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# Copper-catalyzed synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles via intramolecular N–S bond formation

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ABSTRACT

A copper-catalyzed N–S bond formation was utilized to produce 3-substituted-5-amino-1,2,4-thiadiazoles from imidoyl thioureas obtained by reaction of amidine hydrochlorides with isothiocyanates. Moreover, the 1,2,4-thiadiazoles were generated through a one-pot protocol without the isolation of the intermediates. This new method is highly efficient and convenient because it employs the cheap and environmentally friendly copper salt and can be conducted under air.



## 1. Introduction

Copper-catalyzed dehydrogenative heteroatom–heteroatom bond formation using molecular oxygen as the oxidant is highly attractive since copper catalysts are inexpensive, have low toxicity, and are readily available. Molecular oxygen is also a highly atom-economical and environmentally benign oxidant, producing water as the single byproduct.[1] Motivated by these advantages, considerable effort has been invested in this catalytic transformation for the synthesis of heterocyclic compounds and other related useful materials. For example, both 1,2,4-triazoles[2] and 2-*H*-indazoles[3] were generated through a Cu(I) catalyzed C–N/N–N bond formation, and pyrazoles[4] were prepared through a $Cu(OAc)_2$ mediated C–C/N–N bond formation cascade. Additionally, a novel copper-catalyzed approach to aromatic azo compounds from anilines has been developed.[5] Recently, copper(II)-catalyzed oxidative N–N bond formation was used for the synthesis of [1,2,3]triazolo[1,5-*a*]pyridines.[6] Furthermore, copper salts were successfully exploited to yield benzo[*d*]isothiazole-3(2*H*)-ones and 1,2,4-thiadiazoles through intramolecular N–S bond formation,[7] and to make intermolecular N–S bond between thiols and amines or diaryl disulfides and alkylamines, respectively.[8] Although substantial effort has been devoted to exploring the synthesis of heterocycles possessing heteroatom–heteroatom bonds by the copper-catalyzed dehydrogenative transformation, there are a few examples employing the transition metal catalyzed N–S bond formation for the synthesis of heterocycles.[7]

The 1,2,4-thiadiazole moiety is encountered in a myriad of biologically active compounds.[9] For the purpose of building druglike libraries, our laboratory has put effort into synthesizing 3-substituted-5-amino-1,2,4-thiadiazole derivatives **2** using both solution-phase and solid-phase syntheses.[10] Common approaches to the 1,2,4-thiadiazole skeleton **2** from the imidoyl thiourea **1** employed *p*-toluenesulfonyl chloride,[10] diethyl azodicarboxylate (DEAD),[11] diisopropyl azodicarboxylate (DIAD),[12] bromine,[13] iodine,[14] *N*-chlorosuccinimide,[15] hydrogen chloride and hydrogen peroxide as either a coupling reagent or an oxidant.[16] However, these classical methods would produce undesired byproducts or wastes that also complicate the process of purification. With these limitations in mind, we envisioned a copper-catalyzed intramolecular N–S bond formation for the synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles **2** using molecular oxygen as the oxidant.

## 2. Results and discussion

At the outset, we chose imidoyl thiourea **1a** as a model substrate, which was readily available from the reaction of benzamidine hydrochloride with phenyl isothiocyanate (Table 1). We began our investigation by examining Cu(I) salts such as CuI and CuCN as

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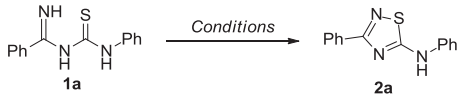
0040-4020/

**Table 1**
Optimization of Cu-catalyzed N–S bond[a]




| Entry | Catalyst | Base | Solvent | Time [h] | Yield **1a**/**2a**[b] [%] |
|---|---|---|---|---|---|
| 1 | CuI | $Cs_2CO_3$ | THF | 16 | 3:54 |
| 2 | CuI | — | THF | 16 | 34:35 |
| 3 | CuCN | $Cs_2CO_3$ | THF | 16 | 21:42 |
| 4 | $CuBr_2$ | $Cs_2CO_3$ | THF | 16 | 0:65 |
| 5 | $Cu(OAc)_2 \cdot H_2O$ | $Cs_2CO_3$ | THF | 16 | 0:72 |
| 6 | $CuSO_4$ | $Cs_2CO_3$ | THF | 16 | 25:52 |
| 7 | $Cu(OTf)_2$ | $Cs_2CO_3$ | THF | 16 | 0:91 |
| 8 | $Cu(OTf)_2$ | $Cs_2CO_3$ | $CH_3CN$ | 1 | 0:81 |
| 9 | $Cu(OTf)_2$ | $Cs_2CO_3$ | DMF | 1 | 0:85 |
| 10[c] | $Cu(OTf)_2$ | $Cs_2CO_3$ | THF | 1 | 0:86 |
| 11[c] | $Cu(OTf)_2$ | — | THF | 6 | 0:84 |
| 12[c,d] | $Cu(OTf)_2$ | $Cs_2CO_3$ | THF | 1 | 45:36 |

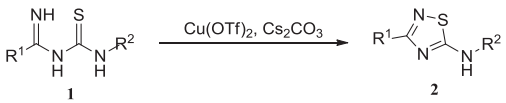
[a] Reaction condition: **1a** (0.5 mmol), base (2 equiv), cat. (5 mol %), and solvent (10 mL) under air at 25 °C.
[b] Isolated yield.
[c] The reactions were carried out at 50 °C.
[d] Under a nitrogen atmosphere.

catalysts (entries 1 and 3). Fortunately, the desired product **2a** was obtained, but the yield was unsatisfactory.

