Chapter 8

Mechanistic Study on the Formation of Compounds from Thioureas

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Additional information is available at the end of the chapter

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Abstract

Formation of 2-(*N*-arylamino)benzothiazole takes place, when *N*,*N*′-diphenylthioureas are treated with polymer-supported tribromide or with iodine-alumina as catalyst under solvent free conditions. However, when *N*-substituted-*N*′-benzoylthioureas are treated with polymer-supported tribromide or with iodine-alumina as catalyst either under various conditions or under solvent free conditions, decomposition takes place to give the respective benzamides and thiobenzamides. Mechanistic study of the formation of these compounds is studied using DFT calculations. It is found that electron donating group at the *para*-position of the aryl group of benzoylthiourea favors the formation of benzamide whereas the presence of electron withdrawing group at *para*-position of the aryl group of benzoylthiourea, formation of thiobenzamide takes place. When the catalyst is changed to diacetoxyiodobenzene (DIB) under similar reaction conditions, benzoxazole amides are formed; expected benzothiazoles or the decomposition products are not obtained. Mechanistic study of the reaction using DFT calculation again shows that the reaction followed through carbodiimide intermediate undergoes the formation of C-O bond in benzoxazole moiety, instead of the expected C-S bond formation of benzothiazole moiety *via* a sequential acylation and deacylation process.

Keywords: mechanism, benzoxazoles, benzothiazoles, decomposition, thioureas, DFT calculations

1. Introduction

Heterocyclic chemistry is the most complex and intriguing branch of organic chemistry, and heterocyclic compounds constitute the largest and most unique family of organic compounds [1–3]. Nitrogen, oxygen, and sulfur are the most common heteroatoms but some other heterocyclic compounds containing selenium, tellurium, phosphorus, arsenic, silicon, boron, etc., are

also widely known. Heterocyclic compounds are present in many natural and non-naturally occurring compounds. Some examples of such compounds are alkaloids, vitamins (vitamin B series and vitamin C), antibiotics, amino acids, hemoglobin, hormones, pigments, and a large number of synthetic drugs and dyes. Several natural drugs such as morphine, codeine, quinine, penicillin, papaverine, atropine, emetine, reserpine, procaine, theophylline, etc., are examples of heterocyclic compounds. Some of the synthetic drugs have shown several therapeutic uses such as antidiabetic, antitubercular, antidepressant, antitumor, anti-HIV, anthelmintic, antibacterial, antifungal, antiviral, antimalarial, antileishmanial, analgesic, anti-inflammatory, anticonvulsant, anticancer, muscle relaxants, lipid peroxidation inhibitor, herbicidal, trypanocidal, fungicidal, and insecticidal activities. Thus, heterocyclic compounds are receiving more and more significance in recent years, particularly owing to their pharmacological as well as synthetic potential.

In recent years, green chemistry has become one of the most important philosophies in chemistry, since it represents a major change in the way we think about practicing chemistry and using chemicals. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. The search for new environmentally benign solvents and catalysts that operate efficiently in them and can be easily recycled is of significant academic and industrial interest. There have been several approaches to access to this problem, e.g., the developments of neat reactions that proceed under various conditions such as microwave irradiation, thermal heating, grinding, sonication, etc., or in organic or inorganic solid-media, or in ionic liquid-media under organic solvent-free reactions. Among the proposed solutions, solvent free conditions are becoming more and more popular and it is often claimed that the best solvent from an ecological point of view is, without a doubt, no solvent. The formation of various compounds from thioureas and their derivatives under different catalysts in solvent free condition is highlighted.

The density functional theory (DFT) method has become one of the most prevalent and efficient tools, as compared to the conventional *ab initio* method (HF), for studying the detailed reaction mechanism in chemical systems during the last two decades. With DFT methods, many catalytic reaction mechanisms have been widely studied in addition to the assignment of experimental spectra. It is to be noted that study of reaction mechanism is important not only for understanding the reaction and its stereochemistry but also for designing new reactions and catalysts. The mechanistic pathways for the decomposition of benzoylthioureas into benzamides and thiobenzamides; and also the conversion of benzoylthioureas into benzoxazoles, instead of forming bezothiazoles, using different catalysts have also been highlighted with the help of DFT calculations.

2. 2-Aminobenzothiazoles from thioureas

Benzothiazoles are an important class of heterocycles that possess a broad range of biological activities [4]. They were studied extensively for their anti-allergic, anti-inflammatory, antitumor, antimicrobial, and analgesic activities. Among those 2-substituted benzothiazole derivatives, the

2-aminobenzothiazoles are one of the most important structural motifs in pharmaceutically active compounds and natural products [5]. A large number of 2-aminobenzothiazole derivatives are also found to be anticancer active and the 2-aminobenzothiazole moieties act as a privileged pharmacophores as well as valuable reactive intermediates [6–8]. For example, *N*-aryl substituted 2-aminobenzothiazole (**A**; R116010) is a potential inhibitor of retinoic acid metabolism for cancer treatment [9]; 6-substituted 2-aminobenzothiazole (**B**) is found to exhibit antifungal activity [10]. Riluzole (**C**) is a 2-aminobenzothiazole compound employed in the treatment of amyotrophic lateral sclerosis [11] and *N*-disubstituted 2-aminobenzothiazole (**D**, HM13N) is used as anti-HIV agent [12]. 2-(*N*-acylamino) benzothiazole derivatives, such as trihydroxybenzoyl-2-aminobenzothiazole (**E**) [12] exhibit significant topoisomerase I inhibitory activity. Moreover, derivatives of 2-aminobenzothiazoles such as benzothiazole-triazole-pyridine conjugated analogs (**F**) [13] showed better anti-TB activity compared to rifampicin (RIF) (**Figure 1**).

The main objectives of benzothiazoles synthesis are not only for the development of more diverse and complex bioactive compounds for biological activity and structure-activity relationship (SAR) studies but also for other applications, such as preparation of dyes. There are several methods for the synthesis of 2-aminobenzothiazoles. The most versatile and economical method involves the treatment of various substituted arylthioureas (which are synthesized *via* treatment of an aromatic amine with isothiocyanate) with oxidizing agent or cyclizing agent using different reaction conditions to yield 2-aminobenzothiazoles.

Recently, several methods have been reported which utilize bromine as catalyst. Basically, cyclization with bromine is achieved by oxidation of aniline, substituted aniline, and arylthiourea in acid or chloroform with alkali thiocyanate. Hugerschoff, in early 1900s, synthesized 2-aminobenzothiazole and found that 1, 3-diarylthiourea can be cyclized with liquid bromine in chloroform to form a 2-aminobenzothiazoles (**Scheme 1**) [14, 15].

This reaction worked well for symmetrical thioureas giving exclusively one product. But, when the same reaction is performed using unsymmetrical 1,3-diaryl thioureas, there is always uncertainty as to on which aryl ring the intramolecular electrophilic substitution would take place to give aminobenzothiazole. Kamel *et al.* have reported the synthesis of 6-chloro-4-(trifluoromethyl) 2-aminobenzothiazole by oxidative cyclization of 4-chloro-2-(trifluoromethyl)phenylthiourea with bromine in chloroform to give an intermediate followed by basification with NH_3 (**Scheme 2**) [16].

Jordan *et al*. have reported the use of benzyltrimethylammoniumtribromide ($PhCH_2NMe_3Br_3$) which is an electrophilic bromine source for the conversion of substituted arylthiourea to 2-aminobenzothiazoles under mild conditions in different solvents with good yields (**Scheme 3**) [17].

Liu *et al.* have reported the metal-free synthesis of 2-aminobenzothiazoles from *N*′-substituted *N*-(2-halophenyl) thioureas *via* a base-promoted cyclization in dioxane (**Scheme 4**) [18]. However, this reaction requires drastic conditions, like heating the vial which was sealed in an oil bath.

The palladium-catalyzed intramolecular cyclization of 2-bromophenylthioureas to synthesize 2-substituted benzothiazoles was also reported. Castillon *et al.* reported Pd- catalyzed cyclization of 2-bromophenylthioamides using $Pd_2(dba)_3$/(2-biphenyl)P(*t*-Bu)$_2$ catalytic system (**Scheme 5**) [19].

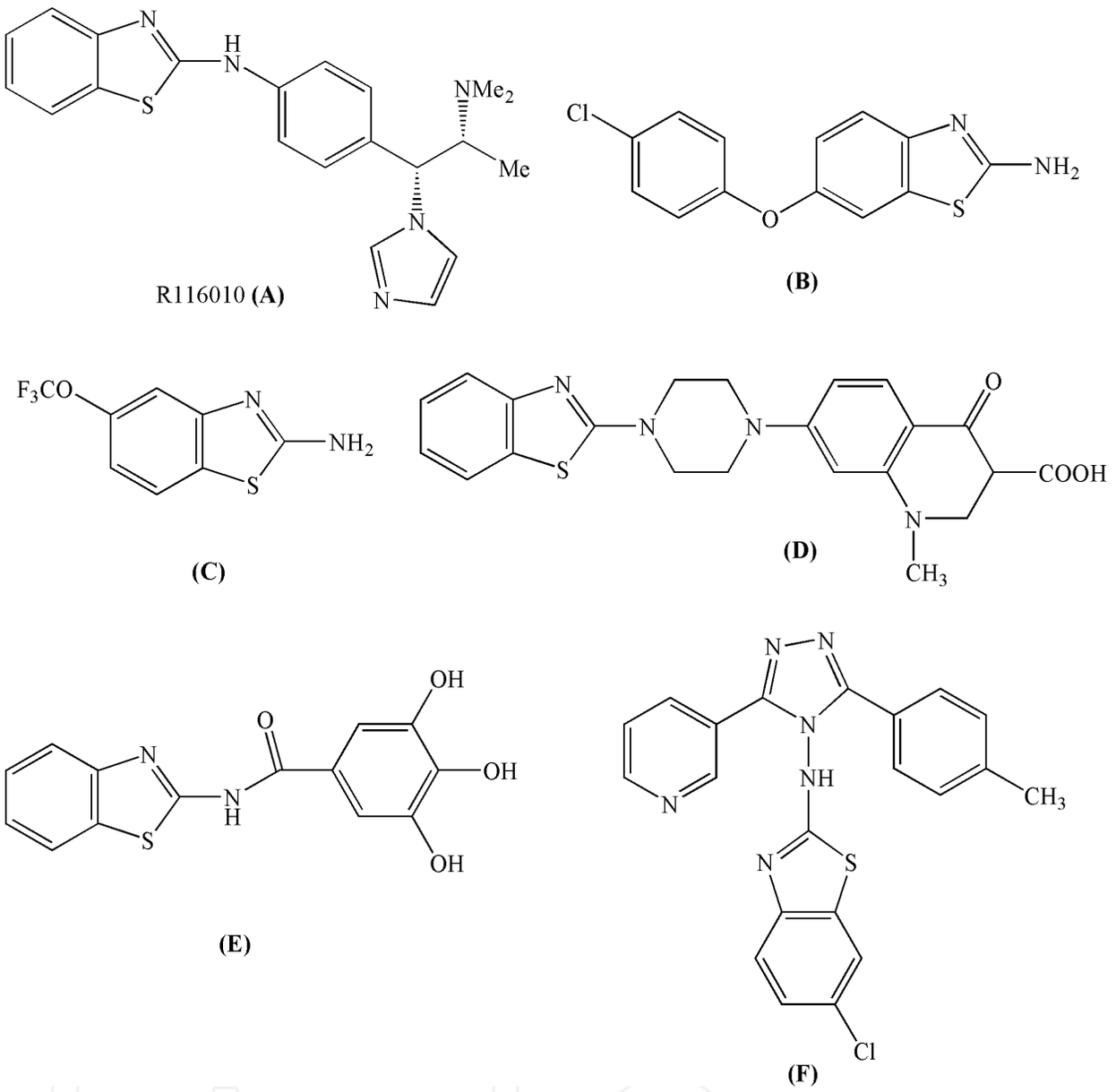
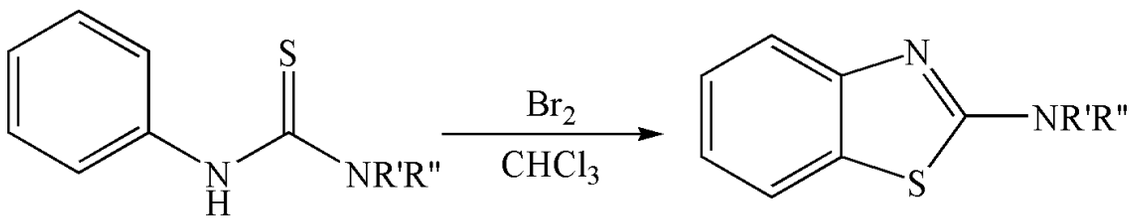


Figure 1. Several *N*-substituted-2-aminobenzothiazole derivatives reported as biologically active compounds and pharmaceutical products.



