One-Pot Synthesis of Five and Six Membered N, O, S-Heterocycles Using a Ditribromide Reagent

Ramesh Yella and Bhisma K. Patel*

Department of Chemistry, Indian Institute of Technology Guwahati, Assam 781 039, India

Received July 6, 2010

In a one-pot procedure, bromine less brominating reagent 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) has been utilized as an efficient desulfurizing agent for the construction of a library of heterocycles containing *N*, *O*, and *S* starting from aryl/alkyl isothiocyanates. In this approach, aryl/alkyl isothiocyanate reacts with *o-phenylenediamine (o*-PD), *o*-aminophenol, and *o*-aminothiophenol to form their monothiourea which on desulfurization with EDPBT led to the formation of corresponding 2-aminobenzimidazoles, 2-aminobenzoxazoles, and 2-aminobenzothiazoles, respectively. An interesting regioselectivity was observed for unsymmetrical thiourea having a naphthyl moiety on the one side and an *ortho* amino or an *ortho* hydroxy phenyl group on the other side giving a completely different product which is mainly dependent on the nature of the nucleophiles (−OH or $-NH_2$). Further, the *bis*-thioureas resulted from the aliphatic 1,2-diamine with 2 equiv of aryl isothiocyanates on treatment with EDPBT gave imidazolidenecarbothioamides, whereas *bis*-thioureas resulted from aromatic 1,2-diamine yielded benzimidazoles with concurrent expulsion of an isothiocyanate unit. This method is simple and applied to various substrates which are amenable to bromination that reveals the desulfurizing ability of EDPBT predominating over its brominating ability. Finally, the spent reagent EDPDB can be recovered, regenerated, and reused without any loss of activity.

Introduction

Tandem reactions involving C−N, C−O, and C−S bond formation are one of the vital tools in combinatorial chemistry for the construction of a library of small molecules. Generally, they involve numerous chemical transformations in one-pot, and the advantages associated with these reactions are minimal workup and minimization of waste generation.[1] The use of molecular bromine is awkward because of its hazardous nature; thus, special care has to be taken for its uses, storage, and transport. To overcome this problem, several bromine less brominating reagents, namely, tribromides, have been developed.[2,3] Among various tribromides, benzyltrimethylammonium tribromide (BTMATB)[3a] and [Bmim]Br_3[3b] have been employed for the construction of 2-aminobenzothiazoles. Over the past decade, we have successfully replaced corrosive and toxic molecular bromine with various organic ammonium tribromides, namely, tetrabutylammonium tribromide, for various synthetically useful organic transformations.[2a,b,4] However, the process is expensive particularly for large scale reactions because of their inherent phase transfer property and, beside others, recycling of the spent reagent. To alleviate some of the problem associated with the existing tribromides, we recently designed the first ditribromide reagent, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT)[5a,b] which is superior to most tribromides and has several advantages over molecular bromine and other known tribromides. This reagent can be easily prepared by heating pyridine and 1,2-dibromoethane in the ratio of 2:1. The resultant 1,1′-(ethane-1,2-diyl)dipyridinium ditribromide (EDPDB)[5a,b] salt on treatment with KBr as the bromide source and Oxone as the oxidizing agent gave the ditribromide reagent 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) in excellent yield.[5a,b] This reagent also has been employed as catalyst/reagent for acylation of alcohols,[5c] regioselective enolate addition to 9-phenyl-9*H*-xanthene-9-ol,[5d,e] in the synthesis of various thiazolidene-2-imine derivatives,[5f,g] synthesis of 1,4-dithiins and 1,4-benzodithiins,[5i] and construction of 1,3-oxathiolan-2-ylidenes[5j] and urazole to triazonediones.[5k] Very recently, we have utilized this reagent to reveal the formation of an *anti*-Hugerschoff product from an aryl-*sec*-alkyl unsymmetrical thiourea having a thioamido guanidino moiety[6] and not the expected Hugerschoff product 2-aminobenzothiazole as has been reported.[3a,b]

In continuation to our ongoing research in heterocyclic synthesis, we have been exploring the thiophilic nature of diacetoxyiodobenzene (DIB) in various organic transformations.[7] In spite of its superiority; the expensive nature of the hypervalent iodine reagent is the major obstacle for large scale requirements. As a part of a continuing effort in our laboratory toward the development of newer methods for the expeditious synthesis of biologically relevant heterocyclic compounds,[5e−g,6b,7b] we became interested in the possibility of developing a novel and efficient method to construct various *N*, *O*, *S* heterocycles utilizing the thiophilic property of EDPBT **3**.

Benzimidazoles are important structural motifs in medicinal chemistry, which involve nearly one-quarter of the top-100 selling drugs. Specifically, 2-amino benzimidazoles can

* To whom correspondence should be addressed. E-mail: patel@iitg.ernet.in.

