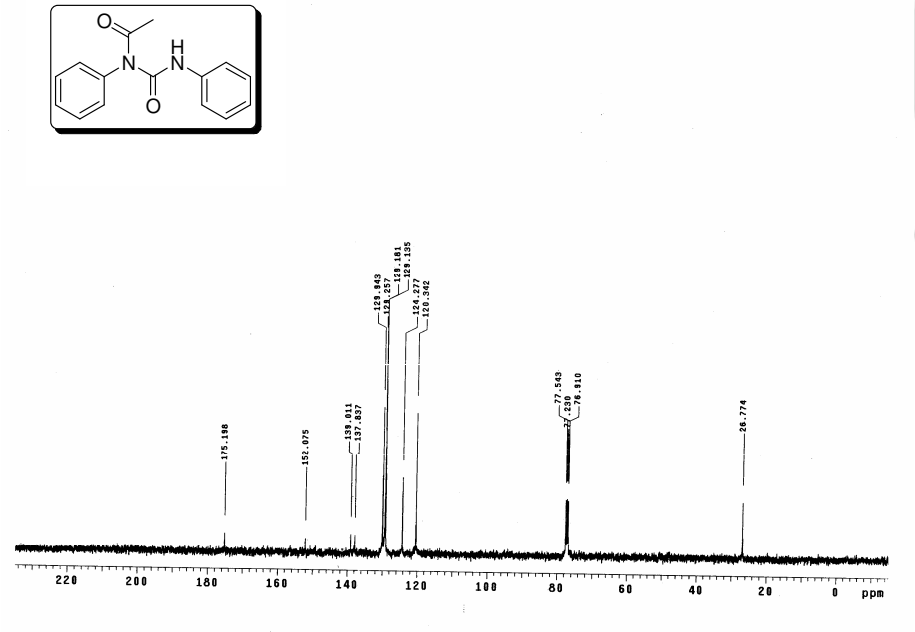
White solid, M.p 68-70 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.2 Hz), 1.22 (m, 16H), 1.57 (m, 2H), 2.14 (t, 2H, *J* = 7.2 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 7.28 (m, 4H), 7.43-7.56 (m, 5H), 11.56 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 24.8, 29.1, 29.4, 29.5, 29.7, 32.1, 37.9, 120.3, 124.2, 129.1, 129.2, 129.4, 129.8, 137.9, 138.4, 152.3, 177.8. IR (KBr): 3120, 2917, 2846, 1717, 1668, 1585, 1550, 1484, 1207, 1160, 1149, 1072, 754 cm^{-1}.

III.7. Selected Spectra

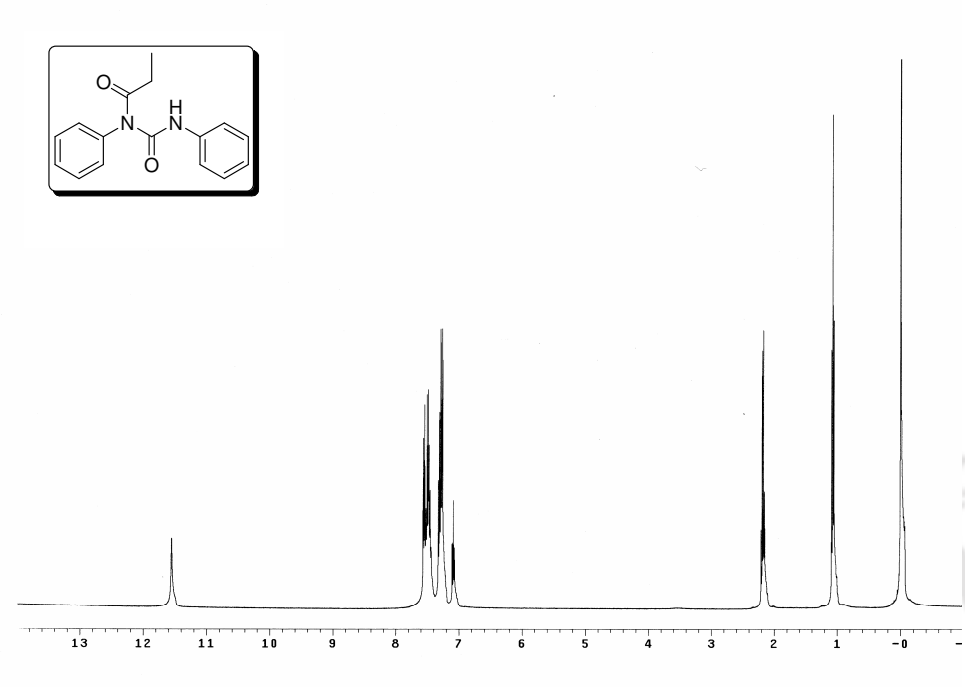
1-Acetyl-1,3-diphenylurea (1a): ^{1}H NMR (400 MHz, $CDCl_3$):



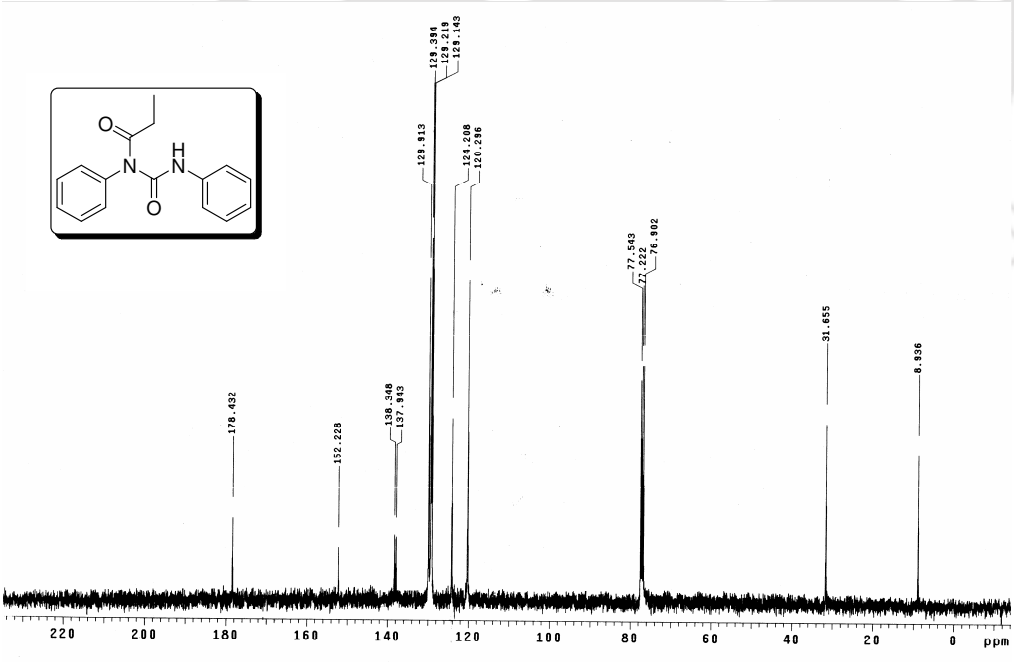
1-Acetyl-1,3-diphenylurea (1a): ^{13}C NMR (100 MHz, $CDCl_3$):



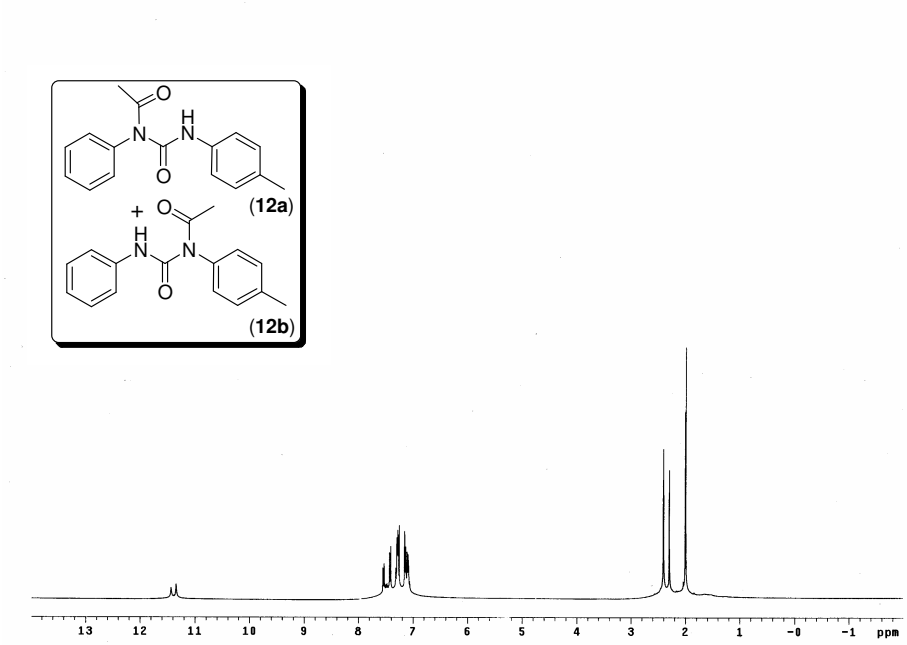
1,3-diphenyl-1-propionyl-urea (1a'): ^{1}H NMR (400 MHz, $CDCl_3$):



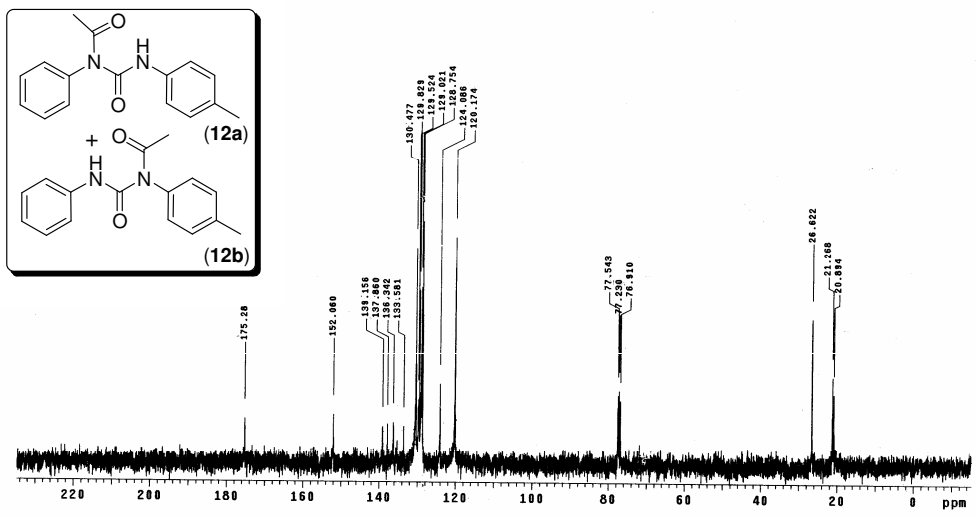
1,3-diphenyl-1-propionyl-urea (1a'): ^{13}C NMR (100 MHz, $CDCl_3$):



1-Acetyl-1-phenyl-3-*p*-tolylurea (12a) + 1-Acetyl-1-*p*-tolyl -3-phenylurea (12b) (55 : 45): ^{1}H NMR (400 MHz, $CDCl_3$):



1-Acetyl-1-phenyl-3-*p*-tolylurea (12a) + 1-Acetyl-1-*p*-tolyl -3-phenylurea (12b) (55 : 45): ^{13}C NMR (100 MHz, $CDCl_3$):

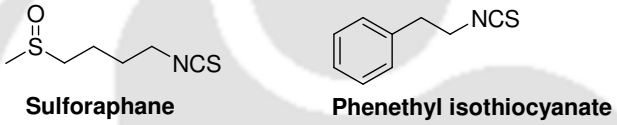


CHAPTER IV

IV. Desulfurization of Dithiocarbamic Acid Salt with Hypervalent Iodine(III): A Facile One-Pot Access to Isothiocyanate and Cyanamide

IV.1. Importance and Applications

Isothiocyanates and cyanamides are important class of compounds that are frequently encountered in a number of natural and biologically active molecules.



Sulforaphane **Phenethyl isothiocyanate**

Figure IV.1.1.

Some isothiocyanates such as sulforaphane and phenethyl isothiocyanate (PEITC) (*Figure IV.1.1*) have antitumor, antimicrobial activities.[1] They have been shown to inhibit carcinogenesis and as such are useful chemo preventive agents against the development and proliferation of cancers. Several sesquiterpene isothiocyanates have been isolated from marine natural products.[2a,b] Allyl isothiocyanate which is responsible for the pungent taste of mustard, horseradish, and wasabi, serves the plant as a defense against herbivores.[2c] Additionally, synthetic isothiocyanates have been proved to have some biological activity such as anti-proliferatives[2d] and enzyme inhibitors for the HIV virus.[2e] They also serve as chemoselective electrophiles in bioconjugate chemistry, particularly for biological assays of DNA and proteins.[3]

On the other hand, cyanamides (RR'N–C≡N) are known to be tumor inhibitors.[4a,b] They are also important intermediates for the synthesis of many biologically active compounds, such as minoxidil,[4c] (*Figure IV.1.2*) known for its ability to reduce hair loss and promote hair re-growth, and as herbicides.[4d,e]

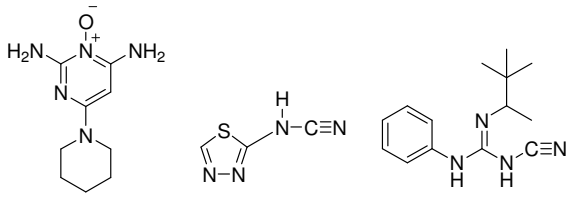


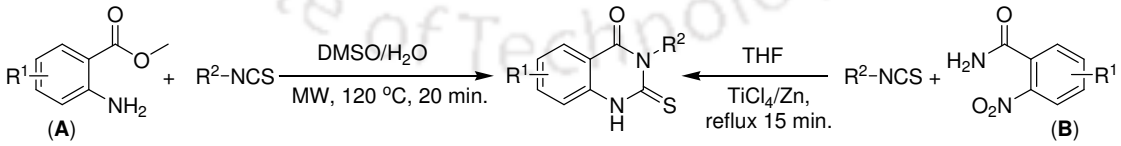
Figure IV.1.2.

The *N*-cyanoamidines, Amitivir and Pinacidil, (*Figure IV.1.2*) are isosteric to α-aminoacids. The compound Amitivir show anti-viral activity, and Pinacidil and similar compounds show anti-diabetes activity.[4f]

IV.1.1. Applications in Organic Synthesis

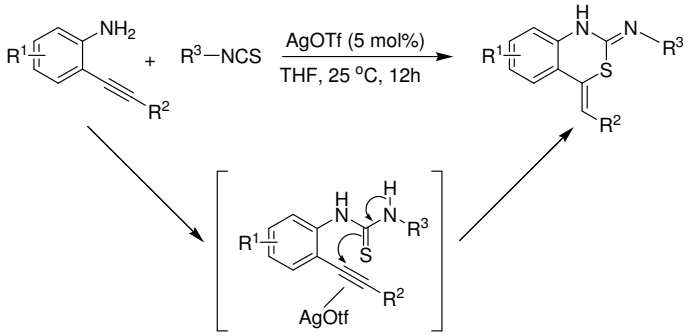
Isothiocyanates are key intermediates especially for the preparation of both sulfur- and nitrogen-containing organic heterocycles.[5] The use of isothiocynates, in the preparation of various heterocycles, has been extensively discussed by Muhkerjee *et. al.* in a chemical review 1991.[5a] Some recent literature reports on use of isothiocyanates in the preparation of a wide range of heterocyclic compounds are reviewed in this section.

Substituted methyl anthranilate (**A**) (*Scheme IV.1.1.1*) was reacted with various isothiocyanates in DMSO/H_2O using microwave irradiation to afford 2-thioxoquinazolinones.[6a] In a modified strategy, 2-thioxoquinazolinones have been prepared by the reaction of nitro-compounds (**B**) (*Scheme IV.1.1.1*) and isothiocyanates induced by low-valent titanium reagent ($TiCl_4$/Zn).[6b]



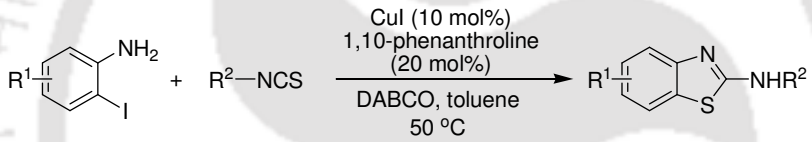
Scheme IV.1.1.1.

Wu and co-worker developed a novel and efficient method for the synthesis of 2,4-dihydro-1*H*-benzo[*d*]-[1,3]thiazine derivatives via AgOTf-catalyzed tandem addition-cyclization reactions of 2-alkynylbenzenamines with isothiocyanates (*Scheme IV.1.1.2*).[6c]



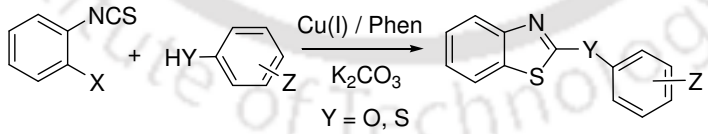
Scheme IV.1.1.2.

In another report, Wu *et. al.* described the copper(I)-catalyzed tandem reactions of 2-iodobenzenamines with isothiocyanates which afforded 2-aminobenzothiazole (*Scheme IV.1.1.3*). The advantages of the method were demanded as the high efficiency, good substrate generality, mild reaction conditions, and experimental ease.[6d]



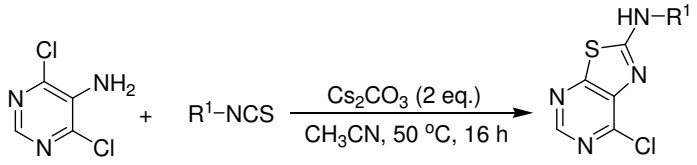
Scheme IV.1.1.3.

Recently, our group disclosed a method to prepare 2-arylthio benzothiazoles and 2-aryloxy benzothiazoles directly from 2-haloaryl isothiocyanates and O or S nucleophiles by a Cu-catalyzed, intramolecular, C-S bond formation (*Scheme IV.1.1.4*).[6e]



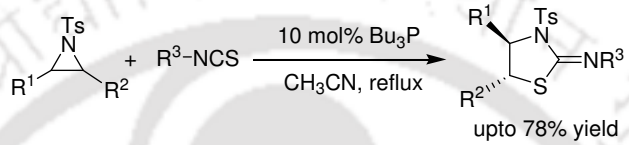
Scheme IV.1.1.4.

Player *et. al.* demonstrated a single-step process for the preparation of 2-amino-7-chlorothiazolo[5,4-*d*]pyrimidines, by the reaction of 4,6-dichloro-5-aminopyrimidine with isothiocyanates in presence of base Cs_2CO_3 (*Scheme IV.1.1.5*).[6f]



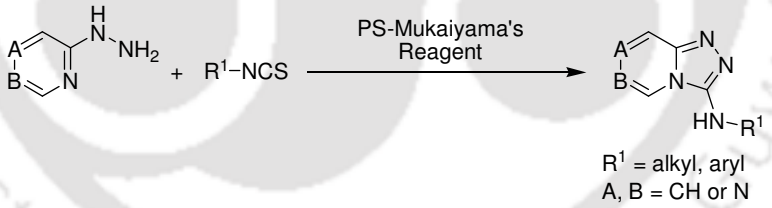
Scheme IV.1.1.5.

Thiazolidinone derivatives have been prepared by organophosphine-catalyzed ring-opening reaction of aziridines with isothiocyanates (*Scheme IV.1.1.6*).[6g]



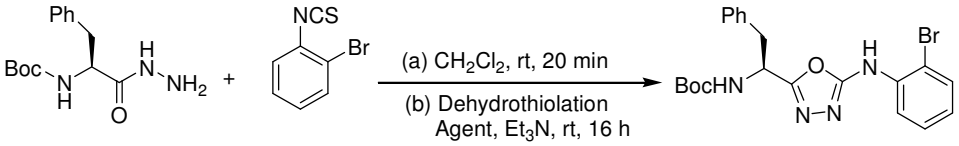
Scheme IV.1.1.6.

The reaction of hydrazinopyridine with isothiocyanate affords the corresponding thiosemicarbazide, which on further *in situ* desulfurization, using polymer-supported Mukaiyama's reagent, gives the final cyclization product 3-amino-[1,2,4]triazolo[4,3-a]pyridine in one-pot methodology (*Scheme IV.1.1.7*).[6h]



Scheme IV.1.1.7.

Batey group developed a synthetic route of 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 IV.1.1.8*). The reactions proceed via initial formation of thiosemicarbazides, followed by dehydrothiolative cyclization to the 1,3,4-oxadiazoles.[6i]

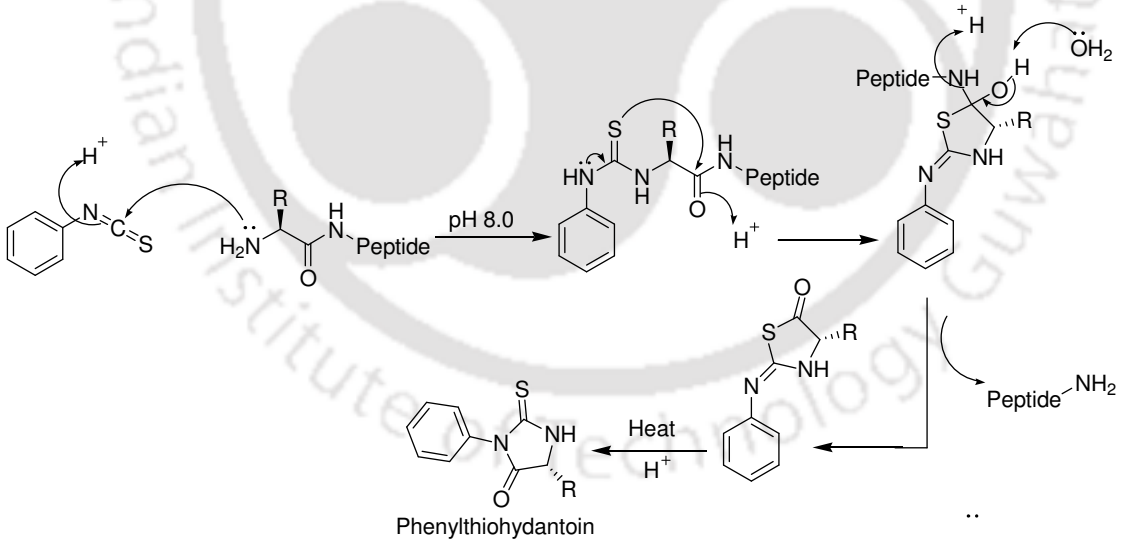


Scheme IV.1.1.8.

Besides these, isothiocyanates have been used for the synthesis of spiro(imidazolidine-2,3'-benzo[b]thiophene)[7a] 3-alkyl 2-thiohydantoins,[7b] N,6-disubstituted-1,3,5-triazine-2,4-diamines,[7c] 1,2,4-thiadiazolidine-3,5-diones[7d] etc.

Isothiocyanates are the key precursors for the synthesis of both symmetrical and unsymmetrical thioureas which are again versatile building blocks for the preparation of various heterocycles.[7e]

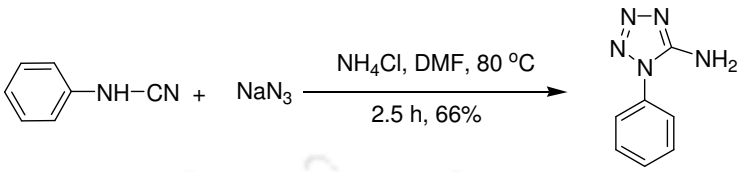
Isothiocyanates are used as reagents in Edman method for sequencing of amino acids in a peptide (*Scheme IV.1.1.9*).[7f-h] Edman degradation proceeds from the *N*-terminus of the protein and able to accurately sequence up to 30 amino acids with modern machines capable of over 99% efficiency per amino acid.



Scheme IV.1.1.9.

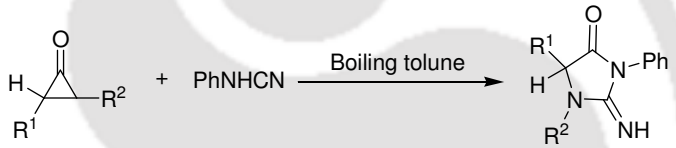
On the other hand, due to its unique reactivity, cyanamide is an important functional group in synthetic organic chemistry. Cyanamides are useful precursors in the synthesis of pharmaceutically important heterocycles.[8]

Kanaoka group used the phenylcyanamide to synthesize tetrazole (*Scheme IV.1.1.10*) which was again used for synthesizing drug with inhibitory activities against ECE (endothelin converting enzyme) in the solubilized fraction from rat lung membrane.[9a]



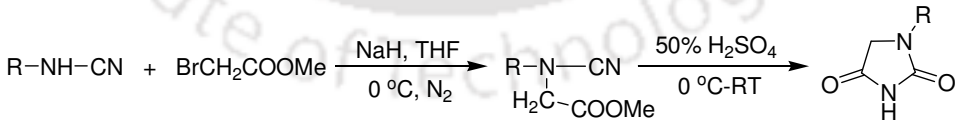
Scheme IV.1.1.10.

The products imidazolidinones, were obtained by acyl–nitrogen bond cleavage of aziridinones with phenyl cyanamide, followed by cyclization involving intramolecular nucleophilic attack on the nitrile (*Scheme IV.1.1.11*).[9b]



Scheme IV.1.1.11.

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 very good to excellent yields (*Scheme IV.1.1.12*).[9c]



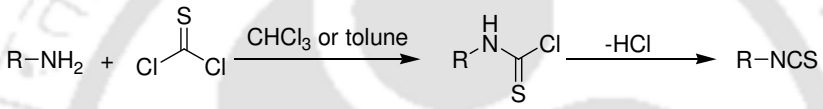
Scheme IV.1.1.12.

Cyanamides are also useful precursors in the synthesis *N*-alkyl or *N*-aryl imides.[9d] Due to the easy removal of the cyano group from cyanamide, they often serve as a useful protecting groups in the synthesis of secondary and tertiary amines containing heterocycles.[10]

Aromatic cyanamides are used as popular ligands for binding with various metals, such as, octaethylporphyrin iron(III) complexes containing cyanamide derivatives as axial ligand,[11a] Rh^{III} polypyridine complexes with phenylcyanamide derivative ligands,[11b] tetraphenylporphyrin manganese(III) complexes of phenylcyanamide ligands,[11c] *cis*-bis(bipyridine) cobalt(III) complexes of phenylcyanamide ligands[11d] etc.

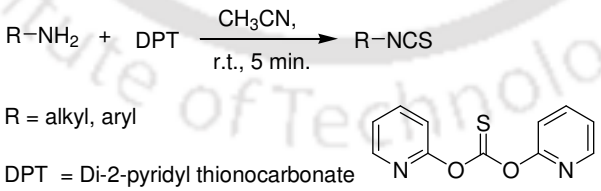
IV.2. Available Synthetic Methods

Isothiocyanates are prepared conventionally by treating amines with thiophosgene. Primary amines reacted with thiophosgene to give unstable thiocarbamoyl chlorides which in turn furnished isothiocyanates (*Scheme IV.2.1*).[12a]



Scheme IV.2.1.