Scheme 1. Hugerschoff synthesis of 2-aminobenzothiazole from 1, 3-diarylthiourea with liquid bromine and chloroform.

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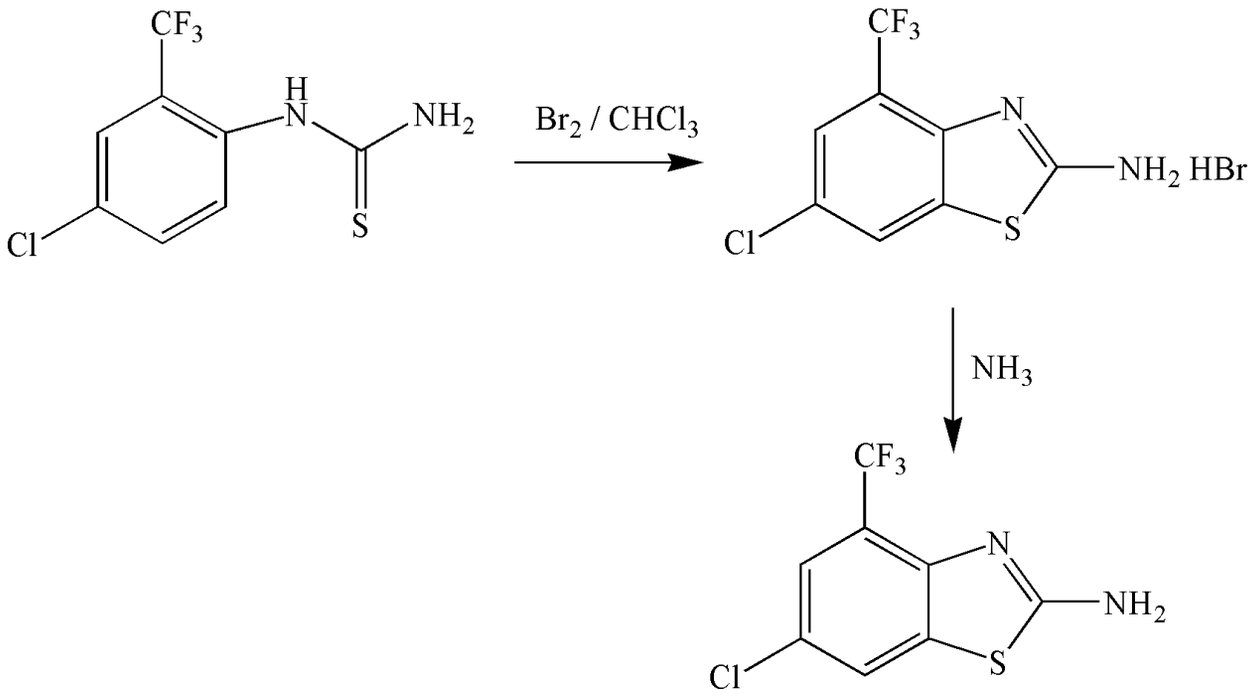
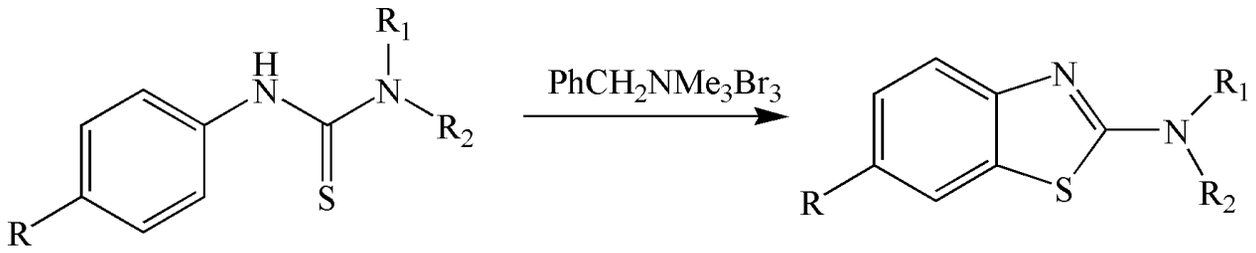
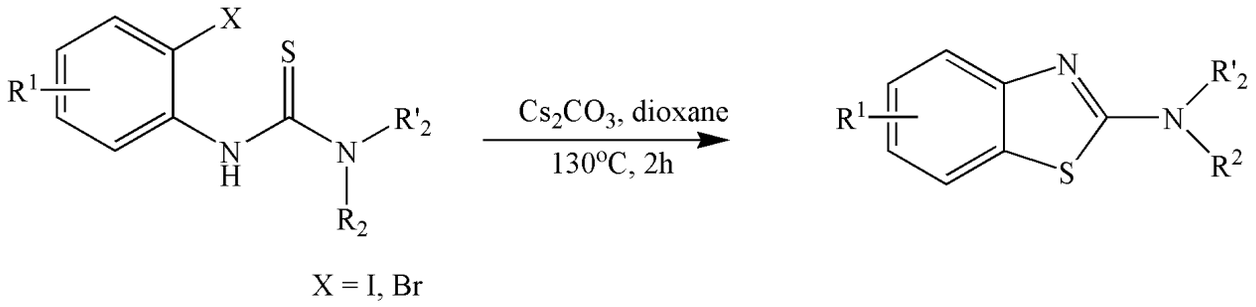


Scheme 2. Oxidative cyclization of phenylthiourea to give 2-aminobenzothiazole.

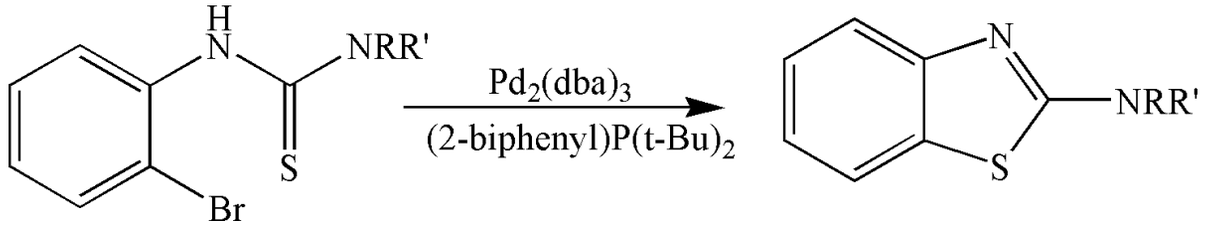


Scheme 3. Synthesis of 2-aminobenzothiazoles using benzyltrimethylammoniumtribromide.

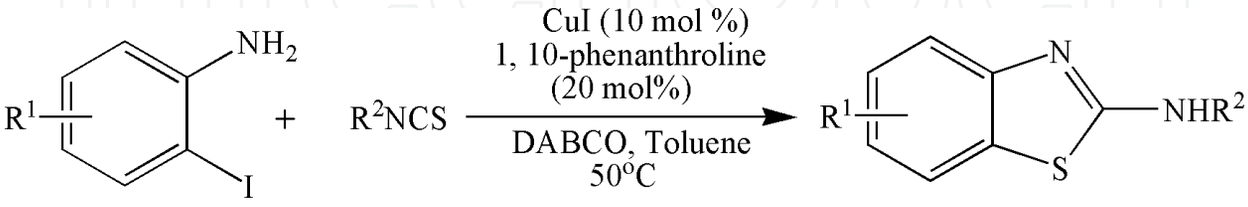


Scheme 4. Synthesis of 2-Substituted Benzothiazoles via a Base-Promoted Cyclization.

However, both a ligand and a base are required to promote the reaction, and the substrates are not readily available. It was reported recently a catalytic synthesis of 2-substituted benzothiazoles from thiobenzanilides in the presence of a palladium catalyst through C-H functionalization or C-S bond formation [20].

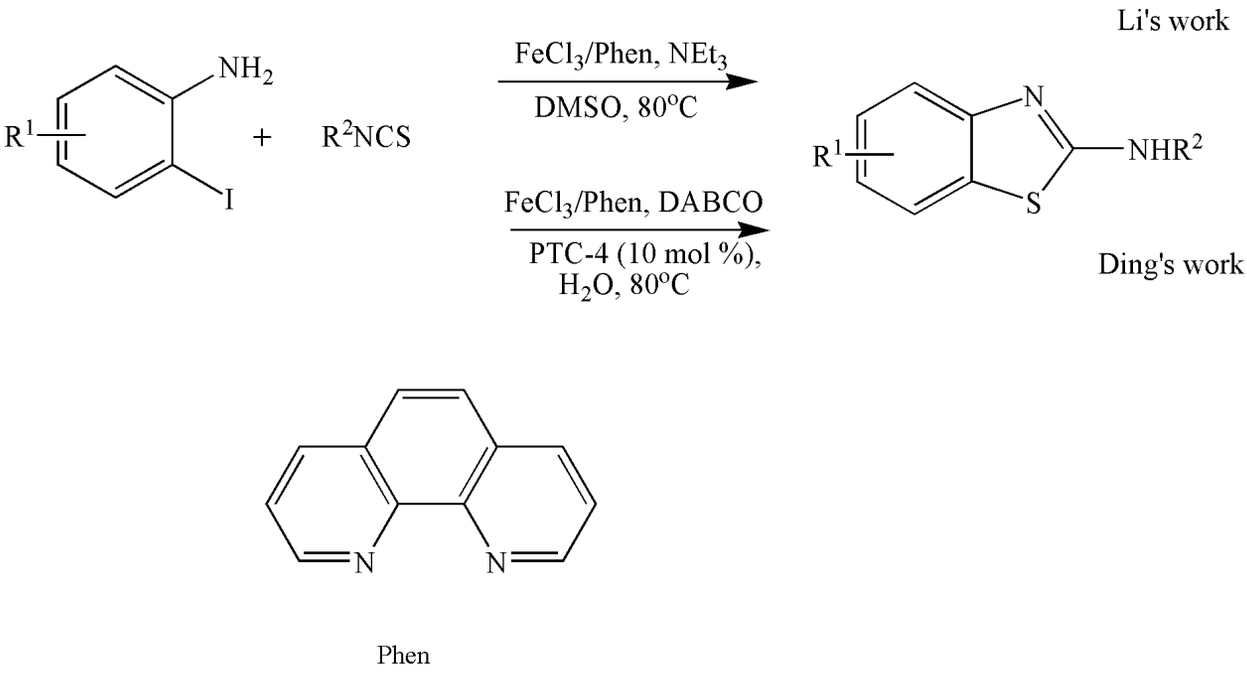


Scheme 5. Synthesis of 2-substituted benzothiazoles through palladium-catalyzed intramolecular cyclization of 2-bromophenylthioureas.



