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A metal-free and a solvent-free synthesis of thio-amides and amides: An efficient Friedel-Crafts arylation of isothiocyanates and isocyanates

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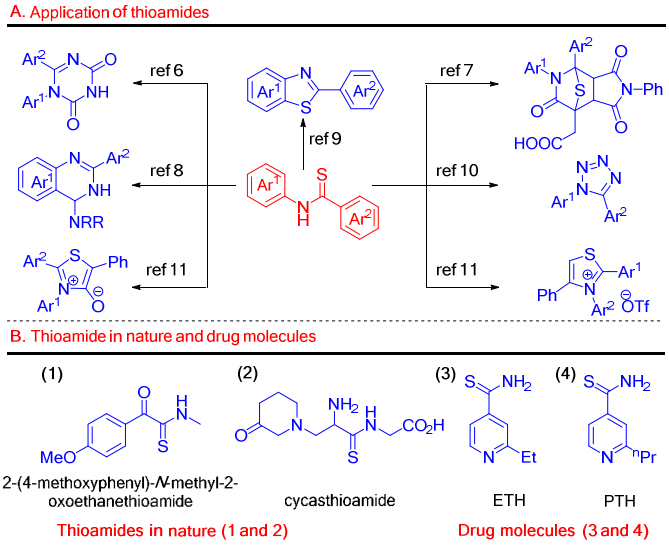
A rapid, metal-free and solvent-free (very low-loading of solvent in few cases) reaction conditions for synthesizing thioamides and amides using the Bronsted super acid such as triflic acid has been developed. This method shows a broad substrate scope with a variety of electron-rich arenes including thiophene derivatives. The reaction works well for both aromatic as well as aliphatic isothiocyantes. Most of the thioamides are obtained in excellent yields in short reaction duration of time and in most of the examples, a simple work up procedure has been developed which does not require further purification.

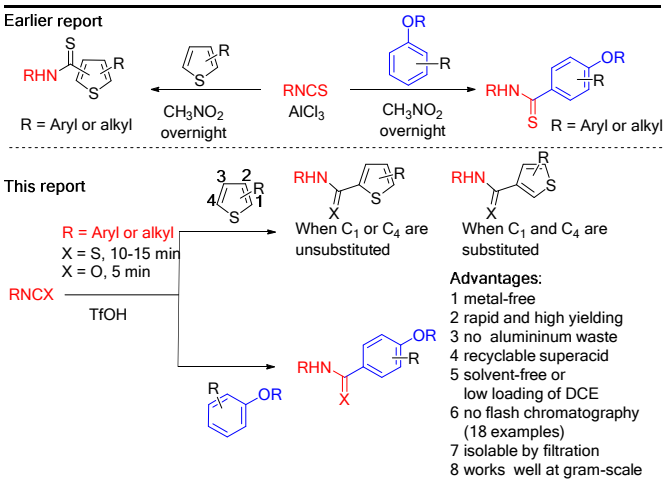
Introduction

Thioamides are important structural motifs that are found in a variety of biologically active molecules[1] and are building blocks for a number of pharmaceutically active compounds.[2] Although a very few thioamide derivatives are found in natural products,[3] the well-known among them is closthioamide, which is a potent antibiotic.[3,4] It has been demonstrated by Hertweck group that the thioamide functional group in the closthioamide is responsible for the antibiotic property of closthioamide, whereas the corresponding amide analogue, closamide, is not a potent antibiotic.[4] Thioamides also find innumerous application as important precursors and intermediates in organic synthesis, which can be attributed to their reactivity.[5] Further, thioamides are important precursor for synthesizing a variety of pharmaceutically important compounds such as 1,3,5-triazine-2,4(1H,3H)-diones,[6] triones,[7] 4-aminoquinazoline derivatives,[8] 2-aryl benzothiazoles,[9] tetrazoles[10] and metal-complex ligand such as mesoionic thiazol-5-ylidenes[11] (Scheme 1, A). Further, they find utility in asymmetric synthesis,[12] vulcanizing agents, lubrication agents etc.[13] Thioamides serve as important ligands and are known to selectively chelate with metal ions.[14] Recently, thioamides were found to exhibit supra molecular polymerization, which is useful in designing novel supra molecular scafolds.[15] The drug molecules used for the treatment of mycobacterium infection (tuberculosis and leprosy) invariably contain thioamide moieties (Scheme 1, B).[16]



Scheme 1 Utility of thioamides

Although, there are number of methods available for synthesizing thioamides, the synthesis of thioamide is still a challenging task. The conventional method of thionation of amides for synthesizing thioamides employs Lawesson's reagent or P_4S_{10}.[17] Similarly,



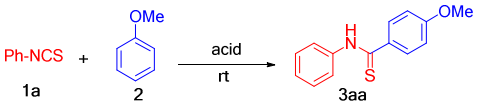
Scheme 2 Syntheiss of thioamides

aldehydes, ketones carboxylic acids and nitriles are converted to their thioamides using reagents such as thiacetamide, thioacid, dithiophosphoric acid etc.[18] Other widely used method for the synthesis of thioamide is the Willgerodt-Kindler reaction, which employs ketones, elemental sulfur and secondary amines.[19] However, most of these methods suffer from limitations such as cumbersome isolation methods, tedious purification procedures and more importantly the by-products of these reactions, which is generated in substantial amount, needs proper disposable measures. Very commonly used sulfur transferring reagents such as Lawesson's reagent and P_4S_{10} are very foul smelling, hazardous, and need proper care and handling till purification of the desired product. Considering the environmental impact and difficulties associated in handling and disposal of these hazardous wastes, the user-friendly and green methods are well sought for synthesizing thioamides. Interestingly, the reaction between phenyl isothiocyanate and arene under Friedel-Crafts conditions is useful method employed for the synthesis of thioamide (Gattermann reaction),[20] which has been modified over the time.[21,22] For example, thioamides and their derivatives have been synthesized by Jadozinski using improved reaction conditions which showed a broad substrate scope.[22] However, these Friedel-Crafts and related methods are also associated with the problems of generating a large amount of aluminum wastes, use of hazard solvent like CS_2 and often result in low yields of the products. Due to these reasons, synthesis of thioamides, still remain as a challenging task. In pursuit of our quest in developing new strategies for synthesizing a variety of sulfur and phosphorous compounds,[23] herein we report a synthesis of thioamides and amides using a simple, rapid and high yielding method that involves reusable catalyst,[24] and readily available starting materials with broad substrate scope. Additionally, a simple method for purification is developed (Scheme 2) and moreover, this method does not generate hazardous waste materials and the TfOH can be recycled.

