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Electrochemical Oxidative Intramolecular N-S Bond Formation: Synthesis of 3-Substituted 5-Amino-1,2,4-thiadiazoles

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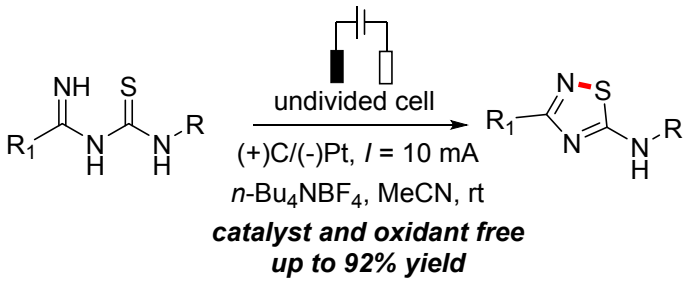


ABSTRACT

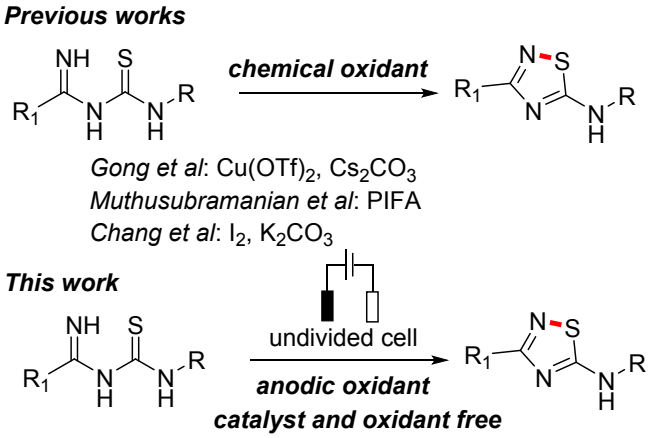
A facile and efficient protocol for the construction of 3-substituted 5-amino-1,2,4-thiadiazoles has been developed through the electro-oxidative intramolecular dehydrogenative N-S bond formation of imidoyl thioureas. Various 1,2,4-thiadiazole derivatives were synthesized in good to excellent yields with broad substrate scope and excellent functional group tolerance under catalyst- and oxidant-free electrolytic conditions at room temperature.

INTRODUCTION

Sulfur-containing compounds are ubiquitous structural motifs in natural products, biologically active compounds, materials and synthetic intermediates.[1] Among them, the 1,2,4-thiadiazole derivatives, which have a wide of biological and pharmaceutical properties.[2] Therefore, the synthesis of 1,2,4-thiadiazole derivatives have received considerable attention. Traditionally, 1,2,4-thiadiazole derivatives can be achieved by the oxidative cyclization of thioamides and thiourea with various metal-catalysts and oxidants.[3] Gong developed an N-S bond formation reaction for the synthesis of 5-amino-1,2,4-thiadiazoles via copper-catalyzed intramolecular dehydrogenative of imidoyl thiourea.[4] Muthusubramanian reported a hypervalent iodine(III)-mediated intramolecular oxidative N-S bond formation of imidoyl thiourea for the synthesis of 5-amino-1,2,4-thiadiazoles.[5] Later, I_2-mediated intramolecular oxidative cyclization for the synthesis of 5-amino-1,2,4-thiadiazoles has also been achieved by Chang.[6] However, most of these methods require stoichiometric oxidants, bases and transition-metal catalysts (scheme 1). In this context, the development of environmentally friendly, atom economy and effective methods without metal catalyst or external oxidant for the synthesis of 5-amino-1,2,4-thiadiazoles are highly desirable.