Scheme 6. Copper-catalyzed tandem reaction of 2-iodoaniline with phenyl isothiocyanate to form 2-aminobenzothiazole.

Recently, the transition-metal (copper or iron)-catalyzed one-pot tandem reactions of 2-halobenzenamines with isothiocyanates for the synthesis of 2-aminobenzothiazoles have received considerable attention because of their efficiency and low costs. For example, Wu *et al.* described a copper-catalyzed tandem reaction between 2-halobenzenamines and isothiocyanates using the CuI (10 mol%)/1,10-phenanthroline (20 mol%) catalytic system to prepare 2-aminobenzothiazoles (**Scheme 6**) [21]. Li and Ding's group reported iron-catalyzed tandem reactions of 2-halobenzenamines and isothiocyanates leading to 2-aminobenzothiazoles (**Scheme 7**) [22, 23].



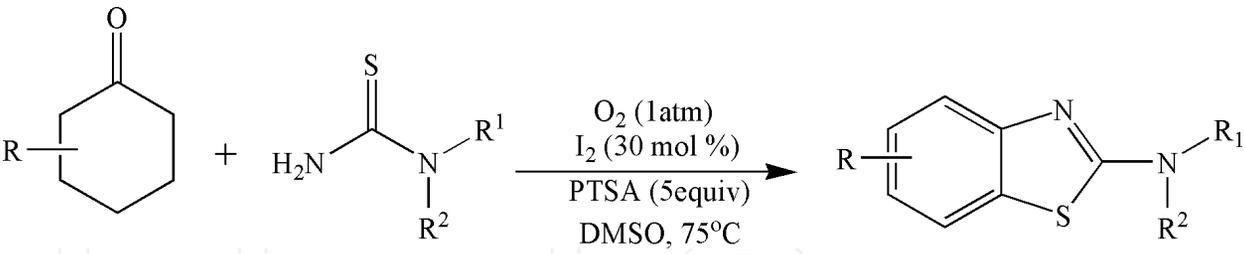
Scheme 7. $FeCl_3$-catalyzed tandem reaction of 2-iodoaniline with phenyl isothiocyanate in water to give 2-aminobenzothiazole.

Meanwhile, the ligand-free copper-catalyzed one-pot tandem reactions of 2-halobenzenamines and isothiocyanates were also reported [24, 25]. However, it should be noted that the copper or iron catalyzed one-pot tandem reactions of 2-halobenzenamines with isothiocyanates generally involve organic solvents such as DMSO, DMF, and toluene which are environmentally unfriendly. Moreover, the reactions which are described above might proceed efficiently; they usually suffer from the use of highly toxic and corrosive reagents, high-costing metal catalysts, and specific ligands. There is also possibility to leave toxic traces of metals in the products. More recently, Jiang *et al.* have reported a metal-free synthesis of 2-aminobenzothiazoles from cyclohexanones and thioureas using catalytic iodine and molecular oxygen as the oxidant under mild conditions (**Scheme 8**) [26].

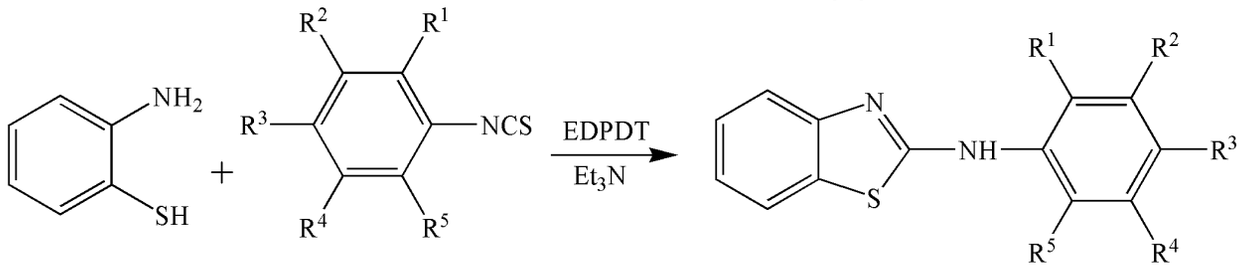
Recently, Patel *et al*. have reported a one-pot procedure for the preparation of 2-aminobenzothiazoles using ditribromide reagent 1,1′-(ethane-1, 2-diyl)dipyridinium bistribromide (EDPBT). In this approach, aryl/alkyl isothiocyanate reacts with *o*-aminothiophenol to form their monothiourea which on desulfurization with EDPBT led to the formation of corresponding 2-aminobenzothiazoles (**Scheme 9**) [27].

Very recently, polymer-supported tribromide has been used as a new solid phase and recyclable catalyst for the one-pot synthesis of 2-(*N*-arylamino)benzothiazole under microwave irradiation (**Scheme 10**) [28].

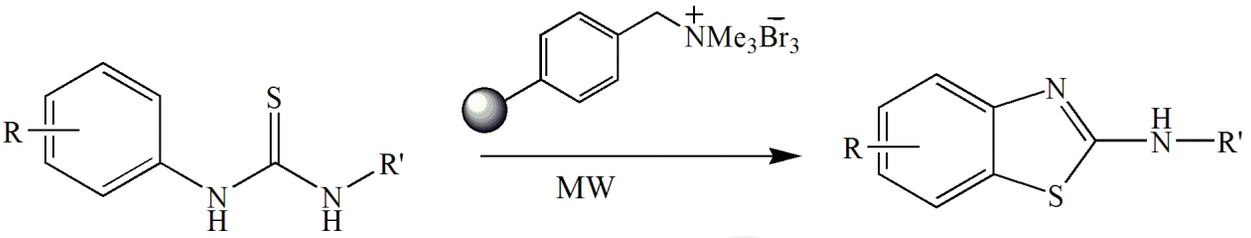
The probable reaction mechanism for the formation of 2-(*N*-arylamino) benzothiazoles through polymer-supported tribromide-mediated intramolecular cyclization of thioureas is given in **Scheme 11**.



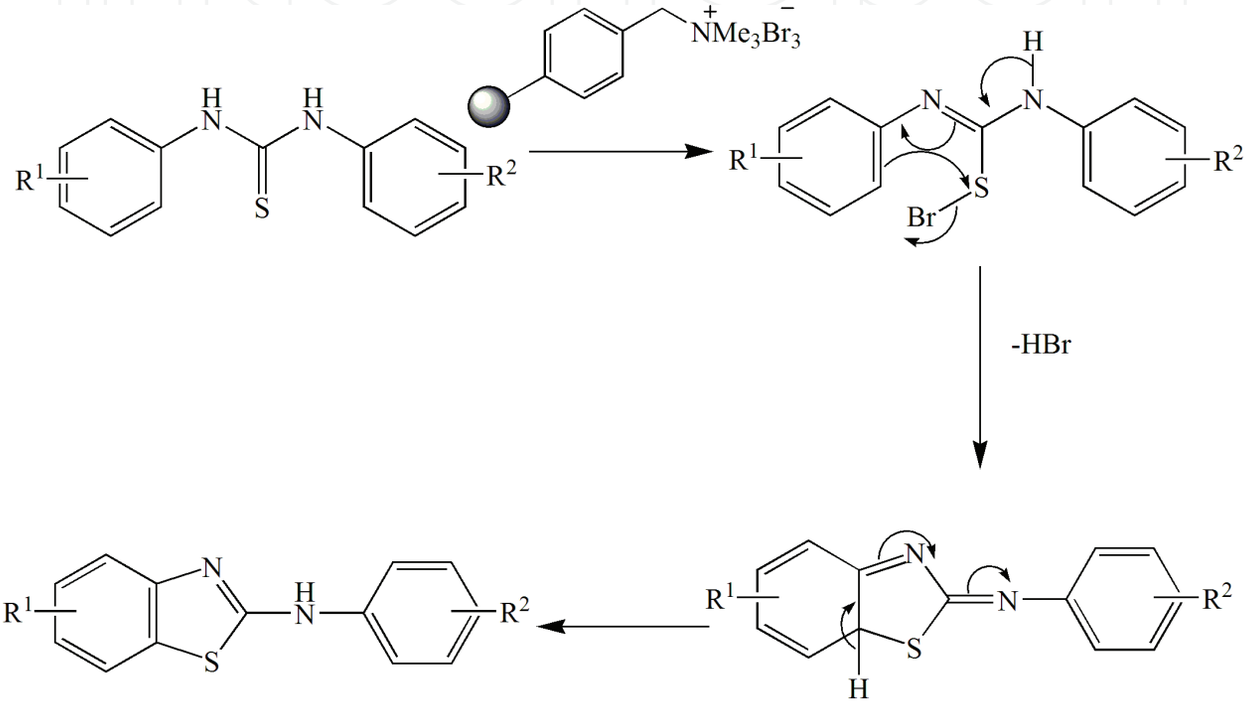
Scheme 8. Metal-free synthesis of 2-aminobenzothiazoles via aerobic oxidative cyclization of cyclohexanones and thioureas.



Scheme 9. One-pot synthesis of 2-aminobenzothiazoles using ditribromide reagent 1, 1′-(ethane-1, 2-diyl)dipyridinium bistribromide (EDPBT).



Scheme 10. One-pot synthesis of 2-(*N*-arylamino)benzothiazoles under microwave irradiation using polymer-supported tribromide.

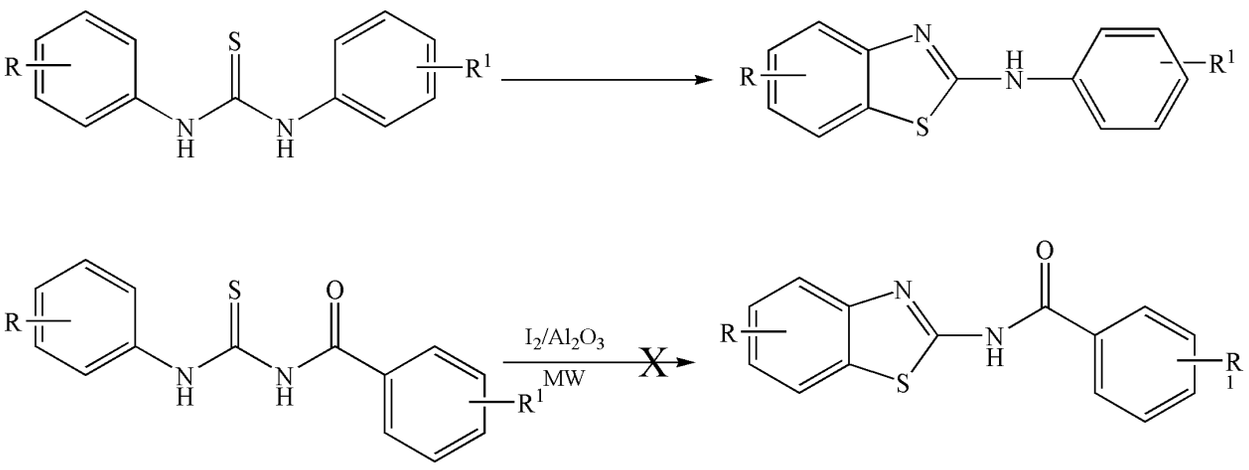


Scheme 11. Plausible reaction mechanism for the formation of 2-(*N*-arylamino) benzothiazoles through polymer supported tribromide–mediated intramolecular cyclization of thioureas.

