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I2-Mediated oxidative C-N and N-S bond formation in water: A metal-free synthesis of 4,5-disubstituted/N-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles

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I_2-Mediated oxidative C-N and N-S bond formation in water: A metal-free synthesis of 4,5-disubstituted/*N*-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles

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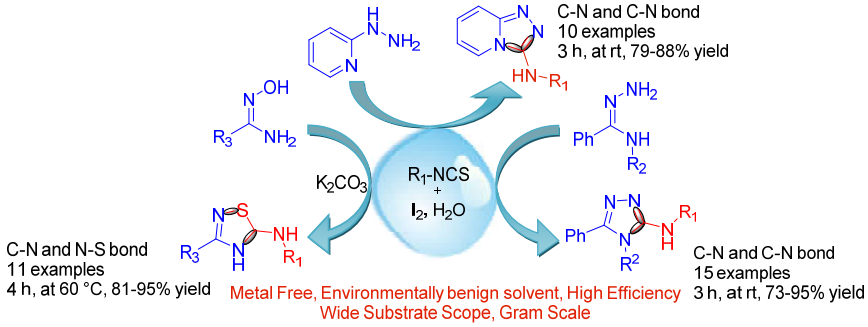


An environmentally benign and convenient strategy for the synthesis of 4,5-disubstituted/*N*-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles from isothiocyanates has been developed. This metal-free method involves I_2-mediated oxidative C-N and N-S bond formations in water. Furthermore, this facile protocol exhibited excellent substrate tolerance in good to high yields and scalable fashion.

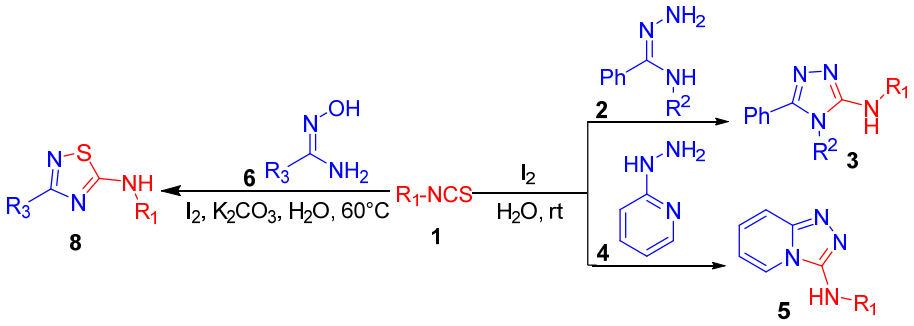
INTRODUCTION

N-Containing heterocyclic molecules constitute an important class of compounds in the fields of material and pharmaceutical chemistry due to their many fold applications. Among them, 1,2,4-triazoles and 1,2,4-thiadiazoles have emerged as an important structural motif present in a large number of functionalized molecules with a broad range of biological activities,

such as antibacterial,[1] anti-inflammatory,[2] antifungal[3] and antiviral.[4] Moreover, they are also found in valuable pharmaceuticals, including sitagliptin,[5] maraviroc,[6] trizaolam,[7] deferasirox[8] and cefozopran.[9] Owing to its broad spectrum of functions, the efficient methods for the synthesis of 1,2,4-triazoles and 1,2,4-thiadiazoles has attracted much attention. The most generally explored synthetic pathways for 1,2,4-triazoles involve cyclodehydration of *N*-acylamidrazone obtained from hydrazines and carboxylic acid derivatives.[10] Whereas, the simple oxidative dimerization of thioamides using various oxidants is very common protocol for the synthesis of 1,2,4-thiadiazoles.[11] Apart from these, some other synthetic methods to access 1,2,4-triazoles or 1,2,4-thiadiazoles were also disclosed.[12] These protocols suffer from one or more drawbacks, such as use of transition-metals, harsh reaction conditions with high temperatures or strong acids, or use of organic solvent. Thus, more general and practical synthetic methods for the preparation of 4,5-disubstituted/*N*-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles are still in high demand.

On the other hand, molecular iodine has attracted considerable attention because of its low toxicity, ready availability, inexpensive in contrast to transition-metal catalysts. As a potent catalyst, iodine is widely used in various organic reactions.[13] Recently, our group developed an efficient and regiospecific protocol by using molecular iodine as a catalyst for the synthesis of *N*-fused 1,2,4-thiadiazoles and 3,4-disubstituted 5-imino-1,2,4-thiadiazoles *via* N-S bond formations.[14a] In addition, the development of reactions in the presence of water has become highly advantageous to meet environmentally friendly processes in life sciences. Inspired by these advances, in connection with previous work and continuation of our studies on the construction of valuable synthetic methodologies for diverse biologically active heterocyclic scaffolds[14b-c] herein, we report a novel and environmentally benign protocol for the formation of

C-N and N-S bond using molecular iodine as an oxidant in water for the synthesis of 4,5-disubstituted/*N*-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles (Scheme 1).



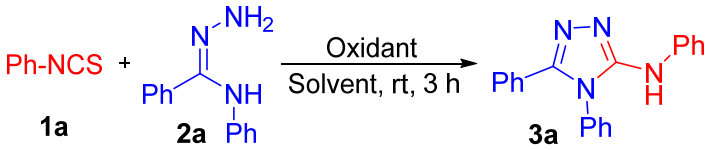
Scheme 1. Synthesis of 4,5-disubstituted/*N*-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles.

RESULTS AND DISCUSSION

We began our study by examining the reaction of phenyl isothiocyanate (**1a**), *N*-phenylbenzamidrazone (**2a**) and iodine (0.5 equiv.) in DMSO at rt for 3 h, provided the desired product **3a** in 38% yield (Table 1, entry 1). To improve the reaction yield, we have screened various solvents under the same conditions. Polar solvents such as DMF and MeOH provided moderate yields (Table 1, entries 2 & 3). Moderate conversions were observed using MeCN and DCM, whereas no reaction took place in EtOAc (Table 1, entries 4-6). The reaction efficiency was observed in a protic solvent, considering the requirements of green chemistry, we attempted the water as solvent. The reaction was significantly accelerated in water to give **3a** in 52% yield (Table 1, entry 7). Subsequently, other iodine containing catalysts were also studied, such as TBAI, KI, NIS and PIDA showed a lower yield of **3a** (Table 1, entries 8-11). Next, we studied on the amount of iodine, raising the quantity of iodine from 0.5 equiv. to 1 equiv. provided the

product **3a** in 92% yield (Table 1, entry 12). However, further increase of iodine did not improve the yield (Table 1, entry 13). Thus, the optimized reaction conditions are isothiocyanate (1.0 mmol), *N*-phenylbenzamidrazone (1.0 mmol) and iodine (1.0 equiv.) in water at room temperature were chosen as the optimum reaction conditions for the synthesis of 4,5-disubstituted 3-amino- 1,2,4-triazoles.

Table 1. Optimization of the reaction conditions.[a]



Entry	Oxidant (mol%)	Solvent	Yield (%)
1	I_2 (50)	DMSO	38
2	I_2 (50)	DMF	31
3	I_2 (50)	MeOH	43
4	I_2 (50)	MeCN	18
5	I_2 (50)	DCM	22
6	I_2 (50)	EtOAc	--
7	I_2 (50)	H_2O	52
8	TBAI (50)	H_2O	30
9	KI (50)	H_2O	26
10	NIS (50)	H_2O	35
11	PIDA (50)	H_2O	trace
12	I_2 (100)	H_2O	92

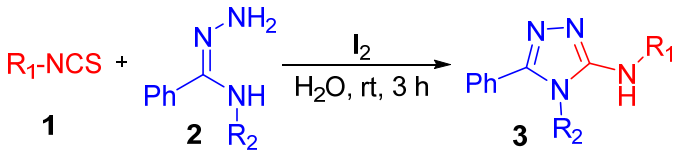
13	I_2 (150)	H_2O	92

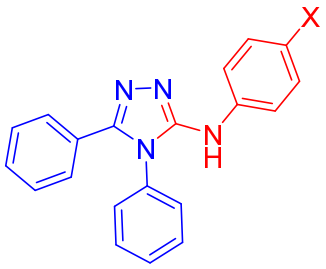
[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol) and oxidant (x mol%) in solvent (2 mL) at room temperature for 3 h.