Results and discussion

The studies were started with a proposal that the the isothiocyanates can react with aromatic systems in the presence of Bronsted acids to form the corresponding thioamides. Hence we began screening studies by treating phenyl isothiocyanate (**1a**, 1 equiv) with excess of TfOH (5 equiv) and excess of anisole (**2a**, 5 equiv) at ambient conditions. The reaction proceeded well to furnish the corresponding thioamide (**3aa**) in

Table 1 Screening studies[a]



Entry	**2a** (equiv)	Bronsted acid (equiv)	Solvent[b]	Time	Yield (%)[c]
1	**5**	**TfOH (5)**	**none**	**10 min**	**96**
2	5	H_2SO_4 (2)	none	12h	57
3	5	H_2SO_4 (10)	none	12h	70
4	5	H_2SO_4 (20)	none	12h	70
5	1.5	H_2SO_4 (10)	none	12h	40
6	5	HCl (10)	none	12h	nr
7	5	$HClO_4$ (10)	none	12h	80
8	1.5	$HClO_4$ (10)	none	12h	trace
9	5	CH_3COOH	CH_3COOH	12	nr
10	5	TFA (5)	none	12h	trace
11	1.5	CH_3SO_3H (2)	none	10 min	4
12	1.5	CH_3SO_3H (2)	none	12h	16
13	1.5	PTSA (2)	none	12h	nr
14	5	TfOH (2)	none	10 min	95
15	5	TfOH (1)	none	2h	65
16	1	TfOH (2)	none	10 min	79
17	1.3	TfOH (2)	none	10 min	83
18	**1.5**	**TfOH (2)**	**none**	**10 min**	**96**
19	**1.5**	**TfOH (2)**	**none**	**5 min**	**96**
20	1.5	TfOH (2)	none	2 min	58
21	1.5	TfOH (1.5)	none	10 min	65
22	1.5	TfOH (2)	DCE	5min	69
23	1.5	TfOH (2)	DCE	10 min	89
24	1.5	TfOH (2)	DCE	15 min	89
25	1.5	TfOH (2)	DCM	15 min	nr
26	1.5	TfOH (2)	CH_3CN	15 min	nr
27	1.5	TfOH (2)	THF	15 min	nr
28	1.5	TfOH (2)	DMF	15 min	nr
29	1.5	TfOH (2)	DMSO	15 min	nr
30	**5**	TfOH (2)	acetone	15 min	

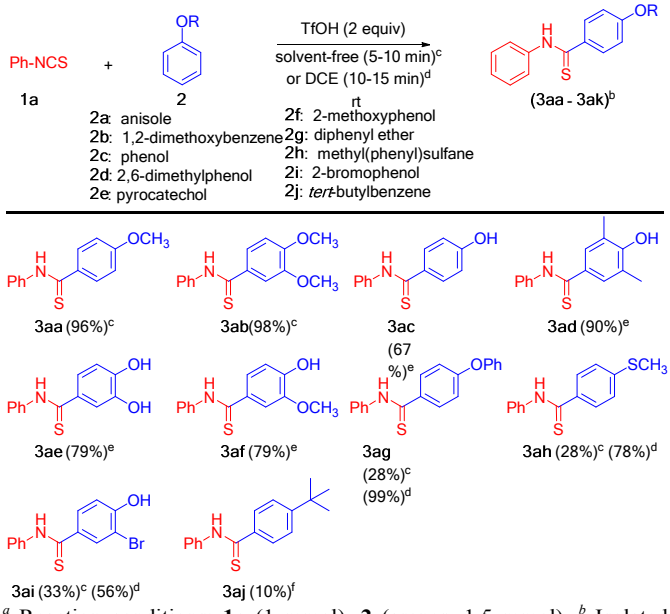
[a] Reaction conditions: **1a** (1 mmol). [b] 0.5 mL of solvent was used. [c] Isolated yields, nr = no reaction.

near quantitative yield in 10 min (96%, entry 1, Table 1). Interestingly, the product was isolated in good purity by filtration after quenching the reaction mixture with water (5 mL). Further screening study was continued to find the suitability of other mineral acids. Although, the similar reaction with H_2SO_4 was promising, the reaction required large amount of acid, excess of anisole and longer reaction time (entries 2-5, Table 1). The reaction with Con. HCl was not fruitful in forming the product **3aa** (entry 6, Table 1). Nevertheless, the reactions using $HClO_4$ afforded the thioamide in 80% yield (entries 7 and 8). Similarly, the reaction of **1a** with **2a** using organic acids such as CH_3COOH, TFA, MeSO3H, or PTSA, formed the corresponding thioamide in lower yields (entries 9-13, Table 1). With the lead that the TfOH serves better than other acids, further optimization studies were conducted to find the optimal reaction conditions using TfOH (entries 14-21). Although, most of the reactions proceeded well under the solvent-free conditions, in few cases the yields obtained in the solvent-free reactions were low. Therefore, solvent screening studies revealed that DCE is the most suitable solvent for the reaction whereas solvents such as CH_3CN, THF, DMF, and

DMSO, or acetone are not suitable solvents as the reactions in these solvents did not afford the expected product (entries 22-30, Table 1).These studies revealed that the reaction of phenylisothiocyanate (**1a**, 1 equiv) and anisole (**2a**, 1.5 equiv) in TfOH (2 equiv) at ambient temperature can lead to the corresponding thioamide (**3aa**) in 5 min (entry 19, Table 1).

The scope of this reaction was explored and the results are presented in the following section. A variety of electron rich arenes (**2a-2j**) were reacted with phenyl isocyante (**1a**) under the optimal reaction conditions. As can be seen in Table 2, anisole (**2a**) and 1,2-dimethoxybenzene (**2b**) underwent a facile reaction with phenylisothiocyanate (**1a**) in a solvent-free conditions furnishing the corresponding thioamides **3aa** and **3ab** in 96 and 98% yield, respectively. However, the reaction of **1a** with phenol (**2c**) 2,6-dimethylphenol (**2d**), pyrocatechol (**2e**), and 2-methoxyphenol (**2f**) required DCE as the solvent to afford the the corresponding thioamides **3ac**, **3ad**, **3ae**, and **3af** in good yields (67, 90, 79 and 79% respectively). Although the solvent-free reactions of **1a** with diphenyl ether (**2g**), and methyl(phenyl)sulfane (**2h**), resulted in the formation of their thioamides **3ag**, and **3ah** in lower yields (28 and 28%, respectively). However, the same reactions in the solvent DCE resulted in the formation of thioamides **3ag**, and **3ah** in 99, and 78%, yields, respectively. The bromosubstituted substrate such as 2-bromophenol (**2i**) was less reactive under the optimal recation conditions and afforded the corresponding thioamide **3ai** in moderate yield (56%). As expected, the reaction of phenylisothiocyanate (**1a**) with *tert*-butylbenzene (**2j**) resulted in the formation of the corresponding thioamide (**3aj**) in low yield (10%).

