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Article

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Hypervalent Iodine(III) Mediated Synthesis of 3-Substituted 5-Amino-1,2,4-thiadiazoles through Intramolecular Oxidative S-N Bond Formation

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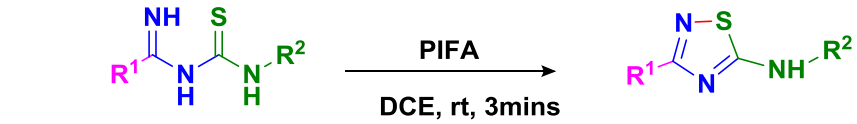


1a 2a

R1 = aryl, heteroaryl, alkyl
R2 = aryl, alkyl

Abstract

An efficient synthesis of 3-substituted-5-arylamino-1,2,4-thiadiazoles through intramolecular oxidative **S-N** bond formation of imidoyl thioureas by phenyliodine(III) bis(trifluoroacetate) is reported. The protocol features metal free approach, broad substrate scope and very short reaction times, good to excellent yields and simple starting materials.

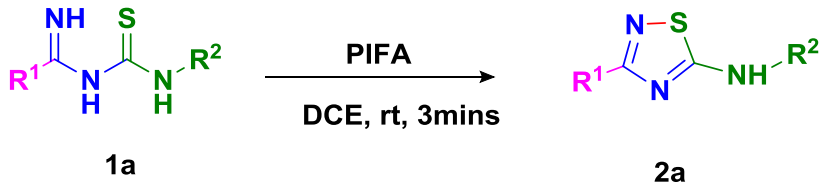
***Keywords*:** 1,2,4 -Thiadiazole; phenyliodine(III) bis(trifluoroacetate); hypervalent iodine(III); oxidative cyclisation.

Introduction

Efficient and convenient procedures for the synthesis of heterocycles through the heteroatom-heteroatom bond [N-X bond (X= N, O, S)] formation are still in high demand as only limited examples are available in the literature for the N-X[1-3] bond formation compared to C-C and C-X bond formation processes. The available metal catalyzed protocols for N-X bond formation have their own disadvantages, the metal contamination in the desired product and harsh reaction conditions being the main limitations.[4] Some metal free approaches [1d, 5] have been developed for the N-X bond formation, in which hypervalent iodine (III) reagents have turned out to be good candidates owing to their environmentally benign nature, low cost and strong oxidizing power.[6] Hypervalent iodine (III) reagents have been employed in the construction of C-C,[7] C-X[8] and N-X[1a, b, 9-11] (X= N, O, S) bond formation protocols. A careful literature survey reveals that only very few reports describe the synthesis of heterocycles through the S-N bond formation using iodine(III) reagents.[11]

1,2,4-Thiadiazole is an important heterocyclic core with a broad spectrum of applications as a pharmacophore and its derivatives serve as pesticides and corrosion inhibitors.[12] In particular, the substituted 1,2,4-thiadiazoles have been reported to have a wide spectrum of biological activity including antibacterial,[13] anti-inflammatory,[14] antiulcerative,[15] anti-rheumatic[16] and antidiabetic.[17] In view of this importance, numerous methodologies have been developed to construct this skeleton. Among them, the simple oxidative dimerization of thio amides using various oxidants is very common.[18] Smith et al. reported the synthesis of 1,2,4-Thiadiazoles by thermolysis of N^3-thiocarbamoylamidrazone ylides.[19] Dürüst et al. reported a cyclocondensation reaction of amidoximes with *N*-substituted thioureas in the presence of KF/Al_2O_3, but the reaction required more time even at reflux temperature.[20] Wehn et al. reported the synthesis of 3-amino-1,2,4-

thiadiazoles *via* a palladium catalyzed Suzuki-Miyaura coupling reaction.[21] Many approaches have been reported to construct 1,2,4-thiadiazole skeleton from imidoyl thioureas.[22-26] Kurzer and Tertiak have employed hydrogen peroxide to prepare 3-alkyl(or aryl)-5-alkyl(or aryl)-amino-1,2,4-thiadiazoles from imidoyl thioureas.[27] Kim et al. developed a copper catalyzed synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles through intramolecular oxidative cyclisation.[28] In continuation of our efforts on the development of useful synthetic methodologies for the construction of heterocycles through mild and eco-friendly protocols using hypervalent iodine (III) reagents,[29] we present an efficient and mild approach for the synthesis of 3-substituted-5-arylamino-1,2,4-thiadiazoles in a very short reaction time at room temperature.



