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Synthesis of 2-Amino-1,3,4-oxadiazoles and 2-Amino-1,3,4-thiadiazoles via Sequential Condensation and I_2-Mediated Oxidative C−O/C−S Bond Formation

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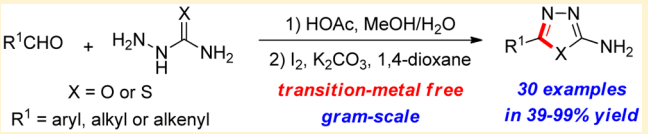
Supporting Information

ABSTRACT: 2-Amino-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles were synthesized via condensation of semicarbazide/thiosemicarbazide and the corresponding aldehydes followed by I_2-mediated oxidative C−O/C−S bond formation. This transition-metal-free sequential synthesis process is compatible with aromatic, aliphatic, and cinnamic aldehydes, providing facile access to a variety of diazole derivatives bearing a 2-amino substituent in an efficient and scalable fashion.

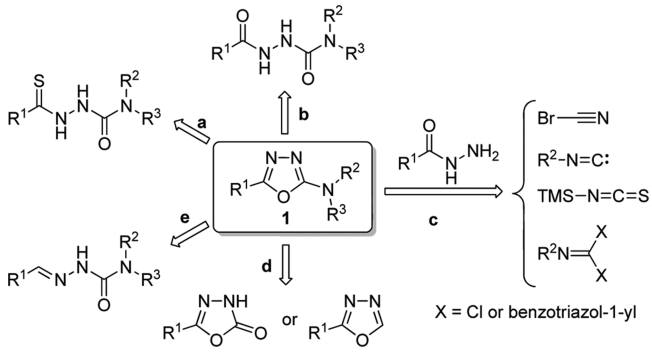


INTRODUCTION

1,3,4-Oxadiazoles and 1,3,4-thiadiazoles are important five-membered nitrogen-containing heterocycles with a wide range of applications[1−4] in medicinal chemistry, material science, and organic synthesis. In particular, these diazole structural motifs bearing a 2-amino substituent are valuable building blocks in drug design. For example, 2-amino-1,3,4-oxadiazole derivatives exhibit a broad spectrum of biological and pharmaceutical activities including antimicrobial,[5a] anticonvulsant and sedative-hypnotic,[5b] antiepileptic,[5c] antitubercular,[5d] antimitotic,[5e] and muscle relaxing.[5f] In addition, they can also be used as histone deacetylase inhibitors[5g] and antagonists of *Pseudomonas* quorum sensing receptor (PqsR).[5h] On the basis of bioisosterism between −S− and −O−,[6] 2-amino-1,3,4-thiadiazole could act as a bioisostere of 2-amino-1,3,4-oxadiazole and, therefore, produce biological properties broadly similar to those of the latter.[7] Thus, development of synthetic methods to access these 2-amino-substituted diazoles is of great importance to the drug discovery community.

To date, various methods have been reported in the literature for the synthesis of 2-amino-1,3,4-oxadiazoles (Scheme 1): (a) cyclodesulfurization of acyl thiosemicarbazide using desulfurating reagents such as carbodiimides,[8a−c] tosyl chloride,[8d] IBX,[8e,f] oxone,[8g] mercury oxide,[8h] methyl iodide,[8i] and ethyl bromoacetate;[8j] (b) cyclodehydration of acyl semicarbazides using $SOCl_2$,[8i] Ph_3P,[9] or $POCl_3$;[10e] (c) reaction of acylhydrazides with reagents, such as cyanogen bromide,[10a,b] isocyanides,[10c] trimethylsilyl isothiocyanate,[10d] isocyanide dichloride,[10e,f] di(benzotriazol-1yl)methanimine;[10g] and (d) direct amination of oxadiazol-2-ones[11a] or 1,3,4-oxadiazoles.[11b−f] Yet, there are still disadvantages associated with these methodologies, such as harsh reaction conditions, the use of expensive and/or toxic reagents, and limited scalability.

