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Synthesis of 5-Amino and 3,5-Diamino Substituted 1,2,4-Thiadiazoles by I_2-Mediated Oxidative N−S Bond Formation

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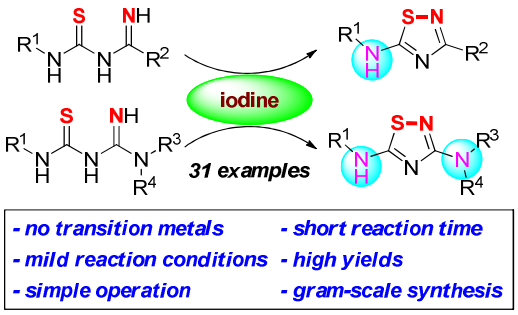
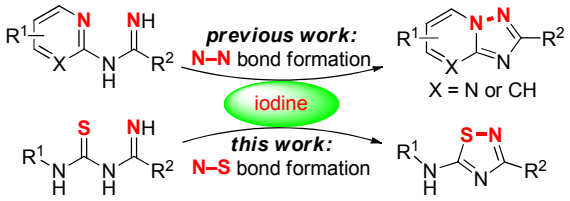


Abstract: An oxidative N–S bond formation reaction has been established for 1,2,4-thiadiazole synthesis employing molecular iodine as the sole oxidant. The features of the present reaction include no use of transition metals, mild reaction conditions, simple operation, and short reaction time. This versatile synthetic approach is broadly applicable to a variety of imidoyl and guanyl thiourea substrates to produce 5-amino and 3,5-diamino substituted 1,2,4-thiadiazole derivatives, respectively, in an efficient and scalable fashion.

▪ Introduction

Oxidative N−S bond formation is a useful synthetic approach for the construction of nitrogen- and sulfur-containing frameworks. In recent years, such transformations were accomplished via copper-catalyzed aerobic oxidation[1] and hypervalent iodine(III)-mediated oxidative cyclization.[2] As an inexpensive and low-toxic reagent, molecular iodine has been successfully employed to construct C−C and C−X (X = N, O, or S) bonds via direct C−H functionalization.[3] However, applications of iodine in heteroatom-heteroatom bond formation reactions remain relatively undeveloped. In 2016, Jiang and Li[4] disclosed an intermolecular [3 + 2] heterocyclization for 1,2,3-thiadiazole synthesis by using the combination of I_2 and O_2 as oxidantion sources. Previously, we also described an I_2/KI-enabled oxidative cyclization of *N*-aryl amidines to synthesize 1,5-fused 1,2,4-triazoles via N−N bond formation[5] (Scheme 1).

Scheme 1. Proposed Route to Access 1,2,4-Thiadiazoles via I_2-Mediated Oxidative N–S Bond Formation Based on the Previous Work



1,2,4-Thiadiazole is an important sulfur-containing heterocylclic moiety occurring frequently in many compounds with diverse biological and pharmaceutical properties,[6] such as enzyme inhibitory,[7] receptor modulation,[8] antiinflammatory[9] antibiotic,[10] fungicidal,[11] antiulcerative,[12] and antidiabetic activities.[13] Among the various synthetic methods reported for 1,2,4-thiadiazole preparation,[6,14] several

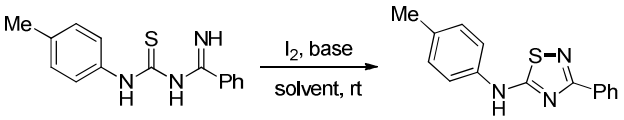
approaches provide access to the 5-amino substituted derivatives through oxidative cyclization using oxidants[2a,15,16] (e.g. PIFA, Br_2, and H_2O_2), Cu(II)-catalyzed dehydrogenative coupling,[17] thermolysis of N^3-thiocarbamoylamidrazone ylides,[18] or KF/Al_2O_3-mediated cyclocondensation of amidoximes with thioureas.[19] However, synthetic pathways towards 3,5-diamino-1,2,4-thiadiazoles are rarely reported in the literature.[20] The existing methods only allow for the synthesis of N^3,N^5-symmetrically substituted derivatives through oxidative annulations of two molecules of the same thiourea precursors. Thus, more general and practical synthetic methods for the preparation of amino substituted 1,2,4-thiadiazoles are still in high demand and would be of great importance to medicinal chemistry research. Encouraged by our previous work[5] on I_2-mediated heteroatom-heteroatom bond construction, herein we developed a versatile and efficient N−S bond formation reaction to access both 5-amino and 3,5-diamino substituted 1,2,4-thiadiazole derivatives from readily available precursors (Scheme 1).

▪ Results and Discussion

The required substrates **3** were readily prepared via the addition reaction of amidines to corresponding isothiocyanates (see Experimental Section). Initially, we took imidoyl thiourea **3b** as the model substrate with which to investigate the I_2-mediated oxidative cyclization for 5-amino-1,2,4-thiadiazole synthesis. The expected product **1b** was formed in absence of base in CH_2Cl_2 at room temperature; however, the conversion was still incomplete after 32 h, giving product **1b** in 89% yield (entry 1, Table 1). Addition of inorganic bases could accelerate the reaction (entries 2−3), with K_2CO_3 resulting in a better yield. Further solvent screening (entries 4−8) suggested that MeCN is the most effective media for this transformation. Nevertheless, both the

conversion rate and the yield of the product were affected in MeCN without base (entry 9).