To enhance the yield, we screened other copper catalysts (entries 4–7). Among them, $Cu(OTf)_2$ showed the best result (entry 7). It was effective in reducing the reaction time by switching solvent or increasing the temperature (entries 8–10). Adding a base seemed to be non-essential, but it evidently facilitated the reaction (entry 1 vs 2 or 10 vs 11). As expected, the reaction did not proceed well under a nitrogen atmosphere (entry 12).[17]

With the data in hand, we next tried to explore the scope and limitations of the optimized reaction conditions (Table 2). Imidoyl thioureas **1** from benzamidine hydrochloride **3** with various isothiocyanates **4** bearing electron-withdrawing (–CN, $-NO_2$, –Cl, $CF_3$) or electron-donating groups ($-OCH_3$, $-CH_3$) were cyclized to the corresponding 1,2,4-thiadiazoles (entries 2–7). Substrates from benzyl or *c*-pentyl isothiocyanate required more of the copper catalyst or changing the solvent from THF to $CH_3CN$ to complete the reaction (entries 8 and 9). Other intermediates **1** from acetamidine hydrochloride, amidinopyridine hydrochlorides, and *S*-benzylisothiouronium chloride also gave the desired products (entries 10–18). Finally, we reduced the catalyst loading from 5 to 0.5 mol %. The similar yield demonstrated the high efficiency of the catalyst (entry 1).

**Table 2**
Synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles[a]



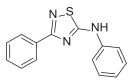
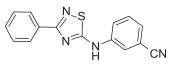
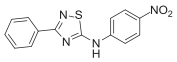
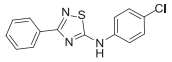
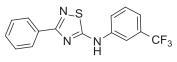
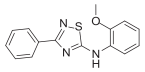
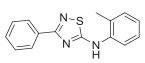
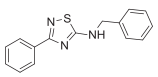
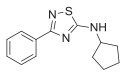
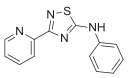
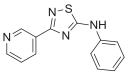
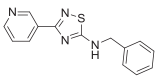
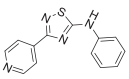
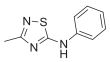
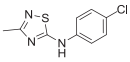
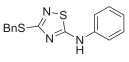
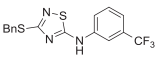
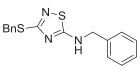

| Entry | **2** | | Time [h] | Yield[b] [%] |
|---|---|---|---|---|
| 1 |  | **2a** | 1 (2)[c] | 86 (85)[c] |
| 2 |  | **2b** | 2 | 79 |
| 3 |  | **2c** | 3 | 60 |
| 4 |  | **2d** | 3 | 80 |
| 5 |  | **2e** | 2 | 87 |
| 6 |  | **2f** | 3 | 67 |
| 7 |  | **2g** | 3 | 57 |

**Table 2** (*continued*)

| Entry | **2** | | Time [h] | Yield[b] [%] |
|---|---|---|---|---|
| 8[d] |  | **2h** | 12 | 77 |
| 9 |  | **2i** | 12 (1)[f] | 34[e] (72)[f] |
| 10[c] |  | **2j** | 3 | 61 |
| 11[c] |  | **2k** | 1 | 81 |
| 12[c,d] |  | **2l** | 6 | 71 |
| 13 |  | **2m** | 1 | 79 |
| 14 |  | **2n** | 3 | 72 |
| 15 |  | **2o** | 3 | 73 |
| 16[g] |  | **2p** | 2 | 55 |
| 17[g] |  | **2q** | 1 | 30 |
| 18[g] |  | **2r** | 3 | 20 |

[a] Reaction condition: **1a** (0.5 mmol), $Cs_2CO_3$ (2 equiv), $Cu(OTf)_2$ (5 mol %), and solvent (10 mL) under air at 50 °C.
[b] Isolated yield.
[c] $Cu(OTf)_2$ (0.5 mol %).
[d] $Cu(OTf)_2$ (10 mol %).
[e] The imidoyl thiourea **1i** was recovered (23%).
[f] $CH_3CN$ was used.
[g] The reaction was carried out at 25 °C.

A one-pot synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles **2** from amidine hydrochlorides **3** and isothiocyanates **4** was reported by Wu and Zhang.[12b] They achieved the reaction by a one-pot two-step process. First, imidoyl thioureas **1** were constructed with Hünig's base in DMF, and then DIAD was employed to form N–S bond. Instead of using this procedure, we attempted the reaction without separating the addition step and the coupling step, which could not be performed with electrophilic DIAD or DEAD. This would be feasible because the copper catalyst could not seriously hamper the reaction in the addition step, and engage in the coupling of N–S bond of the imidoyl thiourea **1** formed in the

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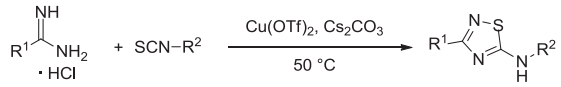
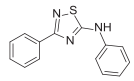
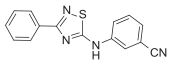
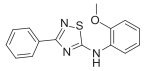
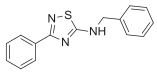
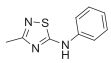
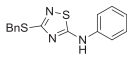
mixture. Six selected substrates were tested, which gave the desired products with moderate yields (Table 3). Noteworthy, the fact that **2n** can be obtained from this one-pot protocol shows it is more versatile for producing the thiadiazoles than the previous method, which failed to render them from acetamidine hydrochloride.[12b]

**Table 3**
One-pot synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles[a]

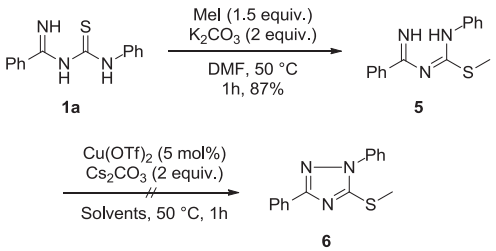



3 4 2

| Entry | 2 | | Solvent | Time [h] | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 |  | **2a** | THF | 6 | 83 |
| 2 |  | **2b** | THF | 6 | 47 |
| 3 |  | **2f** | THF | 6 | 72 |
| 4 |  | **2h** | $CH_3CN$ | 2 | 63 |
| 5 |  | **2n** | $CH_3CN$ | 6 | 58 |
| 6 |  | **2p** | THF | 3 | 45 |

