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One-Pot Synthesis of 3-Aryl-5-amino-1,2,4-thiadiazoles from Imidates and Thioureas via I_2-Mediated Oxidative Construction of N-S Bond

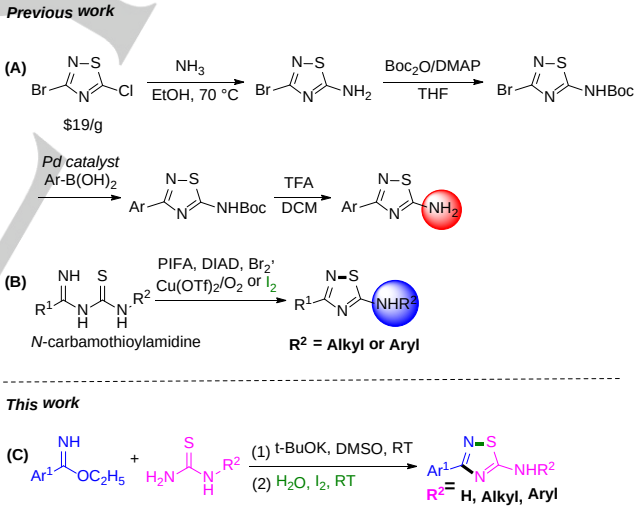
Ling Chai,[a] Zhenzhen Lai,[a] Qiangqiang Xia,[a] Jiangpei Yuan,[a] Qilong Bian,[a] Mingjian Yu,[a] Wenkai Zhang,[a] Yuanqing Xu*[a] and Hao Xu*[a,b]

Abstract: A simple and practical I_2-mediated one-pot synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles from imidates and thioureas has been developed. The protocol undergoes sequential process of base-mediated nuclophilic addition-elimination and I_2-mediated oxidative construction of N-S bond. The merit of this finding is illustrated by readily available and nontoxic substrates, easy approach to 3-aryl-5-amino-1,2,4-thiadiazoles with free or substituted amino group, and I_2-mediated oxidative construction of N-S bond.

Introduction

The demand for 1,2,4-thiadiazole derivatives is growing rapidly in many research fields.[1] In the 1,2,4-thiadiazoles, 3-substituted 5-amino-1,2,4-thiadiazoles show wide applications in medicinal chemistry,[2] and they often occur as the basic skeletons of natural products and pharmaceuticals.[3] The importance of this moiety has prompted the development of many efficient methods for the synthesis of 3-substituted 5-amino-1,2,4-thiadiazoles. In the previous methods, 3-substituted 5-amino-1,2,4-thiadiazoles with free amino group were difficult to be prepared; and drawbacks of hazardous reagents, tedious workups, unavailable starting materials and low yields always existed in the preparation process of such compounds by previous methods.[4] In 2009, a relatively simple method for the synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles with free amino group *via* Pd-catalyzed Suzuki-Miyaura couplings was developed (Scheme 1A).[4e] However, the tedious workups and expensive starting materials still restricted its application. Furthermore for the synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles with substituted amino group, the most common and direct strategy was oxidative heterocyclization of *N*-carbamothioylamidines (Scheme 1B).[5] Typical oxidants for this transformation included hypervalentiodine(Ⅲ) reagents (such as PIFA),[5a] azodicarboxylates (DIAD)[5b] and $Cu(OTf)_2/O_2$.[5c] Meanwhile, *N*-carbamothioylamidines were usually formed from amidines and isothiocyanates (which are toxic).[5] Very recently, molecular iodine (I_2) was also applied in this transformation as a readily available and eco-friendly oxidants;[6] however, the substrates of *N*-carbamothioylamidines were still needed to be prepared beforehand from amidines and isothiocyanates (which are toxic). Therefore, it is highly desired to develop simpler and green methods for the synthesis of 3-substituted 5-amino-1,2,4-thiadiazoles with free or substituted amino group from readily available and nontoxic substrates.

N-S bond construction through oxidative coupling of N-H and S-H bonds has attracted much attention for its atom- and step-economy. Meanwhile hypervalent iodine(Ⅲ) reagents,[5a,7] copper salts[8] or molecular iodine (I_2)[6,9] were employed to promote this transformation. This prompted us to explore the feasibility of synthesizing 3-substituted 5-amino-1,2,4-thiadiazoles from simper substrates under I_2-mediated oxidative conditions. In continuation of our endeavors to develop efficient methods for the synthesis of *N*-heterocycles from nitriles and their derivatives,[9b,10] herein we report a simple one-pot synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles with free or substituted amino group from aromatic imidates and thioureas via I_2-mediated oxidative N-S bond formation.