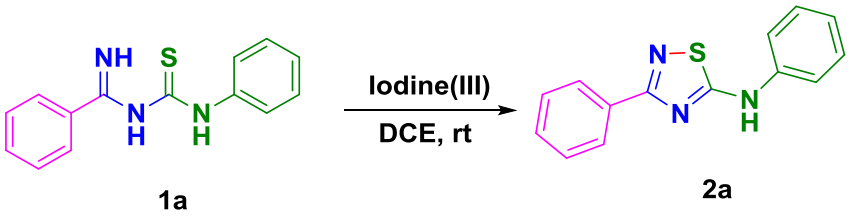
1a 2a

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

Results and Discussion

We initially tested hypervalent iodine (III) reagent, phenyl iodine(III) diacetate (PIDA), for the oxidative cyclisation of imidoyl thiourea **1a**, which has been obtained by the reaction of amidine and phenylisothiocyanate**.** To our delight, the reaction got completed in 5 minutes yielding the expected product **2** (Scheme 1) in 70 % yield in THF (Table 1, entry 1). Encouraged by this result, we studied this conversion with different hypervalent iodine reagents such as 2-iodoxy benzoic acid, Dess Martin periodinane and phenyliodine(III) bis(trifluoroacetate) (Table 1, entries 2, 3 & 4). We also employed other oxidants such as ceric ammonium nitrate, DDQ, potassium perdisulfate and oxone. The yields were good with oxone and DDQ (Table 1, entries 5 & 8), but relatively poor

Table 1. Optimisation of reaction conditions.[a]



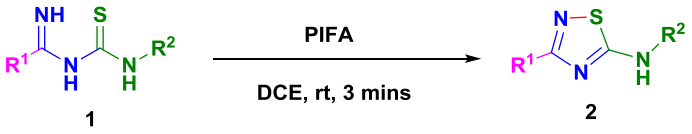
1a 2a

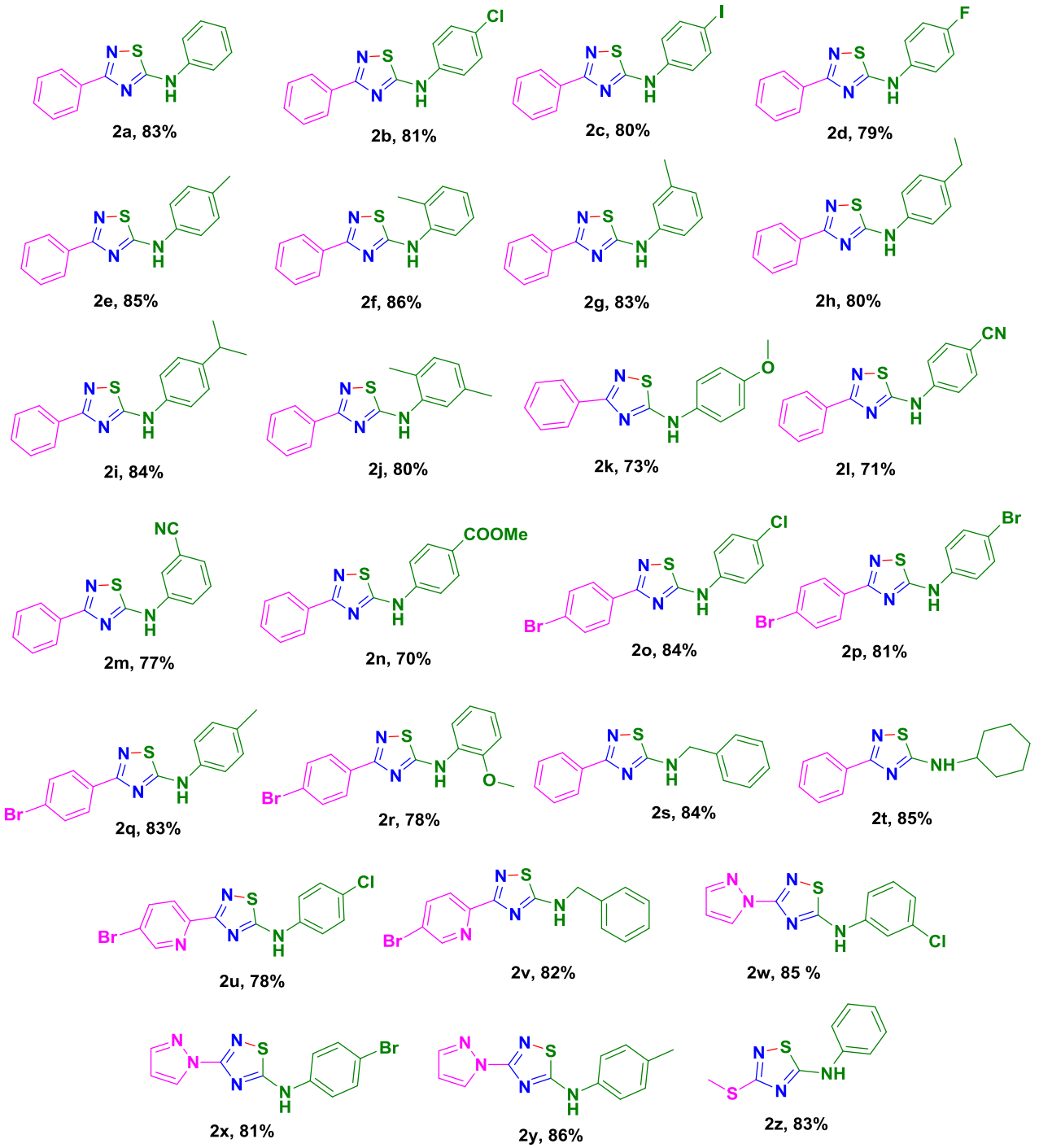
Entry	oxidant	solvent[b]	Time (mins)	Yield (%)[c]
1	PIDA	THF	5	70
2	DMP	THF	3	76
3	IBX	THF	5	73
4	PIFA	THF	3	80
5	Oxone	THF	5	68
6	CAN	THF	5	38
7	$K_2S_2O_8$	THF	3	47
8	DDQ	THF	5	60
9	PIFA[d]	THF	3	62
10	PIFA	DMF	3	65
11	PIFA	MeOH	3	70
12	**PIFA**	**DCE**	**3**	**83**
13	PIFA	MeCN	3	73
14	PIFA	1,4-Dioxane	3	46
15	PIFA	TFA	3	66