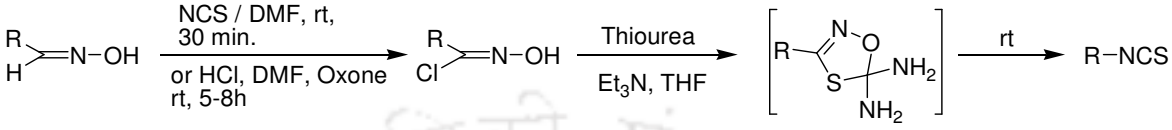
Owing to difficulties in handling thiophosgene, its equivalents have been prepared and employed for this purpose. This method was modified over the years and diethylthiocarbamoyl chloride,[12b] bis(diethylthiocarbamoyl) sulfide or disulfide,[12c] di-2-pyridyl thiocarbonate,[12d-f] 1,1'-(thiocarbonyldioxy)dibenzotriazole,[12g,h] and 1,l'-thiocarbonyl-2,2'-dipyridone.[12i] bis(trichloromethy1) pentathiodiperoxycarbonate[12j] were introduced as the substitute of highly toxic thiophosgene.



Scheme IV.2.2.

The reactions of amines with "thiocarbonyl transfer" reagents like di-2-pyridyl thionocarbonate afford the corresponding isothiocyanates (*Scheme IV.2.2*).[13]

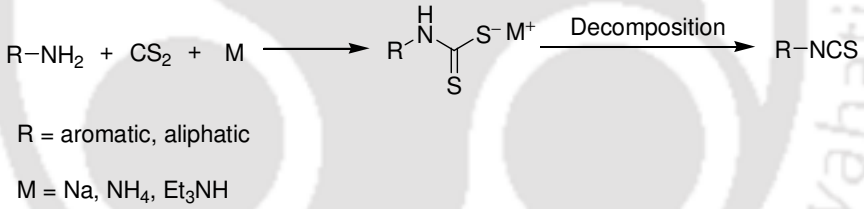
Isothiocyanates were prepared in a one-pot reaction from aldoxime derivatives by successive treatment of aldoxime with *N*-chlorosuccinimide (NCS), thiourea, and triethylamine (*Scheme IV.2.3*). The use of HC1 / DMF / Oxone® system in the reaction instead of NCS was equally effective.[14a]



Scheme IV.2.3.

Another method of preparation of isothiocyanate, with limited substrate scope, is the treatment of 1,3-disubstituted thiourea with strong acids e.g. H_2SO_4 in reflux condition.[14b]

An alternative approach relies on the decomposition of dithiocarbamic acid salts into isothiocyanates promoted by various reagents (*Scheme IV.2.4*).



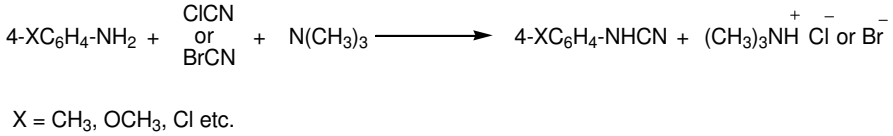
Scheme IV.2.4.

The reagents used are uronium- and phosphonium based coupling agents,[15a-d] tosyl chloride,[15e] di-*tert*-butyl dicarbonate,[15f] hydrogen peroxide,[15g] ethyl chlorocarbonate,[15h] bis(trichloromethyl)carbonate (BTC) and trichloromethyl chloroformate (TCF),[15i] Claycop,[15j] and 2-chloro-1-methylpyridinium salt.[15k]

Very recently, our group has demonstrated a high yielding protocol for the preparation of isothiocyanate by the decomposition of dithiocarbamate salt with various thiophilic reagents such as molecular iodine,[16a] ditribromide[16b] and Michael-acceptor.[16c]

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

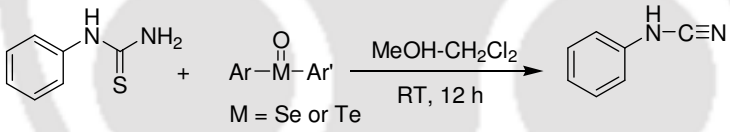
synthesis of cyanamides is the cyanation of amine using cyanogen halides, (*Scheme IV.2.5*) or its synthon (CN^+).[17]



Scheme IV.2.5.

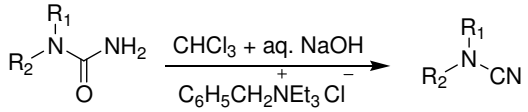
To avoid the use of toxic cyanogen halides, some electrophilic cyanating reagent that can serve as a cyano cation (CN^+) equivalent, have been prepared. The reagents capable of delivering electrophilic cyanogens (CN^+) are 2-chlorobenzyl thiocyanate,[18a] 1-cyanoimidazole,[18b] 2-cyanopyridazin-3-(2*H*)-ones,[18c] 1-cyanobenzotriazole and metal cyanide,[18d] tosylcyanide,[18e,f] thiocyanogen,[18g] and cyanogens azide.[18h]

Cyanamides are obtained from 1-phenylthioureas by using various methods, such as, polymer supported diaryl selenoxide or telluroxide mediated dehydrosulfurization (*Scheme IV.2.6*),[19a] treatment with superoxide (KO_2) in pyridine at 60 ^oC under N_2 for 2 h,[19b] methylation followed by a basic work-up[19c] etc.



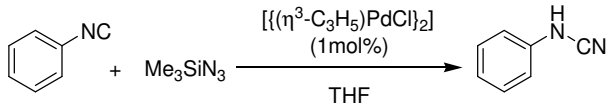
Scheme IV.2.6.

In an alternative approach, cyanamides are obtained from ureas through dehydration method using chloform and NaOH mixture (*Scheme IV.2.7*)[20a] or trichloromethyl chloroformate.[20b]



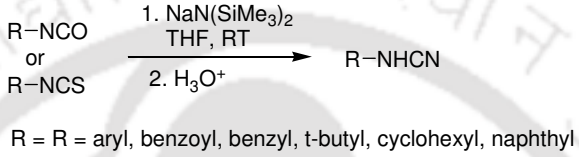
Scheme IV.2.7.

The other less commonly adopted method is the Tiemann rearrangement of amidoximes.[20c]



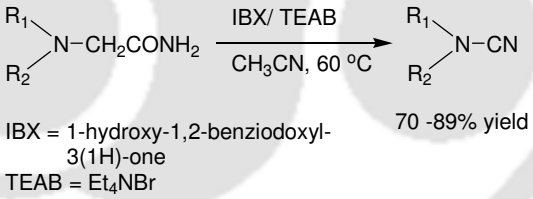
Scheme IV.2.8.

Recently Yamamoto *et.al* have been prepared from organic isocyanides and trimethylsilyl azide via a Si-N bond cleavage catalyzed by [{(η^3-C_3H_5)PdCl}$_2$] (*Scheme IV.2.8*).[20d]



Scheme IV.2.9.

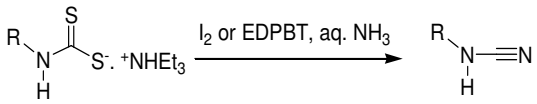
Cyanamides have been prepared in one-pot by reacting isocyanate or isothiocyanate with sodium bis(trimethylsilyl)amide as deoxygenating or desulfurizing agents in THF at room temperature (*Scheme IV.2.9*).[21a,b]



Scheme IV.2.10.

In yet another method, cyanamides have been prepared from *N.N'*-disubstituted glycylamide using a pentavalent iodine reagent in the presence of tetraethylammonium bromide at ambient temperature through one-carbon dehomologation of primary carboxamides (*Scheme IV.2.10*).[21c]

Very recently our group has disclosed a high yielding, environmentally benign method for the preparation of cyanamide from dithiocarbamate salt using molecular iodine and ditribromide reagent 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (*Scheme IV.2.11*).[21d,e]



Scheme IV.2.11.

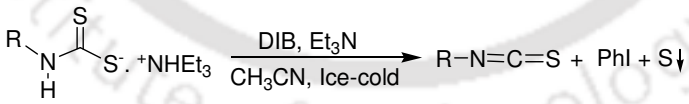
Thus inspite of a plethors of methods available for the synthesis of isothiocyanates and cyanamides due to the immense importance of these heterocumulenes there is always scope for newer and milder strategy for their synthesis.

IV.3. Present Work

Preparation of Isothiocyanate

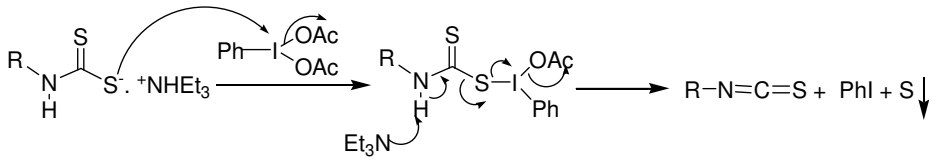
After synthesizing *N*-acylurea from 1,3-disubstituted thiourea using hypervalent iodine(III) reagent (diacetoxyiodo)benzene (DIB) as discussed in the previous sections,[22a] we have been further interested to explore the thiophilic nature of (diacetoxyiodo)benzene (DIB) as an efficient thiophilic / desulfurizing agent for the preparation of isothiocyanate and cyanamide from dithiocarbamate salts.[22b,c]

The use of (diacetoxyiodo)benzene (DIB) overcomes many of the problems associated with the preparation of isothiocyanates. When the dithiocarbamate salt (1 equiv.) was treated with DIB (1 equiv.) in the presence of triethylamine (1.5 equiv.) in acetonitrile, isothiocyanate was obtained in excellent yield (*Scheme IV.3.1*).[22b]



Scheme IV.3.1. *Preparation of isothiocyanate from the dithiocarbamate salt*

Addition of DIB to the suspension of the dithiocarbamate salt must be carried out slowly over a period of 10 – 15 min. The proposed mechanism is shown in *Scheme IV.3.2*. The formation of phenyl iodide and the precipitation of elemental sulfur from the reaction mixture support the mechanism.

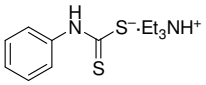
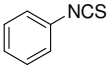
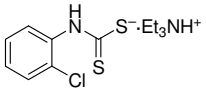
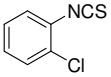
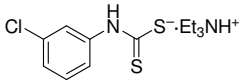
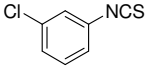
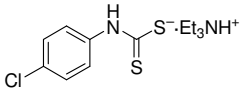
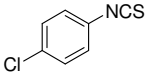
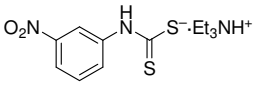
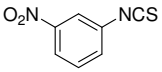
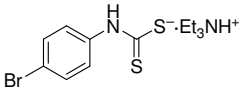
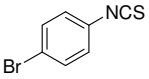
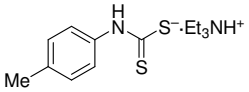
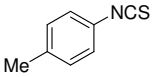
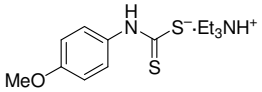
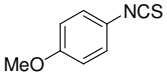
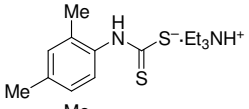
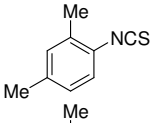
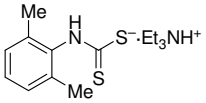
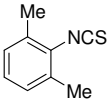
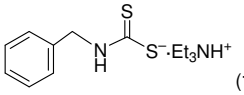
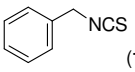
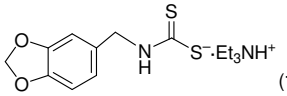
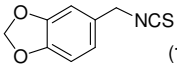
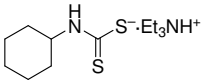
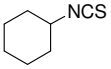
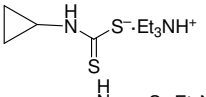
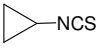
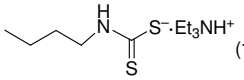
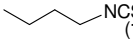


Scheme IV.3.2. *Mechanism of the formation of isothiocyanate from the dithiocarbamate salt*

In these reactions, the most crucial aspect is the preparation of the dithiocarbamic acid salts,[23] and once the dithiocarbamate salts are obtained, DIB proved to be an effective reagent for their decomposition to the desired isothiocyanates in excellent yields.

Several isothiocyanates (*Table IV.3.1*) were successfully prepared in good to excellent yields by utilizing this protocol. As can be seen from *Table IV.3.1*, aromatic substrates containing ortho, meta, and para substituents all gave isothiocyanates in good yields. Recently, we found that regioselective *N*-acylation of unsymmetrical 1,3-disubstituted thiourea is dependent on the p*Ka* of the amine attached to the thioureas.[22a] Based on this observation and the mechanism proposed in *Scheme IV.3.2*, we have reason to believe that an amine with a lower p*Ka* should yield the isothiocyanate faster because of its easy deprotonation. Triethylamine, the base employed for this purpose is sufficiently basic (p*Ka* = 10.78) compared with the aromatic amines used (p*Ka* = 2.46–5.63). The p*Ka* of the NH proton upon formation of the dithiocarbamate salt is expected to decrease further. Hence all the dithiocarbamic acid salts (**1**–**10**) gave the corresponding isothiocyanates (**1a**–**10a**) in excellent yields when triethylamine was used as the base along with DIB. Alkylamines such as *n*-butyl- (p*Ka* = 10.77), cyclohexyl- (p*Ka* = 10.66), benzylamine (p*Ka* = 9.33) and cyclopropylamine (p*Ka* = 9.10), which have comparable basicity to that of triethylamine (p*Ka* = 10.78), yielded isothiocyanates **11a**–**15a** in good yields in shorter reaction times. The attachment of hypervalent iodine to sulfur makes it a much better leaving group and is probably the rate-limiting step in this reaction (*Scheme IV.3.2*). Further, the NH protons of the alkylamines are expected to become more acidic due to the presence of a C=S moiety leading to facile deprotonation by the base triethylamine.

Table IV.3.1. *Preparation of isothiocyanate from dithiocarbamate salt*[a]

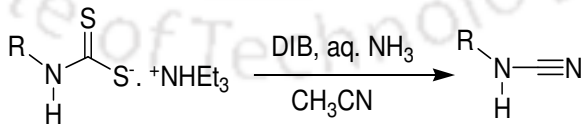
Substrate	Product[b]	Yield (%)[c]
 (**1**)	 (**1a**)	96%
 (**2**)	 (**2a**)	94%
 (**3**)	 (**3a**)	91%
 (**4**)	 (**4a**)	93%
 (**5**)	 (**5a**)	78%
 (**6**)	 (**6a**)	93%
 (**7**)	 (**7a**)	92%
 (**8**)	 (**8a**)	97%
 (**9**)	 (**9a**)	90%
 (**10**)	 (**10a**)	95%
 (**11**)	 (**11a**)	93%
 (**12**)	 (**12a**)	88%
 (**13**)	 (**13a**)	81%
 (**14**)	 (**14a**)	65%
 (**15**)	 (**15a**)	63%

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

In summary, we have developed a general, convenient, and environmentally benign method for the preparation of isothiocyanates from the corresponding dithiocarbamic acid salts. In comparison to the existing methods of the decomposition of the dithiocarbamic acid salts, our procedure is perhaps the simplest yet most efficient method for the synthesis of isothiocyanates. The reagent is readily available and nontoxic, and the precipitated sulfur can be removed easily. Although literature enumerates a number of procedures for the preparation of isothiocyanates, the simplicity, environmental acceptability, and operational simplicity of our procedure makes it a practical alternative.

Preparation of Cyanamide

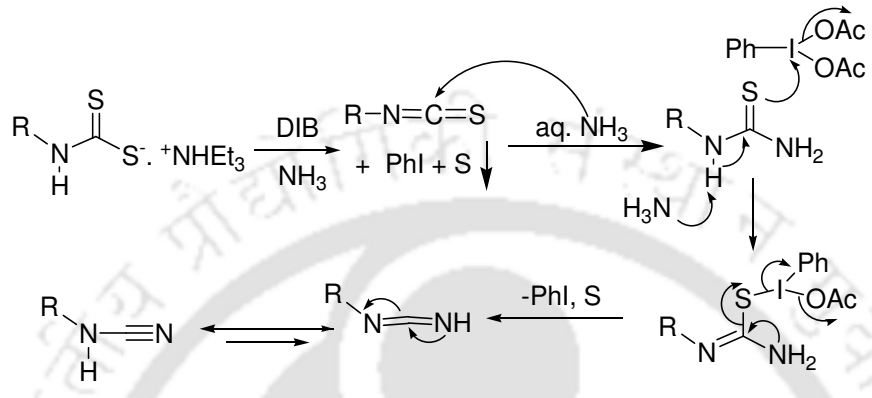
After successfully synthesizing various isothiocyanates, we focused our attention on the synthesis of cyanamides in one-pot. The *in situ* generated isothiocyanates on reaction with various *bis*-nucleophiles gave different heterocycles.[22b] Taking cues from this work, we have reasoned that isothiocyanate can be obtained from dithiocarbamic acid salt and DIB in the presence of aqueous ammonia without using triethylamine. The *in situ* generated isothiocyanate will react further with ammonia giving alkyl or aryl thiourea, which, on oxidative desulfurization with DIB and ammonia, would form organic cyanamide. All these process can be performed in one pot. Herein, we discuss a high yielding 'one-pot' preparation of cyanamides from dithiocarbamate salts using the non-metallic, non-toxic, eco-friendly hypervalent iodine(III) reagent (diacetoxyiodo)benzene (DIB).[22c]



Scheme IV.3.3. *Preparation of cyanamide from the dithiocarbamate salt*

Various dithiocarbamate salts can be prepared easily in high yields from amines following the literature procedure. When a freshly prepared salt of dithiocarbamate salt (2 equiv.) in acetonitrile (5 mL) was treated with aqueous ammonia (25 %) (2 mL) and DIB

(2 equiv.) under an ice-cooled conditions, 1-phenylthiourea was obtained in good yield (*Scheme IV.3.3*). When DIB (2 equiv.) was added to this reaction mixture, phenylcyanamide was isolated in 85% yield. A plausible mechanism for the transformation of dithiocarbamic acid salt to cyanamide is shown in *Scheme IV.3.4*.

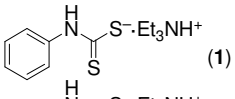
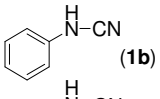
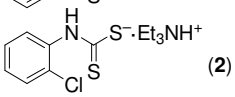
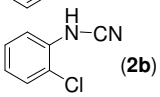
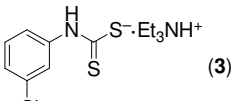
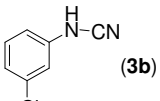
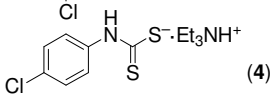
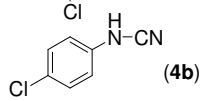
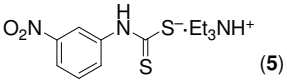
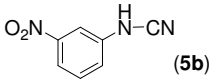
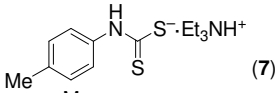
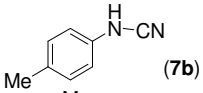
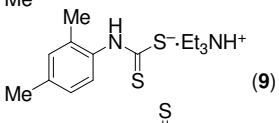
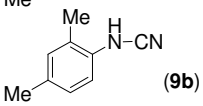
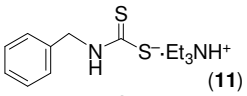
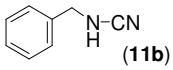
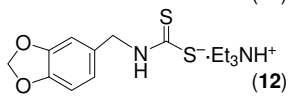
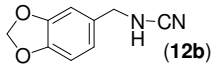
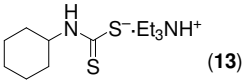
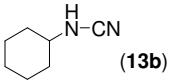
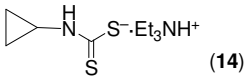
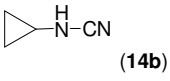
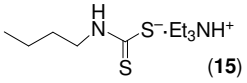
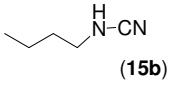


Scheme IV.3.4. *Proposed mechanism for the formation of cyanamide*

The mechanism for the formation of isothiocyanate is expected to be similar to the one proposed above for the isothiocyanate formation (*Scheme IV.3.2.*).[22b] The *in situ* generated isothiocyanate on reaction with aqueous NH_3 would give 1-phenylthiourea. The 1-phenylthiourea on oxidative desulfurization leads to the formation of a carbodiimide type intermediate which is converted to its stable cyanamide analogue (*Scheme IV.3.4*). The precipitation of elemental sulfur supports the mechanism proposed. The formation of isothiocyanate has been confirmed by recording the IR spectra of the crude reaction mixture, which shows a strong peak at 2063 cm^{-1} characteristic of isothiocyanate. Further, when isolated 1-phenylthiourea in acetonitrile was treated with DIB in an aqueous ammonia, it gave cyanamide confirming the intermediacy of phenylisothiocyanate and 1-phenylthiourea in the reaction mixture. It may be mentioned here that the reaction of 1-phenylthiourea with DIB in the absence of any base is reported to give 1,2,4-thiadiazole.[24]

Irrespective of the mechanism involved, the success of the method depends on the strong thiophilic nature of the DIB. Employing this one-pot strategy, we have successfully prepared a series of cyanamides (*Table IV.3.2*) from both aliphatic and aromatic amines.

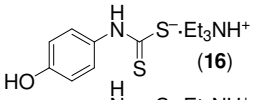
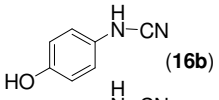
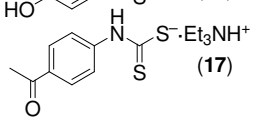
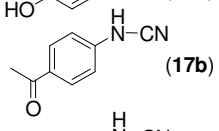
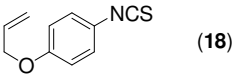
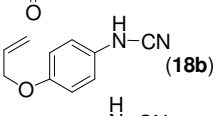
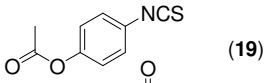
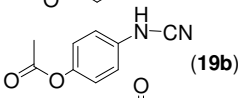
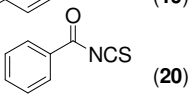
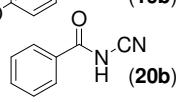
Table IV.3.2. *Preparation of cyanamide from dithiocarbamate salt*[a]

Substrate	Product[b]	Yield (%)[c]
 (**1**)	 (**1b**)	85%
 (**2**)	 (**2b**)	68%
 (**3**)	 (**3b**)	71%
 (**4**)	 (**4b**)	60%
 (**5**)	 (**5b**)	65%
 (**7**)	 (**7b**)	72%
 (**9**)	 (**9b**)	78%
 (**11**)	 (**11b**)	76%
 (**12**)	 (**12b**)	78%
 (**13**)	 (**13b**)	77%
 (**14**)	 (**14b**)	63%
 (**15**)	 (**15b**)	67%

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

Aromatic amines containing various substituents in the phenyl ring (**1–9**) gave corresponding cyanamides (**1b–9b**) in good yields. Benzylic amines **11** and **12** gave a satisfactory yield of corresponding cyanamides **11b** and **12b** respectively. This method was also extremely successful in the preparation of cyclohexyl (**13b**), cyclopropyl (**14b**), and n-butyl (**15b**) cyanamides starting from their parent amine / dithiocarbamate salt.

Table IV.3.3. *Preparation of cyanamide from dithiocarbamate salt*[a]

Substrate	Product[b]	Yield (%)[c]
 (**16**)	 (**16b**)	72%
 (**17**)	 (**17b**)	83%
 (**18**)	 (**18b**)	76%
 (**19**)	 (**19b**)	83%
 (**20**)	 (**20b**)	83%

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

This method is compatible with a number of other functional groups such as –OH, $–NO_2$, and –COR as was tested in substrates **16**, **5**, and **17** giving their corresponding cyanamides **16b**, **5b**, and **17b**, respectively, (*Table IV.3.2* and *Table IV.3.3*). The stability of other functional groups containing substrates such as alkenes **18** and esters **19** were also found to be compatible in the second stage of the reaction giving, respectively, products **18b** and **19b**. It was difficult to get suitable dithiocarbamate salts having these functionalities. Hence, their compatibility was tested from isothiocyanates **18** and **19** having these functionalities. It is heartening to know that both these functionalities survived under the reaction condition giving cyanamides **18b** and **19b**, respectively, in good yields. However in the case of **18b** and **19b**, 0.5 mL of aq NH_3 was used per mmol of the substrate instead of 1 mL of the aq NH_3 used when the reaction started from dithiocarbamate salt. Benzoyl cyanamide **20b** was obtained from benzoyl isothiocyanate **20** in reasonable yield.

In an attempt to synthesize cyanamide of secondary amines such as pyrrolidine, no traces of cyanamide could be detected. Rather, it underwent oxidative dimerization. This is possible because of the inability of the secondary amine to form isothiocyanate, thereby further supporting our mechanism. Thus, by this method, cyanamide of a secondary amine cannot be prepared and this is perhaps the only drawback of the method.

In conclusion, hypervalent iodine reagent DIB serves as an efficient desulfurizing agent for the conversion of dithiocarbamic acid salts to cyanamides. Organic cyanamide in the past was prepared by an arduous method involving toxic and expensive reagents. Although the isolated yield looks moderate considering three steps in one pot, the yields are, in fact, good to excellent. Thus, this is perhaps the most efficient method reported so far for the preparation of organic cyanamides.

IV.4. Experimental Section

IV.4.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1. Page number 48-49.

IV.4.2. General Procedures

IV.4.2.1. Preparation of Phenyl Isothiocyanate (1a) from Dithiocarbamate Salt (1)

Triethylamine (417 µL, 3 mmol) was added to a stirred and ice-cooled suspension of dithiocarbamate **1** (540 mg, 2 mmol) in acetonitrile (5 mL). DIB (644 mg, 2 mmol) was added portionwise over a period of 30 min. A light-yellow precipitate of sulfur started to separate during this period. After the complete addition of DIB, the stirring was stopped to allow complete precipitation of the sulfur. The precipitated sulfur was filtered, and the organic layer was concentrated and admixed with hexane (15 mL). The hexane layer was washed with 1 N HCl (2 x 5 mL) and water (1 x 5 mL). The organic layer was dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified through a short column of silica gel (100% hexane) to give **1a**.

IV.4.2.2. General Procedure for Preparation of Phenyl Cyanamide (1b) from Dithiocarbamate Salt (1)

Aqueous ammonia (25%, 2 mL) was added to a stirred and ice-cooled suspension of dithiocarbamate **1** (540 mg, 2 mmol) in acetonitrile (5 mL). DIB (644 mg, 2 mmol) was added portion-wise over a period of 15 min. A light yellow precipitate of sulfur started to

separate out during this period. After the complete addition of DIB, it was kept stirring for 15 min and conversion to the corresponding 1-phenylthiourea was confirmed by TLC. To the reaction mixture DIB (644 mg, 2 mmol) was added portion-wise over a period of 15 min during which further precipitation of elemental sulfur was observed. The conversion of the 1-phenylthiourea to phenylcyanamide (**1b**) was observed within 10 min of the complete addition of DIB. The reaction mixture was allowed to stand, and the precipitated sulfur was filtered. The organic layer was concentrated and admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with water (25 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified through a short column of silica gel to give the pure product **1b**.