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

Results and Discussion

I_2-mediated one-pot reaction of ethyl benzimidate (**1a**) with thiourea (**2a**) was first chosen as the model to optimize the conditions, which included the bases, solvents and the amount of molecular iodine. As shown in Table 1,*t*-BuOK was proved to be the best base for the first step (entries 1-6), because strong base was helpful to the formation of *N*-carbamothioylamidine intermediate (entry 7; Scheme 1C). However, *t*-BuOK would not benefit the I_2-mediated oxidative coupling for the second step, so a small amount of water (0.1 mL) was needed to quench excess *t*-BuOK (compare entry 1 with 13). Moreover, the effect of

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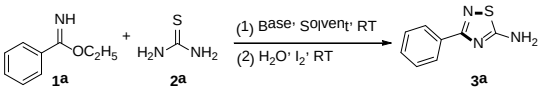
Supporting information for this article is given via a link at the end of the document.

solvents was also investigated, and DMSO provided the highest yield (entries 1, 8-12). When the amount of I_2 was reduced to 0.5 mmol (1 equiv.), a lower yield of product **3a** was obtained (compared entry 1 with 14). The reaction was also performed under I_2-catalyzed oxidative conditions (O_2 balloon, 1 atm), but only a 31% yield of **3a** was obtained (entry 15). Meanwhile it was noted that a high yield could still be provided under a nitrogen atmosphere (entry 17), and the yield of **3a** showed no increasement under an oxygen atmosphere (entry 16). When no I_2 was added in the second step under N_2 atmosphere, only trace amount of **3a** was detected (entry 18). Based on these results (entries 1, 14-18), the main oxidant in this transformation should be molecular iodine (I_2), rather than DMSO or oxygen (O_2).

Table 1. I_2-mediated one-pot synthesis of 3-phenyl-5-amino-1,2,4-thiadiazole (**3a**) from ethyl benzimidate (**1a**) with thiourea (**2a**): optimization of conditions.[a]



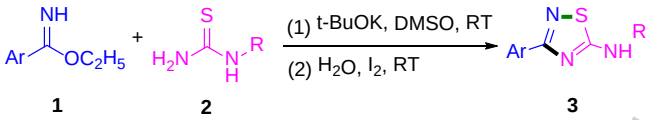
1a 2a 3a

Entry	Base	Solvent	Yield (%)[b]
1	***t*-BuOK**	**DMSO**	**88**
2	EtONa	DMSO	39
3	NaOH	DMSO	60
4	KOH	DMSO	59
5	Cs_2CO_3	DMSO	Trace
6	K_3PO_4	DMSO	Trace
7	--	DMSO	0
8	*t*-BuOK	DMF	35
9	*t*-BuOK	Dioxane	49
10	*t*-BuOK	*t*-$BuOCH_3$	Trace
11	*t*-BuOK	*t*-BuOH	Trace
12	*t*-BuOK	CH_3CN	27
13[c]	*t*-BuOK	DMSO	47
14[d]	*t*-BuOK	DMSO	34
15[e,g]	*t*-BuOK	DMSO	31
16[g]	*t*-BuOK	DMSO	85
17[h]	*t*-BuOK	DMSO	86
18[f,h]	*t*-BuOK	DMSO	trace

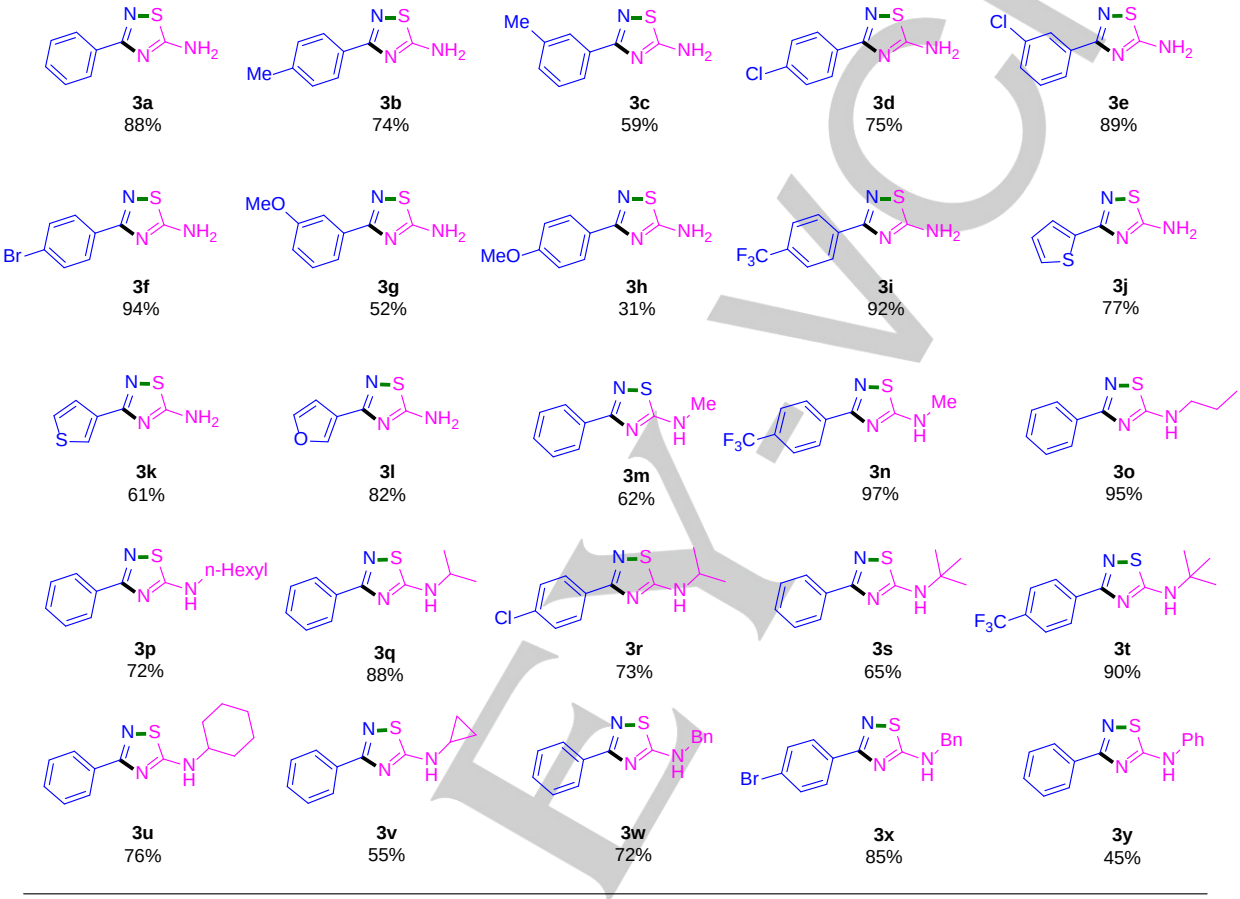
[a] Reaction conditions: without exclusion of air in a sealed Schlenk tube. For the first step, ethyl benzimidate **1a** (0.5 mmol, 75 mg), thiourea **2a** (1 mmol, 76 mg), base (1 mmol), anhydrous solvent (1 mL), reaction time (4 h) at room temperature (~25 °C). For the second step, I_2 (1 mmol, 254 mg), H_2O (0.1 mL), reaction time (10 h) at room temperature (~25 °C). [b] Isolated yield. [c] Without addition of H_2O for the second step. [d] I_2 (0.5 mmol) for the second step. [e] I_2 (0.25 mmol) for the second step. [f] No I_2 was added in the second step. [g] Under a O_2 balloon (1 bar) for the second steps. [h] Under a N_2 balloon (1 bar) for the two steps in a Schlenk tube.