3. Decomposition of benzoylthioureas

When the reaction of *N*,*N*′-diphenylthioureas with iodine-alumina as catalyst was carried out, the expected 2-(*N*-arylamino)benzothiazoles were obtained. However, when *N*-substituted-*N*′-benzoylthioureas are treated with the above catalyst, the expected benzothiazoles are not obtained (**Scheme 12**).

Instead, the decomposition of benzoylthioureas to benzamides and thiobenzamides in a single route using iodine-alumina as catalyst under solvent-free condition takes place. When electron donating group, such as methyl or methoxy group, is present at the *para*-position of the aryl group of benzoylthioureas, benzamides are obtained as major product. When electron withdrawing group, such as chlorine or nitro group, is at *para*-position of the aryl group of benzoylthioureas, thiobenzamides are the favored product. Thus, a simple and efficient process

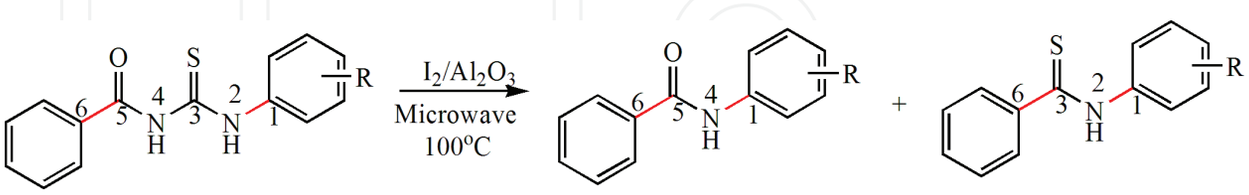


Scheme 12. Reaction of *N,N′*-diphenylthioureas and *N*-substituted-*N′*-benzoylthioureas with iodine-alumina under solvent-free condition

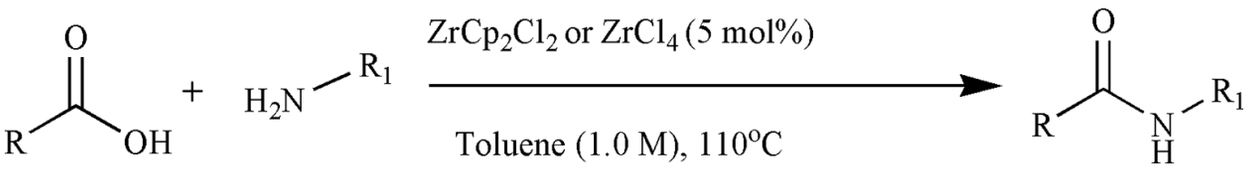
for the conversion of benzoylthioureas to benzamides and thiobenzamides using iodine-alumina as catalyst without any solvent was described (**Scheme 13**) [29].

Amides and thioamides are an important class of building blocks in modern organic synthesis, with broad applications in advanced materials, pharmaceuticals, agrochemicals, and polymers, etc. They are used for the synthesis of various natural products as well as intermediates of organic compounds. Generally, amides are prepared from their corresponding ketoximes by Beckmann rearrangement, and thioamides are prepared by thionation of the corresponding amide analogues by Lawesson's reagent. Liana Allen *et al*. have reported the direct coupling of unactivated carboxylic acids with amines in toluene at 110°C in the absence of catalyst. The use of simple zirconium catalysts at 5.0 mol% loading gave amide formation as little as in 4 h (**Scheme 14**) [30].

Gelens *et al*. have also reported the microwave assistance in the coupling of carboxylic acids with amines. An array of structurally diverse amides was synthesized efficiently by combining (primary and secondary) amines and carboxylic acids in one-pot under solvent-free microwave (MW) conditions (**Scheme 15**) [31].



Scheme 13. Decomposition of benzoylthioureas to benzamides and thiobenzamides using iodine-alumina.

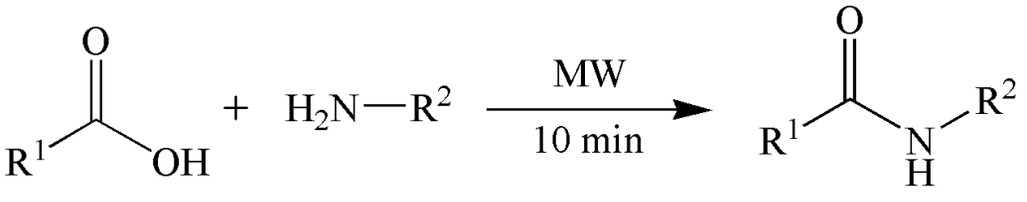


Scheme 14. Direct amide formation from unactivated carboxylic acids with amines using zirconium catalysts.

Very recently, Rajeshwer Vanjari *et al*. have developed a new approach for the synthesis of amides through manganese dioxide-promoted nondirected C-H activation of methylarenes under mild conditions employing *N*-chloroamines as effective coupling partners (**Scheme 16**) [32].

Different synthetic methods have been discovered for the synthesis of thioamides. Among these strategies, thionation of amide analogues with Lawesson's reagent is the most common, but this reaction cannot be classified as an atom economical approach because of crucial limitations: only one oxygen atom is replaced by a sulfur atom, and no other new bond was created. Thus, it is worthwhile to provide a practical and environmentally benign method to synthesize thioamides. Recently, some three component reactions have nicely exploited the use of benzylamine [33], aldehydes [34], and alkyne [35], in combination with elemental sulfur and amine for the synthesis of thioamides (**Scheme 17**).

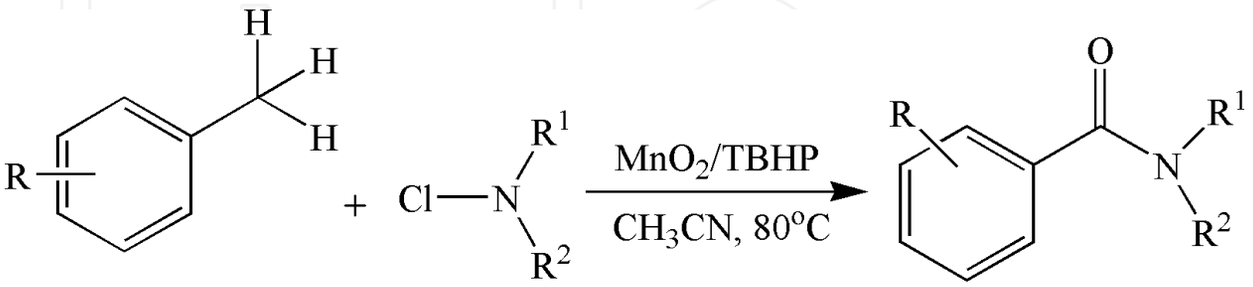
More recently, Guntreddi *et al*. reported a new decarboxylative strategy for the synthesis of thioamides via a three-component reaction involving arylacetic or cinnamic acids, amines, and elemental sulfur powder, without the need of a transition metal and an external oxidant (**Scheme 18**) [36].



R^1= Aryl, alkyl, containing a chiral center

R^2= Aryl, alkyl, containing a chiral center

Scheme 15. Microwave (MW)-assisted amide formation.

