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FACILE ONE-POT PROCEDURE FOR THE SYNTHESIS OF 2-AMINOTHIAZOLE DERIVATIVES

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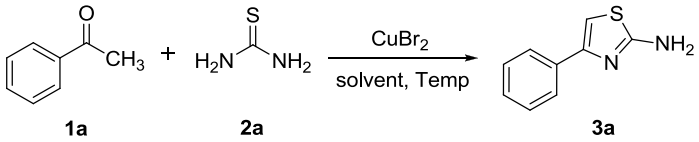
Abstract – A facile, efficient synthesis of 2-aminothiazole derivatives by the reaction of easily available aromatic methyl ketones with thiourea/*N*-substituted thioureas in the presence of copper(II) bromide was developed. The reaction underwent a one-pot α-bromination/cyclization process.

INTRODUCTION

Thiazole derivatives are present in many natural and synthetic products with a wide range of pharmacological activities, such as anticancer, antiviral, antibacterial, antifungal, and anti-inflammatory activities.[1–3] Among them, aminothiazole derivatives possess an antitumor activity through the inhibition of the kinases.[4,5] Aminothiazoles are also known to be ligands of estrogen receptors[6] as well as a novel class of adenosine receptor antagonists.[7] In view of their importance, a variety of approaches to 2-aminothiazole derivatives have been reported. Hantzsch thiazole synthesis, involving the reaction of α-halo carbonyl compounds and thioureas, is still one of the most widely used methods.[8–13]

In recent years, much attention has been paid to one-pot synthesis,[14] which is a strategy to improve the efficiency of a chemical reaction because of avoiding a separation process and purification of the intermediates. However, most of synthetic strategies towards the one-pot preparation of 2-aminothiazole underwent α-iodo ketones[15,16] or α-tosyloxy ketones[17–21] intermediates. In addition, although there are numerous efficient methods for α-bromination carbonyl compounds,[22–28] few reports foucs on the one-pot α-bromination/cyclization process for 2-aminothiazole.[29] Copper(II) bromide was found to be an efficient, simple and inexpensive reagent for the α-bromination of carbonyl compounds.[30,31] Based on the above-motioned results, we herein reported a facile, efficient one-pot synthesis of 2-aminothiazole derivatives via α-bromination/cyclization process from easily available aromatic methyl ketones.

RESULTS AND DISCUSSION



Scheme 1

Table 1. Optimization of reaction condition for the synthesis of **3a** in the presence of K_2CO_3

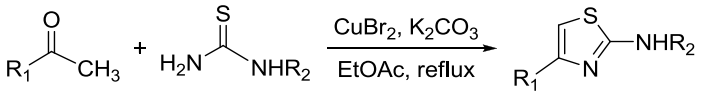
Entry	Solvent	Temp (^oC)	Yield[a] (%)	Entry	Solvent	Temp (^oC)	Yield[a] (%)
1	EtOAc	reflux	87	6	$CHCl_3$	reflux	0
2	MeOH	reflux	80	7	H_2O	60	0
3	EtOH	reflux	82	8	EtOAc	20	0
4	THF	reflux	25	9	EtOAc	reflux	45[b]
5	MeCN	reflux	40	10	EtOAc	reflux	30[c]

[a]Isolated yield based on acetophenone. [b]$NaHCO_3$ as a base. [c]no base was used.

In our initial experiments, acetophenone (**1a**) was used as the model substrate to react with thiourea in different solvents (such as MeOH, EtOH, THF, MeCN, $CHCl_3$, H_2O and EtOAc) in the presence of copper(II) bromide and K_2CO_3 for the preparation of the expected 4-phenylthiazol-2-amine (**3a**) (Scheme 1). As shown in Table 1, it can be seen that the reaction gave the highest yield (87%) in refluxing EtOAc (entry 1). **3a** was also obtained in good yield in MeOH or EtOH (entries 2, 3). However, the reaction gave poor yields in THF and MeCN (entries 4, 5). No reaction occurred in $CHCl_3$, water or in EtOAc at room temperature (entries 6–8). When $NaHCO_3$ or no base was employed, **3a** was isolated only in 45% and 30% yields respectively (entries 9, 10). Its structure was assigned on the basis of ^{1}H NMR and mass spectra. The ^{1}H NMR spectra of **3a** shows a characteristic peak at 6.73 ppm corresponding to the hydrogen of thiazole ring, which are in accordance with the literature.[21]