With this promising result in hand, the scope and generality of the reaction was investigated and the results are summarized in Scheme 2. The reaction is applicable to a wide variety of isothiocyanates under the established reaction conditions, giving the corresponding 4,5-disubstituted 3-amino-1,2,4-triazoles in good to high yields. Simple phenyl isothiocyanate (**1a**) with *N*-phenylbenzamidrazone (**2a**) gave the corresponding 3-amino-1,2,4-triazole (**3a**) in 92% yield (entry **3a**). Electron- donating groups, such as *o*-methoxy, *m*-methoxy, *p*-methoxy, *m*-methyl and *p*-methyl on the phenyl ring of isothiocyanates underwent the reaction efficiently in excellent yields (entries **3b, 3c & 3g-3i**). Meanwhile, the steric hindrance is not obvious for *o*-methoxy group on the phenyl isothiocyanate in this protocol (entry **3i**). On the other hand, phenyl isothiocyanates with electron-deficient groups, like chloro, nitro and trifluoro methyl on para position generated the corresponding 3-amino-substituted 1,2,4-triazoles in good yields (entries **3d-3f & 3j**). These results demonstrate that substitutent's on phenyl isothiocyanates have no bearing on the reaction yield. To our delight, alkyl isothiocyanates such as *tert*-butyl, butyl and alicyclic isothiocyanate like cyclohexyl also reacted smoothly to afford the desired products **3l-3o** in 73% to 76% yield. Furthermore, we investigated the scope of the method by varying the *N*-phenylbenzamidrazones, which proceeded successfully to afford the corresponding 3-amino-1,2,4-triazoles in good yields (entries **3j, 3k, 3m & 3o**). After the successful study of substrate scope, we have evaluated this green methodology towards gram scale level. Importantly, the

methodology can be carried out in gram scale without any complications, and **3a** was isolated in 89% yield, demonstrating the efficiency and practicality of this methodology.

Scheme 2. Synthesis of 4,5-disubstituted 3-amino-substituted 1,2,4-triazoles.[a]





3a, X = H, 92% (89%)[b]

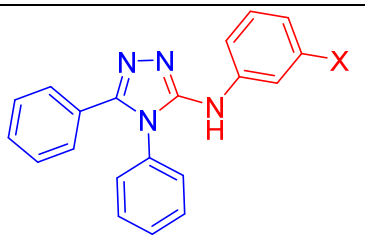
3b, X = Me, 91%

3c, X = OMe, 95%

3d, X = Cl, 87%

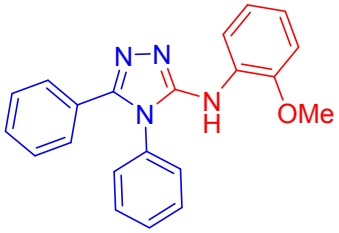
3e, X = NO_2, 82%

3f, X = CF_3, 82%

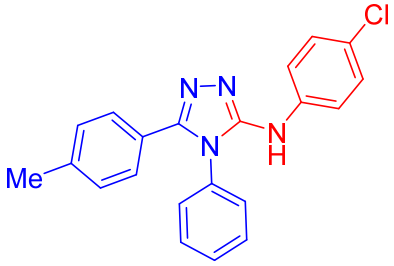


3g, X = Me, 89%

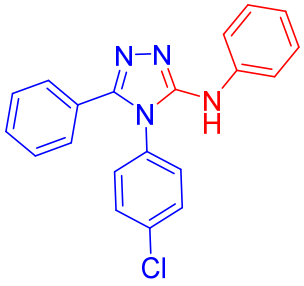
3h, X = OMe, 92%



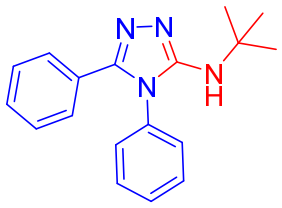
3i, 81%



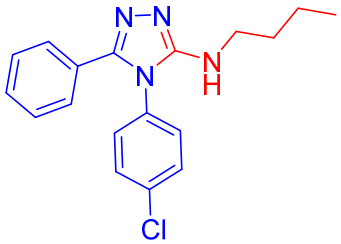
3j, 90%



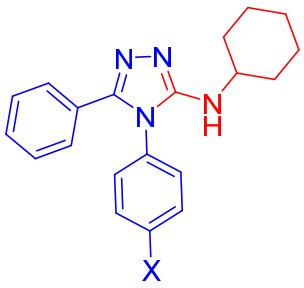
3k, 79%



3l, 76%



3m, 75%



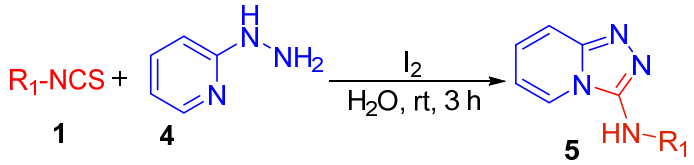
3n, X = H, 76%

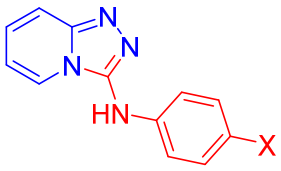
3o, X = Cl, 73%

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol) and iodine (1.0 equiv.) in water at rt for 3 h. [b]Gram scale reaction.

Encouraged by these successful results, the utility of this iodine mediated protocol was further investigated for the synthesis of *N*-fused-3-amino-substituted 1,2,4-triazoles. For this purpose, amidrazone (**2**) was replaced with 2-hydrazinopyridine (**4**) under the established optimized reaction conditions (Scheme 3). Gratifyingly, we were able to prepare the desired product *N*-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5a**) in 87% yield. Furthermore, the substrate scope of phenyl isothiocyanate was examined, both electron-donating and electron-withdrawing groups at different positions of the phenyl ring gave the desired products **5b-5i** in 82% to 88% yields. On replacing the 2-hydrazinopyridine with 2-hydrazineylquinoline was also compatible with the reaction conditions to deliver **5j** in 79% yield. However, the alkyl isothiocyanates didn't provide the desired product under the optimal reaction conditions, only the uncyclized products were observed (Scheme 3, **5k** and **5l**).

Schme 3. Synthesis of *N*-fused-3-amino-1,2,4-triazoles.[a]





5a, X = H, 87% (83%)[b]

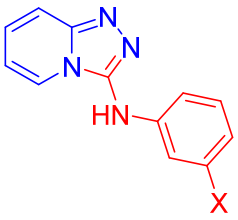
5b, X = Me, 87%

5c, X = OMe, 88%

5d, X = Cl, 85%

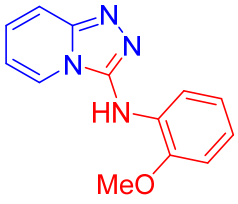
5e, X = F, 83%

5f, X = CF_3, 83%

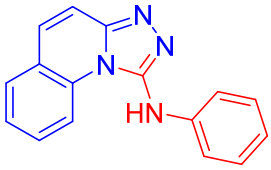


5g, X = Me, 87%

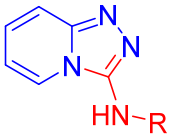
5h, X = OMe, 88%



5i, 82%



5j, 79%



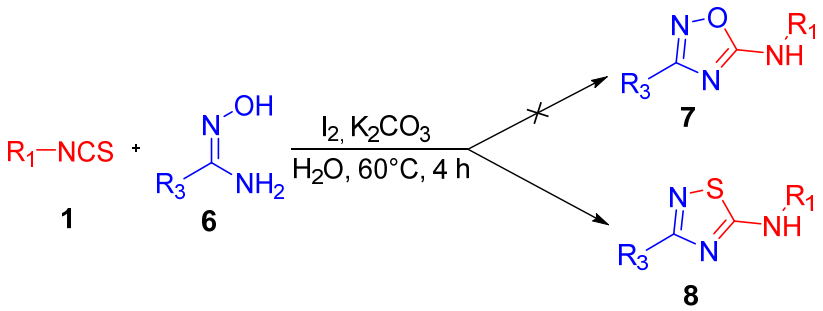
5k, R = propyl, 0%

5l, R = butyl, 0%

[a]Reaction conditions: **1** (1.0 mmol), **4** (1.0 mmol) and iodine (1.0 equiv) in water at rt for 3 h.

[b]Gram scale reaction.