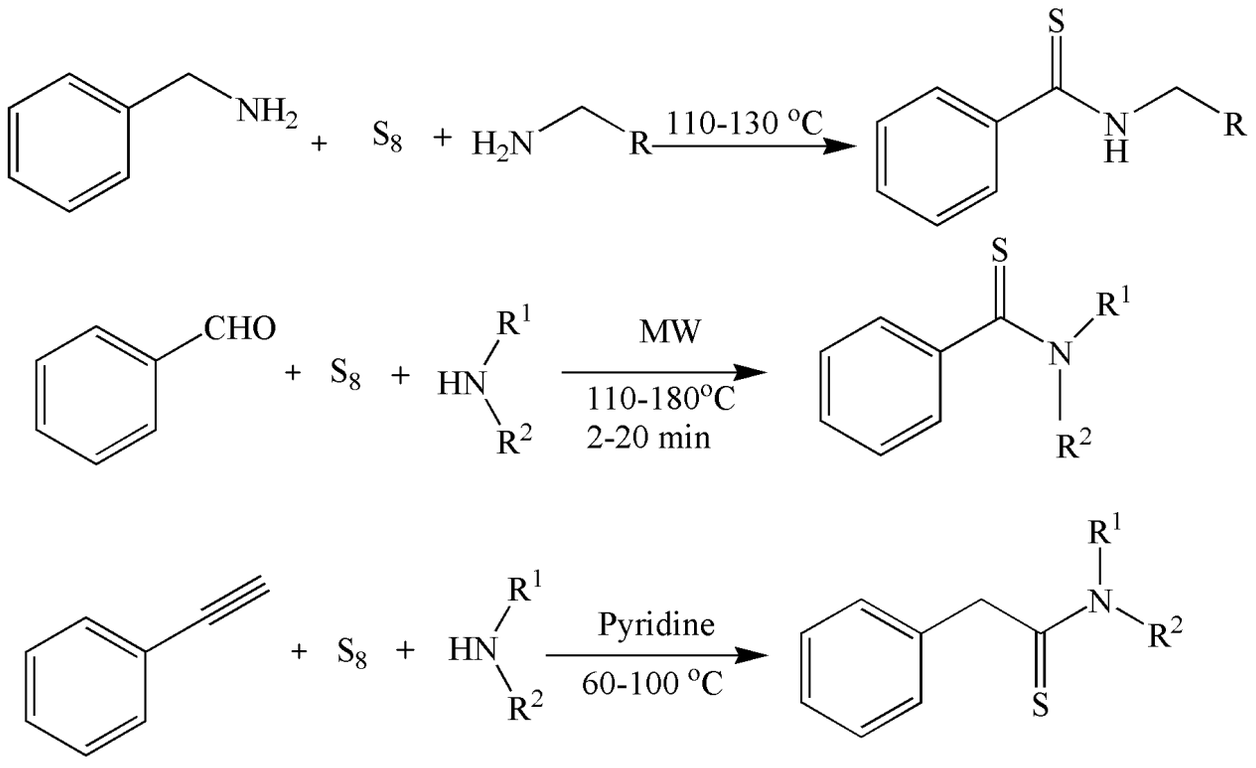


R= Me, OMe, Cl, Br, NO_2

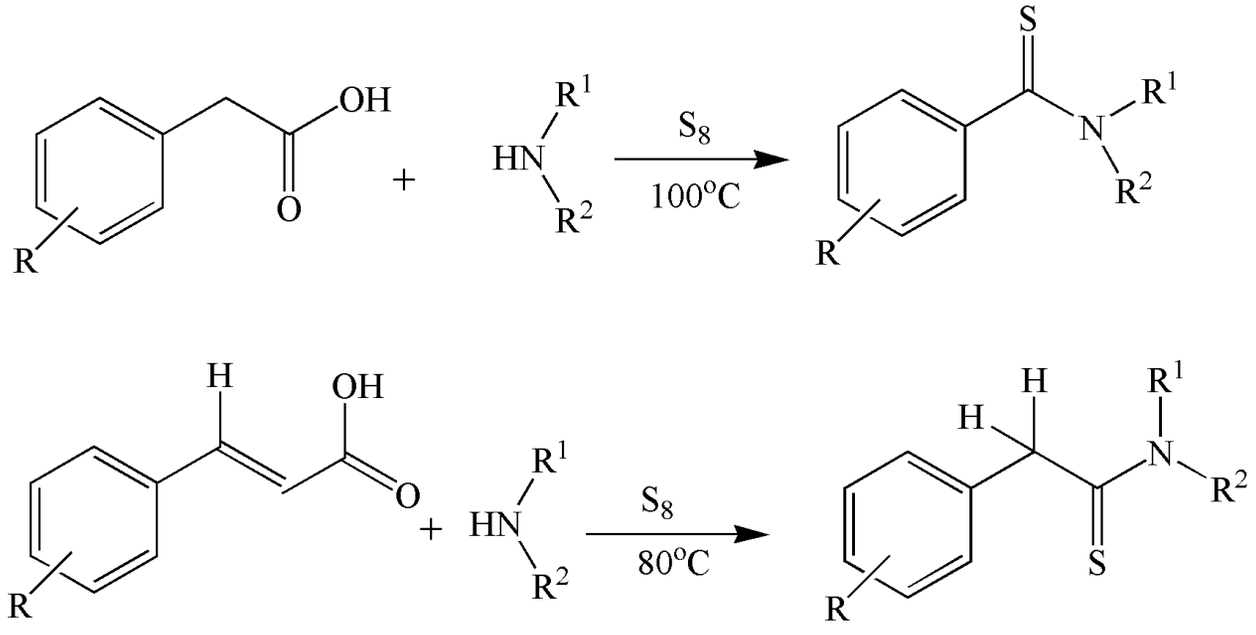
R^1= Benzyi, hexyl, butyl

R^2= Piperidyl, morpholine, Me, H

Scheme 16. Synthesis of amides through manganese dioxide promoted nondirected C-H activation of methylarenes.



Scheme 17. Multicomponent oxidative coupling into thioamides by elemental sulphur under solvent-free condition.



Scheme 18. Synthesis of thioamides via a three-component reaction by decarboxylative method.

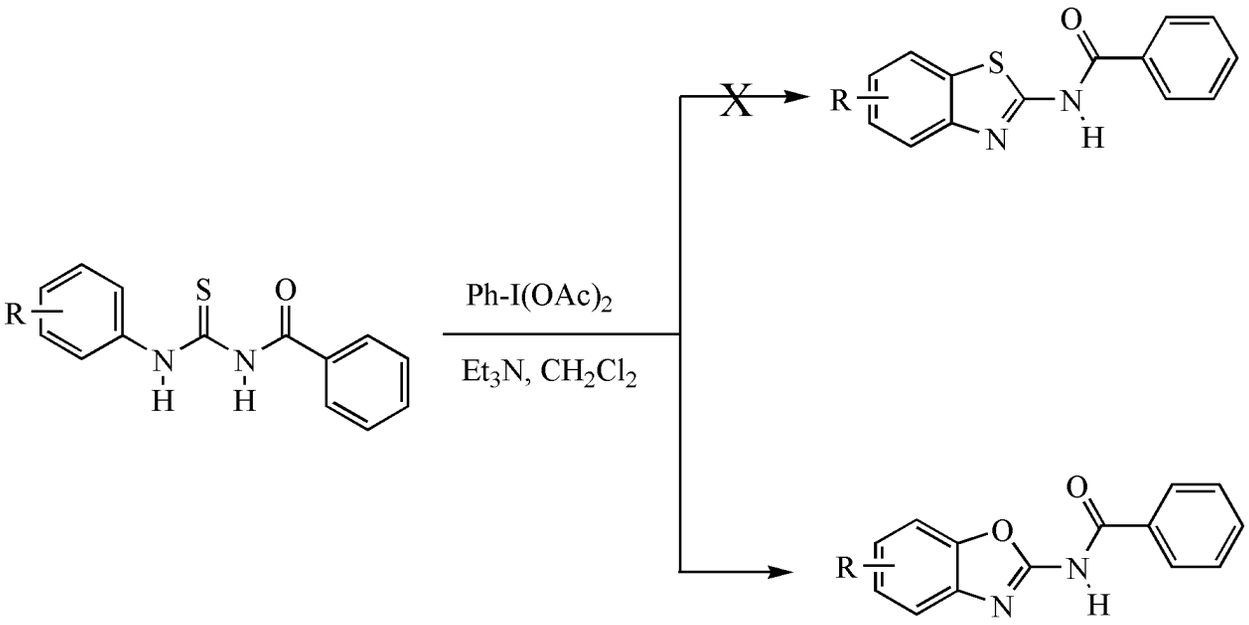
The Beckmann rearrangement generally requires a strong acid, high reaction temperature, harsh reaction conditions, and production of unwanted by-products. Several methodologies to check the reaction conditions, such as, in liquid phase, in vapor phase, in supercritical water, and

in ionic liquids have been developed. However, the drawbacks in such methods are the use of toxic solvents, expensive reagents, long reaction times, low yields, and the production of considerable amounts of by-products. Literature survey reveals that there were many reports for the synthesis of amides and its sulfur containing analogue, thioamides; however, there is no report for the simultaneous synthesis of benzamides and thiobenzamides from benzoylthiourea [29].

4. Benzoxazole amides from benzoylthioureas

When *N*-substituted-*N*′-benzoylthioureas are reacted with diacetoxyiodobenzene (DIB) as catalyst, benzoxazole amides are formed; expected benzothiazoles or the decomposition products are not obtained. Thus, when *N*-benzoylthiourea reacts with hypervalent iodine (III) reagent (DIB), instead of molecular iodine, an unexpected cyclized benzoxazole derivative is formed (**Scheme 19**) [37]. Unlike molecular iodine, DIB as catalyst renders the formation of C-O bond in benzoxazole moiety of substituted *N*-benzoxazol-2-yl-amides, instead of the expected C-S bond formation of benzothiazole moiety. Unexpectedly, the reaction follows different pathways leading to C-O bond formation between carbonyl oxygen and *ortho*-carbon of aryl moiety resulting in oxazole ring formation *via* a sequential acylation and deacylation process.

Benzoxazoles are a class of heterocyclic compounds exhibiting therapeutical activities (**Figure 2**), such as, antifungal agents [38–40], cytotoxic compounds [41], as anti-inflammatory agents [42], as HIV-1 protease inhibitor [43], as an antibiotic [44], as *Cp*IMPDH inhibitors [45], non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTI) [46], and antitumour agents [47].



Scheme 19. Synthesis of benzoxazole amides by the reaction of *N*-substituted-*N*′-benzoylthioureas with diacetoxyiodobenzene (DIB) as catalyst.

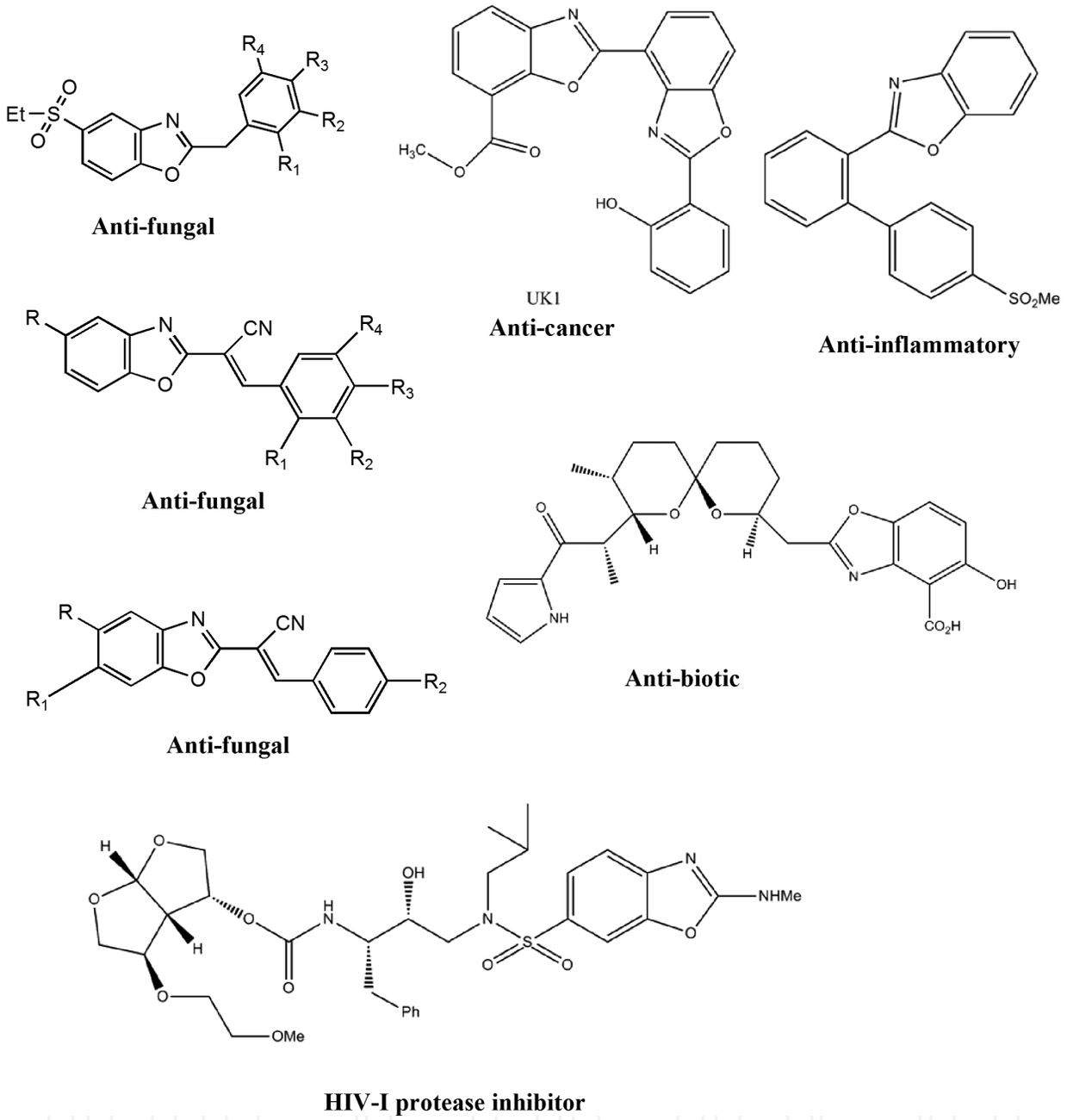
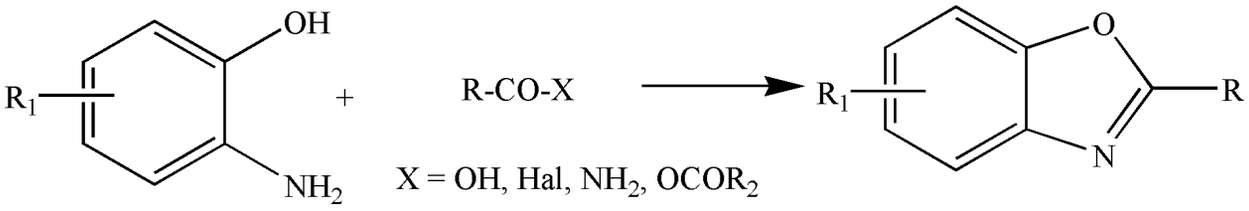


Figure 2. Several benzoxazole derivatives reported as biologically active compounds and pharmaceutical products.