After the optimization of reaction conditions, we next examined the scope and generality of this method to other substrates using different aromatic ketones and *N*-substituted thioureas (Scheme 2). The results are summarized in Table 2. The condensation of different methyl ketones including electron-donating or electron-withdrawing groups (such as -OMe, -OBn, -F and C_6H_5) on the 4-position of phenyl ring with thiourea gave the expected products 4-aryl-2-aminothiazole **3b–e** in good to excellent yields (78–90%, entries 2–5). 2-Acetylnaphthalene also gave the 4-(naphthalen-2-yl)thiazol-2-amine (**3f**) in 82% yield (entry 6). Furthermore, we were pleased to find that *N*-substituted thioureas such as *N*-methylthiourea, *N*-allylthiourea, *N*-phenylthiourea and *N*-(naphthalen-2-yl)thiourea reacted with aryl or heteroaryl methyl ketones afforded the 2-aminothiazole derivatives **3g–u** in good yields (68–88%, entries 7–21). Notably, the reaction of 4'-fluoroacetophenone with *N*-phenylthiourea and *N*-(naphthalen-2-yl)thiourea delivered 4-(4-fluorophenyl)-*N*-phenylthiazol-2-amine (**3s**) and 4-(4-fluorophenyl)-*N*-(naphthalen-2-yl)thiazol-2-

amine (**3u**) in 70% and 68% isolated yields respectively. The slightly lower yields might be attributed to the steric hindrance of *N*-aryl substituted thioureas and electron-withdrawing property of fluorine atom. However, no expected product was isolated using cyclohexanone as a substrate (entry 22).



Scheme 2

Table 2. Synthesis of 2-aminothiazole derivatives **3**

Entry	R_1	R_2	Yield of **3** (%)[a]	Entry	R_1	R_2	Yield of **3** (%)[a]
1	C_6H_5	H	**3a** (87)	12	4-FC_6H_4	Allyl	**3l** (70)
2	4-$MeOC_6H_4$	H	**3b** (90)	13	4-$C_6H_5C_6H_4$	Allyl	**3m** (86)
3	4-$BnOC_6H_4$	H	**3c** (89)	14	2-Naph	Allyl	**3n** (81)
4	4-FC_6H_4	H	**3d** (78)	15	2-Furyl	Allyl	**3o** (83)
5	4-$C_6H_5C_6H_4$	H	**3e** (85)	16	2-Thienyl	Allyl	**3p** (85)
6	2-Naph	H	**3f** (82)	17	C_6H_5	C_6H_5	**3q** (80)
7	C_6H_5	CH_3	**3g** (85)	18	4-$MeOC_6H_4$	C_6H_5	**3r** (84)
8	2-Furyl	CH_3	**3h** (80)	19	4-FC_6H_4	C_6H_5	**3s** (70)
9	2-Thienyl	CH_3	**3i** (75)	20	C_6H_5	2-Naph	**3t** (79)
10	C_6H_5	Allyl	**3j** (85)	21	4-FC_6H_4	2-Naph	**3u** (68)
11	4-$MeOC_6H_4$	Allyl	**3k** (88)	22	Cyclohexanone		—[b]

[a]Isolated yield based on aromatic methyl ketones. [b]No expected product was obtained.

EXPERIMENTAL

All reagents were purchased from commercial suppliers and used without further purification. All solvents were of analytical grade and dried according to published methods and distilled before use. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 300 spectrometers using $CDCl_3$ as the solvent. Chemical shifts are reported relative to TMS (internal standard). Mass spectra were measured on a LCQ Advantage MAX (ESI). IR spectra were obtained as KBr pellet samples on a Nicolet 5700 FTIR spectrometer. The elemental analysis was performed by Perkin Elmer 2400. Melting points were determined on a X-4 micromelting apparatus and are uncorrected.