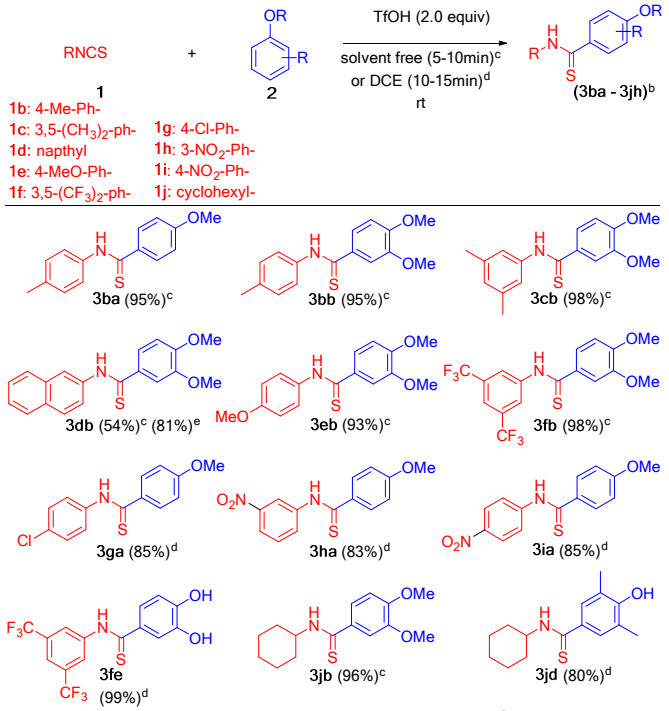
Table 2 Reaction of electron-rich arenes with phenylisothiocyanate[a]



[a] Reaction conditions: **1a** (1 mmol), **2** (arenes, 1.5 mmol). [b] Isolated yields. [c] Solvent free reaction (5-10 min). [d] Solvent free reaction (1h). [e] DCE (0.5 ml, 10-15 min). [f] *tert*-Butyl benzene (1mL, 60° C, 6h). rt = room temperature.

Further scope of this reaction was explored by treating a variety of isothocyanates with anisole or phenol derivatives and results are presented in Table 3. A variety of aromatic isothiocyanates containing electron-donating or electron-withdrawing groups on phenyl ring underwent a facile reaction with electron rich arenes to furnish their corresponding thioamides in excellent yields. Hence, a solvent-free reaction of 1-isothiocyanato-4-methylbenzene (**1b**) with anisole (**2a**) proceeded well to furnish the corresponding thioamide **3ba** in 95% yield. Similarly, a variety of aromatic isothiocyanates such as 1-isothiocyanato-4-methylbenzene (**1b**), 1-isothiocyanato-3,5-dimethylbenzene (**1c**),2-isothiocyanatonaphthalene (**1d**),1-isothiocyanato-4-methoxybenzene (**1e**), and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**1f**) reacted well with 1,2-dimethoxybenzene (**2b**) under a solvent-free condition to afford the corresponding thioamides **3bb**, **3cb**, **3db**, **3eb**, and **3fb** in good to excellent yields (95, 98, 81, 93, and 98% yields, respectively). The reaction of anisole (**2a**) with isothiocyanates such as 1-chloro-4-isothiocyanatobenzene (**1g**), 1-isothiocyanato-3-nitrobenzene (**1h**), and 1-isothiocyanato-4-nitrobenzene (**1i**) in DCE furnished their corresponding thioamides **3ga**, **3ha**, and 3ia in 85, 83 and 85% yields, respectively. The reaction of pyrocatechol (**2e**) with1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**1f**) in DCE resulted in the formation of the thioamide **3fe** in near quantitative yield (99% yield). The reaction of aliphatic isothiocyanate such as cyclohexyl isothiocyanate (**1j**) was found to proceed well with 1,2-dimethoxyanisole (**20b**) and 2,6-dimethylphenol (**2h**) to give the corresponding thioamides **3jb** and **3jd** in excellent yields (96% and 80%, respectively). These successful reaction of pyrocatexchol (**1g**) and dimethylphenol (**2h**) with isocyanates indicate that the reaction of phenols is facile and OH group survives the reaction conditions.

Table 3 Reaction of substituted isothiocyanates[a]

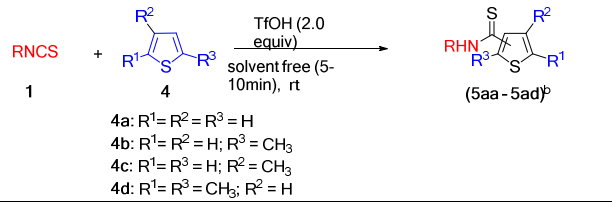


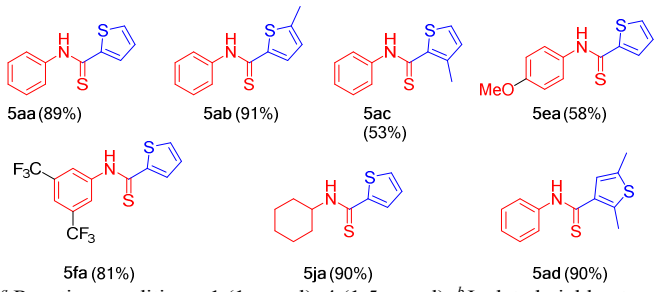
[a] Reaction conditions: **1a** (1 mmol), **2** (arenes, 1.5 mmol). [b] Isolated yields. [c] Solvent-free reaction (5-10 min). [d] DCE (0.5 ml, 10-15 min). [e] Solvent-free reaction (30 min). rt = room temperature.

The successful reaction of a variety of isothiocyanates with electron rich arenes such as anisole and phenol derivatives led

us to explore the reaction of isothiocyanates with unactivated heteroaromatic compounds such as thiophene and its derivatives. As can be seen in Table 4, the reaction of isothiocyanates with thiophene and its derivatives is highly regioselective and a new –C=S bond is formed exclusively at C-2 carbon of thiophene. The reaction of phenylisothiocyanate (**1a**) with thiophene (**4a**), 2-methylthiophene (**4b**), and 3-methylthiophene (**4c**), under a solvent-free condition, resulted in the formation of the corresponding thiocyantaes **5aa**, **5ab**, and **5ac** in good to moderate yields (89, 91, and 53%, respectively). The reaction of isothiocyanates 1-isothiocyanato-4-methoxybenzene (**1e**), and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**1f**) with thiophene (**4a**) furnished their corresponding thioamides **5ea** (58%) and **5fa** (81%). Under the optimal reaction conditions, aliphatic isothiocyanate such as cyclohexylisothiocyanate (**1j**) underwent a facile reaction with thiophene (**4a**) and furnished its thioamide **5ad** in excellent yield (90%). The reaction of 2,5-dimethylthiophene (**4d**) with phenylisothicyanate (**1a**) was also proceeded successfully and afforded the corresponding thioamide **5ad** in good yield (90%).

Table 4 Reaction of thiophene derivatives with isothiocyanatesa

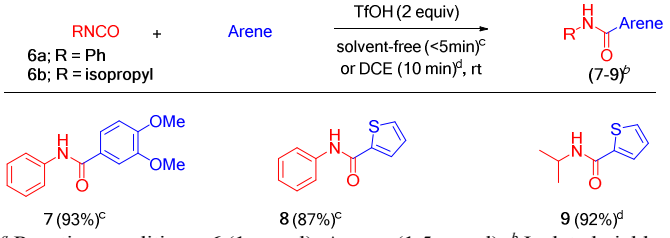




a Reaction conditions: 1 (1 mmol), 4 (1.5 mmol). b Isolated yields, rt = room temperature.

