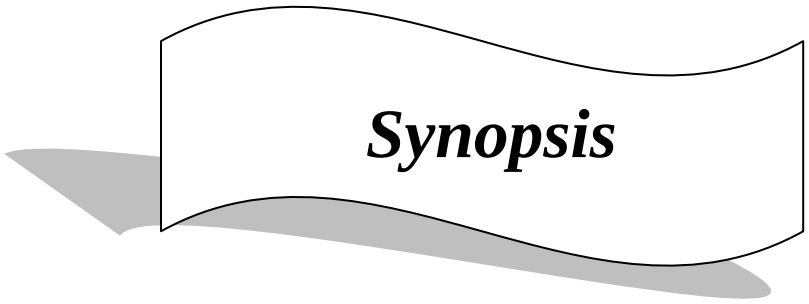

Synopsis

SYNOPSIS

The thesis entitled "**Metal-Free Oxidative Strategies for the Construction of Heterocyclic Compounds: Synthesis of 1,2,4-Thiadiazoles, 2-Aminobenzo[*d*]thiazoles and 1,2,4-Triazolo[1,5-*a*]pyridines**" has been divided into three chapters.

CHAPTER I: I_2-Catalyzed Oxidative N-S Bond Formation: Metal-Free Regiospecific Synthesis of *N*-Fused and 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles.

CHAPTER II: Hypervalent Iodine(III)-Mediated Solvent-Free, Regioselective Synthesis of 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles and 2-Aminobenzo[*d*]thiazoles.

SECTION A: Synthesis of 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles.

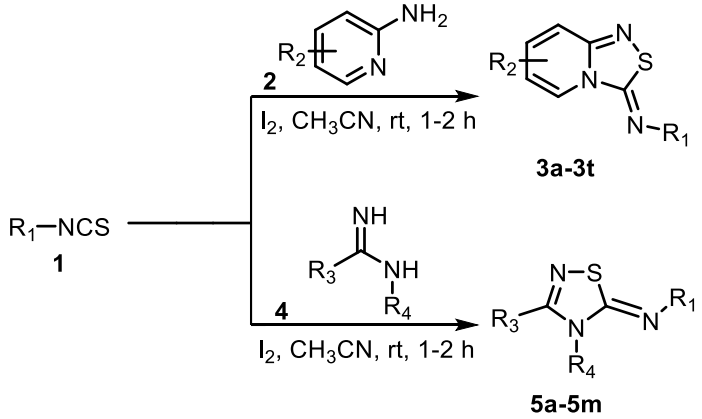
SECTION B: Synthesis of 2-Aminobenzo[*d*]thiazoles.

CHAPTER III: $PhI(OAc)_2$-Mediated Regioselective Synthesis of 5-Guanidino-1,2,4-thiadiazoles and 1,2,4-Triazolo[1,5-*a*]pyridines *via* Oxidative N-S and N-N Bond Formation.

Chapter-I

I_2-Catalyzed Oxidative N-S Bond Formation: Metal-Free Regiospecific Synthesis of *N*-Fused and 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles

This chapter consists of introduction and describes the methods for the construction of *N*-fused and 3,4-disubstituted 5-imino-1,2,4-thiadiazoles as well as previous approaches for the synthesis of 1,2,4-thiadiazoles. Heterocyclic compounds of 1,2,4-thiadiazoles are an important class of organic molecules for medicinal chemistry and are associated with a broad range of biological activity,[1a] including antibacterial,[1b] antiulcerative,[2] antidiabetic,[3] antirheumatic,[4] anti-inflammatory,[5] anti-microbial agents.[6] A family of 1,2,4-thiadiazole derivatives also exhibit fungicidal,[7] and herbicidal activity.[8] Despite their wide applications in pharmacology and organic synthesis, few methods were developed for the synthesis of 1,2,4-thiadiazoles. In this present work, the construction of N-S bond by employing molecular iodine as a catalyst to synthesize biologically important *N*-fused 1,2,4-thiadiazole and 3,4-disubstituted 5-imino-1,2,4-thiadiazole scaffolds (Scheme 1) were envisioned for the first time and the results will be reported.

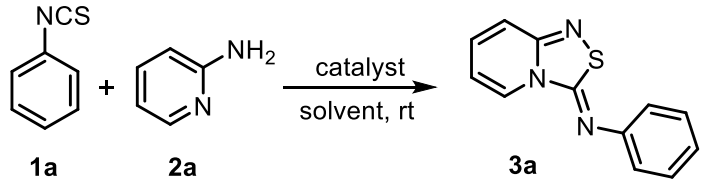


Scheme 1: Synthesis of *N*-fused 1,2,4-thiadiazoles and 3,4-disubstituted 5-imino-1,2,4-thiadiazoles

The initial study started with the reaction of isothiocyanate **1a** with 2-aminopyridine (**2a**) in the presence of iodine (0.2 equiv) with no solvent (neat) at room temperature. Delightfully, the formation of the expected 1,2,4-thiadiazole **3a** was observed in low yield (Table 1, entry 1). The poor yield of **3a** might be due to the low solubility of the reactants. Next, the optimization of reaction conditions with various solvents were established, forward yield improvement and the results are summarized in Table 1. Amongst all, acetonitrile proved to be a better solvent in terms of the reaction time and yield of the product (Table 1, entry 4). The replacement of iodine with other oxidizing catalysts, including KI, TBAI and

NIS resulted in a decreased yield of **3a** (Table 1, entries 8-10). Having established suitable catalyst for synthesis of 1,2,4-thiadiazoles, the quantity of iodine was screened. Raising the loading of iodine resulted in the desired product **3a** in high yields (Table 1, entries 11 and 12), and the use of 50 mol % of catalyst gave the best result (Table 1, entry 12). With the further increasing of iodine from 0.5 to 1.0 equiv, the yield of **3a** not augmented (Table 1, entry 13). Thus, the standardized conditions for this reaction are summarized as follows: **1a** (3 mmol, 1equiv), **2a** (3 mmol, 1 equiv), and I_2 (50 mol %), at rt in CH_3CN in 1-2 h.

Table 1: Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst (mol %)	Solvent	Yield (%)
1	I_2 (20)	-	19
2	I_2 (20)	DCE	32
3	I_2 (20)	1,4-dioxane	41
4	I_2 (20)	CH_3CN	58
5	I_2 (20)	DMF	29
6	I_2 (20)	EtOH	32
7	I_2 (20)	DMSO	30
8	KI (20)	CH_3CN	trace
9	TBAI (20)	CH_3CN	42
10	NIS (20)	CH_3CN	36
11	I_2 (30)	CH_3CN	72
12	**I_2 (50)**	**CH_3CN**	**91**
13	I_2 (100)	CH_3CN	91

[a]Reaction conditions: **1a** (3 mmol, 1 equiv), **2a** (3 mmol, 1 equiv), catalyst (x mol %) and solvent (1 mL) at rt for 1 to 2 h.

Next, the generality of the oxidative synthesis of *N*-fused 1,2,4-thiadiazoles (Table 2) were investigated. A variety of isothiocyanates with different substituents were tested. As expected, all the isothiocyanates gave the corresponding *N*-fused 1,2,4-thiadiazoles in good to excellent yields. Phenyl isothiocyanate (**1a**) gave the desired product **3a** in 91% yield. Further

structural confirmation of **3a** was ascertained by X-ray studies (Figure 1). Aryl isothiocyanates containing groups like -methyl, -methoxy at *para*-, *meta*-, and *ortho*-positions gave better reactivity and provided the corresponding products in good to excellent yields (**3b, 3c, 3h** and **3i**). Conversely, aryl isothiocyanates with electron-withdrawing groups such as -chloro, and -fluoro at *para*-, and *meta*-positions furnished corresponding products in moderate to good yields (**3d**, **3e** and **3j**). It should be noted that aryl isothiocyanates with strong electron-withdrawing groups, including -NO_2, and -CF_3, were well tolerated under the reaction conditions and the desired *N*-fused 1,2,4-thiadiazole products were obtained in good yields (**3f** and **3g**). It was worth mentioning that steric hindrance (**3b, 3c** and **3h-3j**) and electronic factors (**3a-3j**) of phenyl isothiocyanates seemingly exerted a negligible influence on the reaction rate or the yields of the products. An alicyclic isothiocyanate such as cyclopropyl isothiocyanate was also tolerated under these reaction conditions, and the corresponding product **3k** was isolated in 79% yield. Aliphatic isothiocyanates including cyclohexyl methyl, propyl and isopropyl underwent the oxidative reaction to give the corresponding products in good yields (**3l-3n**). To further examine the scope and limitations of the reaction, various 2-aminopyridines with phenyl isothiocyanate (Table 2) was studied. Methyl substituted 2-aminopyridine was well tolerated and the position of the methyl substituent at 4, 5 and 6 did not bear any significant affect on the reaction yield (**3o-3q**). Electron-withdrawing groups such as -chloro and -bromo were compatiable and gave the corresponding products **3r** and **3s** in 87% and 86% yields, respectively. When a strong electron-withdrawing nitro group was used, the desired product **3t** was obtained in 84% yield. It should be noted that the catalytic transformation was successfully conducted in gram scale without any difficulty (Table 2, **3a**).