Electrochemical anodic oxidation, which is environmentally friendly, atom-economical and emerging powerful synthetic methodology[7] has attracted much

attention in the construction of carbon-carbon[8] or carbon-heteroatom[9] or heteroatom-heteroatom[10] bonds for the synthesis of various functional molecules. However, the electrochemical oxidative N-S bond formation is still rare. Yuan reported an electrochemical oxidation of S-H/N-H cross-coupling reaction to produce sulfonamides.[11] More recently, an environmentally method for the synthesis of sulfonamides from amines and thiols was developed via microflow electrochemical oxidative N-S bond formation.[12] Encouraged by previous studies on N-S bond formation reaction[13a-c] and our interest in the electrochemical[13d], herein, we disclose an electrochemical oxidative intramolecular N-S bond formation for the construction of 3-substituted 5-amino-1,2,4-thiadiazoles under catalyst, metal and oxidant-free conditions.

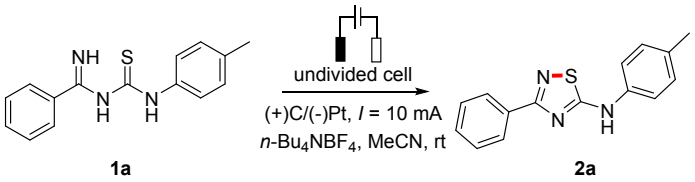


Scheme 1. Synthesis of 5-amino-1,2,4-thiadiazoles

RESULTS AND DISCUSSION

In the initial experiment, imidoyl thiourea **1a** was selected as model substrate to investigate the optimization of the reaction conditions. As shown in **table 1**, in an undivided cell (a two-necked round-bottomed flask) with a carbon rod anode and Pt plate cathode, when 10 mA constant current and 0.03 M *n*-Bu_4NBF_4 electrolyte was used in 10 mL MeCN at room temperature, the desired 5-amino-1,2,4-thiadiazole **2a** was isolated in 85% yield (table 1, entry 1). Encouraged by this result, various electrolytes were also tested such as $LiClO_4$, *n*-Bu_4NPF_6 and KI, no further improved the yield of **2a** was observed (table 1, entries 2-4). Further, the product yield of **2a** was dropped to 53% when 5 mA constant current was used (table 1, entry 5). And, when the constant current was increased from 10 mA to 15 mA, no significant effect of the yield was observed (table 1, entry 6). Next, the effect of the solvents was screened, aqueous MeCN was unsuitable for the electrooxidized N-S bond formation reaction (table 1, entry 7). Using EtOH and DMSO as solvents isolated the corresponding product **2a** in 28% and 47% yields, respectively (table 1, entries 8-9). This result demonstrated that MeCN was the best solvent for this transformation. Graphite and platinum electrode were tested, no improvement yield of **2a** can be achieved (table 1, entries 10-11). Using graphite as the anode and nickel foam as the cathode, the yield of desired product **2a** decreased from 85% to 75% (table 1, entry 12). Additionally, no product was obtained in the absence of current after the reaction (table 1, entry 13).

Table 1. Optimization of reaction conditions[a]