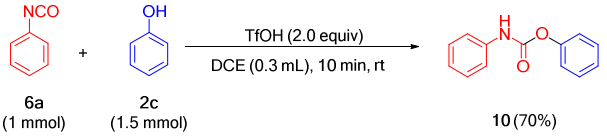
After successful synthesis of thioamides, we turned our attention towards the similar reactions of isocyantes to explore the possibility of synthesizing amides (Table 5). Although, amides are easily accessible *via* a nucleophilic substitution reaction between acyl halides with amines, the present strategy provides an alternative method using Friedel-Crafts type reaction of isocyanate as the amide source to form the corresponding amide. Interestingly, literature survey revealed that there are only a few reports known for the reaction of isocyanates with arenes to obtain amides by employing metal catalysts.[25] As the present strategy provides an opportunity of rapid reaction between isocyante and electron rich arenes and thiophene, to form amides, following experiments have been performed. As can be seen in Table 5 the phenyl isocyanate (**6a**) reacted rapidly (<5min) with 1,2-dimethoxybenzene (**2a**), and thiophene (**4a**) under solvent-free conditions at room temperature to form **7**, and **8** in excellent yields (93, and 87%, respectively). However, the similar reaction of aliphatic isocyanate such as isopropylisocyanate with thiophene in DCE resulted in the formation of the corresponding amide **9** in excellent yield (92%).

Table 5 Reaction of isocyanates with electron-rich arenes and thiophenea



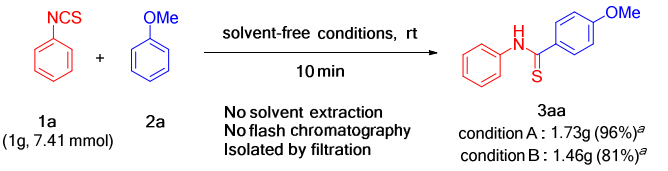
a Reaction conditions: **6** (1 mmol), Arenes (1.5 mmol). b Isolated yields. c Solvent free reaction (<5 min). d DCE (0.5 mL, 10 min).

As isothiocyanates in a reaction with phenol under optimal conditions furnished their corresponding thioamides (Tables 2 and 3), we performed a similar reaction of phenylisocyanate (**6a**) with phenol (**2c**) under the optimal reaction conditions. Contrary to our expectation, this reaction furnished the corresponding carbamate **10** in 70% yield (Scheme 3)



Scheme 3 Reaction of isocyante with phenol

The application of this methodology of synthesizing thioamide has been exemplified in performing a reaction at preparative scale (Scheme 4). Hence, the reaction of phenylisothiocyanate (**1a**, 1g, 7.41 mmol) and anisole (**2a**, 1.04g, 9.63 mmol, 1.3 equiv) was performed in solvent-free conditions. As can be seen, the reaction of **1a** and **2a** under solvent-free conditions at room temperature formed the corresponding thioamide **3aa** in excellent yield (96%, 10 min). A comparison of the reaction of anisole and phenylisothiocyanate in TfOH and H_2SO_4 has been shown in Schme 3. As can be seen, the reaction using H_2SO_4 required excess of anisole (**2a**, 5 equiv**)** and extended reaction time (12 h) to furnish the corresponding thioamide in 81% yield.



Scheme 4 Preparative scale experiment

Conclusions

In summary, we have explored a metal-free Friedel-Crafts type reaction of isothiocyantaes and isocyantes with aromatic systems to obtain the corresponding thioamides as well as amides. The salient feature of these reactions are the reactions are carried out in the absence of solvents and the work-up procedure is very simple, and the reaction furnishes almost analytically pure products, which are isolated by simple filtration and does not need further purification. As thioamides are important building blocks for the synthesis of pharmaceutically important compounds and are useful biologically active compounds, this approach would be

attractive and useful. A preparative scale synthesis has been shown to work equally well.

Experimental section

General experimental procedure for synthesis of thioamides (**3aa, 3ab, 3ad, 3ae, 3ag, 3aj, 3ba-3jh** - 18 example): To a well-stirred, ice cold mixture of isothiocyanate (1 mmol) and arene (1.5 mmol) was added TfOH (2 mmol, 0.18 mL) drop wise during 1 min. The ice bath was then removed and the reaction mixture was stirred for 5-10 min at room temperature (the reaction mixture was stirred for 10-15 min while 0.5 mL of DCE was used as solvent). The reaction was quenched by adding water (3-5 ml) drop wise. The yellow solid precipitated out was filtered through a sintered funnel, washed with hexane (15 mL) and dried to afford pure yellow solid of expected thioamide.

Note 1: If the reaction mixture could not be stirred efficiently or when one of the reactants was a solid (isothiocyanate or arene), then DCE (0.3-0.5 mL for 1mmol of isothiocyanate) was used as solvent to ensure proper stirring during the course of the reaction. For the synthesis of compounds such as **3ac, 3ad, 3ae, 3ha, 3ia, 3fg and 3jh** the DCE (0.5 mL) was used as solvent.

Note 2: When DCE was used as solvent, the reaction mixture was stirred for 10-15 minutes; the reaction mixture was quenched by adding water (3-5 ml) drop wise and followed by addition of 20 mL excess of water. The crude compound was extracted into DCM (10 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated, the yellow solid formed was filtered through a sintered funnel, washed with hexane (15 mL) and dried to afford pure yellow solid of expected thioamide.

Note 3: When the product was not well-precipitated after quenching with water, then 20 mL excess of water was added into the reaction mixture, the crude compound was extracted into DCM (10 mL x 3) and the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the yellow solid formed was filtered through sintered funnel, washed with hexane (15 mL) and dried.

Note 4: The compounds such as **3ac, 3af, 3ai, 5aa, 5ab, 5ac, 5da, 5fa, 5ja, 5ad, 8 and 9** were obtained after purifying the crude compound by silica gel column chromatography.

Gram-scale synthesis of 4-methoxy-N-phenylbenzothioamide (3aa)

Procedure 1. To a well-stirred, ice cold mixture of isothiocyanate (1g, 7.41 mmol) and anisole (1.04g, 9.63 mmol, 1.30 equiv) was added TfOH (14.82 mmol, 2 equiv, 1.30 mL) drop wise during 3 min. The ice bath was then removed and the reaction mixture was stirred for 10 min. The reaction mixture was quenched by adding ice-cold water (50 mL) slowly over a period of 1-2 min. The yellow solid precipitated was filtered through a sintered funnel, washed with hexane (50 mL) and dried to afford pure yellow solid of 4-methoxy-N-phenylbenzothioamide (**3aa**) in 96% yield (1.73g).