Table 2. Optimization of reaction conditions for the synthesis 3-substituted 5-amino-1,2,4-thiadiazoles.[a]



Entry	Iodine (mol%)	Base	temp	Yield (%)
1	I_2 (50)	---	rt	NR

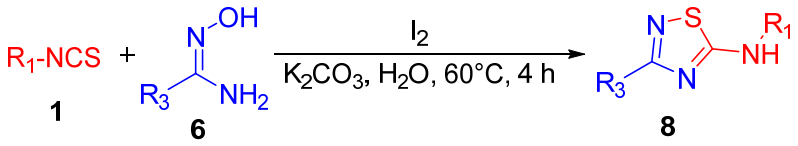
2	I_2 (50)	K_2CO_3	rt	74
3	I_2 (50)	Na_2CO_3	rt	20
4	I_2 (50)	Cs_2CO_3	rt	26
5	I_2 (50)	K_2CO_3	60	90
6	I_2 (100)	K_2CO_3	60	90

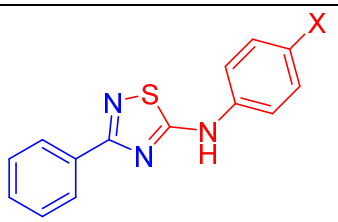
[a]Reaction conditions: **1a** (1.0 mmol), **6a** (1.0 mmol), Base (1.0 mmol) and iodine (x mol%) in water for 4-5 h.

In light of our above consecutive results, we attempted to synthesize 1,2,4-oxadiazoles (**7**) by replacing amidrazones (**2**) with amidoximes (**6**). Surprisingly, we observed the unexpected product 3-substituted 5-amino-1,2,4-thiadiazoles (**8**) in the presence of I_2 (0.5 equiv.) and K_2CO_3 (1 equiv.) at room temperature within 5 h in 74% yield (Table 2, entry 2), while the other bases Na_2CO_3 and Cs_2CO_3 gave the product in 20% and 26% yields respectively (Table 2, entries 3 and 4). However, the unexpected product yield could be improved to 90% by raising the temperature to 60°C in 4 h (Table 2, entry 5). Raising the amount of iodine from 0.5 to 1.0 equiv, the yield of **8a** did not improve (Table 2, entry 6). With the results in hand, we proceeded to investigate the substrate scope on the outcome of the reaction. It was observed that benzamidoxime reacts with different isothiocyanites to furnish the respective products in good to high yields. The phenyl isothiocyanates containing electron-donating groups like methyl and methoxy at ortho, para and meta position provided of the corresponding products in 86% to 95% yield (Scheme 4, entries **8b, 8c, 8f & 8g**). Phenyl isothiocyanites with electron-withdrawing groups on the para-positions like -F and $-NO_2$ generated the corresponding products in 88% and 87% yields respectively (Scheme 4, entries **8d & 8e**). Interestingly, the reaction also proceeded

with propyl and cyclohexyl isothiocyanates to afford the desired compounds **8h** and **8i** in good yields. Furthermore, we investigated the scope of the method with various amidoximes, such as *p*-methy and *p*-chloro benzamidoximes, which proceeded successfully to afford the corresponding products in 91% and 89% yields respectively (Scheme 4, entries **8j & 8k**).

Scheme 4. Synthesis of 3-substituted 5-amino-1,2,4-thiadiazoles.[a]





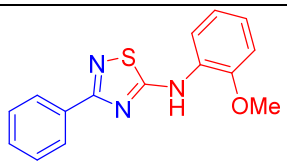
8a, X = H, 90% (88%)[b]

8b, X = Me, 92%

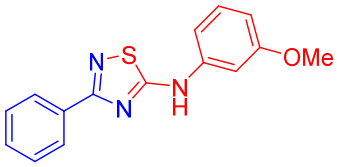
8c, X = OMe, 95%

8d, X = F, 88%

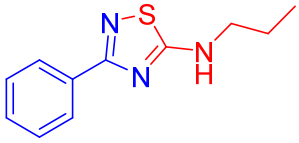
8e, X = NO_2, 87%



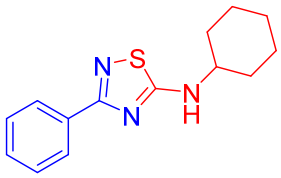
8f, 86%



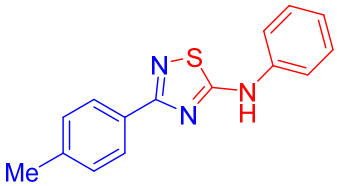
8g, 89%



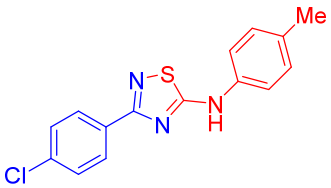
8h, 84%



8i, 81%



8j, 91%

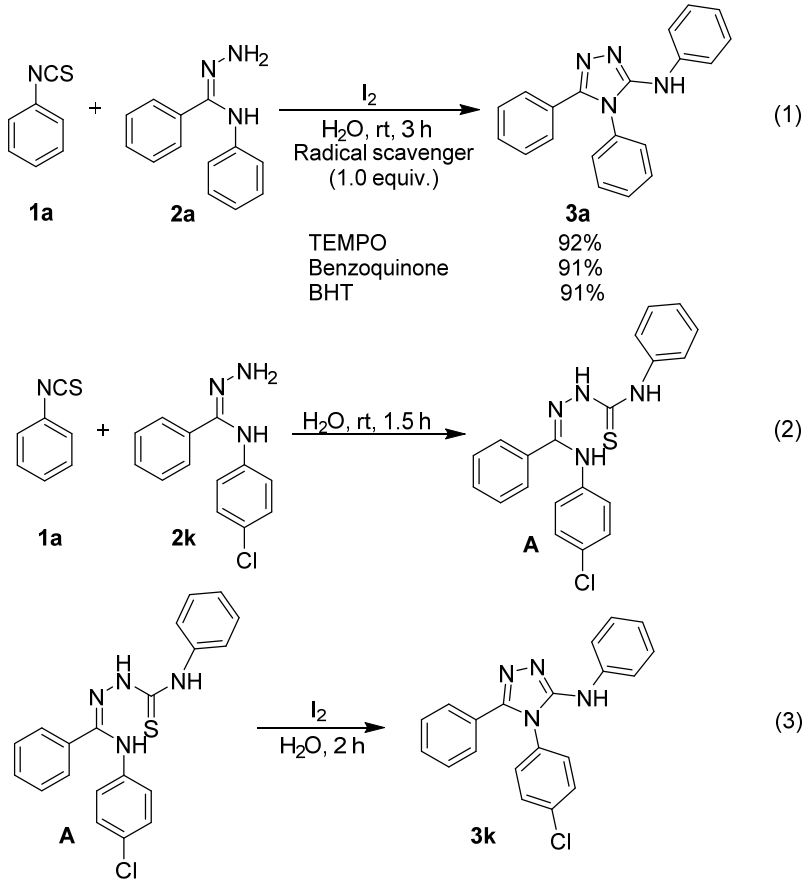


8k, 89%

[a]Reaction conditions: **1** (1.0 mmol), **6** (1.0 mmol), iodine (0.5 equiv.) and K_2CO_3 (1.09 mmol) in water at 60°C for 4 h. [b]Gram scale reaction.

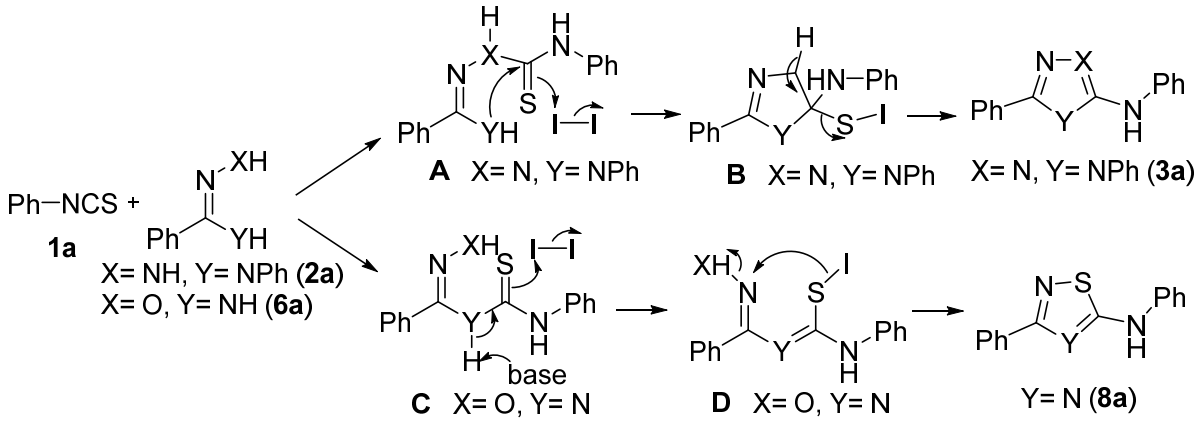
In order to gain more insights into the mechanism of this I_2-catalyzed reaction, a series of control experiments were performed, as shown in Scheme 3. The radical inhibition studies under the standard reaction conditions with TEMPO, benzoquinone and BHT gave the corresponding compound **3a** in 92%, 91% and 91% yields respectively (Scheme 5, eq 1). These results amply proved a radical mechanism can be ruled out. Next, the reaction of **1a** with (*Z*)-*N*-(4-chlorophenyl)benzohydrazonamide (**2k**) was carried out in the absence of I_2 in water for 1.5 h gave the intermediate **A**, whose structure was assigned by 1H, 13C NMR and HRMS (Scheme 5, eq 2). Furthermore, the intermediate **A** under the standard conditions produces **3k**, indicating that **A** might be intermediate for this transformation (Scheme 5, eq 3).