[a]Reaction conditions: Reactant **1** (1.0 mmol), oxidant **2** (1.1 mmol), solvent (3 mL) - stirred at room temperature for 3-5 mins. [b]Abbreviations used in the table: PIDA = phenyl iodine(III) diacetate; DMP = Dess Martin periodinane; IBX = 2-iodoxy benzoic acid; PIFA = phenyliodine(III) bis(trifluoroacetate); CAN = ceric ammonium nitrate; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DCE = 1,2-dichloroethane; THF = tetrahydrofuran; MeCN = acetonitrile; DMF = *N*, *N*-dimethylformamide; TFA = trifluroacetic acid. [c]Isolated yield. [d]Oxidant **2** (2.2 mmol**).**

with ceric ammonium nitrate and potassium perdisulfate (Table 1, entries 5 & 6). Among all the oxidants investigated, PIFA was found to be the best choice (Table 1, entry 4), though the yield

Table 2. Synthesised compounds: **2a-2z.**

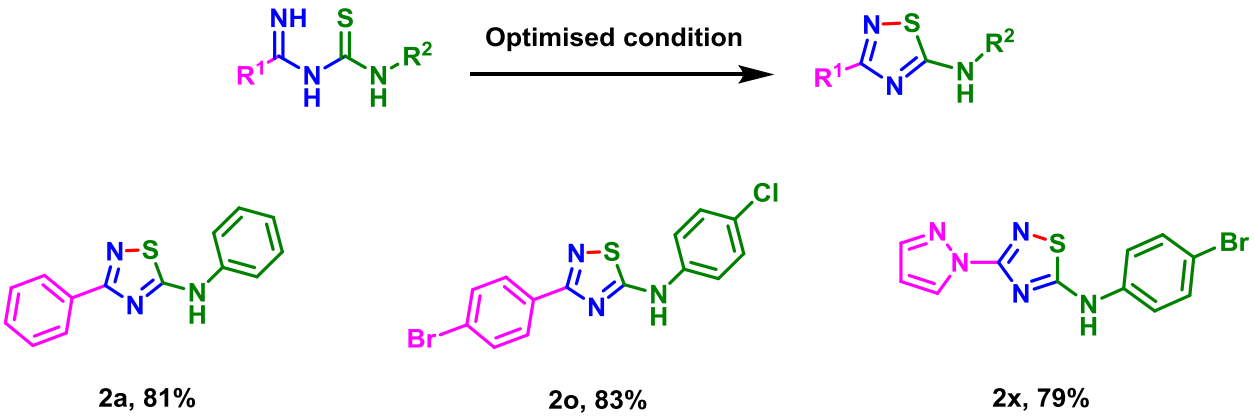




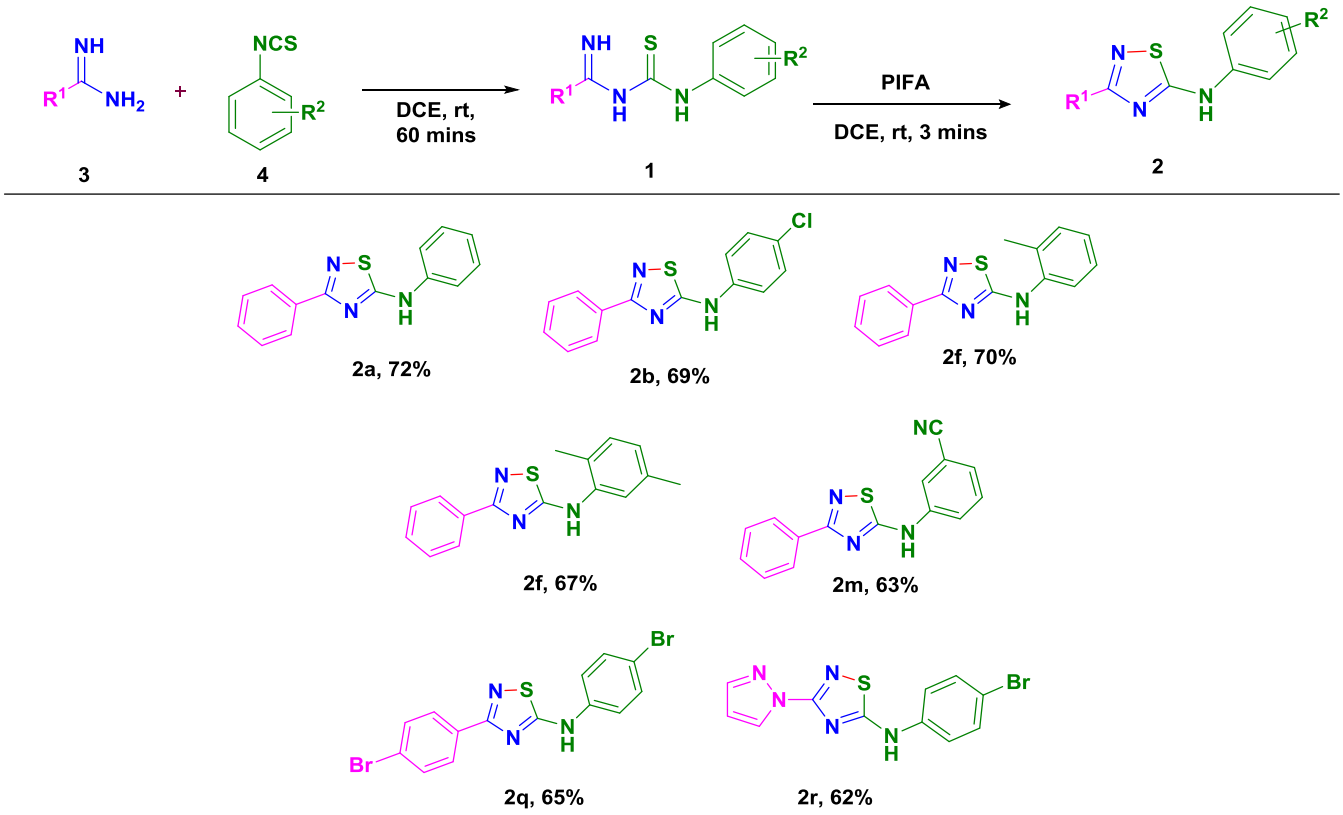
was equally good with DMP (Table 1, entry 2). Increasing the oxidant amount had negative impact on the reaction (Table 1, entry 9) resulting in decreased yield of the product. Though the yield was relatively good with all the polar solvents (Table 1, entry 10, 11, 13 & 15), the best solvent identified was dichloroethane (Table 1, entry 12). With the optimized reaction conditions in hand, we explored the substrate scope of the reaction. The reaction