Scheme 1. Various Methods for the Construction of the 2-Amino-Substituted 1,3,4-Oxadiazole Skeleton



Owing to the easy accessibility of substrates, oxidative cyclization has been extensively used for the synthesis of 1,3,4-oxadiazoles from the corresponding acylhydrazones.[2,12a] However, preparation of 2-amino-substituted 1,3,4-oxadiazoles through direct oxidative cyclization of semicarbazones (path e, Scheme 1) is rarely reported in the literature.[13] This could be due to the presence of the amino group (NH_2) in the substrate (**6**, Scheme 2), which will compete with the oxygen atom during the cyclization process to form byproduct triazolone **8**,[14] and may also lead to undesired byproducts under the oxidation conditions. An ideal methodology for this transformation could not only convert the precursor **6** to the desired oxadiazole **1** selectively but also avoid side reactions of the 2-amino group. Herein, we report such a reaction for the construction of the 2-amino-1,3,4-oxadiazole framework (**1**) via I_2-mediated oxidative cyclization. Moreover, this transition-metal-free protocol can

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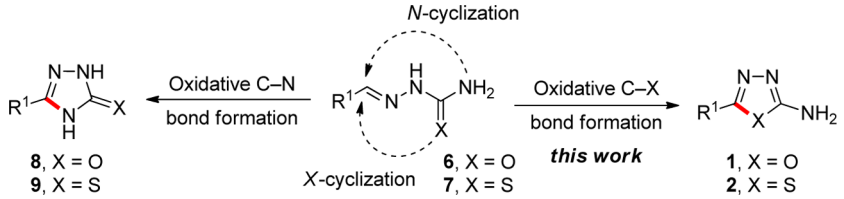
Scheme 2. Two Possible Cyclization Pathways of Semicarbazone 6 or Thiosemicarbazone 7

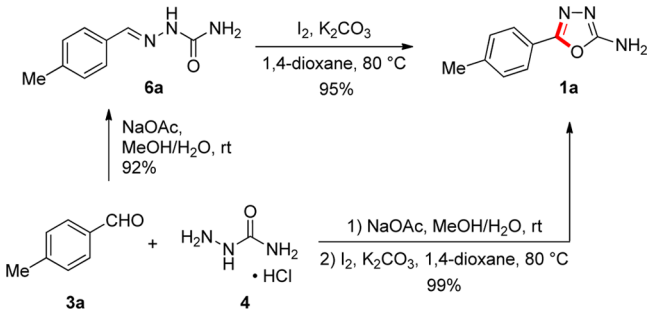


also be utilized to synthesize 2-amino-1,3,4-thiadiazole derivatives from the corresponding thiosemicarbazones **7** via C–S bond formation.

RESULTS AND DISCUSSION

Due to the numerous advantages associated with this eco-friendly element, molecular iodine has been extensively used in organic synthesis.[15] Recently, we have reported I_2-mediated oxidative intramolecular C–O/C–N bond formation reactions for the preparation of 1,3,4-oxadiazoles[12a] and pyrazoles,[12b] respectively. In this work, initially, we investigated the oxidative cyclization of the purified semicarbazone **6a**, which was readily prepared via the condensation of 4-methylbenzaldehyde (**3a**) and aminourea hydrochloride (**4a**) in a mixture of water and methanol (Scheme 3). However, treatment of substrate **6a** with

Scheme 3. Synthesis of 2-Amino-1,3,4-oxadiazole 1a from 4-Methylbenzaldehyde (3a) and Semicarbazide Hydrochloride (4)[a]



[a]Optimal reaction conditions: (1) condensation of **3a** (0.5 mmol) and **4a** (0.5 mmol) in the presence of NaOAc (0.5 mmol) in MeOH/H_2O (1:1) at room temperature; (2) I_2 (0.6 mmol), K_2CO_3 (1.5 mmol), 1,4-dioxane, 80 °C.

I_2 in the presence of K_2CO_3 in dimethylsulfoxide (DMSO)[12a] did not afford the desired 2-amino-1,3,4-oxadiazole **1a** at all. Screening of the reaction solvent indicated that, when it was switched to 1,4-dioxane, the transformation proceeded smoothly at 80 °C. With no need for further optimization, product **1a** was generated in 95% yield (Scheme 3). Next, we attempted to probe the feasibility of sequential synthesis of compound **1a** without purification of the intermediate **6a**. After the first-step condensation of **3a** and **4** was complete (monitored by TLC), the solvents were evaporated under reduced pressure. The resulting crude semicarbazone **6a** was directly subjected to the above optimal reaction conditions (I_2, K_2CO_3, 1,4-dioxane, 80 °C), which also produced product **1a** in equally good yield (99%, Scheme 3). Furthermore, the reaction can be successfully conducted in gram scale (Table 1, entry 1).

With good reaction conditions in hand, we set out to examine the substrate scope of this methodology (Table 1). As illustrated in Table 1, this sequential synthesis protocol works well with a range of benzaldehydes (**3a–k**) bearing *ortho-*, *meta-*, *para-*, or multisubstituents. Under the optimal reaction conditions, both electron-donating groups and electron-withdrawing groups with substituted benzaldehydes were converted to the desired 2-amino-1,3,4-oxadiazoles (**1a–k**) in good to excellent yields. Among them, the 3-trifluoromethylphenyl analogue has been reported as a novel antagonist of PqsR.[5h] Other aromatic aldehydes, such as α-naphthaldehyde, α-picolinaldehyde, and furfural (**3l–n**), also gave the target products (**1l–n**). The structure of 5-naphthyl-substituted 2-amino-1,3,4-oxadiazole (**1l**) was further confirmed by X-ray crystallography (see Supporting Information). In addition, this synthetic process is compatible with both aliphatic (**3o–q**) and cinnamic aldehydes (**3r**), which formed 2-amino-1,3,4-oxadiazoles **1o–r** in satisfactory yields, as well.