Procedure 2. To a well-stirred, ice cold mixture of isothiocyanate (1g, 7.41 mmol) and anisole (4.0g, 37.05 mmol, 5.0 equiv) was added H_2SO_4 (74.1 mmol, 10 equiv, 3.95 mL) drop wise during 5 min. The ice bath was then removed and the reaction mixture was stirred for 12h. The reaction mixture was quenched by adding ice-cold water (50 mL) slowly over the period of 1-2 min. The yellow solid precipitated was filtered through a sintered funnel, washed with hexane (20-30 mL) and dried to afford pure yellow solid of 4-methoxy-N-phenylbenzothioamide **(3aa)** in 81% yield (1.46g).

General experimental procedure for synthesis of amide (7, **8** and **9**): To a well-stirred, ice cold mixture of isocyanate (1 mmol) and arene (1.5 mmol) was added TfOH (2 mmol, 0.18 mL) drop wise during 1 min. The ice bath was then removed and the reaction mixture was stirred for 5 min (the reaction mixture was stirred for 10 mins while using 0.5 mL of DCE as solvent). Then the reaction mixture was quenched by adding water (3-5 mL) drop wise. The white solid precipitated out was filtered through sintered funnel, washed with warm water (15-20 mL) followed by hexane (15-20 mL) and dried to afford white solid.

Note 5: The compound **7** was not further purified after filtration. The compounds **8** and **9** were obtained as a white solid by filtration and further purified by silicagel column chromatography (eluent 10-30% ethylacetate/hexane).

Note 6: For the reaction between isopropyl isocyanate (**6b**) and thiophene (**5a**) the DCE 0.3 mL was used as solvent.

Experimental procedure for synthesising carbomate (**10**). To a well-stirred, ice cold solution of phenyl isocyanate (**6a**, 1 mmol) and phenol (**2c**, 1.5 mmol) in DCE (0.3 mL) was added TfOH (2 mmol, 0.18 mL) drop wise during 1 min. The ice bath was then removed and the reaction mixture was stirred for 10 minutes. The reaction mixture was quenched by adding water (3-5 mL) drop wise followed by the addition of 30 mL of water and the crude compound was extracted into DCM (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4. The crude compound was purified by silica gel chromatography (eluent: 10% EtOAC/Hexane) to afford the product **10** in 70% yield.

4-Methoxy-N-phenylbenzothioamide (3aa).[22b] Yellow solid; Yield - 92% (224 mg); mp: 156-158 ºC (lit.[20b] 153-154 ºC); R_f (30% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3154, 1601, 1507, 1346, 1248. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.54 (brs, 1H), 7.91 (d, J = 6.9 Hz, 2H), 7.77(d, J = 6.0 Hz, 2H), 7.43 (s, 2H), 7.26 (s, 1H), 7.01 (d, J = 7.2 Hz, 2H), 3.83 (s, 3H) ; **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.4, 161.6, 140.2, 134.6, 129.5, 128.4, 126.0, 124.5, 113.1, 55.5. **ESI-HRMS** *(m/z)*: Calculated for $C_{14}H_{13}NOS$ (M + Na): 266.0616, found (M + Na): 266.0615.

3,4-Dimethoxy-N-phenylbenzothioamide (3ab). Yellow solid; Yield - 98% (267 mg); mp: 168-170 ºC (lit[26] 159 ºC); R_f (30% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3159, 1596, 1510, 1329, 1269,1145. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.49 (brs, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.54 (s, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 7.1 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 3.83 (s, 6H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.4, 151.4, 147.7, 140.2, 134.4, 128.4, 126.1, 124.7, 120.8, 111.4, 110.6, 55.7, 55.5. **ESI-HRMS** *(m/z)*: Calculated for $C_{15}H_{15}NO_2S$ (M + Na): 296.0721, found (M + Na): 296.0724.

4-Hydroxy-N-phenylbenzothioamide (3ac).[22b] Yellow solid; Yield - 67% (77 mg); mp: 161-163 ºC (lit[21b]. 164-165

ºC); R_f (30% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3310, 3226, 1599, 1504, 1361, 1192, 1165. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.42 (brs, 1H), 10.11 (brs, 1H), 7.82 (d, J = 7.8 Hz, 2H), 7.75 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 6.82 (d, J = 8.3 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.7, 160.4, 140.3, 133.1, 129.8, 128.4, 126.0, 124.6, 114.5. **ESI-HRMS** *(m/z)*: Calculated for $C_{13}H_{11}NOS$ (M + Na): 252.0459, found (M + Na): 252.0454.

4-Hydroxy-3,5-dimethyl-N-phenylbenzothioamide (3ad). Yellow solid; Yield - 90% (231 mg); mp: 184-186 ºC; R_f (20% EtOAc/hexane) 0.25; **IR** (KBr, cm^{-1}): 3378, 3180, 1595, 1520, 1495, 1484, 1313, 1170. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.37 (brs, 1H), 8.92 (brs, 1H), 7.75 (d, J = 6.6 Hz, 2H), 7.56 (s, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.0 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 197.0, 156.4, 140.4, 133.1, 128.3, 128.2, 125.9, 124.5, 123.3, 16.7. **ESI-HRMS** *(m/z)*: Calculated for $C_{15}H_{15}NOS$ (M + Na): 280.0772, found (M + Na): 280.0775.

3,4-Dihydroxy-N-phenylbenzothioamide (3ae). Yellow solid; Yield - 79% (97 mg); mp: 161-163 ºC; R_f (30% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3243, 1599, 1503, 1268, 1145, 1021. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.36 (brs, 1H), 9.45 (brs, 2H), 7.73 (s, 2H), 7.42-7.40 (m, 3H), 7.24 (d, J = 6.8 Hz, 2H), 6.78 (d, J = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.9, 148.9, 144.5, 140.4, 133.6, 128.4, 125.9, 124.5, 119.2, ,116.1, 114.5. **ESI-HRMS** *(m/z)*: Calculated for $C_{13}H_{11}NO_2S$ (M + Na): 268.0408, found (M + Na): 268.0408.

4-Hydroxy-3-methoxy-N-phenylbenzothioamide (3af). Yellow solid; Yield - 78% (202 mg); mp:158-160 ºC; R_f (30% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3175, 1591, 1505, 1274, 1173.**^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.40 (brs, 1H), 9.74 (brs, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.54 (s, 1H), 7.46-7.40 (m, 3H), 7.25 (t, J = 7.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.6, 149.9, 146.7, 140.3, 133.1, 128.4, 126.1, 124.8, 121.4, 114.5, 112.1, 55.7. **ESI-HRMS** *(m/z)*: Calculated for $C_{14}H_{13}NO_2S$ (M + Na): 282.0565, found (M + Na): 282.0565.

4-Phenoxy-N-phenylbenzothioamide (3ag).[22b] Yellow solid; Yield - 99% (302 mg); mp: 131-132 ºC (lit[22b] 127-129 ºC) R_f (10% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3337, 1591, 1500, 1490, 1347, 1264. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.67 (brs, 1H), 7.91 (d, J = 7.7 Hz, 2H), 7.79 (d, J = 7.5 Hz, 2H), 7.47-7.41 (m, 4H), 7.28-7.20(m, 2H), 7.10 (d, J = 7.5 Hz, 2H) 7.04 (d, J = 7.7 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.3, 159.4, 155.7, 140.1, 137.2, 130.3, 129.7, 128.5, 126.2, 124.35, 124.31, 119.5, 117.1. **ESI-HRMS** *(m/z)*: Calculated for $C_{19}H_{15}NOS$ (M + Na): 328.0772, found (M + Na): 328.0770.