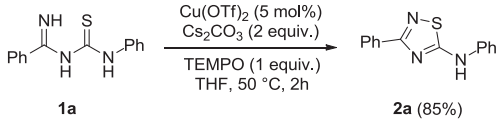
[a] Reaction condition: **3** (0.5 mmol), **4** (0.5 mmol), $Cs_2CO_3$ (3 equiv), $Cu(OTf)_2$ (5 mol %), and solvent (10 mL) under air at 50 °C.
[b] Isolated yield.

As noted in the Introduction, copper salts can be applied to connect nitrogen atom to nitrogen atom. Therefore, we suspected that **1a** could be transformed to the triazole under the optimized condition. But we observed only one spot being the thiadiazole in the mixture by TLC. Further, **1a** of the sulfur atom protected with methyl **5** was conducted under the condition to investigate whether **6** could be formed, but no reaction took place (Scheme 1). This N–N oxidative coupling reaction of the substrates is currently under investigation in our laboratory.

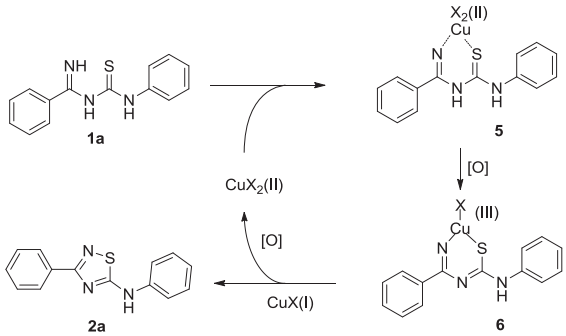



**Scheme 1.** Attempted N–N bond formation of **5**.

Copper-catalyzed reaction can be occurred via a single electron transfer process or an organometallic pathway.[1,14] Based on literature reports,[2b,4,7a,8] a plausible mechanism for the Cu(II)-catalyzed formation of N–S bond is depicted in Scheme 3. A radical pathway could be ruled out because stoichiometric radical scavenger (TEMPO) did not inhibit the reaction at all (Scheme 2).[7c] Initially, a copper catalyst coordinates with imidoyl thiourea **1a**. Subsequently, an oxidative Cu–S and Cu–N bond formation would occur, and a reductive elimination of the copper species **6** makes N–S bond, affording the thiadiazole **2** and a reduced copper.




**Scheme 2.** N–S bond formation in the presence of TEMPO.




**Scheme 3.** Proposed mechanism for the N–S bond formation of the imidoyl thiourea.

## 3. Conclusion

In summary, we have developed the copper-catalyzed synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles **2** via intramolecular N–S bond formation of imidoyl thiourea **1** or directly from amidines **3** and isothiocyanates **4**. This method could be an appealing alternative strategy to substitute the prevalent methods, as it is economical, easy to handle, and requires environmentally friendly reagents.

## 4. Experimental

### 4.1. General

All reactions were carried out under open-flask conditions in which no precautions were taken to exclude air and moisture from the reaction mixture. All commercial reagents and solvents were used as received without further purification. The reactions were monitored by thin-layer chromatography (TLC). Column chromatography was performed with silica gel (230–400 mesh). $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a 500 MHz spectrometer. Proton chemical shift values ($\delta$) are given in parts per million and referenced to tetramethylsilane at 0.00 ppm as an internal standard. Carbon chemical shifts are reported to the residual peak of $CDCl_3$ at 77.2 ppm and DMSO-$d_6$ at 39.5 ppm. Low-resolution mass spectra were obtained on a Triple Quadrupole Mass spectrometer using a technique of electronspray ionization. IR spectra were recorded on an FTIR-ATR spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). High-resolution mass spectra were obtained using a TOF LC/MS system.

### 4.2. Preparation of imidoyl thioureas (1)

*4.2.1. N-(Phenylcarbamothioyl)benzimidamide (**1a**).* To a suspension of benzamidine hydrochloride (10.0 mmol) in dichloromethane were added phenyl isothiocyanate (10.0 mmol) and triethylamine (30.0 mmol), and stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the resulting solid was washed with the solvent (diethyl ether/hexane, v/v=1:3) to afford the product (1.89 g, 74%). Light yellow solid; mp 118–120 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.64–10.70 (m, 1H), 8.86–7.30 (m, 9H), 7.26–7.09 (m, 1H), 6.91–5.93 (m, 1H); LC/MS (ESI) *m*/*z* 256 $[M+H]^+$.

*4.2.2. N-((3-Cyanophenyl)carbamothioyl)benzimidamide (**1b**).* To a suspension of benzamidine hydrochloride (2.0 mmol) in dichloromethane were added 3-cyanophenyl isothiocyanate (2.0 mmol) and triethylamine (6.0 mmol), and stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. After removal of the solvent in vacuum, the resulting solid was washed with diethyl ether to afford the product (477 mg, 85%). Light yellow solid; mp 151–153 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.12–9.91 (m, 2H), 9.64–8.64 (m, 1H), 8.48–7.37 (m, 8H); LC/MS (ESI) *m*/*z* 281 $[M+H]^+$.