IV.5. References

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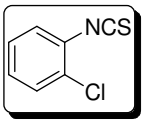
IV.6. Spectral Data

1-Isothiocyanato-benzene (1a):

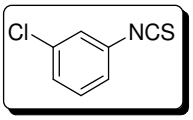
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.8, 127.4, 129.6, 131.3, 135.3. IR (KBr): 3064, 2164, 2063, 1591, 1489, 1474, 1451, 1070, 927, 905, 749, 684 cm^{-1}.

1-Chloro-2-isothiocyanato-benzene (2a):



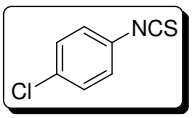
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 3H), 7.39 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.9, 126.4, 126.6, 127.6, 128.0, 130.1, 131.7. IR (KBr): 3066.4, 2562, 2126, 2053, 1582, 1472, 1442, 1068, 937, 750, 723, 660 cm^{-1}.

1-Chloro-3-isothiocyanato-benzene (3a):



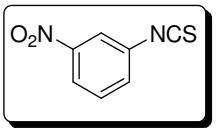
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.12 (m, 1H), 7.21-7.28 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.8, 125.7, 127.4, 130.3, 132.4, 134.9, 137.5. IR (KBr): 3060, 2560, 2230, 2197, 2071, 1931, 1585, 1572, 1470, 1423, 1070, 1089, 960, 864, 776, 751, 672, 532 cm^{-1}.

1-Chloro-4-isothiocyanato-benzene (4a):



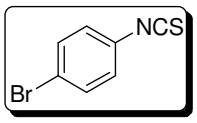
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, 2H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.0, 129.8, 130.0, 133.0, 136.8. IR (KBr): 3082, 2928, 2175, 2126, 2086, 1482, 1089, 928, 824, 495 cm^{-1}.

1-Isothiocyanato-3-nitro-benzene (5a):



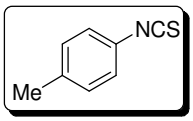
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 2H), 8.06 (s, 1H), 8.11-8.14 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.7, 121.9, 130.6, 131.6, 133.3, 139.6, 148.8. IR (KBr): 3091, 3074, 2227, 2161, 2106, 1526, 1470, 1348, 1302, 892, 809, 736, 665 cm^{-1}.

1-Bromo-4-isothiocyanato-benzene (6a):



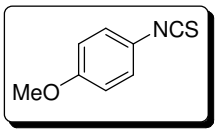
M.p. 58 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, 2H, *J* = 8.8 Hz), 7.47 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.8, 127.2, 130.5, 132.8, 136.9. IR (KBr): 3074, 2925, 2171, 2071, 1578, 1478, 1474, 1399, 1067, 1011, 923, 818, 490, 438 cm^{-1}.

1-Isothiocyanato-4-methyl-benzene (7a):



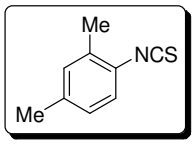
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 7.06-7.13 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 125.4, 128.2, 130.1, 134.4, 137.4. IR (KBr): 2920, 2094, 1503, 929, 812, 790, 497 cm^{-1}.

1-Isothiocyanato-4-methoxy-benzene (8a):



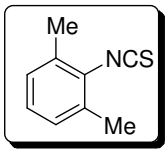
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 6.85 (d, 2H, *J* = 8.8 Hz), 7.16 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 114.6, 123.2, 126.8, 133.7, 158.4. IR (KBr): 3000, 2956, 2835, 2170, 2098, 1580, 1599, 1503, 1459, 1440, 1292, 1251, 1179, 1166, 1028, 927, 824, 614, 513 cm^{-1}.

1-Isothiocyanato-2,4-dimethyl-benzene (9a):



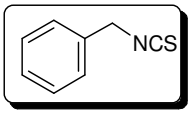
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.33 (s, 3H), 6.96 (d, 1H, *J* = 9.2 Hz), 7.01 (s, 1H), 7.07 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 21.1, 125.6, 127.4, 131.2, 134.6, 137.4. IR (KBr): 2920, 2131, 2085, 1490, 1455, 1379, 1229, 1036, 947, 901, 875, 812 cm^{-1}.

1-Isothiocyanato-2,6-dimethyl-benzene (10a):



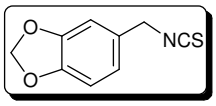
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 6H), 7.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 126.8, 127.9, 129.4, 134.8, 135.6. IR (KBr): 2920, 2148, 2086, 1592, 1469, 1442, 1379, 1165, 1032, 924, 770, 747, 719, 550 cm^{-1}.

1-Isothiocyanatomethyl-benzene (11a):



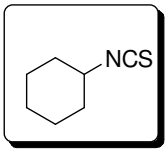
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (s, 2H), 7.31-7.41 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 126.7, 128.2, 128.8, 131.8, 134.1. IR (KBr): 3033, 2925, 2175, 2094, 1454, 1347, 1028, 700, 574 cm^{-1}.

5-(Isothiocyanatomethyl)benzo[d][1,3]dioxole (12a):



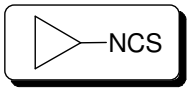
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59 (s, 2H), 5.98 (s, 2H), 6.74-6.80 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.7, 101.5, 107.7, 108.6, 120.7, 128.0, 132.1, 147.8, 148.2. IR (KBr): 2895, 2087, 1503, 1445, 1369, 1322, 1251, 1101, 1028, 924 cm^{-1}.

Isothiocyanato-cyclohexane (13a):



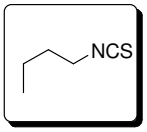
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28-1.96 (m, 10H), 3.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 24.9, 33.0, 34.4, 55.2, 129.6. IR (KBr): 2937, 2858, 2175, 2102, 2060, 1450, 1361, 1320, 986, 891, 720, 702 cm^{-1}.

Isothiocyanatocyclopropane (14a):



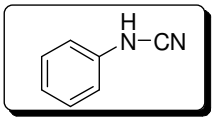
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (m, 2H), 0.93 (m, 2H), 2.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.4, 26.0, 129.5. IR (KBr): 2857, 2080, 1648, 1639, 1351, 1008, 809, 619 cm^{-1}.

1-Isothiocyanato-n-butane (15a):



^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.4 Hz), 1.47-1.37 (m, 2H), 1.69-1.61 (m, 2H), 3.42 (t, 2H, *J* = 6.6 Hz). ^{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, 116, 753 cm^{-1}.

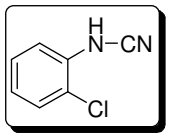
Phenylcyanamide (1b):



^{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, $CDCl_3$):

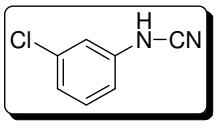
δ 112.2, 115.5, 123.6, 129.8, 137.4. IR (KBr): 3175, 2919, 2227, 1600, 1501, 1249, 748, 689 cm^{-1}. $C_7H_6N_2$ (118.13): calcd C, 71.17; H, 5.12; N, 23.71. Found: C, 71.27; H, 5.09; N, 23.67

2-Chloro-phenyl cyanamide (2b):



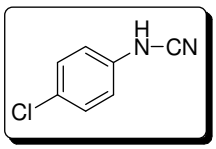
M.p 101-103 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.56 (br s, 1H), 7.05 (m, 1H), 7.31 (m, 2H), 7.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.0, 116.2, 120.4, 124.5, 128.6, 129.9, 134.3. IR (KBr): 3163, 2921, 2243, 1598, 1500, 1426, 1295, 1049 cm^{-1}. $C_7H_5ClN_2$ (152.58): calcd C 55.10, H 3.30, N 18.36; found C 55.11, H 3.32, N 18.29.

3-Chloro-phenyl cyanamide (3b):



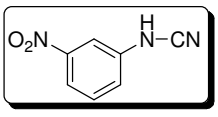
M.p 93-95 °C, ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (m, 1H), 7.03 (m, 2H), 7.26 (t, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.1, 113.8, 115.9, 124.0, 130.9, 135.7, 138.7. IR (KBr): 3154, 2910, 2237, 1602, 1513, 1423, 1256 cm^{-1}. $C_7H_5ClN_2$ (152.58): calcd C 55.10, H 3.30, N 18.36; found C 55.10, H 3.29, N 18.29. MS (ESI): 152 (M^+).

4-Chloro-phenyl cyanamide (4b):



M.p 95 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz). ^{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}. $C_7H_5ClN_2$ (152.58): calcd C 55.10, H 3.30, N 18.36; found C 55.09, H 3.33, N 18.32.

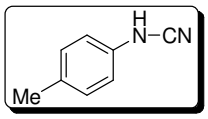
3-Nitro-phenyl cyanamide (5b):



Yellow Solid: M.p 133-135 °C, ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.38 (d, 1H, *J* = 8.4 Hz), 7.52 (t, 1H, *J* = 8.4 Hz), 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, 871 cm^{-}

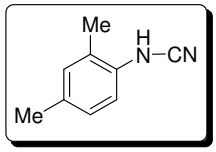
[1]. $C_7H_5N_3O_2$ (163.14): calcd C 51.54, H 3.09, N 25.76; found C 51.58, H 3.12, N 25.71; MS (ESI): 163 (M^+).

_p_-Tolyl cyanamide (7b):



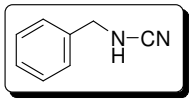
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H. CH_3), 6.91 (d, 2H, *J* = 8.4 Hz), 7.10 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 112.4, 115.5, 130.3, 133.2, 134.9. IR (KBr): 3165, 2950, 2228, 1620, 1515, 1249 cm^{-1}. $C_8H_8N_2$ (132.17): calcd C 72.70, H 6.10, N 21.20; found C 72.73, H 6.08, N 21.15.

2,4-Dimethyl-phenyl cyanamide (9b):



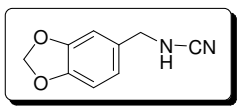
M.p 115-119 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 6.74 (br s, 1H, NH), 6.93 (s, 1H), 6.99 (d, 1H, *J* = 8.0 Hz), 7.05 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 20.7, 112.8, 115.7, 124.7, 127.9, 131.8, 133.2, 133.3. IR (KBr): 3186, 2915, 2233, 1599, 1512, 1433, 1271, 1031 cm^{-1}. $C_9H_{10}N_2$ (146.19): calcd C 73.94, H 6.89, N 19.16; found C 73.87, H 6.86, N 19.14. MS (ESI): 146 (M^+);

Benzyl cyanamide (11b):



Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (d, 2H, CH_2, *J* = 5.2 Hz), 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}. $C_8H_8N_2$ (132.17): calcd C 72.70, H 6.10, N 21.19; found C 72.66, H 6.13, N 21.11.

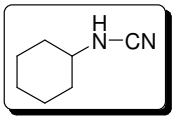
Benzo[1,3]dioxol-5-ylmethyl-cyanamide (12b):



M.p 82-84 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05 (d, 2H, CH_2, *J* = 5.2 Hz), 4.57 (br s, 1H), 5.94 (s, 2H, OCH_2), 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,

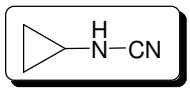
2952, 2897, 2220, 1500, 1445, 1038, 925, 809 cm^{-1}. $C_9H_8N_2O_2$ (176.18): calcd C 61.36, H 4.58, N 15.90; found C 61.41, H 4.61, N 15.85.

Cyclohexyl-cyanamide (13b):



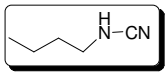
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (m, 5H), 1.61 (m, 1H), 1.78 (m, 2H), 1.95 (m, 2H), 3.09 (m, 1H), 3.91 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 25.1, 32.6, 54.3, 115.9. IR (KBr): 3196, 2933, 2857, 2217, 1453, 1367, 1167 cm^{-1}. $C_7H_{12}N_2$ (124.19): calcd C 67.70, H 9.74, N 22.56; found C 67.67, H 9.70, N 22.50.

Cyclopropyl-cyanamide (14b):



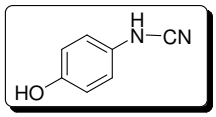
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 (m, 4H, 2 x CH_2), 2.71 (m, 1H, CH), 5.10 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.1, 26.9, 116.3. IR (KBr): 3206, 2224, 1571, 1471, 1358, 1238, 101 $4cm^{-1}$. $C_4H_6N_2$ (88.11): calcd C 58.52, H 7.37, N 34.12; found C 58.49, H 7.40, N 34.06.

***n*-Butyl-cyanamide (15b):**



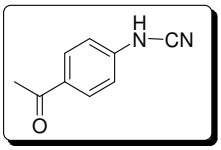
Gummy: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, 3H, CH_3, J = 7.6 Hz), 1.40 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 3.06 (m, 2H, CH_2), 4.61 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 19.5, 31.7, 45.7, 117.2. IR (KBr): 3207, 2961, 2875, 2221, 1614, 1463, 1373, 1171 cm^{-1}. $C_5H_{10}N_2$ (98.15): calcd C 61.19, H 10.27, N 28.54; found C 61.22, H 10.23, N 28.48.

4-Hydroxy-phenyl cyanamide (16b):



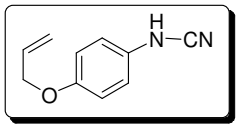
M.p 259-261 ^oC, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 5.67 (br s, 1H), 6.77 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 8.8 Hz), 8.98 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.8, 115.6, 115.8, 129.5, 152.2. IR (KBr): 3213, 2992, 2230, 1613, 1519, 1444, 1258, 1224 cm^{-1}. $C_7H_6N_2O$ (134.14): calcd C 62.68, H 4.51, N 20.88; found C 62.72, H 4.55, N 20.83.

4-Acetyl-phenylcyanamide (17b):



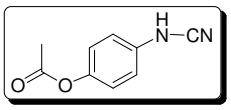
M.p 153-157 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.56 (s, 3H, CH_3), 7.08 (d, 2H, *J* = 8.8 Hz), 7.91 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 25.9, 110.9, 114.5, 129.8, 131.2, 142.9, 196.2. IR (KBr): 3188, 2966, 2228, 1666, 1599, 1585, 1411, 1362, 1278, 1176, 962 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^+).

4-(Allyloxy)-phenyl cyanamide (18b):



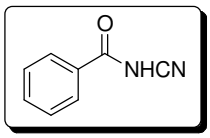
M.p 66-70 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49 (d, 2H, *J* = 4.4 Hz), 5.29 (d, 1H, *J* = 10.8 Hz), 5.40 (d, 1H, *J* = 17.2 Hz), 6.02 (m, 1H), 6.87 (d, 2H, *J* = 8.4 Hz), 6.93 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.5, 112.4, 116.1, 116.9, 118.1, 130.7, 133.2, 155.0. IR (KBr): 3148, 3079, 2954, 2887, 2214, 1510, 1240, 1172, 1108, 1014, 994 cm^{-1}. $C_{10}H_{10}N_2O$ (174.20): calcd C 68.95, H 5.79, N 16.08; found C 68.91, H 5.77, N 16.00. MS (ESI): 174 (M^+).

4-Cyanamide-phenylacetate (19b):



M.p 95-97 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 6.93 (d, 2H, *J* = 8.8 Hz), 7.02 (d, 2H, *J* = 8.8 Hz), 7.08 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 111.5, 116.5, 122.9, 135.4, 146.4, 170.7. IR (KBr): 3168, 3100, 2974, 2233, 1754, 1610, 1512, 1374, 1226, 1202, 1164, 1014 cm^{-1}. $C_9H_8N_2O_2$ (176.18): calcd C 61.36, H 4.58, N 15.90; found C 61.40, H 4.61, N 15.8.

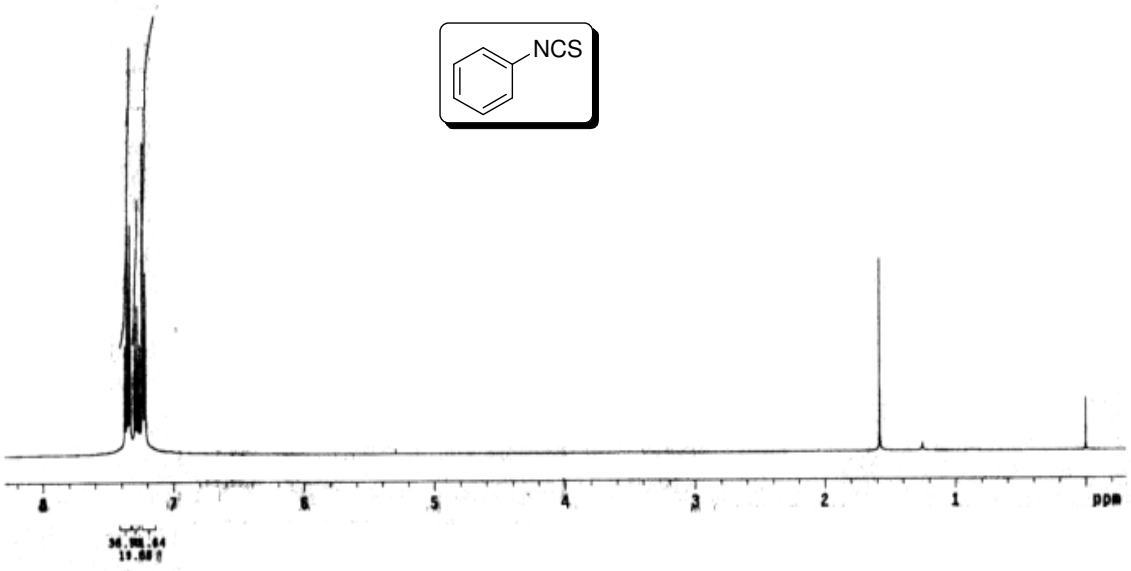
N-Cyanobenzamide (20b):



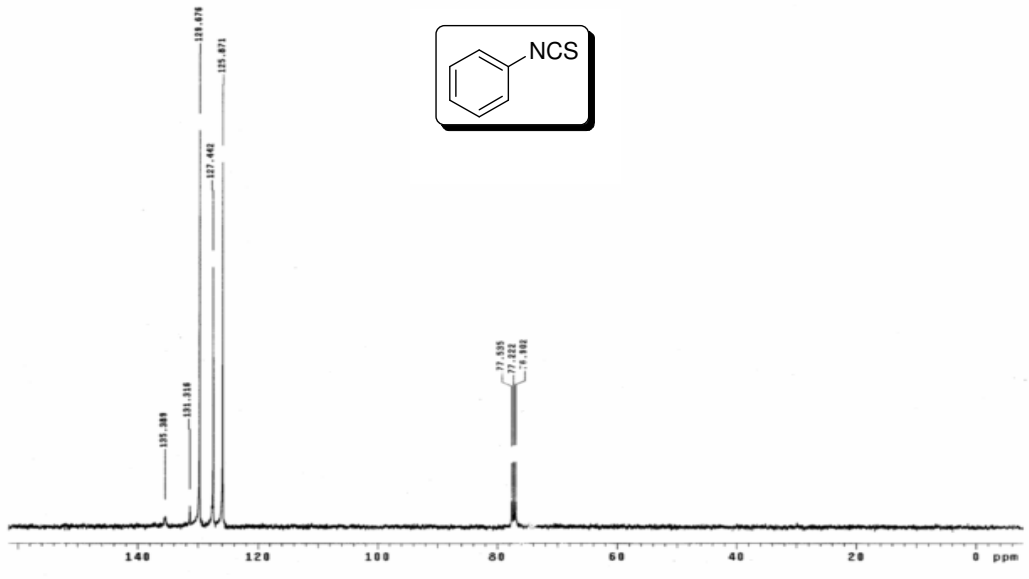
M.p 135-137 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (t, 2H, *J* = 7.6 Hz), 7.62 (t, 1H, *J* = 7.8 Hz), 7.95 (m, 2H), 10.11 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 108.7, 128.5, 128.8, 130.2, 133.8, 166.9. IR (KBr): 3242, 2254, 1678, 1463, 1268, 1099, 706, 593 cm^{-1}. $C_9H_8N_2O_2$ (176.18): calcd C 65.75, H 4.14, N 19.17; found C 65.78, H 4.10, N 19.18.

IV.7. Selected Spectra

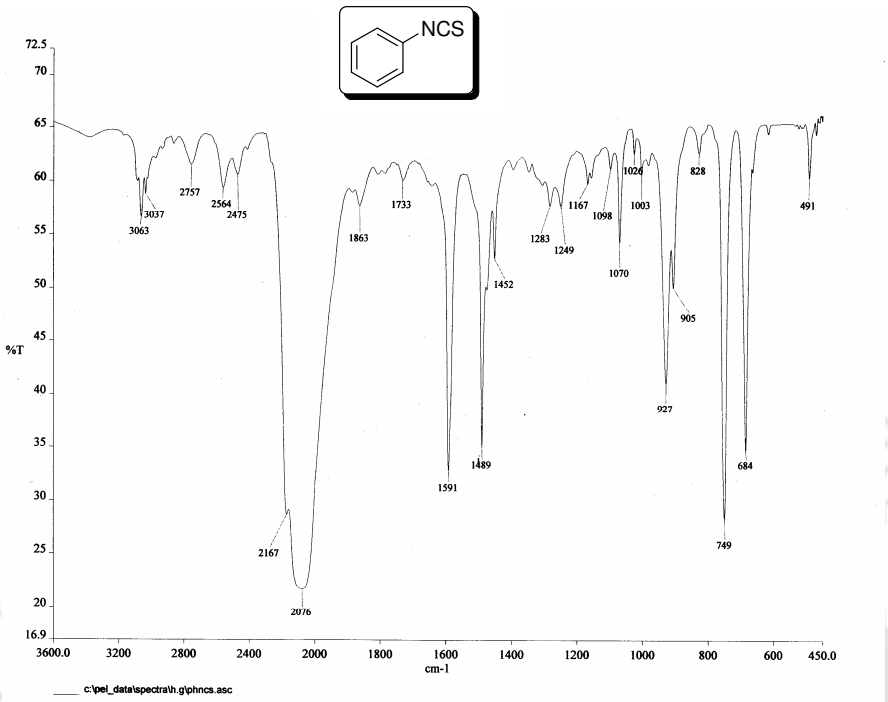
1-Isothiocyanato-benzene (1a): ^{1}H NMR (400 MHz, $CDCl_3$):



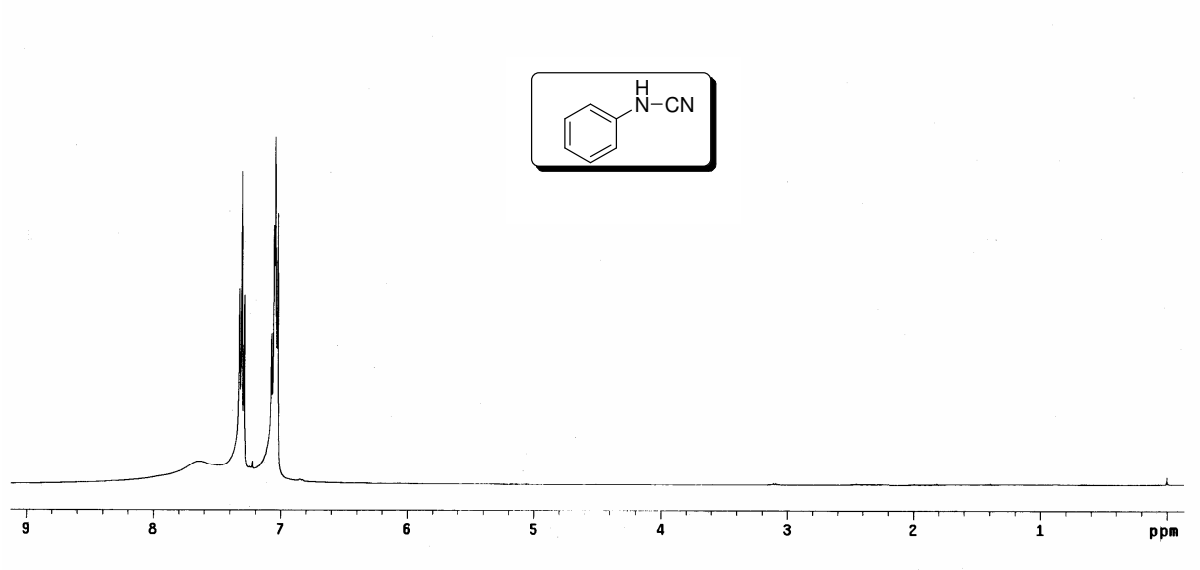
1-Isothiocyanato-benzene (1a): ^{13}C NMR (100 MHz, $CDCl_3$):



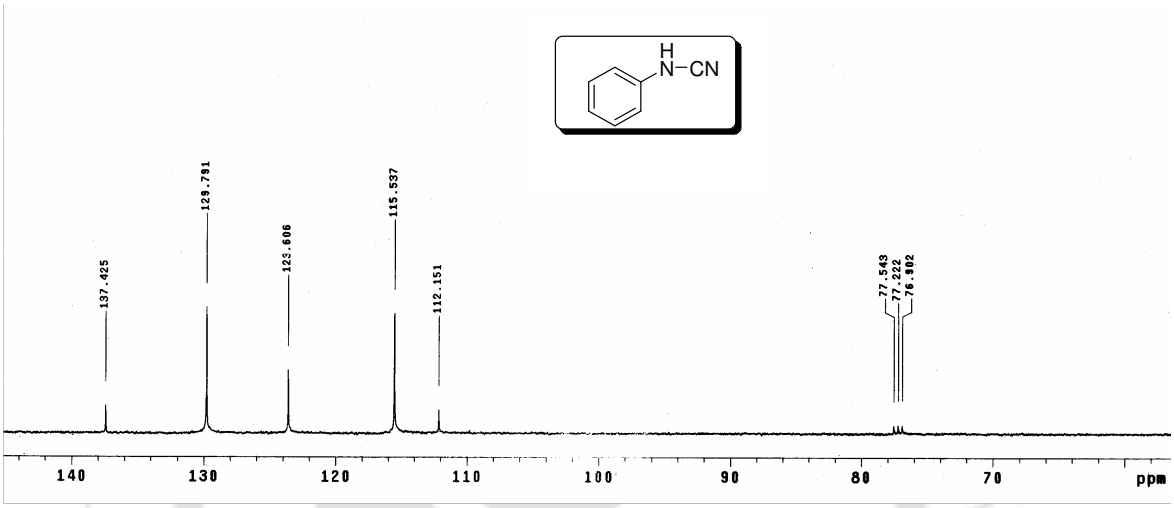
1-Isothiocyanato-benzene (1a): IR(KBr):



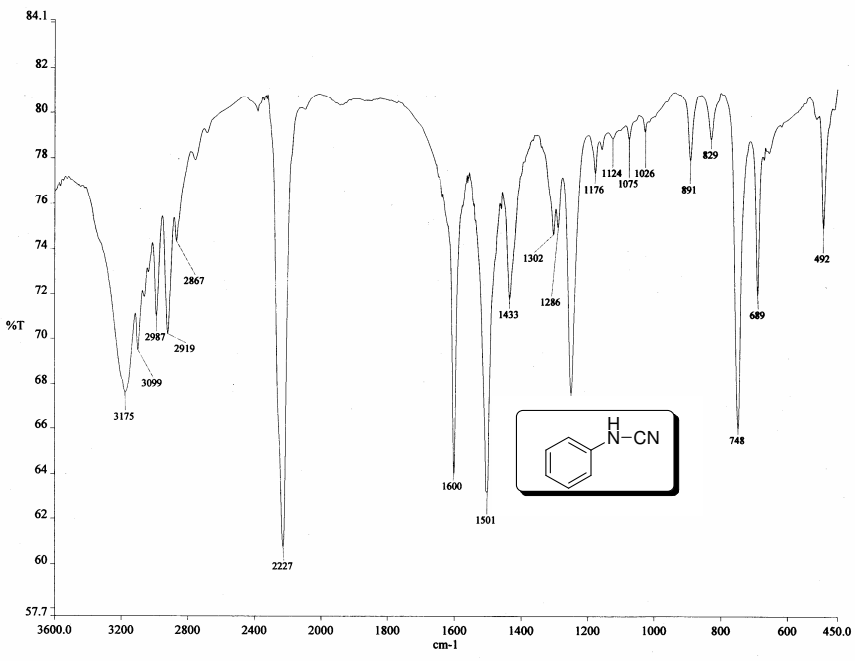
Phenyl cyanamide (1b): ^{1}H NMR (400 MHz, $CDCl_3$):



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



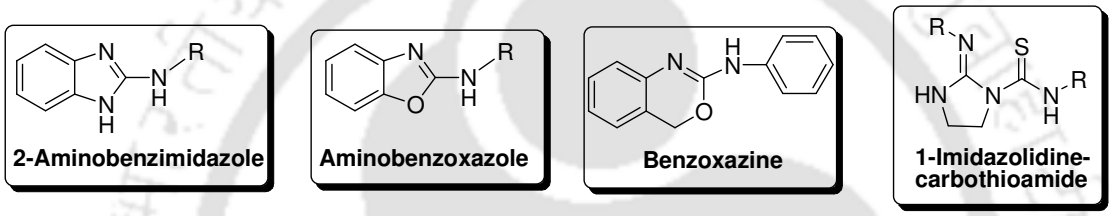
Phenyl cyanamide (1b): IR(KBr):



CHAPTER V

V. Hypervalent Iodine(III) Mediated Desulfurization: A Novel Strategy for the Construction of Heterocycles

In this chapter, we will discuss the synthesis of four types of heterocycles namely, 2-aminobenzimidazole, aminobenzoxazole, benzoxazine and 1-imidazolidinecarbothioamide mediated by hypervalent iodine(III) reagent, (diacetoxyiodo)benzene (DIB) by a desulfurizaton strategy.