The scope of I_2-mediated one-pot synthesis of 5-amino-1,2,4-thiadiazoles was investigated under the optimized condition (*t*-BuOK as base, DMSO as solvent, 2 equiv. of I_2 as oxidant). As shown in Table 2, a series of 5-amino-1,2,4-thiadiazole products were synthesized in moderate to good yields at room temperature. For the substrate of imidates, the benzimidates with electron-withdrawing groups showed higher reactivity (Br, CF_3; **3f, 3i, 3n, 3t, 3x**), perhaps because electron-withdrawing groups made benzimidates easier to be attacked by thiourea; meanwhile the reactivity of benzimidates with electron-donating groups (CH_3, OCH_3; **3b, 3c, 3g, 3h**) was lower than others. The position of substituent on the benzyl group (*meta* and *para* position) affected the yields of **3** as well; for the weak electron-donating group of methyl, the *para*-substituted benzimidates provided higher yields (compare **3b** and **3c**), due to lower steric hindrance; however for chlorine atom and methoxyl group, the opposite case was presented (compare **3d** with **3e**, **3g** with **3h**), maybe because the strong electron-withdrawing inductive effect of chlorine atom activated the substrate of imidates, and strong electron-donating conjugative effect of methoxyl group deactivated the substrate respectively. Furthermore, the heteroarylimidates were also tolerated well in this transformation (**3j-3l**). For the substrate of alkyl-substituted thioureas, the steric hindrance of substituent groups did not affect the yield of products **3** significantly, even thioureas with *t*-butyl group worked well for this transformation. But there were still some limitations, for example, the aliphatic imidates like benzyl and *n*-butyl imidates failed to provide the intended products (Scheme S1 in the Supporting Information).

Table 1. I_2-mediated one-pot synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles[a,b]

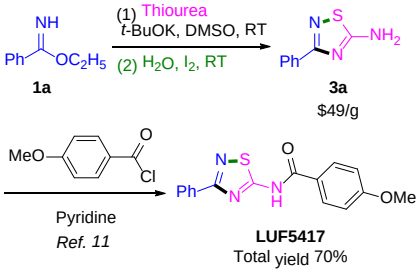


1 2 3



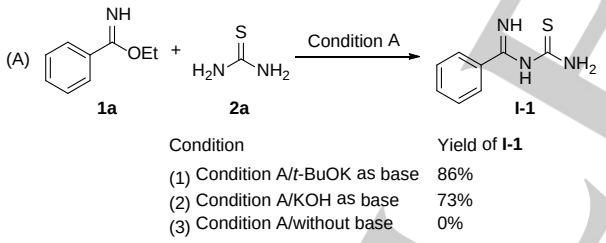
[a] Reaction conditions: without exclusion of air in a sealed Schlenk tube. For the first step, imidate **1** (0.5 mmol, 75 mg), thiourea **2** (1 mmol, 76 mg), *t*-BuOK (1 mmol, 112 mg), anhydrous DMSO (1 mL), reaction time (4 h) at room temperature (~25 °C). For the second step, I_2 (1 mmol, 254 mg), H_2O (0.1 mL), reaction time (10 h) at room temperature (~25 °C). [b] Isolated yield.

As shown in Table 2, the tolenrance of diverse functional groups implied the potential for modification for the synthesis of downstream 3-substituted 5-amino-1,2,4-thiadiazole products under I_2-mediated conditions. To further demonstrate the utility of this synthetic protocol, we applied it into the preparation of *N*-(3-phenyl-1,2,4-thiadiazol-5-yl)-4-methoxybenzamide (**LUF5417**). In van Muijlwijk-Koezen's work, a series of thiodiazolobenzamide compounds was synthesized as potent and selective adenosine receptor antagonists, especially **LUF5417** showing a K_i value of 82 nM at the adenosine A_3 receptor;[11] and the excellent activity of **LUF5417** was also proved in Kim's work.[4d] But the starting material of **3a**, used for the synthesis of **LUF5417**, was expensive and hard to be prepared. By our method, **3a** could be prepared easily; and **LUF5417** was synthesized from readily available ethyl benzimidate in 70% yield over two steps (Scheme 2).