Various methods have been reported in the literature for the synthesis of benzoxazoles starting from 2-aminophenol precursors with carboxylic acid derivatives, such as carboxylic acids, acid chlorides, acid anhydrides, and amides (**Scheme 20**), or by reacting 2-aminophenols with aldehydes followed by oxidation (**Scheme 21**) [48–51].

In most cases, 2-aminophenols are used as the starting materials for the preparation of 2-arylbenzoxazoles. However, the synthesis of *N*-benzoxazol-2-yl-amides is very limited [52] and the synthesis of *N*-benzoxazol-2-yl-amides starting from *N*′-benzoylthiourea using hypervalent iodine(III) reagents (DIB) is recently reported [37].



Scheme 20. Synthesis of benzoxazoles from 2-aminophenol with carboxylic acid derivatives, acid chlorides, and amides.

Scheme 21. Synthesis of benzoxazoles from 2-aminophenol with aldehydes followed by oxidation.

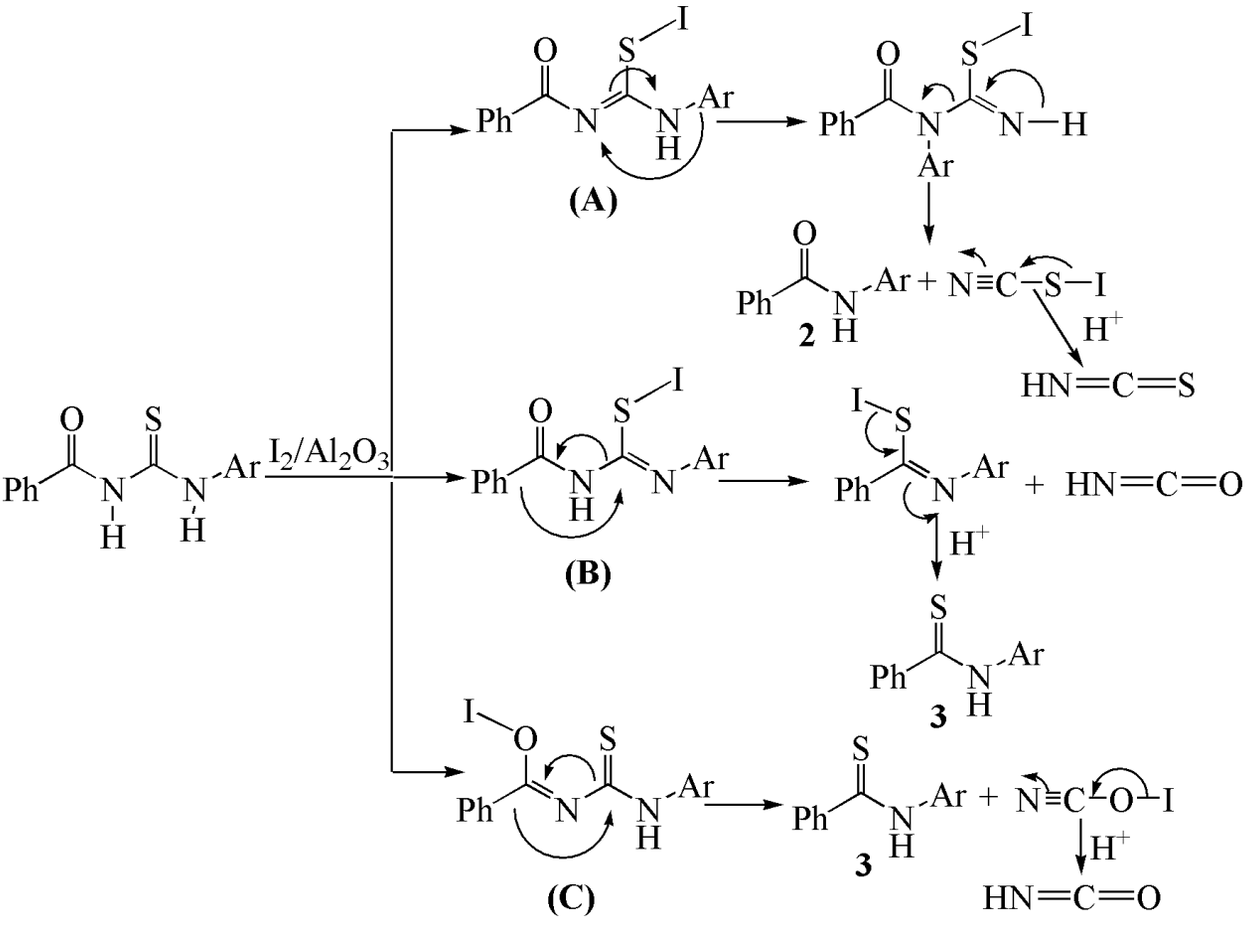
5. DFT calculations

With the help of density functional theory (DFT), the electronic structure of organic compounds could be expressed by electron density functional. DFT calculation is recently applied to the study of various reaction mechanisms, *viz*. the reaction mechanisms of the Pd(II)-catalyzed oxidative carbocyclization-alkoxycarbonylation of bisallenes to construct seven-membered carbocycles have been theoretically investigated with the aid of density DFT calculations [53]; the coupling reaction mechanisms of the Rh(III)-catalyzed redox-neutral C7-selective aryl C-H functionalization of indolines with alkynes and alkenes have been theoretically investigated [54]; the mechanism of NHC catalyzed annulation reactions involving an α,β-unsaturated acyl azolium and β-naphthol has been studied using DFT methods [55]; DFT calculations have been performed on Rh(III)-catalyzed phosphoryl-directed oxidative C-H activation/cyclization to investigate the detailed mechanism [56]; DFT calculations were also employed to investigate the energetics of several reaction paths for the Fries rearrangement of aryl formates promoted by boron trichloride [57]; the reactions of hypochlorous acid (HOCl) with ammonia, (di)methyl-amine, and heterocyclic amines have been studied computationally using double-hybrid DFT methods [58]; the mechanisms and chemo- and stereo-selectivities of PBu3-catalyzed intramolecular cyclizations of N-allylic substituted α-amino nitriles leading to functionalized pyrrolidines (5-endo-trig cyclization, Mechanism A) and their competing reaction leading to another kind of pyrrolidine (5-exo-trig cyclization, Mechanism B) have been investigated using DFT [59]; a systematic theoretical study has been carried out to understand the mechanism and stereoselectivity of N-heterocyclic carbene (NHC)-catalyzed intramolecular-crossed benzoin reaction of enolizable ketoaldehyde using DFT calculations [60]. A simple and convenient method for the construction of substituted cycloheptenones from 1-bromoocta-1,7-diene-3-ols has been developed. The reaction involves Pd(0)-catalyzed intramolecular 7-exo-trigcyclization followed by Pd (II)-catalyzed oxidation of cyclic alcohol. The course of the reaction pathway has been evaluated using DFT calculations [61].

5.1. DFT calculations for the formation of benzamides and thiobenzamides

The mechanism for the decomposition of benzoylthioureas to benzamides and thiobenzamides in a single route using iodine-alumina as catalyst under solvent-free condition was studied with DFT calculations; all the structures were optimized by hybrid density functional B3LYP [62, 63] using the segmented all-electron relativistically contracted Def2-TZVP(−df) basis set with the help of ORCA [64]. The DFT calculation shows that the formations of both benzamides and thiobenzamides with by-products, *viz.*, isothiocyanate and isocyanate, respectively, are endothermic. The formation of benzamide and isothiocyanate involves lower energy. Thus, it was found that the formation of benzamide product is a thermodynamically favored reaction although it is observed from the experimental results that both the products are formed, except in *N*-2-pyridinyl-*N*′-benzoylthiourea where only the energetically favored benzamide product is formed [29].

The plausible mechanism for the formation of benzamides and thiobenzamides is shown in **Scheme 22**. To understand the mechanistic pathway, three most probable iodide intermediates **A**, **B**, and **C** formed after reaction with diiodine (I_2) molecule were considered (**Scheme 22** and **Table 1**). The I-I bond in diiodine is often known to be perturbed by thiones and form iodides. The formation of iodide intermediate through oxygen atom **C** is being ruled out because of its



Scheme 22. Plausible mechanism for the formation of benzamides and thiobenzamides.

relatively high energy compared to those of intermediates **A** and **B** (examples of O-I bond formation of diiodine with ketones are not found in the literature).

The results show that the intermediate (**A**) has the lowest energy which indicates that it is the most probable intermediate and the optimized structure is shown in (**Figure 3**). The results further show that for all the reactions theoretically considered, the intermediate (**A**) has the lowest energy, except for *p*-chlorinated molecule, which indicates that it is the most probable intermediate (**Table 1**).

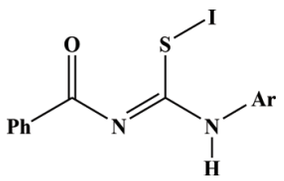
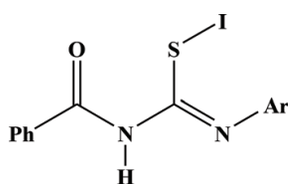
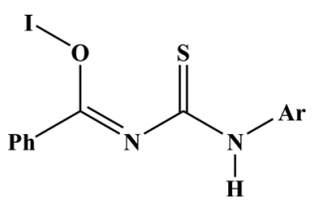
Intermediates	Structure	Relative energy (kcal)
A		0.0
B		0.5
C		35.2

Table 1. Relative energies of different intermediates for parent molecule.

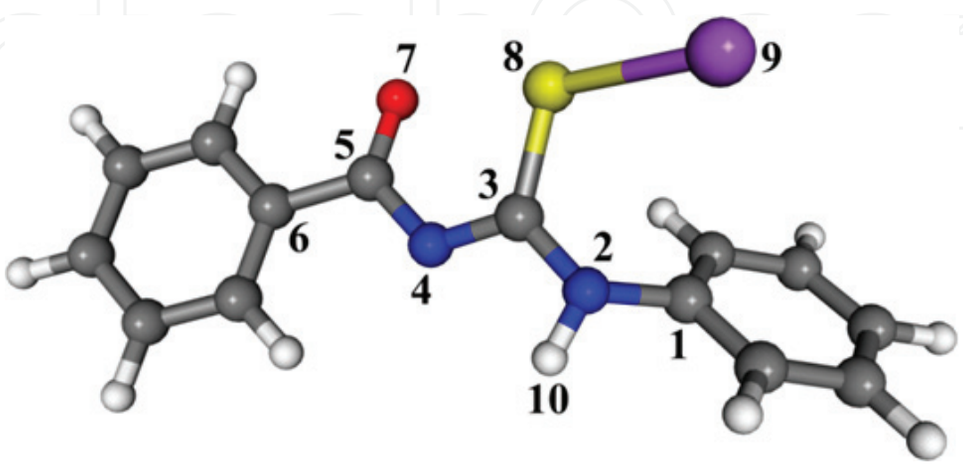


Figure 3. Optimized structure of A.