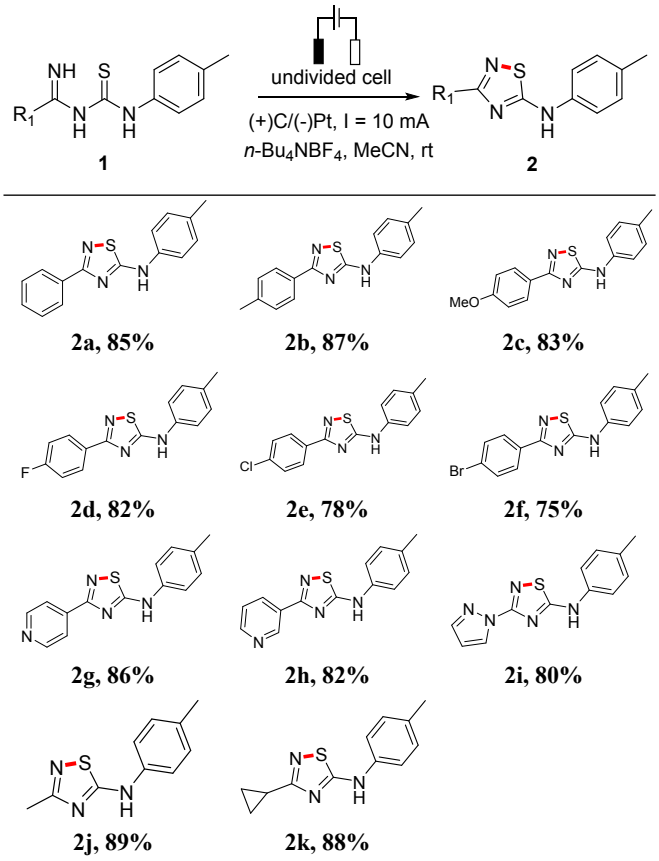
Entry	Variation from the standard conditions	Yield [%]
1	none	85
2	$LiClO_4$ instead of *n*-$BuNBF_4$	42
3	*n*-Bu_4NPF_6 instead of *n*-Bu_4NBF_4	56
4	KI instead of *n*-Bu_4NBF_4	51
5[b]	I = 5 mA instead of I = 10 mA (3.7 F/mol)	53
6[b]	I = 15 mA instead of I = 10 mA (2.8 F/mol)	82
7	MeCN/H_2O (4:1) instead of MeCN	Trace
8	EtOH instead of MeCN	28
9	DMSO instead of MeCN	47
10	(+)C/(−)C instead of (+)C/(−)Pt	66
11	(+)Pt/(−)Pt instead of (+)C/(−)Pt	72
12	(+)C/(−)Ni instead of (+)C/(−)Pt	75
13	no electric current, 24 h	N. R.

[a]Reaction conditions: carbon rod anode, Pt plate cathode (1cm×1cm), undivided cell, I = 10 mA (J_{anode}

= 10 mA/cm^2), **1a** (0.3 mmol), *n*-Bu_4NBF_4 (0.3 mmol), MeCN (10 mL), under air atmosphere at room temperature for 2.5 h, 3.1 F/mol. [b]Until complete consumption of **1a**.

With the optimized protocol in hand, we explored the scope of the electrochemical N-S bond formation reaction with various imidoyl thioureas **1** synthesized from different amidines with 4-methylphenyl isothiocyanate. As shown in **table 2**, a variety of imidoyl thioureas **1** with electron-donating groups, electron-withdrawing groups and halogens on the aryamidines side were investigated which were converted to the desired products **2a-2f** in good yields. In addition, 4-pyridine (**1g**), 3-pyridine (**1h**) and pyrazole (**1i**) of imidoyl thioureas, were also compatible and produced the desired products **2g**, **2h** and **2i** in 80-86% yield. Importantly, alkyl of imidoyl thioureas were tolerated in this transformation, and the corresponding products **2j** and **2k** were generated in 89% and 88% yield, respectively.

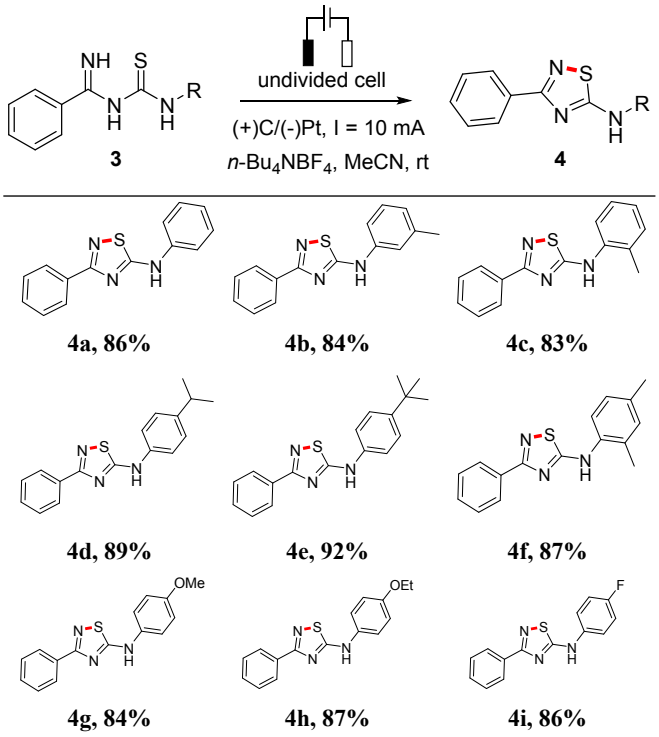
Table 2. Substrate Scope of 5-Amino-1,2,4-thiadiazole Synthesis[a]