Scheme 5. Control experiments.



On the basis of these experimental results and previous reports,[15] a plausible reaction mechanism for the formation of 4,5-disubstituted 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiadiazoles is proposed as shown in Scheme 6. Initially, **1a** condensed with **2a** in water to afford intermediate **A**. Next an intramolecular attack on the carbon atom by the NH group gave the intermediate **B** through the formation of S-I bond, which on cleavage of HI and S gave the desired product **3a**. Whereas **1a** condensed with **6a** to afford intermediate **C** the intermediate **C** reacts with iodine under basic condition generates the plausible iodo species **D**. Then the S-I bond cleaves in intermediate **D** gave the desired **8a** with formation of a new N-S bond.

Scheme 6. Proposed reaction mechanism.



CONCLUSION

In conclusion, we have developed a metal-free and ecofriendly strategy for the oxidative C-N and N-S bond formation for the synthesis of 4,5-disubstituted/*N*-fused 3-amino-1,2,4-triazoles and 4,5-disubstituted 5-amino-1,2,4-thiadiazoles from isothiocyanates for the first time. Furthermore, this efficient and operationally simple protocol features nontoxic and inexpensive

molecular iodine as the catalyst and water as an environmentally friendly solvent. Moreover, the wide variety of substrate tolerance in good to excellent yields and amenable to gram-scale synthesis of our method allowed the construction of library of compounds.

EXPERIMENTAL SECTION

General information and Reagents:

The glassware to be used in reactions was thoroughly washed and dried in an oven and the experiments were carried out with required precautions. Chemicals and all solvents were obtained from commercial suppliers and used without further purification. ^{1}H-NMR was measured on Bruker Avance-300, Varian Unity-400 MHz and Avance New-500 MHz and ^{13}C-NMR was measured with Varian Unity-400 MHz (100 MHz) and with Avance New-500 MHz (125 MHz), as specified and referred as the internal standard to TMS (tetramethylsilane). Chemical shifts (δ) are given in ppm and J values are given in Hz. High Resolution Mass Spectra (HRMS) were performed on a high resolution magnetic sector mass spectrometer. TLC analysis was performed on Merck silica gel 60 F_{254} plates. Column chromatography was performed on silica gel (100-200 mesh) from Merck. Melting points were measured using melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

The Scale-up Reaction:

The mixture of isothiocyanate (**1a**) (7.4 mmol), *N*-phenylbenzamidrazone (**2a**) (7.4 mmol)/2-hydrazinopyridine (**4a**) (7.4 mmol) and I_2 (100 mol%, 933 mg, 7.4 mmol) in water (15 mL) was stirred magnetically at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate

twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc : hexane as eluents to afford corresponding product **3a/5a.**

Typical procedure for the synthesis of intermediate A:

The mixture of phenyl isothiocyanate (**1a**) (1.0 mmol, 135mg) and *N*-phenylbenzamidrazone (**2k**) (1.0 mmol, 245mg) in water (2 mL) was stirred magnetically at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was treated with $NaHCO_3$ and extracted with EtOAc. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc : hexane as eluents to afford corresponding product **A.**

(*Z*)-2-(((4-chlorophenyl)amino)(phenyl)methylene)-*N*-phenylhydrazinecarbothioamide (**A**): White solid; Mp 165-167 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.48 (s, 1H), 9.91 (s, 1H), 9.12 (s, 1H), 7.62 (t, J = 8.5 Hz, 4H), 7.37 (dd, J = 14.9, 7.8 Hz, 5H), 7.19 (d, J = 8.4 Hz, 3H), 6.65 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.4, 142.2, 140.1, 139.0, 132.9, 129.7, 128.8, 128.5, 128.2, 128.0, 125.1, 125.0, 120.9; HRMS (ESI) calcd for $C_{20}H_{17}N_4ClS$ $[M+H]^+$: 381.0935; found: 381.0962.

Typical procedure for the synthesis of 4,5-disubstituted 3-amino-1,2,4-triazoles 3a-3o:

The mixture of isothiocyanate (**1**) (1.0 mmol), *N*-phenylbenzamidrazone (**2**) (1.0 mmol) and I_2 (100 mol%, 126 mg, 1.0 mmol) in water (2 mL) was stirred magnetically at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated and

the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc : hexane as eluents to afford corresponding product **3a-3o.**

N,4,5-Triphenyl-4H-1,2,4-triazol-3-amine (**3a**):[16] White solid; Yield: 92% (287 mg); Mp 210-211 °C; eluent: hexane/ethyl acetate 70:30; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.55-7.50 (m, 5H), 7.43-7.40 (m, 2H), 7.35-7.31 (m, 5H), 7.23 (t, J = 7.9 Hz, 2H), 6.87 (t, J = 7.3 Hz, 1H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.9, 150.0, 141.6, 133.3, 129.9, 129.6, 129.1, 128.5, 128.4, 128.3, 127.7, 127.4, 120.4, 117.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{17}N_4$ 313.1447; Found 313.1437.

4,5-Diphenyl-N-(p-tolyl)-4H-1,2,4-triazol-3-amine (**3b**): White solid; Yield: 91% (299 mg); Mp 198-200 °C; eluent: hexane/ethyl acetate 72:28; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.54-7.53 (m, 3H), 7.42-7.40 (m, 4H), 7.34-7.30 (m, 5H), 7.04 (d, J = 8.3 Hz, 2H), 2.22 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 152.2, 149.8, 138.9, 133.3, 129.9, 129.6, 129.2, 129.0, 128.9, 128.4, 128.3, 127.6, 127.4, 117.2, 20.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_4$ 327.1604; Found 327.1593.

N-(4-Methoxyphenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3c**): White solid; Yield: 95% (324 mg); Mp 178-180 °C; eluent: hexane/ethyl acetate 68:32; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.55-7.53 (m, 3H), 7.49 (d, J = 9.0 Hz, 2H), 7.42 (dd, J = 6.4, 3.1 Hz, 2H), 7.35-7.29 (m, 5H), 6.84 (d, J = 9.0 Hz, 2H), 3.70 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 153.6, 152.6, 149.5, 134.6, 133.3, 129.9, 129.6, 129.0, 128.4, 128.3, 127.6, 127.5, 119.0, 113.7, 55.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_4O$ 343.1553; Found 343.1544.

N-(4-Chlorophenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3d**): White solid; Yield: 87% (301 mg); Mp 178-180 °C; eluent: hexane/ethyl acetate 74:26; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.59-7.54 (m, 5H), 7.44-7.41 (m, 2H), 7.38-7.27 (m, 7H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.7, 150.0, 140.5, 133.1, 129.9, 129.7, 129.2, 128.4, 128.3, 127.7, 127.3, 123.8, 118.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}ClN_4$ 347.1058; Found 347.1049.

N-(4-Nitrophenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3e**): Yellow solid; Yield: 82% (292 mg); Mp 270-272 °C; eluent: hexane/ethyl acetate 67:33; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.15 (d, J = 9.3 Hz, 2H), 7.64 (d, J = 9.2 Hz, 2H), 7.55-7.54 (m, 3H), 7.45 (dd, J = 6.4, 3.1 Hz, 2H), 7.44-7.34 (m, 5H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 151.5, 150.9, 148.9, 140.3, 133.4, 130.4, 129.9, 128.9, 128.8, 128.4, 127.5, 125.7, 116.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}N_5O_2$ 358.1298; Found 358.1288.