Table 1. Optimization of the Reaction Conditions for the Synthesis of 5-Amino-1,2,4-thiadiazole 1b[a]



3b **1b**

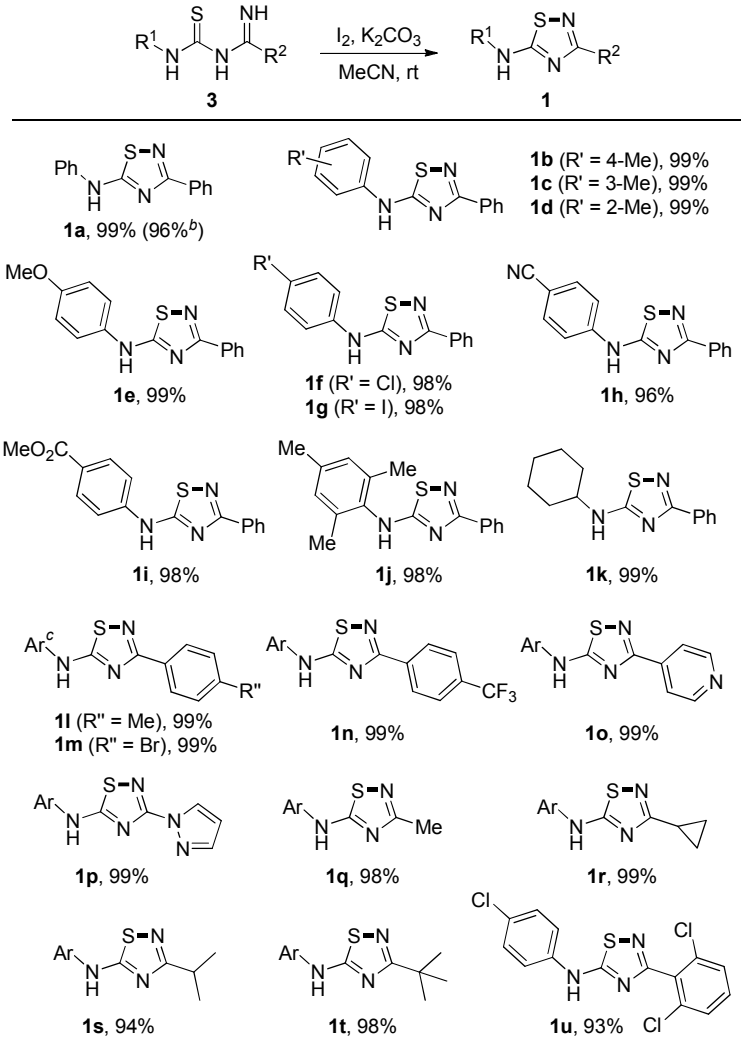
entry	base	solvent	time	yield[b]
1	–[c]	CH_2Cl_2	32 h	89%
2	$NaHCO_3$	CH_2Cl_2	6 h	90%
3	K_2CO_3	CH_2Cl_2	5 h	99%
4	K_2CO_3	DMSO	6 h	90%
5	K_2CO_3	DCE	17 h	82%
6	K_2CO_3	1,4-dioxane	7 h	82%
7	K_2CO_3	toluene	21 h	97%
8	**K_2CO_3**	**MeCN**	**15 min**	**99%**
9	–	MeCN	5 h	87%

[a]Reaction conditions unless specified otherwise: **3b** (0.5 mmol), iodine (0.6 mmol), base (0.75 mmol), solvent (5 mL), rt. [b]Isolated yields are given. [c]In the absence of base.

Having established the optimal reaction conditions (entry 8 in Table 1), we sought to examine the substrate scope and the generality of this methodology for thiadiazole synthesis. A range of imidoyl thioureas **3** were subjected to the above oxidative cyclization conditions, and all were smoothly and efficiently converted into the desired 5-amino-1,2,4-thiadiazoles **1** (Scheme 2). Taking the synthesis of **1a** as an example, the reaction was successfully conducted on the gram scale. It is compatible with both electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) on the N^5-phenyl ring (R^1) (**1a**–**j**). The good functional group tolerance allows for the presence of a carboxylic ester moiety in the substrate, as in **1i**. The

N^5-cyclohexylamino-1,2,4-thiadiazole (**1k**) was also prepared from the corresponding precursor in an excellent yield. Moreover, both 2-aryl and 2-alkyl substituted 5-amino-1,2,4-thiadiazoles (**1l**–**u**) were synthesized under these mild reaction conditions in high yields. Among them, the 3-(2,6-dichlorophenyl)-5-(4-chloroanilino) analogue (**1u**) has previously been demonstrated with potent fungicidal and squalene epoxidase inhibitory activity.[11]