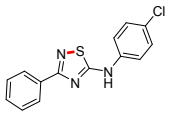


[a]Reaction conditions: carbon rod anode, Pt plate cathode (1cm×1cm), undivided cell, I = 10 mA (J_{anode} = 10 mA/cm^2), **1** (0.3 mmol), *n*-Bu_4NBF_4 (0.3 mmol), MeCN (10 mL), under air atmosphere at room temperature for 2.5 h, 3.1 F/mol.

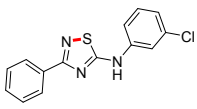
Furthermore, the imidoyl thioureas **3** from isothiocyanates with benzamidine were investigated the compatibility of the electrochemical dehydrogenative N-S bond formation protocol in **table 3**. The imidoyl thioureas **3** from aryl isothiocyanates with various functional groups such as, Me, *i*-Pr, *t*-Bu, OMe, OEt, F and Cl were tolerated and afford the 1,2,4-thiadiazoles **4a-4k** in good yields. Generally, the imidoyl thioureas **3** with electron-donating groups (Me, OMe, OEt) shown higher reactivity than electron-withdrawing groups (F, Cl). Additionally, imidoyl thioureas **3l** and **3m** from naphthyl and benzyl isothiocyanate underwent the reaction smoothly and produce the **4l** and **4m** in 85% and 78% yield, respectively. Moreover, 2-alkyl substituted desired products **4n** and **4o** have been synthesized under the electrochemical conditions in good yields. However, a complex mixture of **4p** was obtained, when imidoyl thiourea with alkenyl group was tested.

Table 3. Substrate Scope of 5-Amino-1,2,4-thiadiazole Synthesis[a]

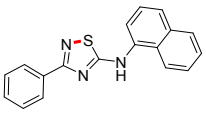




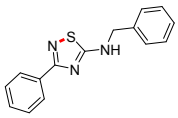
4j, 83%



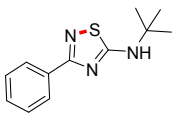
4k, 74%



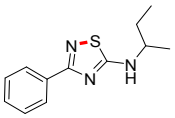
4l, 85%



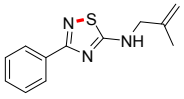
4m, 78%



4n, 84%



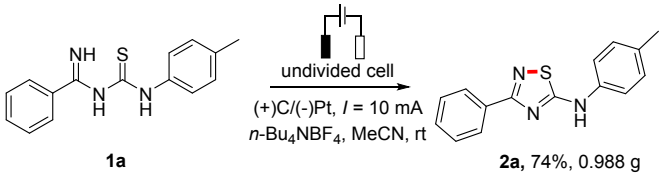
4o, 80%



4p, complex mixture

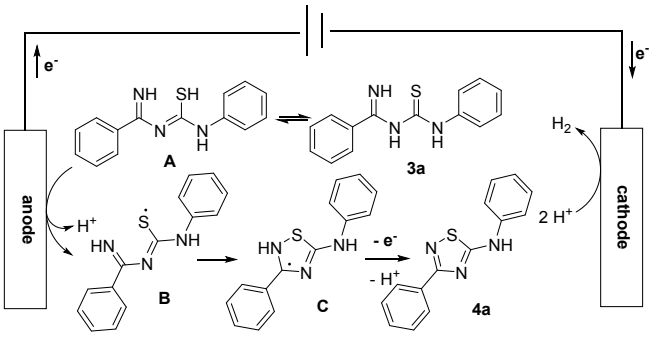
[a]Reaction conditions: carbon rod anode, Pt plate cathode (1cm×1cm), undivided cell, I = 10 mA (J_{anode} = 10 mA/cm^2), **3** (0.3 mmol), n-Bu_4NBF_4 (0.3 mmol), MeCN (10 mL), under air atmosphere at room temperature for 2.5 h, 3.1 F/mol.