10.1021/cc100124q © 2010 American Chemical Society
Published on Web 08/18/2010

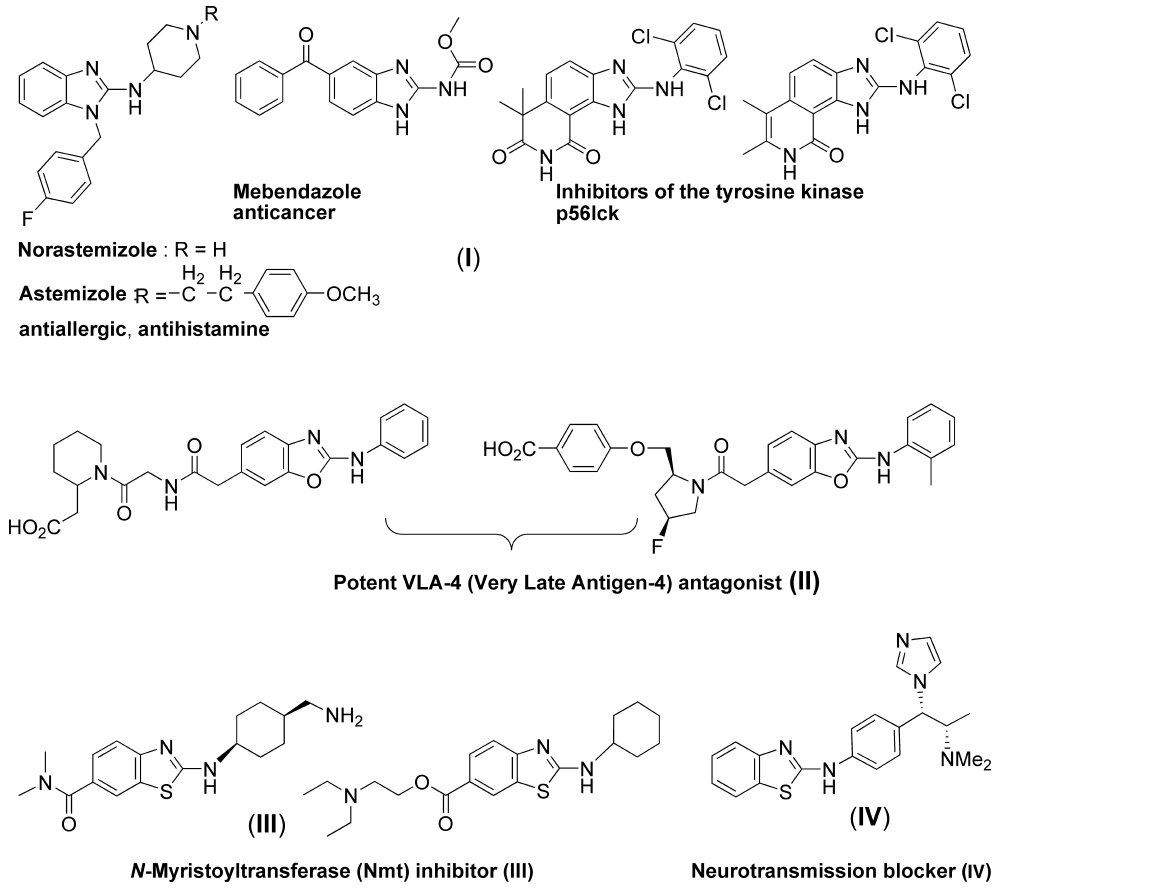


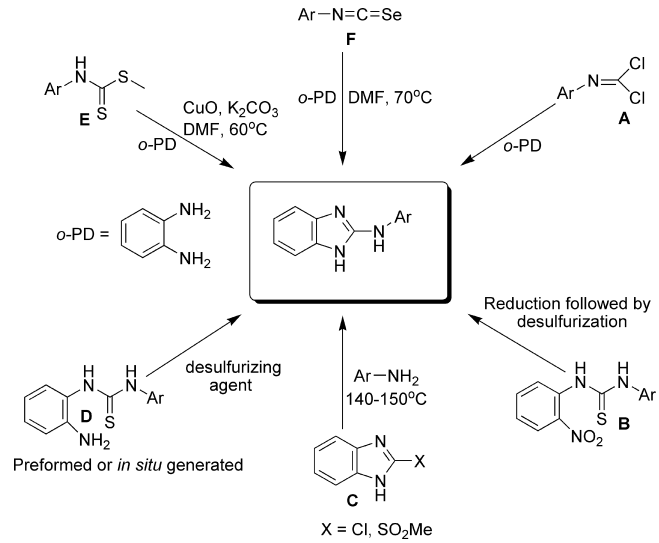
Figure 1. Bioactive benzofused *N*, *O*, *S* heterocycles.

be found in a number of biologically active molecules.[8] Several compounds from this class have been used as anticancer,[9a] antihistamine,[9b] and antiviral agents.[9c−e] Some examples of pharmaceutically interesting benzofused *N*, *O*, *S* heterocycles[9−11] are shown in Figure 1 (I−IV).

The conventional methods for the preparation of 2-aminobenzimidazoles are by the reaction of arylcarbonimidoyl dichlorides which in turn are prepared by the chlorination of aryl isothiocyanate, with *o*-phenylenediamines in a suitable solvent **A**[12a] (Scheme 1), reductive cyclization of nitrothioureas **B**[12b] (Scheme 1), S_NAr reaction of chlorobenzimidazole or methylsulfonyl benzimidazole with an amine nucleophiles **C**[12c,d] (Scheme 1) under solvent-free conditions. The most commonly adopted method for the synthesis of 2-aminobenzimidazole involves the cyclodesulfurization of a preformed or in situ generated monothioureas **D**. The reported desulfurizing agents include carbodiimides,[13a,b] tosylchloride,[13c] methyl iodide,[13d] mercury(II) oxide,[13e] mercury(II) chloride,[13f] and DIB.[7b] In addition to this, copper(I)/(II) salts have also been employed for the condensation of dithiocarbamate **E** with *o*-phenylenediamine (*o*-PD) at high temperature.[13g,h] Very recently, Xie et al. reported the synthesis of benzimidazoles from a toxic isoselenocyanates in dimethylformamide (DMF) at high temperature **F**.[13i]

As part of our interests in the chemistry of heterocyclic compounds and development of newer methods by replacing the toxic reagents with greener reagents,[6,14] we herein disclose the thiophilicity/desulfurizing ability of bromineless brominating reagent (EDPBT) **3** in the synthesis of a

Scheme 1. Available Synthetic Methods for the Preparation of 2-Aminobenzimidazole(**A**−**F**)[12,13]



spectrum of biologically active benzofused *N*, *O*, *S* heterocycles and study the regioselectivity of its formation.