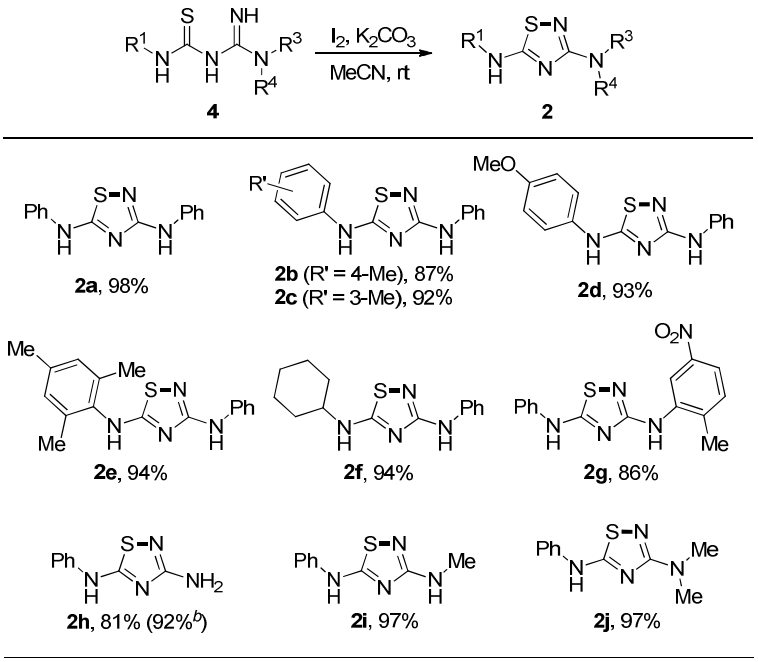
Scheme 2. Substrate Scope for 5-Amino-1,2,4-thiadiazole Synthesis[a]



[a]Reaction conditions: **3** (0.5 mmol), iodine (0.6 mmol), K_2CO_3 (0.75 mmol), MeCN, rt, 15 min (isolated yields are given). [b]The yield of gram-scale synthesis (5 mmol). [c]Ar = 4-methylphenyl.

Furthermore, this synthetic protocol can be extended to the preparation of 3,5-diamino substituted 1,2,4-thiadiazole derivatives. The required guanyl thiourea substrates **4** were obtained through the addition of guanidines to isothiocyanates (see Experimental Section). Then, I_2-mediated oxidative cyclization of these substrates afforded a series of N^3,N^5-symmetrically and N^3,N^5-asymmetrically substituted 3,5-diamino-1,2,4-thiadiazoles (**2a**−**j**) in good yields (Scheme 3). The structure of N^5-mesityl analogue **2e** was further confirmed by X-ray crystallography (see Supporting Information). The present reaction works well with both *N*-aryl and *N*-alkyl (R^1, R^3 and R^4) substituted guanyl thioureas. It is worth to mention that the substrate bearing no substituents at R^3 or R^4 position was also successfully cyclized into the expected product (**2h**). In addition, the synthesis of **2h** in CH_2Cl_2 gave slightly better than the one in MeCN did, but the former required much longer reaction time.

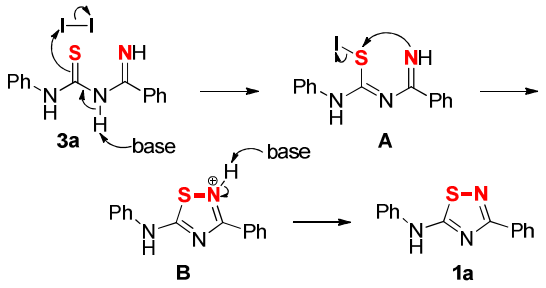
Scheme 3. Substrate Scope for 3,5-Diamino-1,2,4-thiadiazole Synthesis[a]



[a]Reaction conditions: **4** (0.5 mmol), iodine (0.6 mmol), K_2CO_3 (0.75 mmol), MeCN, rt, 15 min (isolated yields are given). [b]The yield of the reaction preformed in CH_2Cl_2 for 16 h.

Based on these experimental results along with our previous work of I_2-mediated oxidative N–N bond formation,[5] a tentative reaction mechanism for this intramolecular N–S formation reaction is proposed (Scheme 4). Taking the formation of thiadiazole **1a** as an example, the base-promoted oxidative iodination of substrate **3a** generates a plausible iodo species **A**. Then the S−I bond in iodide **A** cleaves, and consequently an ammonium ion B is formed via a S_N2'-type cyclization of **A** with a new N−S bond formed. Finally, the subsequent deprotonation by base affords the 5-amino-1,2,4-thiadiazole framework **1a**.

Scheme 4. Proposed Mechanism for the Formation of 1,2,4-Thiadiazole 1a



▪ Conclusion

In summary, we have established an I_2-mediated oxidative N−S bond formation reaction for 1,2,4-thiadiazole synthesis. This practical and transition-metal-free synthetic approach works well with a wide range of imidoyl and guanyl thiourea substrates and can be safely conducted on the gram scale. The features such as high efficiency, mild reaction conditions, simple operation, and short reaction time make it an attractive alternative for the preparation of 5-amino-1,2,4-thiadiazoles. Moreover, for the first time, this synthetic method provides a direct access to both

N^3,N^5-symmetrically and N^3,N^5-asymmetrically substituted 3,5-diamino-1,2,4-thiadiazole derivatives.

▪ Experimental Section

General Information. ^{1}H 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 (ppm) with tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; hept, heptet; m, multiplet. The coupling constants (*J*) are reported in hertz (Hz). Melting points were determined on a micromelting point apparatus without corrections. Infrared (IR) spectra were obtained on an FT-IR spectrometer. High-resolution mass spectra (HRMS-ESI) were obtained on a Q-TOF mass spectrometer. Flash column chromatography was performed over silica gel 200−300 mesh, and the eluent was a mixture of EtOAc and petroleum ether (PE). CH_2Cl_2 and EtOH was analytical reagent grade and used without any pretreatment.

General Procedure A for the Preparation of Substrates 3. A mixture of an amidine salt (2.0 mmol), the corresponding isothiocyanate (2.2 mmol), and K_2CO_3 (414 mg, 3.0 mmol) in CH_2Cl_2 (10 mL) (for **3n** and **3s**, EtOH was used) was stirred at room temperature for 12 h, then quenched with H_2O (10 mL), and extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford the substrate **3**.