IV.1. Importance and Applications

2-(*N*-substituted)-aminobenzimidazoles are widely used structural motifs in medicinal chemistry as well as in drug discovery and 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.[3] Some examples of pharmaceutically interest molecules are shown below (*Figure V.1.1*).

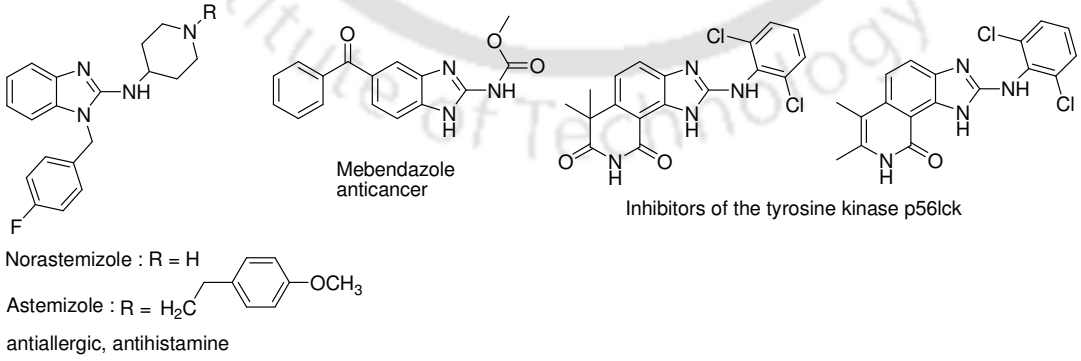


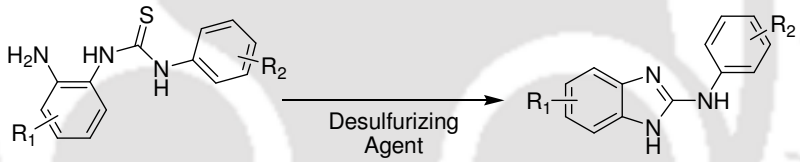
Figure V.1.1

The 2-aminobenzoxazole moiety is a popular building block for the construction of pharmaceutically interesting compounds. 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.[4]

The oxazine analogous ring system is of great interest in modern organic chemistry because it can be used as a masked carboxylic acid,[5a] chiral ligand for asymmetric synthesis,[5b] versatile synthetic intermediate[5c] and therapeutic agent.[5d] 1-Imidazolidinecarbothioamides are useful as insecticides, particularly for the control of *Epilachna varivestis*.[5e]

V.2. Available Synthetic Methods

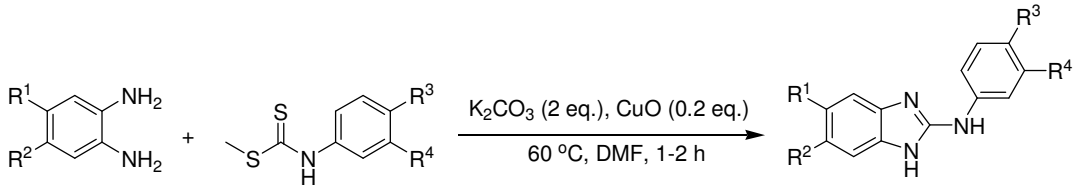
The most commonly adopted method for the synthesis of 2-(*N*-substituted)-aminobenzimidazoles involves the cyclodesulfurization of preformed monothioureas (*Scheme V.2.1*).



Scheme V.2.1.

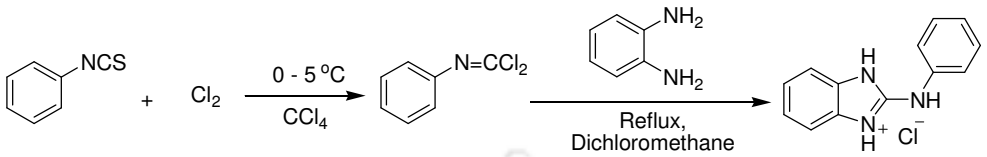
The reported desulfurization agents include carbodiimides,[6] tosyl chloride,[7a] methyl iodide,[7b] mercury(II) oxide,[7c] mercury(II) chloride,[7d] and copper(I) chloride.[7e]

In another approach, benzimidazoles have been prepared by the reaction of dithiocarbamates and *o*-phenylenediamines promoted by catalytic CuO (*Scheme V.2.2*).[8a]



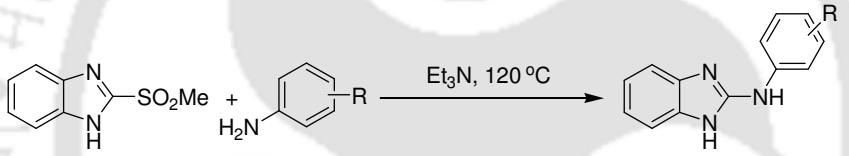
Scheme V.2.2.

2-Aryl aminobenzimidazoles have been obtained by reacting phenyl- and *p*-chlorophenylcarbonimidoyl dichlorides, which are prepared by chlorination of phenyl isothiocyanate with *o*-phenylenediamines in a suitable solvent (*Scheme V.2.3*).[8b]



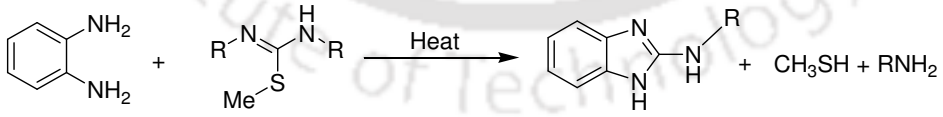
Scheme V.2.3.

A variety of 2-substituted benzimidazoles has been prepared by the reaction of 2-methylsulfonyl benzimidazole with an amine nucleophile under a solvent-free condition (*Scheme V.2.4*).[8c]



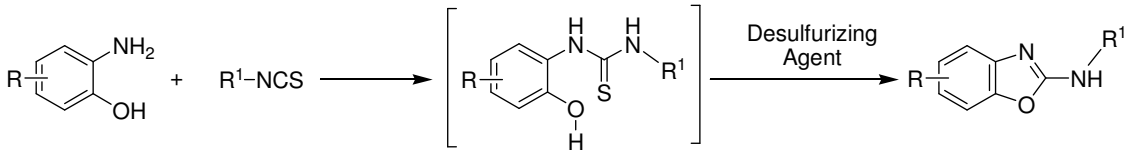
Scheme V.2.4.

The reaction between *o*-phenylenediamine and methyl isodiphenylthiourea at 145 ^{o}C afforded 2-anilino-benzimidazol with the separation of mercaptan and aniline (*Scheme V.2.5*).[8d]



Scheme V.2.5.

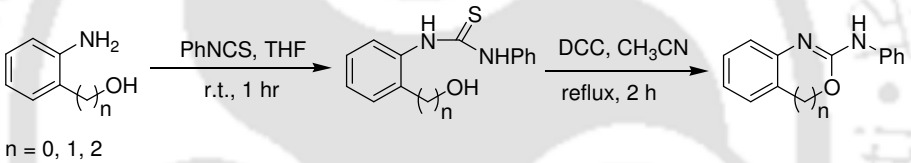
The general method used for the synthesis of aminobenzoxazoles is the cyclodesulfurization of *N*-substituted 2-hydroxyphenylthioureas (*Scheme V.2.6*).



Scheme V.2.6.

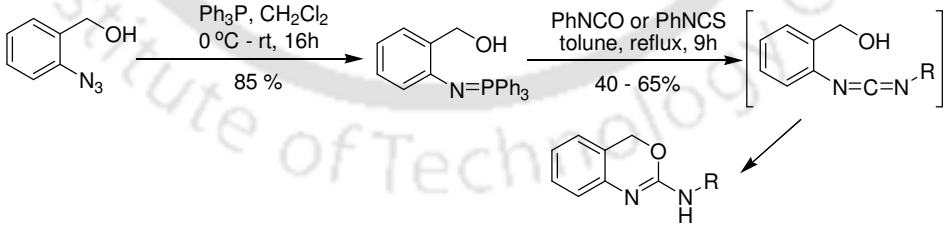
The cyclodesulfurization reagents include NiO,[9] HgO,[10] $AgNO_3$,[11a,b] KO_2,[11c,d] salts of transition metals,[11e] and dicyclohexylcarbodiimide (DCC).[11f] Oxidative cyclodesulfurization by using aqueous hydrogen peroxide and LiOH has recently been reported to give excellent yields of the products.[11g]

Another important class of compounds, benzoxazines, has been prepared by using DCC as the desulfurization agent from the substituted thiourea moiety in quite good yield (*Scheme V.2.7*).[12a]



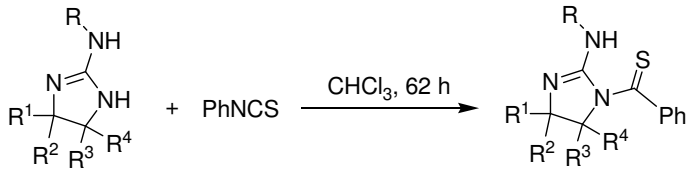
Scheme V.2.7.

In another report, benzoxazines have been obtained by an arduous tandem aza-Wittig/heterocumulene-mediated annulation strategy (*Scheme V.2.8*).[12b]



Scheme V.2.8.

Only two methods have been reported for synthesis of 1-imidazolidinecarbothioamides, one involves the use of a toxic mercury salt from *bis*(urea) and the other by the treatment of 2-methylamino-2-imidazoline with isothiocyanate (*Scheme V.2.9*).[13]



Scheme V.2.9.

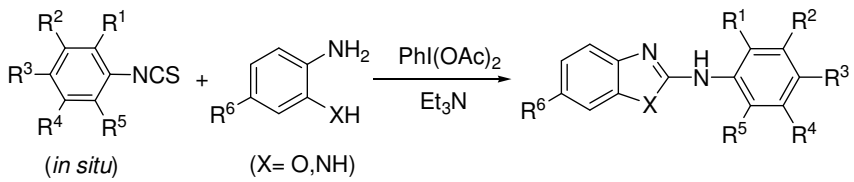
Thus there is lot of interest and challenges in the synthesis of the above mentioned heterocycles.

V.3. Present Work

One of the most important achievements in hypervalent iodine oxidation reactions is the synthesis of various heterocyclic compounds. As a part of our group's continuous efforts to synthesize various N, O, S containing five or six membered heterocycles,[14] we have utilized the desulfurizing ability of hypervalent iodine(III) reagent, (diacetoxyiodo)benzene (DIB) to synthesize four types of heterocycles *viz.* 2-aminobenzimidazole, aminobenzoxazole, benzoxazine and 1-imidazolidinecarbothioamide.

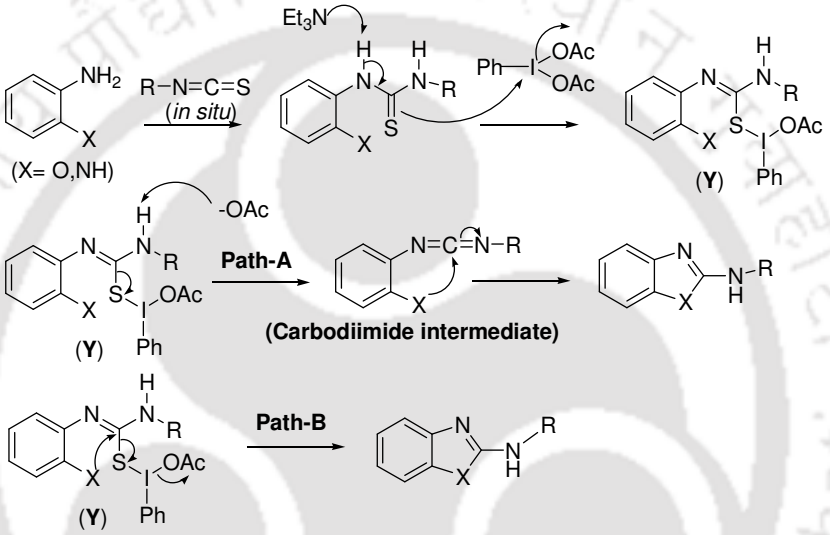
We developed a high yielding protocol for the synthesis of a wide variety of isothiocyanates starting from dithiocarbamate salts using thiophilic hypervalent iodine(III) reagent, (diacetoxyiodo)benzene as discussed in the previous sections.[15a] After successfully synthesizing various isothiocyanates, we focused our attention on the synthesis of 2-aminobenzimidazole.

Because isothiocyanate can be generated from a dithiocarbamate salt by using DIB, which has desulfurization ability,[15a,b] we decided to develop a one-pot procedure for the synthesis of 2-aminobenzimidazole by treating *o*-phenylenediamine with the *in situ* generated isothiocyanates (*Scheme V.3.1*). The resultant monothiourea was treated with another equivalent of DIB to give the desired benzimidazole in good yield.



Scheme V.3.1. *Synthesis of 2-aminobenzimidazole/benzoxazole*

The sulfur atom of the thiourea attacks the thiophilic iodine of $PhI(OAc)_2$ displacing one of its acetate groups to give intermediate **Y** (*Scheme V.3.2*). Reductive β-elimination of the λ^3-iodane intermediate (path A, *Scheme V.3.2*) with the expulsion of sulfur produced a carbodiimide intermediate, which reacted intramolecularly with the *o*-amino group to yield the desired product, as shown in *Scheme V.3.2*. The precipitation of elemental sulfur and formation of phenyl iodide support the proposed mechanism. Alternatively, a mechanism involving direct intramolecular cyclization at the iminium carbon atom (path B) cannot be ruled out.



Scheme V.3.2. *Mechanism of formation of benzimidazole / benzoxazole*

This strategy has successfully been applied to the preparation of various benzimidazoles (**1b-10b**), as shown in *Table V.3.1*.The structure of the product **1b** was confirmed by X-ray crystallography (*Figure V.3.1*). The success of this strategy lies in the selective formation of monothiourea from *o*-phenylenediamine in the presence of 1 equiv. of the *in situ* generated isothiocyanate.

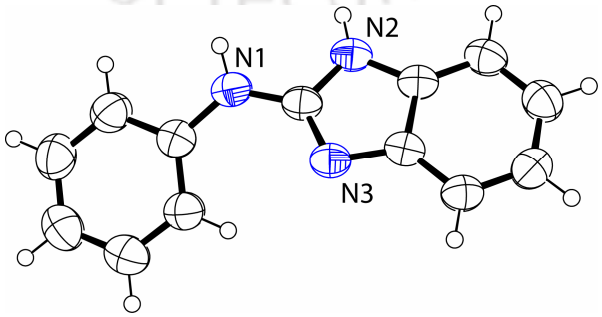
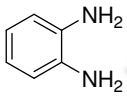
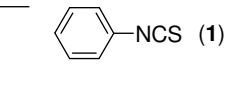
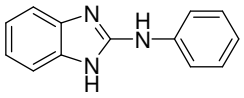
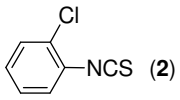
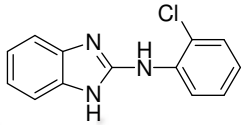
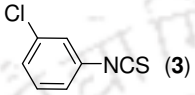
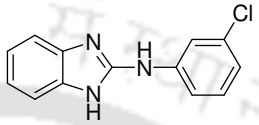
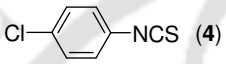
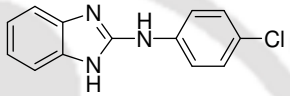
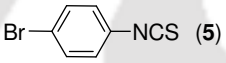
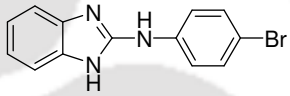
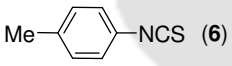
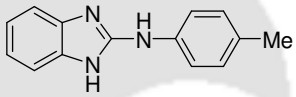
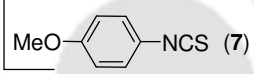
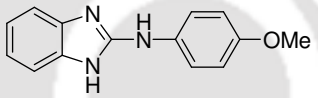
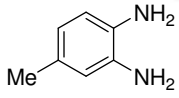
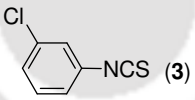
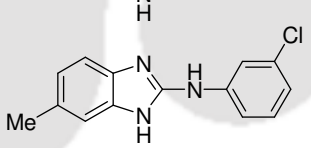
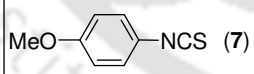
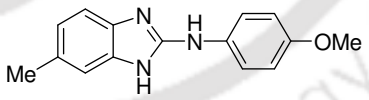
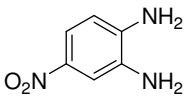
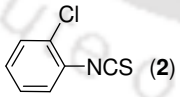
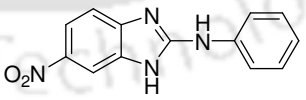


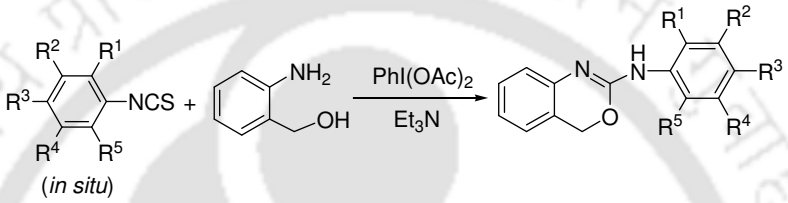
Figure V.3.1. *The ORTEP view with the atomic numbering scheme of (**1b**)*

Table V.3.1. *Preparation of 2-aminobenzimidazole*[a]

Substrate	Product[b]	Yield (%)[c]
 +  (**1**)	 (**1b**)	71%
+  (**2**)	 (**2b**)	70%
+  (**3**)	 (**3b**)	73%
+  (**4**)	 (**4b**)	69%
+  (**5**)	 (**5b**)	65%
+  (**6**)	 (**6b**)	75%
+  (**7**)	 (**7b**)	69%
 +  (**3**)	 (**8b**)	64%
+  (**7**)	 (**9b**)	68%
 +  (**2**)	 (**10b**)	62%

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

The successful synthesis of benzimidazole prompted us to apply this strategy to the synthesis of aminobenzoxazoles. Thus, the strategy applied to the synthesis of 2-aminobenzimidazole was also applied to the synthesis of aminobenzoxazoles. The *in situ* generated isothiocyanate (*Scheme V.3.1*) was treated with *o*-aminophenol to yield the monothiourea. The resultant monothiourea, on treatment with another equivalent of DIB, produced the desired aminobenzoxazoles. The mechanism is expected to be similar to the one proposed in *Scheme V.3.2*. Several aminobenzoxazole derivatives (**1c**–7**c**) (*Table V.3.2*) were successfully prepared in excellent yields in shorter reaction times.



Scheme V.3.3. *Synthesis of benzoxazine*

Another important class of compounds, benzoxazines (**1d**–**3d**), has also been prepared by using DIB in one-pot strategy (*Scheme V.3.3*). The structure of the product **1d** was confirmed by X-ray crystallography (*Figure V.3.2*).

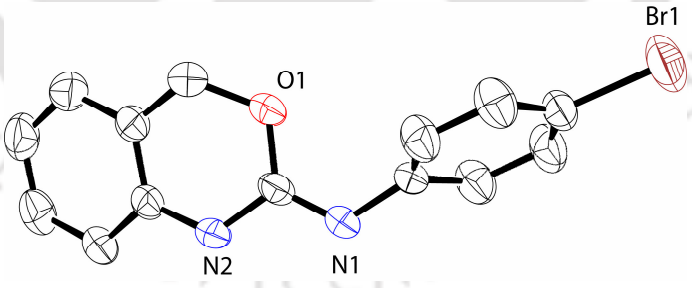
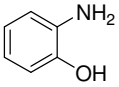
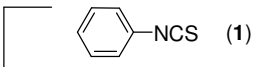
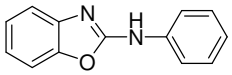
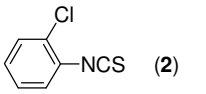
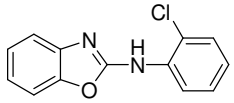
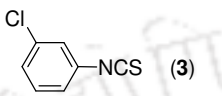
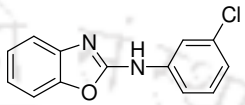
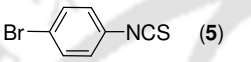
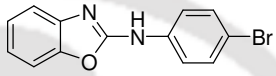
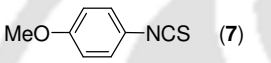
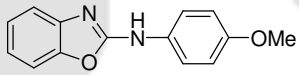
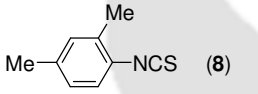
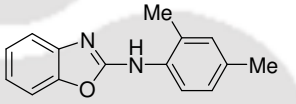
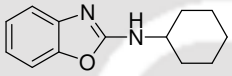
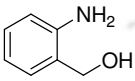
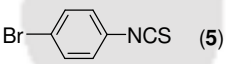
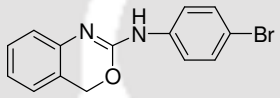
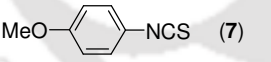
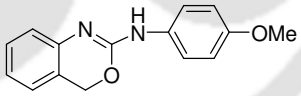
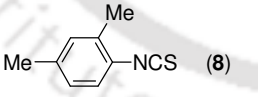
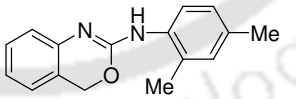
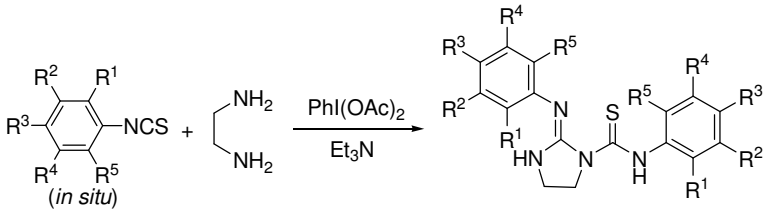


Figure V.3.1. *The ORTEP view with the atomic numbering scheme of (**1d**)*

Table V.3.2. *Preparation of* aminobenzoxazole[a]

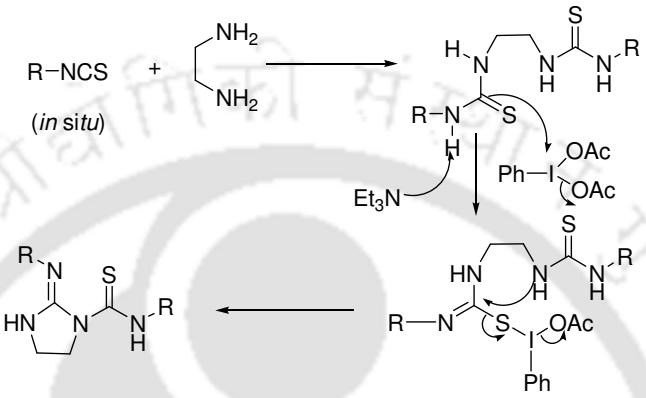
Substrate		Product[b]		Yield (%)[c]
	 (**1**)		(**1c**)	70%
	 (**2**)		(**2c**)	67%
	 (**3**)		(**3c**)	73%
	 (**5**)		(**4c**)	69%
	 (**7**)		(**5c**)	71%
	 (**8**)		(**6c**)	65%
	 (**9**)		(**7c**)	72%
	 (**5**)		(**1d**)	66%
	 (**7**)		(**2d**)	68%
	 (**8**)		(**3d**)	71%

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



Scheme V.3.4. *Preparation of 1-imidazolidinecarbothioamide*

The most interesting aspect of this investigation is the synthesis of 1-imidazolidinecarbothioamides. The *in situ* generated isothiocyanate (2 equiv.), when treated with ethylenediamine (1 equiv.), gave *bis*(thiourea), which, on reaction with DIB, gave an excellent yield of imidazolidinecarbothioamide (*Scheme V.3.4*). The mechanism for the formation of imidazolidinecarbothioamide is shown in (*Scheme V.3.5*).



Scheme V.3.5. *Mechanism of 1-imidazolidinecarbothioamide formation*

As a result of this success, the strategy was applied to the synthesis of other imidazolidinecarbothioamides (**1e**–**6e**) in good yields, as shown in *Table V.3.3*. The structure of **6e** was confirmed by X-ray crystallography (*Figure V.3.3*).