Results and Discussion

In an initial experiment, the in situ generated thiourea, obtained by treating phenyl isothiocyanate **1a**[7b,14c,d] (1 equiv) with *o*-phenylenediamine **2a** (*o*-PD) (1 equiv), followed by the addition of Et_3N (3 equiv) and subsequent treatment with EDPBT **3** (0.5 equiv) in THF afforded the product 2-aminobenzimidazole **4a** in 81% yield. A mechanism as shown

Scheme 2. Proposed Mechanism for the Formation of Benzimidazole/Benzoxazole and Benzothiazole

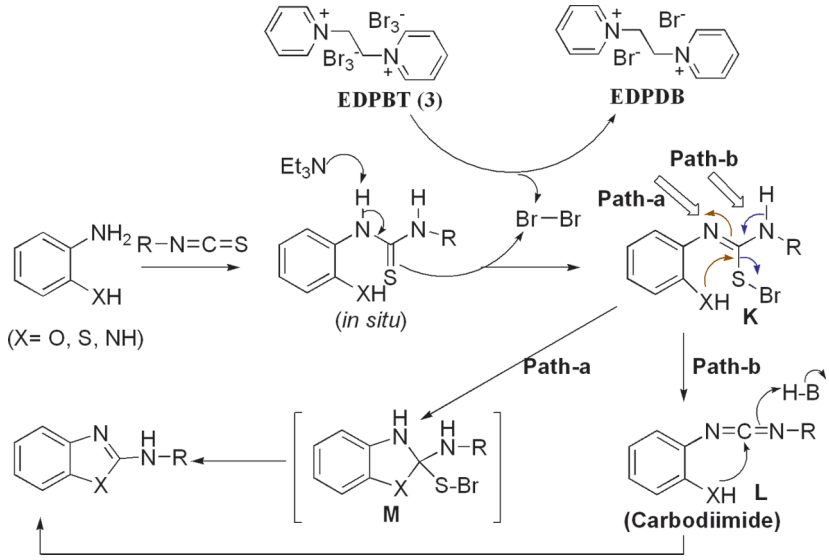
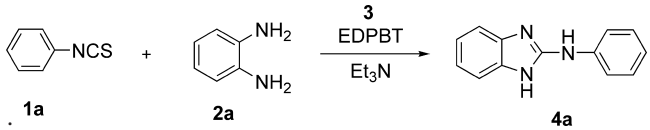


Table 1. Screening of Different Bromine Equivalents Using CH_3CN Solvent



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

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

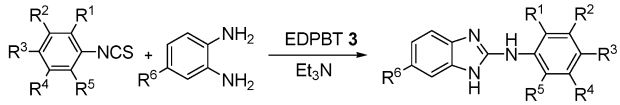
in Scheme 2 can be proposed to account for the formation of the product **4a**. The soft sulfur atom of the in situ generated thiourea first attacks on the thiophilic bromine forming a S−Br type of species **K** (Scheme 2).[5h] An intramolecular attack of the amino nucleophile (where X = NH) as shown in path-a (Scheme 2) should yield the intermediate **M** which on elimination would give the desired benzimidazole **4a**. Alternatively, a reductive elimination as shown in path-b to form the intermediate carbodiimide **L** cannot be ruled out. Subsequent intramolecular attack of the *o*-amino group onto carbodiimide would generate the desired product **4a**.

Among the various solvents tested such as CH_2Cl_2, Dioxane, tetrahydrofuran (THF), CH_3CN, MeOH, DMF, and dimethylsulfoxide (DMSO), solvents CH_2Cl_2 and CH_3CN were found equally effective in giving good yields (86%, 90%) in short reaction time but for convenience CH_3CN was chosen for all other reactions. Further, the efficacy of the reagent/method was compared with some known tribromides including molecular bromine (Table 1, entries 3−8) using Et_3N as the base and CH_3CN as the solvent. As can be seen from Table 1, irrespective of the brominating reagents used, the formation of the 2-aminobenzimidazole **4a** is the predominant product. On the basis of the overall isolated yield (Table 1), EDPBT **3** was found to be the best among the various reagents assessed. In addition to this, the reagent is a stable crystalline solid, easy to prepare, handle, and maintain the desired stoichiometry. Further, the advantage of storage, transport, and recyclability of the spent reagent makes this reagent superior to toxic, fuming liquid bromine. Thus, further supporting our argument about the superiority of the reagent.[6c]

Following this protocol a library of benzimidazoles (**4a**−**4l**) were synthesized in good yields as shown in Table 2. It was observed that aryl isothiocyanates having moderately electron withdrawing groups (such as halide groups) (Table 2, entries **1b**-**1f**) as well as electron donating groups (such as alkyl groups) (Table 2, entries **1g**-**1i**) reacts efficiently with various aromatic 1,2-diamines possessing electron withdrawing substituents (-NO_2) (Table 2, entry **2b**) or electron donating (Me)(Table 2, entry **2c**) giving corresponding benzimidazoles **4c**, **4l**, **4e**, and **4i** in good yields as shown in Table 2. The success of this strategy mainly lies on the selective formation of monothiourea resulted from 1 equiv of isothiocyanate **1** and *o*-phenylenediamine **2**.

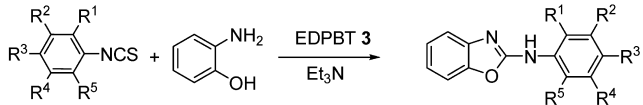
The successful synthesis of benzimidazoles prompted us to synthesize another interesting class of compound, namely, benzoxazole. In particular, 2-aminobenzoxazole moiety is a popular building block for the construction of pharmaceutically important compounds[10a] for instance, as shown in Figure 1 (entry II). These classes of compounds are vital as drug candidates, and their use is currently explored for the treatment of diseases such as HIV, neurodegeneration, and inflammation.[15] The most commonly adopted method for the synthesis of 2-aminobenzoxazoles is by the cyclodesulfurization of preformed thiourea having an *o*-phenolic group. The reported cyclodesulfurization agents includes, NiO,[16a] HgO,[16b−d] $AgNO_3$,[17a,b] KO_2[18a,b] salts of transition metals,[18c] and dicyclohexylcarbodiimide (DCC),[18d] aq H_2O_2,[18e] DIB.[7b] More recently it has been prepared by the direct amination of benzoxazoles using Cu-catalyst.[18f] Because of the toxicity and high cost associated with reported reagents, they cannot