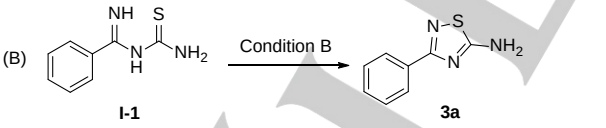


Scheme 2. The application of I_2-mediated one-pot method in the synthesis of **LUF5417**

In order to explore the mechanism for the I_2-mediated synthesis of 5-amino-1,2,4-thiadiazoles, the following control experiments were performed. Expected intermediate **I-1** could be prepared successfully from **1a** and **2a** in the presence of *t*-BuOK (Scheme 3A); and the strong base was helpful to the formation of intermediate **I-1**. For the transformation from **I-1** to **3a**, the molecular iodine (I_2) played a key oxidative role, and a good yield of **3a** could be provided under I_2-mediated conditions (entries 6-7 in Scheme 3B). Interestingly, the addition of base should have benefitted the transformation by the proposed reaction mechanism below (Scheme 4). However when the base was added and only DMSO was used as the solvent, a lower yield of **3a** was obtained (entries 2-4 in Scheme 3B); the results implied the basicity and nucleophilicity of base in DMSO solution was much stronger than in the DMSO/H_2O solution,[12] due to weak solvation effect of base in DMSO solution; so that the **I-1** was destroyed and transformed into other by-products. Moreover when the DMSO/H_2O was used as the solvent, the base of KOH could dissolve well in the aqueous reaction solution, and deprotonate **I-1**; then the addition of base was beneficial to the transformation (entries 5-7 in Scheme 3B). In addition, a 76% yield of **3a** could be obtained under base-free conditions in DMSO/H_2O solution (entry 5 in Scheme 3B); this result implied that the transformation from **I-1** to **3a** could also proceed under base-free conditions. Nonetheless, the addition of base could accelerate the reaction obviously [compare entry 5 with 7 in Scheme 3B; 76% (10 h) vs 86% (20 min)]. At last, to verify the existence of generated iodide, we attempted to capture the iodide with water solution of $AgNO_3$, then a yellow deposition could be obtained (please see Figure S1 in the Supporting Information).



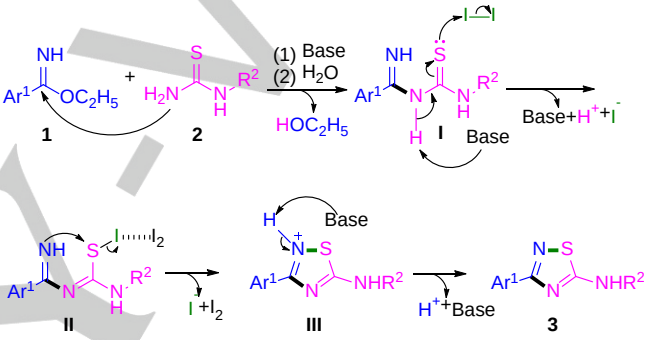
Condition	Yield of **I-1**
(1) Condition A/*t*-BuOK as base	86%
(2) Condition A/KOH as base	73%
(3) Condition A/without base	0%



Condition	Yield of **3a**
(1) Condition B/without I_2	0%
(2) Condition B/*t*-BuOK as base	40%
(3) Condition B/*t*-BuOK (1.5 mmol) as base	36%
(4) Condition B/KOH as base	48%
(5) Condition B/without base/DMSO/H_2O (1/0.1, 1.1 mL) as solvent	76%
(6) Condition B/KOH as base/DMSO/H_2O (1/0.1, 1.1 mL) as solvent	90%
(7) Condition B/KOH as base/DMSO/H_2O (1/0.1, 1.1 mL)/20 min	86%

Scheme 3. Control experiments for mechanism study [Condition A: without exclusion of air in a sealed Schlenk tube. Ethyl benzimidate **1a** (3 mmol, 448 mg), thiourea **2a** (6 mmol, 457 mg), base (6 mmol), anhydrous DMSO (1 mL), reaction time (4 h) at room temperature (~25 °C); Condition B: **I-1** (0.5 mmol, 90 mg), I_2 (1.1 mmol, 279 mg), base (1 mmol), DMSO (1 mL) as solvent, reaction time (10 h) at room temperature (~25 °C)].

A possible mechanism is suggested for synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles (Scheme 4). At first, intermolecular nucleophilic attack of thiourea **2** to imidate **1** in the presence of base (*t*-BuOK) leads to intermediate **I** (*N*-carbamothioylamidine),then subsequent oxidative iodination of **I** furnishes the iodide **II**.[6,8b] Afterword, the S-I bond cleaves under I_2-mediated conditions, and a new N-S bond is formed after intramolecular nucleophilic attack of imino group to sulfur atom in iodide **II**, to afford protonated intermediate **III.** Finally, deprotonation of **III** in the presence of base affords the target product 5-amino-1,2,4-thiadiazole **3a**.