Subsequently, to further illustrate the scalability of this dehydrogenative N-S bond formation protocol, a gram-scale reaction was evaluated in **scheme 2**. To our delight, 5 mmol of **1a** was treated under the electrochemical conditions in 100 mL MeCN, and the desired product **2a** was isolated in 74% yield.

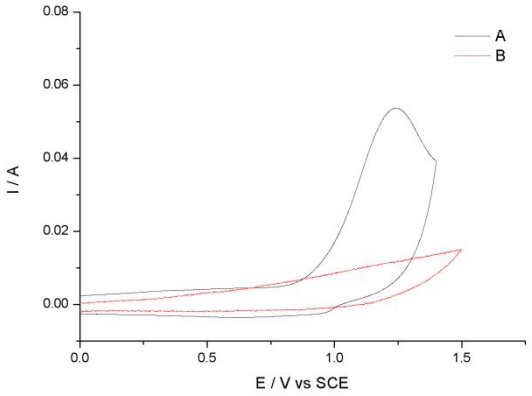


Scheme 2. Gram-scale experiments

According to the previous work[14] and experimental results[15], a plausible mechanism for this dehydrogenative N-S bond formation is proposed in **scheme 3**. The imidoyl thiourea **3a** could isomerize to the thioiminol **A** which was then oxidized at the anode to formed the radical intermediate **B** *via* single electron transfer (SET) process. The radical intermediate **B** afford in an anodic was supported by the CV experiments (**scheme 4**). Then, the radical cation **B** underwent radical cyclization to produce the intermediate **C**. Finally, the desired product **4a** was obtained by oxidative rearomatization of the intermediate **C**.



Scheme 3. Proposed Reaction Mechanism



Scheme 4. Cyclic voltammograms, scan rate: 25 mV/s. A) **1a** (0.3 mmol) + *n*-Bu_4NBF_4 (0.3 mmol) in MeCN (10 mL); B) *n*-Bu_4NBF_4 (0.3 mmol) in MeCN (10 mL)

In summary, we have demonstrated an efficient and atom-economic protocol for the construction of 3-substituted 5-amino-1,2,4-thiadiazoles *via* electrochemical oxidative dehydrogenative of N-S bond formation. This electrochemical strategy provides a simple and efficient method for the synthesis of 1,2,4-thiadiazole derivatives in good to excellent yields with broad substrate scope under mild conditions, which avoids use of metal catalysts and stoichiometric oxidants.

EXPERIMENTAL SECTION

General methods: ^{1}H (400 MHz), ^{13}C{^{1}H} (101 MHz) spectra were recorded on a Bruker 400MHz spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as internal standard. HRMS was recorded on a Bruker micrOTOF-Q II. Melting points are uncorrected. The Pt plate electrode (1cm×1cm×0.15cm), Ni plate electrode

(1cm×1.5cm×0.15cm) and carbon rod electrode (0.4cm×6cm) were obtained from Shanghai yueci Electronic Technology Co., Ltd, China.

General procedure for synthesis of imidoyl thioureas 1 or 3: [4, 5] Amidine (0.3 mmol), isothiocyanate (0.33 mmol), and K_2CO_3 (0.45 mmol, 62 mg) in 2 mL dichloromethane, and stirred for 20 h at room temperature. Upon completion of the reaction, the mixture was washed with water, and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated, and afford the target products without further purification.