*4.2.3. N-((4-Nitrophenyl)carbamothioyl)benzimidamide (**1c**).* To a suspension of benzamidine hydrochloride (4.0 mmol) in dichloromethane were added 4-nitrophenyl isothiocyanate (4.0 mmol) and triethylamine (8.8 mmol), and stirred for 12 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the resulting solid was washed with diethyl ether to afford the product (1.081 g, 90%). Yellow solid; mp 161–163 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.01 (br s, 1H), 10.55 (br s, 1H), 9.43 (br s, 1H), 8.22 (d, *J*=9.1 Hz, 2H), 8.08–7.87 (m, 4H), 7.63 (t, *J*=7.3 Hz, 1H), 7.56 (t, *J*=7.5 Hz, 2H); LC/MS (ESI) *m*/*z* 301 $[M+H]^+$.

*4.2.4. N-((4-Chlorophenyl)carbamothioyl)benzimidamide (**1d**).* To a suspension of benzamidine hydrochloride (2.0 mmol) in dichloromethane were added 4-chlorophenyl isothiocyanate (2.0 mmol) and triethylamine (4.4 mmol), and stirred for 16 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the resulting solid was washed with diethyl ether to afford the product (435 mg, 75%). White solid; mp 156–158 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.80–10.87 (m, 1H), 8.99–8.15 (m, 1H), 8.10–7.12 (m, 8H), 6.94–6.17 (m, 1H); LC/MS (ESI) *m*/*z* 290 $[M+H]^+$.

*4.2.5. N-((3-(Trifluoromethyl)phenyl)carbamothioyl)benzimidamide (**1e**).* To a suspension of benzamidine hydrochloride (2.0 mmol) in dichloromethane were added 3-(trifluoromethyl)phenyl isothiocyanate (2.0 mmol) and triethylamine (4.4 mmol), and stirred for 12 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the resulting solid was washed with the solvent (diethyl ether/hexane, v/v=1:2) to afford the product (453 mg, 70%). White solid; mp 154–156 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.43 (s, 1H), 9.22–7.76 (m, 4H), 7.71–7.29 (m, 5H), 7.07–6.11 (m, 1H); LC/MS (ESI) *m*/*z* 324 $[M+H]^+$.

*4.2.6. N-((2-Methoxyphenyl)carbamothioyl)benzimidamide (**1f**).* To a suspension of benzamidine hydrochloride (4.0 mmol) in acetonitrile were added 2-methoxyphenyl isothiocyanate (4.0 mmol) and triethylamine (8.8 mmol), and stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. After removal of the solvent in vacuum, the residue was purified by column chromatography to afford the product as a light yellow oil (924 mg, 81%). The oily compound became a light yellow solid after two days. Light yellow solid; mp 99–101 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.61–10.40 (m, 1H), 9.27–8.53 (m, 1H), 8.21–7.72 (m, 2H), 7.66–7.33 (m, 3H), 7.24–6.04 (m, 4H), 4.11–3.75 (m, 3H); LC/MS (ESI) *m*/*z* 286 $[M+H]^+$.

*4.2.7. N-(o-Tolylcarbamothioyl)benzimidamide (**1g**).* To a suspension of benzamidine hydrochloride (3.0 mmol) in acetonitrile were added *o*-tolyl isothiocyanate (3.0 mmol) and triethylamine (7.5 mmol), and stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the resulting solid was washed with diethyl ether to afford the product (480 mg, 59%). Pale yellow solid; mp 116–117 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.93–10.62 (m, 1H), 8.68–8.02 (m, 1H), 7.97–7.04 (m, 9H), 6.87–5.96 (m, 1H), 2.57–2.10 (m, 3H); LC/MS (ESI) *m*/*z* 270 $[M+H]^+$.

*4.2.8. N-(Benzylcarbamothioyl)benzimidamide (**1h**).* To a suspension of benzamidine hydrochloride (3.0 mmol) in acetonitrile were added benzyl isothiocyanate (3.0 mmol) and triethylamine (6.6 mmol), and stirred for 12 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the solvent (diethyl ether/hexane, v/v=2:1) was poured to the residue. The precipitated solid was collected and washed with the solvent (445 mg, 55%). Pale yellow solid; mp 104–106 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.74–10.59 (m, 1H), 8.35–7.75 (m, 2H), 7.62–7.27 (m, 8H), 7.08–5.98 (m, 1H), 5.11–4.67 (m, 2H); LC/MS (ESI) *m*/*z* 270 $[M+H]^+$.

*4.2.9. N-(Cyclopentylcarbamothioyl)benzimidamide (**1i**).* To a suspension of benzamidine hydrochloride (1.7 mmol) in acetonitrile were added cyclopentyl isothiocyanate (1.7 mmol) and triethylamine (3.74 mmol), and stirred for 12 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the residue was purified by column chromatography to afford the product (219 mg, 52%). Colorless solid; mp 133–135 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 12.38–10.32 (m, 2H), 8.13–7.77 (m, 2H), 7.63–7.38 (m, 3H), 6.88–5.94 (m, 1H), 4.75–4.44 (m, 1H), 2.34–1.95 (m, 2H), 1.84–1.29 (m, 6H); LC/MS (ESI) *m*/*z* 248 $[M+H]^+$.

*4.2.10. N-(Phenylcarbamothioyl)pyridine-2-carboximidamide (**1j**).* To a solution of 2-amidinopyridine hydrochloride (1.58 mmol) in solvent (acetonitrile/MeOH, v/v=1:1) were added phenyl isothiocyanate (1.58 mmol) and triethylamine (3.48 mmol), and stirred for 2 h at 50 °C. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum,

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diethyl ether was added to the residue. The oily compound becomes solid. The resulting solid was collected and washed with the solvent (140 mg, 35%). White solid; mp 120–122 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.48–10.69 (m, 1H), 8.83–7.61 (m, 5H), 7.53–7.10 (m, 5H); LC/MS (ESI) *m*/*z* 257 $[M+H]^+$.