Encouraged by the success of 2-amino-1,3,4-oxadiazole synthesis, we sought to further extend the scope of this practical approach by replacing semicarbazide hydrochloride **4** with thiosemicarbazide **5** to prepare 2-amino-1,3,4-thiadiazoles. Upon the completion of the condensation of thiosemicarbazide **5** and the corresponding aldehyde **3**, the reaction mixture was concentrated and then redissolved in 1,4-dioxane, followed by the treatment with molecular iodine and potassium carbonate. To our delight, stirring the resulting mixture at the refluxing temperature for 1–4 h (see the Experimental Section) produced the desired 2-amino-1,3,4-thiadiazole **2** with a new C–S bond formed. This sequential synthesis protocol also tolerates aromatic, aliphatic, and cinnamic aldehydes to provide a series of 2-amino-1,3,4-thiadiazole derivatives in moderate to good yields (Table 2).

CONCLUSIONS

In summary, we have developed a practical I_2-mediated oxidative C–O/C–S bond formation methodology for the synthesis of 2-amino-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. Under the optimal sequential synthesis conditions, semicarbazide/thiosemicarbazide and the corresponding aldehydes were smoothly converted into the desired diazoles **1** and **2** without purification of the condensation intermediates. This versatile and transition-metal-free protocol allows the efficient synthesis of a variety of aryl-, alkyl-, and alkenyl-substituted diazole derivatives bearing a 2-amino group in a scalable fashion.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz (100 MHz for ^{13}C NMR) spectrometer. Chemical shift values are given in parts per million with tetramethylsilane as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets. The coupling constants (*J*) are reported in hertz (Hz). Melting points were determined on a micromelting point apparatus without corrections. Flash column chromatography was performed over silica gel 200–300

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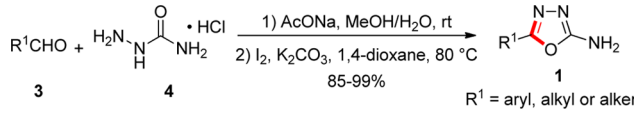
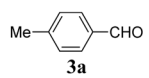
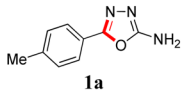
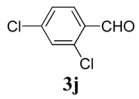
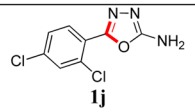
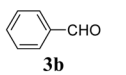
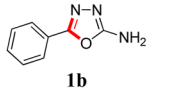
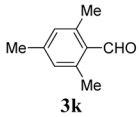
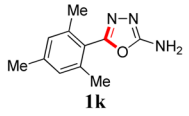
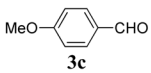
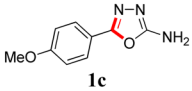
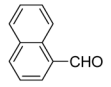
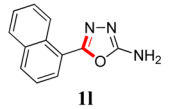
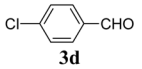
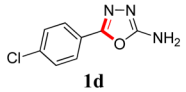
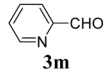
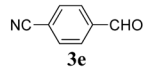
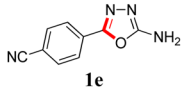
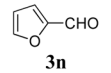
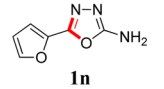
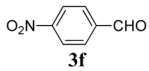
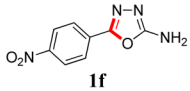
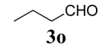
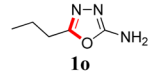
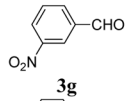
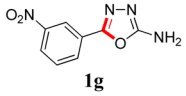
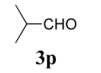
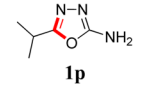
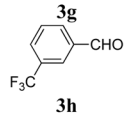
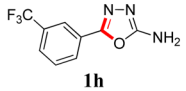
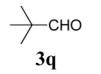
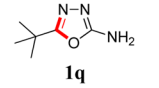
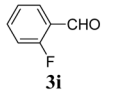
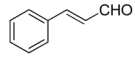
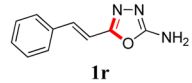
Table 1. Synthesis of 2-Amino-1,3,4-oxadiazoles 1[a]