General procedure for synthesis of 2 or 4: In 25 mL two-necked round bottom flask, with carbon rod anode, Pt plate cathode (1cm×1cm), 0.3 mmol imidoyl thiourea **1** or **3,** *n*-Bu_4NBF_4 (0.3 mmol, 99 mg) and MeCN (10 mL). The mixture was magnetic stirred with constant current 10 mA at room temperature for 1-2 hour. Upon completion of the reaction, the mixture was concentrated in vacuo and the residue was purified by column chromatography (EtOAc/n-Hexane=1:10) to afford the desired products **2** or **4**.

3-phenyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2a**).[6] White solid, mp 154-156 °C, yield: 85% (68 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.24 – 8.14 (m, 2H), 7.48 – 7.39 (m, 3H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.11 – 7.03 (m, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.6, 169.5, 136.8, 134.6, 133.0, 130.4, 130.2, 128.7, 128.1, 119.1, 21.0.

N,3-di-p-tolyl-1,2,4-thiadiazol-5-amine (**2b**).[6] White solid, mp 180-183 °C, yield: 87% (73 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 19.8 Hz, 1H), 8.18 – 8.01 (m, 2H), 7.25 – 7.15 (m, 4H), 7.13 – 7.08 (m, 2H), 2.39 (s, 3H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.2, 169.5, 140.3, 136.7, 134.4, 130.4, 130.3, 129.3, 127.9, 118.9, 21.5, 20.9.

3-(4-methoxyphenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2c**). White solid, mp 145-147 °C, yield: 83% (74 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (2brs, 1H), 8.12 (d, *J* = 8.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.5, 169.2, 161.2, 136.9, 134.4, 130.4, 129.7, 125.9, 119.1, 114.0, 55.5, 21.0. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{16}N_3OS$ $[M+H]^+$ 298.1009, found 298.1003.

3-(4-fluorophenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2d**). White solid, mp 198-200 °C, yield: 82% (70 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.38 – 8.13 (m, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.42 – 7.34 (m, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 180.0, 168.1, 162.6, 138.1, 132.8, 130.5, 130.4, 130.1, 118.5, 116.4 (d, *J* = 22.0 Hz), 21.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.56. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{13}FN_3S$ $[M+H]^+$ 286.0809, found 286.0813.

3-(4-chlorophenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2e**).[6] White solid, mp 220-222 °C, yield: 78% (70 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.32 – 8.13 (m, 2H), 7.67 – 7.58 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 180.2, 168.3, 138.2, 135.7, 133.0, 132.4, 130.7, 130.1, 129.8, 118.8, 21.3.

3-(4-bromophenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2f**).[6] White solid, mp 240-242 °C, yield: 75% (78 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.19 – 8.09 (m, 2H), 7.79 – 7.74 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 180.0, 168.0, 137.9, 132.7, 132.4, 132.3, 130.3, 130.0, 124.2, 118.5, 21.0.

3-(pyridin-4-yl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2g**).[3] White solid, mp 240-242 °C, yield: 86% (69 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.72 (d, *J* = 6.0 Hz, 2H), 8.02 (d, *J* = 6.2 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 7.4 Hz, 2H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 181.2, 167.7, 151.2, 140.0, 138.2, 133.1, 130.3, 122.2, 118.7, 21.1.

3-(pyridin-3-yl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2h**).[3] 78% White solid, mp 238-240 °C, yield: 82% (66 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.27 – 7.11 (m, 8H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.4, 180.4, 137.3, 136.0, 134.5, 130.2, 130.0, 129.5, 126.5, 125.6, 125.6.

3-(1H-pyrazol-1-yl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2i**).[5] White solid, mp 200-202 °C, yield: 80% (62 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.30 (d, *J* = 5.6 Hz, 1H), 7.53 (s, 1H), 7.28 – 7.12 (m, 4H), 6.46 – 6.35 (m, 1H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 183.3, 158.5, 142.9, 136.3, 135.6, 130.4, 128.9, 121.0, 108.0, 21.1.

3-methyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2j**).[6]

White solid, mp 144-147 °C, yield: 89% (55 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.19 – 7.11 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 182.3, 169.5, 137.0, 134.9, 130.4, 119.8, 20.9, 19.1.