*4.2.11. N-(Phenylcarbamothioyl)pyridine-3-carboximidamide (**1k**).* To a suspension of 3-amidinopyridine hydrochloride (2 mmol) in acetonitrile were added phenyl isothiocyanate (2 mmol) and triethylamine (6 mmol), and stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, diethyl ether and dichloromethane were added to the residue. The oily compound becomes solid. The resulting solid was collected and washed with diethyl ether (420 mg, 82%). Light yellow solid; mp 131–133 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.97–10.49 (m, 1H), 9.20–8.40 (m, 3H), 8.30–7.59 (m, 2H), 7.52–7.15 (m, 5H), 7.03–6.03 (m, 1H); LC/MS (ESI) *m*/*z* 257 $[M+H]^+$.

*4.2.12. N-(Benzylcarbamothioyl)pyridine-3-carboximidamide (**1l**).* To a suspension of 3-amidinopyridine hydrochloride (2 mmol) in acetonitrile were added benzyl isothiocyanate (2 mmol) and triethylamine (6 mmol), and stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, diethyl ether and dichloromethane were added to the residue. After heating the solution at 50 °C, diethyl ether was added. After repeating it twice, the resulting solid was collected and washed with diethyl ether (438 mg, 81%). Pale yellow crystalline solid; mp 97–99 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.21 (br s, 1H), 9.17–8.90 (m, 1H), 8.81–8.60 (m, 1H), 8.36–7.91 (m, 1H), 7.81–7.07 (m, 7H), 6.41 (br s, 1H), 4.96–4.70 (m, 2H); LC/MS (ESI) *m*/*z* 271 $[M+H]^+$.

*4.2.13. N-(Phenylcarbamothioyl)pyridine-4-carboximidamide (**1m**).* To a suspension of 4-amidinopyridine hydrochloride (2 mmol) in acetonitrile were added phenyl isothiocyanate (2 mmol) and triethylamine (6 mmol), and stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the resulting solid was collected and washed with diethyl ether (410 mg, 80%). Yellow solid; mp 161–162 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.77–10.70 (m, 1H), 8.98–7.99 (m, 4H), 7.52–7.29 (m, 4H), 7.24–7.15 (m, 1H), 6.88–6.08 (m, 1H); LC/MS (ESI) *m*/*z* 257 $[M+H]^+$.

*4.2.14. N-(Phenylcarbamothioyl)acetimidamide (**1n**).* To a solution of acetamidine hydrochloride (3.7 mmol) in methanol were added phenyl isothiocyanate (3.7 mmol) and potassium hydroxide (7.4 mmol), and stirred for 0.5 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the residue was purified by column chromatography to afford the product (222 mg, 31%). Pale yellow solid; mp 89–91 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.30–7.87 (m, 1H), 7.72–7.53 (m, 1H), 7.51–7.28 (m, 3H), 7.26–7.08 (m, 1H), 6.06 (br s, 1H), 2.26–2.06 (m, 3H); LC/MS (ESI) *m*/*z* 194 $[M+H]^+$.

*4.2.15. N-((4-Chlorophenyl)carbamothioyl)acetimidamide (**1o**).* To a suspension of acetamidine hydrochloride (2.9 mmol) in acetonitrile were added 4-chlorophenyl isothiocyanate (3 mmol) and potassium carbonate (6 mmol), and stirred for 0.5 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the resulting solid was collected and washed with diethyl ether (304 mg, 46%). Pale yellow solid; mp 122–124 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.37–7.89 (m, 2H), 7.66–7.53 (m, 1H), 7.48–7.29 (m, 3H), 7.25–7.17 (m, 1H), 6.10 (br s, 1H), 2.60–1.79 (m, 3H); LC/MS (ESI) *m*/*z* 228 $[M+H]^+$.

*4.2.16. Benzyl N-(phenylcarbamothioyl)carbamimidothioate (**1p**).* To a solution of *S*-benzylisothiourea hydrochloride (2.6 mmol) in the solvent (acetone/water, 8:1=v/v, 18 mL) were added phenyl isothiocyanate (2 mmol) and potassium hydroxide (1 mmol), and refluxed for 1 h. Acetone was removed under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. The precipitated solid was collected by filtration, and washed with water and the solvent (diethyl ether/methanol, v/v=2:1) (362 mg, 60%). White solid; mp 114–116 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.45–8.07 (m, 1H), 7.70–6.99 (m, 10H), 4.38–4.01 (m, 2H); LC/MS (ESI) *m*/*z* 302 $[M+H]^+$.

*4.2.17. Benzyl N-{[3-(trifluoromethyl)phenyl]carbamothioyl}-carbamimidothioate (**1q**).* To a suspension of *S*-benzylisothiourea hydrochloride (2 mmol) in dichloromethane were added 3-(trifluoromethyl)phenyl isothiocyanate (2 mmol) and triethylamine (2.4 mmol), and stirred for 12 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the residue was purified by column chromatography to afford the product (517 mg, 70%). White solid; mp 112–114 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.62–8.06 (m, 1H), 8.00–6.98 (m, 9H), 4.63–3.73 (m, 2H); LC/MS (ESI) *m*/*z* 370 $[M+H]^+$.

*4.2.18. Benzyl N-(benzylcarbamothioyl)carbamimidothioate (**1r**).* To a suspension of *S*-benzylisothiourea hydrochloride (3 mmol) in acetonitrile were added benzyl isothiocyanate (3 mmol) and triethylamine (6.6 mmol), and stirred for 16 h at room temperature. The reaction mixture was concentrated under reduced pressure. Water was added to the crude mixture, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuum, the residue was purified by column chromatography to afford the product (871 mg, 92%). Pale yellow oil; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.48–7.19 (m, 9H), 7.14–6.79 (m, 1H), 4.91–4.57 (m, 2H), 4.34–4.03 (m, 2H). LC/MS (ESI) *m*/*z* 316 $[M+H]^+$.