Scheme 4. Possible mechanism for synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles

Conclusions

We have developed a simple and practical I_2-mediated one-pot method for synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles. The protocol used readily available imidates and thioureas as the starting materials, economical and environmentally friendly molecular iodine (I_2) as the oxidant. The one-pot reactions underwent sequential base-mediated nuclophilic addition-elimination to form the intermediate of *N*-carbamothioylamidines, and I_2-mediated oxidative heterocyclization of *N*-carbamothioylamidines to give the corresponding products. 3-Substituted 5-amino-1,2,4-thiadiazoles with free amino group were difficult to be prepared by previous methods; and drawbacks of hazardous reagents, tedious workups, unavailable starting materials and low yields always existed in the preparation process of such compounds. Meanwhile for the synthesis of 3-substituted 5-amino-1,2,4-thiadiazoles with substituted amino group, the oxidative heterocyclization of *N*-carbamothioylamidines was the most common and direct strategy; but the *N*-carbamothioylamidines were usually prepared from amidines and isothiocyanates (which are toxic). In addition, the application of molecular iodine (I_2) in the oxidative cross-coupling of N-H and S-H is rare. Given this, A simple and green method for the synthesis of 3-aryl-

5-amino-1,2,4-thiadiazoles with free or substituted amino group from readily available and nontoxic substrates has been developed in this paper. In light of the wide application of the products and easy workup approach, this method will attract much attention in relevantly academic and industrial fields.

Experimental Section

General experimental procedures: All reactions were carried out under air. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm,$CHCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm) or were recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 39.51 ppm).

General procedure for synthesis of compounds (3a-3y): Thiourea **2** (1 mmol), *t*-BuOK (1 mmol, 112 mg) and DMSO (1 mL) were added into a 10 mL reaction tube charged with a magnetic stirrer. Then the aromatic imidate **1** (0.5 mmol) was added into the tube,and the tube was sealed and stirred for 4 h under room temperature for the first step. After that, 100 uL water and iodine (1 mmol, 254 mg) was added into the tube; the mixture was stirred for 10 h at room temperature for the second step. The resulting solution was quenched with saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography on silica gel employing petroleum ether/ EtOAc as eluent to afford target product (**3a-3y**).

3-Phenyl-1,2,4-thiadiazol-5-amine (3a):[6c] Eluent: petroleum ether/ethyl acetate (4:1). Yield 78 mg (88%). White solid, mp 155-156 °C (lit.[6c] m.p. 155-156 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.27-7.90 (m, 4H), 7.63-7.26 (m, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 184.0, 168.8, 133.6, 130.2, 129.0, 127.8. ESI-MS $[M+H]^+$ *m/z* 178.13.

3-(*p*-Tolyl)-1,2,4-thiadiazol-5-amine (3b): Eluent: petroleum ether/ethyl acetate (4:1). Yield 71 mg (74%). White solid, mp 167-168 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.01 (s, 2H), 7.95 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.8, 168.9, 139.8, 131.1, 129.6, 127.8, 21.4. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{11}H_{12}N_2S$ 192.0590, found 192.0585.

3-(*m*-Tolyl)-1,2,4-thiadiazol-5-amine (3c): Eluent: petroleum ether/ethyl acetate (4:1). Yield 56 mg (59%). White solid, mp 148-149 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.03 (s, 2H), 7.93-7.82 (m, 2H), 7.39-7.30 (m, 1H), 7.29-7.22 (m, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.9, 169.0, 138.1, 133.6, 130.8, 128.9, 128.4, 125.0, 21.5. ESI-HRMS $[M+H]^+$*m/z* calcd for $C_9H_{10}N_3S$ 192.0590, found 192.0604

3-(*p*-Chlorophenyl)-1,2,4-thiadiazol-5-amine (3d): Eluent: petroleum ether/ethyl acetate (4:1). Yield 79 mg (75%). White solid, mp 189.7-190.9 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.22-8.05 (m, 4H), 7.57 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 184.1, 167.7, 134.9, 132.38 , 129.5, 129.2. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_8H_7ClN_3S$ 212.0044, found 212.0054.

3-(*m*-Chlorophenyl)-1,2,4-thiadiazol-5-amine (3e): Eluent: petroleum ether/ethyl acetate (4:1). Yield 94 mg (89%). White solid, mp 189.7-190.9 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.11 (s, 2H), 8.08-7.91 (m, 2H), 7.58-7.43 (m, 2H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.7, 166.8, 135.0, 133.3, 130.6, 129.5, 127.0, 125.9. ESI-HRMS $[M+H]^+$*m/z* calcd for $C_8H_7ClN_3S$ 212.0044, found 212.0052.

3-(*p*-Bromophenyl)-1,2,4-thiadiazol-5-amine (3f):[13] Eluent: petroleum ether/ethyl acetate (4:1). Yield 120 mg (94%). White solid, mp 202-203 °C (lit.[13] mp 197.9-199.1 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.09 (s, 2H), 7.98 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 184.1, 167.8, 132.7, 132.1, 129.8, 123.7. ESI-MS $[M+H]^+$*m/z* 255.90.

3-(*m*-Methoxyphenyl)-1,2,4-thiadiazol-5-amine (3g): Eluent: petroleum ether/ethyl acetate (4:1). Yield 54 mg (52%). White solid, mp 124.1-126.4 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.04 (s, 2H), 7.69-7.62 (m, 1H), 7.62-7.57 (m, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.06-6.97 (m, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.5, 168.2, 159.3, 134.5, 129.7, 119.7, 115.7, 112.2, 55.1. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_9H_{10}N_3OS$ 208.0539, found 208.0533.