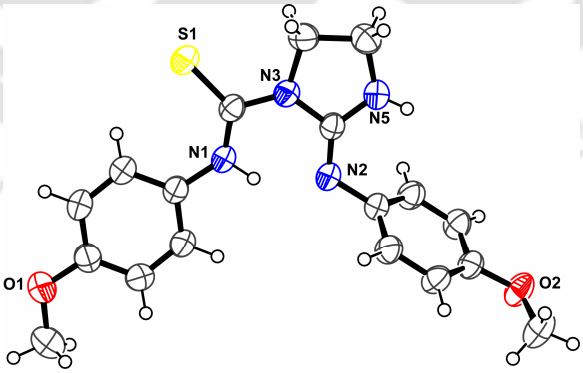
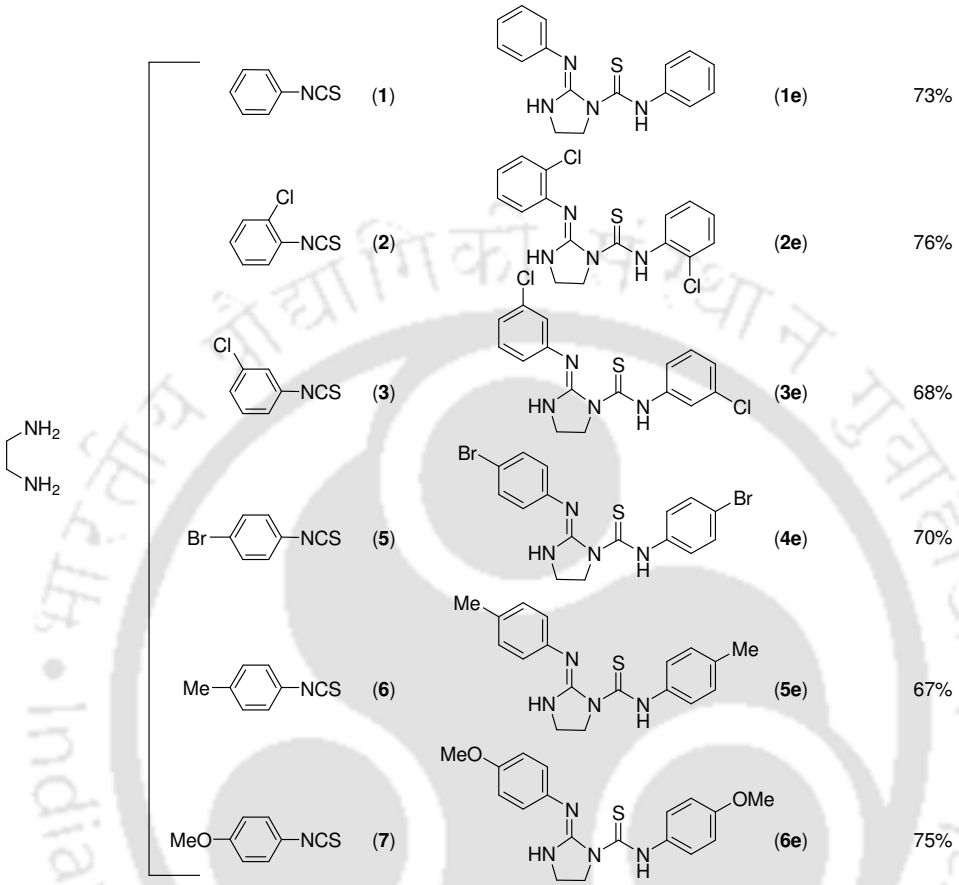
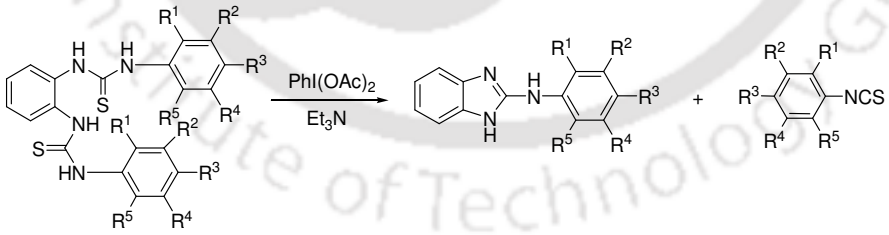


Figure V.3.3. *The ORTEP view with the atomic numbering scheme of (6**e**)*

Table V.3.3. *Synthesis of imidazolidenecarbothioamides*[a]

Substrate	Product[b]	Yield(%)[c]
		
(1)	(**1e**)	73%
(2)	(**2e**)	76%
(3)	(**3e**)	68%
(5)	(**4e**)	70%
(6)	(**5e**)	67%
(7)	(**6e**)	75%

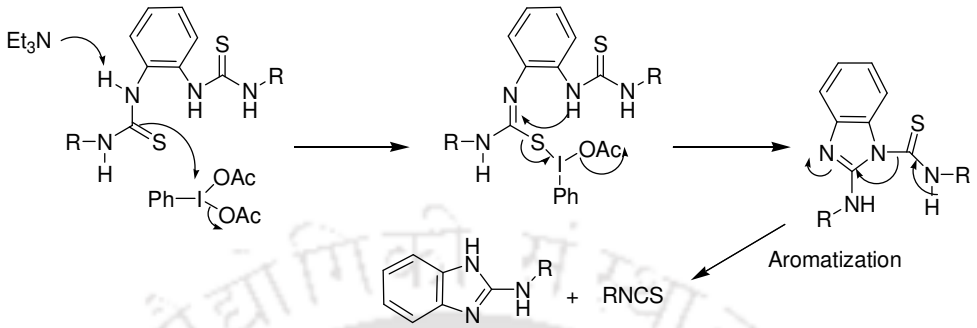
[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.



Scheme V.3.6. *Reactivity of aromatic 1,2-bisthiourea with DIB*

When the flexible ethylenediamine was replaced by a rigid aromatic system such as *o*-phenylenediamine, the reactivity changed completely to give benzimidazole and isothiocyanate instead of imidazolidinecarbothioamide (*Scheme V.3.6*). The *bis*(thioureas) of *o*-phenylenediamine (*Scheme V.3.6*) were prepared according to a modified literature procedure, and the reaction was performed starting from the isolated *bis*(thioureas). In this

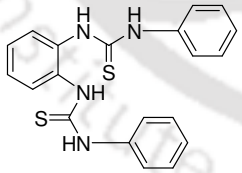
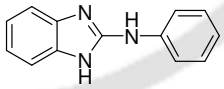
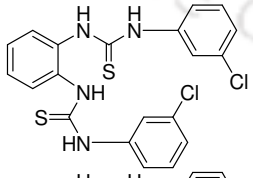
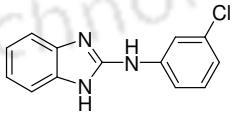
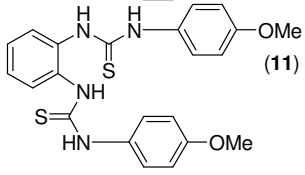
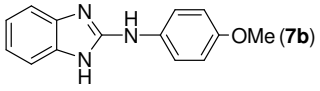
case the intermediate imidazolidinecarbothioamide rapidly lost one equivalent of isothiocyanate to give benzimidazole (*Scheme V.3.7*).



Scheme V.3.7. *Mechanism of formation of benzimidazole and isothiocyanate from aromatic 1,2-bis(thiourea)*

The driving force for this reaction is the gain in the aromatic character of the product benzimidazole as a result of the loss of isothiocyanate (*Scheme V.3.7*), which was not observed with the analogous aliphatic ethylenediaminebis(thioureas) (*Scheme V.3.5*). This reaction was tested to other *bis*(thioureas) and the corresponding benzimidazoles (**1b**, **3b**, and **7b**) was obtained in good yields, as shown in *Table V.3.4*.

Table V.3.4. *Synthesis of 2-aminobenzimidazole*[a]

Substrate	Product[b]	Yield (%)[c]
 (**9**)	 (**1b**)	93%
 (**10**)	 (**3b**)	92%
 (**11**)	 (**7b**)	94%

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

In conclusion, we have demonstrated the multifaceted use of (diacetoxyiodo)benzene for various synthetically useful organic transformations. In the past most of these reactions were carried out in several steps using toxic heavy metals or expensive reagents. It has been demonstrated here that the reactions can be carried out under mild conditions using hypervalent iodine reagent DIB. Although the overall isolated yields look moderate, considering that the reactions are multistep processes, the yields are in fact good to excellent. An interesting difference in reactivity was observed for the *bis*(thioureas) of aliphatic and aromatic 1,2-diamines, the former giving 1-imidazolidinecarbothioamide and the latter benzimidazole and isothiocyanate.

V.4. Experimental Section

IV.4.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1. page 48-49.

V.4.2. General Procedures

V.4.2.1. General Procedure for the One-Pot Preparation of Bezimidazole (1b) Starting from the Corresponding Dithiocarbamate Salt

Phenyl isothiocyanate was prepared *in situ* from the corresponding dithiocarbamate salt (540 mg, 2 mmol) following the standard procedure stated in Chapter IV, Section IV.4.2.1 and was used as such without any further purification.

o-Phenylenediamine (216 mg, 2 mmol) was added to the above *in situ* generated phenylisothiocyanate. Complete conversion to corresponding mono-thiourea was confirmed by TLC (30 to 60 minute). To this reaction mixture was added triethylamine (278 μL, 2 mmol) followed by portion wise addition of DIB (644 mg, 2 mmol) over a period of 10-15 minutes. Conversion of thiourea to benzimidazole was observed within 5-10 minutes with concomitant precipitation of sulfur. The reaction mixture was allowed to stand and the precipitated sulfur was filtered; organic layer was evaporated and admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with water (2 x 5 mL). The

organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column to give the pure product **1b**.

V.4.2.2. General Procedure for the One-Pot Preparation of N-2-Phenyl-1,3-benzoxazol-2-amine (1c) Starting from the Dithiocarbamate Salt

Phenyl isothiocyanate was prepared *in situ* from the corresponding dithiocarbamate salt (540 mg, 2 mmol) following the standard procedure stated in Chapter IV, Section IV.4.2.1 and was used as such without any further purification.

o-Aminophenol (218 mg, 2 mmol) was added to the above *in situ* generated phenylisothiocyanate. Complete conversion to corresponding thiourea was confirmed by TLC (30 to 60 minute). To this reaction mixture was added triethylamine (278 µL, 2 mmol) followed by portion wise addition of DIB (644 mg, 2 mmol) over a period of 10-15 minutes. Conversion of thiourea to benzoxazole was observed within 5-10 minutes with concomitant precipitation of sulfur. The reaction mixture was allowed to stand and the precipitated sulfur was filtered; organic layer was evaporated and admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column to give the pure product **1c**.

V.4.2.3. General Procedure for the One-Pot Preparation *N*-(4-Bromophenyl)-4H-benzo[d] [3,1]oxazin-2-amine (2d) Starting from Dithiocarbamate Salt

Similar to General Procedure V.4.2.2, except 2-amino-bezyl alcohol was used instead of *o*-aminophenol to give product **2d**.

V.4.2.3. General Procedure for the One-Pot Preparation of *N*-Phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (1e) Starting From the Corresponding Dithiocarbamate Salt

Phenyl isothiocyanate was prepared *in situ* from the corresponding dithiocarbamate salt (540 mg, 2 mmol.) following the standard procedure stated in Chapter IV, Section IV.4.2.1 and was used as such without any further purification.

Ethylenediamine (1 mmol, 68 μL) was added to the above reaction mixture. Complete conversion to *bis*-thiourea was observed (30 minutes). To this reaction mixture, triethylamine (139 μL, 1 mmol) was added followed by portionwise addition of DIB (322 mg, 1 mmol) over a period of 10-15 minutes. Conversion of *bis*-thiourea to N-phenyl-2-(phenylimino)imidazolidine-1-carbothioamide (**1e**) was observed with concomitant precipitation of sulfur (5 minutes). The reaction mixture was allowed to stand for 5 minutes and the precipitated sulfur was filtered; organic layer evaporated and admixed with ethyl acetate (15 mL). The ethyl acetate layer was washed with water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column to give pure product **1e**.

V.5. References

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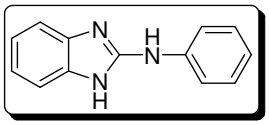
V.6. Spectral Data

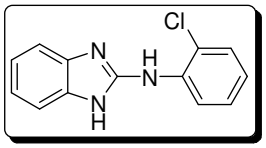
***N*-Phenyl-1*H*-benzo[*d*]imidazol-2-amine (1b):**



M.p. 150-152 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.29 (br s, 1H), 6.92 (t, 1H, *J* = 7.6 Hz), 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, 693, 497 cm^{-1}.

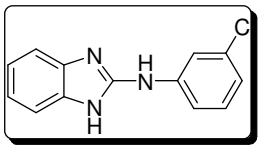
Crystal data for 1b: Crystal dimension (mm): 0.30 x 0.28 x 0.23. $C_{26}H_{22}N_6$, Mr = 418.50. orthorhombic, space group Pbca; a = 8.5445(4) Å, b = 10.9972(6) (2) Å, c = 22.4895(12) Å; α = 90.00°, β = 90.00°, γ = 90.00°, V = 2113.24(19) $Å^3$; Z = 4; ρ_{cal} = 1.315 mg/m^3; μ(mm^{-1}) = 0.081; *F (000)* = 880; Reflection collected / unique = 24797 / 2602; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0421, wR2 =0.1175, R indices (all data) R1 = 0.0745, wR2 = 0.1481; Goodness of fit = 0.768. CCDC # 699840.

***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 (br s, 1 H), 6.89 (t, 1 H, *J* = 7.2 Hz), 7.07 (m, 2 H), 7.25–7.38 (m, 4 H), 8.66 (d, 1H, *J* = 6.8 Hz). ^{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}. $C_{13}H_{10}ClN_3$ (243.70): calcd C 64.07, H 4.14, N 17.24; found C 64.11, H 4.19, N 17.18.

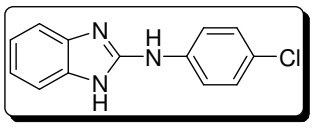
***N*-(3-Chlorophenyl)-1*H*-benzo[*d*]imidazol-2-amine (3b):**



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, 1H, *J* = 8.0 Hz), 7.36 (m, 2H), 7.51 (m, 1H), 7.75 (t, 1H, *J* = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.8, 115.6, 117.2,

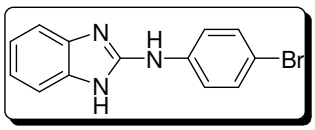
117.7, 120.7, 121.1, 129.9, 130.4, 141.6, 150.4. IR (KBr): 3394, 2923, 1591, 1559, 1459, 1241, 1193, 776, 747 cm^{-1}.

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



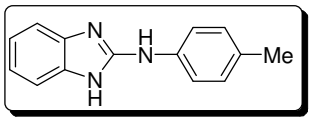
M.p. 178-180 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.40 (br s, 1H), 7.06 (m, 2H), 7.24 (m, 2H, *J* = 8.4 Hz) 7.34 (m, 2H), 7.62 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.5, 118.9, 120.5, 125.7, 128.6, 136.9, 138.7, 150.4. IR (KBr): 3048, 2916, 1646, 1593, 1567, 1517, 1488, 1461, 1426, 1384, 1266, 1251, 1089, 1009, 841, 819, 742, 701, 501, 479 cm^{-1}.

_N_-(4-Bromophenyl)-1_H_-benzo[_d_]imidazol-2-amine (5b):



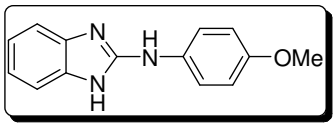
M.p. 213-215 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.80 (br s, 1H), 7.03 (m, 2H), 7.34 (m, 2H), 7.36 (d, 2H, *J* = 8.4 Hz), 7.64 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 112.1, 112.3, 118.7, 120.0, 131.0, 136.6, 139.0, 149.9. IR (KBr): 3154, 3048, 2921, 1644, 1604,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

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



M.p. 192-194 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 6.90 (d, 2H, *J* = 8.0 Hz), 7.06 (m, 4H), 7.20 (m, 2H), 9.33 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 112.4, 121.2, 121.9, 130.2, 134.3, 135.1, 135.8, 151.8. IR (KBr): 3057, 2921, 2854, 1660, 1629, 1607, 1567, 1514, 1475, 1410, 1270, 1044, 812, 656, 613, 499 cm^{-1}.

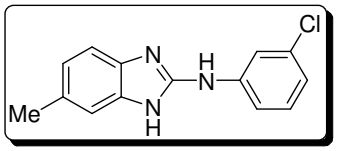
_N_-(4-Methoxyphenyl)-1_H_-benzo[_d_]imidazol-2-amine (7b):



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, 2H, *J* = 8.8 Hz), 7.01 (m, 2H), 7.30 (m, 2H), 7.50 (d, 2H, *J* = 8.8 Hz). ^{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,

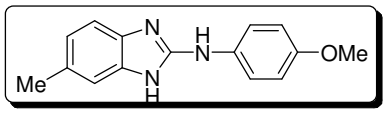
1514, 1461, 1393, 1314, 1274, 1175, 1026, 915, 806, 741, 593 cm^{-1}.

_N_-(3-Chlorophenyl)-6-methyl-1_H_-benzo[_d_]imidazol-2-amine(8b):



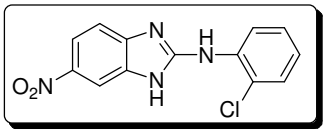
M.p. 95-97 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.41 (s, 3H), 4.62 (br s, 1H), 6.92 (t, 2H, *J* = 8.0 Hz), 7.21 (m, 3H), 7.44 (m, 1H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 21.6, 112.5, 112.8, 116.4, 118.0, 121.8, 122.4, 130.2, 130.9, 134.4, 134.6, 136.1, 141.2, 150.1. 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 65.11, H 4.73, N 16.22. MS (ESI): MH^+, found 258.08.

_N_-(4-Methoxyphenyl)-1_H_-benzo[_d_]imidazol-2-amine (9b):



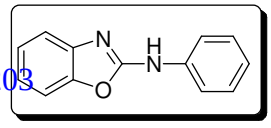
M.p. 180 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.76 (s, 3H), 4.12 (br s, 1H), 6.84 (d, 2H, *J* = 8.8 Hz), 7.01 (m, 2H), 7.30 (m, 2H), 7.50 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6): δ 55.1, 109.5, 112.1, 114.0, 120.0, 133.1, 137.2, 151.6, 154.5. IR (KBr): 2921, 2832, 1623,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

_N_-(2-Chlorophenyl)-4-Nitro-1_H_-benzo[_d_]imidazol-2-amine (10b):



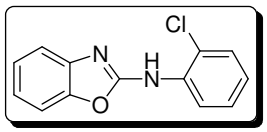
M.p. 213-215 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 4.62 (s, 1H), 7.01 (t, 1H, *J* = 7.6 Hz), 7.35 (t, 1H, *J* = 7.8 Hz), 7.41 (t, 2H, *J* = 8.0 Hz), 8.02 (m, 1H), 8.25 (s, 1H), 8.63 (t, 1H, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 108.0, 111.8, 116.6, 119.4, 121.2, 122.3, 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}. $C_{13}H_9ClN_4O_2$ (288.69): Calcd C 54.09, H 3.14, N 19.41; found C 54.11, H 3.10, N 19.43.

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



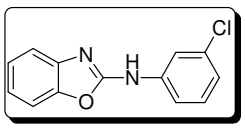
M.p. 176-178 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.05 (m, 2H), 7.19 (t, 1H, *J* = 7.6 Hz), 7.32 (m, 3H), 7.46 (d, 1H, *J* = 7.8 Hz), 7.71 (m, 2H), 9.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 108.6, 116.7, 118.1, 121.4, 122.4, 123.8, 128.9, 138.4, 142.5, 147.4, 158.4. IR (KBr): 3162, 2922, 1659, 1601, 1574, 1502, 1459, 1375, 1249, 1225, 1164, 1003, 972, 892, 739, 686, 636, 504 cm^{-1}.

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



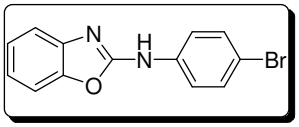
M.p. 109-111 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.09 (m, 1H), 7.22 (m, 1H), 7.31 (m, 1H), 7.43 (m, 3H), 7.58 (d, 1H, *J* = 8.0Hz), 7.84 (s, 1H), 8.57 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 109.1, 117.6, 119.4, 121.9, 122.3, 123.5, 124.2, 127.9, 129.2, 134.5, 142.2, 147.6, 157.1. IR (KBr): 3230, 3029, 1661, 1589, 1571, 1531, 1458, 1339, 1317, 1245, 1229, 1166, 1055, 1003, 969, 920, 743, 707, 630, 494 cm^{-1}. $C_{13}H_9ClN_2O$ (244.68): Calcd C 63.82, H 3.71, N 11.45; found C 63.87, H 3.67, N 11.37.

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



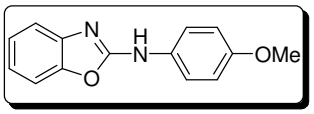
M.p. 184-186 °C, ^{1}H NMR: (400 MHz, $CDCl_3$ + DMSO-d_6): δ 6.99 (d, 1H, *J* = 8.0 Hz), 7.12 (t, 1H, *J* = 7.6 Hz), 7.22 (t, 1H, *J* = 7.6 Hz), 7.28 (t, 1H, *J* = 8.4 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.46 (d, 1H, *J* = 7.6 Hz), 7.63 (d, 1H, *J* = 7.4 Hz), 7.92 (s, 1H), 10.35 (s, 1H). ^{13}C NMR (100 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 63.82, H 3.71, N 11.45; found C 63.85, H 3.76, N 11.39.

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



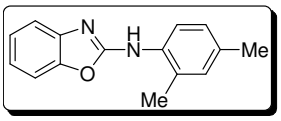
M.p. 219-221 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 7.10 (t, 1H, *J* = 8.0 Hz), 7.20 (t, 1H, *J* = 7.6 Hz), 7.32 (d, 1H, *J* = 8.0 Hz), 7.42-7.48 (m, 3H), 7.69 (d, 2H, *J* = 8.8 Hz), 10.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 108.5, 114.1, 116.7, 119.4, 121.4, 123.7, 131.4, 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}.

_N_-2-(4-Methoxyphenyl)-1,3-benzoxazol-2-amine (5c):



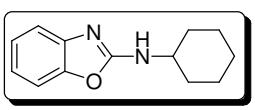
M.p. 136-138 °C, ^{1}H NMR: (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.80 (s, 3H), 6.90 (d, 2H, *J* = 8.8 Hz), 7.06 (t, 1H, *J* = 7.6 Hz), 7.18 (t, 1H, *J* = 7.6 Hz), 7.29 (d, 1H, *J* = 8.0 Hz), 7.42 (d, 1H, *J* = 7.6 Hz), 7.59 (d, 2H, *J* = 8.8 Hz), 9.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 55.5, 108.7, 114.3, 116.6, 120.4, 121.2, 123.9, 131.6, 42.6, 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}. $C_{14}H_{12}N_2O_2$ (240.26): Calcd C 69.99, H 5.03, N 11.66; found C 70.08, H 5.09, N 11.57.

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



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, 1H, *J* = 7.2 Hz), 7.29 (d, 1H, *J* = 8.0 Hz), 7.38 (d, 1H, *J* = 7.2 Hz), 7.74 (d, 1H, *J* = 8.0 Hz). ^{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}. $C_{15}H_{14}N_2O$ (238.28): Calcd C 75.61, H 5.92, N 11.76; found C 75.60, H 5.96, N 11.77.

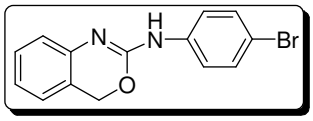
_N_-Cyclohexylbenzo[*d*]oxazol-2-amine (7c):



M.p. 112-114 °C, ^{1}H NMR: (400 MHz, $CDCl_3$ + DMSO-d_6): δ 1.18-1.48 (m, 5H), 1.65 (m, 1H), 1.77 (m, 2H), 2.11 (m, 2H), 3.73 (m, 1H), 5.87 (d, 1H, *J* = 7.6 Hz), 6.99 (t, 1H, *J* = 7.4 Hz),

7.13 (t, 1H, *J* = 6.8 Hz), 7.22 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 24.8, 25.5, 33.4, 52.0, 108.5, 115.8, 120.3, 123.7, 143.2, 148.3, 161.8. IR (KBr): 3183, 2920, 2854, 1651, 1585, 1462, 1354, 1285, 1241, 1147, 1113, 1007, 889, 737, 632 cm^{-1}. $C_{13}H_{16}N_2O$ (216.28): Calcd C 72.19, H 7.46, N 12.95; found C 72.21, H 7.45, N 12.97.

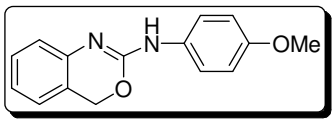
***N*-(4-Bromophenyl)-4H-benzo[d] [3,1]oxazin-2-amine (1d):**



M.p. 182-184 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 5.20 (s, 2H), 6.99 (m, 3H), 7.22 (m, 1H), 7.29-7.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 67.7, 115.3, 120.7, 122.2, 123.1, 123.9, 129.1, 131.8, 139.6, 140.6, 151.4. IR (KBr): 3166, 3053, 2992, 2872, 1695, 1682, 1600, 1496, 1480, 1456, 1408, 1394, 1315, 1267, 1245, 1206, 1169, 1069, 1025, 1007, 885, 839, 754, 692, 663 cm^{-1}.

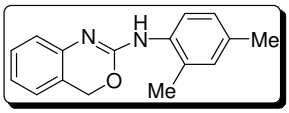
Crystal data for 1d: Crystal dimension (mm): 0.42 x 0.32 x 0.20. $C_{14}H_{11}BrN_2O$, Mr = 303.16, Triclinic, space group P-1; a = 5.8193(2) Å, b = 8.1460(2) Å, c = 14.2820(4) Å; α = 106.093(2)°, β = 92.257(2)°, γ = 94.748(2)°, V = 646.89(3)Å^3; Z = 2; ρ_{cal} = 1.556 mg/m^3; μ(mm^{-1}) = 3.166; *F (000)* = 304; Reflection collected / unique = 2889 / 1947; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0430, wR2 = 0.1026 R indices (all data) R1 = 0.0703 wR2 = 0.1134, Goodness of fit = 1.057. CCDC # 775675

***N*-(4-Methoxyphenyl)-4H-benzo[d] [3,1]oxazin-2-amine (2d):**



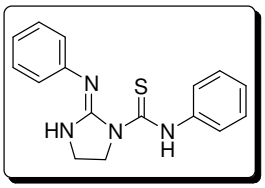
M.p. 150-152 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.78 (s, 3H), 5.19 (s, 2H), 6.84 (d, 2H, *J* = 9.2 Hz), 6.98 (m, 3H), 7.20 (m, 1H), 7.40 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 55.4, 67.5, 114.0, 120.9, 121.0, 122.2, 122.5, 123.6, 128.9, 132.7, 141.5, 152.3, 155.5. 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)-4H-benzo[d][1,3]oxazin-2-amine (3d):



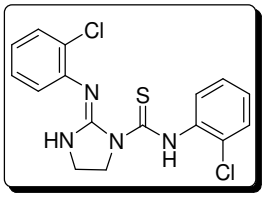
M.p. 163-166 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.30 (s, 3H), 5.14 (s, 2H), 6.80 (d, 1H, *J* = 8.0 Hz), 6.92-6.99 (m, 4H), 7.15 (t, 1H, *J* = 7.2 Hz), 7.31 (d, 1H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 21.0, 67.8, 120.1, 120.6, 122.5, 123.8, 124.0, 127.2, 129.2, 130.9, 131.3, 134.1, 135.8, 141.2, 152.5. IR (KBr): 3159, 3043, 2956, 2836, 1681, 1600, 1511, 1496, 1461, 1405, 1268, 1239, 1206, 1028, 885, 837, 755, 697, 594, 528 cm^{-1}. $C_{16}H_{16}N_2O$ (252.31): Calcd C 76.16, H 6.39, N 11.10; found C 76.11, H 6.41, N 11.11.