### 4.3. General procedure for the synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles from imidoyl thioureas (2)

Imidoyl thiourea **1** (0.5 mmol) and $Cs_2CO_3$ (1.0 mmol) were dissolved in THF or $CH_3CN$ (10 mL), and $Cu(OTf)_2$ was added to the solution with stirring (the amount of Cu cat. is described in Table 2). The mixture was stirred at the temperature described in Table 2. After completion of the reaction as indicated by TLC, the solvent was evaporated and quenched with water, extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered. The residue (or the resulting solid) was either purified by column chromatography using ethyl acetate and hexanes as eluents (**2a**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i**, **2n**, **2o**, **2p**, **2q**, **2r**) or washed with diethyl ether to give the product (**2b**, **2c**, **2j**, **2k**, **2l**, **2m**).

*4.3.1. N,3-Diphenyl-1,2,4-thiadiazol-5-amine (**2a**).* White solid (109 mg, 86%); mp 174–176 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.26 (s,

1H), 8.21 (dd, *J*=6.6, 3.0 Hz, 2H), 7.49–7.38 (m, 5H), 7.24 (d, *J*=7.9 Hz, 2H), 7.16 (t, *J*=7.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 180.8, 169.6, 139.3, 133.1, 130.3, 130.1, 128.8, 128.2, 124.5, 118.6. LC/MS (ESI) *m*/*z* 254 $[M+H]^+$; IR (ATR): $\nu$=3225, 2965, 1598, 1556, 1449, 1442, 1348, 751, 710, 690; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{10}N_3S$ $[M-H]^-$ 252.0601, found 252.0584.

*4.3.2. 3-[(3-Phenyl-1,2,4-thiadiazol-5-yl)amino]benzonitrile (**2b**).* Pale yellow solid (110 mg, 79%); mp 221–223 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.23 (dd, *J*=6.6, 3.0 Hz, 2H), 7.94 (s, 1H), 7.75 (s, 1H), 7.60 (dd, *J*=8.3, 1.5 Hz, 1H), 7.54 (t, *J*=7.9 Hz, 1H), 7.50–7.46 (m, 3H), 7.44 (d, *J*=7.6 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 178.7, 168.5, 140.4, 132.5, 130.8, 130.3, 128.8, 127.5, 126.2, 122.2, 120.2, 118.7, 112; LC/MS (ESI) *m*/*z* 279 $[M+H]^+$; IR (ATR): $\nu$=3289, 2239, 1599, 1526, 1424, 1334, 783, 703; HRMS (ESI) *m*/*z* calcd for $C_{15}H_9N_4S$ $[M-H]^-$ 277.0553, found 277.0539.

*4.3.3. N-(4-Nitrophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2c**).* Yellow solid (89 mg, 60%); mp 216–218 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.68 (s, 1H), 8.34 (d, *J*=9.2 Hz, 2H), 8.24 (dd, *J*=7.2, 2.3 Hz, 2H), 7.95 (d, *J*=9.2 Hz, 2H), 7.60–7.49 (m, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 178.5, 168.7, 145.3, 141.5, 132.4, 130.5, 128.9, 127.7, 125.7, 117.4; LC/MS (ESI) *m*/*z* 299 $[M+H]^+$; IR (ATR): $\nu$=3225, 3218, 3063, 1615, 1563, 1521, 1330, 1244, 1109, 847, 819, 704; HRMS (ESI) *m*/*z* calcd for $C_{14}H_9N_4O_2S$ $[M-H]^-$ 297.0452, found 297.0457.

*4.3.4. N-(4-Chlorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2d**).* White solid (115 mg, 80%); mp 196–198 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.20 (d, *J*=3.6 Hz, 2H), 7.98 (s, 1H), 7.54–7.44 (m, 3H), 7.39 (d, *J*=8.2 Hz, 2H), 7.30–7.21 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 180.2, 169.6, 137.7, 132.8, 130.3, 129.9, 129.5, 128.6, 128.0, 119.7; LC/MS (ESI) *m*/*z* 288 $[M+H]^+$; IR (ATR): $\nu$=3129, 1600, 1526, 1427, 1347, 1156, 828, 713; HRMS (ESI) *m*/*z* calcd for $C_{14}H_9ClN_3S$ $[M-H]^-$ 286.0211, found 286.0221.

*4.3.5. 3-Phenyl-N-[3-(trifluoromethyl)phenyl]-1,2,4-thiadiazol-5-amine (**2e**).* White solid (140 mg, 87%); mp 124–126 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.74 (s, 1H), 8.21 (dd, *J*=6.6, 3.1 Hz, 2H), 7.59–7.40 (m, 6H), 7.38 (d, *J*=7.5 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 180.3, 169.9, 139.8, 132.8,f 132.4 (q, $J_{C-F}$=32.7 Hz), 130.6, 130.5, 128.9, 128.3, 123.7 (q, $J_{C-F}$=275.1 Hz), 121.2, 120.8 (q, $J_{C-F}$=3.7 Hz), 115.4 (q, $J_{C-F}$=3.9 Hz); LC/MS (ESI) *m*/*z* 322 $[M+H]^+$; IR (ATR): $\nu$=3207, 3087, 1607, 1526, 1459, 1331, 1153, 1111, 895, 700; HRMS (ESI) *m*/*z* calcd for $C_{15}H_9F_3N_3S$ $[M-H]^-$ 320.0475, found 320.0495.

*4.3.6. N-(2-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2f**).* White solid (95 mg, 67%); mp 96–98 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.42 (s, 1H), 8.30–8.19 (m, 2H), 7.66–7.57 (m, 1H), 7.52–7.40 (m, 3H), 7.13–7.03 (m, 2H), 6.99–6.91 (m, 1H), 3.91 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 179.6, 169.6, 148.1, 133.2, 130.3, 128.9, 128.7, 128.2, 123.7, 121.4, 116.3, 110.8, 56.0; LC/MS (ESI) *m*/*z* 284 $[M+H]^+$; IR (ATR): $\nu$=3378, 1601, 1512, 1459, 1421, 1296, 1247, 1025, 745, 702; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}N_3OS$ $[M+H]^+$ 284.0852, found 284.0854.