General Procedure B for the Preparation of Substrates 4. A mixture of an guanidine salt (2.4 mmol), the corresponding isothiocyanate (2.0 mmol), and K_2CO_3 (553 mg, 4.0 mmol) in EtOH (10 mL) was stirred at room temperature for 12 h (for

4f−**i**, it was performed at 70 °C for 3 h), and then concentrated under reduced pressure. The resulting residue was treated with H_2O (15 mL) and extracted with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to give the substrate **4**.

General Procedure C for the Synthesis of Products 1 and 2. A stirred solution of the substrates **3** or **4** (0.5 mmol) in MeCN (5 mL) was treated with iodine (153 mg, 0.6 mmol) and K_2CO_3 (104 mg, 0.75 mmol) in sequence, and then stirred at room temperature for 15 min. The reaction was quenched with 5% $Na_2S_2O_3$ (5 mL), diluted with H_2O (10 mL), and extracted with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and then purified through silica gel column chromatography to afford the product **1** or **2**.

*N,3-Diphenyl-1,2,4-thiadiazol-5-amine (**1a**).* Eluent: EtOAc/PE 10:90; yield: 126 mg, 99%; white solid, mp 174−176 °C (lit[2a] 170−173 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.22−8.20 (m, 2H), 7.45−7.39 (m, 5H), 7.24 (d, J = 7.6 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 169.2, 139.1, 132.8, 130.2, 129.9, 128.6, 128.0, 124.4, 118.4; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{14}H_{12}N_3S$ 254.0746, found 254.0746.

*3-Phenyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**1b**).* Eluent: EtOAc/PE 17:83; yield: 132 mg, 99%; white solid, mp 153−155 °C (lit[21] 156−157 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.20−8.18 (m, 2H), 7.44−7.43 (m, 3H), 7.20 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 169.2, 136.6, 134.6, 132.8, 130.4, 130.2, 128.6, 128.0, 119.0, 20.9; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{15}H_{14}N_3S$ 268.0903, found 268.0899.

*3-Phenyl-N-(m-tolyl)-1,2,4-thiadiazol-5-amine (**1c**).* Eluent: EtOAc/PE 17:83; yield: 132 mg, 99%; off-white solid, mp 113−114 °C (lit[2a] 110−113 °C); ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.21−8.19 (m, 2H), 7.44−7.42 (m, 3H), 7.28−7.25 (m, 1H), 7.03−7.01 (m, 1H), 6.96−6.94 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 169.3, 140.0, 139.1, 132.9, 130.2, 129.6, 128.6, 128.1, 125.2, 119.5, 115.3, 21.4; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{15}H_{14}N_3S$ 268.0903, found 268.0906.

*3-Phenyl-N-(o-tolyl)-1,2,4-thiadiazol-5-amine (**1d**).* Eluent: EtOAc/PE 17:83; yield: 132 mg, 99%; white solid, mp 173−175 °C (lit[2a] 168−171 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.13−8.11 (m, 2H), 7.46 (d, J = 7.6 Hz, 1H), 7.41−7.25 (m, 5H), 7.18 (t, J = 7.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 169.7, 137.8, 132.9, 131.5, 130.5, 130.0, 128.5, 127.9, 127.6, 126.2, 121.0, 17.7; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{15}H_{14}N_3S$ 268.0903, found 268.0897.

*N-(4-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**1e**).*[2a] Eluent: EtOAc/PE 17:83; yield: 140 mg, 99%; white solid, mp 144−145 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.17−8.15 (m, 2H), 7.56−7.50 (m, 5H), 7.02−7.00 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.1, 169.0, 155.8, 133.8, 133.3, 130.6, 129.2, 128.0, 120.2, 115.1, 55.8; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{15}H_{14}N_3OS$ 284.0852, found 284.0856.

*N-(4-Chlorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**1f**).* Eluent: EtOAc/PE 25:75; yield: 141 mg, 98%; white solid, mp 197−199 °C (lit[2a] 194−196 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 8.20−8.18 (m, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.53−7.47 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.3, 169.0, 139.2, 133.1, 130.7, 129.7, 129.2, 128.1, 126.8, 119.7; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{14}H_{11}ClN_3S$ 288.0357, found 288.0357.

*N-(4-Iodophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**1g**).*[2a] Eluent: EtOAc/PE 17:83; yield: 186 mg, 98%; white solid, mp 210−212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.20−8.18 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.54−7.52 (m,

5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.2, 169.0, 140.1, 138.4, 133.1, 130.7, 129.2, 128.1, 120.4, 86.4; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{14}H_{11}IN_3S$ 379.9713, found 379.9693.

4-((3-Phenyl-1,2,4-thiadiazol-5-yl)amino)benzonitrile ***(1h)***.[2a] Eluent: EtOAc/PE 25:75; yield: 134 mg, 96%; white solid, mp 194-196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 8.23−8.21 (m, 2H), 7.89 (s, 4H), 7.56−7.53 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.0, 169.1, 143.9, 134.3, 133.0, 130.8, 129.3, 128.1, 119.6, 118.2, 104.6; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{15}H_{11}N_4S$ 279.0699, found 279.0697.