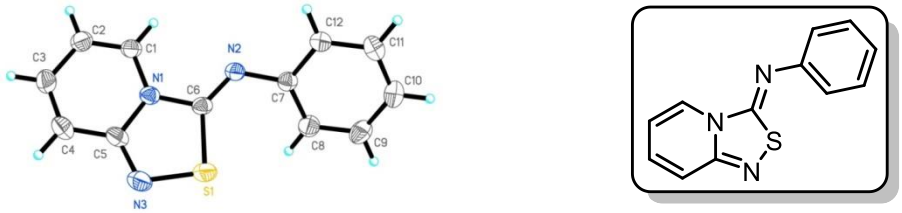
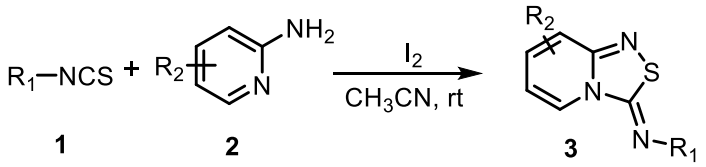
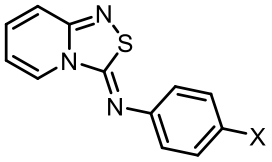


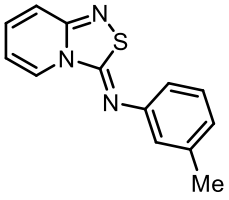
Figure 1: Crystal structure of the compound **3a**

Table 2: Synthesis of *N*-fused 1,2,4-thiadiazoles[a]

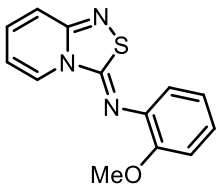




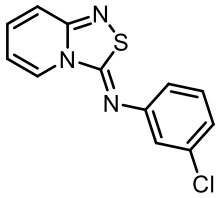
3a, X = H, 91% (89%)[b]
3b, X = Me, 90%
3c, X = OMe, 95%
3d, X = Cl, 88%
3e, X = F, 88%
3f, X = NO_2, 85%
3g, X = CF_3, 82%



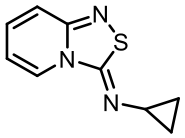
3h, 82%



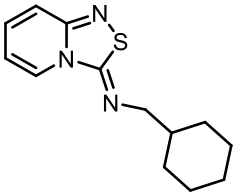
3i, 82%



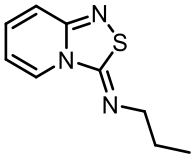
3j, 86%



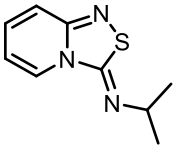
3k, 79%



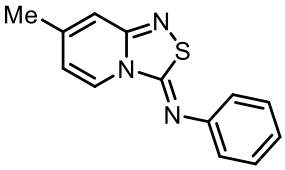
3l, 78%



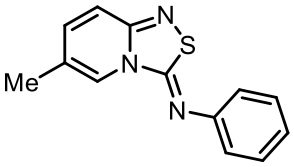
3m, 76%



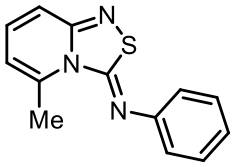
3n, 76%



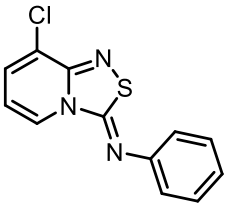
3o, 86%



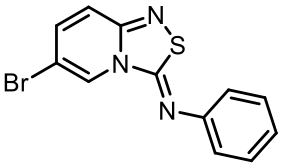
3p, 86%



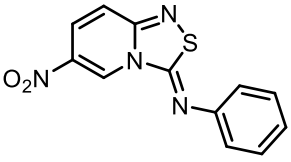
3q, 86%



3r, 87%



3s, 86%



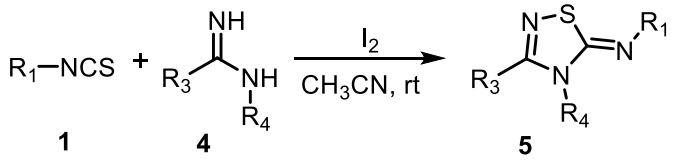
3t, 84%

[a]Reaction conditions: **1** (3 mmol, 1 equiv), **2** (3 mmol, 1 equiv), I_2 (50 mol %) and CH_3CN (1 mL) at rt for 1to 2 h. [b]The reaction was conducted on gram-scale.

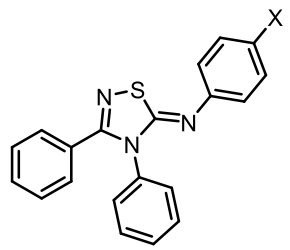
In light of successful oxidative cyclization process for the synthesis of *N*-fused 1,2,4-thiadiazoles, further the scope of this practical approach was extended by replacing 2-

aminopyridine (**2**) with *N*-phenyl benzamidines (**4**) to prepare 3,4-disubstituted 5-imino-1,2,4-thiadiazoles under the optimal reaction conditions. Gratifyingly, following the above protocol, 3,4-disubstituted 5-imino-1,2,4-thiadiazoles were prepared efficiently. As shown in Table 3, this protocol tolerates a variety of aryl isothiocyanates with different *N*-phenyl benzamidines. No significant substituent effect was observed, excellent yields were obtained for arylisothiocyanates having both electron-donating and electron-withdrawing substituents with different *N*-phenyl benzamidines. This methodology worked equally well with alicyclic isothiocyanate such as cyclopropyl in good yield (**5l**). Fortunately, the reaction worked equally well with aliphatic isothiocyanates including butaryl, isopropyl and propyl gave corresponding 3,4-disubstituted 5-imino-1,2,4-thiadiazoles in good yields (**5i**, **5k** and **5m**). Compound **5k** was fully characterized by X-ray analysis (Figure 2).

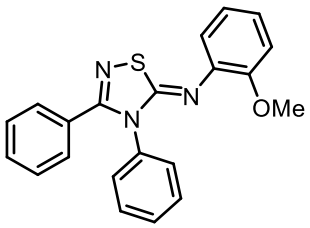
Table 3: Synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles[a]



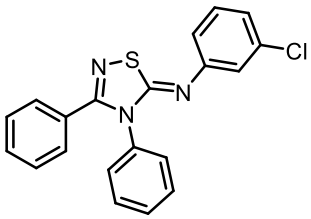
1 **4** **5**



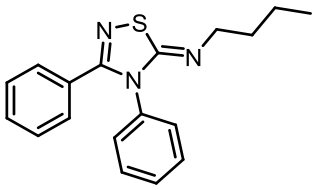
5a, X = H, 89%
5b, X = Me, 90%
5c, X = OMe, 90%
5d, X = Cl, 87%
5e, X = NO_2, 86%
5f, X = CF_3, 82%



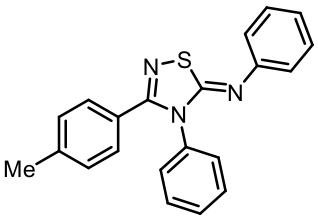
5g, 82%



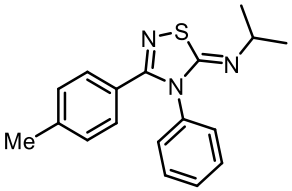
5h, 87%



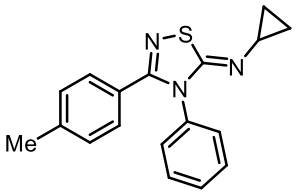
5i, 74%



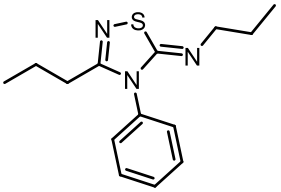
5j, 76%



5k, 75%



5l, 76%



5m, 73%

[a]Reaction conditions: **1** (1.5 mmol, 1 equiv), **4** (1.5 mmol, 1 equiv), I_2 (50 mol %) and CH_3CN (1 mL) at rt for 1to 2 h.

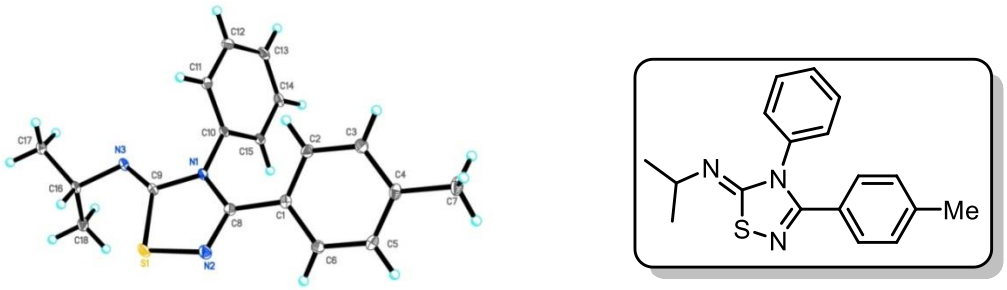
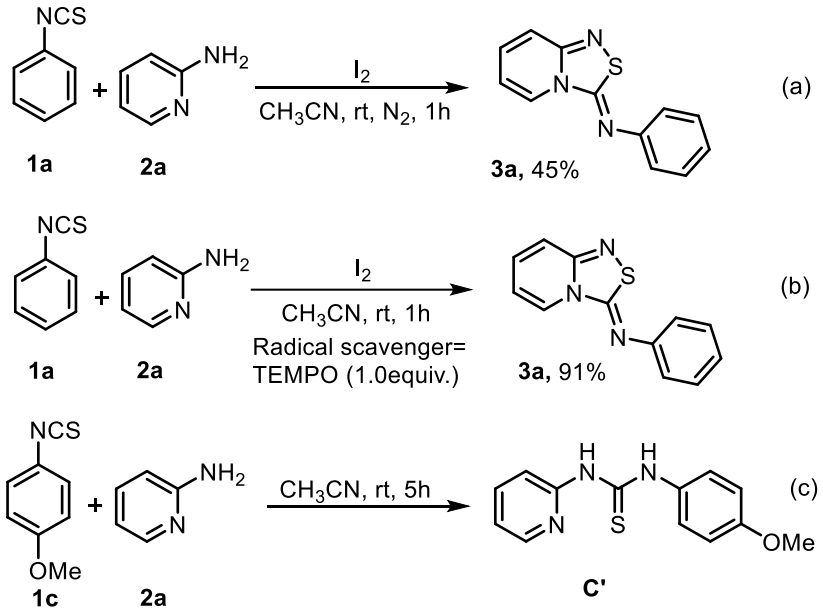
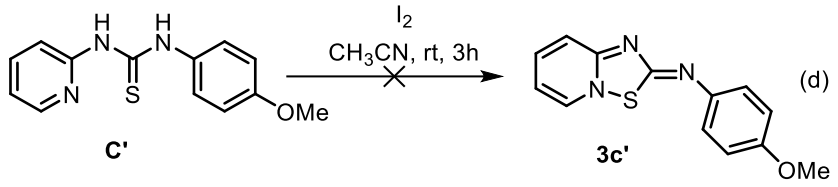


Figure 2: Crystal structure of the compound **5k**

To further probe the mechanism, control experiments were conducted as shown in Scheme 2. When the phenyl isothiocyanate (**1a**) reaction with 2-aminopyridine (**2a**) under optimized conditions in inert atmosphere the reaction was dramatically inhibited and only 45% yield of the desired product **3a** was isolated, which suggested air (oxygen) is necessary for this reaction (Scheme 2a). As expected, when 2,2,6,6-tetramethylpiperdine-1-oxide (TEMPO, a well-known radical inhibitor) was added to the reaction, no considerable effect was observed (Scheme 2b), demonstrating that a radical mechanism was ruled out. When the phenyl isothiocyanate (**1c**) was reacted with 2-aminopyridine (**2a**) in the absence of I_2 intermediate **C'** (Scheme 2c) was obtained, which was confirmed by ^1H, ^{13}C NMR, HRMS and X-ray analysis (Figure 3). However **C'** did not produce **3c'** in the presence of I_2 (Scheme 2d). Thus, it may be deduced that the present protocol is highly regiospecific and affords **3c** exclusively.