3-cyclopropyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2k**).[6] White solid, mp 135-137 °C, yield: 88% (61 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.07 – 7.01 (m, 2H), 2.27 (s, 3H), 2.03 (ddd, *J* = 13.2, 8.3, 4.9 Hz, 1H), 0.99 (dt, *J* = 6.2, 3.1 Hz, 2H), 0.89 (dt, *J* = 8.3, 3.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 181.3, 174.9, 137.0, 134.5, 130.4, 119.2, 21.0, 13.7, 9.0.

N,3-diphenyl-1,2,4-thiadiazol-5-amine (**4a**).[5] White solid, mp 174-175 °C, yield: 86% (65 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.15 – 8.12 (m, 2H), 7.39 – 7.32 (m, 5H), 7.20 – 7.16 (m, 2H), 7.13 – 7.07 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 180.8, 169.5, 139.2, 133.0, 130.3, 130.0, 128.7, 128.1, 124.5, 118.5.

3-phenyl-N-(m-tolyl)-1,2,4-thiadiazol-5-amine (**4b**).[5] White solid, mp 108-110 °C, yield: 84% (67 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.27 – 8.13 (m, 2H), 7.42 (dd, *J* = 5.1, 1.8 Hz, 3H), 7.26 – 7.20 (m, 1H), 7.00 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.87 (s, 1H), 2.24 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 181.3, 169.3, 140.0, 139.2, 132.9, 130.3, 129.7, 128.7, 128.2, 125.3, 119.6, 115.3, 21.5.

3-phenyl-N-(o-tolyl)-1,2,4-thiadiazol-5-amine (**4c**).[5] White solid, mp 167-170 °C, yield: 83% (66 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.15 – 8.06 (m, 2H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.23 (m, 4H), 7.18 (td, *J* = 7.4, 1.2 Hz, 1H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 183.2, 169.7, 137.9, 133.0, 131.6, 130.9, 130.1, 128.6, 127.9, 127.7, 126.4, 121.3, 17.8.

N-(4-isopropylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4d**).[5] White solid, mp 130-132 °C, yield: 89% (79 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.17 – 8.07 (m, 2H), 7.39 – 7.31 (m, 3H), 7.18 – 7.12 (m, 2H), 7.10 – 7.03 (m, 2H), 2.83 (hept, *J* = 6.9 Hz, 1H), 1.18 (s, 3H), 1.16 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 181.4, 169.5, 145.5, 137.0, 133.0, 130.2, 128.7, 128.1, 127.9, 119.0, 33.7, 24.1.

N-(4-(tert-butyl)phenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4e**). White solid, mp 145-147 °C, yield: 92% (85 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.23 – 8.15 (m, 2H), 7.42 – 7.31 (m, 5H), 7.13 – 7.07 (m, 2H), 1.30 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 181.5, 169.4, 147.7, 136.7, 132.9, 130.2, 128.6, 128.1, 126.7, 118.7, 34.5, 31.4. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{20}N_3S$ $[M+H]^+$ 310.1372, found 310.1368

N-(2,4-dimethylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4f**). White solid, mp 132-135 °C, yield: 87% (73 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.07 (d, *J* = 6.8 Hz, 2H), 7.40 – 7.28 (m, 4H), 7.13 – 7.06 (m, 2H), 2.34 (s, 3H), 2.24 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 184.1, 169.8, 136.8, 135.4, 133.0, 132.3, 131.8, 130.0, 128.5, 128.2, 127.9, 122.6, 21.1, 17.7. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{16}N_3S$ $[M+H]^+$ 282.1059, found 282.1054.

N-(4-methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4g**).[5] White solid, mp 117-120 °C, yield: 84% (71 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.20 – 8.12 (m, 2H), 7.41 (dd, *J* = 5.2, 2.0 Hz, 3H), 7.22 – 7.18 (m, 2H), 6.95 – 6.89 (m, 2H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 182.9, 169.7, 157.3, 133.1, 132.5, 130.2, 128.7, 128.1, 122.2, 115.2, 55.7.