Methyl 4-((3-phenyl-1,2,4-thiadiazol-5-yl)amino)benzoate ***(1i)***.[2a] Eluent: EtOAc/PE 33:67; yield: 153 mg, 98%; off-white solid, mp 213−215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (s, 1H), 8.24−8.21 (m, 2H), 8.04 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.56−7.53 (m, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.1, 169.1, 166.2, 144.2, 133.0, 131.4, 130.8, 129.3, 128.1, 123.7, 117.5, 52.4; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{16}H_{14}N_3O_2S$ 312.0801, found 312.0804.

N-Mesityl-3-phenyl-1,2,4-thiadiazol-5-amine ***(1j)***. Eluent: EtOAc/PE17:83; yield: 145 mg, 98%; off-white solid, mp 199−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (br, s, 1H), 8.05−8.03 (m, 2H), 7.38−7.28 (m, 3H), 6.98 (s, 2H), 2.33 (s, 3H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 169.9, 138.8, 136.3, 133.9, 133.0, 129.9, 128.3, 127.7, 21.1, 17.9; IR (film) 2916(w), 1568(m), 1470(m), 1427(m), 1340(m), 1118(m), 703(s), 688(s); HRMS *(m/z)* $[M + H]^+$ calcd for $C_{17}H_{18}N_3S$ 296.1216, found 296.1217.

N-Cyclohexyl-3-phenyl-1,2,4-thiadiazol-5-amine ***(1k)***. Eluent: EtOAc/PE 17:83; yield: 128 mg, 99%; white solid, mp 126−127 °C (lit[18] 120−122 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17−8.14 (m, 2H), 7.44−7.41 (m, 3H), 6.10 (br, s, 1H), 3.25−3.18 (m,

1H), 2.10−2.07 (m, 2H), 1.77−1.74 (m, 2H), 1.65−1.62 (m, 1H), 1.43−1.19 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 169.8, 133.2, 129.9, 128.5, 127.9, 56.2, 32.6, 25.3, 24.6; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{14}H_{18}N_3S$ 260.1216, found 260.1216.

*N,3-Di-p-tolyl-1,2,4-thiadiazol-5-amine (**1l**).* Eluent: EtOAc/PE 20:80; yield: 138 mg, 98%; white solid, mp 180−182 °C (lit[19] 180−182 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br, s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.14−7.11 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 169.5, 140.2, 136.7, 134.4, 130.4, 130.3, 129.3, 127.9, 118.9, 21.5, 20.9; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{16}H_{16}N_3S$ 282.1059, found 282.1065.

*3-(4-Bromophenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**1m**).* Eluent: EtOAc/PE 17:83; yield: 171 mg, 99%; white solid, mp 238−239 °C (lit[2a] 241−243 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.9, 168.0, 137.9, 132.7, 132.4, 132.3, 130.3, 130.0, 124.1, 118.4, 20.9; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{15}H_{13}BrN_3S$ 346.0008, found 346.0018.

*N-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-thiadiazol-5-amine (**1n**).* Eluent: EtOAc/PE 17:83; yield: 161 mg, 96%; off-white solid, mp 234−236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 8.36 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.1, 167.5, 137.8, 136.7, 132.8, 130.5 (q, $J_{C\text{-}F}$ = 32.0 Hz), 130.3, 128.7, 126.3, (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.6 (q, $J_{C\text{-}F}$ = 270.6 Hz), 118.5, 20.9; IR (film) 3238(w), 1561(m), 1444(m), 1314(m), 1129(vs), 1103(m), 709(s), 658(s); HRMS *(m/z)* $[M + H]^+$ calcd for $C_{16}H_{13}F_3N_3S$ 336.0777, found 336.0795.

*3-(Pyridin-4-yl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**1o**).* Eluent: EtOAc/PE 25:75; yield: 132 mg, 99%; off-white solid, mp 241−243 °C; ^{1}H NMR (400 MHz, DMSO-d_6)

δ 11.06 (s, 1H), 8.76−8.75 (m, 2H), 8.05−8.04 (m, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.3, 167.0, 151.0, 139.7, 137.7, 132.9, 130.3, 121.9, 118.5, 20.9; IR (film) 2854(w), 1640(m), 1445(s), 1359(s), 806(m), 698(vs); HRMS *(m/z)* $[M + H]^+$ calcd for $C_{14}H_{13}N_4S$ 269.0855, found 269.0855.

*3-(1H-pyrazol-1-yl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**1p**).*[2a] Eluent: EtOAc/PE 50:50; yield: 127 mg, 99%; light yellow solid, mp 200−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.29 (d, J = 2.8 Hz, 1H), 7.52 (s, 1H), 7.24−7.16 (m, 4H), 6.39 (t, J = 2.4Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 158.4, 142.5, 136.4, 135.7, 130.4, 129.1, 121.0, 108.0, 21.0; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{12}H_{12}N_5S$ 258.0808, found 258.0811.

*3-Methyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**1q**).*[16] Eluent: EtOAc/PE 17:83; yield: 103 mg, 98%; off-white solid, mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 169.5, 137.0, 134.9, 130.4, 119.7, 20.9, 19.1; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{10}H_{12}N_3S$ 206.0746, found 206.0741.

*3-Cyclopropyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**1r**).* Eluent: EtOAc/PE 17:83; yield: 115 mg, 99%; off-white solid, mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 2.34 (s, 3H), 2.14−2.07 (m, 1H), 1.09−1.05 (m, 2H), 0.99−0.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 174.5, 136.8, 134.5, 130.3, 119.1, 20.9, 13.6, 8.9; IR (film) 2918(w), 1556(m), 1440(m), 1359(s), 814(m); HRMS *(m/z)* $[M + H]^+$ calcd for $C_{12}H_{14}N_3S$ 232.0903, found 232.0901.