General procedure for the synthesis of 2-aminothiazole derivatives 3

To a solution of aromatic ketones (1.0 mmol) in EtOAc (15 mL) was added $CuBr_2$ (447 mg, 2.0 mmol) and the reaction mixture was allowed to reflux for 3–6 h until the starting material disappeared (detected

by TLC or crude ^{1}H NMR). Then thiourea/*N*-substituted thioureas (2.0 mmol) and potassium carbonate (276 mg, 2.0 mmol) was added to the mixture and heating was continued for another 5 h. After the reaction was completed, 20 mL water was added and extracted with another 30 mL EtOAc (two times). The organic layer was combined and dried over anhydrous $MgSO_4$, filtered, concentrated, and the residue was purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent to give **3**.

4-Phenylthiazol-2-amine (**3a**): Mp 149–150 °C (lit.,[12] 150–151 °C). IR (KBr) (ν_{max}, cm^{-1}): 3433, 3256, 1598, 1522, 1336, 1034, 712. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.76–7.74 (m, 2H), 7.41–7.29 (m, 3H), 6.73 (s, 1H), 5.14 (s, 2H, NH_2). ESI-MS: *m/z* 175.73 $[M+H]^+$.

4-(4-Methoxyphenyl)thiazol-2-amine (**3b**): Mp 206–207 °C (lit.,[12] 206–207 °C). IR (KBr) (ν_{max}, cm^{-1}): 3436, 3271, 1624, 1528, 1245, 1175. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70 (d, 2H, *J*=8.7 Hz), 6.92 (d, 2H, *J*=8.7 Hz), 6.58 (s, 1H), 5.30 (s, 2H, NH_2), 3.83 (s, 3H). ESI-MS: *m/z* 206.14 $[M+H]^+$.

4-(4-(Benzyloxy)phenyl)thiazol-2-amine (**3c**): Mp 162–163 °C. IR (KBr) (ν_{max}, cm^{-1}): 3419, 3110, 1604, 1493, 1239, 1034. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.70 (d, 2H, *J*=8.7 Hz), 7.46–7.32 (m, 5H), 6.98 (d, 2H, *J*=8.7 Hz), 6.59 (s, 1H), 5.09 (s, 2H), 5.01 (s, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 167.1, 158.4, 151.0, 136.9, 128.6, 128.0, 127.8, 127.5, 127.3, 114.9, 101.1, 70.0. ESI-MS: *m/z* 282.47 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; Found: C, 68.01; H, 5.04; N, 9.96.

4-(4-Fluorophenyl)thiazol-2-amine (**3d**): Mp 103–104 °C (lit.,[12] 102–103 °C). IR (KBr) (ν_{max}, cm^{-1}): 3450, 3285, 3114, 1630, 1528, 1484, 1336. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.75–7.70 (m, 2H), 7.10–7.03 (m, 2H), 6.65 (s, 1H), 5.15 (s, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 167.8, 162.6 (d, $^1J_{C\text{-}F}$=245.3 Hz), 150.2, 130.9 (d, $^4J_{C\text{-}F}$=3.3 Hz), 127.7 (d, $^3J_{C\text{-}F}$=8.0 Hz), 115.6 (d, $^2J_{C\text{-}F}$=21.5 Hz), 102.1. ESI-MS: *m/z* 194.09 $[M+H]^+$.

4-(Biphenyl-4-yl)thiazol-2-amine (**3e**)[16]: Mp 202–203 °C. IR (KBr) (ν_{max}, cm^{-1}): 3434, 3258, 1602, 1524, 1317, 1034, 751, 709. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.87–7.83 (m, 2H), 7.65–7.61 (m, 4H), 7.48–7.32 (m, 3H), 6.78 (s, 1H), 5.06 (s, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 167.2, 150.8, 140.7, 140.5, 133.5, 128.8, 127.3, 127.0, 126.4, 102.9. ESI-MS: *m/z* 253.06 $[M+H]^+$.