4,5-Diphenyl-N-(4-(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-amine (**3f**): White solid; Yield: 82% (311 mg); Mp 230-232 °C; eluent: hexane/ethyl acetate 68:32; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.59-7.54 (m, 5H), 7.44 (dd, J = 6.7, 2.9 Hz, 2H), 7.39-7.31 (m, 5H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.1, 150.5, 145.3, 133.1, 129.9, 129.8, 129.3, 128.3, 127.8, 127.2, 125.9 (d, J= 3 Hz), 122.9, 120.4 (d, J= 32 Hz), 116.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}F_3N_4$ 381.1321; Found 381.1314.

4,5-Diphenyl-N-(m-tolyl)-4H-1,2,4-triazol-3-amine (**3g**): White solid; Yield: 89% (290 mg); Mp 196-198 °C; eluent: hexane/ethyl acetate 73:27; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.54 (s, 3H), 7.37 (d, J = 29.2 Hz, 9H), 7.10 (t, J = 7.7 Hz, 1H), 6.69 (d, J = 7.2 Hz, 1H), 2.24 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.9, 149.9, 141.5, 137.6, 133.3, 129.9, 129.6, 129.1, 128.4, 128.3, 127.7, 127.4, 121.16, 117.4, 114.1, 21.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_4$ 327.1604; Found 327.1594.

N-(3-Methoxyphenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3h**): White solid; Yield: 92% (314 mg); Mp 203-205 °C; eluent: hexane/ethyl acetate 68:32; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.55-7.54 (m, 3H), 7.42-7.40 (m, 2H), 7.32-7.31 (m, 5H), 7.18 (t, J = 2.1 Hz, 1H), 7.13-7.10 (m, 2H), 6.47-6.44 (m, 1H), 3.71 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 160.2, 152.3, 150.5, 143.2, 133.7, 130.4, 130.2, 129.8, 129.6, 128.9, 128.8, 128.2, 127.8, 110.0, 106.6, 103.2, 55.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_4O$ 343.1553; Found 343.1542.

N-(2-Methoxyphenyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3i**): White solid; Yield: 81% (277 mg); Mp 203-205 °C; eluent: hexane/ethyl acetate 69:31; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (d, J = 8.0 Hz, 1H), 7.62-7.60 (m, 3H), 7.53-7.49 (m, 2H), 7.37-7.35 (m, 5H), 6.97-6.89 (m, 4H), 3.70 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 151.7, 150.1, 147.2, 133.7, 130.9, 130.6, 130.0, 129.7, 129.0, 128.4, 128.0, 127.6, 121.5, 121.3, 116.5, 111.1, 56.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_4O$ 343.1553; Found 343.1541.

N-(4-Chlorophenyl)-4-phenyl-5-(p-tolyl)-4H-1,2,4-triazol-3-amine (**3j**): White solid; Yield: 90% (324 mg); Mp 210-212 °C; eluent: hexane/ethyl acetate 75:25; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.58-7.53 (m, 5H), 7.40 (dd, J = 6.3, 2.7 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.26 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 151.5, 150.1, 140.6, 138.8, 133.2, 129.9, 129.7, 128.9, 128.4, 128.3, 127.6, 124.4, 123.8, 118.5, 20.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}N_4Cl$ 361.1214; Found 361.1206.

4-(4-Chlorophenyl)-N,5-diphenyl-4H-1,2,4-triazol-3-amine (**3k**): White solid; Yield: 79% (273 mg); Mp 259-260 °C; eluent: hexane/ethyl acetate 75:25; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.37-7.34 (m, 5H); 7.24 (t, J = 7.9 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ

151.9, 149.7, 141.3, 134.3, 132.2, 130.4, 130.0, 129.2, 128.5, 128.4, 127.8, 127.2, 120.5, 117.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}N_4Cl$ 347.1058; Found 347.1049.

N-(tert-Butyl)-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3l**): White solid; Yield: 76% (221 mg); Mp 198-200 °C; eluent: hexane/ethyl acetate 72:28; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53-7.51 (m, 3H), 7.33-7.23 (m, 7H), 4.60 (s, 1H), 1.36 (s, 9H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 154.0, 148.6, 133.78, 130.0, 129.3, 128.7, 128.2, 128.0, 127.6, 127.3, 51.5, 28.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{21}N_4$ 293.1760; Found 293.1749.

N-Butyl-4-(4-chlorophenyl)-5-phenyl-4H-1,2,4-triazol-3-amine (**3m**): White solid; Yield: 75% (244 mg); Mp 162-164 °C; eluent: hexane/ethyl acetate 70:30; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (d, J = 8.6 Hz, 2H), 7.39-7.25 (m, 7H), 5.89 (t, J = 5.6 Hz, 1H), 3.22 (dd, J = 13.1, 6.7 Hz, 2H), 1.53 (dd, J = 14.5, 7.5 Hz, 2H), 1.36-1.24 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 160.8, 153.9, 139.2, 137.7, 135.3, 134.1, 133.6, 132.6, 47.7, 36.1, 24.7, 19.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}N_4Cl$ 327.1371; Found 327.1363.

N-Cyclohexyl-4,5-diphenyl-4H-1,2,4-triazol-3-amine (**3n**): White solid; Yield: 76% (241 mg); Mp 202-204 °C; eluent: hexane/ethyl acetate 71:29; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52-7.51 (m, 3H), 7.39-7.24 (m, 7H), 5.23 (d, J = 7.8 Hz, 1H), 3.39 (s, 1H), 1.95 (s, 2H), 1.67-1.56 (m, 3H), 1.17 (d, J = 49.1 Hz, 5H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 155.19, 148.87, 133.75, 130.00, 129.29, 128.62, 128.27, 128.04, 127.78, 127.26, 52.03, 32.34, 25.37, 24.93; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_4$ 319.1917; Found 319.1905.

4-(4-Chlorophenyl)-N-cyclohexyl-5-phenyl-4H-1,2,4-triazol-3-amine (**3o**): White solid; Yield: 73% (256 mg); Mp 203-204 °C; eluent: hexane/ethyl acetate 72:28; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, J = 8.2 Hz, 2H), 7.36-7.26 (m, 7H), 5.45 (d, J = 7.6 Hz, 1H), 3.50 (s, 1H), 1.93 (d, J = 15.2 Hz, 2H), 1.68 (s, 2H), 1.58 (d, J = 12.5 Hz, 1H), 1.25 (dd, J = 19.5, 10.2 Hz, 4H), 1.07

(d, J = 10.7 Hz, 1H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 171.9, 155.1, 148.7, 133.8, 132.6, 130.0, 130.0, 128.7, 128.3, 127.6, 127.4, 52.0, 32.3, 25.4, 24.9, 21.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}N_4Cl$ 353.1527; Found 353.1518.

Typical procedure for the synthesis of *N*-fused-3-amino-1,2,4-triazoles 5a-5j:

The mixture of phenyl isothiocyanate (**1**) (1.0 mmol) and 2-hydrazinopyridine (**4**) (1.0 mmol) and I_2 (100 mol%, 126 mg, 1.0 mmol) in water (2 mL) was stirred magnetically at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc : hexane as eluents to afford corresponding product **5a-5j.**

N-Phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5a**):[17] Pale yellow solid; Yield: 87% (182 mg); Mp 229-230 °C; eluent: hexane/ethyl acetate 61:39; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.35 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 9.3 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.26 (dd, J = 9.0, 6.7 Hz, 1H), 6.95-6.90 (m, 2H); $^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6) δ 146.7, 144.7, 141.8, 129.4, 127.0, 123.1, 120.9, 116.6, 115.9, 112.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}N_4$ 211.0978; Found 211.0972.

N-(p-Tolyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5b**):[17] White solid; Yield: 87% (194 mg); Mp 265-267 °C; eluent: hexane/ethyl acetate 60:40; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.32 (d, J = 6.9 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.23 (dd, J = 8.6, 6.5 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 6.88 (t, J = 6.6 Hz, 1H), 2.26 (s, 3H); $^{13}C\{^{1}H\}$NMR (100

MHz, DMSO-d_6) δ 146.6, 145.0, 139.3, 129.8, 129.6, 126.8, 123.0, 116.8, 116.0, 112.6, 20.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{13}N_4$ 225.1134; Found 225.1129.

N-(4-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5c**):[18] White solid; Yield: 88% (211 mg); Mp 240 °C; eluent: hexane/ethyl acetate 58:42; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.31 (d, J = 7.0 Hz, 1H), 7.56 (dd, J = 19.6, 9.1 Hz, 3H), 7.21 (dd, J = 8.8, 6.4 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 6.87 (t, J = 6.5 Hz, 1H), 3.73 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 154.0, 146.5, 145.4, 135.0, 126.8, 122.9, 118.4, 115.9, 114.7, 112.5, 55.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{13}N_4O$ 241.1083; Found 241.1077.