entry	aldehyde (**3**)	product (**1**)	yield[b]	entry	aldehyde (**3**)	product (**1**)	yield[b]
1	 **3a**	 **1a**	99% (91%[c])	10	 **3j**	 **1j**	91%
2	 **3b**	 **1b**	97%	11	 **3k**	 **1k**	86%
3	 **3c**	 **1c**	94%	12	 **3l**	 **1l**	99%
4	 **3d**	 **1d**	96%	13	 **3m**	 **1m**	89%
5	 **3e**	 **1e**	96%	14	 **3n**	 **1n**	90%
6	 **3f**	 **1f**	99%	15	 **3o**	 **1o**	85%
7	 **3g**	 **1g**	90%	16	 **3p**	 **1p**	85%
8	 **3h**	 **1h**	99%	17	 **3q**	 **1q**	95%
9	 **3i**	 **1i**	95%	18	 **3r**	 **1r**	89%

[a]Optimal reaction conditions: (1) condensation of **3** (0.5 mmol) and **4** (0.5 mmol) in the presence of NaOAc (0.5 mmol) in MeOH/H_2O (1:1) at room temperature; (2) I_2 (0.6 mmol), K_2CO_3 (1.5 mmol), 1,4-dioxane, 80 °C. [b]Isolated yields. [c]The reaction was conducted on gram scale (8 mmol scale).

mesh, and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE). High-resolution mass spectra (HRMS-ESI) were obtained on a Q-TOF mass spectrometer. 1,4-Dioxane was dried over 4 Å molecular sieves before use.

General Procedure for the Synthesis of 2-Amino-1,3,4-oxadiazoles 1. To a stirred solution of semicarbazide hydrochloride (**4**, 0.5 mmol) and sodium acetate (0.5 mmol) in H_2O (1 mL) was added a solution of the aldehyde (**3**, 0.5 mmol) in MeOH (1 mL). After being stirred at room temperature for 10 min, the solvent was evaporated under reduced pressure, and the resulting residue was redissolved in 1,4-dioxane (5 mL), followed by addition of potassium carbonate (1.5 mmol) and iodine (0.6 mmol) in sequence. The reaction mixture was stirred at 80 °C until the conversion was complete (monitored by TLC, 1−4.5 h). After being cooled to room temperature, it was treated with 5% $Na_2S_2O_3$ (20 mL) and extracted with CH_2Cl_2/MeOH (10:1, 10 mL × 4). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The given residue was purified through silica gel column chromatography using a mixture of EtOAc and petroleum ether as eluent to afford the corresponding 2-amino-1,3,4-oxadiazoles **1** in 85−99% yield.

*5-(p-Tolyl)-1,3,4-oxadiazol-2-amine (**1a**):* 0.5 mmol scale, yield 87 mg, 99%; 8 mmol scale, yield 1.28 g, 91%; white solid, mp 261−262 °C (lit.[10d] mp 261−263 °C); R_f = 0.35 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 7.6 Hz, 2H), 7.17 (br s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.1, 157.8, 140.6, 130.2, 125.4, 122.1, 21.4; HRMS (m/z) [M + Na]$^+$ calcd for $C_9H_9N_3ONa$ 198.0638, found 198.0633.

*5-Phenyl-1,3,4-oxadiazol-2-amine (**1b**):* yield 78 mg, 97%; white solid, mp 242−243 °C (lit.[13e] mp 241−242 °C); R_f = 0.40 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82−7.79 (m, 2H), 7.54−7.52 (m, 3H), 7.26 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 157.7, 130.8, 129.6, 125.4, 124.8; HRMS (m/z) [M + H]$^+$ calcd for $C_8H_8N_3O$ 162.0662, found 162.0661.

*5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-amine (**1c**):* yield 90 mg, 94%; white solid, mp 252−253 °C (lit.[13e] mp 252−253 °C); R_f = 0.25 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76−7.72 (m, 2H), 7.16 (br s, 2H), 7.10−7.07 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 161.2, 157.7, 127.2, 117.4, 115.1, 55.8; HRMS (m/z) [M + Na]$^+$ calcd for $C_9H_9N_3O_2Na$ 214.0587, found 214.0584.

*5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-amine (**1d**):* yield 94 mg, 96%; white solid, mp 260−262 °C (lit.[10d] mp 260−264 °C); R_f = 0.40 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.33 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.4, 157.0, 135.3, 129.8, 127.2, 123.6; HRMS (m/z) [M + Na]$^+$ calcd for $C_8H_6ClN_3ONa$ 218.0092, found 218.0092.