*3-Isopropyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**1s**).*[22] Eluent: EtOAc/PE 17:83; yield: 110 mg, 94%; off-white solid, mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ

8.80 (br, s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 3.06 (hept, *J* = 7.2 Hz, 1H), 2.35 (s, 3H), 1.31 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 178.4, 137.0, 134.7, 130.4, 119.6, 32.7, 21.4, 20.9; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{12}H_{16}N_3S$ 234.1059,found 234.1061.

3-(tert-Butyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine ***(1t)***. Eluent: EtOAc/PE 17:83; yield: 121 mg, 98%; off-white solid, mp 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (br, s, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 2.34 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 180.9, 136.9, 134.2, 130.3, 118.8, 36.9, 29.4, 20.8; IR (film) 2961(w), 1608(m), 1558(s), 1361(s), 816(m); HRMS *(m/z)* $[M + H]^+$ calcd for $C_{13}H_{18}N_3S$ 248.1216, found 248.1217.

N-(4-Chlorophenyl)-3-(2,6-dichlorophenyl)-1,2,4-thiadiazol-5-amine ***(1u)***.[11] Eluent: EtOAc/PE 20:80; yield: 154 mg, 93%; light yellow solid, mp 216−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (br, s, 1H), 7.33−7.29 (m, 3H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 164.8, 137.8, 135.2, 132.7, 130.9, 130.2, 129.7, 128.0, 120.9; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{14}H_9Cl_3N_3S$ 355.9577, found 355.9590 .

N^3,N^5-Diphenyl-1,2,4-thiadiazole-3,5-diamine ***(2a)***.[20b] Eluent: EtOAc/PE 17:83; yield: 131 mg, 98%; white solid, mp 203−205 °C (lit[1] 203−205 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 9.74 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 8.4 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.89 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.8, 162.7, 141.5, 140.4, 129.7, 129.0, 123.2, 121.0, 118.2, 117.3; HRMS *(m/z)* $[M + H]^+$ calcd for $C_{14}H_{13}N_4S$ 269.0855, found 269.0867.

N^3-Phenyl-N^5-(p-tolyl)-1,2,4-thiadiazole-3,5-diamine ***(2b)***.[23] Eluent: EtOAc/PE 17:83; yield: 123 mg, 87%; white solid, mp 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$

mixture of tautomers, *peaks of the minor one) δ 8.41* (br, s, 0.2H), 8.33 (s, 0.8H), 7.55 (d, J = 7.6 Hz, 1.6H), 7.43−7.39 (m, 0.8H), 7.33−7.29 (m, 2.4H), 7.21−7.19 (m, 2.2H), 7.16−7.14* (m, 0.2H), 7.11−7.08 (m, 2H), 6.99 (t, J = 7.6 Hz, 0.8H), 2.35 (s, 2.4H), 2.30* (s, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$ mixture of tautomers) major isomer δ 179.5, 162.2, 140.0, 136.5, 134.6, 130.4, 129.1, 121.9, 119.1, 117.6, 20.9; minor isomer δ 178.9, 161.9, 139.0, 137.5, 131.5, 129.9, 129.5, 124.5, 118.6, 117.9, 20.7; HRMS (m/z) $[M + H]^+$ calcd for $C_{15}H_{15}N_4S$ 283.1012, found 283.1011.

N^3-Phenyl-N^5-(m-tolyl)-1,2,4-thiadiazole-3,5-diamine ***(2c)***. Eluent: EtOAc/PE 17:83; yield: 130 mg, 92%; white solid, mp 161−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$ mixture of tautomers, *peaks of the minor one) δ 8.48 (br, s, 1H), 7.55 (d, J = 7.6 Hz, 1.8H), 7.43−7.26 (m, 4.3H), 7.22−7.15* (m, 0.7H), 7.02−6.97 (m, 3.4H), 6.81* (d, J = 7.6 Hz, 0.1H), 2.36 (s, 2.6H), 2.33* (s, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$ mixture of tautomers) major isomer δ 178.9, 161.6, 140.1, 139.9, 138.86, 129.7, 129.1, 125.4, 122.0, 119.4, 117.6, 115.6, 21.5; minor isomer δ 178.8, 161.7, 139.8, 138.92, 129.9, 128.9, 124.5, 123.0, 118.6, 118.3, 114.8, 21.6; IR (film) 3080(w), 2960(w), 1515(s), 1439(s), 1362(m), 727(m), 676(m); HRMS *(m/z)* $[M + H]^+$ calcd for $C_{15}H_{15}N_4S$ 283.1012, found 283.1017.

N^5-(4-Methoxyphenyl)-N^3-phenyl-1,2,4-thiadiazole-3,5-diamine ***(2d)***. Eluent: EtOAc/PE 17:83; yield: 139 mg, 93%; off-white solid, mp 187−189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.68 (s, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.88 (t, J = 7.6 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.3, 162.7, 155.7, 141.6, 133.8, 129.0, 120.9, 120.4, 117.3, 114.9, 55.8; IR (film) 3080(w), 2961(w), 1536(s), 1440(s), 751(m), 695(m); HRMS *(m/z)* $[M + H]^+$ calcd for $C_{15}H_{15}N_4OS$ 299.0961, found 299.0974.