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



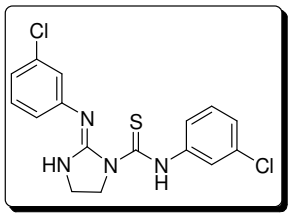
M.p. 190-192 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.46 (t, 2H, *J* = 7.9 Hz), 4.45 (t, 2H, *J* = 8.0 Hz), 5.39 (s, 1H), 7.02 (m, 2H), 7.08 (t, 1H, *J* = 6.4 Hz), 7.19 (t, 1H, *J* = 7.2 Hz), 7.35 (m, 4H), 7.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 38.4, 48.4, 122.6, 123.7, 124.4, 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, 577, 502 cm^{-1}. $C_{16}H_{16}N_4S$ (296.40): Calcd C 64.84, H 5.44, N 18.90, S 10.82; found C 64.78, H 5.36, N 18.79, S 10.73.

2-(2-Chlorophenylimino)-_N_-(2-chlorophenyl)imidazolidine-1-carbothioamide (2e):



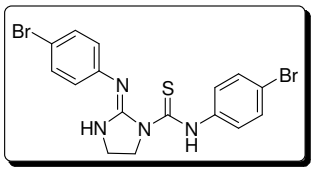
M.p. 147-149 °C, ^{1}H NMR: (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.48 (t, 2H, *J* = 8.0 Hz), 4.42 (t, 2H, *J* = 8.4 Hz), 6.24 (s, 1H), 7.02 (m, 1H), 7.15 (m, 2H), 7.21-7.30 (m, 2H), 7.39 (m, 2H), 8.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 38.1, 48.3, 123.6, 124.1, 126.2, 126.6, 127.3, 127.4, 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}. $C_{16}H_{14}Cl_2N_4S$ (365.28): Calcd C 52.61, H 3.86, N 15.34, S 8.78 found C 52.66, H 3.83, N 15.29, S 8.73.

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



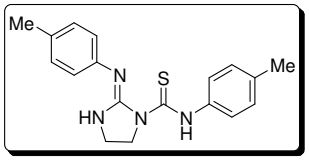
M.p. 138-140 °C, ^{1}H NMR: (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.46 (t, 2H, *J* = 7.6 Hz), 4.41 (t, 2H, *J* = 7.6 Hz), 5.82 (s, 1H), 6.92 (m, 1H), 7.04-7.08 (m, 2H), 7.14 (m, 1H), 7.27 (m, 2H), 7.47 (m, 1H), 7.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 38.3, 48.4, 121.2, 122.4, 122.9, 123.7, 124.1, 125.6, 129.5, 130.5, 133.9, 134.7, 140.2, 147.8, 152.1, 178.6. IR (KBr): 2894, 1667, 1586, 1560, 1474, 1403, 1376, 1322, 1294, 1133, 1078, 898, 828, 791, 679, 581 cm^{-1}. $C_{16}H_{14}Cl_2N_4S$ (365.28): Calcd C 52.61, H 3.86, N 15.34, S 8.78 found C 52.68, H 3.87, N 15.28, S 8.74.

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



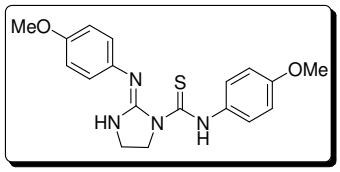
M.p. 180-182 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.47 (t, 2H, *J* = 7.6 Hz), 4.44 (t, 2H, *J* = 8.4 Hz), 4.78 (s, 1H), 6.89 (d, 2H, *J* = 8.4 Hz), 7.45 (m, 4H), 7.52 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 38.6, 48.7, 117.2, 119.0, 124.6, 126.1, 131.9, 132.9, 138.3, 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}. $C_{16}H_{14}Br_2N_4S$ (454.19): Calcd C 42.31, H 3.11, N 12.34, S 7.06; found C 42.35, H 3.08, N 12.27, S 7.00.

2-(*p*-Tolylimino)-*N*-(*p*-tolylphenyl)imidazolidine-1-carbothioamide (5e):



M.p. 142-144 °C, ^{1}H NMR: (400 MHz, $CDCl_3$ + DMSO-d_6): δ 2.32 (s, 3H), 2.33 (s, 3H), 3.43 (t, 2H, *J* = 8.0 Hz), 4.42 (t, 2H, *J* = 7.6 Hz), 5.34 (s, 1H), 6.90 (d, 2H, *J* = 8.0 Hz), 7.14 (m, 4H), 7.45 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 20.8, 21.0, 38.4, 48.4, 122.4, 124.5, 129.1, 130.0, 133.0, 135.4, 136.6, 143.8, 152.0, 178.9. IR (KBr): 3017, 2918, 2850, 1670, 1624, 1565, 1507, 1471, 1408, 1364, 1315, 1285, 1262, 1127, 1076, 822, 807, 765, 690, 509 cm^{-1}. $C_{18}H_{20}N_4S$ (324.45): Calcd C 66.64, H 6.21, N 17.27, S 9.88; found C 66.69, H 6.25, N 17.19, S 9.83.

2-(4-Methoxyphenylimino)-*N*-(4-methoxyphenyl)imidazolidine-1-carbothioamide (6e):

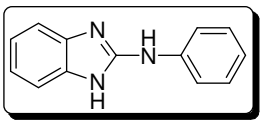


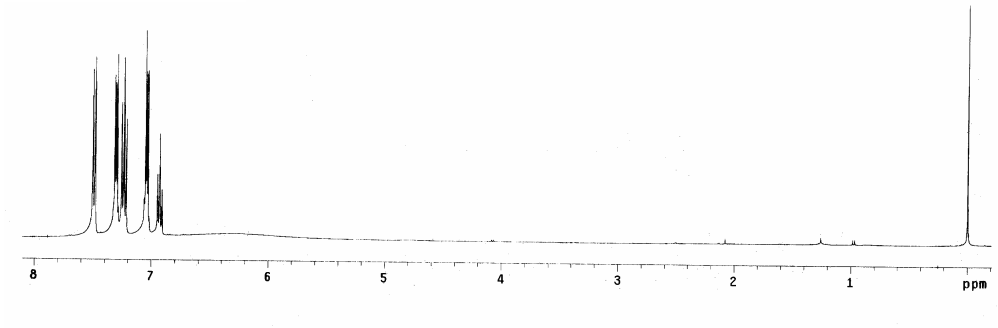
M.p. 126-128 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 3.44 (t, 2H, *J* = 7.6 Hz), 3.78 (s, 3H), 3.80 (s, 3H), 4.42 (t, 2H, *J* = 8.0 Hz), 5.48 (s, 1H), 6.80-6.96 (m, 6H), 7.45 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 29.4, 38.3, 48.3, 55.3, 113.6, 114.5, 123.3, 126.0, 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}. $C_{18}H_{20}N_4O_2S$ (356.45): Calcd C 60.65, H 5.66, N 15.72, S 9.00; found C 60.69, H 5.71, N 15.67, S 8.93.

Crystal data for 6e: Crystal dimension (mm): 0.52 x 0.34 x 0.18. $C_{18}H_{20}N_4O_2S$, Mr = 356.44, Monoclinic, space group P2(1)/c; a = 8.5759(3) Å, b = 23.5834(9) Å, c = 9.2172(4) Å; α = 90.00°, β = 104.572(2)°, γ = 90.00°, V = 1804.20(12) Å^3; Z = 4; ρ_{cal} = 1.312 mg/m^3; μ(mm^{-1}) = 0.198; *F (000)* = 752; Reflection collected / unique = 16995 / 4004; Refinement method = Full-matrix least-squares on F^2; Final R indices [I>2σ_I] R1 = 0.0379, wR2 = 0.0961 R indices (all data) R1 = 0.0531 wR2 = 0.1046, Goodness of fit = 1.041. CCDC # 699841.

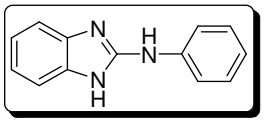
V.7. Selected Spectra

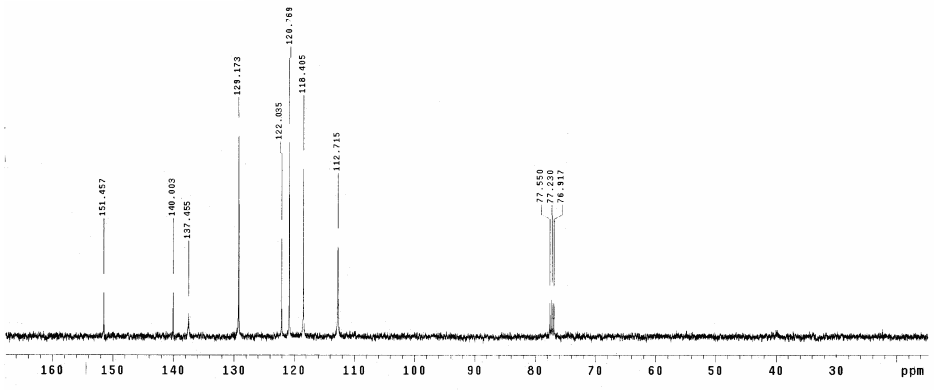
***N*-Phenyl-1H-benzo[d]imidazol-2-amine (1b): ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6):**



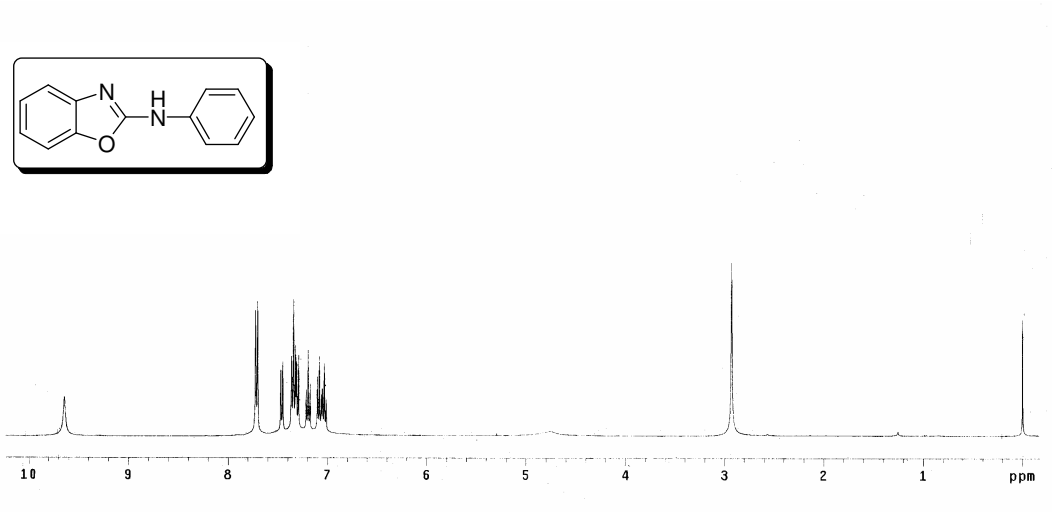


***N*-Phenyl-1H-benzo[d]imidazol-2-amine (1b): ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6):**

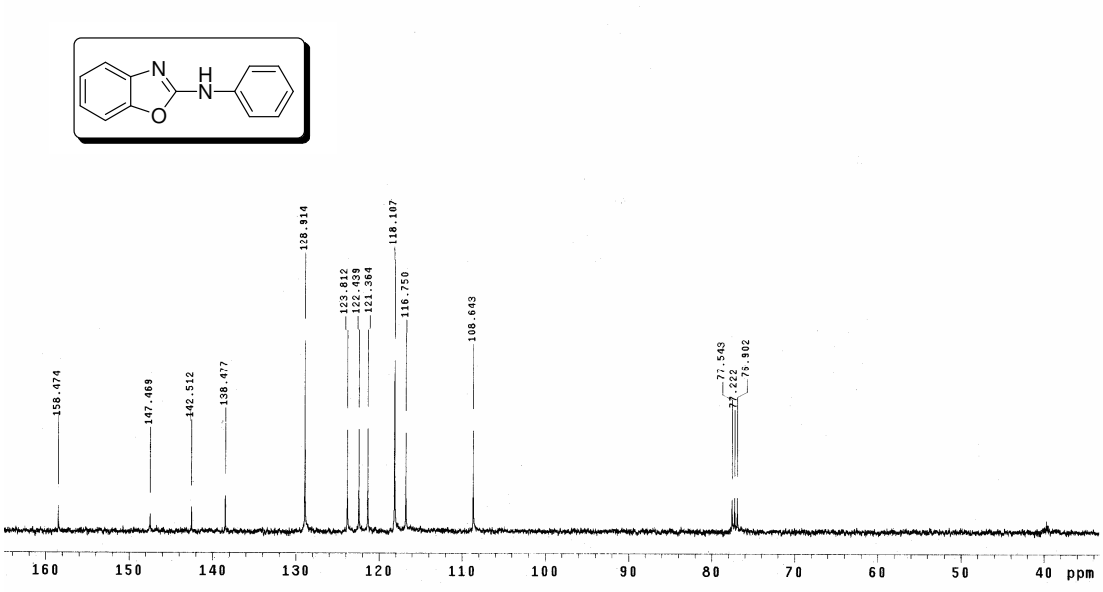




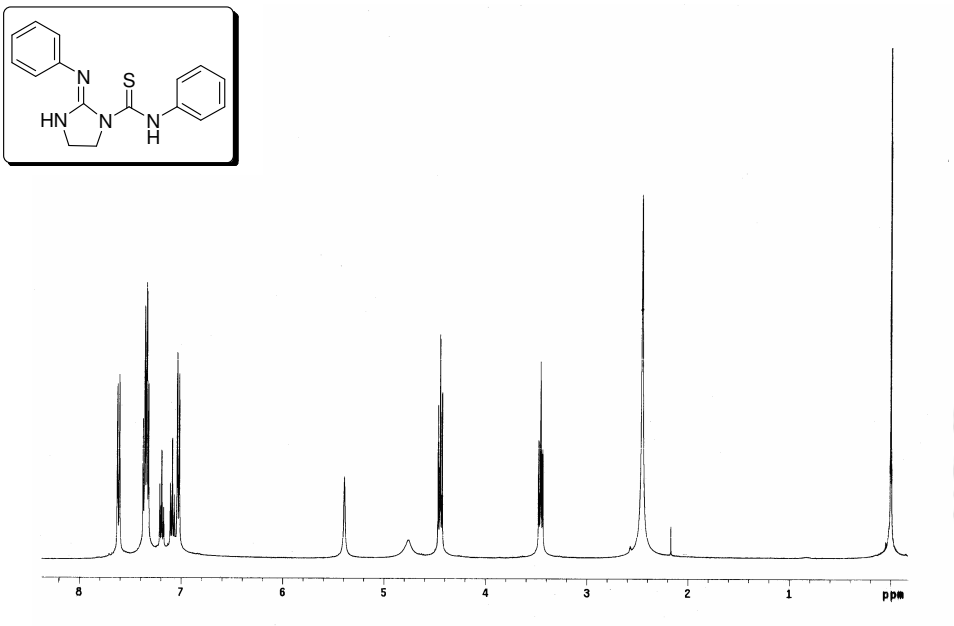
N-2-Phenyl-1,3-benzoxazol-2-amine (1c): ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6):



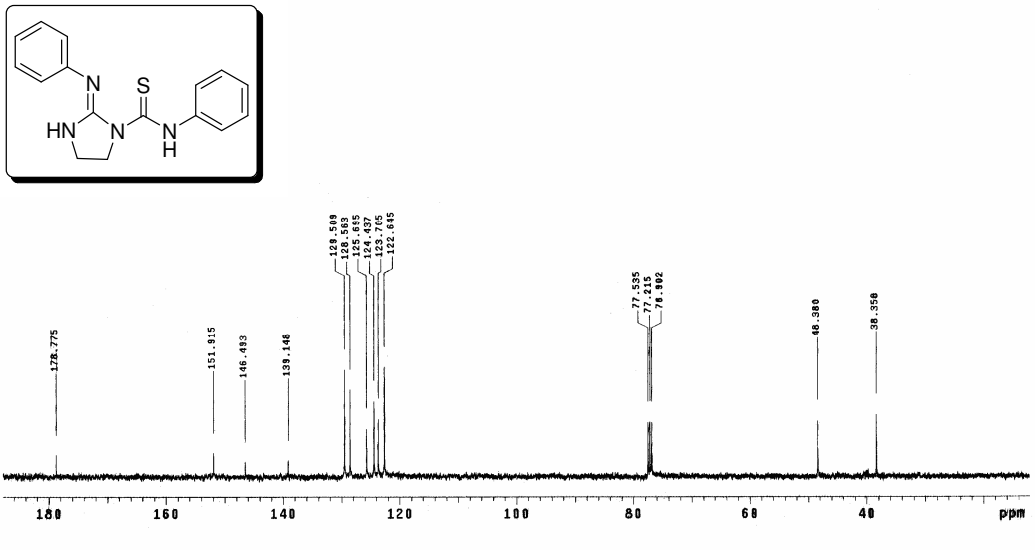
N-2-Phenyl-1,3-benzoxazol-2-amine (1c): ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6):



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



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

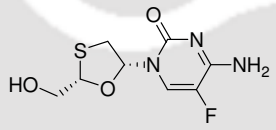


CHAPTER VI

VI. A New Facile Synthetic Method for the Construction of 1,3-Oxathiolan-2-ylidenes

VI.1. Importance and Applications

1,3-Oxathiolan-2-ylidenes having an exocyclic imine group can be used in organic synthesis for the preparation of biologically active compounds.[1] The 2-imino-1,3-oxathiolane core is present in compounds with potential bioactivities.[2] It is reported that the 1,3-oxathiolan moiety containing compound, (-)-*cis*-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (524W91), inhibits Hepatitis B Virus replication in primary human hepatocytes (*Figure VI.1.1*).[3]



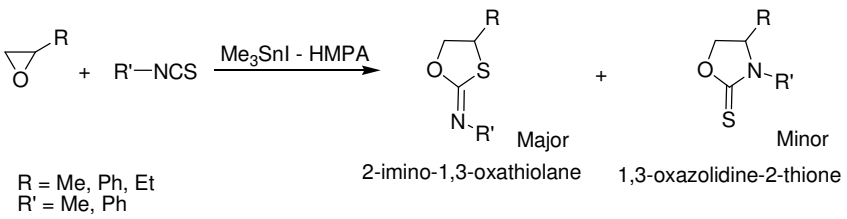
(-)-Cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

Figure VI.1.1

VI.2. Available Synthetic Methods

The heterocycles, 1,3-oxathiolan-2-ylidenes, were initially prepared by the reaction of alkylthiocyanates or acetyl and benzoyl isothiocyanates with epoxides[4] and subsequently by the 1,3-cycloaddition of heterocumulenes, such as isothiocyanates with oxiranes under various reaction conditions.[5]

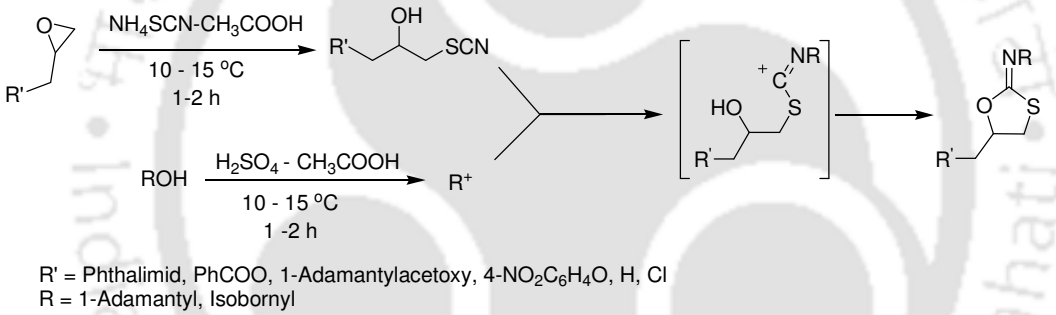
Akio Baba *et. al.* demonstrated the preparation of 2-imino-1,3-oxathiolane (or 1,3-oxathiolan-2-ylidenes) by the reaction of monosubstituted oxiranes and the heterocumulenes, phenyl isothiocyanate, using the catalyst, trialkyltin iodides coordinated by phosphine oxides (*Scheme VI.2.1*). The catalyst, Me_3SnI-HMPA system, effected a regioselective cycloaddition to give 4-substituted 2-imino-1,3-oxathiolane and 3,4-disubstituted 1,3-oxazolidine-2-thione (*Scheme VI.2.1*).[6a]



Scheme VI.2.1.

The basic skeleton of 1,3-oxathiolan-2-ylidenes is unstable and has been isolated as its *N*-acyl or *N*-carbamoyl derivatives.[6b,c]

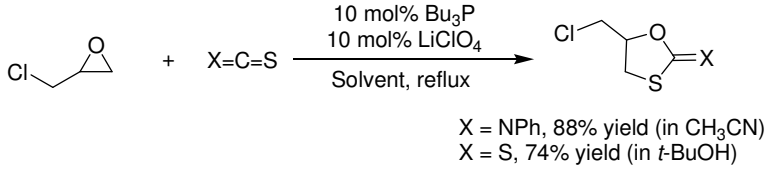
Taking advantage of the faster alkylation of the thiocyano group compared to the intramolecular cyclization of 2-hydroxythiocyanates, an alternative strategy, for the synthesis of *N*-alkyl-1,3-oxathiolan-2-ylidenes has been achieved from 2-hydroxythiocyanates and 1-adamantyl or tertiarybutyl alcohols (*Scheme VI.2.2*).[7]



Scheme VI.2.2.

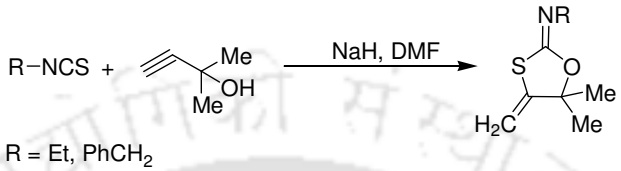
In all these cases the *N*-alkyl-1,3-oxathiolan-2-ylidenes exist as a mixture of *cis*- / *trans*- isomers around the imine double bond.[8]

Hou *et. al.* reported organophosphine-catalyzed reaction of heterocumulenes with epoxides, providing corresponding heterocycles 1,3-oxathiolan-2-ylidenes in good yields (*Scheme VI.2.3*).[9a]



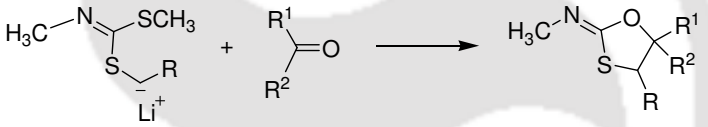
Scheme VI.2.3.

In another strategy, 2-methyl but-3-yne-2-ol reacts with benzyl isothiocyanate to give the oxathiolan-2-ylidene moiety having an exocyclic double bond obtained by intramolecular attack of sulphur on the terminal acetylene (*Scheme VI.2.4*).[9b] It is reported that in this transformation when the isothiocyanate group is bound to a sp^2 carbon atom, it gives oxazolidine unit instead of oxathiolan-2-ylidene moiety.



Scheme VI.2.4.

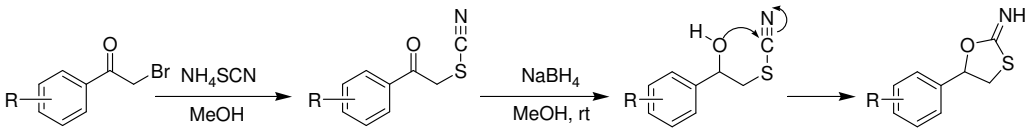
Reactions of lithiated salts of dithioalkylimines with carbonyl compounds give the oxathiolan-2-ylidene skeleton (*Scheme VI.2.5*).[9c]



Scheme VI.2.5.

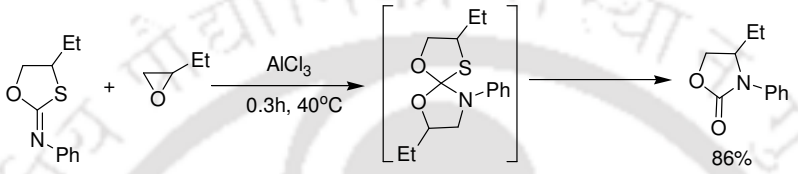
The synthesis of 2-imino-5-chloro-1,3-oxathiolanes, 2-imino-1,3-oxathioles and 1,3-thiazolin-2-ones from *N*-aryl and *N*-alkyl-S-chloroisothiocarbamoyl chlorides and ketones has been reported.[9d]

Gotor and co-workers developed a *one-pot*, three-step procedure to efficiently access the promising 2-imino-1,3-oxathiolane. The *in situ* generated α-thiocyanate ketones from the corresponding halogenated compounds were reduced with sodium borohydride to hydroxy thiocyanate intermediate which on intramolecular cyclization gives 2-imino-1,3-oxathiolane derivative (*Scheme VI.2.6*).[9e]



Scheme VI.2.6.

However, the drawbacks using above strategies are the requirement of expensive and specially designed substrates, reagents and catalysts and elevated temperatures. The use of polar solvents is accompanied by undesirable reactions such as trimerization of the isocyanate. Aromatic and aliphatic isothiocyanates usually do not give oxathiolane-2-ylidenes because of the facile conversion to 2-oxazolidinones in the presence of oxiranes.[9f] Strong Lewis acids such as $AlCl_3$ readily caused this transformation in an 86% yield (*Scheme VI.2.7*).[9g]



Scheme VI.2.7.

Unlike in the synthesis of N-aryl-1,3-oxathiolane-2-ylidenes the reaction of isocyanates with oxiranes catalysed by Lewis acids can not be used for the preparation of *N*-alkyl derivatives.[10] 1,3-Oxathiolan-2-ylidenes are formed only by the cycloaddition of activated isothiocyanates such as acetyl and benzoyl isothiocyanates with oxiranes.