3-(*p*-Methoxyphenyl)-1,2,4-thiadiazol-5-amine (3h):[6d] Eluent: petroleum ether/ethyl acetate (3:1). Yield 32 mg (31%). White solid, mp 185.5-187.1 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.16-7.82 (m, 4H), 7.08-6.87 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.3, 168.2, 160.4, 128.9, 126.1, 113.9, 55.2. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_9H_{10}N_3OS$ 208.0539, found 208.0550.

3-[*p*-(Trifluoromethyl)phenyl]-1,2,4-thiadiazol-5-amine (3i):[13] Eluent: petroleum ether/ethyl acetate (4:1). Yield 113 mg (92%). White solid, mp 166-168 °C (lit.[13] mp 149.8-151.9 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.27 (d, *J* = 8.1 Hz, 2H), 8.17 (s, 2H), 7.84 (d, *J* = 8.2Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.9,

167.0, 136.6, 129.7 (q, *J* = 31.6 Hz), 128.9, 128.0, 125.6 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.0 Hz). ESI-MS $[M+H]^+$ *m/z* 246.20.

3-(Thiophen-2-yl)-1,2,4-thiadiazol-5-amine (3j): Eluent: petroleum ether/ethyl acetate (4:1). Yield 71 mg (77%). White solid, mp 193.3-194.9 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.10 (s, 2H), 7.68-7.57 (m, 2H), 7.26-7.01 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.7, 164.2, 137.5, 129.0, 128.4, 127.9. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_6H_6N_3S_2$ 183.9998, found 183.9990.

3-(Thiophen-3-yl)-1,2,4-thiadiazol-5-amine (3k): Eluent: petroleum ether/ethyl acetate (4:1). Yield 56 mg (61%). White solid, mp 192.8-195.0 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.13-7.87 (m, 3H), 7.64-7.52 (m, 2H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.7, 165.5, 136.4, 127.4, 127.2, 126.8. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_6H_6N_3S_2$183.9998, found 184.0000.

3-(Furan-3-yl)-1,2,4-thiadiazol-5-amine (3l): Eluent: petroleum ether/ethyl acetate (2:1). Yield 69 mg (82%). White solid, mp 175.1-176.3 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.06 (s, 2H), 7.80 (s, 1H), 6.99-6.83 (m, 1H), 6.68-6.54 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.7, 160.9, 148.9, 144.8, 112.2, 111.7. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_6H_6N_3OS$ 168.0226, found 168.0221.

***N*-Methyl-3-phenyl-1,2,4-thiadiazol-5-amine (3m):**[6a] Eluent: petroleum ether/ethyl acetate (5:1). Yield 59 mg (62%). White solid, mp 141-143 °C (lit.[6a] mp 155 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.46 (s, 1H), 8.21-7.98 (m, 2H), 7.56-7.40 (m, 3H), 2.97 (d, *J* = 4.7 Hz, 3H). ^{13}C NMR (100MHz, d_6-DMSO, 25 °C) δ 184.4, 169.1, 133.7, 130.2, 129.0, 128.0, 32.0. ESI-MS $[M+H]^+$ *m/z* 191.98.

***N*-Methyl-3-[*p*-(trifluoromethyl)phenyl]-1,2,4-thiadiazol-5-amine (3n)**: Eluent: petroleum ether/ethyl acetate (10:1). Yield 126 mg (97%). White solid, mp 160.2-162.8 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.56 (s, 1H), 8.30 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 3.01 (d, *J* = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 184.6, 167.6, 137.0, 130.2 (q, *J* = 31.7 Hz), 128.7, 128.6, 126.0 (q, *J* = 3.7 Hz), 123.3, 120.6, 32.0. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{10}H_9F_3N_3S$ 260.0464, found 260.0468.

3-Phenyl-*N*-(*n*-propyl)-1,2,4-thiadiazol-5-amine (3o):[14] Eluent: petroleum ether/ethyl acetate (50:1). Yield 104 mg (95%). White solid, mp 84.4-85.3 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.56 (s, 1H), 8.20-7.98 (m, 2H), 7.60-7.28 (m, 3H), 3.30 (d, *J* = 6.9 Hz, 2H), 1.78-1.48 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.7, 169.0, 133.7, 130.2, 129.0, 127.9, 47.6, 22.3, 11.8. ESI-MS $[M+H]^+$ *m/z* 220.07.

***N*-(*n*-Hexyl)-3-phenyl-1,2,4-thiadiazol-5-amine (3p):** Eluent: petroleum ether/ethyl acetate (15:1). Yield 63 mg (72%). White solid, mp 46.6-48.3 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.54 (s, 1H), 8.24-7.94 (m, 2H), 7.61-7.32 (m, 3H), 1.71-1.52 (m, 2H), 1.45-1.17 (m, 6H), 0.97-0.76 (m, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.6, 169.0, 133.7, 130.2, 129.0, 127.9, 45.7, 31.4, 28.9, 26.4, 22.5, 14.4. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{14}H_{20}N_3S$ 262.1372, found 262.1366.