Intermediates	Mayer bond order				
	C1-N2	N2-C3	C3-N4	N4-C5	C5-C6
A	0.9092	1.1663	1.5143	1.3996	0.9238
B	1.1027	1.8061	0.9953	1.1750	0.9085
C	1.0134	1.1414	1.0373	1.9322	0.9493

Table 2. Mayer bond order for selected bonds (atom numbering is shown in **Figure 3**) for parent molecule.

To study the possibility of breaking the molecular backbone, the strength of different bonds were considered based on the Mayer bond order [65], which indicates a number of electron pairs that constitute a bond. When considering the backbone structure, C1-N2 has the least Mayer bond order in intermediate **A** while C5-C6 has the least bond order in the intermediates **B** and **C** (**Table 2**).

In case of the *p*-chlorinated molecule, an electron withdrawing substituent at the *para*-position of the aryl group, the intermediate **B** is the energetically most favored intermediate (**Table 4**). This indicates that the migration of the phenyl group in *p*-chlorinated molecule to attack the thiocarbonyl carbon is the favored step, which on further rearrangement gives the product thiobenzamide. The proposed steps are supported by the experimental results where the thiobenzamide is the major product. The probable reason for the formation of appreciable amount of the benzamide product, although not the favored step mechanistically, could be that the benzamide product is thermodynamically more stable than the thiobenzamide product. The formation of benzamide occurs through the intermediate **A** by the migration of the aryl group as the C1-N2 bond order is the least in intermediate **A**.

For other substituted molecules also, C5-C6 has the least bond order in the intermediate **B** as mentioned earlier. This explains that the formation of the thiobenzamide product is due to the migration of the phenyl group following the similar steps as in *p*-chlorinated molecule. However, when the electron withdrawing *p*-chlorinated aryl group is replaced by *p*-methylated aryl group, the benzamide product is the major one. The reason for the reaction in this case could be that the formation of benzamide product is preferred by breaking the C1-N2 bond in intermediate **A** than the mechanistically favored step by breaking C5-C6 bond in intermediate **B (**as in *p*-chlorinated molecule). This is so because the intermediate **A** has lower energy than **B** (**Table 3**). It is also interesting to note that when an electron donating group methyl is at the *ortho*-position in the aryl group, the intermediate **A** which has lowest energy has the least bond order at C5-C6 bond. This makes the breaking of C1-N2 bond in intermediate **A** less probable, thus rendering the formation of thiobenzamide product as the major product. Similar result is obtained in *o*-pyridinated molecule.

Thus, the DFT studies showed that the formation of benzamide was due to the migration of the aryl group (in intermediate **A**) while the formation of thiobenzamide may be due to the migration of the phenyl group (in intermediate **B**). It was found that the formation of benzamide product is the thermodynamically favored reaction, although it is observed from the experimental results that both the products are formed, except in *N*-2-pyridinyl-*N*′-benzoylthiourea where only the energetically favored benzamide product is formed.

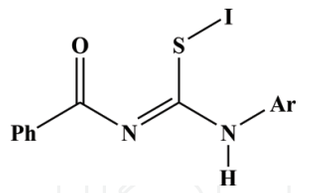
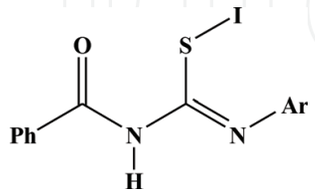
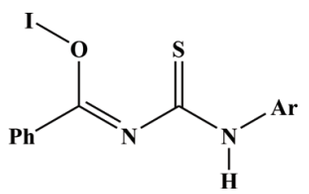
Structure	*p*-Chlorinated molecule		*p*-Methylated molecule	
	Intermediate	Relative energy (kcal)	Intermediate	Relative energy (kcal)
	A_p-Cl	0.2	A_p-Me	0.0
	B_p-Cl	0.0	B_p-Me	0.7
	C_p-Cl	35.0	C_p-Me	35.5

Table 3. Relative energies of different intermediates for *p*-chlorinated and *p*-methylated molecules.

Intermediates	Mayer bond order				
	C1-N2	N2-C3	C3-N4	N4-C5	C5-C6
***p*-Chlorinated molecule**					
A_p-Cl	0.9138	1.1550	1.5238	1.3918	0.9254
B_p-Cl	1.1197	1.7945	1.0017	1.1714	0.9103
C_p-Cl	1.0194	1.1321	1.0436	1.9265	0.9495
***p*-Methylated molecule**					
A_p-Me	0.9047	1.1728	1.5131	1.4038	0.9261
B_p-Me	1.1200	1.8032	0.9944	1.1719	0.9076
C_p-Me	1.0081	1.1453	1.0359	1.9327	0.9498
***o*-Methylated molecule**					
A_o-Me	0.9585	1.1536	1.5098	1.4015	0.9236
B_o-Me	1.1379	1.7861	0.9979	1.1722	0.9090
C_o-Me	0.9087	1.1397	1.0361	1.9337	0.9413
***o*-Pyridinated molecule**					
A_o-Py	1.0052	1.1535	1.5311	1.3810	0.9264
B_o-Py	1.0588	1.8130	1.0024	1.1710	0.9111
C_o-Py	1.0440	1.1511	1.0501	1.9346	0.9517

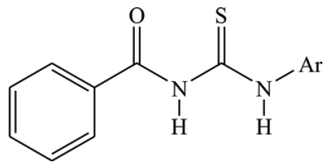
Table 4. Mayer bond order for selected bonds for the *p*-chlorinated, *p*-methylated *o*-methylated molecules and the *o*-pyridinated molecules. (atom numbering is shown in **Figure 3**).

5.2. DFT calculations for the formation of benzoxazoles

Density functional calculations were performed at a B3LYP/Def2-TZVP(−df) level of theory using ORCA to study the reaction mechanism for the formation of benzoxazole amides from benzoylthioureas in presence of DIB as catalyst and the role of substitution with electron withdrawing/donating group at different positions of the phenyl ring on the reaction. The plausible mechanism for the formation of *N*-benzoxazol-2-yl-amides from benzoylthioureas is shown in **Scheme 18**. The final product benzoxazole amide is formed after a series of acylation and deacylation occurring in tandem, as illustrated in **Scheme 18**, with the formation of a number of intermediates. At first, the acylation occurs due to the formation of carbodiimide from *N*′-benzoylthiourea. During carbodiimide formation, the molecule is oxidized by DIB to give 1 mole each of acetic acid, sulfur atom, and phenyl iodide where iodine is reduced from +3 to +1 oxidation state. There are two possible pathways, namely, Path A and Path B, for the formation of carbodiimide from *N*′-benzoylthiourea through the formation of intermediates A and B, respectively. The attack of sulfur atom of thiocarbonyl on the thiophilic iodine of diacetoxyiodobenzene is initiated by the deprotonation of either of the NH protons lying on either side of the thiocarbonyl group. The deprotonation of N4 atom results in intermediate A, while the deprotonation of N2 atom results in intermediate B. To determine which pathway is the favored one, the relative energies of intermediates A and B were calculated (**Table 5**). It is observed that the intermediate B is the thermodynamically favored intermediate in most of the reactions except for substitution at *ortho*-position with chlorine and at *meta*-position with both electron withdrawing chlorine and donating methyl groups. This shows that the position of substitution plays a bigger role than the type of substituent in determining the pathway to give carbodiimide. It may be mentioned that earlier in our work for iodide intermediate [49], the relative energy of the deprotonated product from N4 atom was slightly less than that obtained from N2 atom. However, the energy difference between the two in the previous work was appreciably small with maximum of 3.0 kcal/mole. In the present case, the difference in relative energy between the two intermediates increases by two fold (**Table 5**) although the deprotonated product from N2 atom generally becomes more stable as shown in mechanistic pathways for the formation of benzoxazole amides (**Scheme 23**).

The carbodiimide thus formed is acylated at carbodiimide carbon which after rearrangement gives the acylated intermediate (**C**). The conversion from the acylated intermediate **C** to the final product here also can follow either of two possible routes: Route 1, which is deacylation by hydrolysis followed by cyclization, to give benzoxazole derivative (**D**′) through oxidation of deacylated product by another molecule of DIB or Route 2, which undergoes cyclization through oxidation of acylated intermediate **C** by another molecule of DIB, to give acylated benzoxazole derivative (**E**) followed by deacylation on hydrolysis. The cyclization to give oxazole ring also is initiated by deprotonation of NH atom as in the first reaction.

To determine which route the reaction follows, one needs theoretical consideration of each step of deacylation then cyclization (Route 1) or cyclization then deacylation (Route 2). One way to determine which route the reaction follows is to compare the energetics of each step undergoing in either route (**Table 6**). Comparison of energies of reactions for the first step through Route 1 (deacylation) and Route 2 (cyclization by oxidation of DIB) shows that the initial deacylation (Route 1) is exothermic and thermodynamically favored over oxazole cyclization through Route 2