VI.3. Present Work

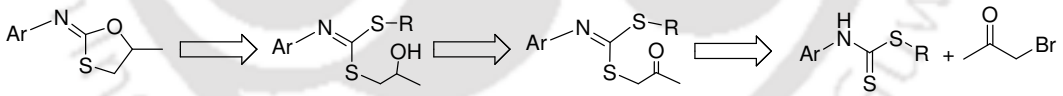
We have been utilizing tetrabutylammonium tribromide for bromination[11] and for various other organic transformations.[12]

Recently we synthesised a new ditribromide reagent, 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) which is superior to all known tribromides and has several advantages over molecular bromine and other tribromides[13] such as higher bromine content per molecule, higher bromination efficiency, selectivity, reduced phase transfer property, and quantitative recovery of the spent reagent. In addition to acting as an excellent brominating agent, it has been utilized as a catalyst for the acylation of alcohols[12d] and preparation of isothiocyanate,[14a] and cyanamide[14b] through desulfurization of dithiocarbamic acid salt.

During last few years our group is actively involved in the synthesis of five or six membered heterocycles having biologically active skeleton, using various techniques such as copper catalysis,[15a-c] hypervalent iodine(III) mediated oxidative cyclization[15d] and other thiophilic reagents.[15e]

The reagent 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) is an excellent source of bromine and capable of brominating varieties of organic substrates. So, we thought to utilize this reagent for the synthesis of various heterocycles. Earlier EDPBT has been utilized for the synthesis of various thiazolidene-2-imine derivatives[16a,b] and the same strategy was further extended to the preparation of pifithrin-α analogues.[16c] Very recently we have reported the synthesis of 2-aminothiazole using EDPBT.[14b] In this section we describe the utility of this reagent for the synthesis of a variety of 1,3-oxathiolan-2-ylidenes.

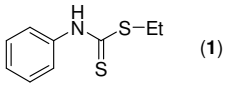
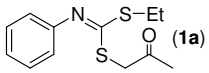
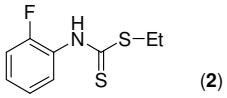
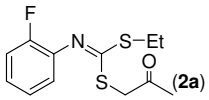
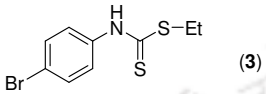
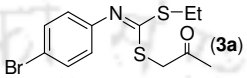
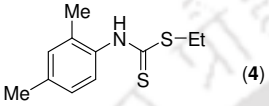
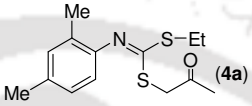
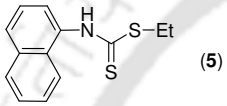
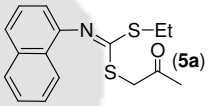
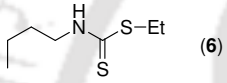
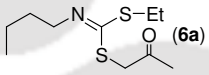
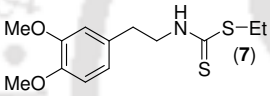
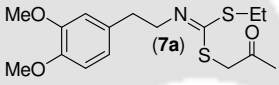
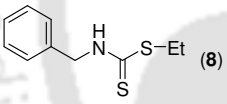
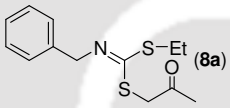
During the formation of thiazolidine-2-imine, the soft sulfur atom of the thiourea attacks the soft electrophilic site of bromomethyl carbon of the α-bromoketone.[16a,c] Taking cues from the reactivity of thioureas,[16] the leaving ability of a thiol attached to an imine functionality[17] and the α-brominating ability of ketones using 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT)[13] we envisaged a retrosynthetic scheme for the construction of 1,3-oxathiolan-2-ylidenes (*Scheme VI.3.1*).



Scheme VI.3.1. *Retrosynthetic analysis of oxathiolan-2-ylidenes*

As expected, the dithiocarbamic acid ester **1**, (*Table VI.3.1, Scheme VI.3.1*) reacted with the α-bromoketone formed by the reaction of acetone with EDPBT in the presence of triethylamine to give the addition product **1a** (*Table VI.3.1*) containing a carbonyl functionality within 0.5 h at room temperature. Similarly, various other adducts **2a**-**8a** of different dithiocarbamic acid esters **2**-**8** were prepared employing this strategy in good yields as shown in *Table VI.3.1*.

Table VI.3.1. *S-Alkylation*[a] *of dithiocarbamic acid ester*

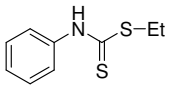
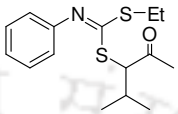
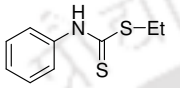
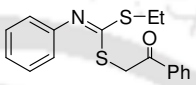
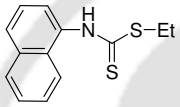
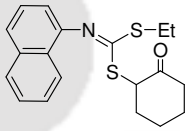
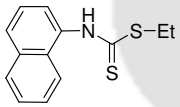
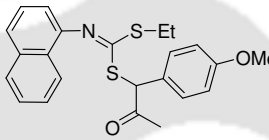
Substrate	Product[b]	Yield (%)[c]
 (**1**)	 (**1a**)	82
 (**2**)	 (**2a**)	78
 (**3**)	 (**3a**)	94
 (**4**)	 (**4a**)	95
 (**5**)	 (**5a**)	81
 (**6**)	 (**6a**)	80
 (**7**)	 (**7a**)	86
 (**8**)	 (**8a**)	78

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

Haloketones, such as 3-bromo-4-methyl-pentane-2-one, 2-bromo-1-phenyl-ethanone, 2-bromo-cyclohexanone and 1-bromo-1-(4-methoxy-phenyl)-propan-2-one were prepared from their parent ketones using EDPBT.[13] These α-haloketones were then reacted with dithiocarbamic acid esters **1** and **5** in the presence of triethylamine in acetonitrile to provide adducts **9a**-**12a** as shown in *Table VI.3.2*. Adducts **1a**-**12a** were obtained exclusively as their Z-isomer. *S*-Alkylation of dithiocarbamic acid esters involves base (triethylamine) mediated abstraction of the NH proton, hence an E_2 type of reaction which will be favorable if the NH and C=S are *anti* to each other. We have shown in an analogous system having a thioimido or a thioamido functionality, that during the formation of the thiazole-2-imine, the imine double bonds were found to have the *Z*-conformation (eight crystal structures).[16] Further no diastereomeric products could be

detected even in ^{1}HNMR of the crude. Adducts **9a**, **11a** and **12a** were obtained as racemic products since they were prepared from the corresponding racemic bromo compounds.

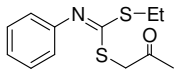
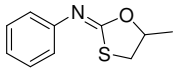
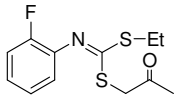
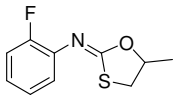
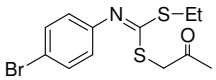
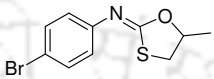
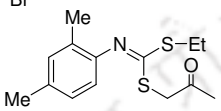
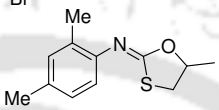
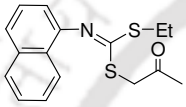
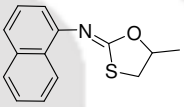
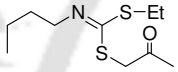
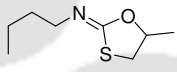
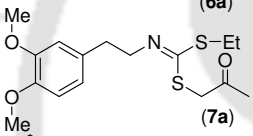
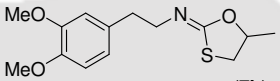
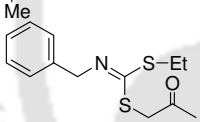
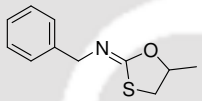
Table VI.3.2. *S-Alkylation*[a] *of dithiocarbamic acid ester*

Substrate	Product[b]	Yield (%)[c]
 (**1**)	 (**9a**)	75
 (**1**)	 (**10a**)	80
 (**5**)	 (**11a**)	75
 (**5**)	 (**12a**)	60

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

Having successfully achieved the first step in our strategy we then attempted to reduce the adduct **1a** using sodium borohydride in a methanolic medium. The carbonyl group of **1a** was reduced selectively without affecting the imine functionality. The reduced product (**1a'**) was isolated and characterized, however, it slowly cyclized to give the 1,3-oxathiolan-2-ylidene **1b** with concomitant liberation of odorous mercaptoethanol at room temperature. However, by performing the reduction of **1a** in methanolic KOH, the carbonyl reduction was faster and complete cyclization was achieved by carrying out the reaction at 60 ^{o}C. When the leaving group was changed from -SEt to -SMe or -SCH_2Ph the reaction rate and yield were found to be similar. Keeping in mind the cost factors, and the ease of preparation and handling difficulties, we used -SEt as the leaving group for all the other substrates.

Table VI.3.3. *Formation of 1,3-oxathiolan-2-ylidene*[a]

Substrate	Product[b]	Yield (%)[c]
 (**1a**)	 (**1b**)	67
 (**2a**)	 (**2b**)	55
 (**3a**)	 (**3b**)	67
 (**4a**)	 (**4b**)	54
 (**5a**)	 (**5b**)	55
 (**6a**)	 (**6b**)	55
 (**7a**)	 (**7b**)	56
 (**8a**)	 (**8b**)	69

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

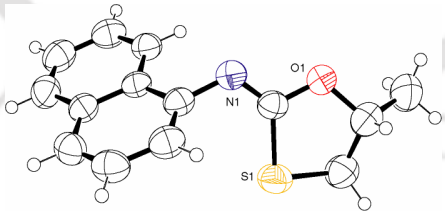
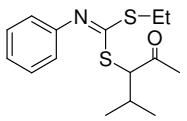
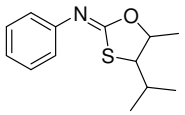
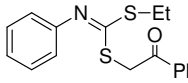
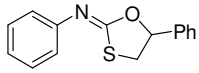
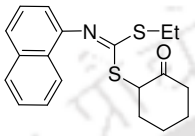
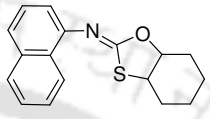
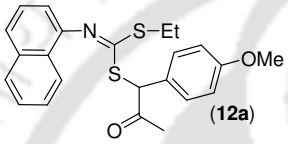
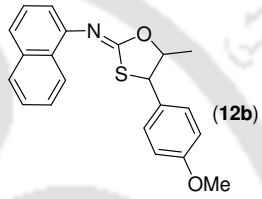


Figure VI.3.1. *ORTEP view of (**5b**) with the atom numbering scheme*

The versatility of this synthetic method is demonstrated with substrates **1a**-**12a** as shown in *Table VI.3.3* and *Table VI.3.4*. Although quantitative conversion was observed by GC and from the crude yield, the isolated product yield was much lower.

***Table VI.3.4**. Formation of 1,3-oxathiolan-2-ylidene*[a]

Substrate	Product[b]	Yield (%)[c]
 (**9a**)	 (**9b**)	45
 (**10a**)	 (**10b**)	50
 (**11a**)	 (**11b**)	45
 (**12a**)	 (**12b**)	40

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

Compared to the aryl systems **1a**-**5a**, the alkyl **6a**, veratryl **7a** and benzyl **8a** systems reacted faster. This observation is comparable to the cycloaddition of $PhCH_2NCS$ and PhNCS, where the later is more reactive than the former towards cycloaddition with propylene oxide.[5e] The presence of the 1,3-oxathiolan-2-ylidene skeleton is shown in the single crystal X-ray structure of **5b**, *Figure VI.3.1*. The versatility of this methodology has been demonstrated successfully using ketones other than acetone as shown with substrates **9a-12a** (*Table VI.3.4*) giving the corresponding 1,3-oxathiolan-2-ylidenes **9b-12b** in moderate yields (*Table VI.3.4*). Products **1b-8b** and **10b** were obtained as racemic mixtures whereas products **9b**, **11b** and **12b** were obtained as diastereomeric mixtures.

In conclusion, we have reported herein an efficient method for the *S*-alkylation of dithiocarbamic acid esters with α-bromoketones under basic conditions. Subsequently we developed an efficient synthetic method for the construction of 1,3-oxathiolan-2-ylidenes by reduction of the addition product of dithiocarbamic acid esters with α-bromoketones. This method is convenient in terms of simplicity and general applicability.

VI.4. Experimental Section

VI.4.1. Instrumentation and Characterization

As described in Chapter II, Section II.5.1. page 48-49.

VI.4.2. General Procedures

VI.4.2.1. General Procedure for S-Alkylation: (Z)-Ethyl 2-xopropyl phenyldithioimidocarbonate (1a)

1,1'-(Ethane-1,2-diyl)dipyridinium bistribromide EDPBT (3 mmol) was added to acetone (5 mL) and the mixture stirred for 10 minutes, during this period the bromination of acetone was complete as judged from the disappearance of the orange color of EDPBT and precipitating out of the spent reagent 1,1'-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB). The supernatant containing the bromo ketone was then filtered into a solution of phenyldithiocarbamic acid ethyl ester **1** (5 mmol) in acetone (5 mL) and triethylamine (10 mmol) and was kept stirred at room temperature. The reaction was complete within 0.5 h as judged from the TLC. After completion of the reaction, the solvent was evaporated and ethyl acetate (20 mL) was added. The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over silica gel to give an 82% yield of (*Z*)-ethyl 2-oxopropyl phenyldithioimidocarbonate (**1a**).

VI.4.2.2. General Procedure for the Reductive Cyclization of (Z)-Ethyl 2-oxopropyl phenyldithioimidocarbonate (1a) to *Rac*-N-[(2Z)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (1b)

To a solution of (*Z*)-ethyl 2-oxopropyl phenyldithioimidocarbonate (**1a**) (0.762 g, 3 mmol) in methanol (5 mL) was added KOH (0.168 g, 3 mmol) followed by portionwise addition of sodium borohydride (0.057 g, 1.5 mmol) over a period of 5 minutes at 0 ^{o}C. After stirring for 0.5 h, the reaction mixture was heated at 60 ^{o}C for 5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, methanol was evaporated and the product was extracted with ethyl acetate (2 x 25 mL). The organic layer

was separated and dried over anhydrous sodium sulfate and concentrated. Further purification was accomplished by column chromatography over a short column of basic alumina using a mixture of hexane and ethyl acetate as eluent. The product, *rac-N*-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (**1b**) was obtained in 67% yield.

VI.5. References

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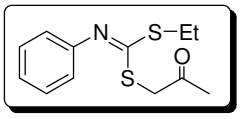
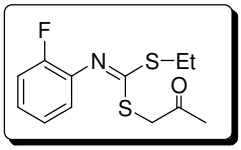
VI.6. Spectral Data

(*Z*)-Ethyl 2-oxopropyl phenyldithioimidocarbonate (1a):



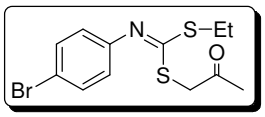
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, 3H, *J* = 7.6 Hz), 2.30 (s, 3H), 3.07 (q, 2H, *J* = 7.6 Hz), 3.90 (s, 2H), 6.83 (d, 2H, *J* = 7.6 Hz), 7.09 (m, 1H), 7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8, 26.6, 29.3, 42.0, 120.4, 124.3, 129.1, 149.3, 161.1, 202.3. IR (KBr): 3058, 2968, 2927. 1718, 1577, 1354, 1208, 1151, 943, 762, 695 cm^{-1}. HRMS (ESI): MH$^+$, found 254.3959, $C_{12}H_{16}NOS_2$ requires 254.3965.

(*Z*)-Ethyl 2-oxopropyl 2-fluorophenyldithioimidocarbonate(2a):



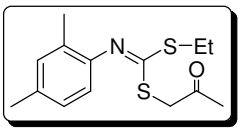
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, 3H, *J* = 7.2 Hz), 2.28 (s, 3H), 3.08 (q, 2H, *J* = 7.2 Hz), 3.91 (s, 2H), 6.84 (br s, 1H), 7.03 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 26.8, 29.0, 41.9, 116.1, 122.4, 124.3, 125.4, 136.9, 151.5, 154.0, 163.7, 202.3. IR (KBr): 3061, 2971, 2930, 2873, 1715, 1574, 1485, 1451, 1355, 1239, 1151, 1102, 950, 850, 756, 727, 577 cm^{-1}. HRMS (ESI): MH$^+$, found 272.3865, $C_{12}H_{15}FNOS_2$ requires 272.3870.

(*Z*)-Ethyl 2-oxopropyl 4-bromophenyldithioimidocarbonate (3a):



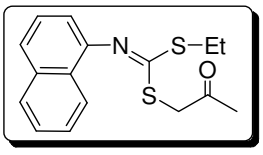
^{1}H NMR (400 MHz $CDCl_3$): δ 1.33 (t, 3H, *J* = 7.6 Hz), 2.30 (s, 3H), 3.09 (q, 2H, *J* = 7.6 Hz), 3.90 (s, 2H), 6.72 (d, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 6.8 Hz). ^{13}CNMR (100 MHz, $CDCl_3$): δ 14.8, 26.8, 29.3, 42.1, 117.4, 122.2, 132.2, 148.3, 161.4, 202.0. IR (KBr): 2971, 2925, 1721, 1568, 1486, 1368, 1214, 1158, 958, 830 cm^{-1}. HRMS (ESI): MH^+, found 333.2920, $C_{12}H_{14}BrNOS_2$ requires 333.2926.

(*Z*)-Ethyl 2-oxopropyl-1,4-dimethylphenyldithioimidocarbonate (4a):



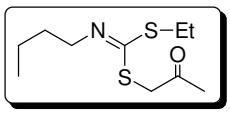
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.2 Hz), 2.03 (s, 3H), 2.27 (s, 3H), 2.29 (s, 3H), 3.07 (q, 2H, *J* = 7.2 Hz), 3.90 (s, 2H), 6.58 (d, 1H, *J* = 8.0 Hz), 6.93 (d, 1H, *J* = 8.0 Hz), 6.98 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 14.9, 17.7, 21.0, 26.5, 29.2, 41.8, 119.3, 127.0, 128.3, 131.4, 133.8, 145.7, 159.3, 202.2. IR (KBr): 2967, 2925, 2871, 1715, 1573, 1354, 1211, 1150, 1120, 950, 934, 816, 724, 613 cm^{-1}. HRMS (ESI): MH^+, found 282.4507, $C_{14}H_{20}NOS_2$ requires 282.4501.

(*Z*)-Ethyl 2-oxopropyl 1-napthyldithioimidocarbonate (5a):



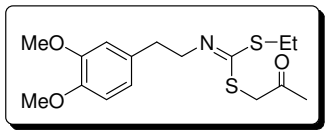
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (m, 3H), 2.24 (s, 3H), 2.97 (m, 2H), 4.00 (s, 2H), 6.78 (m, 1H), 7.39 (m, 3H), 7.52 (m, 1H), 7.61 (m, 1H), 7.75 (m, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 14.9, 26.8, 29.6, 42.3, 115.1, 123.6, 124.5, 125.9, 126.5, 126.6, 127.8, 128.2, 134.5, 146.0, 161.4, 202.3. IR (KBr): 3061, 2971, 2930, 2873, 1715, 1574, 1485, 1451, 1355, 1239, 1151, 1102, 950, 850, 756, 727, 577 cm^{-1}. HRMS (ESI): MH^+, found 304.4557, $C_{16}H_{18}NOS_2$ requires 304.4563

(*Z*)-Ethyl 2-oxopropyl n-butyldithioimidocarbonate (6a):



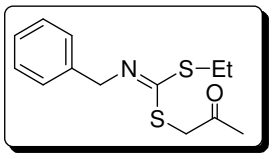
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, J = 7.2 Hz), 1.22-1.30 (m, 7H), 2.26 (s, 3H), 2.88 (q, 1H, J = 7.2 Hz), 2.99 (q, 2H, J = 7.6 Hz), 3.26 (q, 1H, J = 6.0 Hz), 3.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 15.1, 16.0, 25.8, 28.8, 32.0, 40.5, 53.7, 163.8, 201.6. IR (KBr): 2935, 2873, 1716, 1685, 1562, 1481, 1373, 1271, 979, 753 cm^{-1}. HRMS (ESI): MH^+, found 234.4055, $C_{10}H_{20}NOS_2$ requires 234.4061.

(*Z*)-Ethyl 2-oxopropyl 3,4-dimethoxyphenethyldithioimidocarbonate (7a):



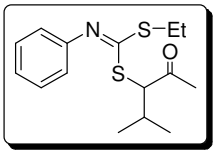
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, 3H, J = 7.6 Hz), 2.11 (s, 3H), 2.81 (t, 2H, J = 7.2 Hz), 3.04 (q, 2H, J = 7.2 Hz), 3.56 (t, 2H, J =7.6 Hz), 3.66 (s, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 6.71 (m, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 15.4, 26.5, 28.8, 36.6, 41.2, 54.7, 55.9, 56.0, 111.4, 112.3, 120.8, 132.9, 147.5, 148.9, 155.6, 203.2. IR (KBr): 2931, 2834, 1716, 1587, 1515, 1464, 1353, 1262, 1236, 1156, 1028, 921, 806, 763, 577 cm^{-1}. HRMS (ESI): MH^+, found 342.5019, $C_{16}H_{24}NO_3S_2$ requires 342.5025.

(*Z*)-Ethyl 2-oxopropyl benzyldithioimidocarbonate (8a):



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, 3H, J = 7.6 Hz), 2.19 (s, 3H), 3.21 (q, 2H, J = 7.6 Hz), 3.82 (s, 2H), 4.62 (s, 2H), 7.34 (m, 5H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 15.3, 26.7, 29.0, 41.3, 56.7, 126.8, 127.7, 128.3, 139.7, 156.8, 200.1. IR (KBr): 3029, 2969, 2928, 2872, 1717, 1574, 1452, 1353, 1151, 1017, 929, 734, 699 cm^{-1}. HRMS (ESI): MH^+, found 268.4241, $C_{13}H_{18}NOS_2$ requires 268.4233.

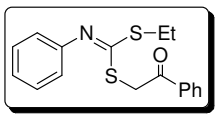
***Rac*-(*Z*)-Ethyl 4-methyl-2-oxopentan-3-yl phenyldithioimidocarbonate (9a):**



^{1}H NMR (400 MHz, $CDCl_3$): 0.91-1.41 (m, 9H), 2.31 (s, 3H), 3.58 (m, 2H), 3.20 (m, 1H), 3.91 (brs, 1H), 6.82 (m, 2H), 7.10 (m, 1H), 7.30 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 14.8, 19.7, 22.7, 26.7, 29.3, 61.3, 120.4, 124.1,

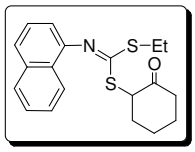
128.9, 149.9, 160.1, 200.1. IR (KBr): 3049, 2963, 2868, 1706, 1576, 1459, 1352, 1262, 1209, 1157, 944, 761, 695, 604 cm^{-1}. HRMS (ESI): MH^+, found 296.4755, $C_{15}H_{22}NOS_2$ requires 296.4769.

(*Z*)-Ethyl 1-benzoyl phenyldithioimidocarbonate (10a):



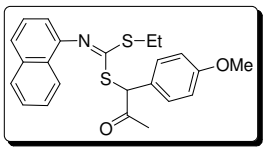
^{1}H NMR (400 MHzCDCl$_3$): δ 1.22 (t, 3H, *J* = 7.2 Hz), 2.99 (q, 2H, *J* = 7.2 Hz), 4.52 (s, 2H), 6.73 (d, 2H, *J* = 5.6 Hz), 6.98 (t, 1H, *J* = 7.2 Hz), 7.20 (t, 2H, *J* = 8 Hz), 7.37 (t, 2H, *J* = 7.6 Hz), 7.48 (t, 1H, *J* = 7.2 Hz), 7.91 (s, 2H). ^{13}CNMR (100 MHz, CDCl$_3$): δ 13.5, 26.7, 39.3, 120.4, 124.2, 128.6, 128.9, 129.1, 133.7, 136.9, 149.4, 163.0, 197.7. IR (KBr): 3060, 2967, 2917, 1681, 1637, 1566, 1484, 1445, 1377, 1259, 1198, 1094, 949, 746, 598 cm^{-1}. HRMS (ESI): MH^+, found 316.4669, $C_{17}H_{18}NOS_2$ requires 316.4673.

(*Z*)-Ethyl 2-oxocyclohexyl phenyldithioimidocarbonate (11a):



^{1}H NMR (400 MHz, CDCl$_3$): δ 1.18 (m. 2H), 1.62 (m, 6H), 2.37 (m, 3H), 3.07 (m, 2H), 4.60 (m, 1H), 6.88 (m, 1H), 7.37-7.85 (m, 6H). ^{13}CNMR (100 MHz, CDCl$_3$): δ 14.7, 25.4, 26.7, 34.9, 41.8, 55.4, 114.8, 123.5, 126.6, 126.7, 127.0, 127.6, 128.0, 128.7, 134.3, 146.2, 160.7, 205.8. IR (KBr): 3055, 2931, 2864, 1713, 1588, 1569, 1447, 1389, 1289, 1263, 1122, 1058, 1015, 942, 908, 797, 774, 731, 648, 605, 546 cm^{-1}. HRMS (ESI): MH^+, found 344.5213, $C_{19}H_{22}NOS_2$ requires 344.5209.

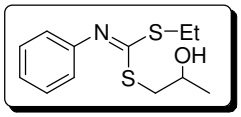
(*Z*)-Ethyl 1-(4-methoxyphenyl)-2-oxopropyl phenyldithioimidocarbonate (12a):



^{1}H NMR (400 MHz, CDCl$_3$): δ 1.16 (t, 3H, *J* = 6.4 Hz), 2.13 (s, 3H), 2.95 (q, 2H, *J* = 6 Hz), 3.72 (s, 3H), 5.62 (s, 1H), 6.81 (m, 3H), 7.22-7.41 (m, 5H), 7.52 (d, 1H, *J* = 8 Hz), 7.59 (d, 1H, *J* = 6.8 Hz), 7.73 (m, 1H) . ^{13}CNMR (100 MHz, CDCl$_3$): δ 14.8, 26.6, 26.9, 55.5, 60.2, 114.4, 115.0, 123.6, 124.3, 124.7, 125.8, 126.3, 126.5, 128.1, 130.5, 130.6,

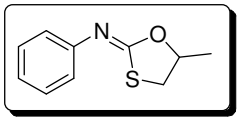
133.0, 134.4, 146.3, 160.2, 202.6. IR (KBr): 3049, 2967, 2838, 1716, 1574, 1506, 1455, 1388, 1349, 1252, 1176, 1154, 1032, 946, 775, 729, 607 cm^{-1}. HRMS (ESI): MH^+, found 410.5809, $C_{23}H_{24}NO_2S_2$ requires 410.5801.

***(Z)*-Ethyl 2-hydroxypropyl phenyldithioimidocarbonate (1a'):**



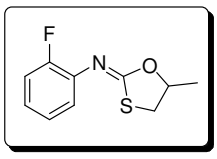
^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (m, 6H), 3.04 (m, 4H), 3.20 (br s, 1H), 4.11 (brs, 1H), 6.86 (d, 2H, *J* = 7.2 Hz), 7.09 (t, 1H, *J* = 7.6 Hz), 7.30 (t, 2H, *J* = 8.0 Hz). IR (KBr): 3364, 3059, 2970, 2927, 2870, 1651, 1574, 1485, 1448, 1261, 1207, 1165, 1107, 1071, 946, 762, 695 cm^{-1}.