***N*-Isopropyl-3-phenyl-1,2,4-thiadiazol-5-amine (3q):**[15] Eluent: petroleum ether/ethyl acetate (15:1). Yield 96 mg (88%). Colorless oil. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.48 (d, *J* = 6.8 Hz, 1H), 8.17-8.02 (m, 2H), 7.57-7.35 (m, 3H), 3.83 (s, 1H), 1.25 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 182.5, 169.0, 133.7, 130.2, 129.0, 127.9, 48.0, 22.6. ESI-MS $[M+H]^+$ *m/z* 220.05.

***N*-Isopropyl-3-(*p*-chlorophenyl)-1,2,4-thiadiazole (3r)**: Eluent: petroleum ether/ethyl acetate (10:1). Yield 93 mg (73%). White solid, mp 134.2-136.1 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.51 (d, *J* = 7.2 Hz, 1H), 8.19-8.00 (m, 2H), 7.62-7.43 (m, 2H), 3.83 (s, 1H), 1.25 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 182.5, 167.8, 134.9, 132.4, 129.6, 129.1, 48.0, 22.6. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{11}H_{13}ClN_3S$ 254.0513, found 254.0504.

***N*-(tert-Butyl)-3-phenyl-1,2,4-thiadiazol-5-amine (3s)**: Eluent: petroleum ether. Yield 76 mg (65%). White solid, mp 108.9-109.9 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.34 (s, 1H), 8.22-8.02 (m, 2H), 7.56-7.38 (m, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 181.1, 168.6, 133.8, 130.2, 129.0, 127.9, 53.7, 28.7. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{12}H_{16}N_3S$ 234.1059, found 234.1096.

***N*-(tert-Butyl)-3-[*p*-(trifluoromethyl)phenyl]-1,2,4-thiadiazol-5-amine (3t)**: Eluent: petroleum ether/ethyl acetate (10:1). Yield 136 mg (90%). White solid, mp 117.4-118.3 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.46 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 181.9, 166.6, 136.7, 129.6 (q, *J* = 31.2, 30.6 Hz), 128.0, 125.6 (q, *J* = 3.8 Hz), 125.5 (q, *J* = 272.1 Hz), 53.3, 28.1. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{13}H_{15}F_3N_3S$ 302.0933, found 302.0940.

***N*-Cyclohexyl-3-phenyl-1,2,4-thiadiazol-5-amine (3u):**[5]Eluent: petroleum ether/ethyl acetate (20:1). Yield 99 mg (76%). White solid, mp 127.9-128.8 °C(lit.[5] 126-127 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.64-8.40 (m, 1H), 8.18-8.02 (m, 2H), 7.57-7.35 (m, 3H), 3.52 (s, 1H), 2.11-1.91 (m, 2H), 1.82-1.63 (m, 2H), 1.64-1.50 (m, 1H), 1.45-1.13 (m, 5H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 182.5, 169.0, 133.7, 130.2, 129.0, 127.9, 45.2, 32.4, 25.6, 24.7. ESI-MS $[M+H]^+$ *m/z* 260.11.

***N*-Cyclopropyl-3-phenyl-1,2,4-thiadiazol-5-amine (3v):**[14] Eluent: petroleum ether/ethyl acetate (10:1). Yield 60 mg (55%). White solid, mp 183.2-183.8 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 9.04 (s, 1H), 8.19-7.87 (m, 2H), 7.60-7.30 (m, 3H), 2.73-2.60 (m, 1H), 0.86-0.72 (m, 2H), 0.68-0.55 (m, 2H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 186.1, 169.6, 133.7, 130.3, 129.1, 127.9, 27.3, 7.1. ESI-MS $[M+H]^+$ *m/z* 218.06.

***N*-Benzyl-3-phenyl-1,2,4-thiadiazol-5-amine (3w):**[4c] Eluent: petroleum ether/ethyl acetate (10:1). Yield 96 mg (72%). White solid, mp 109.3-110.8 °C (lit.[4c] mp 103-105 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 8.99 (s, 1H), 8.09 (m, *J* = 6.9, 2.2 Hz, 2H), 7.54-7.33 (m, 7H), 7.33-7.24 (m, 1H), 4.60 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.7, 168.8, 138.5, 133.6, 130.3, 129.0, 129.0, 128.1, 128.0, 127.8, 49.0. ESI-MS $[M+H]^+$ *m/z* 268.08.

***N*-Benzyl-3-(*p*-bromophenyl)-1,2,4-thiadiazol-5-amine (3x):** Eluent: petroleum ether/ethyl acetate (10:1). Yield 147 mg (85%). White solid, mp 132.8-134.0 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 9.03 (s, 1H), 8.19-7.83 (m, 2H), 7.72-7.61 (m, 2H), 7.46-7.33 (m, 4H), 7.33-7.24 (m, 1H), 4.60 (d, *J* = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 183.8, 167.8, 138.4, 132.6, 132.1, 129.9, 129.0, 128.1, 127.8, 123.8, 49.0. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_{13}BrN_3S$ 346.0008, found 346.0000.

***N*,3-Diphenyl-1,2,4-thiadiazol-5-amine (3y):**[6a] Eluent: petroleum ether/ethyl acetate (20:1). Yield 57 mg (45%). White solid, mp 176-179 °C (lit.[6a] mp 172 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 11.07 (s, 1H), 8.30-8.05 (m, 2H), 7.73-7.61 (m, 2H), 7.58-7.49 (m, 3H), 7.48-7.39 (m, 2H), 7.16-7.05 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 179.6, 169.0, 140.3, 133.2, 130.7, 129.9, 129.2, 128.0, 123.4, 118.1. ESI-MS $[M-H]^-$ *m/z* 252.33.