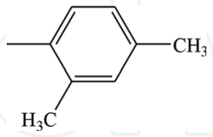
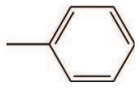
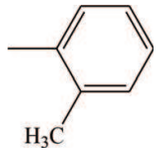
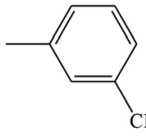
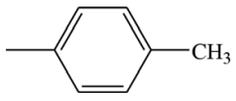
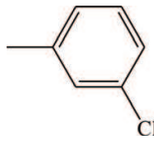
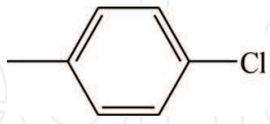
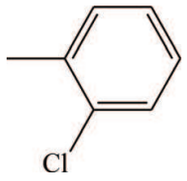
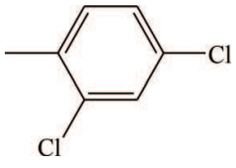
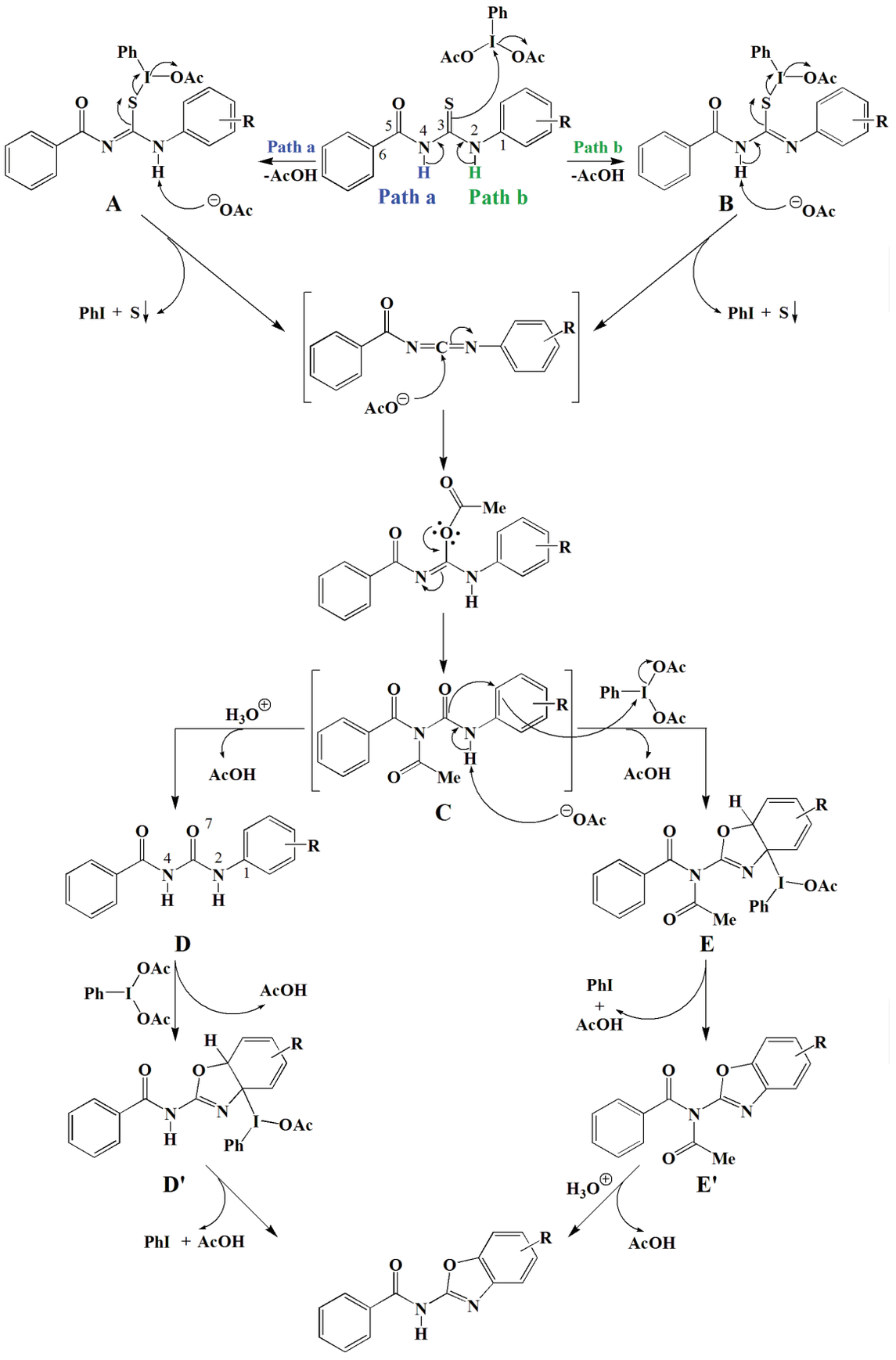
Entry number	Ar	Relative energy of B (kcal/mole)
1		−6.230
2		−7.571
3		−7.236
4		0.952
5		−7.416
6		1.695
7		−7.466
8		0.892
9		−5.000

Table 5. Relative energies of intermediates B with respect to A.

http://dx.doi.org/10.5772/intechopen.73664



Scheme 23. Mechanistic pathways for the formation of benzoxazole amides.

Entry number	Energy of reaction (kcal/mole)					
	Route 1			Route 2		
	C to D	D to D′	D′ to 2	C to E	E to E′	E′ to 2
1	−22.81	52.02	−79.23	52.23	−84.65	−17.60
2	−24.66	57.52	−81.42	55.53	−86.40	−17.70
3	−24.55	53.96	−81.50	52.12	−86.46	−17.75
4	−24.61	56.30	−79.75	54.34	−84.67	−17.72
5	−24.57	56.41	−80.15	53.78	−84.54	−17.56
6	−24.88	57.55	−79.68	55.48	−85.48	−17.02
7	−24.91	57.46	−80.33	55.33	−85.27	−17.84
8	−28.23	57.48	−81.85	52.68	−86.76	−18.52
9	−25.05	57.63	−80.15	55.72	−85.48	−17.81

Table 6. Energy of reaction through Route 1 and Route 2.

which is endothermic. The Route 1 is favored more on substitution with both electron withdrawing as well as donating groups at all positions, that is, *ortho*-, *meta*- and *para*-positions. Further, it is observed that the deacylation of chlorinated derivative of **C** at *ortho*-position is the most exothermic and the least at *meta*-position. This is because of higher conjugation at *ortho*- and *para*-positions where the electron withdrawing nature of chlorine favors the deacylation more. On the other hand, it is reverse for methylated derivative, that is, the reaction is most exothermic when substituted at *meta*-position and least at *ortho*-position. In case of methylated derivative, the electron donating nature of methyl group disfavors the deacylation when substituted at *ortho*- and *para*-positions where the conjugation is more. On dimethylation, both at *ortho*- and *para*-positions of **C**, the exothermic energy is further reduced. However, the exothermic energy for the dichlorination at *ortho*- and *para*-positions of **C** is less than that for substitution at *ortho*-position although it is higher than those for substitutions at *meta*- and *para*-positions.

The deacylation of **C** gives the deacylated intermediate **D** that has two acidic hydrogen atoms which are bonded to N2 and N4 nitrogen atoms as before. Considering the acidity of the hydrogen atoms, it is found that the hydrogen atom attached to N2 nitrogen atom is more acidic than that attached to N4 atom as is indicated by the Mulliken atomic charges of the hydrogen atoms (**Table 7**). This deprotonation of the proton of N2 atom initiates the attack of carbonyl oxygen O7 atom on *ortho*-carbon of the aryl group (the attack of *ortho*-carbon atom is discussed in detail later), leading to the formation of cyclized intermediate **D′** containing oxazole ring and the reduction of another molecule of DIB from +3 to +1 oxidation state of iodine by the attack of C1 carbon atom of **D** on the iodine of DIB. The attack of O7 atom on *ortho*-carbon and C1 atom on iodine of DIB is such that the two attacks are anti-periplanar. Therefore, the hydrogen attached to the *ortho*-carbon and iodine bonded to C1 atom lie on the same side of the molecular plane.

Upon cyclization to form oxazole ring of **D′**, the aromaticity of the benzene ring is lost as the hybridizations of the attacked *ortho*-carbon as well as that of C1 atom change from sp^2- to sp^3-hybridization. Hence, this cyclization process to give **D′** is endothermic. It is observed that the

Entry number	Mulliken charge of hydrogen atom bonded to	
	N2	N4
1	0.2982	0.2679
2	0.3002	0.2657
3	0.2984	0.2686
4	0.301	0.2654
5	0.3011	0.2653
6	0.3016	0.2675
7	0.3018	0.2671
8	0.3061	0.2658
9	0.3073	0.2671

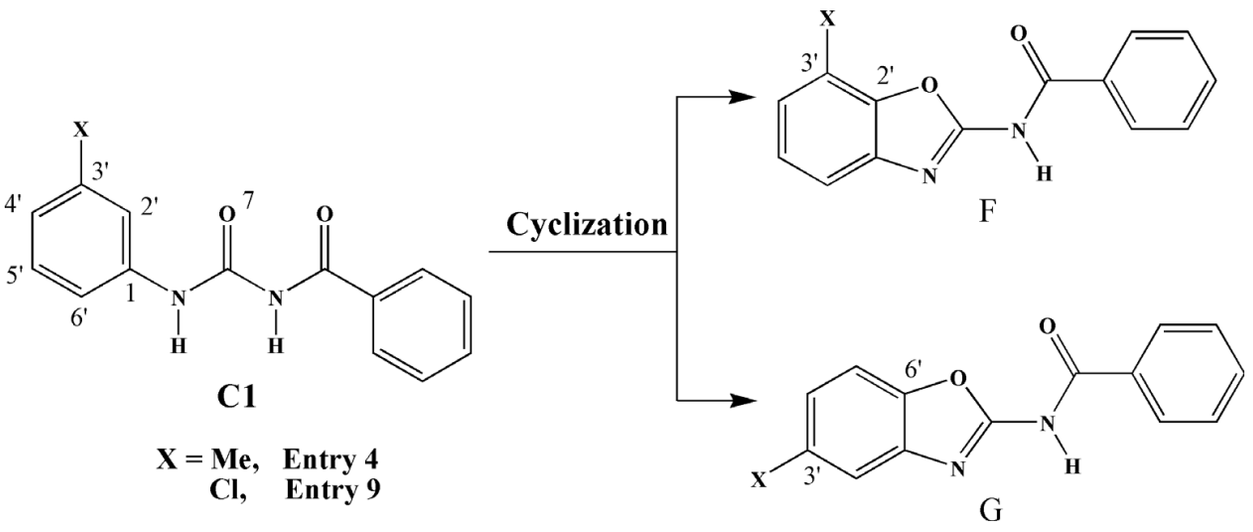
Table 7. Mulliken atomic charge of the hydrogen atoms attached to N2 and N4 atoms of D.

energy involved is affected by the substitution with electron withdrawing/donating groups at different positions of the benzene ring. For methyl-substituted derivative, the cyclization energy involved is greatest when substituted at *para*-position and least at *ortho*-position; while for chlorinated derivative, the energy involved is highest at *meta*-position and least at *para*-position.

The aromaticity is regained upon subsequent deprotonation of sp^3-hybridized *ortho*-carbon and bond breaking between C1 carbon and iodine giving the final product with the release of phenyl iodide and acetic acid. This aromatization to give benzoxazole derivative is exothermic (**Table 6**). For both electron-withdrawing chlorine and -donating methyl-substituted derivatives, the exothermic energy is highest when substituted at *ortho*-position and least at *meta*-position.

There is further interesting result from the reaction when there is substitution at the *meta*-position (3′-position) of the starting material as there are two possible products (**Scheme 24**) formed due to presence of two *ortho*-carbon atoms (2′ and 6′ carbon atoms) available for attack. The first product (**F**) is formed due to attack of O7 atom (initiated by deprotonation of N2 proton) on 2′ *ortho*-carbon atom while the second product (**G**) is formed due to attack on 6′ *ortho*-carbon. When considering the Mayer bond order between carbon and oxygen, the O7-C2′ bond of the first product (**F**) is stronger than the O7-C6′ bond of the second product (**G**) for both methylated and chlorinated derivative. However, the first product (**F**) is energetically slightly favored by 0.85 kcal/mole for the methylated derivative, while the second product (**G**) is favored by 0.35 kcal/mole for the chlorinated derivative, although in both derivatives the products have almost same energy. As the products have equivalent energies, it is inferred that both products may be formed for entry 4 (methylated derivative) and 6 (chlorinated derivative).

When *N*-substituted-*N*′-benzoylthioureas are reacted with diacetoxyiodobenzene (DIB) as catalyst, benzoxazole amides are formed; expected benzothiazoles or the decomposition products are not obtained. Unlike molecular iodine, DIB as catalyst renders the formation of C-O bond in benzoxazole moiety of substituted *N*-benzoxazol-2-yl-amides, instead of the expected C-S bond formation of benzothiazole moiety. DFT calculations showed the reaction followed through carbodiimide intermediate. The carbodiimide further undergoes a series of acylation, deacylation, and cyclization in tandem to give the final product, benzoxazole amides.



Scheme 24. Two possible products for the *meta*-substituted derivative.

Thus, the density functional calculations showed the reaction followed through carbodiimide intermediate formed by the oxidation of *N*′-benzoylthiourea by DIB. The carbodiimide intermediate thus formed undergoes a series of acylation and deacylation in tandem, leading to cyclization to form oxazole ring of substituted *N*-benzoxazol-2-yl-amide, due to C-O bond formation as a result of attack of carbonyl oxygen on *ortho*-carbon aryl moiety, instead of the expected C-S bond formation to give benzothiazole moiety.

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