Table 2. Reaction of *o*-Phenylenediamine **2** (*o*-PD) with Isothiocyanates **1** Using EDPBT[a]

Substrate		Product[b]	Yield (%)[c]
			
1[a-i] + **2[a-c]**	EDPBT **3**, Et_3N	**4[a-l]**	
1a, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H;		**2a** (R^6 = H)	**4a**	90%
1b, R^1 = Cl, R^2 = H, R^3 = H, R^4 = H, R^5 = H;		**2a** (R^6 = H)	**4b**	88%
1b, R^1 = Cl, R^2 = H, R^3 = H, R^4 = H, R^5 = H;		**2b** (R^6 = NO_2)	**4c**	76%
1c, R^1 = H, R^2 = Cl, R^3 = H, R^4 = H, R^5 = H;		**2a** (R^6 = H)	**4d**	80%
1c, R^1 = H, R^2 = Cl, R^3 = H, R^4 = H, R^5 = H;		**2c** (R^6 = Me)	**4e**	81%
1d, R^1 = H, R^2 = H, R^3 =Cl, R^4 = H, R^5 = H;		**2a** (R^6 = H)	**4f**	83%
1e, R^1 = H, R^2 = H, R^3 = Br, R^4 = H, R^5 = H;		**2a** (R^6 = H)	**4g**	79%
1f, R^1 = H, R^2 = H, R^3 = I, R^4 = H, R^5 = H;		**2a** (R^6 = H)	**4h**	82%
1g, R^1 = H, R^2 = H, R^3 = Me, R^4 = H, R^5 = H;		**2c** (R^6 = Me)	**4i**	84%
1h, R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, R^5 = H		**2a** (R^6 = H);	**4j**	77%
1i, R^1 = H, R^2 = H, R^3 = OMe , R^4 = H, R^5 = H;		**2a** (R^6 = H);	**4k**	75%
1i, R^1 = H, R^2 = H, R^3 = OMe, R^4 = H, R^5 = H;		**2b** (R^6 = NO_2)	**4l**	79%

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

Table 3. Reaction of *o*-Aminophenol **5** with Isothiocyanates **1** Using EDPBT[a]

Substrate		Product[b]	Yield (%)[c]
			
1[a,c,e,f,h,i-k] + **5**	EDPBT **3**, Et_3N	**6[a-h]**	
1a, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H;			**6a**	82%
1c, R^1 = H, R^2 = Cl, R^3 = H, R^4 = H, R^5 = H;			**6b**	85%
1e, R^1 = H, R^2 = H, R^3 = Br, R^4 = H, R^5 = H;			**6c**	87%
1f, R^1 = H, R^2 = H, R^3 = I, R^4 = H, R^5 = H;			**6d**	81%
1h, R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, R^5 = H;			**6e**	79%
1i, R^1 = H, R^2 = H, R^3 = OMe , R^4 = H, R^5 = H;			**6f**	78%
1j, R^1 = Me, R^2 = H, R^3 = Me, R^4 = H, R^5 = H;			**6g**	80%
1k, R^1 = Me, R^2 = H, R^3 = H, R^4 = H, R^5 = Me;			**6h**	82%
1l, Benzyl isothiocyanate;			**6i**	69%
1m, Cyclohexyl isothiocyanate;			**6j**	67%

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

be applied for large scale reactions. Therefore we explored the above strategy of benzimidazoles synthesis for the synthesis of benzoxazole as shown in Table 3.

The in situ generated monothiourea resulted from aryl isothiocyanate **1a** (Scheme 2) and *o*-amino phenol **5** when treated with 0.5 equiv of EDPBT **3** gave the desired *N*-2-phenyl-1,3-benzoxazol-2-amines **6a** in excellent yield. The

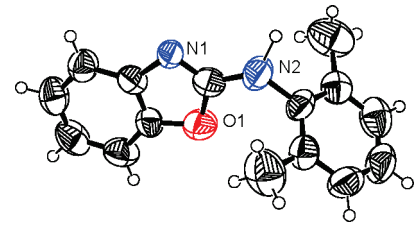
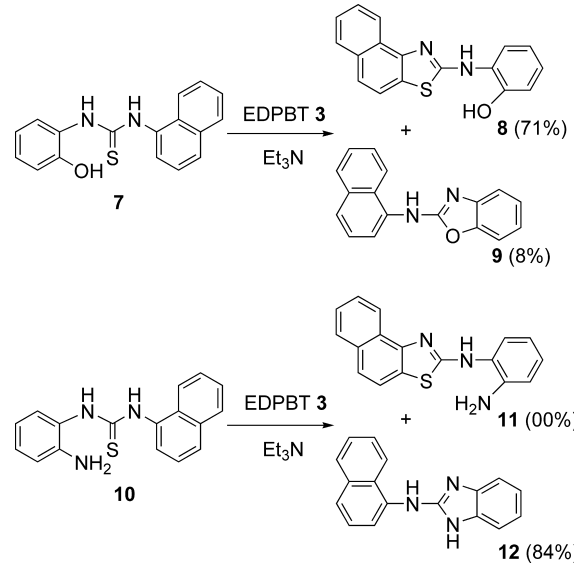


Figure 2. ORTEP view with the atomic numbering scheme of **6h**.[19a]

Scheme 3. Differential Reactivity of Naphthyl-Phenyl Thiourea **7** and **10**



mechanism is expected to be similar to the above (Scheme 2) proposed mechanism. Several aminobenzoxazole derivatives (**6b**−**6j**) have been successfully prepared from the isothiocyanates **1** substituted with electron-poor (Table 3, entries **1c**, **1e**, **1f**) and rich substituents (Table 3, entries **1h**-**1k**) in excellent yields in shorter reaction times as shown in Table 3. The structure of the *N*-2-(2,6-dimethylphenyl)-1,3-benzoxazol-2-amine **6h** has been further confirmed by X-ray crystallography (Figure 2).[19a] In addition to aryl isothiocyanates, reactions of alkyl isothiocyanates for instance, benzyl isothiocyanate **1l**, and cyclohexyl isothiocyanate **1m** also proceeded smoothly to give rise to their corresponding aminobenzoxazoles **6i** and **6j** in good yields.