*N^5-Mesityl-N^3-phenyl-1,2,4-thiadiazole-3,5-diamine (**2e**).* Eluent: EtOAc/PE 17:83; yield: 146 mg, 94%; off-white solid, mp 166−167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (br, s, 1H), 9.58 (s, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 6.96 (s, 2H), 6.84 (t, J = 7.6 Hz, 1H), 2.25 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 162.5, 140.1, 138.8, 136.3, 133.0, 129.8, 129.0, 121.8, 117.6, 21.1, 17.9; IR (film) 3264(w), 1517(s), 1445(m), 1335(m), 742(s), 689(m); HRMS *(m/z)* [M + H]$^+$ calcd for $C_{17}H_{19}N_4S$ 311.1325, found 311.1334.

*N^5-Cyclohexyl-N^3-phenyl-1,2,4-thiadiazole-3,5-diamine (**2f**).* Eluent: EtOAc/PE 17:83; yield: 129 mg, 94%; white solid, mp 128−129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.18 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 8.0 Hz, 2H), 6.83 (t, J = 7.2 Hz, 1H), 3.47 (br, s, 1H), 1.99−1.95 (m, 2H), 1.74−1.71 (m, 2H), 1.59−1.56 (m, 1H), 1.32−1.17 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 162.4, 140.2, 129.0, 121.6, 117.4, 55.7, 32.9, 25.3, 24.6; IR (film) 3267(w), 2927(w), 1520(vs), 1443(m), 1336(m), 748(s), 697(m); HRMS *(m/z)* [M + H]$^+$ calcd for $C_{14}H_{19}N_4S$ 275.1325, found 275.1312.

*N^3-(2-Methyl-5-nitrophenyl)-N^5-phenyl-1,2,4-thiadiazole-3,5-diamine (**2g**).* Eluent: EtOAc/PE 25:75; yield: 141 mg, 86%; yellow solid, mp 235−237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 9.03 (br, s, 2H), 7.80−7.78 (m, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.5, 162.6, 146.6, 140.3, 140.2, 136.2, 131.6, 129.7, 123.3, 118.3, 116.9, 114.2, 18.8; IR (film) 3268(w), 2929(w), 1521(vs), 1444(m), 1333(m), 750(m), 735(m); HRMS *(m/z)* [M + H]$^+$ calcd for $C_{15}H_{14}N_5O_2S$ 328.0863, found 328.0862.

*N^5-Phenyl-1,2,4-thiadiazole-3,5-diamine (**2h**).*[21] Eluent: EtOAc/PE 33:67; yield: 78 mg, 81% (yield of the reaction in CH_2Cl_2 for 16 h: 88 mg, 92%); off-white solid, mp

210−212 °C (lit[1] 214−215 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.53−7.51 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.26 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.7, 167.2, 140.6, 129.6, 122.7, 117.9; HRMS *(m/z)* $[M + H]^+$ calcd for $C_8H_9N_4S$ 193.0542, found 193.0545.

*N^3-Methyl-N^5-phenyl-1,2,4-thiadiazole-3,5-diamine (**2i**).*[24] Eluent: EtOAc/PE 25:75; yield: 100 mg, 97%; off-white solid, mp 137-138 °C (lit[1] 137-138 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br, s, 1H), 7.41−7.39 (m, 2H), 7.18 (d, J = 7.2 Hz, 2H), 7.13 (t, J = 7.6 Hz, 1H),4.91 (br, s, 1H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 166.9, 139.2, 129.8, 124.1, 118.4, 29.9; HRMS *(m/z)* $[M + H]^+$ calcd for $C_9H_{11}N_4S$ 207.0699, found 207.0698.

*N^3,N^3-Dimethyl-N^5-phenyl-1,2,4-thiadiazole-3,5-diamine (**2j**).* Eluent: EtOAc/PE 25:75; yield: 107 mg, 97%; off-white solid, mp 176−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br, s, 1H), 7.37 (t, J = 8.0 Hz, 2H), 7.19−7.17 (m, 2H), 7.11 (t, J = 7.6 Hz, 1H), 3.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 168.1, 139.3, 129.7, 123.8, 118.1, 38.8; IR (film) 2925(w), 1533(s), 1465(m), 1381(m), 1220(m), 755(m), 689(s); HRMS *(m/z)* $[M + H]^+$ calcd for $C_{10}H_{13}N_4S$ 221.0855, found 221.0853.

▪ Associated Content

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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▪ References

(1) (a) Zhu, H.; Yu, J. T.; Cheng, J. *Chem. Commun.* **2016**, *52*, 11908. (b) Lee, C.; Wang, X.; Jang, H. Y. *Org. Lett.* **2015**, *17*, 1130. (c) Chen, F. J.; Liao, G.; Li, X.; Wu, J.; Shi, B. F. *Org. Lett.* **2014**, *16*, 5644. (d) Wang, Z.; Kuninobu, Y.; Kanai, M. *J. Org. Chem.* **2013**, *78*, 7337.

(2) (a) Mariappan, A.; Rajaguru, K.; Merukan Chola, N.; Muthusubramanian, S.; Bhuvanesh, N. *J. Org. Chem.* **2016**, *81*, 6573. (b) Anand, D.; Patel, O. P. S.; Maurya, R. K.; Kant, R.; Yadav, P. P. *J. Org. Chem.* **2015**, *80*, 12410. (c) Rattanangkool, E.; Krailat, W.; Vilaivan, T.; Phuwapraisirisan, P.; Sukwattanasinitt, M.; Wacharasindhu, S. *Eur. J. Org. Chem.* **2014**, 4795. (d) Ma, W. B.; Li, S. N.; Zhou, Z. H.; Shen, H. S.; Li, X.; Sun, Q.; He, L.; Xue, Y. *Eur. J. Org. Chem.* **2012**, 1554.