Scheme 2: Control experiments

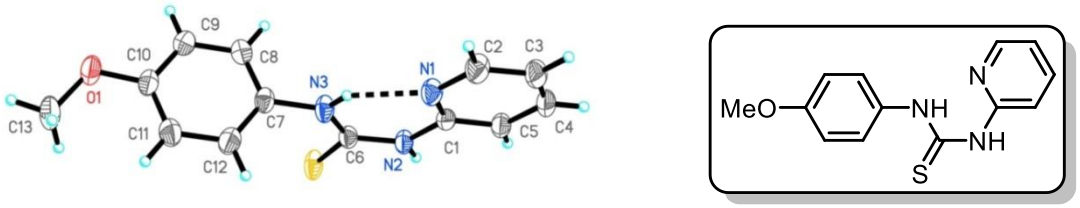
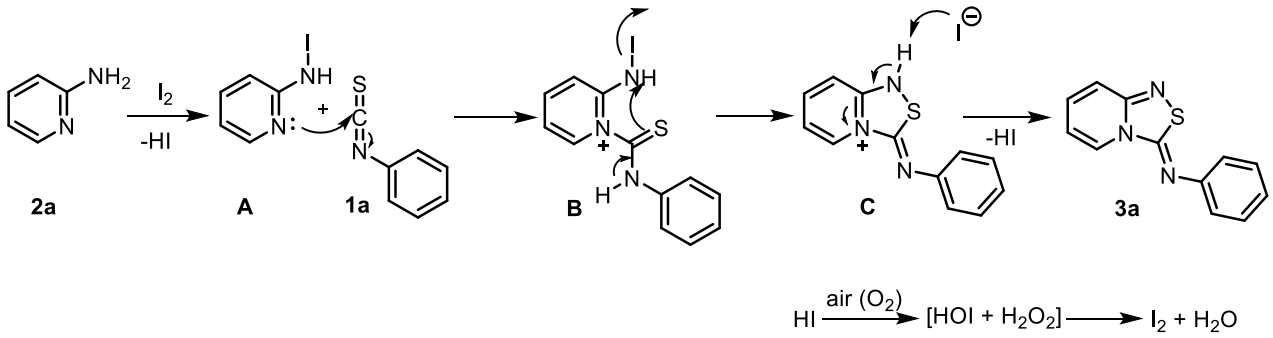


Figure 3: Crystal structure of intermediate **C'**

Based on results presented above, and previous reports,[9] a plausible mechanism was proposed and shown in Scheme 3. First step for the formation of product **3a** involves 2-aminopyridine (**2a**) reaction with iodine gives intermediate **A**, a nucleophilic attack of nitrogen of pyridine ring on phenyl isothiocyanate (**1a**) to form cationic intermediate **B**. The intramolecular nucleophilic ring-closing of intermediate **B** gives intermediate **C**. Finally proton abstraction takes place to give the corresponding derivative **3a**. Under aerobic conditions iodine was regenerated.



Scheme 3: A plausible mechanism for the preparation of **3a**

In summary, a novel and convenient iodine catalyzed oxidative protocol for the N-S bond formation towards the regiospecific synthesis of *N*-fused 1,2,4-thiadiazole and 3,4-disubstituted 5-imino-1,2,4-thiadiazole derivatives was developed for the first time. This versatile and transition-metal-free one-pot protocol features a broad substrate scope, inexpensive and nontoxic molecular iodine as the catalyst, no addition of any ligand, base, or additive is need and with easy workup procedure. The developed synthetic approach can be easily scaled up to gram scale, thereby providing the possibility for the scaled production of diverse *N*-fused 1,2,4-thiadiazole and 3,4-disubstituted 5-imino-1,2,4-thiadiazole derivatives.

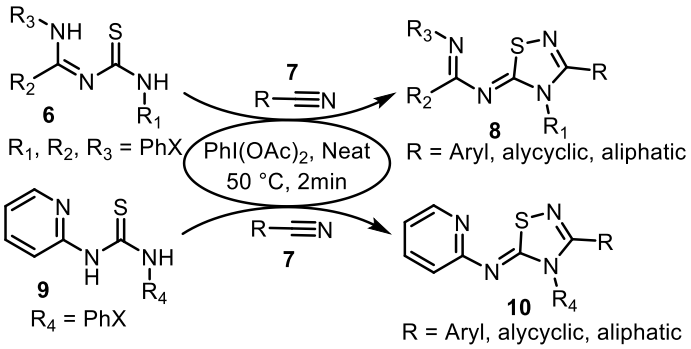
Chapter-II

Hypervalent Iodine(III)-Mediated Solvent-Free, Regioselective Synthesis of 3,4-Disubstituted 5-Imino-1,2,4-thiadiazoles and 2-Aminobenzo[*d*]thiazoles

This chapter consists of introduction and describes the synthetic protocols for the construction of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles and 2-aminobenzo[*d*]thiazoles as well as previous approaches for the synthesis of 5-imino-1,2,4-thiadiazoles and benzo[*d*]thiazoles. This chapter has been divided into two sections.

Section-A: **Synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles**

The present section gives the detailed description on the synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles. The heterocyclic compounds of 5-imino-1,2,4-thiadiazoles regulates many aspects of neuronal function, such as gene expression, neurogenesis, synaptic plasticity, neuronal structure, and neuronal death and survival.[10] Recently, hypervalent iodine reagents have found a wide range of applications in organic transformations due to their ready availability, easy handling, low toxicity and reactivity similar to heavy metals.[11] In particular, phenyliodine(III) diacetate (PIDA) has been successfully employed in the construction of C-C, C-N, C-O, C-S and also N-S bonds.[12] On the other hand, organic transformations under solvent-free conditions have gained significant attention in recent years.[13] This is because solvent-free reactions usually need shorter reaction times, lower costs with reduced pollution and simple workup procedures.[14] As part of our ongoing project to investigate efficient synthetic methods for heterocycles[15] herein, a metal-free, solvent-free, regiospecific protocol for the construction of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles through C-N, N-S bond formation by employing PIDA under neat conditions (Scheme 4) is reported.

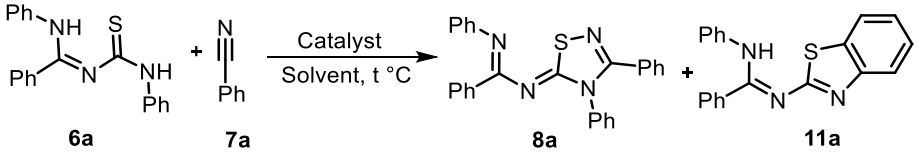


Scheme 4: Synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles

The required substrates imidoyl thioureas were readily prepared from the corresponding amidine and phenylisothiocynate. Initially imidoyl thiourea (**6a**, 1.0 equiv.)

and benzonitrile (**7a**, 1.0 equiv.) and PIDA (1.0 equiv.) in DMSO at 50 °C was chosen as model reaction to explore and optimize the reaction conditions. Surprisingly, an unexpected minor product benzo[*d*]thiazole (**11a**) was observed along with the desired 1,2,4-thiadiazole (**8a**) under these conditions (Table 4, entry 1). Aiming to accomplish better yield of **8a** and suppress the formation of **11a**, the reaction was screened under diverse conditions and the results are summarized in Table 4. Performing the reaction in the presence of various solvents, such as DMF, DCE and THF, led to inferior results (Table 4, entries 2-4). The reaction also failed to improve the yield of **8a** with the protic solvents such as MeOH, IPA (Table 2.1, entries 5 and 6). Notably, in all cases **11a** was also observed in 21-34% yield. Next, the reaction was examined in chlorobenzene and toluene which offered **8a** in 79% and 76% yields respectively in 1h along with **11a** in minor amount (Table 4, entries 7 and 8). Delightfully, when the reaction was carried out under neat reaction conditions we discovered that only **8a** in 88% yield was obtained (Table 4, entry 9). In addition, the reaction was investigated in different oxidants including PIFA, PhIO, I_2 and CAN under neat condition. All these oxidants were not suitable for this transformation (Table 4, entries 10-13). Increasing the amount of PIDA did not affect the product yield but when the amount of PIDA was decreased, significantly lower yield was obtained (Table 4, entries 14 and 15). Next, reaction temperature affects were also studied. Poor yield was obtained when reaction was conducted at 35 °C and raising the temperature to 65 °C showed that no improvement can be achieved (Table 4, entries 16 and 17). Thus the optimal reaction conditions were set to be imidoyl thiourea (**6a**) (1.0 equiv.) and benzonitrile (**7a**) (1.2 equiv.) and PIDA (1.0 equiv.) at 50 °C under neat conditions.

Table 4: Optimization of reaction conditions



6a **7a** **8a** **11a**

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Yield **8a** (%)[c]	Yield **11a** (%)[c]
1[a]	PIDA (100)	DMSO	50	55	21
2[a]	PIDA (100)	DMF	50	47	23
3[a]	PIDA (100)	DCE	50	45	30
4[a]	PIDA (100)	THF	50	49	34

5[a]	PIDA (100)	MeOH	50	30	22
6[a]	PIDA (100)	IPA	50	36	25
7[a]	PIDA (100)	PhCl	50	79	8
8[a]	PIDA (100)	Toluene	50	76	10
9[b]	**PIDA (100)**	**neat**	**50**	**88**	**--**
10[b]	PIFA (100)	neat	50	26	38
11[b]	PhIO (100)	neat	50	17	21
12[b]	I_2 (100)	neat	50	--	--
13[b]	CAN (100)	neat	50	Trace	--
14[b]	PIDA (150)	neat	50	88	--
15[b]	PIDA (50)	neat	50	72	--
16[b]	PIDA (100)	neat	35	79	--
17[b]	PIDA (100)	neat	65	88	--

a) Reaction conditions: **6a** (0.6 mmol, 1.0 equiv.), **7a** (0.6 mmol, 1.0 equiv.) and PIDA (1.0 equiv.) under neat condition at 50 °C for 2 min.