A noteworthy aspect is that the unsymmetrical naphthyl-hydroxyphenylthiourea **7** generated from the 1-napthyl isothiocyanate and 2-aminophenol **5**, when treated with EDPBT, gave the 2-(naphtho[1,2-*d*]thiazol-2-ylamino)phenol **8** as the major product rather than the expected *N*-(naphthalen-1-yl)benzo[*d*]oxazol-2-amine **9** (Scheme 3). The predominate formation of benzothiazole **8** can be in part because of the intramolecular electrophilic substitution of the activated naphthyl ring, and poor nucleophilicity of −OH group. This observation is analogous to Hugerschoff reaction known since 1901.[20] To ascertain the later effect, that is, nucleophilicity plays the role in the product formation, the −OH nucleophile was replaced with a $-NH_2$ nucleophile by designing the substrate **10**. Interestingly, the substrate **10** having an amino group under an identical condition gave exclusively *N*-(naphthalen-1-yl)-

1*H*-benzo[*d*]imidazol-2-amine **12** without giving any traces of benzothiazole **11** which is further confirmed by its mass spectra,[13a] thus supporting our assumption that nucleophilicity is equally important in deciding the course of the reaction (Scheme 3).

In another set of experiments, the scope of this strategy was applied to the synthesis of benzothiazoles. Benzothiazoles are privileged organic compounds because of their recognition in biological and therapeutic activities. Specifically, 2-aminobenzothiazoles are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development for the treatment of diabetes,[21a] epilepsy,[21b−d] inflammation,[22a] amyotrophic lateral sclerosis,[22b] analgesia,[22c] tuberculosis,[22d] and viral infections.[22e] Some of representative examples of biologically important aminobenzothiazoles are shown in Figure 1 (III and IV).[10b−e,11]

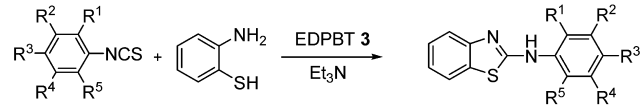
The Hugherschoff reaction is known to produce 2-aminobenzothiazole from 1,3-diaryl thiourea and liquid bromine in chloroform.[20] This reaction works well for symmetrical thioureas giving exclusively one product.[3a] But when the same reaction is performed using unsymmetrical 1,3-diaryl thioureas there is always uncertainty as to on which aryl ring the intramolecular electrophilic substitution would take place to give aminobenzothiazole. To improve the selectivity in product formation, intramolecular ligand assisted copper and palladium catalyzed C−S bond formation between arylhalide and thiourea functionality has been employed for the synthesis of aminobenzothiazole.[23] So far only two methods have been reported using desulfurization strategy[24] for the preparation of aminobenzothiazoles.

The in situ generated monothiourea from aryl isothiocyanate and *o*-aminothiophenol **13** (Scheme 2), when treated with 0.5 equiv of EDPBT **3**, afforded the desired aminobenzothazole **14a** in good yield. The proposed mechanism is similar to that of benzimidazole and benzoxazole as shown in Scheme 3. Various benzothiazoles **14b**-**14f** were obtained under our standard experimental conditions, irrespective of the nature of the substituents attached to the isothiocyanates (Table 4, entry **1e**, **1g**, **1i**, **1j**, and **1k**). Further, the structure of **14d** was confirmed by X-ray crystallography (Figure 3).[19b] In addition to aryl isothiocyanates, alkyl isothiocyanate such as cyclohexyl isothiocyanate **1m** (Table 4) also proceeded smoothly to give product **14g**.

Benzoxazines are yet another member of the heterocycle family which have been synthesized by an analogous desulfurization strategy using expensive DCC[18d] and DIB[7b] as the desulfurizing agent. Another literature method in the preparation of benzoxazines involves an arduous tandem *aza*-Wittig/heterocumulene-mediated annulation strategy.[25] A series of these important heterocycles **16a**−**16f** were prepared under our optimized experimental conditions as shown in Table 5. The structure of the product **16f** has been confirmed by X-ray crystallography (See Supporting Information).

There exist several possibilities for bis-thiourea when separated by two carbon spacer. The S−Br form on one side could be attacked by any one of the two nitrogen nucleophiles from the adjacent thiourea either giving a five membered or a seven membered ring. Alternatively, sulfur atom from the adjacent thiourea can attack to give a seven membered ring or form an eight membered disulfide ring. However, hypervalent iodine mediated reaction of similar substrate gave 1-imidazolidinecarbothioamide as the exclusive product.[7b] Thus we were interested to see if the reagent EDPBT behaves similar to the hypervalent iodine DIB or gives a different product. The aryl isothiocyanate **1** (2 equiv) was treated with

Table 4. Reaction of *o*-Aminothiophenol **13** with Isothiocyanates **1** Using EDPBT[a]

Substrate	Product[b]	Yield (%)[c]
		
1[a,e,g,i-k] + **13** (EDPBT **3**, Et_3N)	**14[a-f]**	
1a, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**14a**	81%
1e, R^1 = H, R^2 = H, R^3 = Br, R^4 = H, R^5 = H;	**14b**	84%
1g, R^1 = H, R^2 = H, R^3 = Me, R^4 = H, R^5 = H;	**14c**	80%
1i, R^1 = H, R^2 = H, R^3 = OMe , R^4 = H, R^5 = H;	**14d**	74%
1j, R^1 = Me, R^2 = H, R^3 = Me, R^4 = H, R^5 = H;	**14e**	72%
1k, R^1 = Me, R^2 = H, R^3 = H, R^4 = H, R^5 = Me;	**14f**	74%
1m, Cyclohexyl isothiocyanate;	**14g**	68%