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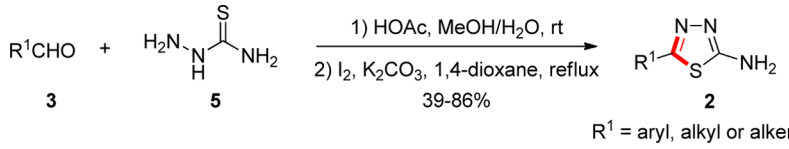
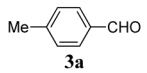
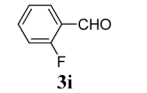
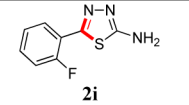
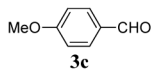
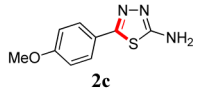
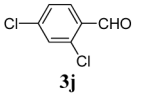
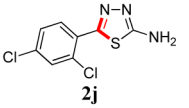
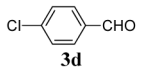
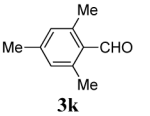
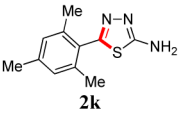
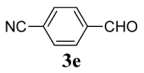
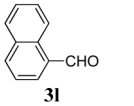
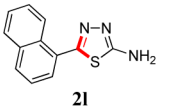
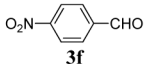
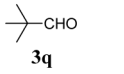
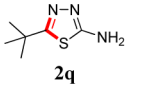
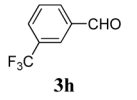
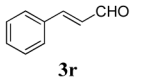
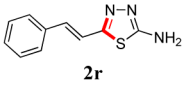
Table 2. Synthesis of 2-Amino-1,3,4-thiadiazoles 2[a]



entry	aldehyde (**3**)	product (**2**)	yield[b]	entry	aldehyde (**3**)	product (**2**)	yield[b]
1	 **3a**	 **2a**	81%	7	 **3i**	 **2i**	84%
2	 **3c**	 **2c**	54%	8	 **3j**	 **2j**	81%
3	 **3d**	 **2d**	60%	9	 **3k**	 **2k**	81%
4	 **3e**	 **2e**	65%	10	 **3l**	 **2l**	70%
5	 **3f**	 **2f**	74%	11	 **3q**	 **2q**	76%
6	 **3h**	 **2h**	86%	12	 **3r**	 **2r**	39%

[a]Optimal reaction conditions: (1) condensation of **3** (0.5 mmol) and **5** (0.5 mmol) in the presence of HOAc (0.5 mmol) in MeOH/H_2O (1:1) at room temperature; (2) I_2 (0.75 mmol), K_2CO_3 (1.6 mmol), 1,4-dioxane, reflux. [b]Isolated yields.

*4-(5-Amino-1,3,4-oxadiazol-2-yl)benzonitrile (**1e**):*[8g] yield 90 mg, 96%; white solid, R_f = 0.40 (EA/PE 75:25); mp 255−257 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01−7.99 (m, 2H), 7.95−7.93 (m, 2H), 7.49 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ164.9, 156.6, 133.7, 128.7, 125.9, 118.8, 112.7; HRMS (m/z) [M + Na]$^+$ calcd for $C_9H_6N_4ONa$ 209.0434, found 209.0434.

*5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-amine (**1f**):* yield 102 mg, 99%; yellow solid, mp 251−252 °C (lit.[13e] mp 250−251 °C); R_f = 0.40 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38−8.35 (m, 2H), 8.04−8.01 (m, 2H), 7.54 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 156.5, 148.3, 130.2, 126.4, 125.0; HRMS (m/z) [M + H]$^+$ calcd for $C_8H_7N_4O_3$ 207.0513, found 207.0523.

*5-(3-Nitrophenyl)-1,3,4-oxadiazol-2-amine (**1g**):* yield 93 mg, 90%; yellow solid, mp 252−253 °C (lit.[13e] mp 253−254 °C); R_f = 0.35 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (t, J = 2.0 Hz, 1H), 8.34 (ddd, J = 8.4, 2.4, 0.8 Hz, 1H), 8.23−8.20 (m, 1H), 7.84 (t, J = 8.0 Hz, 1H), 7.47 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 156.2, 148.6, 131.6, 131.3, 126.2, 125.1, 119.8; HRMS (m/z) [M + Na]$^+$ calcd for $C_8H_6N_4O_3Na$ 229.0332, found 229.0332.

*5-(3-(Trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-amine (**1h**):*[5h] yield 114 mg, 99%; white solid, mp 229−230 °C; R_f = 0.55 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.40 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 156.6, 131.1, 130.3 (q, J_{C-F} = 32.1 Hz), 129.2, 127.2, 125.8, 124.1 (q, J_{C-F} = 271.1 Hz), 121.6 (q, J_{C-F} = 3.9 Hz); HRMS (m/z) [M + H]$^+$ calcd for $C_9H_7F_3N_3O$ 230.0536, found 230.0539.