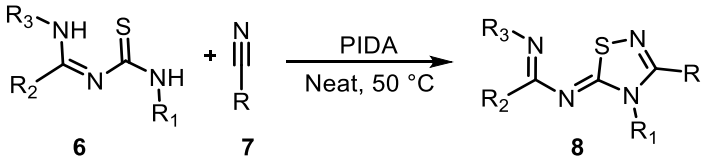
b) Reaction conditions: **6a** (0.6 mmol, 1.0 equiv.), **7a** (0.7 mmol, 1.2 equiv.) and PIDA (1.0 equiv.) under neat condition at 50 °C for 2 min.

c) Isolated yield.

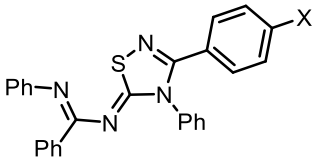
With the optimized reaction conditions in hand, the scope and generality of synthetic protocol was explored and the results are summarized in Table 5. As anticipated, all the benzonitriles gave the corresponding 3,4-disubstituted 5-imino-1,2,4-thiadiazoles in good to excellent yields. Benzonitriles with electron-donating groups like -methyl and -methoxy at *ortho*, *para* and *meta* positions gave the corresponding products **8b**, **8c**, **8h** and **8j** in good to high yields. It was noted that *ortho*-substituted benzonitriles gave a yield similar to that of *para* subsitituted benzonitrile. The reaction with halogen substituent on benzonitriles such as -F, -Cl and -Br afforded the products **8d**-**8f** in good yields. Benzonitriles with strong electron-withdrawing groups like *p*-CF_3 and *m*-NO_2 generated the corresponding thiadiazoles **8g** and **8i** in 78% and 80% yields respectively. In addition, the heteronitrile such as thiophene-2-carbonitrile gave **8o** in 79% yield. Interestingly, alicyclic and aliphatic nitriles like cyclohexyl, butaryl and methyl reacted smoothly to give the desired products **8p**-**8v** in reasonable good yields. The structure of the compound **8j** was confirmed by single-crystal X-ray analysis (Figure 4). Next, the scope of the protocol by varying the imidoyl thiourea was investigated, which proceeded successfully to afford the corresponding 3,4-disubstituted 5-

imino-1,2,4-thiadiazoles in moderate to good yields. As described in Table 5, all imidoyl thiourea substrates bearing electron-rich substituents such as -Me and -OMe on the aryl ring and electron-deficient substrates like -Cl, -Br and -NO_2 on the aryl ring with different nitriles gave the desired products in moderate to good yields (Table 5, entries **8k**-**8n** and **8r**-**8v**). Imidoyl thioureas bearing aryl group with electron-withdrawing substituents gave considerably higher yields than those with electron-donating groups.

Table 5: Synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles[a,b]



6 **7** **8**



8a, X = H, 88%

8b, X = Me, 90%

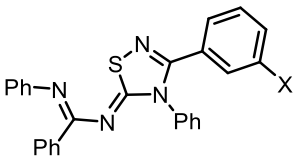
8c, X = OMe, 91%

8d, X = F, 86%

8e, X = Cl, 87%

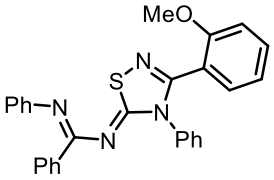
8f, X = Br, 86%

8g, X = CF_3, 78%

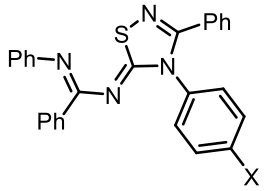


8h, X = OMe, 89%

8i, X = NO_2, 80%

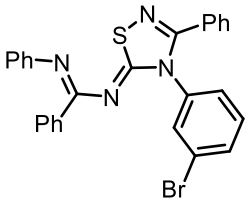


8j, 90%

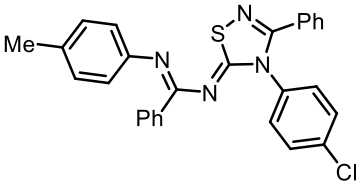


8k, X = OMe, 78%

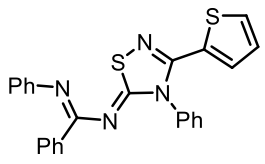
8l, X = NO_2, 90%



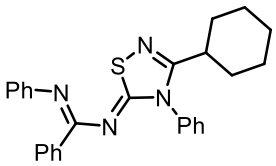
8m, 84%



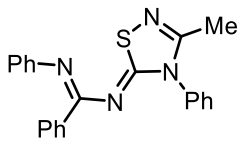
8n, 87%

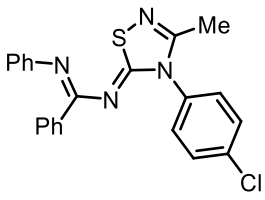


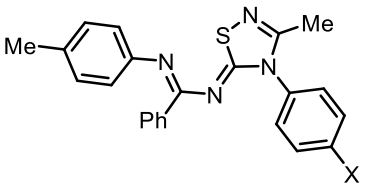
8o, 79%



8p, 76%





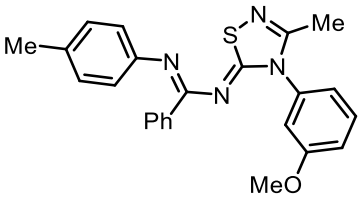


8q, 86%

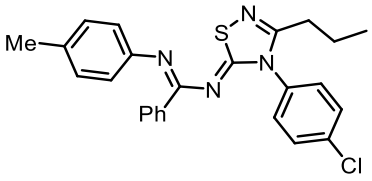
8r, 88%

8s, X = Me, 87%

8t, X = Cl, 91%



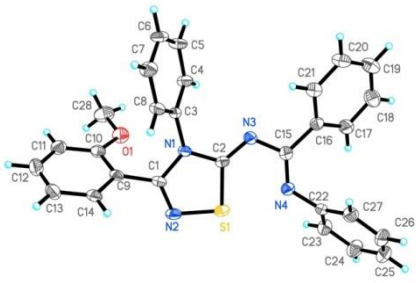
8u, 82%



8v, 83%

a) Reaction conditions: **6** (0.6 mmol), **7** (0.7 mmol) and PIDA (1.0 equiv.) under neat conditions at 50 °C for 2 min.

b) Isolated yield.



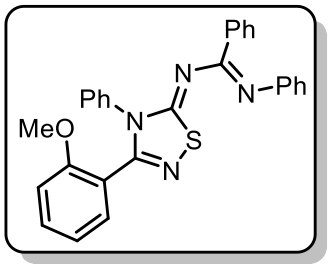


Figure 4: Crystal structure of the compound **8j**

The design of molecules having potent polyheterocyclic scaffolds that emerge as novel drugs in discovery process is ever challange. In light of the above successive results and advances of polyheterocyclic compounds, the methodology towards the synthesis of 3,4-disubstituted 2-pyridinyl 5-imino-1,2,4-thiadiazoles (**10**) could also be expanded. It is glad to observe the formation of desired product **10a** in 90% yield. Next, the scope and generality of the reaction (Table 6) was investigated. Benzonitriles bearing electron-donating groups like -Me and -OMe and electron-withdrawing groups such as -F, -Cl and -CF_3 were well tolerated and the desired products **10b**-**10f** were obtained in good to high yields. Gratifyingly, alicyclic and aliphatic nitriles such as cyclohexly, pentyl and methyl were also good partners in this transformation (Table 6, entries **10j**-**10l**). Furthermore, various pyridinylthioureas with substitutents on aryl ring (R_4) such as methyl, chloro and nitro groups also were well tolerated to yield the desired products (Table 6, entries **10g**-**10i**). The structure of compound **10h** was further confirmed by X-ray analysis (Figure 5).

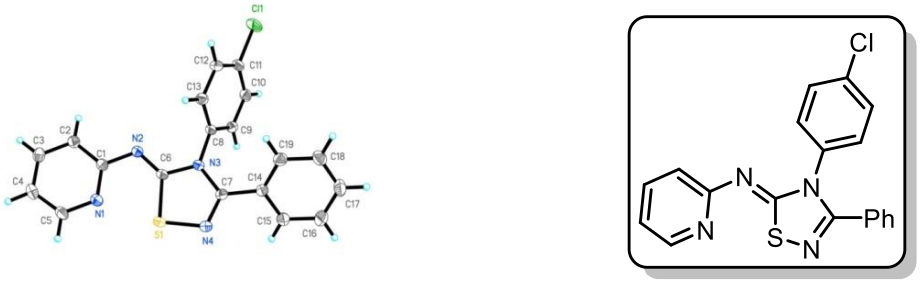
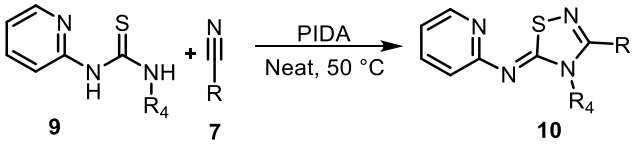
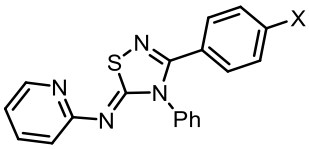


Figure 5: Crystal structure of the compound **10h**

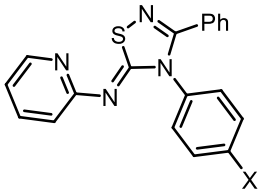
Table 6: Synthesis of 3,4-disubstituted 2-pyridinyl 5-imino-1,2,4-thiadiazoles[a,b]