4-(Methylthio)-N-phenylbenzothioamide (3ah). Yellow solid; Yield - 78% (202 mg); mp: 162-163 ºC; R_f (20% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3152, 1587, 1521, 1338, 1249. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.67 (brs, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.27 (t, J = 7.28 Hz, 1H), 2.53 (s, 3H) ; **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.5, 142.4, 140.1, 138.4, 128.5, 128.1, 126.2, 124.6, 124.4, 14.3. **ESI-HRMS** *(m/z)*: Calculated for $C_{14}H_{13}NS_2$ (M + Na): 282.0387, found (M + Na): 282.0388.

3-Bromo-4-hydroxy-N-phenylbenzothioamide (3ai). Yellow solid; Yield - 56% (172 mg); mp: 174-176 ºC. R_f (30% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3345, 3115, 1594, 1532, 1497, 1405. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.56 (brs, 1H), 11.00 (brs, 1H), 8.06 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.20 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 194.9, 156.9, 140.1, 134.3, 132.3, 129.0, 128.5, 126.2, 124.5, 115.3, 108.6. **ESI-HRMS** *(m/z)*: Calculated for $C_{13}H_{10}BrNOS$ (M + Na): 329.9564, found (M + Na): 329.9564.

4-(*tert*-Butyl)-N-phenylbenzothioamide (3aj).[22b] Yellow solid; Yield - 16% (43 mg); mp: 131-132 ºC (lit[22b] 136-137 ºC); R_f (5% EtOAc/hexane) 0.5; **IR** (KBr, cm^{-1}): 1618, 1586, 1340, 1261, 1207. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.67 (brs, 1H), 7.85 (d, J = 7.7 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 7.14 Hz, 1H), 1.32 (s, 9H) ; **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 197.4, 153.6, 140.1, 128.4, 127.3, 126.1, 124.8, 123.9, 34.6, 30.9. **ESI-HRMS** *(m/z)*: Calculated for $C_{17}H_{19}NS$ (M + Na): 292.1136, found (M + Na): 292.1136.

4-Methoxy-N-(p-tolyl)benzothioamide (3ba). Yellow solid; Yield - 95% (244 mg); mp: 174-176 ºC (lit.[27] 172 ºC); R_f (20% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3164, 1600, 1510, 1244. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.47 (brs, 1H), 7.9 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 7.7 Hz, 2H), 7.22 (d, J = 7.5 Hz, 2H), 7.00 (d, J = 8.2 Hz, 2H), 3.83 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.1, 161.6, 137.7, 135.3, 134.6, 129.4, 128.8, 124.4, 113.1, 55.4, 20.7. **ESI-HRMS** *(m/z)*: Calculated for $C_{15}H_{15}NOS$ (M + Na): 280.0772, found (M + Na): 280.0768.

3,4-Dimethoxy-N-(p-tolyl)benzothioamide (3bb). Yellow solid; Yield -95% (273 mg); mp: 163-165 ºC; R_f (20% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3197, 1596, 1512, 1269, 1145. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.43 (brs, 1H), 7.62 (d, J = 7.9 Hz, 2H), 7.53 (s, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.03 (d, J = 8.9 Hz, 1H), 3.83 (s, 6H), 2.32 (s, 3H) ; **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.1, 151.3, 147.7, 137.7, 135.4, 134.4, 128.8, 124.6, 120.8, 111.4, 110.5, 55.7, 55.5, 20.7. **ESI-HRMS** *(m/z)*: Calculated for $C_{16}H_{17}NO_2S$ (M + Na): 310.0878, found (M + Na): 310.0876.

***N*-(3,5-Dimethylphenyl)-3,4-dimethoxybenzothioamide (3cb).** Yellow solid; Yield - 98% (295 mg); mp: 156-157 ºC; R_f (30% EtOAc/hexane) 0.5; **IR** (KBr, cm^{-1}): 3195, 1595, 1513, 1274, 1173, 1145. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.40 (brs, 1H), 7.54-7.52 (m, 2H), 7.34 (s, 2H), 7.02 (d, J = 8.2 Hz, 1H), 6.91 (s, 1H), 3.83 (s, 6H), 2.29 (s, 6H) ; **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.3, 151.3, 147.7, 140.1, 137.5, 134.5, 127.6, 122.4, 120.9,111.3, 110.6, 55.7, 55.5, 20.9. Calculated for $C_{17}H_{19}NO_2S$ (M + Na): 324.1034, found (M + Na): 324.1033.

3,4-Dimethoxy-N-(naphthalen-2-yl)benzothioamide (3db). Yellow solid; Yield - 81% (262 mg); mp: 151-153 ºC; R_f (30% EtOAc/hexane) 0.4; **IR** KBr, cm^{-1}): 3243, 1599, 1503, 1347, 1268, 1145. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.70 (brs, 1H), 8.01- 7.96 (m, 2H), 7.82 – 7.77 (m, 3H), 7.55 (brs, 4H), 7.10 (s, 1H), 3.87 (s, 6H) ; **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 198.5, 151.7, 147.8, 136.9, 133.8, 132.9, 129.2, 128.2, 127.6, 126.4, 126.3, 125.4, 123.2, 121.2, 111.5,

110.6, 55.8, 55.6. **ESI-HRMS** *(m/z)*: Calculated for $C_{19}H_{17}NO_2S$ (M + Na): 346.0878, found (M + Na): 346.0876.

3,4-Dimethoxy-N-(4-methoxyphenyl)benzothioamide (3eb).[28] Yellow solid; Yield - 93% (282 mg); mp: 164-165 ºC (lit.[29] 154-155 °C); R_f (30% EtOAc/hexane) 0.25; **IR** (KBr, cm^{-1}): 3163, 1514, 1270, 1146. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.40 (brs, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.54 (s, 2H), 7.03 (d, *J* = 9.0 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 6H), 3.78 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 195.8, 157.2, 151.3, 147.7, 134.3, 133.2, 126.2, 120.8, 113.5,111.3, 110.5, 55.7, 55.5, 55.3. **ESI-HRMS** *(m/z)*: Calculated for $C_{16}H_{17}NO_3S$ (M + Na): 326.0827, found (M + Na): 326.0823.