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

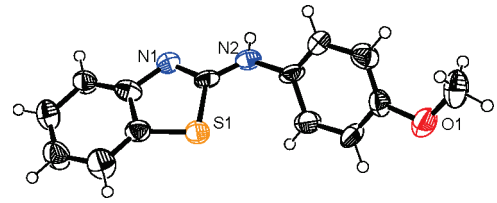
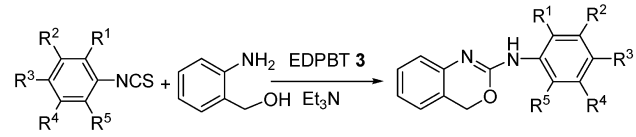


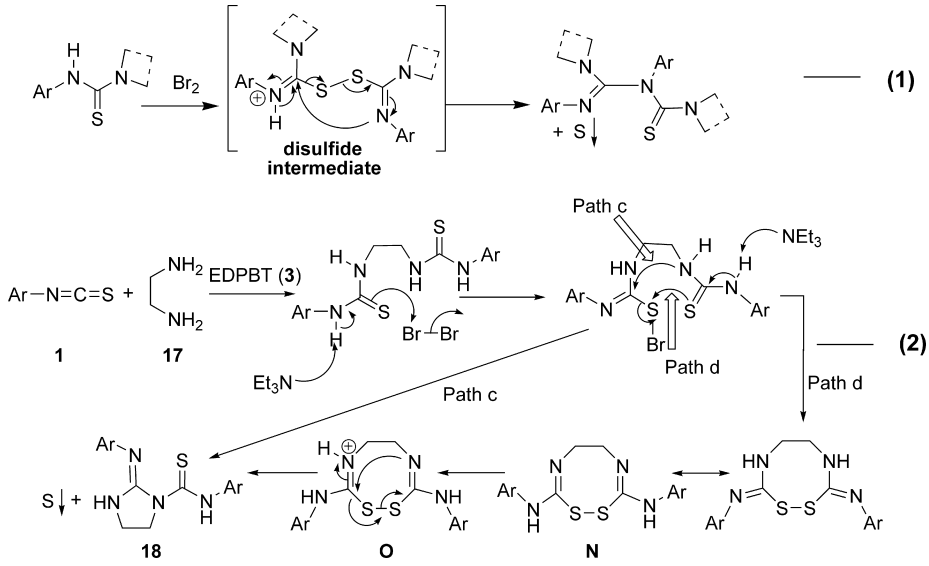
Figure 3. ORTEP view with the atomic numbering scheme of **14d**.[19b]

Table 5. Reaction of *o*-Aminobenzyl Alcohol **15** with Isothiocyanates **1** Using EDPBT[a]

Substrate	Product[b]	Yield (%)[c]
		
1[a,e,f,h-j] + **15** (EDPBT **3**, Et_3N)	**16[a-f]**	
1a, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**16a**	76%
1e, R^1 = H, R^2 = H, R^3 = Br, R^4 = H, R^5 = H;	**16b**	72%
1f, R^1 = H, R^2 = H, R^3 = I, R^4 = H, R^5 = H;	**16c**	75%
1h, R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**16d**	70%
1i, R^1 = H, R^2 = H, R^3 = OMe, R^4 = H, R^5 = H;	**16e**	74%
1j, R^1 = Me, R^2 = H, R^3 = Me, R^4 = H, R^5 = H;	**16f**	70%

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

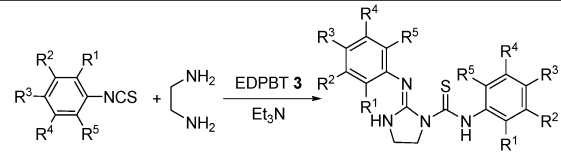
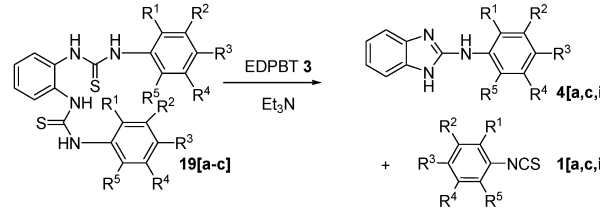
Scheme 4. Alternative Mechanism for the Formation of 1-Imidazolidinecarbothioamide



ethylenediamine **17** (1 equiv) to give *bis*-thiourea which on reaction with EDPBT gave excellent yield of imidazolidinecarbothioamide **18a** (Scheme 4). This is perhaps the most important part of this methodology since there are few synthetic methods available for 1-imidazolidinecarbothioamide. Only three methods have been reported so far for the synthesis of this class of compounds. The first is the desulfurization strategy of *bis*-thioureas using toxic mercury salt[26a] or expensive hypervalent iodine (DIB)[7b] and the other involves the treatment of 2-methylamino-2-imidazoline with isothiocyanate.[26b] Because of limited synthetic methods available these compounds are relatively unexplored in medicinal chemistry but some are known to be valuable insecticides, usually for the control of Epilachna varivestis.[27] A plausible mechanism for the formation of imidazolidinecarbothioamide involves the attack of the internal nitrogen of the adjacent thiourea on to the iminium carbon of the other thiourea displacing S−Br as shown in Scheme 4, eq 2, path c. This mechanism is similar to the hypervalent iodine mediated reaction recently reported by us.[7b] Recently we have reported the formation of an *anti*-Hugerschoff product from an unsymmetrical aryl-alkyl thiourea which is believe to go via an iminium disulfide intermediate (Scheme 4, eq 1). One of the imine nitrogen then attacks on to the adjacent iminium carbon with the concurrent expulsion of the elemental sulfur to give the desired product (Scheme 4, eq 1). This mechanism has been supported by a crossover experiment.[6a] Thus, taking cues from the above mechanism, the following mechanism involving an eight membered disulfide **N** intermediate cannot be ruled out (Scheme 4, eq 2). One of the iminium nitrogen undergo protonation which is attacked by the other imine nitrogen **O** in an intramolecular fashion followed by the expulsion of sulfur to yield the stable product **18a** shown in Scheme 4, eq 2.