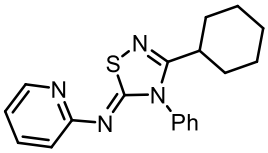
9 **7** **10**



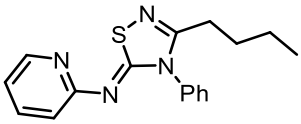
10a, X = H, 90%
10b, X = Me, 91%
10c, X = OMe, 91%
10d, X = F, 85%
10e, X = Cl, 81%
10f, X = CF_3, 74%



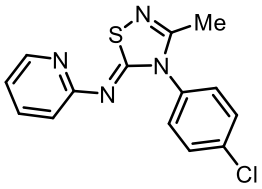
10g, X = Me, 87%
10h, X = Cl, 89%
10i, X = NO_2, 86%



10j, 78%



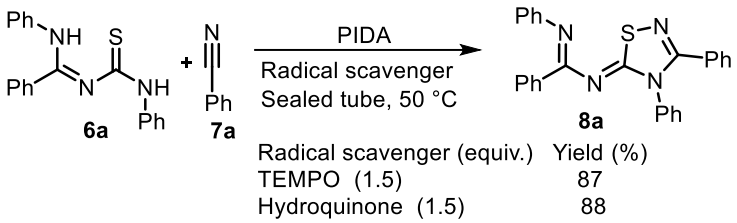
10k, 81%



10l, 86%

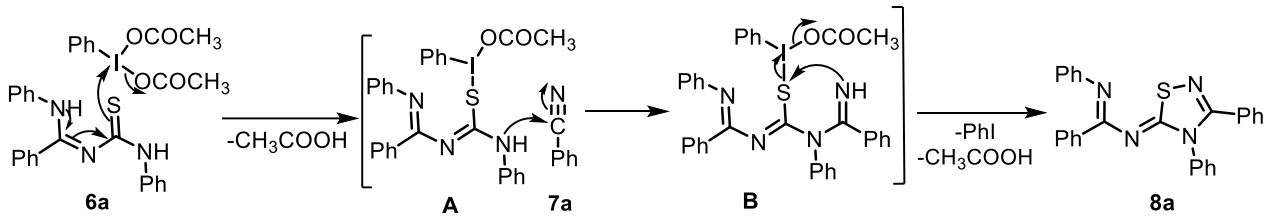
a) Reaction conditions: **9** (0.8 mmol), **7** (1.0 mmol) and PIDA (1.0 equiv.) under neat condition at 50 °C for 2 min.
b) Isolated yield.

In order to explore the reaction mechanism, the radical trapping experiments were conducted in the presence of radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and hydroquinone under the optimized conditions and no considerable effect was observed. These results indicated that the reaction proceeds through an ionic mechanism (Scheme 5). A reaction between **6a** and **7a** in the absence of PIDA was performed but the reaction did not provide the desired product.



Scheme 5: Control experiments

On the basis of these experimental results and previous reports,[16] a mechanism has been proposed for this regioselective synthesis, by taking the formation of **8a** as an example (Scheme 6). Initially, the imidoyl thiourea (**6a**) reacts with PIDA which provides intermediate **A** up on the removal of AcOH. Intermediate **A** reacts with benzonitrile (**7a**) to afford intermediate **B**, followed by intramolecular nucleophilic attack of NH group on the sulfur atom with the loss of iodobenzene and AcOH resulting in the desired product **8a**.



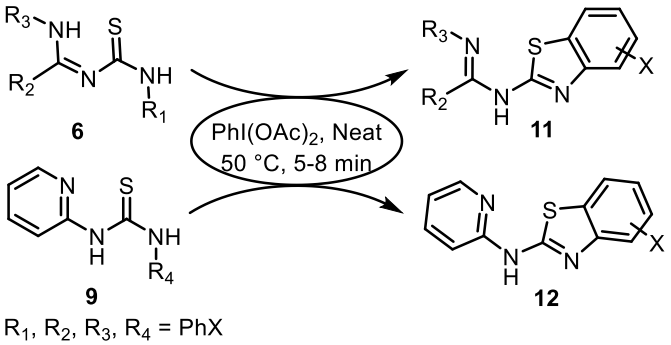
Scheme 6: Proposed reaction mechanism

In conclusion, a novel and efficient method for the synthesis of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles was developed and the results are described. This method includes a PIDA-mediated regioselective oxidative C-N and N-S bond formation under neat conditions. This methodology proceeded with high efficiency and wide functional group tolerance affording the corresponding products in good to excellent yields. The key features such as regioselectivity, solvent-free and metal-free reaction conditions with atom economy in short reaction time makes it an attractive alternative for the preparation of 3,4-disubstituted 5-imino-1,2,4-thiadiazoles.

Section-B: **Synthesis of 2-Aminobenzo[*d*]thiazoles**

The present section gives the detailed description on the synthesis of 2-aminobenzo[*d*]thiazoles. The C-S bond formations in heterocycles were fundamental to the art of organic synthesis, represents a key strategy for the synthesis of a broad range of biologically important molecules and functional materials.[17] In recent years, an increasing number of 2-substituted benzothiazoles have been designed and synthesized for biological evaluations, as the 2-amino benzothiazole motif is one of the privileged structure in medicinal

chemistry and reported to be cytotoxic in cancer cells.[18] In the present work a metal-free, solvent-free, regiospecific protocol for the construction of the C-S bond by employing PIDA under neat conditions for the synthesis of 2-aminobenzo[*d*]thiazoles (Scheme 7) was developed and the results will be reported.



Scheme 7: Synthesis of 2-aminobenzo[*d*]thiazoles

As discussed in the section-A, the optimized reaction conditions for the synthesis of 1,2,4-thiadiazoles (**8**) from imidoyl thioureas (**6**) and nitriles (**7**) one of the byproducts 2-aminobenzo[*d*]thiazoles was observed, with the help of the optimization reaction conditions herein we focused on the formation of byproduct 2-amino-benzo[*d*]thiazoles (**11**). Against this background, an experiment was performed with **6a** in the absence of benzonitrile (**7a**) under the optimized reaction conditions which resulted in the corresponding 2-amino-benzo[*d*]thiazole (**11a**) in 81% yield. The structure of compound **11a** was confirmed by single-crystal X-ray analysis (Figure 6).

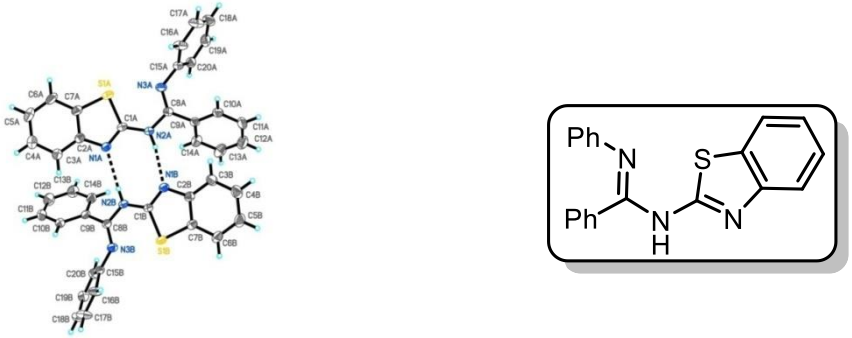
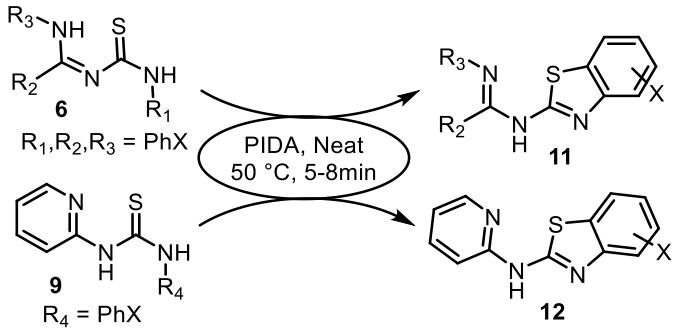


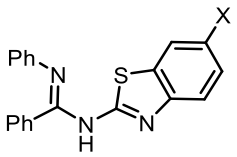
Figure 6: Crystal structure of the compound **11a**

With these optimum reaction conditions in hand, the scope of the reaction with various substituted imidoyl thioureas (Table 7) was investigated. Fortunately, imidoyl thiourea bearing both electron-rich and electron-deficient groups like -Me, -OMe, -F and -Cl on aryl ring (R_1 and R_2) reacted smoothly to give the corresponding product benzo[*d*]thiazoles in good yields (Table 7, entries **11b**-**11g**). Next, the scope of the reaction

with pyridinyl thiourea under the optimized reaction conditions for the synthesis of pyridinyl 2-aminobenzo[*d*]thiazoles **12** was probed. Interestingly, pyridinyl 2-aminobenzo[*d*]thiazoles was obtained in good yields, which was in agreement with the literature.[19] Moreover, the reaction of pyridinyl thiourea bearing electron donating and withdrawing groups on aryl ring (R_4) afforded the corresponding products **12b**-**12e** in good to fare yields.