***N*-(3,5-*bis*(Trifluoromethyl)phenyl)-3,4-dimethoxybenzothioamide (3fb).** Yellow solid; Yield - 98% (400 mg); mp: 159-161 ºC. R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}) 3289, 1512, 1377, 1279, 1263, 1164, 1130. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.89 (brs, 1H), 8.63 (s, 2H), 7.99 (s, 1H), 7.61-7.58 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 3.853 (s, 3H) 3.847 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 197.9, 152.0, 147.8, 141.9, 134.1, 130.3 (q, *J* = 32.8 Hz), 124.5, 123.6 (q, *J* = 278.9 Hz), 121.3, 119.0, 111.4, 110.7, 55.8, 55.6; **ESI-HRMS** *(m/z)*: Calculated for $C_{17}H_{13}F_6NO_2S$ (M + H): 410.0649, found (M + H): 410.0659.

***N*-(4-Chlorophenyl)-4-methoxybenzothioamide (3ga).** Yellow solid; Yield - 79% (220 mg); mp: 186-187 ºC; R_f (20% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3149, 2973, 1601, 1504, 1488, 1305, 1246, 1175, 837. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.47 (brs, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 3.83 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 196.76, 161.79, 139.12, 134.43, 129.84, 129.57, 128.39, 126.12, 113.23, 55.52; **ESI-HRMS** *(m/z)*: Calculated for $C_{14}H_{12}ClNOS$ (M + H): 278.0406, found (M + Na): 278.0404.

4-Methoxy-N-(3-nitrophenyl)benzothioamide (3ha). Yellow solid; Yield - 83% (119 mg); mp: 152-154 ºC; R_f (20% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3345, 1602, 1521, 1345, 1259. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.60 (brs, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 3.83 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 197.5, 162.0, 147.5, 141.2, 134.3, 130.5, 129.8, 129.7, 120.5, 118.6, 113.3, 55.6. **ESI-HRMS** *(m/z)*: Calculated for $C_{14}H_{12}N_2O_3S$ (M + Na): 311.0466, found (M + Na): 311.0467.

4-Methoxy-N-(4-nitrophenyl)benzothioamide (3ia). Yellow solid; Yield - 85% (122 mg); mp: 191-193 ºC; R_f (20% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3134, 1596, 1506, 1340, 1305, 1252, 1171. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.19 (brs, 1H), 8.29 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 7.8 Hz, 2H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 3.84 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 197.9, 162.1, 146.1, 143.9, 134.7, 129.8, 124.2, 123.9, 113.3, 55.6. **ESI-HRMS** *(m/z)*: Calculated for $C_{14}H_{12}N_2O_3S$ (M + Na): 311.0466, found (M + Na): 311.0464.

***N*-(3,5-*bis*(Trifluoromethyl)phenyl)-3,4-dihydroxybenzothioamide (3fe).** Yellow solid; Yield-99% (189 mg); R_f (40% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3307, 1608, 1515, 1381, 1277. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm) 11.76 (brs, 1H), 9.79 (brs, 1H), 9.37 (brs, 1H), 8.62 (s, 2H), 7.94 (s, 1H), 7.469 (d, *J* = 1.8 Hz, 1H), 7.33 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz , 1H), 6.81 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 198.1, 149.6, 144.7, 142.0, 133.1, 130.2 (q, *J* = 32.9 Hz), 124.3, 123.17 (q, *J* = 271 Hz), 119.6, 118.7, 116.2, 114.6; **ESI-HRMS** *(m/z)*: Calculated for $C_{14}H_{12}BrNOS$ (M + Na): 343.9721, found (M + Na): 343.9721.

***N*-Cyclohexyl-3,4-dimethoxybenzothioamide (3jb).** Yellow solid; Yield - 96% (268 mg); mp: 162-164 ºC; R_f (20% EtOAc/hexane) 0.25; **IR** (KBr, cm^{-1}): 3228, 3193, 2936, 2854, 1541, 1510, 1268, 1242, 1144, 1021. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 9.78 - 9.77 (m, NH, 1H), 7.38-7.35 (m, 2H), 6.97 (d, *J* = 8.8 Hz, 1H), 4.44-4.37 (m, CHNH, 1H), 3.80 (s, 6H), 1.98-1.96 (m, 2H); 1.78-1.75 (m, 2H), 1.65-1.62 (m, 1H), 1.45-1.27 (m, 4H), 1.19-1.11 (m, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 194.7, 151.0, 147.6, 133.8, 120.3, 111.6, 110.4, 55.7, 55.5, 55.0, 30.7, 25.1, 24.8; **ESI-HRMS** *(m/z)*: Calculated for $C_{15}H_{21}NO_2S$ (M + Na): 302.1191, found (M + Na): 302.1194.

***N*-Cyclohexyl-4-hydroxy-3,5-dimethylbenzothioamide (3jd).**[22b] Yellow solid; Yield - 80% (210 mg); mp: 212-214 ºC (lit.[22b] 222-224 ºC); R_f (20% EtOAc/hexane) 0.25; **IR** (KBr, cm^{-1}): 3249, 3054, 2933, 1547, 1393, 1324, 1209, 1178. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 9.63-9.62 (m, NH, 1H), 8.75 (brs, OH, 1H), 7.39 (s, 2H), 4.38 (brs, CHNH, 1H), 2.19 (s, 6H), 1.95-1.93 (m, 2H); 1.77-1.74 (m, 2H), 1.65-1.62 (m, 1H), 1.40-1.27 (m, 4H), 1.15-1.12 (m, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 195.1, 155.8, 132.2, 127.9, 123.1, 54.8, 30.7, 25.2, 24.8, 16.6;. **ESI-HRMS** *(m/z)*: Calculated for $C_{15}H_{21}NOS$ (M + Na): 286.1242, found (M + H): 286.1245.

***N*-Phenylthiophene-2-carbothioamide (5aa).**[22a] Yellow solid; Yield - 89% (195 mg); mp: 94-97 ºC (lit.[22a] 94-95 °C); R_f (10% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3294, 1544, 1375, 1350, 1172. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.54 (brs, 1H), 7.88 (brs, 1H), 7.85 (d, *J* = 5.0 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.23-7.21 (m, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 186.7, 148.2, 139.4, 134.8, 128.5, 128.2, 126.4, 125.1, 125.0. **ESI-HRMS** *(m/z)*: Calculated for $C_{11}H_9NS_2$ (M + H): 220.0255, found (M + Na): 220.025.

5-Methyl-N-phenylthiophene-2-carbothioamide (5ab). Yellow solid; Yield - 91% (212 mg); mp: 123-125 ºC R_f (20% EtOAc/hexane) 0.5; **IR** (KBr, cm^{-1}): 1517, 1446, 1335; **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.39 (brs, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 2.46 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 186.5, 149.2, 145.7, 139.5, 128.5, 126.9, 126.2, 125.2, 125.1, 15.4. **ESI-HRMS** *(m/z)*: Calculated for $C_{12}H_{11}NS_2$ (M + Na): 256.0231, found (M + Na): 256.0238.