Synthesis of 4-methoxy-*N*-(3-phenyl-1,2,4-thiadiazol-5-yl)benzamide (LUF5417) from 3a[11]: 5-Amino-3-phenyl-1,2,4-thiadiazole **3a** (4 mmol, 709 mg) was dissolved in dry pyridine (1.8 mL) at a 10 mL three-neck flask. The mixture was cooled to 0 °C, and 4-methoxybenzoyl chloride (5.9 mmol, 1.0 g) was dropwise added. The solution solidified gradually within 0.5 h. And then the solid was dissolved in a mixture of EtOAc/water (1/1, 80 mL). The water layer was removed, and the organic layer was washed subsequently with 40 mL of 1 M HCl, 40 mL of 5% $NaHCO_3$ solution and 40 mL of brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel employing petroleum ether/ EtOAc (10:1) as eluent, and white crystal of 4-methoxy-*N*-(3-phenyl-1,2,4-thiadiazol-5-yl)benzamide **(LUF5417)** was obtained. Yield 984 mg (79%). White solid, mp 174.7-176.0 °C (lit.[11] mp 177 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 13.45 (s, 1H), 8.39-8.08 (m, 4H), 7.74-7.38 (m, 3H), 7.24-7.02 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 177.0, 167.3, 166.4, 163.8, 133.3, 131.2, 130.7, 129.3, 127.9, 123.1, 114.6, 56.1. ESI-MS $[M-H]^-$ m/z 310.08.

Synthesis of *N*-carbamothioylbenzimidamide (I-1): Thiourea **2a** (6 mmol, 457 mg), *t*-BuOK (6 mmol, 673 mg) and DMSO (6 mL) were added into a 25 mL round-bottom flask charged with a magnetic stirrer. Then the benzoimidate **1a** (3 mmol, 448 mg) was added into the flask; and the flask was sealed and stirred for 4 h under room temperature. After that, the resulting solution was quenched with saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography on silica gel employing petroleum ether/ EtOAc (2:1) as eluent to afford target product *N*-carbamothioylbenzimidamide **(I-1)**. Yield 462 mg (86%). Pale green solid, mp 150.9-152.1 °C. ^{1}H NMR (400 MHz, d_6-DMSO, 25 °C) δ 10.29 (s, 1H), 8.73 (s, 1H), 8.43-8.29 (m, 1H), 8.28-8.12 (m, 1H), 8.02-7.90 (m, 2H), 7.61-7.39 (m, 3H). ^{13}C NMR (100 MHz, d_6-DMSO, 25 °C) δ 192.1, 162.5, 135.7, 132.0, 128.7, 127.9. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_8H_{10}N_3S$ 180.0590, found 180.0584.

Synthesis of 3a from I-1: **I-1** (0.5 mmol, 90 mg), DMSO (1 mL), H_2O (0.1 mL), KOH (1 mmol, 56 mg) and iodine (1.1 mmol, 279 mg) were sequentially added into a 10 mL reaction tube charged with a magnetic stirrer. The mixture was stirred for 10 h at room tempereture. The resulting solution was quenched with saturated aqueous solution of $Na_2S_2O_3$. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography on silica gel employing petroleum ether/ EtOAc (4:1) as eluent to afford target product **3a** (80 mg, 90%).

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Keywords: I_2-mediated • one-pot synthesis • oxidative construction of N-S bond • 5-amino-1,2,4-thiadiazole • imidate

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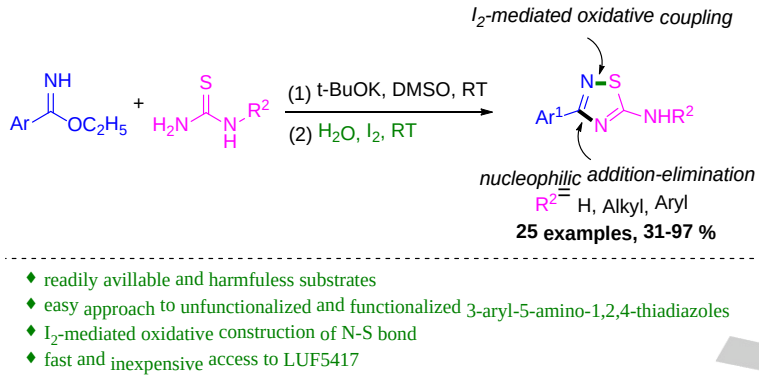

- readily avillable and harmfuless substrates
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Heterocycles*

Ling Chai, Zhenzhen Lai, Qiangqiang Xia, Jiangpei Yuan, Qilong Bian, Mingjian Yu, Wenkai Zhang, Yuanqing Xu, Hao Xu**

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One-Pot Synthesis of 3-Aryl-5-amino-1,2,4-thiadiazoles from Imidates and Thioureas via I_2-Mediated Oxidative Construction of N-S Bond

A simple and practical I_2-mediated one-pot synthesis of 3-aryl-5-amino-1,2,4-thiadiazoles from imidates and thioureas has been developed. The protocol undergoes sequential process of base-mediated nuclophilic addition-elimination and I_2-mediated oxidative construction of N-S bond.