Table 7: Synthesis of 2-aminobenzo[*d*]thiazoles[a,b]



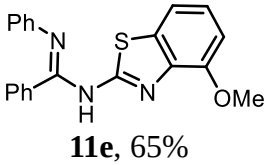


11a, X = H, 81%

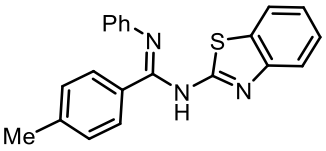
11b, X = Me, 83%

11c, X = OMe, 83%

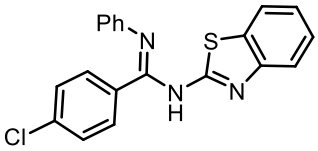
11d, X = F, 74%



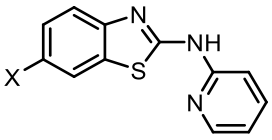
11e, 65%



11f, 73%



11g, 72%

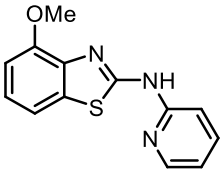


12a, X = H, 77%

12b, X = Me, 88%

12c, X = OMe, 87%

12d, X = NO_2, 54%



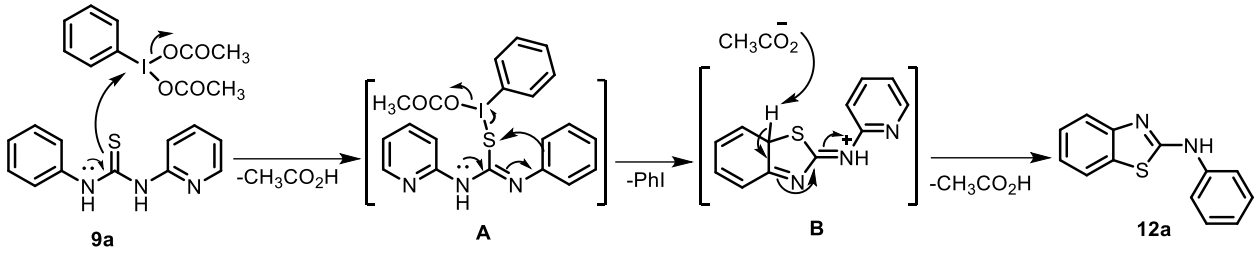
12e, 79%

a) Reaction conditions: **6** (0.6 mmol) or **9** (0.8 mmol) and PIDA (1.0 equiv.) under neat condition at 50 °C for 5-8 min.

b) Isolated yield.

On the basis of these experimental results (Scheme 5) and previous report,[19] a mechanism has been proposed for this regioselective synthesis, by taking the formation of **12a** as an example (Scheme 8). The first step involves the nucleophilic attack of the sulfur on PIDA to displace one molecule of CH_3COOH and give intermediate **A**. The sulfur atom is

then attacked by the electron-rich *ortho* position of the benzene ring to provide cationic intermediate **B**, which aromatizes to give *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine **12a**.



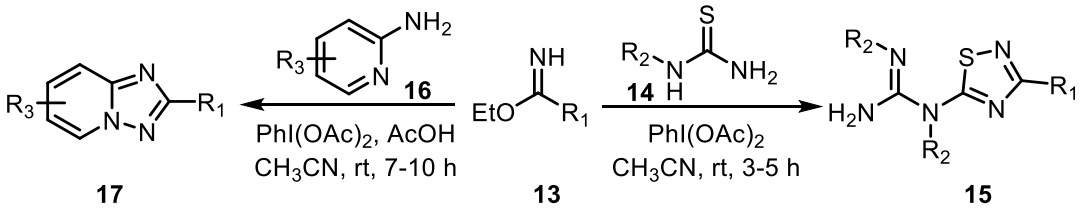
Scheme 8: Proposed reaction mechanism

In conclusion, a novel and efficient method for the synthesis of 2-aminobenzo[*d*]thiazoles was developed and described. This method includes a PIDA-mediated regioselective oxidative C-S bond formation under neat conditions. This methodology proceeded with high efficiency and wide functional group tolerance, affording the corresponding products in good to excellent yields. The key features such as regioselectivity, solvent-free and metal-free reaction conditions with atom economy in short reaction time makes it an attractive alternative for the preparation of 2-aminobenzo[*d*]thiazoles.

Chapter-III

$PhI(OAc)_2$-Mediated Regioselective Synthesis of 5-Guanidino-1,2,4-thiadiazoles and 1,2,4-Triazolo[1,5-*a*]pyridines *via* Oxidative N-S and N-N Bond Formation

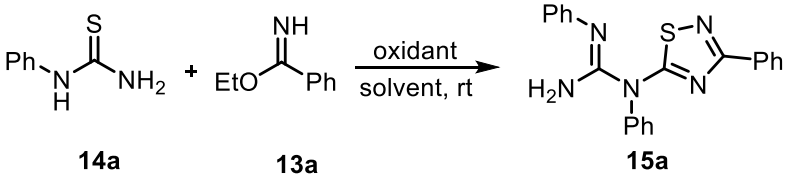
This chapter consists of introduction and construction of 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazoles as well as previous approaches for the synthesis of 1,2,4-thiadiazoles and 1,2,4-triazoles. Heterocyclic compounds such as 1,2,4-thiadiazoles and 1,2,4-triazoles are considered as very significant nitrogen-based heterocyclic scaffolds due to their important biological activities and these can be used as key skeletons in many pharmaceuticals with anticancer,[20] antifungal,[21] antibacterial[22] and anti-inflammatory activities.[23] Due to their broad applications in medicinal and pharmaceutical area, the synthesis of 1,2,4-thiadiazoles and 1,2,4-triazoles have attracted great attention. In a continuation of our previous efforts for constructing of heterocyclic compounds by using metal-free iodine/hypervalent iodine oxidants,[24] an efficient and regioselective N-S and N-N bond formations for the synthesis of 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazolo[1,5-*a*]pyridines using $PhI(OAc)_2$ (Scheme 9) was developed and the results will be presented here.



Scheme 9: Synthesis of 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazolo[1,5-*a*]pyridines

Initially phenylimidate (**13a**) (1.0 equiv.), phenylthiourea (**14a**) (2.0 equiv.) and $PhI(OAc)_2$ (1.0 equiv.) in CH_2Cl_2 at room temperature were selected as a model reaction to explore and screen the reaction conditions. The desired product 5-guanidino-1,2,4-thiadiazole **15a** was formed in very low yield (Table 8, entry 1). To enhance the yield of the product, several solvents such as $CHCl_3$, DMF, DMSO, CH_3CN and PhCl were studied and the results revealed that CH_3CN was superior to other solvents (Table 8, entries 2-6). Next, the investigation by studying various oxidants like $PhI(OCOCF_3)_2$, PhIO, I_2 and TBAI (Table 8, entries 7-10) was conducted. The stronger oxidant $PhI(OCOCF_3)_2$ could not provide a better yield of the product **15a** (Table 8, entry 7) and PhIO was found to be less potent under the studied conditions (Table 8, entry 8). Oxidants like I_2 and TBAI were also inefficient to provide the desired product (Table 8, entries 9 and 10). Having acceptable oxidant for the synthesis of guanidino thiadiazoles, further focused on the quantity of $PhI(OAc)_2$. Raising the equivalance of $PhI(OAc)_2$ resulted in improved yields of product **15a** (Table 8, entries 11 & 12), and the use of 2 equivalance of oxidant gave the best result (Table 8, entry 12). However, with the further increasing of $PhI(OAc)_2$ from 2 to 2.5 equiv, the yield of **15a** did not increase (Table 8, entry 13). Thus, the established conditions are: 1 equiv of **13a** and 2 equiv of **14a** with 2 equiv of $PhI(OAc)_2$ in the presence of acetonitrile (Table 8, entry 12).

Table 8: Optimization of reaction conditions[a]



Entry	Oxidant (x equiv)	Solvent	Yield (%)[b]
1	$PhI(OAc)_2$ (1)	CH_2Cl_2	18
2	$PhI(OAc)_2$ (1)	$CHCl_3$	10

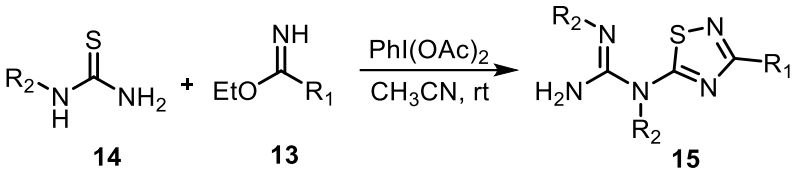
3	$PhI(OAc)_2$ (1)	DMF	15
4	$PhI(OAc)_2$ (1)	DMSO	28
5	$PhI(OAc)_2$ (1)	CH_3CN	40
6	$PhI(OAc)_2$ (1)	Ph-Cl	Trace
7	$PhI(OCOCF_3)_2$ (1)	CH_3CN	25
8	PhIO (1)	CH_3CN	20
9	I_2 (1)	CH_3CN	15
10	TBAI (1)	CH_3CN	NR
11	$PhI(OAc)_2$ (1.5)	CH_3CN	72
12	**$PhI(OAc)_2$ (2)**	**CH_3CN**	**90**
13	$PhI(OAc)_2$ (2.5)	CH_3CN	90

[a]Reaction conditions: **13a** (2 mmol, 1 equiv), **14a** (4 mmol, 2 equiv), catalyst (x equiv) and solvent (1 mL) at rt for 3 to 5 h. [b]Isolated yield.

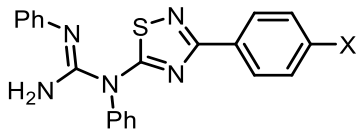
Under the optimal reaction conditions (Table 8, entry 12), the generality and functional group compatibility of this transformation for the synthesis 5-guanidino-1,2,4-thiadiazoles was explored and the results are summarized in Table 9. A wide variety of imidates with various substituents were explored. As anticipated, all the imidates gave the corresponding 5-guanidino-1,2,4-thiadiazoles in good to high yields. Phenylimidates with electron-donating groups like -methyl and -methoxy at *para* and *meta* positions afford the corresponding products **15b**, **15c** and **15f** in good to excellent isolated yields. Conversely, the reaction progressed with halogen substituent on phenylimidates such as -F and -Cl at *para*, *meta* and *ortho* positions to afford the products **15d**, **15e**, **15g** and **15h** in moderate to good yields. Gratifyingly, *ortho*-substituted electron-withdrawing phenylimidate afford the yield similar to that of *para*-subsitituted phenylimidate. In addition, the heteroimidate like thiophene-2-carbimidate gave **15i** in 86% yield. Notably, an alicyclic imidate such as cyclohexyl imidate was also found compatible to the reaction conditions to deliver the corresponding product **15j** in 82% yield. In the case of aliphatic propyl imidate, the corresponding product **15k** was obtained in moderate yield. To extend the scope of the substrates and find limitations of the reaction, various phenylthioureas with phenylimidate were further studied, which proceeded proficiently to afford the corresponding 5-guanidino-1,2,4-thiadiazoles in good to excellent

yields. As mentioned in Table 9, all phenylthiourea substrates bearing electron-donating substituents such as -Me and -OMe at *para*, *meta* and *ortho* positions gave the corresponding products **15l**, **15o** and **15p** in good to high yields. Electron-withdrawing substrate like -Cl on the aryl ring with imidate gave the desired product in very good yield (Table 9, entry **15m**). Phenylthiourea with strong electron-withdrawing group like -NO_2 generated the corresponding thiadiazole **15n** in 80% yield. It should be observed that the oxidative cyclization was satisfyingly conducted in gram scale without any complication (Table 9, **15a**). The structure of product **15e** was unambiguously secured by the X-ray diffraction analysis (Figure 7).