N-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5d**): White solid; Yield 85% (207 mg); Mp 220-221 °C; eluent: hexane/ethyl acetate 61:39; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.35 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 8.7 Hz, 3H), 7.36 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 8.9, 6.7 Hz, 1H), 6.92 (t, J = 6.6 Hz, 1H); ^{13}C{^{1}H}NMR (125 MHz, DMSO-d_6) δ 146.7, 144.5, 140.7, 129.2, 127.1, 124.3, 123.0, 118.2, 115.9, 112.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{10}N_4Cl$ 245.0588; Found 245.0582.

N-(4-Fluorophenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5e**):[17] White solid; Yield : 83% (189 mg); Mp 246-248 °C; eluent: hexane/ethyl acetate 62:38; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.34 (d, J = 7.1 Hz, 1H), 7.63-7.60 (m, 3H), 7.26-7.22 (m, 1H), 7.19-7.15 (m, 2H), 6.92-6.89 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6) δ 158.2, 155.8, 146.6, 144.9, 138.2, 127.0, 123.0, 118.2 (d, J=7 Hz), 116.0, 115.9 (d, J= 5 Hz), 112.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{10}FN_4$ 229.0884; Found 229.0877.

N-(4-(Trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5f**):[17] White solid; Yield: 83% (230 mg); Mp 240-241°C; eluent: hexane/ethyl acetate 60:40; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.37 (d, J = 6.9 Hz, 1H), 7.73-7.66 (m, 5H), 7.32-7.30 (m, 1H), 6.95 (t, J = 6.6

Hz, 1H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 146.5, 144.9, 143.4, 126.8, 126.3 (d, *J*= 3 Hz), 122.7 (d, *J*= 32 Hz), 120.5, 120.1, 115.7 (d, *J*= 217 Hz), 115.5, 112.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{10}F_3N_4$ 279.0852; Found 279.0842.

N-(m-Tolyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5g**): White solid; Yield: 87% (194 mg); Mp 216-218 °C; eluent: hexane/ethyl acetate 62:38; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.33 (d, *J* = 6.7 Hz, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.40 (s, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.19-7.17 (m, 2H), 6.90 (t, *J* = 6.4 Hz, 1H), 6.74 (d, *J* = 7.0 Hz, 1H), 2.30 (s, 3H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 146.2, 144.2, 141.3, 138.1, 128.8, 126.4, 122.5, 121.2, 116.6, 115.4, 113.4, 112.2, 21.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{13}N_4$ 225.1134; Found 225.1128.

N-(3-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5h**): White solid; Yield: 88% (211 mg); Mp 205-207 °C; eluent: hexane/ethyl acetate 60:40; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.34 (t, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 9.3 Hz, 1H), 7.26-7.19 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 6.6 Hz, 1H), 6.51 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.75 (s, 3H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 159.9, 146.1, 144.1, 142.5, 129.7, 126.6, 122.6, 115.4, 112.3, 108.7, 105.9, 102.1, 54.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{13}N_4O$ 241.1083; Found 241.1078.

N-(2-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**5i**): White solid; Yield: 82% (196 mg); Mp 106-108 °C; eluent: hexane/ethyl acetate 60:40; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.23 (d, *J* = 7.0 Hz, 1H), 7.64 (d, *J* = 9.3 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.30-7.26 (m, 1H), 7.05 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.93-6.85 (m, 3H), 3.89 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6) δ 148.3, 147.5, 144.7, 131.7, 127.3, 123.6, 121.4, 121.1, 116.4, 115.7, 112.6, 111.6, 56.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{13}N_4O$ 241.1083; Found 241.1077.

N-Phenyl-[1,2,4]triazolo[4,3-a]quinolin-1-amine (**5j**): White solid; Yield: 79% (205 mg); Mp 259-260 °C; eluent: hexane/ethyl acetate 64:36; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H),

8.51 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 9.6 Hz, 1H), 7.62 (t, *J* = 8.7 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 2H), 6.87 (d, *J* = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 147.8, 146.7, 143.9, 131.3, 129.3, 129.2, 128.9, 126.0, 124.0, 120.2, 116.2, 115.4, 114.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{13}N_4$ 261.1134; Found 261.11264.

Typical procedure for the synthesis of 3-substituted 5-amino-1,2,4-thiadiazoles 8a-8k:

The mixture of phenyl isothiocyanate (**1**) (1.0 mmol) and amidoximes (**6**) (1.0 mmol), I_2 (50 mol%, 63 mg, 0.5 mmol) and K_2CO_3 (1.0 mmol) in water (2 mL) was stirred magnetically at 60°C. After completion of the reaction as monitored by TLC, The reaction mixture was cooled to room temperature and then quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc : hexane as eluents to afford corresponding product **8a-8k.**

N,3-Diphenyl-1,2,4-thiadiazol-5-amine (**8a**):[19] White solid; Yield: 90% (227 mg); Mp 174-176 °C; eluent: hexane/ethyl acetate 90:10; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.20-8.18 (m, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 6.4 Hz, 3H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 179.1, 168.5, 139.8, 132.7, 130.1, 129.3, 128.7, 127.5, 122.9, 117.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{12}N_3S$ 254.0746; Found 254.0740.

3-Phenyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**8b**):[19] White solid; Yield: 92% (245 mg); Mp 153-155 °C; eluent: hexane/ethyl acetate 92:8; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.19-8.17 (m, 2H), 7.55-7.48 (m, 5H), 7.24 (d, *J* = 8.3 Hz, 2H), 2.30 (s, 3H); $^{13}C\{^{1}H\}$NMR (75

MHz, DMSO-d_6) δ 179.2, 168.5, 137.4, 132.7, 132.0, 130.0, 129.7, 128.7, 127.5, 117.8, 20.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3S$ 268.0902; Found 268.0895.

N-(4-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8c**):[20] White solid; Yield: 95% (268 mg); Mp 144-145 °C; eluent: hexane/ethyl acetate 90:10; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.19-8.16 (m, 2H), 7.58-7.50 (m, 5H), 7.02 (d, J = 9.0 Hz, 2H), 3.77 (s, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 179.6, 168.5, 155.3, 133.2, 132.8, 130.0, 128.6, 127.5, 119.7,114.5, 55.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3OS$ 284.0852; Found 284.0844.

N-(4-Fluorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8d**):[19] White solid; Yield: 88% (238 mg); Mp 170-173 °C; eluent: hexane/ethyl acetate 90:10; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.19 (d, J = 5.9 Hz, 2H), 7.71 (dd, J = 8.6, 4.6 Hz, 2H), 7.52 (d, J = 6.6 Hz, 3H), 7.28 (t, J = 8.7 Hz, 2H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 179.1, 168.5, 159.3, 156.2, 136.3, 132.7, 130.1, 128.7, 127.5, 119.5 (d, J= 7 Hz), 115.9 (d, J= 226 Hz); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}N_3FS$ 272.0652; Found 272.0644.

N-(4-Nitrophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8e**):[21] Yellow solid; Yield: 87% (259 mg); Mp 216-218 °C; eluent: hexane/ethyl acetate 85:15; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.33 (d, J = 9.1 Hz, 2H), 8.25-8.24 (m, 2H), 7.95 (d, J = 9.1 Hz, 2H), 7.55 (d, J = 5.3 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, DMSO-d_6) δ 178.4, 168.6, 145.2, 141.5, 132.4, 130.4, 128.8, 127.6, 125.6, 117.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}N_4O_2S$ 299.0597; Found 299.0589.

N-(2-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8f**):[21] White solid; Yield: 86% (243 mg); Mp 96-98 °C; eluent: hexane/ethyl acetate 88:12; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.49 (d, J = 6.9 Hz, 1H), 8.19-8.17 (m, 2H), 7.54-7.49 (m, 3H), 7.11-7.05 (m, 3H), 3.90

(s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6) δ 179.97, 168.4, 148.9, 133.4, 130.4, 129.4, 129.2, 127.9, 124.0, 121.2, 119.4, 111.7, 56.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3OS$ 284.0852; Found 284.0866

N-(3-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**8g**): White solid; Yield: 89% (251 mg); Mp 123-125 °C; eluent: hexane/ethyl acetate 90:10; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.19 (d, J = 3.3 Hz, 2H), 7.52 (s, 3H), 7.37 (d, J = 14.1 Hz, 2H), 7.16 (s, 1H), 6.70 (d, J = 6.4 Hz, 1H), 3.82 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6) δ 179.5, 168.9,160.5, 141.4, 133.2, 130.7, 130.6, 129.2, 127.9, 110.4, 108.7, 104.1, 55.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}N_2OS$ 284.0852; Found 284.0846.