proceeded well with substrates having both electron-withdrawing as well as electron-donating groups in the aryl rings. Subsequently, we varied the amidine part with heteroaryl rings as well resulting in good yields of **2**. A library of synthesized compounds is listed in Table 2. The structure of products **2** were unambiguously assigned by spectral and analytical data, and that of **2f** was confirmed by single crystal X-ray analysis (See supporting information).[30]

The scalability of the reaction has been tested with three compounds (Scheme 2) and the results are encouraging.

Scheme 2. Gram- scale synthesis.

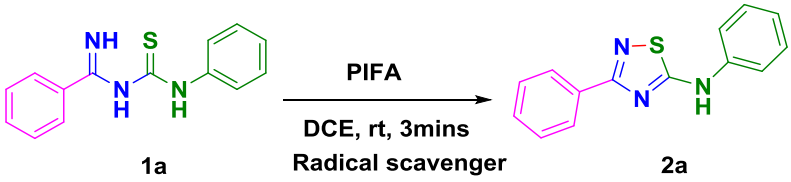


Scheme 3. One-pot synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles.



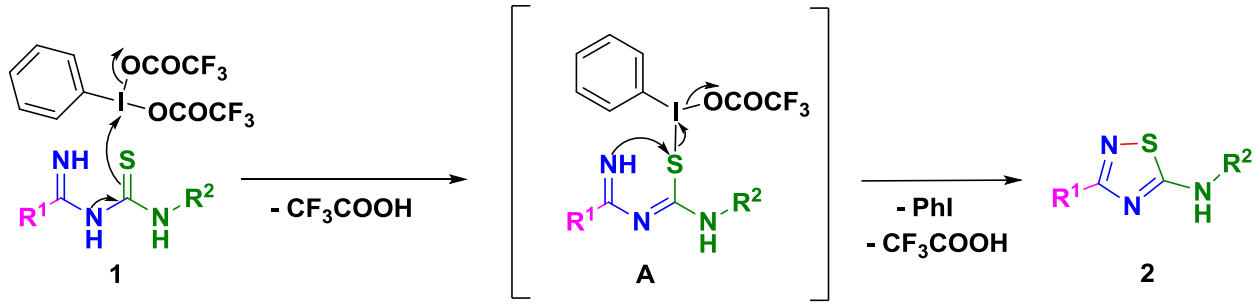
An attempt to carry out this oxidative cyclisation in a one pot fashion by allowing amidine **3** to react with phenylisothiocyanate **4** followed by the addition of the hypervalent iodine (III) reagent in the same reaction vessel did not affect the yield significantly (Scheme 3). Under the optimized reaction conditions, when the control experiments were carried out with radical scavengers like TEMPO (2,2,6,6-tetramethylpiperdine-1-oxide) and hydroquinone, no considerable effect was observed ruling out the radical mechanism favoring the ionic mechanism (Scheme 4).