Table 9: Synthesis of 5-guanidino-1,2,4-thiadiazoles[a,b]



14 **13** **15**



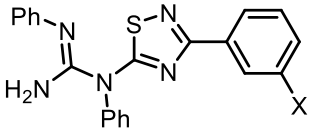
15a, X = H, 90% (85%)[c]

15b, X = Me, 92%

15c, X = OMe, 91%

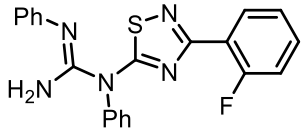
15d, X = F, 87%

15e, X = Cl, 90%

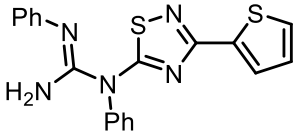


15f, X = Me, 85%

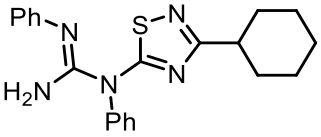
15g, X = Cl, 87%



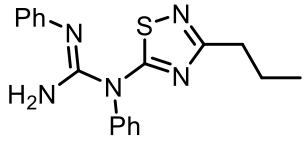
15h, 83%



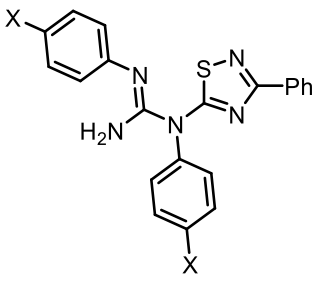
15i, 86%



15j, 82%



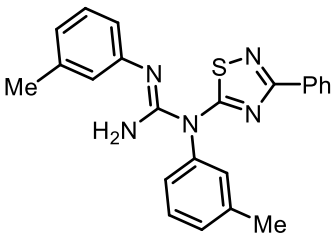
15k, 83%



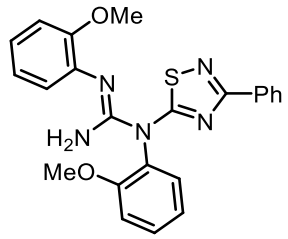
15l, X = OMe, 88%

15m, X = Cl, 90%

15n, X = NO_2, 80%



15o, 85%



15p, 78%

[a]Reaction conditions: **13** (2 mmol, 1 equiv), **14** (4 mmol, 2 equiv), PIDA (2 equiv) and CH_3CN (1 mL) at rt for 3 to 5 h. [b]Isolated yield. [c]The reaction was conducted on gram scale.

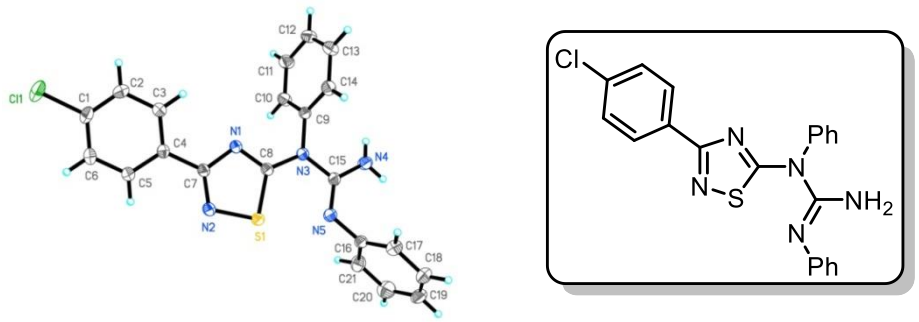
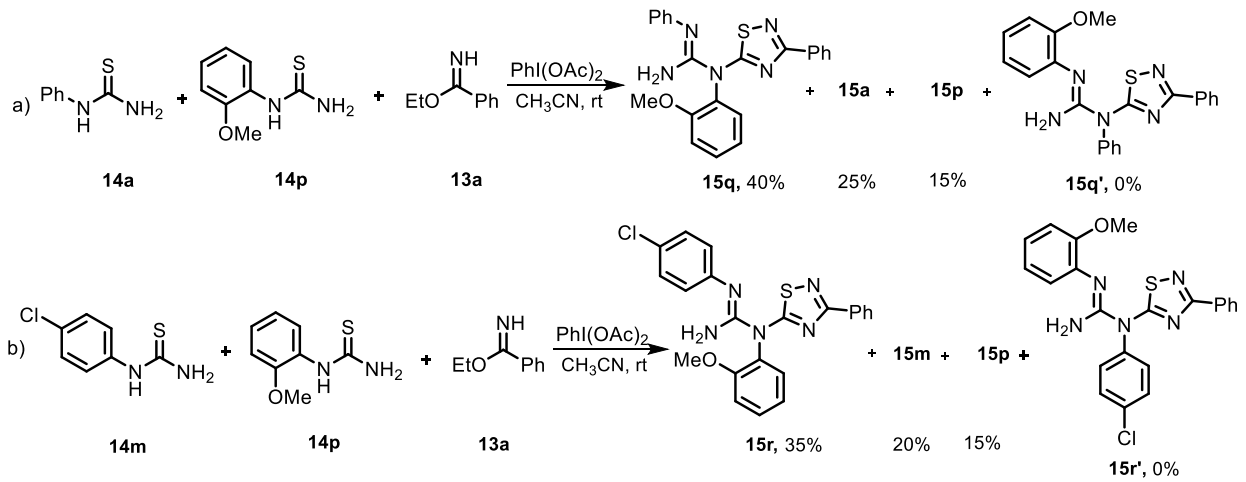


Figure 7: Crystal structure of the compound **15e**

Further, checked if this protocol works equally well when a mixture of thioureas were used. Thus, when the reaction was conducted between 1 equiv of **14a** and 1 equiv of **14p** with 1 equiv of phenylimidate (**13a**) under the established reaction conditions, a mixture of products **15q** in 40% yield along with **15a** and **15p** in 25% and 15% yields respectively were obtained. This indicates cross-dimerization of phenylthioureas takes place to furnish the corresponding product **15q** (confirmed by its crystallographic analysis, Figure 8) along with homo-dimerized products **15a** and **15p** (Scheme 10a). The regioisomeric **15q**, namely **15q'** was not observed mainly due to the electronic factors of electron-donating *ortho*-methoxy group on the phenyl, which prefers to stay substituted to nitrogen atom of the 1,2,4-thiadiazole ring as it facilitates in its formation which is not the case with **15q'**. To substantiate this, conducted another experiment with a substrate possessing electron-withdrawing substrate like **14m** (1 equiv) and **14p** (1 equiv) with **13a** (1 equiv) under the same reaction conditions (Scheme 10b). Isolated similar set of products, **15r** in 35% yield along with **15m** and **15p** in 20% and 15% respectively. This clearly states that the donating-group containing aryl moiety prefers to remain as *N*-substitutent of 1,2,4-thiadiazole ring, while the withdrawing-group bearing aryl group decorates the guanidino nitrogen.



Scheme 10: Synthesis of cross-dimerization products of 5-guanidino-1,2,4-thiadiazoles

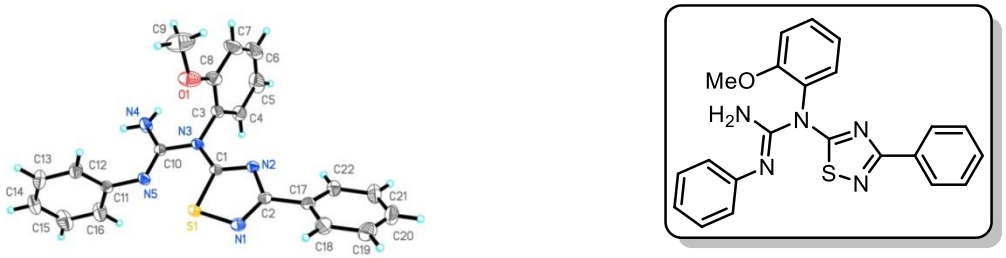
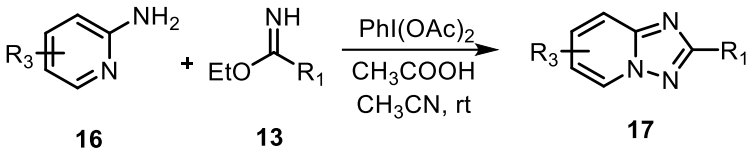


Figure 8: Crystal structure of compound **15q**

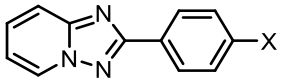
The aforementioned results prompted us to test the fate of the more challenging and further extend the scope of this practical approach by replacing phenylthioureas (**14**) with 2-aminopyridines (**16**) under the standard conditions to prepare 1,2,4-triazolo[1,5-*a*]pyridines (**17**) gave in good yields. Then studied the equivalence of $PhI(OAc)_2$ and use of additive CH_3COOH for the enhancement of rate of reaction. Finally, the optimum reaction conditions as: 1 equiv of **13** and 1 equiv of **16** with 1 equiv of $PhI(OAc)_2$ in the presence of 1 equiv of the additive CH_3COOH in acetonitrile solution at room temperature. As shown in Table 10, this protocol tolerates a variety of phenylimidates with 2-aminopyridines. No significant substituent effect was observed, and excellent yields were obtained for phenylimidates having both electron-donating and electron-withdrawing substituents with 2-aminopyridines. It is worth noting that heterocyclic substituent such as thienyl ring (**17l**) could also well survive the process with 80% yield. This methodology worked equally well with alicyclic imidates such as cyclohexyl and cyclopropyl, and good yields were observed (**17m** and **17n**). Fortunately, the reaction worked equally well with aliphatic imidates, including propyl and isopropyl and which gave corresponding 1,2,4-triazolo[1,5-*a*]pyridines in good yields (**17o** and **17p**). The heterocyclic ring of 2-aminopyridine was found to be tolerant of both electron-

donating group such as methyl (**17q**) and electron-withdrawing group such as halogen (**17r**). Reactions of halogen-containing substrates negatively affected the reaction yields compared to the methyl-containing substrate, which was due to the relatively low nucleophilicity of the pyridines affected by the halogens (**17q**-**17t**). Here also compound **17a** was synthesized in gram scale successfully.