3-Phenyl-N-propyl-1,2,4-thiadiazol-5-amine (**8h**): White solid; Yield: 84% (183 mg); Mp 82-84 °C; eluent: hexane/ethyl acetate 95:5; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.11-8.07 (m, 2H), 7.50-7.43 (m, 3H), 3.30 (d, J = 5.9 Hz, 2H), 1.64 (dd, J = 14.3, 7.2 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 183.1, 168.5, 133.1, 129.7, 128.4, 127.4, 47.0, 21.8, 11.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{14}N_3S$ 220.0902; Found 220.0895.

N-Cyclohexyl-3-phenyl-1,2,4-thiadiazol-5-amine (**8i**):[19] White powder; Yield: 81% (209 mg); mp 126-127 °C; eluent: hexane/ethyl acetate 94:6; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.10 (s, 2H), 7.45 (s, 3H), 3.52 (s, 1H), 2.00 (s, 2H), 1.72 (s, 2H), 1.57 (s, 1H), 1.30 (t, J = 32.6 Hz, 5H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 182.0, 168.4, 133.2, 129.6, 128.4, 127.4, 54.4, 31.9, 25.1, 24.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{18}N_3S$ 260.1215; Found 260.1210.

N-Phenyl-3-(p-tolyl)-1,2,4-thiadiazol-5-amine (**8j**): White solid; Yield; 91% (242 mg); Mp 187-188 °C; eluent: hexane/ethyl acetate 94:6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.07

(d, J = 8.1 Hz, 2H), 7.65 (d, J = 7.9 Hz, 2H), 7.44 (t, J = 7.9 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 2.38 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6) δ 179.4, 169.0, 140.3, 140.3, 130.6, 129.9, 129.8, 128.0, 123.3, 118.1, 21.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3S$ 268.0902; Found 268.0896.

3-(4-Chlorophenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**8k**): White solid; Yield: 89% (267 mg); Mp 220-222 °C; eluent: hexane/ethyl acetate 95:5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.18-8.15 (m, 2H), 7.59-7.57 (m, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 2.30 (s, 3H); $^{13}C\{^{1}H\}$NMR (75 MHz, DMSO-d_6) δ 179.4, 167.3, 137.3, 134.7, 132.2, 131.5, 129.7, 129.2, 128.8, 117.9, 20.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}ClN_3S$ 302.0513; Found 302.0505.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Bhat, A. R.; Bhat, G. V.; Shenoy, G. G. Synthesis and In-Vitro Antimicrobial Activity of New 1,2,4-Triazoles. *J. Pharm. Pharmacol.* **2001**, *53*, 267-272. (b) Katica, C. R.; Vesna, D.; Vlado, K.; Dora, G. M.; Aleksandra, B. Synthesis, Antibacterial and Antifungal Activity of 4-Substituted-5-aryl-1,2,4-triazoles. *Molecules* **2001**, *6*, 815-824. (c) Holla, B. S.; Poorjary, K. N.; Rao, B. S.; Shivananda, M. K. New bis-Aminomercaptotriazoles and bis-Triazolothiadiazoles as Possible Anticancer Agents. *Eur. J. Med. Chem.* **2002**, *3*, 511-517. (d) Yamanaka, T.; Ohki, H.; Ohgaki, M.; Okuda, S.; Toda, A.; Kawabata, K.; Inoue, S.; Misumi, K.; Itoh, K.; Satoh, K.; U. S. Patent US 2005004094 A1, **2005**.

(2) (a) Bekircan, O.; Gumurkcuoglu, N. Synthesis of Some 3,5-Diphenyl-4*H*-1,2,4-triazole Derivatives as Antitumor Agents. *Indian J. Chem.* **2005**, *44B*, 2107-2113. (b) Siddiqui, A. A.; Arora, A.; Siddiqui, N.; Misra, A. Synthesis of Some 1,2,4-Triazoles as Potential Antifungal Agents. *Indian J. Chem.* **2005**, *44B*, 838-841. (c) Boschelli, D. H.; Connor, D. T.; U. S. Patent US 2005114958A, **2005**.

(3) (a) Collin, X.; Sauleau, A.; Coulon, J. 1,2,4-Triazolo Mercapto and Aminonitriles as Potent Antifungal Agents. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2601-2605. (b) Lamrence, E. K.; U. S. Patent 4, 263, 312, **1981**. (c) Rollas, S.; Kalyoncuoglu, N.; Sur-Altiner, D.; Yegenoglu, Y. 5-(4-Aminophenyl)-4-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones: Synthesis and Antibacterial and Antifungal Activities. *Pharmazie* **1993**, *48*, 308-309.

(4) (a) Clercq, E. De. Antiviral Drugs in Current Clinical Use. *J. Clin. Virol.* **2004**, *30*, 115-133. (b) Kucukguzel, I.; Tatar, E.; Kucukguzel, S. G.; Rollas, S.; Clercq, E. De. Synthesis

of Some Novel Thiourea Derivatives Obtained from 5-[(4-Aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and Evaluation as Antiviral/Anti-HIV and Anti-Tuberculosis Agents. *Eur. J. Med. Chem.* **2008**, *43*, 381-392.

(5) Bo, Y.; Lin, C.; Ruiying, F.; Zhiping, G. Luteolytic Effects of DL111-IT in Pregnant Rats. *Eur. J. Pharmacol*. **1999**, *380*, 145-152.

(6) Naveen, M.; Upendar Reddy, Ch.; Iqbal, J.; Pal, M. Synthesis of Dipeptidyl Peptidase-4 Inhibitors: A Brief Overview. *Tetrahedron* **2010**, *66*, 4919-4938.

(7) Li, C.-S.; An, C.-Y.; Li, X.-M.; Gao, S.-S.; Cui, C.-M.; Sun, H.-F.; Wang, B.-G. Triazole and Dihydroimidazole Alkaloids from the Marine Sediment-Derived Fungus Penicillium Paneum SD-44. *J. Nat. Prod.* **2011**, *74***,** 1331-1334.

(8) Nisbet-Brown, E.; Olivieri, N. F.; Giardina, P. J.; Grady, R. W.; Neufeld, E. J.; Sechaud, R.; Krebs-Brown, A. J.; Anderson, J. R.; Alberti, D.; Sizer, K. C.; Nathan, D. G. Effectiveness and Safety of ICL670 in Iron-Loaded Patients with Thalassaemia: A Randomised, Double-Blind, Placebo-Controlled, Dose-Escalation Trial. *Lancet* **2003**, *361*, 1597-1602.

(9) Iizawa, Y.; Okonogi, K.; Hayashi, R.; Iwahi, T.; Yamazaki, T.; Imada, A. Therapeutic Effect of Cefozopran (SCE-2787), a New Parenteral Cephalosporin, Against Experimental Infections in Mice. *Antimicrob. Agents Chemother.* **1993**, *37*, 100-105.

(10) (a) Larsen, S. D.; DiPaolo, B. A. Traceless Solid-Phase Synthesis of 1,2,4-Triazoles Using a Novel Amine Resin. *Org. Lett.* **2001**, *3*, 3341-3344. (b) Stocks, M. J.; Cheshire, D. R.; Reynolds, R. Efficient and Regiospecific One-Pot Synthesis of Substituted 1,2,4-Triazoles. *Org. Lett.* **2004**, *6*, 2969-2971. (c) Balsells, J.; DiMichele, L.; Liu, J.; Kubryk, M.; Hansen,

K.; Armstrong, J. D. Synthesis of [1,2,4]Triazolo[4,3-*r*]piperazines *via* Highly Reactive Chloromethyloxadiazoles. *Org. Lett.* **2005**, *7*, 1039-1042.