Scheme 4. Control experiments



Radical scavenger (mmol)	Yield (%)
TEMPO(1.5)	83
Hydroquinone(1.5)	83

Based on this and the previous literature report,[1c] a mechanism has been proposed for the formation of **2** as depicted in Scheme 5. The imidoyl thiourea reacts with PIFA to form an intermediate **A**, followed by the nucleophilic attack on the sulfur atom by the NH-group with the removal of trifluoro acetic acid and iodobenzene resulting in the required product **2**.



Scheme 5. Proposed mechanism for the intramolecular oxidative S-N bond formation.

Conclusion

In summary, we have developed an efficient protocol for the synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles through intramolecular oxidative S-N bond formation by hypervalent iodine (III) reagent, PIFA.

Experimental Section

General methods

All solvents were purchased from commercial sources and used without further purification. The melting points were measured in open capillary tubes and are uncorrected. Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ and DMSO-D6 using TMS as an internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (*J* values) are reported in Hertz (Hz) and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), sept (septet), m (multiplet), bs (broad singlet), bd (broad doublet). ^{13}C NMR spectra were routinely run with broadband decoupling. Pre coated silica gel on aluminum plates were used for TLC analysis with a mixture of petroleum ether (60-80^{o}C) and ethyl acetate as eluent. Elemental analyses were performed on an Elemental CHNS analyzer.

Synthesis of *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amines (2a-2z):

General procedure

A mixture of *N*-(phenylcarbamothioyl)benzimidamide **1a** (255 mg, 1.0 mmol) and $PhI(OCOCF_3)_2$ (430 mg, 1.1 mmol) was taken in a 10 ml round bottom flask in 1,2-dichloroethane (3 mL) and stirred at room temperature for 3 minutes. The completion of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed. Then the reaction mass was washed with sodium bicarbonate solution and extracted with dichloromethane (3 times). After drying over sodium sulfate, dichloromethane was removed under vacuum. Crude product was purified by column chromatography using petroleum ether − ethyl acetate (70: 30) as the eluent to afford compound **2a**.

Characterization data for compounds (2a-2z)

N,3-Diphenyl-1,2,4-thiadiazol-5-amine ***(2a).***[26] Isolated as white solid (210 mg, 83%); mp 170 – 173^{o}C; IR (KBr): ν = 3231, 2967, 1602, 1566, 1453 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.22 – 8.20 (m, 2H), 7.45 – 7.41 (m, 3H), 7.39 – 7.36 (m, 2H), 7.21 (d, *J* = 7.7 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 169.3, 139.1, 132.8, 130.1, 129.8, 128.6, 128.0, 124.3, 118.4. ESI-MS m/z calcd $[M+H]^+$ 253.07, found 254.12.

N-(4-Chlorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine ***(2b).***[26] Isolated as white solid (232 mg, 81%); mp 194 – 196 ^{o}C; IR (KBr): ν = 3222, 3080, 1604, 1560, 1490 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.26 – 8.22 (m, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.47- 7.44 (m, 3H), 7.35 – 7.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 168.9, 138.4, 132.8, 129.5, 128.7, 128.0, 127.5, 127.0, 118.8.

N-(4-Iodophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine ***(2c).*** Isolated as light brown solid (302 mg, 80%) ; mp 180 – 183 ^{o}C; IR (KBr): ν =3220, 3068, 1594, 1551, 1458, 714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 10.17 (s, 1H), 8.24 – 8.21 (m, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.46 – 7.44 (m, 3H), 7.38 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 168.9, 139.5, 137.5, 132.7, 129.5, 128.0, 127.5, 119.5, 84.9. Anal. Calcd for: $C_{14}H_{10}IN_3S$: C, 44.34; H, 2.66; N, 11.08 %. Found: C, 44.32; H, 2.69; N, 11.11%. ESI-MS m/z calcd $[M+H]^+$ 379.96, found 380.01.

N-(4-Fluorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine ***(2d).*** Isolated as white solid (207 mg, 79%); mp 170 – 173^{o}C; IR (KBr): ν =3228, 3080, 1597, 1548, 1466 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 10.17 (s, 1H), 8.25 – 8.22 (m, 2H), 7.60 – 7.55 (m, 2H), 7.47 – 7.44 (m, 3H), 7.08 (t, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 169.2, 158.4(d, $^{1}J_{C-F}$ = 241.5Hz)

136.2, 133.1, 129.6, 127.9, 119.6(d, $^{3}J_{C\text{-}F}$ = 8.5Hz), 115.6 (d, $^{2}J_{C\text{-}F}$ = 22.5Hz). Anal. Calcd for: $C_{14}H_{10}FN_3S$: C, 61.98; H, 3.72; N, 15.49 %. Found: C, 61.89; H, 3.68; N, 15.42 %.