After successfully synthesizing imidazolidinecarbothioamide, the strategy was applied to electron poor (Table 6, **1b**, **1c**, **1e**, and **1f**) and electron rich (Table 6, **1h**-**1j**) isothiocyanates giving the products **18b**-**18h** in good to excellent yields, as shown in Table 6. The structure of **18f** was confirmed by X-ray crystallography (See Supporting Information).

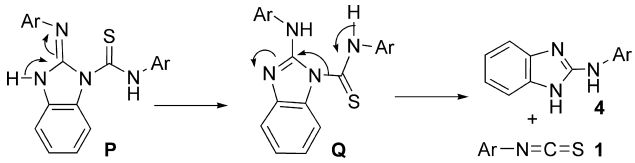
Table 6. Synthesis of Imidazolidenecarbothioamides and Benzimidazole[a]

Substrate	Product[b]	Yield (%)[c]
		
1[a-c, e-g,h-j] + **17** (EDPBT **3**, Et_3N)	**18[a-h]**	
1a, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**18a**	78%
1b, R^1 = Cl, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**18b**	83%
1c, R^1 = H, R^2 = Cl, R^3 =H, R^4 = H, R^5 = H;	**18c**	81%
1e, R^1 = H, R^2 = H, R^3 = Br, R^4 = H, R^5 = H;	**18d**	77%
1f, R^1 = H, R^2 = H, R^3 = I, R^4 = H, R^5 = H;	**18e**	75%
1h, R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**18f**	79%
1i, R^1 = H, R^2 = H, R^3 = OCH_3, R^4 = H, R^5 = H;	**18g**	77%
1j, R^1 = Me, R^2 = H, R^3 = Me, R^4 = H, R^5 = H;	**18h**	80%
		
19[a-c] (EDPBT **3**, Et_3N)	**4[a,c,i]** + **1[a,c,i]**	
19a, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**4a**	91%
19b, R^1 = H, R^2 = Cl, R^3 = H, R^4 = H, R^5 = H;	**4c**	90%
19c, R^1 = H, R^2 = H, R^3 = OMe, R^4 = H, R^5 = H;	**4i**	92%

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

We were further interested to see if an aromatic 1,2-diamine such as *o*-phenylenediamine **2** (*o*-PD) behaves similar to the aliphatic 1,2-diamine **17**. Interestingly, the *bis*-thiourea obtained by the treatment of *o*-phenylenediamine **2** (*o*-PD) and aryl isothiocyanate **1** gave benzimidazole **4** and

Scheme 5. Reactivity of Aromatic 1,2-*bis*-Thiourea with EDPBT



aryl isothiocyanate **1** instead of the expected imidazolidinecarbothioamide. Various *bis*-thioureas (Table 6, entry **19a**−**c**) were reacted under the present experimental condition and in each case a benzimidazole **4** (Table 6, **4a**, **4c**, and **4i**) and an aryl isothiocyanate **1** (Table 6, **1a**, **1c**, and **1i**) were isolated. In this case the intermediate imidazolidinecarbothioamide **P** (Scheme 5) which is non-aromatic in character rapidly loses a molecule of isothiocyanate **1** giving benzimidazole **4**. The driving force for this reaction seems to be the gain in the aromatic character of the product benzimidazole because of loss of an isothiocyanate from the intermediate **Q** (Scheme 5).

Conclusion

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

Experimental Section

General Procedure for Preparation of *N*-phenyl-1*H*-benzo[*d*]imidazol-2-amines (4a). To a solution of phenyl isothiocyanate **1a** (270 mg, 2 mmol.) in CH_3CN (6 mL) was added *o*-phenylenediamine **1a** (216 mg, 2 mmol), at room temperature. Formation of monothiourea was observed within 30 min as judged from thin layer chromatography (TLC). To this reaction mixture was added triethylamine (835 μL, 6 mmol) followed by portion wise addition of EDPBT (666 mg, 1 mmol) over a period of 10−15 min. The reaction was kept at room temperature for stirring, and complete conversion to benzimidazole **4a** was observed within 30 min with concomitant precipitation of sulfur as can be judged from TLC and disappearance of orange color of EDPBT. After completion of the reaction, the solvent was evaporated and the reaction mixture was admixed with ethyl acetate (15 mL) and water 8 mL. The water layer containing the spent reagent 1,1′-(ethane-1,2-diyl)dipyridinium ditribromide (EDPDB) was collected separately for recycling. The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The pure product was isolated by silica gel column (1:4 ethylacetate/hexane) to give the product **4a**[7b,13c,i] (377 mg, 90%). Mp 150−152 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 6.29 (brs, 1H), 6.92 (t, J = 7.6 Hz, 1H), 7.04 (m, 2H), 7.23 (m, 2H), 7.30 (m, 2H), 7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 112.7, 118.4, 120.7, 122.0, 129.1, 137.4, 140.0, 151.4; IR (KBr) 3053, 2917, 1635, 1603, 1573, 1531, 1498, 1456, 1270, 1233, 1184, 1045, 898, 754, 743 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{11}N_3$: C 74.62, H 5.30, N 20.08; found C 74.66, H 5.32, N 20.11.

Spectral Data for Selected Compounds. *N*-(2-Chlorophenyl)-4-nitro-1*H*-benzo[*d*]imidazol-2-amine (4c). Mp 213-215 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 4.58 (s, 1H), 7.01 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 8.0 Hz, 2H), 8.02 (m, 1H), 8.25 (s, 1H), 8.63 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 108.0, 111.8, 116.6, 119.4, 121.2, 122.3, 127.1, 128.5, 135.3, 141.0, 153.2; IR (KBr) 3374, 3312, 2924, 1609, 1567, 1532, 1468, 1450, 1362, 1324, 1124, 1070, 1026, 869, 820, 737 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_9ClN_4O_2$: C 54.09, H 3.14, N 19.41; found C 54.06, H 3.16, N 19.44.