*4.3.7. N-(2-Methylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2g**).* White solid (76 mg, 57%); mp 171–173 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.15 (dd, *J*=7.4, 1.9 Hz, 2H), 8.02 (s, 1H), 7.46 (d, *J*=7.9 Hz, 1H), 7.44–7.36 (m, 3H), 7.36–7.24 (m, 2H), 7.18 (t, *J*=7.5 Hz, 1H), 2.34 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 182.8, 169.8, 137.9, 133.1, 131.7, 130.3, 130.2, 128.7, 128.1, 127.8, 126.2, 120.8, 17.9; LC/MS (ESI) *m*/*z* 268 $[M+H]^+$; IR (ATR): $\nu$=3182, 1563, 1425, 1337, 1281, 1070, 766, 702; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}N_3S$ $[M-H]^-$ 266.0757, found 266.0780.

*4.3.8. N-Benzyl-3-phenyl-1,2,4-thiadiazol-5-amine (**2h**).* White solid (103 mg, 77%); mp 103–105 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.17–8.12 (m, 2H), 7.46–7.30 (m, 8H), 6.61 (s, 1H), 4.51 (d, *J*=5.6 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 184.6, 170.1, 136.3, 133.4, 130.1, 129.1, 128.7, 128.4, 128.1, 127.8, 50.6; LC/MS (ESI) *m*/*z* 268 $[M+H]^+$; IR (ATR): $\nu$=3208, 3126, 1592, 1574, 1343, 1291, 1067, 1023, 979, 779, 736, 700; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}N_3S$ $[M-H]^-$ 266.0757, found 266.0754.

*4.3.9. N-Cyclopentyl-3-phenyl-1,2,4-thiadiazol-5-amine (**2i**).* White solid (88 mg, 72%); mp 101–102 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.26–8.08 (m, 2H), 7.48–7.36 (m, 3H), 6.01 (d, *J*=6.0 Hz, 1H), 3.83–3.68 (m, 1H), 2.14–2.00 (m, 2H), 1.78–1.53 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 184.1, 170.1, 133.5, 130.0, 128.6, 128.1, 58.5, 33.1, 23.8; LC/MS (ESI) *m*/*z* 246 $[M+H]^+$; IR (ATR): $\nu$=3184, 1573, 1467, 1347, 1287, 1101, 1024, 785, 704; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}N_3S$ $[M-H]^-$ 244.0914, found 244.0909.

*4.3.10. N-Phenyl-3-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (**2j**).* White solid (78 mg, 61%); mp 239–241 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.65 (d, *J*=4.4 Hz, 1H), 8.57 (s, 1H), 8.26 (d, *J*=7.9 Hz, 1H), 7.80 (td, *J*=7.7, 1.6 Hz, 1H), 7.43 (t, *J*=7.9 Hz, 2H), 7.34 (dd, *J*=6.9, 5.0 Hz, 1H), 7.26–7.14 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 181.7, 168.8, 150.9, 150.0, 139.3, 137.0, 130.1, 124.9, 124.7, 123.2, 119.1; LC/MS (ESI) *m*/*z* 255 $[M+H]^+$; IR (ATR): $\nu$=3261, 3200, 1621, 1592, 1511, 1493, 1432, 1348, 1243, 1136, 746, 696; HRMS (ESI) *m*/*z* calcd for $C_{13}H_9N_4S$ $[M-H]^-$ 253.0553, found 253.0567.

*4.3.11. N-Phenyl-3-(pyridin-3-yl)-1,2,4-thiadiazol-5-amine (**2k**).* White solid (103 mg, 81%); mp 238–240 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.15 (s, 1H), 9.35 (s, 1H), 8.71 (s, 1H), 8.49 (d, *J*=7.8 Hz, 1H), 7.67 (d, *J*=7.9 Hz, 2H), 7.63–7.52 (m, 1H), 7.45 (t, *J*=7.7 Hz, 2H), 7.12 (t, *J*=7.3 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 179.4, 166.3, 150.9, 148.5, 139.7, 134.8, 129.5, 128.4, 124.0, 123.1, 117.8; LC/MS (ESI) *m*/*z* 255 $[M+H]^+$; IR (ATR): $\nu$=3191, 2745, 1569, 1456, 1443, 1396, 1359, 1117, 818, 751, 717; HRMS (ESI) *m*/*z* calcd for $C_{13}H_9N_4S$ $[M-H]^-$ 253.0553, found 253.0569.

*4.3.12. N-Benzyl-3-(pyridin-3-yl)-1,2,4-thiadiazol-5-amine (**2l**).* White solid (95 mg, 71%); mp 169–171 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.79 (s, 1H), 8.47 (d, *J*=7.9 Hz, 1H), 8.30 (d, *J*=3.2 Hz, 2H), 7.47–7.26 (m, 6H), 4.51 (d, *J*=5.3 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 185.1, 167.6, 150.0, 149.9, 136.3, 135.3, 129.1, 129.1, 128.4, 128.2, 123.5, 50.8; LC/MS (ESI) *m*/*z* 269 $[M+H]^+$; IR (ATR): $\nu$=3062, 1578, 1452, 1400, 1191, 1027, 758, 700; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{11}N_4S$ $[M-H]^-$ 267.0710, found 267.0709.