(3) (a) Zi, W.; Zuo, Z.; Ma, D. *Acc. Chem. Res.* **2015**, *48*, 702. (b) Zhao, J.; Gao, W.; Chang, H.; Li, X.; Liu, Q.; Wei, W. *Chin. J. Org. Chem.* **2014**, *34*, 1941. (c) Ren, Y.-M.; Cai, C.; Yang, R.-C. *RSC Adv.* **2013**, *3*, 7182. (d) Parvatkar, P. T.;

Parameswaran, P. S.; Tilve, S. G. *Chem. Eur. J.* **2012**, *18*, 5460. (e) Veisi, H. *Curr. Org. Chem.* **2011**, *15*, 2438.

(4) Fan, W.; Li, Q.; Li, Y.; Sun, H.; Jiang, B.; Li, G. *Org. Lett.* **2016**, *18*, 1258.

(5) Song, L.; Tian, X.; Lv, Z.; Li, E.; Wu, J.; Liu, Y.; Yu, W.; Chang, J. *J. Org. Chem.* **2015**, *80*, 7219.

(6) Castro, A.; Castaño, T.; Encinas, A.; Porcal, W.; Gil, C. *Bioorg. Med. Chem.* **2006**, *14*, 1644.

(7) (a) Dahlin, J. L.; Nissink, J. W.; Strasser, J. M.; Francis, S.; Higgins, L.; Zhou, H.; Zhang, Z.; Walters, M. A. *J. Med. Chem.* **2015**, *58*, 2091. (b) Martinez, A.; Alonso, M.; Castro, A.; Pérez, C.; Moreno, F. J. *J. Med. Chem.* **2002**, *45*, 1292.

(8) (a) Göblyös, A.; de Vries, H.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2005**, *48*, 1145. (b) van den Nieuwendijk, A. M. C. H.; Pietra, D.; Heitman, L.; Göblyös, A.; Ijzerman, A. P. *J. Med. Chem.* **2004**, *47*, 663. (c) Fawzi, A. B.; Macdonald, D.; Benbow, L. L.; Smith-Torhan, A.; Zhang, H.; Weig, B. C.; Ho, G.; Tulshian, D.; Linder, M. E.; Graziano, M. P. *Mol. Pharmacol.* **2001**, *59*, 30.

(9) Unangst, P. C.; Shrum, G. P.; Connor, D. T.; Dyer, R. D.; Schrier, D. J. *J. Med. Chem.* **1992**, *35*, 3691.

(10) Iizawa, Y.; Okonogi, K.; Hayashi, R.; Iwahi, T.; Yamazaki, T.; Imada, A. *Antimicrob. Agents Chemother.* **1993**, *37*, 100.

(11) Kumita, I.; Niwa, A. *J. Pestic. Sci.* **2001**, *26*, 60.

(12) Kharimian, K.; Tam, T. F.; Leung-Toung, R. C.; Li, W. PCT Int. Appl. WO1999051584 A1, 1999.

(13) Johnstone, C.; Mckerrecher, D.; Pike, K. G.; Waring, M. J. PCT Int. Appl. WO2005121110 A1, 2005.

(14) Frija, L. M. T.; Pombeiro, A. J. L.; Kopylovich, M. N. *Eur. J. Org. Chem.*, *Early View*, DOI: 10.1002/ejoc.201601642.

(15) Zyabrev, V. S.; Rensky, M. A.; Rusanov, E. B.; Drach, B. S. *Heteroatom Chem.* **2003**, *14*, 474.

(16) Kurzer, F.; Tertiuk, W. *J. Chem. Soc.* **1959**, 2851.

(17) Kim, H.-Y.; Kwak, S. H.; Lee, G.-H.; Gong, Y.-D. *Tetrahedron* **2014**, *70*, 8737.

(18) Smith, R. F.; Feltz, T. P. *J. Heterocycl. Chem.* **1981**, *18*, 201.

(19) Dürüst, Y.; Yıldırım, M.; Aycan, A. *J. Chem. Res.* **2008**, 235.

(20) (a) Castro, A.; Castaño, T.; Encinas, A.; Porcal, W.; Gil, C. *Bioorg. Med. Chem.* **2006**, *14*, 1644. (b) Castro, A.; Encinas, A.; Gil, C.; Bräse, S.; Porcal, W.; Pérez, C.; Moreno, F. J.; Martínez, A. *Bioorg. Med. Chem.* **2008**, *16*, 495. (c) Mamaeva, E. A.; Bakibaev, A. A. *Tetrahedron* **2003**, *59*, 7521.

(21) Kihara, Y.; Kabashima, S.; Uno, K.; Okawara, T.; Yamasaki, T.; Furukawa, M. *Synthesis* **1990**, *11*, 1020.

(22) Bracha, P.; Lovich, M. Israeli Patent, IL35743 A, 1974.

(23) Akiba, K.-Y.; Tsuchiya, T.; Ochiumi, M.; Inamoto, N. *Tetrahedron Lett.* **1975**, *16*, 455.

(24) Kurzer, F. *J. Chem. Soc.* **1956**, 2345.