***N*-(3-Chlorophenyl)-6-methyl-1*H*-benzo[*d*]imidazol-2-amine (4e).** Mp 95−97 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 2.41 (s, 3H), 4.62 (brs, 1H), 6.92 (t, J = 8.0 Hz, 2H), 7.21 (m, 3H), 7.44 (m, 1H), 7.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 21.6, 112.5, 112.8, 116.4, 118.0, 121.8, 122.4, 130.2, 130.9, 134.4, 134.6, 136.1, 141.2, 150.1; IR (KBr) 2921, 1648, 1594, 1558, 1478, 1275, 1094, 912, 856, 798, 770, 678, 594 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{12}ClN_3$: C 65.25, H 4.69, N 16.30; found C 65.21, H 4.73, N 16.22.

***N*-2-(2-Methoxyphenyl)-1,3-benzoxazol-2-amine (6e).** Mp 106 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.89 (d, J = 8.0 Hz, 1H), 7.00−7.13 (m, 3H), 7.22 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H,), 7.66 (brs, 1H), 8.41 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 109.1, 110.2, 117.6, 121.5, 122.5, 123.7, 124.3, 127.6, 142.9, 147.5, 147.9, 157.9; IR (KBr) 3388, 2926, 1638, 1606, 1578, 1528, 1456, 1346, 1254, 1242, 1213, 1165, 1115, 982, 740 cm^{-1}; HRMS (ESI) *m*/*z* 241.1328 (MH^+); elemental analysis calcd (%) for $C_{14}H_{12}N_2O_2$: C 69.99, H 5.03, N 11.66; found C 69.94, H 5.07, N 11.61.

2-(Naphtho[1,2-d]thiazol-2-ylamino)phenol (8). Mp 216−218 °C, ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 6.92−6.99 (m, 3H), 7.50−7.65 (m, 3H), 7.74 (t, J = 7.2 Hz, 1H), 7.90 (t, J = 7.0 Hz, 1H), 8.12 (d, J = 7.2 Hz, 1H), 8.52 (t, J = 7.2 Hz, 1H), 9.41 (brs, 1H), 10.2 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 115.6, 117.8, 118.8, 119.0, 121.4, 122.7, 122.8, 124.1, 124.5, 125.1, 125.4, 127.0, 127.9, 130.9, 146.1, 162.9; IR (KBr) 3418, 2255, 2128, 1649, 1542, 1456, 1393, 1368, 1048, 1025, 1002, 826, 764 cm^{-1}; HRMS (ESI): *m*/*z* 293.3685 (MH^+); elemental analysis calcd (%) for $C_{17}H_{12}N_2OS$:C 69.84, H 4.14, N 9.58, S 10.97; found C 69.88, H 4.11, N 9.66, S 10.92.

Benzothiazol-2-yl-(2,4-dimethyl-phenyl)-amine (14e). Mp 135 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.37 (s, 3H), 7.10 (m, 3H), 7.26 (m, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 21.2, 118.9, 121.0, 122.0, 125.2, 126.2, 128.0, 132.2, 133.3, 135.9, 136.9, 152.0, 168.2; IR (KBr) 3063, 2851, 1618, 1607, 1568, 1449, 1268, 1217, 1126, 906 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{14}N_2S$:C 70.83, H 5.55, N 11.01, S, 12.61; found C 70.79, H 5.58, N 11.05, S, 12.66.

***N*-(2,4-dimethylphenyl)-4*H*-benzo[*d*] [3,1]oxazin-2-amine (16f).** Mp 163−166 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.30 (s, 3H), 5.14 (s, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.92−6.99 (m, 4H), 7.15 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 21.0, 67.8, 120.1, 120.6, 122.5,123.8, 124.0, 127.2, 129.2, 130.9, 131.3, 134.1, 135.8, 141.2, 152.5; IR (KBr) 2976, 2917, 2865, 1680, 1650, 1598, 1484, 1457, 1402, 1305, 1268, 1251, 1206, 1251, 1206, 1123, 1031, 908, 831,756 cm^{-1}; HRMS (ESI) m/z 253.1348 (MH^+); elemental analysis calcd (%) for $C_{16}H_{16}N_2O$: C 76.16, H 6.39, N 11.10; C 76.19, H 6.42, N 11.04.

2-(2-Methoxyphenylimino)-*N*-(2-methoxyphenyl)imidazolidine-1-carbothioamide (18f). Mp 153 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (t, J = 7.6 Hz, 2H), 3.76 (s, 3H), 3.83 (s, 3H), 4.44 (t, J = 7.6 Hz, 2H), 4.71 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.98 (m, 3H), 7.04−7.15 (m, 3H), 8.47 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.6, 48.8, 55.9, 56.2, 111.0, 112.5, 120.1, 121.6, 124.5, 124.7, 124.8, 125.9, 128.8, 135.3, 151.3, 151.4, 151.9, 178.2; IR (KBr) 3403, 2938, 2898, 2835, 1669, 1607, 1564, 1495, 1475, 1398, 1371, 1323, 1295, 1247, 1108, 1046, 1026, 910, 748 cm^{-1}; HRMS (ESI): m/z 379.1217 (M+Na^+); elemental analysis calcd (%) for $C_{18}H_{20}N_4O_2S$: C 60.65, H 5.66, N 15.72, S 9.00; found C 60.60, H 5.60, N 15.77, S 9.09.

Acknowledgment. B.K.P. acknowledges the support of this research by the Department of Science and Technology (DST) (SR/S1/OC-79/2009), New Delhi, and the Council of Scientific and Industrial Research (CSIR) (01(2270)/08/EMR-II). R.Y. thanks the CSIR for fellowships. Thanks are due to the Central Instruments Facility (CIF) IIT Guwahati for Mass and NMR spectra, and DST-FIST for the XRD facility.

Supporting Information Available. Detailed experimental procedures, general information, and analytical data of all compounds, and the copies of their ^{1}H NMR and ^{13}C NMR, crystallographic information of **16f** and **18f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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