*5-(2-Fluorophenyl)-1,3,4-oxadiazol-2-amine (**1i**):*[8g] yield 85 mg, 95%; white solid, mp 213-214 °C; R_f = 0.45 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (td, J = 7.6, 1.6 Hz, 2H), 7.61−7.55 (m, 1H), 7.44−7.35 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5 (d, J_{C-F} = 0.9 Hz), 158.9 (d, J_{C-F} = 252.7 Hz), 154.1 (d, J_{C-F} = 5.2 Hz), 132.9 (d, J_{C-F} = 8.3 Hz), 128.8 (d, J_{C-F} = 1.9 Hz), 125.5 (d, J_{C-F} = 3.6 Hz), 117.3 (d, J_{C-F} = 20.6 Hz), 113.0 (d, J_{C-F} = 12.0 Hz); HRMS (m/z) [M + H]$^+$ calcd for $C_8H_7FN_3O$ 180.0568, found 180.0577.

*5-(2,4-Dichlorophenyl)-1,3,4-oxadiazol-2-amine (**1j**):* yield 105 mg, 91%; white solid, mp 209−210 °C (lit.[16] mp 210−211 °C); R_f = 0.50 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84−7.82 (m, 2H), 7.60 (dd, J = 8.8, 2.0 Hz, 1H), 7.41 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 154.9, 135.9, 132.2, 131.6, 130.9, 128.4, 122.8; HRMS (m/z) [M + Na]$^+$ calcd for $C_8H_5Cl_2N_3ONa$ 251.9703, found 251.9705.

*5-Mesityl-1,3,4-oxadiazol-2-amine (**1k**):* yield 87 mg, 86%; white solid, mp 247−248 °C; R_f = 0.50 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (br s, 2H), 7.00 (s, 2H), 2.28 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 156.2, 140.2, 138.3, 128.9, 122.4, 21.2, 20.3; HRMS (m/z) [M + Na]$^+$ calcd for $C_{11}H_{13}N_3ONa$ 226.0951, found 226.0951.

*5-(Naphthalen-1-yl)-1,3,4-oxadiazol-2-amine (**1l**):*[17] yield 105 mg, 99%; yellow solid, mp 175−176 °C; R_f = 0.60 (EA/PE 75:25); ^{1}H NMR (400 MHz, CD_3OD) δ 9.01 (d, J = 8.8 Hz, 1H), 7.99−7.97 (m, 2H), 7.92 (d, J = 7.6 Hz, 1H), 7.62−7.50 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.0, 158.3, 133.9, 131.2, 129.5, 128.3, 127.2, 126.7, 126.2, 125.5, 124.6, 120.5; HRMS (m/z) [M + Na]$^+$ calcd for $C_{12}H_9N_3ONa$ 234.0638, found 234.0638.

*5-(Pyridin-2-yl)-1,3,4-oxadiazol-2-amine (**1m**):*[5f] yield 72 mg, 89%; white solid, mp 250−252 °C; R_f = 0.15 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (dt, J = 4.8, 1.6 Hz, 1H), 8.00−7.94 (m, 2H), 7.53−7.49 (m, 1H), 7.42 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 157.7, 150.2, 144.0, 137.9, 125.3, 121.5; HRMS (m/z) [M + Na]$^+$ calcd for $C_7H_6N_4ONa$ 185.0434, found 185.0432.

*5-(Furan-2-yl)-1,3,4-oxadiazol-2-amine (**1n**):* yield 68 mg, 90%; yellow solid, mp 222−223 °C (lit.[5f] mp 225−226 °C); R_f = 0.45 (EA/

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PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (m, 1H), 7.33 (br s, 2H), 7.00 (d, J = 3.6 Hz, 1H), 6.72−6.70 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 151.1, 145.7, 139.8, 112.5, 111.6; HRMS (m/z) [M + Na]$^+$ calcd for $C_6H_5N_3O_2Na$, 174.0274, found 174.0270.

*5-Propyl-1,3,4-oxadiazol-2-amine (**1o**):*[13a] yield 54 mg, 85%; white solid, mp 145−146 °C; R_f = 0.25 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (br s, 2H), 2.59 (t, J = 7.6 Hz, 2H), 1.62 (sext, J = 7.6 Hz, 2H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 159.5, 26.8, 19.9, 13.8; HRMS (m/z) [M + Na]$^+$ calcd for $C_5H_9N_3ONa$ 150.0638, found 150.0634.