3-Phenyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine ***(2e).*** Isolated as off-white solid (225 mg, 85%); mp 120 – 123 ^{o}C; IR (KBr): ν = 3234, 3085, 1605, 1564, 1512 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.20 – 8.17 (m, 2H), 7.43 – 7.41 (m, 3H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 169.3, 136.7, 134.4, 132.9, 130.3, 130.1, 128.5, 127.9, 119.0, 20.8. Anal. Calcd for: $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72 %. Found: C, 67.43; H, 4.87; N, 15.76 %. ESI-MS m/z calcd $[M+H]^+$ 268.08, found 268.14.

3-Phenyl-N-(o-tolyl)-1,2,4-thiadiazol-5-amine ***(2f).***[26] Isolated as white solid (228 mg, 86%); mp 168 – 171^{o}C; IR (KBr): ν = 3218, 3078, 1605, 1559, 1486 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.13 (m, 2H), 8.04 (bs, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.41 – 7.39 (m, 2H), 7.35 – 7.26 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 169.4, 137.8, 132.8, 131.4, 130.7, 130.0, 128.4, 127.8, 127.5, 126.2, 121.2, 17.6.

3-Phenyl-N-(m-tolyl)-1,2,4-thiadiazol-5-amine ***(2g).*** Isolated as off-white solid (220 mg, 83%); mp 110 – 113 ^{o}C; IR (KBr): ν = 3228, 3089, 1596, 1548, 1476 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.10 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.31 (m, 4H), 7.25 – 7.27 (m, 1H), 7.20 – 7.15 (m, 1H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 169.2, 139.9, 139.1, 132.8, 130.1, 129.5, 128.5, 128.0, 125.1, 119.5, 115.2, 21.4. Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72 %. Found: C, 67.42; H, 4.95; N, 15.69 %.

N-(4-Ethylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine ***(2h).*** Isolated as white solid (223 mg, 80%); mp 140 – 143 ^{o}C; IR (KBr): ν = 3223, 3070, 1596, 1555, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.22 – 8.19 (m, 2H), 7.68 – 7.44 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.5 Hz,

2H), 2.66 (q, *J*=7.5 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 169.4, 140.8, 136.9, 133.1, 130.0, 129.1, 128.5, 128.0, 118.9, 28.0, 15.2. Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93 %. Found: C, 68.27; H, 5.39; N, 14.97 %. ESI-MS m/z calcd $[M+H]^+$ 282.10, found 282.33.

N-(4-Isopropylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine ***(2i).*** Isolated as white solid (246 mg, 84%); mp 130 – 132 ^{o}C; ν = 3216, 3092, 1601, 1560, 1520, 1453 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.19 (d, *J* = 5.3 Hz, 2H), 7.43 (d, *J* = 2.1 Hz, 3H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.98 – 2.83 (m, 1H), 1.26 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.4, 169.1, 145.4, 136.9, 132.7, 130.1, 128.5, 128.0, 127.7 119.0, 33.5, 23.9. Anal. Calcd for: $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22 %. Found: C, 69.16; H, 5.77; N, 14.27 %. ESI-MS m/z calcd $[M+H]^+$ 296.11, found 296.33.

N-(2,5-Dimethylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine ***(2j).*** Isolated as white solid (234 mg, 80%); mp 135 – 137 ^{o}C; IR (KBr): ν = 3227, 3026, 1586, 1548, 1442 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.10 (dd, *J* = 7. 9, 1.6 Hz, 2H), 7.42 – 7.31 (m, 4H), 7.14 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 2.37 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 169.6, 137.5, 137.5, 132.9, 131.3, 129.9, 128.4, 127.8, 127.5, 127.0, 121.9, 21.1, 17.2. Anal. Calcd for: $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93 %. Found: C, 68.33; H, 5.39; N, 14.90 %. ESI-MS m/z calcd $[M+H]^+$ 282.10, found 282.17.

N-(4-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine ***(2k).*** Isolated as white solid (196 mg, 73%); mp 116 – 118 ^{o}C; IR (KBr): ν = 3230, 3079, 1603, 1548, 1512, 1421 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 9.94 (s, 2H), 8.22 – 8.20 (m, 2H), 7.46 – 7.43 (m, 5H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 169.3, 156.2, 133.1, 129.7, 128.2,

127.8, 127.1, 120.8, 114.6, 55.4. Anal. Calcd for: $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83 %. Found: C, 63.52; H, 4.66; N, 14.78 %.

4-((3-Phenyl-1,2,4-thiadiazol-5-yl)amino)benzonitrile ***(2l).*** Isolated as white solid (196 mg, 71%); mp 208 – 210 ^{o}C; IR (KBr): ν = 3230, 3091, 2234, 1602, 1560, 1428 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 10.91 (s, 1H), 8.23 – 8.21 (m, 2H), 7.80 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.45 – 7.42 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 169.3, 143.4, 133.1, 132.7, 129.8, 128.2, 127.7, 119.0, 117.4, 104.4. Anal. Calcd for: $C_{15}H_{10}N_4S$: C, 64.73; H, 3.62; N, 20.13 %. Found: C, 64.70; H, 3.66; N, 20.08 %. ESI-MS m/z calcd $[M+H]^+$ 279.06, found 279.14.