N-(4-ethoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4h**). White solid, mp 135-137 °C, yield: 87% (78 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.15 – 7.98 (m, 2H), 7.38 – 7.27 (m, 3H), 7.13 – 7.03 (m, 2H), 6.85 – 6.74 (m, 2H), 3.94 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 183.1, 169.7, 156.7, 133.0, 132.4, 130.2, 128.6, 128.0, 122.2, 115.6, 63.9, 14.9. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{16}N_3OS$ $[M+H]^+$ 298.1009, found 298.1003.

N-(4-fluorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4i**).[5] White solid, mp 170-172 °C, yield: 86% (70 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.30 – 8.17 (m, 2H), 7.79 – 7.70 (m, 2H), 7.60 – 7.52 (m, 3H), 7.36 – 7.28 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 180.1, 169.5, 158.8 (d, *J* = 240.4 Hz), 137.3 (d, *J* = 3.0 Hz), 133.7, 131.2, 129.7, 128.5, 120.5 (d, *J* = 8.1 Hz), 117.0 (d, *J* = 23.2 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -119.75.

N-(4-chlorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4j**).[5] White solid, mp 194-196 °C, yield: 83% (71 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.20 – 8.18 (m, 2H), 7.72 (d, *J* = 8.9 Hz, 2H), 7.53 – 7.48 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 179.6, 169.1, 139.5, 133.2, 130.7, 129.7, 129.2, 128.3, 126.9, 119.7.

N-(3-chlorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4k**).[5] White solid, mp 156-158 °C, yield: 74% (64 mg). ^{1}H NMR (400 MHz, CDCl3) δ 8.58 (s, 1H), 8.21 – 8.18 (m, 2H), 7.46 – 7.43 (m, 3H), 7.31 – 7.26 (m, 2H), 7.15 – 7.09 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.6, 140.3, 135.6, 132.8, 130.9, 130.5, 130.4, 128.8, 128.1, 124.3, 118.6, 116.2.

N-(naphthalen-1-yl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4l**).[5] White solid, mp 150-152 °C, yield: 85% (77 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.04 – 7.89 (m, 3H), 7.85 – 7.78 (m, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.58 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.48 – 7.36 (m, 3H), 7.23 – 7.15 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 184.4, 169.9, 135.5, 134.7, 132.9, 130.0, 128.8, 128.4, 127.9, 127.9, 127.3, 127.1, 127.0, 125.87, 121.4, 119.7.

N-benzyl-3-phenyl-1,2,4-thiadiazol-5-amine (**4m**).[3] White solid, mp 100-103 °C, yield: 78% (62 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.03 (m, 2H), 7.35 – 7.23 (m, 8H), 6.85 (s, 1H), 4.40 (d, *J* = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 184.7, 169.9, 136.2, 133.3, 130.1, 129.0, 128.6, 128.3, 128.0, 127.7, 50.6.

N-(tert-butyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4n**). Yellow liquid, yield: 84% (59 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.12 – 8.02 (m, 2H), 7.32 – 7.23 (m, 5H), 7.04 – 7.00 (m, 2H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.6, 169.3, 133.3, 129.9, 128.6, 128.0, 53.2, 28.6. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{16}N_3S$ $[M+H]^+$ 234.1059, found 234.1063.

N-(sec-butyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**4o**). Yellow liquid, yield: 80% (56 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.03 (m, 2H), 7.35 (dd, *J* = 5.2, 2.0 Hz, 3H), 5.98 (d, *J* = 8.5 Hz, 1H), 3.25 (dh, *J* = 8.3, 6.4 Hz, 1H), 1.52 (qd, *J* = 7.4, 6.3 Hz, 2H), 1.20 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 184.0, 170.0, 133.3, 130.0, 128.6, 128.0, 55.3, 29.7, 20.3, 10.5. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{16}N_3S$ $[M+H]^+$ 234.1059, found 234.1056.

Supporting Information Available: The copies of ^{1}H and ^{13}C{^{1}H} NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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