*5-Isopropyl-1,3,4-oxadiazol-2-amine (**1p**):*[13a] yield 54 mg, 85%; white solid, mp 181−182 °C; R_f = 0.25 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (br s, 2H), 2.96 (heptet, J = 6.8 Hz, 1H), 1.21 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 163.6, 25.8, 20.2; HRMS (m/z) [M + Na]$^+$ calcd for $C_5H_9N_3ONa$ 150.0638, found 150.0639.

*5-(tert-Butyl)-1,3,4-oxadiazol-2-amine (**1q**):*[18] yield 67 mg, 95%; white solid, mp 193−194 °C; R_f = 0.30 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (br s, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 163.9, 32.0, 28.2; HRMS (m/z) [M + Na]$^+$ calcd for $C_6H_{11}N_3ONa$ 164.0794, found 164.0791.

*(E)-5-Styryl-1,3,4-oxadiazol-2-amine (**1r**):*[8g] yield 83 mg, 89%; yellow solid, mp 249−251 °C; R_f = 0.30 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70−7.67 (m, 2H), 7.43−7.33 (m, 3H), 7.26 (br s, 2H), 7.17 (d, J = 16.4 Hz, 2H), 7.10 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 158.1, 135.6, 134.3, 129.5, 129.3, 127.7, 111.3; HRMS (m/z) [M + Na]$^+$ calcd for $C_{10}H_9N_3ONa$ 210.0638, found 210.0638.

General Procedure for the Synthesis of 2-Amino-1,3,4-thiadiazoles 2. To a stirred solution of thiosemicarbazide (**5**, 0.5 mmol) and acetic acid (0.5 mmol) in H_2O (1 mL) was added a solution of the aldehyde (**3**, 0.5 mmol) in MeOH (1 mL). After being stirred at room temperature for 30 min, the solvent was evaporated under reduced pressure, and the resulting residue was redissolved in 1,4-dioxane (5 mL), followed by addition of potassium carbonate (1.6 mmol) and iodine (0.75 mmol) in sequence. The reaction mixture was heated to reflux under nitrogen atmosphere until the conversion was complete (monitored by TLC, 1−4 h). After being cooled to room temperature, it was treated with 5% $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (15 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The given residue was purified through silica gel column chromatography using a mixture of EtOAc and petroleum ether as eluent to afford the corresponding 2-amino-1,3,4-thiadiazoles **2** in 39−86% yield.

*5-(p-Tolyl)-1,3,4-thiadiazol-2-amine (**2a**):* yield 78 mg, 81%; white solid, mp 215−216 °C (lit.[19] mp 214−216 °C); R_f = 0.50 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, J = 8.4 Hz, 2H), 7.36 (br s, 2H), 7.27 (d, J = 7.6 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.6, 156.9, 139.7, 130.1, 128.7, 126.7, 21.3; HRMS (m/z) [M + Na]$^+$ calcd for $C_9H_9N_3SNa$ 214.0409, found 214.0406.

*5-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-amine (**2c**):* yield 56 mg, 54%; white solid, mp 191−193 °C (lit.[20] mp 192−194 °C); R_f = 0.40 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71−7.67 (m, 2H), 7.31 (br s, 2H), 7.04−7.00 (m, 2H), 3.81 (s, 3H),; ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 160.7, 156.7, 128.2, 124.0, 114.9, 55.7; HRMS (m/z) [M + Na]$^+$ calcd for $C_9H_9N_3OSNa$ 230.0359, found 230.0357.

*5-(4-Chlorophenyl)-1,3,4-thiadiazol-2-amine (**2d**):* yield 64 mg, 60%; white solid, mp 224−225 °C (lit.[21] mp 224−226 °C); R_f = 0.55 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.48 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 155.5, 134.4, 130.3, 129.6, 128.3; HRMS (m/z) [M + Na]$^+$ calcd for $C_8H_6ClN_3SNa$ 233.9863, found 233.9858.

*4-(5-Amino-1,3,4-thiadiazol-2-yl)benzonitrile (**2e**):*[7f] yield 66 mg, 65%; white solid, mp 243−244 °C; R_f = 0.40 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96−7.90 (m, 4H), 7.66 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 155.0, 135.5, 133.5, 127.2, 118.9, 111.9; HRMS (m/z) [M + Na]$^+$ calcd for $C_9H_6N_4SNa$ 225.0205, found 225.0206.

*5-(4-Nitrophenyl)-1,3,4-thiadiazol-2-amine (**2f**):* yield 82 mg, 74%; brown solid, mp 250−252 °C (lit.[20] mp 250−252 °C); R_f = 0.50 (EA/PE 75:25); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 7.73 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.4, 154.5, 147.8, 137.2, 127.5, 124.9; HRMS (m/z) [M + H]$^+$ calcd for $C_8H_7N_4O_2S$ 223.0284, found 223.0281.