3-((3-Phenyl-1,2,4-thiadiazol-5-yl)amino)benzonitrile ***(2m).***[26] Isolated as yellow solid (213 mg, 77%); mp 223 – 226 ^{o}C; IR (KBr): ν = 3236, 2238, 1599, 1540, 1449 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 10.61 (s, 1H), 8.27 - 8.24 (m, 2H), 8.10 (s, 1H), 7.91 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 – 7.45 (m, 4H), 7.33 (d, *J* = 6.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-D_6) δ 178.6, 169.1, 140.5, 132.6, 129.7, 129.7, 128.2, 127.6, 125.5, 121.5, 120.3, 118.5, 112.4.

Methyl 4-((3-phenyl-1,2,4-thiadiazol-5-yl)amino)benzoate ***(2n).*** Isolated as white solid (216 mg, 70%); mp 179 – 182^{o}C; IR (KBr): ν = 3228, 3068, 1720, 1602, 1556, 1432 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.27 – 8.26 (m, 2H), 8.07 (d, *J* = 7.4 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.48 – 7.46 (m, 3H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 168.6, 165.8, 143.4, 132.4, 130.3, 129.3, 127.8, 127.2, 123.0, 116.2, 51.2. Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50 %. Found: C, 61.76; H, 4.24; N, 13.46 %.

3-(4-Bromophenyl)-N-(4-chlorophenyl)-1,2,4-thiadiazol-5-amine ***(2o).*** Isolated as pale yellow solid (307 mg, 84%); mp 174 – 176^{o}C; IR (KBr): ν = 3226, 3080, 1606, 1557, 1491, 1440 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 10.50 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.2 Hz,

4H), 7.34 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-D_6) δ 178.6, 167.1, 137.8, 131.3, 130.6, 128.6, 128.1, 126.3, 123.2, 118.3. Anal. Calcd for: $C_{14}H_9BrClN_3S$: C, 45.86; H, 2.47; N, 11.46 %. Found: C, 45.82; H, 2.49; N, 11.40 %.

N, 3-Bis(4-bromophenyl)-1,2,4-thiadiazol-5-amine ***(2p).*** Isolated as pale yellow solid (331 mg, 81%); mp 179 – 181^{o}C; IR (KBr): ν = 3231, 3080, 1600, 1554, 1493, 1443 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 10.60 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 2H), 7.62 – 7.57 (m, 4H), 7.50 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-D_6) δ 179.0, 167.8, 138.8, 131.8, 131.5, 131.1, 129.0, 123.7, 119.2, 114.6. Anal. Calcd for: $C_{14}H_9Br_2N_3S$: C, 40.90; H, 2.21; N, 10.22 %. Found: C, 40.96; H, 2.18; N, 10.18 %.

3-(4-Bromophenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine ***(2q).*** Isolated as white solid (286 mg, 83%); mp 241 – 243^{o}C; IR (KBr): ν = 3224, 3054, 1592, 1565, 1438 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 10.30 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-D_6) δ 180.3, 168.3, 138.2, 132.9, 132.8, 132.1, 130.2, 130.1, 124.3, 118.7, 21.2. Anal. Calcd for: $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.14 %. Found: C, 52.07; H, 3.44; N, 12.17 %.

N-(2-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine ***(2r).*** Isolated as white solid (281 mg, 78%); mp 120 – 123^{o}C; IR (KBr): ν = 3237, 3065, 1600, 1570, 1439 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.12 – 8.10 (m, 2H), 7.60 – 7.57 (m, 3H), 7.11 – 7.08 (m, 2H), 6.96 (d, *J* = 7.2 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 168.4, 148.0, 132.0, 131.7, 129.6, 128.7, 124.5, 123.7, 121.3, 116.4, 110.7, 55.8. Anal. Calcd for: $C_{15}H_{12}BrN_3OS$: C, 49.74; H, 3.34; N, 11.60 %. Found: C, 49.68; H, 3.30; N, 11.65 %.

N-Benzyl-3-phenyl-1,2,4-thiadiazol-5-amine ***(2s).***[26] Isolated as white solid (223 mg, 84%); mp 101 – 104°C; IR (KBr): ν = 3218, 3098, 1594, 1570, 1436, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15-8.12 (m, 2H), 7.40-7.38 (m, 2H), 7.34-7.26 (m, 6H), 7.01 (s, 1H), 4.47 (d, *J* = 5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7, 169.8, 136.1, 133.1, 129.9, 128.9, 128.4, 128.1, 127.9, 127.6, 50.4. ESI-MS m/z calcd $[M+H]^+$ 268.08, found 268.15.

N-Cyclohexyl-3-phenyl-1,2,4-thiadiazol-5-amine ***(2t).***[22b] Isolated as white solid (218 mg, 85%); mp 113 – 115 °C; IR (KBr): ν = 3190, 3062, 2985,1577, 1503, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.14 (m, 2H), 7.43 – 7.41 (m, 3H), 5.91 (d, *J* = 7.7 Hz, 1H), 3.28 – 3.18 (m, 1H), 2.17 – 2.09 (m, 2H), 1.82 – 1.75 (m, 2H), 1.42 – 1.25 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.4, 169.8, 133.2, 129.8, 128.4, 127.9, 56.2, 32.5, 25.2, 24.5. ESI-MS m/z calcd $[M+H]^+$ 260.11, found 260.33.