***Rac*-*N*-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (1b):**



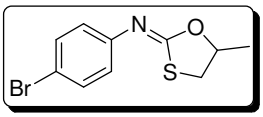
^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, 3H, *J* = 6.4 Hz), 3.05 (app.t, 1H, *J* = 9.2 Hz), 3.36 (dd, 1H, *J* = 5.6 Hz), 4.75 (m, 1H), 6.96 (d, 2H, *J* = 7.2 Hz), 7.10 (t, 1H, *J* = 7.2 Hz), 7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 37.7, 78.6, 121.3, 124.1, 129.0, 149.0, 163.6. IR (KBr): 3057, 3030, 2980, 2935, 2855, 1651, 1593, 1488, 1159, 1102, 1022, 949, 770, 697, 658, 593 cm^{-1}. HRMS (ESI): MH^+, found 194.2749, $C_{10}H_{12}NOS$ requires 194.2757.

***Rac*-2-fluoro-*N*-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (2b):**



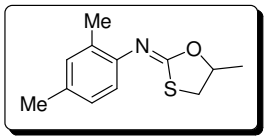
^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (d, 3H, *J* = 6.0 Hz), 3.05 (app.t, 1H, *J* = 10.0 Hz), 3.35 (dd, 1H, *J* = 5.6 Hz), 4.76 (m, 1H), 6.94 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 38.2, 79.8, 116.2, 116.4, 123.4, 124.5, 125.4, 136.9, 153.1, 155.5, 163.3. IR (KBr): 3033, 2977, 2927, 2869, 1651, 1488, 1453, 1242, 1161, 1097, 1024, 950, 836, 755, 653, 588 cm^{-1}. HRMS (ESI): MH^+, found 212.2667, $C_{10}H_{11}FNOS$ requires 212.2674.

***Rac*-4-bromo-*N*-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (3b):**



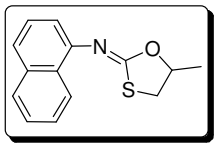
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (d, 3H, *J* = 6.4 Hz), 3.09 (app.t, 1H, *J* = 10.0 Hz), 3.41 (dd, 1H, *J* = 5.6 Hz), 4.77 (m, 1H), 6.85 (d, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 38.0, 79.1, 117.3, 123.3, 132.2, 148.2, 164.3. IR (KBr): 2991, 2935, 1680, 1634, 1486, 1388, 1250, 1163, 1096, 958, 835, 605 cm^{-1}. HRMS (ESI): MH^+, found 273.1665, $C_{10}H_{11}BrNOS$ requires 273.1670.

***Rac*-2,4-dimethyl-*N*-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (4b):**



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, 3H, *J* = 6.0 Hz), 2.17 (s, 3H), 2.29 (s, 3H), 3.05 (app.t, 1H, *J* = 10.0 Hz), 3.35 (dd, 1H, *J* = 5.2 Hz), 4.75 (m, 1H), 6.75 (d, 1H, *J* = 7.6 Hz), 6.98 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 19.3, 21.0, 37.9, 79.0, 120.4, 127.3, 130.0, 131.4, 133.9, 145.6, 163.2. IR (KBr): 2979, 2923, 2865, 1651, 1497, 1454, 1382, 1239, 1162, 1092, 1024, 951, 821, 634 cm^{-1}. HRMS (ESI): MH^+, found 222.3117, $C_{12}H_{16}NOS$ requires 222.3113.

***Rac*-*N*-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene] naphthalene-1-amine (5b):**

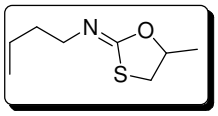


Crystalline solid, M.p. 87-89 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (d, 3H, *J* = 6.0 Hz), 3.05 (app.t, 1H, *J* = 10.0 Hz), 3.36 (dd, 1H, *J* = 6.0 Hz), 4.83 (m, 1H), 7.00 (d, 1H, *J* = 7.2 Hz), 7.43 (m, 3H), 7.61 (d, 1H, *J* = 8.4 Hz), 7.81 (d, 1H, *J* = 7.2 Hz), 8.05 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 38.0, 79.3, 115.9, 123.9, 124.5, 125.7, 126.0, 126.4, 127.8, 128.0, 134.4, 146.0, 164.1. IR (KBr): 3016, 2926, 2861, 1657, 1496, 1451, 1402, 1095, 1050, 875, 824, 804, 687, 605 cm^{-1}. HRMS (ESI): MH^+, found 244.3302, $C_{14}H_{14}NOS$ requires 244.3307.

Crystallographic description of (5b): Crystal dimensions (mm): 0.28 x 0.20 x 0.17. $C_{14}H_{13}NOS$, Mr = 243.31. Monoclinic, space group P2(1)/n; a = 7.8987(2) Å, b = 14.0972(4) Å, c = 11.5295(3)

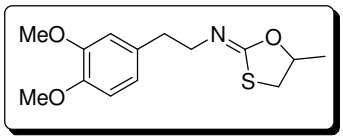
Å; α = 90.00°, β = 106.7410(10)°, γ = 90.00°, V = 1229.39(6) Å^3; Z = 4; ρ_{cal} = 1.315 mg/m^3; μ(mm^{-1}) = 0.245; *F (000)* = 512; Reflections collected / unique = 3047 / 2281; refinement method = full-matrix least-squares on F^2; final R indices [I>2σ_I] R1 = 0.0579, wR2 = 0.1306, R indices (all data) R1 = 0.0414, wR2 =0.1155; goodness of fit = 1.033. CCDC # 676901.

***Rac*-*N*-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene] n-butylamine (6b):**



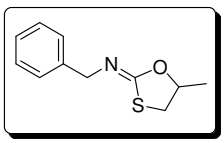
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 7.2 Hz), 1.33 (m, 2H), 1.43 (d, 3H, *J* = 6.0 Hz), 1.52 (m, 2H), 3.01-3.07 (m, 3H) 3.33 (dd, 1H, *J* = 5.2 Hz), 4.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 19.1, 20.4, 32.9, 37.6, 53.5, 79.9, 161.0. IR (KBr): 2950, 2935, 2873, 1680, 1542, 1460, 1383, 1168, 1076, 748, 636 cm^{-1}. HRMS (ESI): MH$^+$, found 174.2859, $C_8H_{16}NOS$ requires 174.2865.

***Rac*-2-(3,4-dimethoxyphenyl)-*N*-[(2*Z*-5-methyl-1,3-oxathiolan-2-ylidene]ethanamine (7b):**



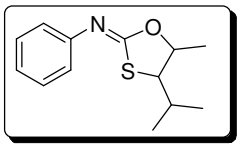
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (d, 3H, *J* = 6.4 Hz), 2.78 (t, 2H, *J* = 7.6 Hz), 2.94 (app.t, 1H, *J* = 9.6 Hz), 3.28 (m, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 4.57 (m, 1H), 6.71 (m, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 19.3, 37.0, 37.8, 51.0, 55.8, 56.0, 77.6, 111.3, 112.3, 120.9, 132.9, 147.5, 148.8, 162.2. IR (KBr): 2935, 2832, 1696, 1675, 1516, 1460, 1271, 1020, 748 cm^{-1}. HRMS (ESI): MH$^+$, found 282.3821, $C_{14}H_{20}NO_3S$ requires 282.3829.

***Rac*-N-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene] phenylmethanamine (8b):**



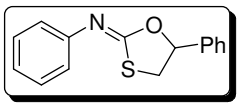
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, 3H, *J* = 6.0 Hz), 3.05 (app.t, 1H, *J* = 9.6 Hz), 3.38 (dd, 1H, *J* = 5.6 Hz), 4.35 (d, 2H, *J* = 6.8 Hz), 4.61 (m, 1H), 7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 38.0, 57.5, 80.5, 126.8, 127.7, 128.4, 139.7, 162.8. IR (KBr): 3027, 2978, 2931, 2869, 1663, 1452, 1352, 1156, 1122, 1089, 1051, 1022, 929, 735, 699, 641 cm^{-1}. HRMS (ESI): MH$^+$, found 208.3035, $C_{11}H_{14}NOS$ requires 208.3037.

***Rac-N*-[(2*Z*)-4-isopropyl-5-methyl-1,3-oxathiolan-2-ylidene]aniline (*diastereomeric mixture*) (9b):**



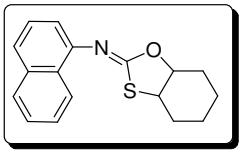
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (m, 6H), 1.40 (d, 3H, *J* = 6.0 Hz), 1.90 (m, 1H), 3.31 (m, 1H), 4.52 (m, 1H), 6.99 (m, 2H), 7.11 (t, 1H, *J* = 7.2 Hz), 7.32 (t, 2H, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 20.0, 21.3, 31.3, 61.9, 80.9, 121.6, 124.2, 129.2, 149.5, 163.4. IR (KBr): 3054, 2963, 2868, 1651, 1595, 1544, 1447, 1315, 1229, 1110, 1064, 948, 769, 696, 642 cm^{-1}. HRMS (ESI): MH^+, found 236.3509, $C_{13}H_{18}NOS$ requires 236.3513.

***Rac-N*-[(2*Z*)-5-phenyl-1,3-oxathiolan-2-ylidene] aniline (10b):**



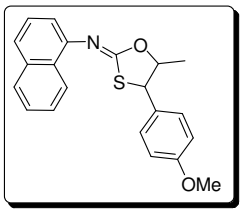
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.29 (app.t, 1H, *J* = 10.8 Hz), 3.53 (dd, 1H, *J* = 4.8 Hz), 5.53 (app.t, 1H, *J* = 6 Hz), 6.81 (s, 2H), 6.94-6.99 (m, 3H), 7.16-7.57 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.7, 83.4, 118.9, 121.6, 123.7, 126.1, 128.9, 129.5, 138.1, 154.3, 163.9. IR (KBr): 3054, 2950, 1648, 1604, 1541, 1497, 1445, 1314, 1229, 1067, 754, 694 cm^{-1}. HRMS (ESI): MH^+, found 254.3466, $C_{15}H_{14}NOS$ requires 256.3477.

***Rac-N*-[(2Z)-hexahydro-1,3-benzoxathiol-2-ylidene]naphthalene-1-amine (*diastereomeric mixture*) (11b):**



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12-1.55 (m, 4H), 1.79 (m, 2H), 2.30 (m, 2H), 3.39 (m, 1H), 4.56 (m, 1H), 6.91 (m, 1H), 7.20-7.84 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 20.4, 23.6, 28.0, 47.1, 81.5, 115.8, 121.0, 123.5, 124.6, 126.7, 128.1, 128.6, 128.8, 134.3, 145.9, 164.4. IR (KBr): 3054, 2937, 2859, 1650, 1574, 1536, 1504, 1393, 1358, 1259, 1184, 1114, 1013, 964, 907, 774, 729, 642 cm^{-1}. HRMS (ESI): MH^+, found 283.3925, $C_{17}H_{18}NOS$ requires 284.4013.

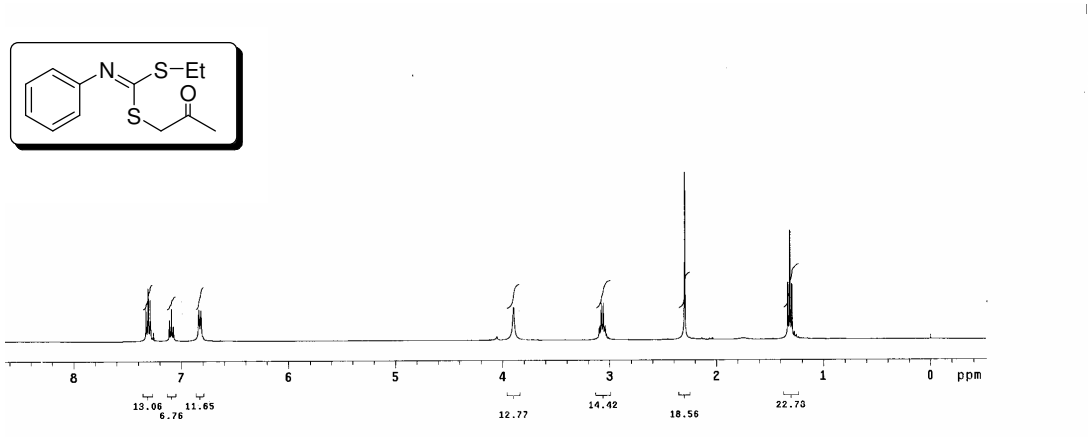
***Rac-N*-[{2*Z*}-4-(4-methoxyphenyl)-5-methyl-1,3-oxathiolan-2-ylidene] napthalene-1-amine phenylmethanamine (*diastereomeric mixture*) (12b):**



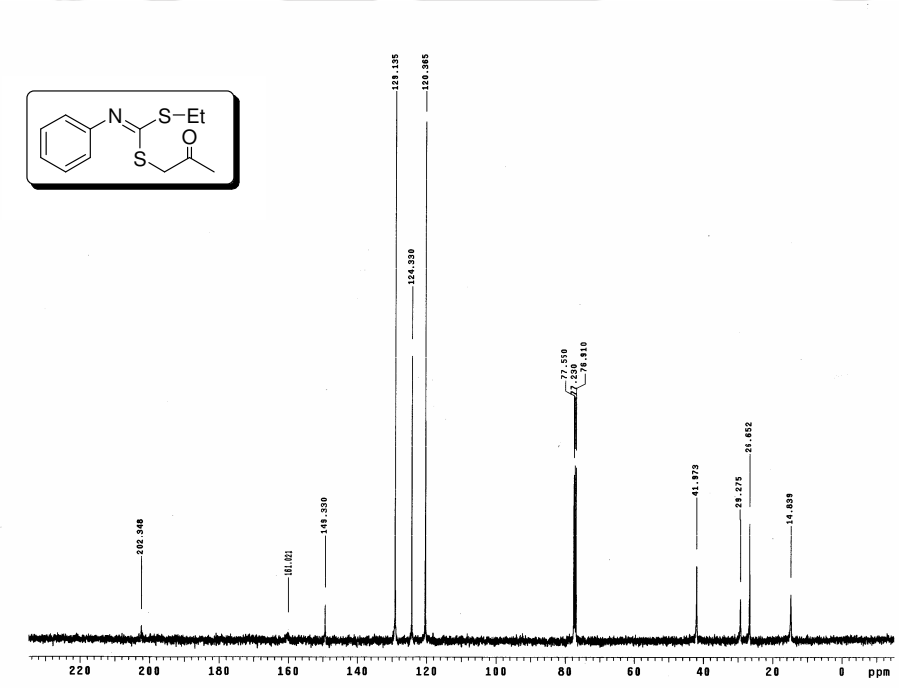
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (m, 3H), 3.62 (s, 3H), 4.46 (d, 1H, *J* = 5.6 Hz), 4.86 (m, 1H), 6.71 (t, 2H, *J* = 8.4), 7.00 (m, 2H), 7.13 (m, 1H), 7.30 (m, 1H), 7.38 (m, 2H), 7.50 (d, 1H, *J* = 8.4 Hz), 7.70 (m, 1H), 8.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 54.8, 55.5, 82.5, 114.2, 115.9, 123.8, 124.6, 125.7, 126.0, 126.4, 128.3, 128.4, 128.9, 129.6, 134.4, 145.9, 159.8, 164.2. IR (KBr): 3056, 2961, 2836, 1651, 1574, 1512, 1462, 1393, 1304, 1248, 1179, 1073, 1032, 943, 802, 777, 734, 654 cm^{-1}. HRMS (ESI): MH^+, found 350.4549, $C_{21}H_{20}NO_2S$ requires 350.4545.

VI.7. Selected Spectra

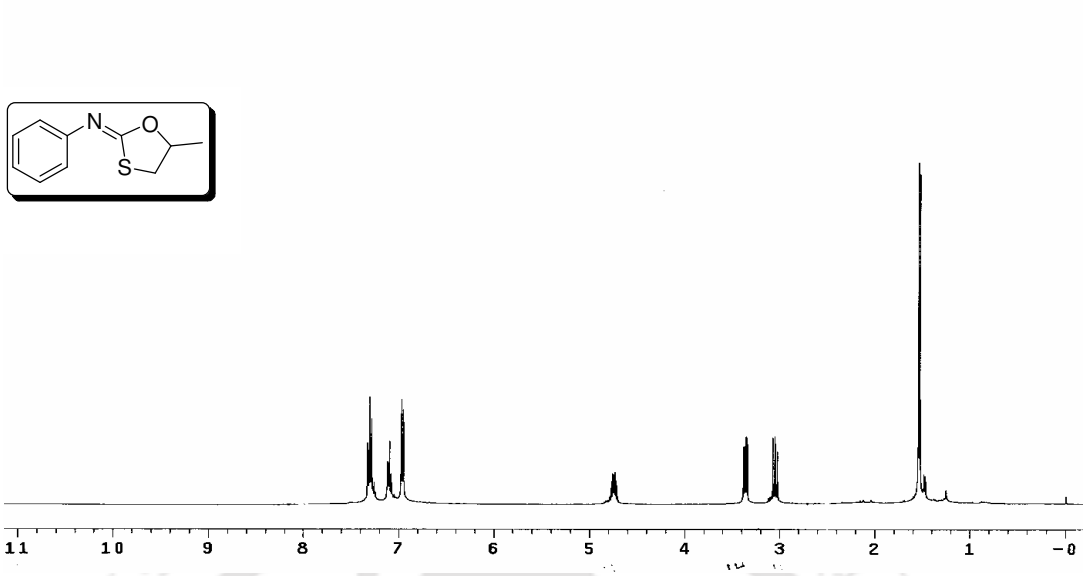
(*Z*)-Ethyl 2-oxopropyl phenyldithioimidocarbonate (1a): ^{1}H NMR (400 MHz, $CDCl_3$):



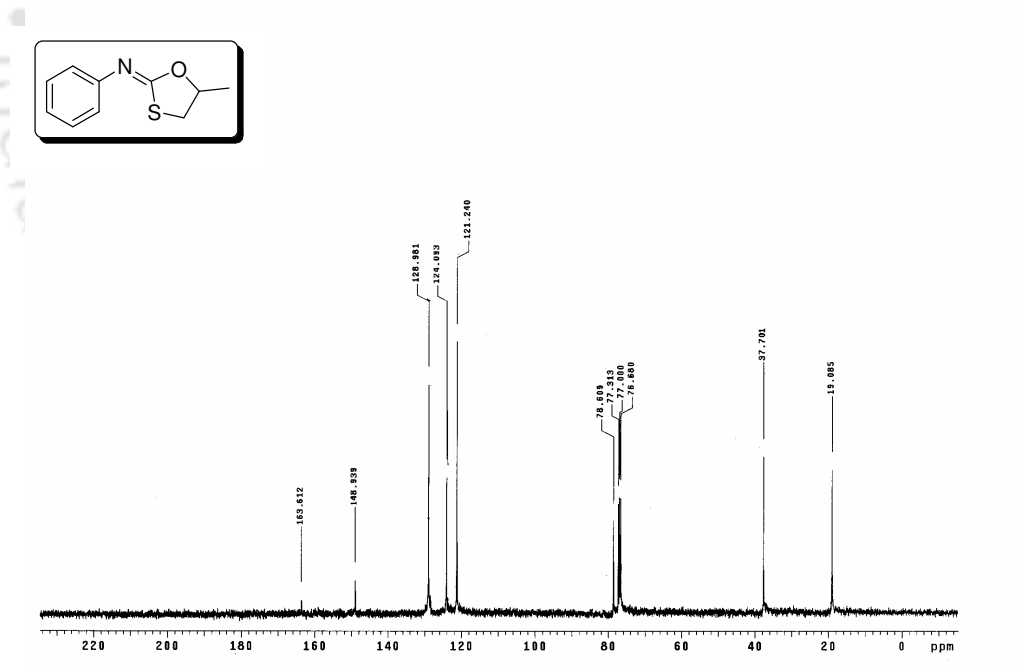
(*Z*)-Ethyl 2-oxopropyl phenyldithioimidocarbonate (1a): ^{13}C NMR (100 MHz, $CDCl_3$):



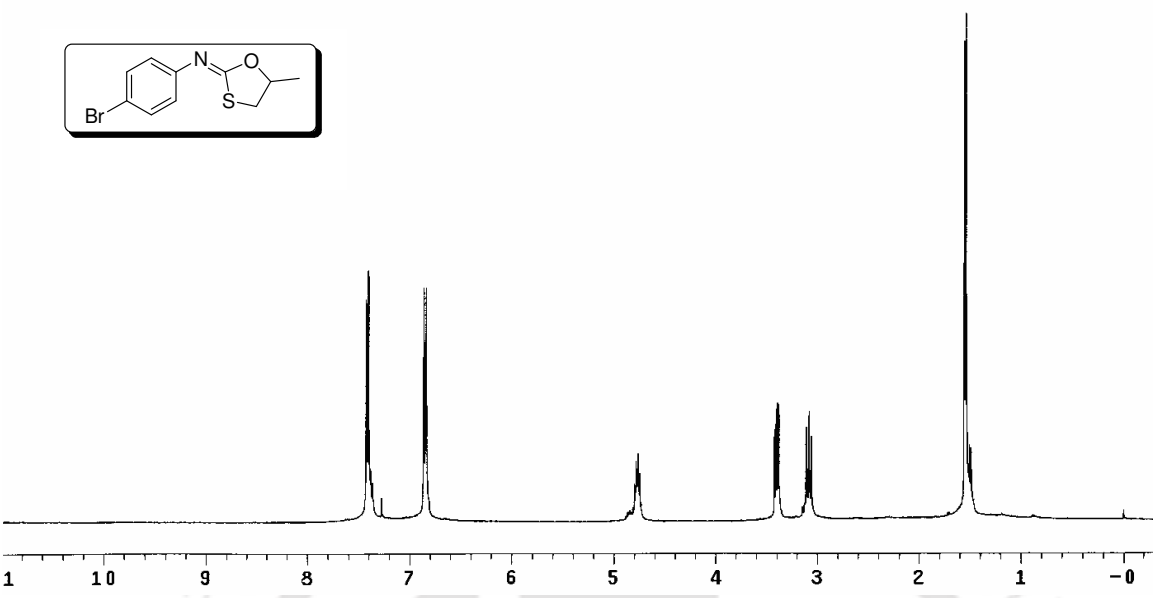
***Rac*-N-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (1b): ^{1}H NMR (400 MHz, $CDCl_3$):**



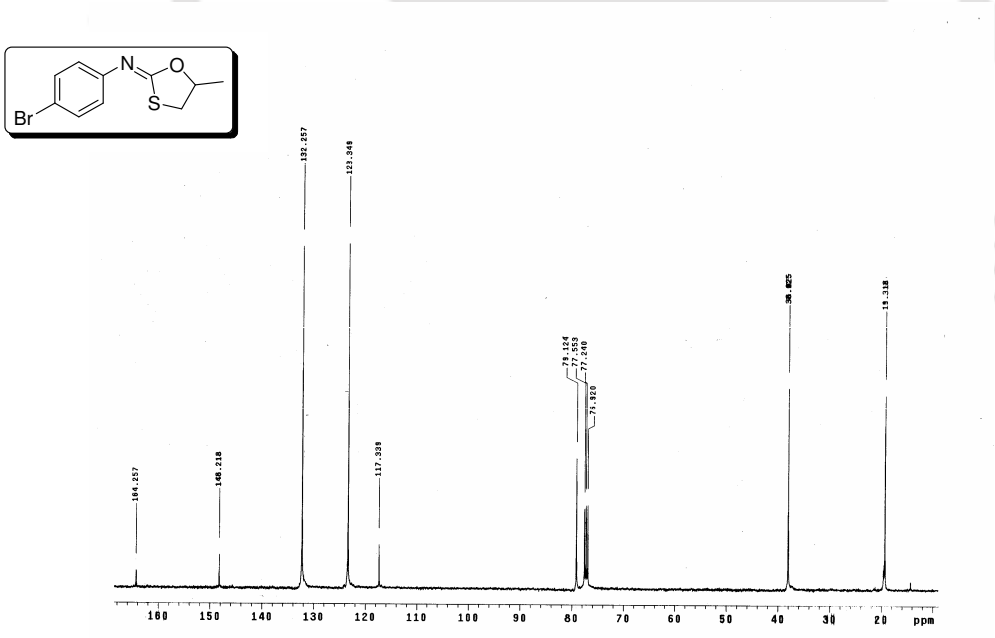
***Rac*-N-[(2Z)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (1b): 13C NMR (100 MHz, CDCl3):**



***Rac*-4-bromo-N-[(2*Z*)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (3b): ^{1}H NMR (400 MHz, $CDCl_3$):**



***Rac*-4-bromo-N-[(2Z)-5-methyl-1,3-oxathiolan-2-ylidene]aniline (3b): ^{13}C NMR (100 MHz,CDCl3):**



LIST OF PUBLICATIONS

1. '**Hypervalent Iodine(III) Mediated Oxidation of Aldoximes to *N*-Acetoxy or *N*-Hydroxy amides**' **Harisadhan Ghosh,** Bhisma K. Patel* *Org. Biomol. Chem.,* **2010**, *8*, 384-390.
2. **'Hypervalent Iodine(III)-Mediated Regioselective N-Acylation of 1,3-Disubstituted Thioureas'** C. B. Singh, **Harisadhan Ghosh**, Siva Murru, Bhisma K. Patel* *J. Org. Chem.,* **2008**, *73*, 2924-2927.
3. **'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**, 6189-6196.
4. **'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 Letters,* **2009,** *50*, 2407–2410.
5. **'A New Facile Synthetic Method for the Construction of 1,3-Oxathiolan-2-ylidenes' Harisadhan Ghosh**, C. B. Singh, Siva Murru, Veerababurao Kavala, Bhisma K. Patel* *Tetrahedron Letters,* **2008,** *49*, 2602–2606.
6. **'Oxidative Desulfurization of Disubstituted Thioureas Using Pb(II) salts and Investigation of p*Ka* Dependent Regioselective N-Acylation' Harisadhan Ghosh**, Soumya Sarkar, Abdur Rezzak Ali, Bhisma K. Patel* *Journal of Sulfur Chemistry,* **2010***, 31*, 1-11.
7. **'1,3-Disubstituted Thiourea: Versatile Building Block for the Construction of Heterocycles' Harisadhan Ghosh**, *Synlett Spotlight*, **2009**, 2882**.**
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**, 1849-1851.
9. **'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*, 1-14.
10. **'Intra- and Intermolecular C-S Bond Formation Using a Single Catalytic System: First Direct Access to Arylthiobenzothiazoles'** Siva Murru, **Harisadhan Ghosh**, Santosh K. Sahoo, Bhisma K. Patel* *Org. Lett.,* **2009,** *11*, 4254-4257.
11. **'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.
12. '**A Greener Synthetic Protocol for the Preparation of Carbodiimide**' Abdur Rezzak Ali, **Harisadhan Ghosh**, Bhisma K. Patel* *Tetrahedron Letters,* **2010,** *51*, 1019-1021.
13. '**The Thiocarbonyl 'S' is Softer Than Thiolate 'S': A Catalyst-free One-pot Synthesis of Isothiocyanates in Water'** Latonglila Jamir, Abdur Rezzak Ali, **Harisadhan Ghosh**, Francis A. S. Chipem, Bhisma K. Patel* *Org. Biomol. Chem*., **2010**, *8*, 1674-1678.