4-Methyl-N-phenylthiophene-2-carbothioamide (5ac). Yellow solid; Yield - 53% (123 mg); mp: 93-95 ºC (lit.[22c] 70-71 °C in CCl_4); R_f (20% EtOAc / hexane) 0.3; **IR** (KBr, cm^{-1}): 3189, 1506, 1206, 714, 696. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.48 (brs, 1H), 7.79 (s, 2H), 7.63 (d, *J* = 5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 6.965 (d, *J* = 4 Hz, 1H), 2.38 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 189.2, 142.4, 139.7, 135.3, 131.1, 128.9, 128.6, 126.2, 123.6, 15.4; **ESI-HRMS** *(m/z)*: Calculated for $C_{12}H_{11}NS_2$ (M + Na): 256.0231, found (M + H): 256.0233.

***N*-(4-Methoxyphenyl)thiophene-2-carbothioamide (5ea).**[22a] Yellow solid ; Yield - 58% (144 mg); mp: 123-125 ºC (lit.[22a] 129-130.5 °C); R_f (30% EtOAc/hexane) 0.5; **IR** (KBr, cm^{-1}): 3244, 1511, 1362, 1247, 1238. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.45 (brs, 1H), 7.86 (d, J = 3.5 Hz, 1H), 7.83 (d, J = 5.0 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.21 (t, J = 4.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 186.3, 157.4, 148.1, 134.6, 132.4, 128.2, 126.6, 124.7, 113.7, 55.3;. **ESI-HRMS** *(m/z)*: Calculated for $C_{12}H_{11}NOS_2$ (M + Na): 272.0180, found (M + Na): 272.0179.

***N*-(3,5-*bis*(Trifluoromethyl)phenyl)thiophene-2-carbothioamide (5fa).** Yellow solid; Yield - 81% (287 mg); mp: 104-106 ºC; R_f (10% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3327, 1560, 1378, 1277, 1173, 1128. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.86 (brs, 1H), 8.55 (s, 2H), 8.00 (s, 1H), 7.27 (t, J = 4.44 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 187.9, 147.7, 141.2, 135.9, 130.3(q, J = 33.0 Hz), 128.5, 126.0, 125.0, 123.1 (q, J = 271.0 Hz), 119.3, 119.1; **ESI-HRMS** *(m/z)*: Calculated for $C_{13}H_7F_6NS_2$ (M + H): 356.0002, found (M + H): 356.0005.

***N*-Cyclohexylthiophene-2-carbothioamide (5ja).** yellow solid ; Yield - 70% (158 mg); mp:122-124 ºC; R_f (10% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3272, 2921, 2852, 1537, 1531, 983. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 9.84-9.82 (m, NH, 1H), 7.74-7.71 (m, 2H), 4.37-4.34 (m, CHNH, 1H), 1.95-1.92 (m, 2H); 1.78-1.75 (m, 2H), 1.65-1.62 (m, 1H), 1.44-1.24 (m, 4H), 1.19-1.12 (m, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 185.0, 147.3, 133.7, 127.9, 124.1, 54.9, 30.8, 24.8; **ESI-HRMS** *(m/z)*: Calculated for $C_{11}H_{15}NS_2$ (M + Na): 248.0544, found (M + H): 248.0570.

2,5-Dimethyl-N-phenylthiophene-3-carbothioamide (5ad).[22a] Yellow solid; Yield - 90% (222 mg); mp: 93-95 ºC (lit.[22a] 93-93.5 °C); R_f (10% EtOAc/hexane) 0.3; **IR** (KBr, cm^{-1}): 3222, 1539, 1490, 1387, 1351. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 11.53 (brs, 1H), 7.84 (d, J = 7.8 Hz, 2H), 7.43-7.40 (m, 2H), 7.25 (t, J = 7.2 Hz, 1H), 6.89 (s, 1H), 2.46 (s, 3H), 2.38 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 192.1, 141.3, 139.6, 134.7, 134.5, 128.5, 127.1, 126.1, 123.6, 14.6, 14.1; **ESI-HRMS** *(m/z)*: Calculated for $C_{13}H_{13}NS_2$ (M + Na): 270.0387, found (M + Na): 270.0386.

3,4-Dimethoxy-N-phenylbenzamide (7).[30] White solid; Yield -93% (239 mg); mp: 164-166 ºC (lit.[31] 160-162 °C); R_f (30% EtOAc/hexane) 0.2; **IR** (KBr, cm^{-1}): 3318, 1646, 1512, 1320, 1271; **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 10.07 (brs, 1H), 7.76 (d, J = 7.9 Hz, 2H), 7.62 (d, J = 8.3 Hz, 1H), 7.54 (s, 1H), 7.37-7.33 (m, 2H), 7.10-7.07 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 164.9, 151.6, 148.3, 139.3, 128.6, 127.0, 123.5, 121.0, 120.5, 111.0, 110.9, 55.7, 55.6; **ESI-HRMS** *(m/z)*: Calculated for $C_{15}H_{15}NO_3$ (M + Na): 280.0950, found (M + H): 280.0951.

***N*-Phenylthiophene-2-carboxamide (8).**[30] White solid; Yield - 86% (174 mg); mp: 140-141 ºC (lit.[30] 136-138 °C); R_f (20% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3307, 1632, 1616, 1596, 1538, 1445, 1322. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), **10.22 (brs, 1H),** 8.02 (d, J = 3.4 Hz, 1H), 7.85 (d, J = 4.8 Hz, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 4.3 Hz, 1H), 7.10 (t, J = 7.28 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 159.90, 140.07, 138.71, 131.88, 129.11, 128.70, 128.08, 123.78, 120.41. **ESI-HRMS** *(m/z)*: Calculated for $C_{11}H_9NOS$ (M + Na): 226.0303, found (M + H): 226.0291.

***N*-Isopropylthiophene-2-carboxamide (9).** White solid; Yield - 92% (155 mg); mp: 139-142° C (lit.[32] 138-140 °C); R_f (30% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3288, 2971, 1614, 1539. **^{1}H NMR** (400 MHz, DMSO- d_6): δ (ppm), 8.20 (d, J = 7.0 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.70-7.69 (m, 1H), 7.12-7.10 (m, 1H), 4.08-3.99 (m, 1H), 1.15 (d, J = 6.6 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO- d_6): δ (ppm) 160.2, 140.5, 130.4, 127.74, 127.72, 41.0, 22.3; **ESI-HRMS** *(m/z)*: Calculated for $C_8H_{11}NOS$ (M + Na): 192.0459, found (M + Na): 192.0456.

4-Hydroxy-*N*-phenylbenzamide (10).[33] White solid; Yield - 70% (153 mg); mp: 125-127 ºC (lit[34]. 126-127 ºC); R_f (10% EtOAc/hexane) 0.4; **IR** (KBr, cm^{-1}): 3044, 1718, 1598, 1534, 1491, 1318, 1224, 1202. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.45 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.4 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 7.1 Hz, 1H), 7.20 (m, 2H), 7.11 (t, J = 7.3 Hz, 1H), 6.94 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 151.6, 150.5, 137.3, 129.4, 129.1, 125.7, 123.9, 121.6, 118.7. **ESI-HRMS** *(m/z)*: Calculated for $C_{13}H_{11}NO_2$ (M + Na): 236.0687, found (M + Na): 236.0688.

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