(11) (a) Shah, A. A.; Khan, Z. A.; Choudhary, N.; Loholter, C.; Schafer, S.; Marie, G. P. L.; Faroog, U.; Witulski, B.; Wirth, T. Iodoxolone-Based Hypervalent Iodine Reagents. *Org. Lett.* **2009**, *11*, 3578-3581. (b) Cashman, J.-R.; Hanzlik, R.-P. Oxidation and Other Reactions of Thiobenzamide Derivatives of Relevance to Their Hepatotoxicity. *J. Org. Chem.* **1982**, *47*, 4645-4650. (c) Patil, P. C.; Bhalerao, D. S.; Dangate, P. S.; Akamanchi, K. G. IBX/TEAB-Mediated Oxidative Dimerization of Thioamides: Synthesis of 3,5-Disubstituted 1,2,4-Thiadiazoles. *Tetrahedron Lett.* **2009**, *50*, 5820-5822. (d) Khosropour, A.-R.; Noei. A Convenient Strategy for the Synthesis of 3,5-Diaryl-1,2,4-thiadiazoles: Oxidative Dimerization of Arylthioamides using CC-DMSO in PEG-400. *Monatsh. Chem.* **2010**, *141*, 649-651. (e) Xu, Y.; Chen, J.; Gao, W.; Jin, H.; Ding, J.; Wu, H. Solvent-Free Synthesis of 3,5-Di(hetero)aryl-1,2,4-thiadiazoles by Grinding of Thioamides Under Oxidative Conditions. *J. Chem. Res.* **2010**, *34*, 151-153. (f) Cheng, D.; Luo, R.; Zheng, W.; Yan, J. Highly Efficient Oxidative Dimerization of Thioamides to 3,5-Disubstituted 1,2,4-Thiadiazoles Mediated by DDQ. *Synth. Commun.* **2012**, *42*, 2007-2013.

(12) (a) Madhur, S.; Joshi, F.; Christopher, P. Construction of 1,2,4-Triazole Derivatives *via* Cyclocondensation of Alkylidene Dihydropyridines and Aryldiazonium Salts. *Org. Lett.* **2016**, *18*, 5916-5919. (b) Murali Mohan, G.; Tharmalingam, P. Copper(II)-Catalyzed Aerobic Oxidative Synthesis of Substituted 1,2,3- and 1,2,4-Triazoles from Bisarylhydrazones *via* C-H Functionalization/C-C/N-N/C-N Bonds Formation. *J. Org. Chem.* **2012**, *77*, 5063-5073. (c) Zhengkai, C.; Hongli, L.; Weipeng, D.; Maozhong, M.; Hongjun, R. I_2-Catalyzed Oxidative Coupling Reactions of Hydrazones and Amines and

the Application in the Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazoles. *Org. Lett.* **2016**, *18*, 1334-1337. (d) Bechara, W. S.; Khazhieva, I. S.; Elsa, R.; Charette, A. B. One-Pot Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles *via* the Addition of Hydrazides to Activated Secondary Amides. *Org. Lett.* **2015**, *17*, 1184-1187. (e) Arumugam, M.; Kandasamy, R.; Noufal, M. C.; Shanmugam, M.; Nattamai, B. Hypervalent Iodine(III) Mediated Synthesis of 3-Substituted 5-Amino-1,2,4-thiadiazoles through Intramolecular Oxidative S-N Bond Formation. *J. Org. Chem.* **2016**, *81*, 6573-6579.

(13) (a) Finkbeiner, P.; Nachtsheim, B. J. Iodine in Modern Oxidation Catalysis. *Synthesis* **2013**, *45,* 979-999. (b) Zhang, Z.-H; Liu, Q.-B. Organic Reaction Catalyzed by Molecular Iodine. *Prog. Chem.* **2006**, *18,* 270-280. (c) Banerjee, A. K.; Vera, W.; Mora, H.; Laya, M. S.; Bedoya, L.; Cabrera, E. V. Iodine in Organic Synthesis. *J. Sci. Ind. Res.* **2006**, *65,* 299-308. (d) Wang, S.-Y. Molecular Iodine. *Synlett* **2004**, 2642-2643. (e) Zhang, J.; Wu, X.; Gao, Q.; Geng, X.; Zhao, P.; Wu, Y.-D.; Wu, A. Diamination/Oxidative Cross-Coupling/Bicyclization of Anilines and Methyl Ketones: Direct I_2-Promoted Synthesis of 1,2-Fused Oxindoles. *Org. Lett*. **2017**, *19*, 408-411. (f) Naresh, G.; Kant, R.; Narender, T. Molecular Iodine Promoted Divergent Synthesis of Benzimidazoles, Benzothiazoles, and 2-Benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines. *J. Org. Chem*. **2014**, *79*, 3821-3829. (g) Lv, Z.; Liu, J.; Wei, W.; Wu, J.; Yu, W.; Chang, J. Iodine-Mediated Aryl C-H Amination for the Synthesis of Benzimidazoles and Pyrido[1,2-*a*]benzimidazoles. *Adv. Synth. Catal.* **2016**, *358*, 2759-2766. (h) Cui, H.; Liu, X.; Wei, W.; Yang, D.; He, C.; Zhang, T.; Wang, H. Molecular Iodine-Mediated Difunctionalization of Alkenes with Nitriles and Thiols Leading to β-Acetamido Sulfides. *J. Org. Chem.* **2016**, *81*, 2252-2260.

(14) (a) Nagaraju, T.; Nagesh, J.; Radha Krishna, P.; Sridhar, B.; Mangarao, N. 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. *J. Org. Chem.* **2017**, *82*, 5310-5316. (b) Mangarao, N.; Ramu, T.; Srinivas, N.; Siddaiah, V. Synthesis of 1,2,4-Triazoles, *N*-Fused 1,2,4-Triazoles and 1,2,4-Oxadiazoles *via* Molybdenum Hexacarbonyl-Mediated Carbonylation of Aryl Iodides. *Adv. Synth. Catal*. **2016**, *358*, 520-525. (c) Mangarao, N.; Ramu, T.; Srinuvasarao, R.; Prasanthi, S.; Siddaiah, V. A Simple and Efficient Synthesis of 3,4,5-Trisubstituted/*N*-Fused 1,2,4-Triazoles *via* Ceric Ammonium Nitrate Catalyzed Oxidative Cyclization of Amidrazones with Aldehydes Using Polyethylene Glycol as a Recyclable Reaction Medium. *Synthesis* **2015**, 517-525.

(15) (a) Naresh, G.; Kant, R.; Narender, T. Molecular Iodine Promoted Divergent Synthesis of Benzimidazoles, Benzothiazoles and 2-Benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines. *J. Org. Chem.* **2014**, *79*, 3821-3829. (b) Wenhui, Z.; Yingcai, D.; Zhaogang, B.; Ping, X.; Baojun, X.; Qiujie, T.; Wei, W.; Aihua, Z. One-Pot Three-Component Synthesis of Alkylthio-/Arylthio- Substituted Imidazo[1,2-*a*]pyridine Derivatives *via* C(sp^2)-H Functionalization. *Adv. Synth. Catal.* **2017**, *359*, 2215-2221.

(16) Natarajan, A.; Yuhong, G.; Haribabu, A.; Gerhard, W.; Halperin, J. A.; Michael, C. Synthetic Studies Toward Aryl-(4-aryl-4*H*-[1,2,4]triazole-3-yl)-amine from 1,3-Diarylthiourea as Urea Mimetics. *J. Org. Chem.* **2005**, *70*, 6362-6368.

(17) Pandurangan, K.; Aletti, A. B.; Montroni, D.; Kitchen, J. A.; Miguel, M.-C.; Salvador, B.; Thorfinnur, G.; Scanlan, E. M. Supramolecular Anion Recognition Mediates One-Pot Synthesis of 3-Amino-[1,2,4]-triazolo Pyridines from Thiosemicarbazides. *Org. Lett.* **2017**, *19*, 1068-1071.

(18) Comas, H.; Bernardinelli, G.; Swinnen, D. A Straightforward, One-Pot Protocol for the Synthesis of Fused 3-Aminotriazoles. *J. Org. Chem.* **2009**, *74*, 5553-5558.

(19) Mariappan, A.; Rajaguru, K.; Merukan Chola, N.; Muthusubramanian, S.; Bhuvanesh, N. Hypervalent Iodine(III) Mediated Synthesis of 3-Substituted 5-amino-1,2,4-thiadiazoles Through Intramolecular Oxidative S-N Bond Formation. *J. Org. Chem.* **2016**, *81*, 6573-6579.

(20) Wang, B.; Meng, Y.; Zhou, Y.; Ren, L.; Wu, J.; Yu, W.; Chang, J. Synthesis of 5-Amino and 3,5-Diamino Substituted 1,2,4-Thiadiazoles by I_2-Mediated Oxidative N-S Bond Formation. *J. Org. Chem.* **2017**, *82*, 5898-5903.

(21) Kim, H.-Y.; Kwak, S. H.; Lee, G.-H.; Gong, Y.-D. Copper-Catalyzed Synthesis of 3-Substituted-5-amino-1,2,4-thiadiazoles *via* Intramolecular N-S Bond Formation. *Tetrahedron* **2014**, *70*, 8737-8743.