*5-(3-(Trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-amine (**2h**):*[22] yield 105 mg, 86%; white solid, mp 144−146 °C; R_f = 0.40 (EA/PE 50:50); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.58 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 155.1, 132.4, 130.9, 130.8 (q, J_{C-F} = 1.4 Hz), 130.3 (q, J_{C-F} = 31.9 Hz), 126.3 (q, J_{C-F} = 3.8 Hz), 124.3 (q, J_{C-F} = 271.2 Hz), 122.4 (q, J_{C-F} = 3.8 Hz); HRMS (m/z) [M + Na]$^+$ calcd for $C_9H_6F_3N_3SNa$ 68.0127, found 268.0123.

*5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-amine (**2i**):*[23] yield 82 mg, 84%; white solid, mp 210−212 °C; R_f = 0.35 (EA/PE 50:50); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (td, J = 8.0, 1.6 Hz, 1H), 7.52−7.48 (m, 1H), 7.47 (br s, 2H), 7.41−7.32 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.4 (d, J_{C-F} = 4.5 Hz), 158.3 (d, J_{C-F} = 247.0 Hz), 148.9 (d, J_{C-F} = 7.9 Hz), 131.8 (d, J_{C-F} = 8.5 Hz), 128.1 (d, J_{C-F} = 2.7 Hz), 125.6 (d, J_{C-F} = 3.2 Hz), 119.1 (d, J_{C-F} = 11.9 Hz), 116.7 (d, J = 21.6 Hz); HRMS (m/z) [M + Na]$^+$ calcd for $C_8H_6FN_3SNa$ 218.0159, found 218.0159.

*5-(2,4-Dichlorophenyl)-1,3,4-thiadiazol-2-amine (**2j**):* yield 100 mg, 81%; white solid, mp 223−224 °C (lit.[24] mp 225 °C); R_f = 0.45 (EA/PE 50:50); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 8.4 Hz, 1H), 7.99 (s, 1H), 7.55 (dd, J = 8.4, 2.0 Hz, 1H), 7.52 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.7, 151.0, 135.0, 131.7, 131.6, 130.3, 129.1, 128.4; HRMS (m/z) [M + H]$^+$ calcd for $C_8H_6Cl_2N_3S$ 245.9654, found 245.9654.

*5-Mesityl-1,3,4-thiadiazol-2-amine (**2k**):*[25] yield 89 mg, 81%; white solid, mp 273−274 °C; R_f = 0.40 (EA/PE 50:50); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (br s, 2H), 6.96 (s, 2H), 2.27 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 153.9, 139.2, 137.7, 128.6, 127.7, 21.1, 20.2; HRMS (m/z) [M + H]$^+$ calcd for $C_{11}H_{14}N_3S$ 220.0903, found 220.0907.

*5-(Naphthalen-1-yl)-1,3,4-thiadiazol-2-amine (**2l**):*[26] yield 80 mg, 70%; yellow solid, mp 207−208 °C; R_f = 0.25 (EA/PE 50:50); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 8.0 Hz, 1H), 8.05−8.01 (m, 2H), 7.74 (dd, J = 7.2, 1.2 Hz, 1H), 7.66−7.57 (m, 3H), 7.47 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 156.0, 134.0, 130.4, 130.2, 129.1, 128.9, 127.8, 126.9, 126.1, 125.9; HRMS (m/z) [M + H]$^+$ calcd for $C_{12}H_{10}N_3S$ 228.0590, found 228.0590.

*5-(tert-Butyl)-1,3,4-thiadiazol-2-amine (**2q**):* yield 79 mg, 76%; white solid, mp 180−181 °C (lit.[27] mp 181−184 °C); R_f = 0.25 (EA/PE 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (br s, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 168.2, 36.1, 30.7; HRMS (m/z) [M + H]$^+$ calcd for $C_6H_{12}N_3S$ 158.0746, found 158.0748.

*(E)-5-Styryl-1,3,4-thiadiazol-2-amine (**2r**):*[28] yield 40 mg, 39%; yellow solid, mp 230−232 °C; R_f = 0.20 (EA/PE 50:50); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65−7.63 (m, 2H), 7.43 (br s, 2H), 7.41−7.32 (m, 4H), 7.06 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.0, 157.2, 136.2, 134.7, 129.2, 129.0, 127.3, 120.0; HRMS (m/z) [M + Na]$^+$ calcd for $C_{10}H_9N_3SNa$ 226.0409, found 226.0402.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of compounds **1** and **2**, and X-ray structure and data of compound **1l** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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