3-(5-Bromopyridin-2-yl)-N-(4-chlorophenyl)-1,2,4-thiadiazol-5-amine ***(2u).*** Isolated as brown solid (285 mg, 78%); mp 228 – 231°C; IR (KBr): ν = 3179, 3063, 3027, 1590, 1490, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-D_6) δ 10.54 (s, 1H), 8.80 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.01 – 7.96 (m, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-D_6)) δ 179.3, 166.8, 150.1, 148.6, 138.8, 138.0, 128.4, 126.9, 124.2, 121.0, 118.7. Anal. Calcd for $C_{13}H_8BrClN_4S$: C, 42.47; H, 2.19; N, 15.24 %. Found: C, 42.50; H, 2.13; N, 15.28 %.

N-Benzyl-3-(5-bromopyridin-2-yl)-1,2,4-thiadiazol-5-amine ***(2v).*** Isolated as white solid (283 mg, 82%); mp 221 – 224 °C; IR (KBr): ν = 3233, 3088, 3032, 1601, 1534, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-D_6) 8.64 (d, *J* = 2.1 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.89 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.37 (m, 5H), 4.56 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-D_6)) δ 183.0,

166.2, 149.2, 148.5, 138.2, 136.4, 127.4, 126.6, 126.4, 123.7, 120.1, 48.2. Anal. Calcd for $C_{14}H_{11}BrN_4S$: C, 48.43; H, 3.19; N, 16.14 %. Found: C, 48.40; H, 3.21; N, 16.11 %.

N-(3-Chlorophenyl)-3-(1H-pyrazol-1-yl)-1,2,4-thiadiazol-5-amine ***(2w).*** Isolated as off-white solid (235 mg, 85%); mp 220 – 222 ^{o}C; IR (KBr): ν = 3267, 3148, 3087, 1614, 1544, 1473, 1432 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) 10.85 (s, 1H), 8.36 (bd, *J* = 2.1 Hz, 1H), 7.76 (s, 1H), 7.64 (s, 1H), 7.45 – 7.44 (m, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.47 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-D_6) δ 179.5, 157.4, 142.3, 140.2, 134.3, 129.9, 129.5, 122.9, 117.9, 115.9, 107.3. Anal. Calcd for $C_{11}H_8ClN_5S$: C, 47.57; H, 2.90; N, 25.22 %. Found: C, 47.53; H, 2.93; N, 25.27 %.

N-(4-Bromophenyl)-3-(1H-pyrazol-1-yl)-1,2,4-thiadiazol-5-amine ***(2x).*** Isolated as white solid (259 mg, 81%); mp 221 – 224 ^{o}C; IR (KBr): ν = 3226, 3060, 3025, 1615, 1490, 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-D_6) 10.72 (s, 1H), 8.35 (bd, *J* = 2.4 Hz, 1H), 7.75 (s, 1H), 7.47 (s, 4H), 6.47 – 6.45 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-D_6) δ 178.9, 156.9, 141.8, 137.8, 131.2, 129.1, 119.1, 114.7, 106.9. Anal. Calcd for $C_{11}H_8BrN_5S$: C, 41.01; H, 2.50; N, 21.74 %. Found: C, 41.06; H, 2.47; N, 21.69 %.

3-(1H-Pyrazol-1-yl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine ***(2y).*** Isolated as Pale yellow solid (219 mg, 86%); mp 180 – 183 ^{o}C; IR (KBr): ν = 3220, 3073, 1606, 1548, 1457 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 8.98 (s, 1H), 8.30 (s, 1H), 7.57 (s, 1H), 7.24 – 7.15 (m, 4H), 6.41 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 182.7, 158.1, 142.3, 136.6, 135.3, 130.1, 129.1, 120.9, 107.9, 20.9. Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; N, 27.22 %. Found: C, 56.06; H, 4.34; N, 27.16 %.

3-(Methylthio)-N-phenyl-1,2,4-thiadiazol-5-amine ***(2z).*** Isolated as white solid (184 mg, 83%); mp 80 – 83°C; IR (KBr): ν = 3223, 2968, 1592, 1545, 1451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.42 – 7.37 (m, 2H), 7.34 – 7.31 (m, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 180.2, 168.1, 139.4, 129.4, 123.8, 118.5, 14.3. Anal. Calcd for $C_9H_9N_3S_2$: C, 48.41; H, 4.06; N, 18.82 %. Found: C, 48.46; H, 4.03; N, 18.78 %.

ASSOCIATED CONTENT

Supporting Information

^1H, ^{13}C NMR, ESI-Mass spectra (PDF) and X-ray crystal data of compound **2f** (CIFs). This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) CCDC No. 1478589 contains the supplementary crystallographic data for the compound **2f**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.