*4.3.13. N-Phenyl-3-(pyridin-4-yl)-1,2,4-thiadiazol-5-amine (**2m**).* White solid (100 mg, 79%); mp 215–217 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.17 (s, 1H), 8.77 (s, 2H), 8.07 (d, *J*=5.3 Hz, 2H), 7.67 (d, *J*=7.9 Hz, 2H), 7.45 (t, *J*=7.9 Hz, 2H), 7.13 (t, *J*=7.4 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 179.6, 166.6, 150.6, 139.6, 139.2, 129.5, 123.2, 121.5, 117.8. LC/MS (ESI) *m*/*z* 255 $[M+H]^+$; IR (ATR): $\nu$=3190, 2761, 1622, 1461, 1362, 1003, 822; HRMS (ESI) *m*/*z* calcd for $C_{13}H_9N_4S$ $[M-H]^-$ 253.0553, found 253.0555.

*4.3.14. 3-Methyl-N-phenyl-1,2,4-thiadiazol-5-amine (**2n**).* Pale yellow solid (69 mg, 72%); mp 112–114 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.16 (s, 1H), 7.47–7.39 (m, 2H), 7.26–7.22 (m, 2H), 7.21–7.16 (m, 1H), 2.47 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 181.6, 169.8, 139.5,

130.1, 124.8, 119.1, 19.2; LC/MS (ESI) *m/z* 192 $[M+H]^+$; IR (ATR): $\nu$=3225, 2960, 1598, 1545, 1453, 1197, 1001, 807, 746, 715; HRMS (ESI) *m/z* calcd for $C_9H_8N_3S$ $[M-H]^-$ 190.0444, found 190.0443.

*4.3.15. N-(4-Chlorophenyl)-3-methyl-1,2,4-thiadiazol-5-amine (**2o**).* Pale yellow solid (82 mg, 73%); mp 166–168 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.12 (s, 1H), 7.39 (d, *J*=8.6 Hz, 2H), 7.22 (d, *J*=8.7 Hz, 2H), 2.46 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 181.4, 170.0, 138.1, 130.1, 130.0, 120.6, 19.3; LC/MS (ESI) *m/z* 226 $[M+H]^+$; IR (ATR): $\nu$=3229, 2810, 2101, 1604, 1560, 1429, 1334, 1301, 1089, 805, 746; HRMS (ESI) *m/z* calcd for $C_9H_7ClN_3S$ $[M-H]^-$ 224.0055, found 224.0075.

*4.3.16. 3-(Benzylthio)-N-phenyl-1,2,4-thiadiazol-5-amine (**2p**).* White solid (82 mg, 55%); mp 148–150 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.48 (s, 1H), 7.41 (dd, *J*=13.2, 7.4 Hz, 4H), 7.31 (t, *J*=7.4 Hz, 2H), 7.28–7.24 (m, 1H), 7.22 (d, *J*=7.8 Hz, 2H), 7.18 (t, *J*=7.4 Hz, 1H), 4.45 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 181.0, 167.5, 139.0, 137.3, 130.1, 129.2, 128.7, 127.6, 125.0, 119.1, 36.3; LC/MS (ESI) *m/z* 300 $[M+H]^+$; IR (ATR): $\nu$=3229, 3081, 1598, 1541, 1414, 1218, 747, 683; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}N_3S_2$ $[M-H]^-$ 298.0467, found 298.0468.

*4.3.17. 3-(Benzylthio)-N-[3-(trifluoromethyl)phenyl]-1,2,4-thiadiazol-5-amine (**2q**).* Pale yellow solid (55 mg, 30%); mp 123–125 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.33 (s, 1H), 7.56 (s, 1H), 7.55–7.45 (m, 2H), 7.42 (d, *J*=7.3 Hz, 3H), 7.31 (t, *J*=7.4 Hz, 2H), 7.28–7.24 (m, 1H), 4.45 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 180.9, 167.6, 139.7, 137.0, 132.5 (q, $J_{C-F}$=32.9 Hz), 130.7, 129.2, 128.7, 127.7, 123.7 (q, $J_{C-F}$=272.6 Hz), 122.0, 121.4 (q, $J_{C-F}$=3.7 Hz), 116.2 (q, $J_{C-F}$=3.9 Hz), 36.3; LC/MS (ESI) *m/z* 368 $[M+H]^+$; IR (ATR): $\nu$=3209, 3084, 1573, 1459, 1335, 1217, 1169, 1115, 967, 793, 695; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}F_3N_3S_2$ $[M-H]^-$ 366.0341, found 366.0318.

*4.3.18. N-Benzyl-3-(benzylsulfanyl)-1,2,4-thiadiazol-5-amine (**2r**).* White solid (31 mg, 20%); mp 106–107 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.46–7.09 (m, 11H), 4.44 (d, *J*=5.7 Hz, 2H), 4.38 (s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 184.4, 167.4, 137.4, 136.1, 129.2, 129.1, 128.7, 128.4, 128.0, 127.5, 50.5, 36.1; LC/MS (ESI) *m/z* 314 $[M+H]^+$; IR (ATR): $\nu$=3201, 3113, 1596, 1430, 1258, 1195, 1189, 1063, 767, 692; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}N_3S_2$ $[M-H]^-$ 312.0635, found 312.0614.

### 4.4. One-pot procedure for the synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles (2)

Amidine hydrochloride **3** (0.5 mmol), isothiocyanate **4** (0.5 mmol) and $Cs_2CO_3$ (1.5 mmol), and solvent (10 mL) were added to a flask. With stirring, $Cu(OTf)_2$ (5 mol %) was added to the solution. After completion of the reaction as indicated by TLC, the solvent was evaporated and quenched with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and purified by column chromatography to give the product using hexanes and ethyl acetate as eluents.

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### Supplementary data

Copies of $^1$H spectra for **1**, copies of $^1$H and $^{13}$C NMR spectra for **2** and optimization of reaction conditions for the synthesis of **2p**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.09.023.

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