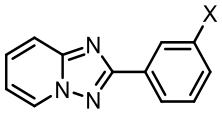
Table 10: Synthesis of 1,2,4-triazolo[1,5-*a*]pyridines[a,b]



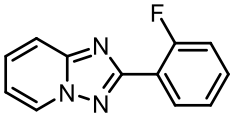
16 **13** **17**



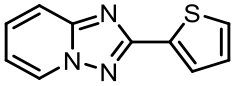
17a, X = H, 92% (87%)[c]
17b, X = Me, 94%
17c, X = OMe, 90%
17d, X = F, 85%
17e, X = Cl, 91%
17f, X = CF_3, 90%



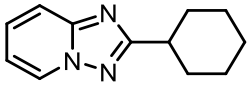
17g, X = Me, 91%
17h, X = Cl, 89%
17i, X = Br, 82%
17j, X = NO_2, 78%



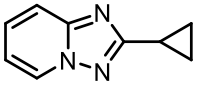
17k, 78%



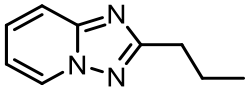
17l, 80%



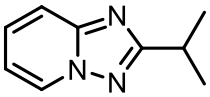
17m, 86%



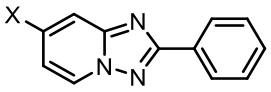
17n, 80%



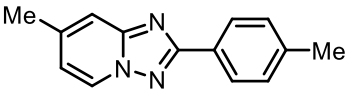
17o, 82%



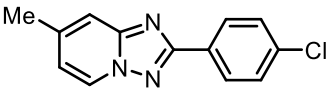
17p, 81%



17q, X = Me, 92%
17r, X = Cl, 85%



17s, 92%

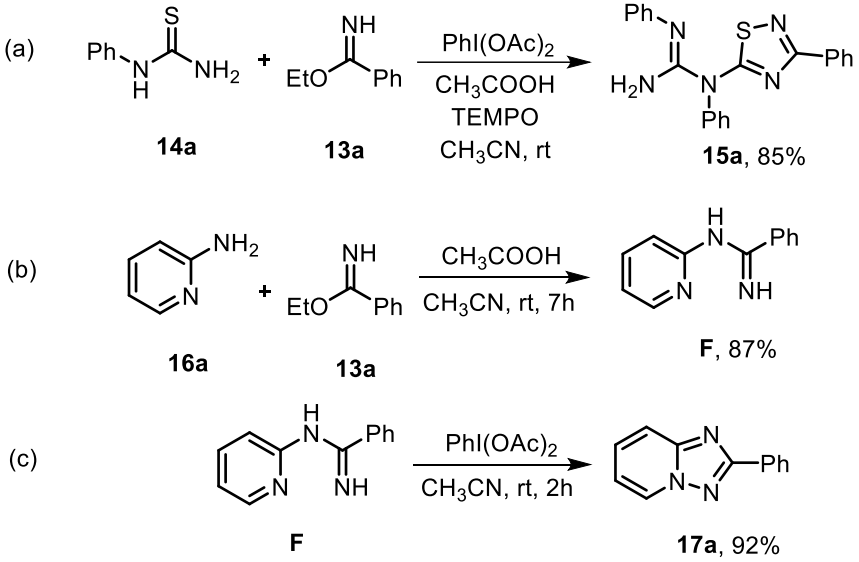


17t, 94%

[a]Reaction conditions: **13** (2 mmol, 1 equiv), **16** (2 mmol, 1 equiv), PIDA (1 equiv), CH_3COOH (1 equiv) and CH_3CN (1 mL) at rt for 7 to 10 h. [b]Isolated yield. [c]The reaction was conducted on gram scale.

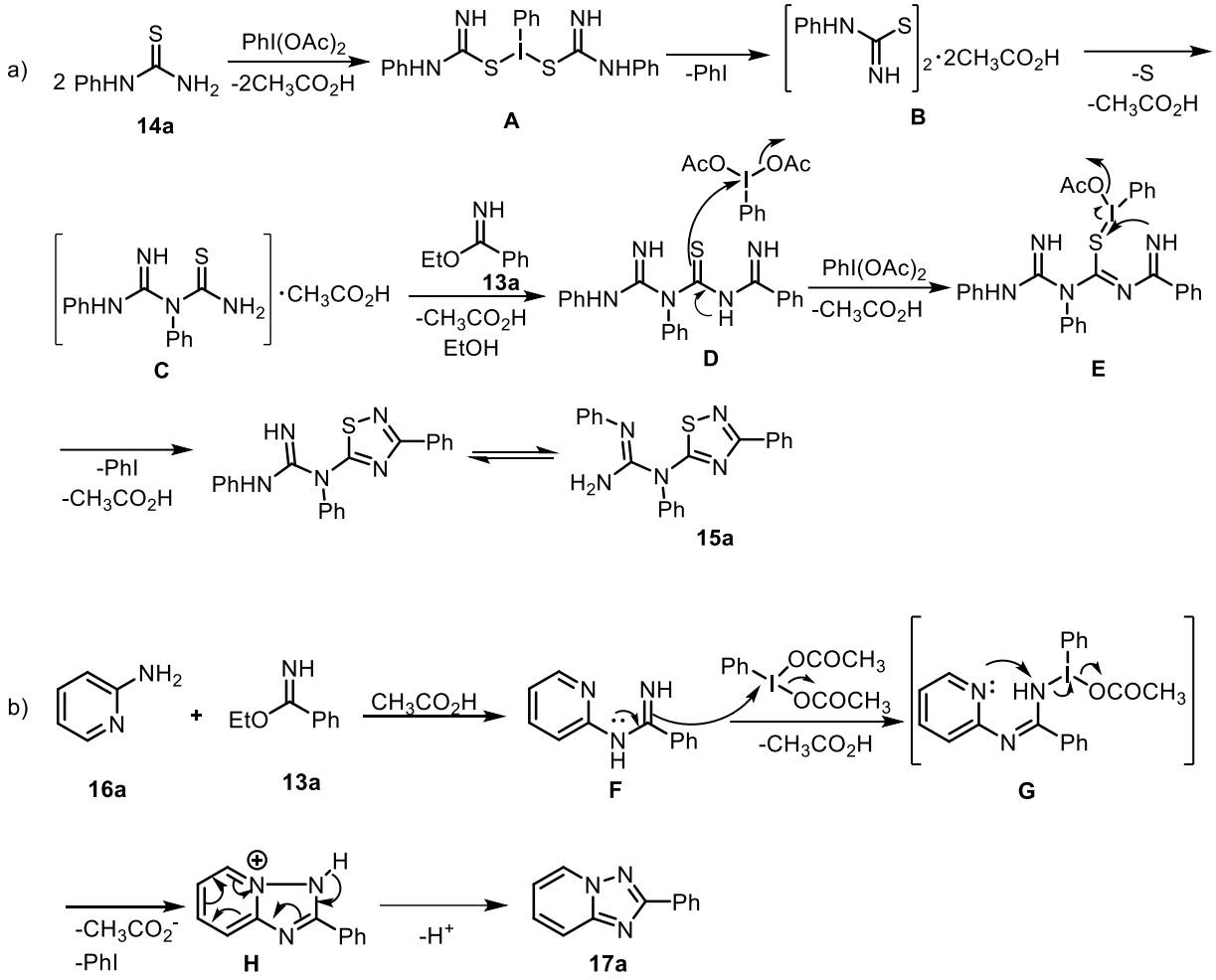
To gain a better understanding of the reaction mechanism, a series of control experiments were carried out under the standard reaction conditions (Scheme 11). When the

control experiment was carried out with radical scavenger such as TEMPO (2,2,6,6-tetramethylpiperdine-1-oxide), did not influence the reaction rate and outcome of the product yield, which suggests that the favouring of ionic mechanism (Scheme 11a). When the phenylimidate (**13a**) and 2-aminopyridine (**16a**) undergoes reaction in presence of acetic acid with the absence of $PhI(OAc)_2$, intermediate *N*-(pyridin-2-yl)-imidamide (**F**) (Scheme 11b) was obtained. This intermediate **F** reacts with $PhI(OAc)_2$ gave the desired product **17a** in 92% yield (Scheme 11c).



Scheme 11: Control experiments

On the basis of existing literature reports[25] and the experimental results, a plausible reaction mechanism for the formation of 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazolo[1,5-*a*]pyridines is proposed (Scheme 12). Initially, **14a** undergoes reaction with $PhI(OAc)_2$ to afford polyvalent iodine intermediate **A**, which undergoes iodobenzene elimination and dimerizes to form 1,6-diphenyl-dithioformamidine **B**. Then the intermediate **B** on sulfur atom elimination forms amidinothiourea **C**. Next, intermediate **C** reacts with **13a** to give a thiourea intermediate **D** which undergoes reaction with second equivalent of $PhI(OAc)_2$ to form the intermediate **E** which on intramolecular nucleophilic attack of the NH group on sulphur followed by isomerization affords the desired guanidino thiadiazole **15a** (Scheme 12a). Whereas **13a** condensed with **16a** to afford intermediate *N*-(pyridin-2-yl)-imidamide **F** in presence of acetic acid, the intermediate **F** reacts with $PhI(OAc)_2$ generates the intermediate **G** with the releasing of acetic acid and then intramolecular nucleophilic attack of the nitrogen atom of the pyridine ring to give ammonium ion **H**, which affords the required product **17a** after rearomatization through the elimination of a proton (Scheme 12b).



Scheme 12: Proposed reaction mechanism

In conclusion, a novel and convenient approach for the construction of 5-guanidino-1,2,4-thiadiazoles and 1,2,4-triazolo[1,5-*a*]pyridines was developed under mild conditions through oxidative N-S and N-N bond formation from thioureas/2-aminopyridines and imidates for the first time in this chapter. The use of environmentally benign $PhI(OAc)_2$ reagent makes this protocol green and highly practical. Moreover, this method provides metal-free, regioselectivity, high functional group tolerance, mild reaction conditions and scalability as the attractive features.

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