4-(Naphthalen-2-yl)thiazol-2-amine (**3f**): Mp 150–151 °C (lit.,[13] 153–154 °C). IR (KBr) (ν_{max}, cm^{-1}): 3432, 3258, 1602, 1524, 1317. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.31 (s, 1H), 7.90–7.80 (m, 4H), 7.50–7.43 (m, 2H), 6.86 (s, 1H), 5.21 (s, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 167.3, 151.2, 133.6, 133.0, 131.8, 128.3, 128.2, 127.6, 126.2, 125.9, 125.0, 123.9, 103.4. ESI-MS: *m/z* 226.60 $[M+H]^+$.

***N*-Methyl-4-phenylthiazol-2-amine** (**3g**): Mp 125–126 °C (lit.,[13] 136–137 °C). IR (KBr) (ν_{max}, cm^{-1}): 3447, 3209, 1596, 1449, 1398, 1329. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.81–7.78 (m, 2H), 7.41-7.31 (m, 3H), 6.71 (s, 1H), 5.74 (s, 1H, NH), 2.99 (d, 3H, *J*=4.2 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C:171.6, 151.6, 135.1, 128.4, 127.6, 126.0, 100.3, 32.1. ESI-MS: *m/z* 190.71 $[M+H]^+$.

***N*-Methyl-4-(furan-2-yl)thiazol-2-amine** (**3h**): Mp 103–104 °C. IR (KBr) (ν_{max}, cm^{-1}): 3207, 3117, 1572,

1449. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.40 (dd, 1H, J_1=1.8 Hz, J_2=0.6 Hz), 6.68 (s, 1H), 6.63 (dd, 1H, J_1=3.3 Hz, J_2=0.6 Hz), 6.44 (dd, 1H, J_1=3.3 Hz, J_2=1.8 Hz), 5.86 (s, 1H, NH), 3.00 (d, 3H, J=4.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 172.0, 150.5, 143.0, 141.7, 111.3, 106.1, 100.0, 32.4. ESI-MS: *m/z* 180.71 $[M+H]^+$. Anal. Calcd for $C_8H_8N_2OS$: C, 53.31; H, 4.47; N, 15.54; Found: C, 53.26; H, 4.51; N, 15.58.

***N*-Methyl-4-(thiophen-2-yl)thiazol-2-amine** (**3i**)[20]: Mp 108–109 °C. IR (KBr) (ν_{max}, cm^{-1}): 3450, 3213, 3104, 1588, 1399, 1287. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.33 (dd, 1H, J_1=3.3 Hz, J_2=1.2 Hz), 7.21 (dd, 1H, J_1=5.4 Hz, J_2=1.2 Hz), 7.02 (dd, 1H, J_1=5.4 Hz, J_2=3.3 Hz), 6.60 (s, 1H), 6.07 (s, 1H, NH), 2.96 (d, 3H, J=4.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 171.5, 145.9, 138.9, 127.4, 124.3, 123.3, 99.3, 32.3. ESI-MS: *m/z* 196.76 $[M+H]^+$.

***N*-Allyl-4-phenylthiazol-2-amine** (**3j**): Mp 72–73 °C (lit.,[13] 73 °C). IR (KBr) (ν_{max}, cm^{-1}): 3449, 3194, 2966, 1581, 1416, 1321, 915, 702. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.81–7.77 (m, 2H), 7.40–7.28 (m, 3H), 6.71 (s, 1H), 6.00–5.87 (m, 1H), 5.61 (s, 1H, NH), 5.37–5.30 (m, 1H), 5.24–5.19 (m, 1H), 3.9 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 170.1, 151.3, 134.9, 133.5, 128.4, 127.5, 126.0, 116.9, 100.6, 48.2. ESI-MS: *m/z* 216.50 $[M+H]^+$.

***N*-Allyl-4-(4-methoxyphenyl)thiazol-2-amine** (**3k**): Mp 89–90 °C. IR (KBr) (ν_{max}, cm^{-1}): 3221, 2954, 1573, 1414, 1328, 1236, 1021. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.72 (d, 2H, J=9.0 Hz), 6.90 (d, 2H, J=9.0 Hz), 6.57 (s, 1H), 5.96–5.86 (m, 1H), 5.67 (s, 1H, NH), 5.36–5.29 (m, 1H), 5.22–5.18 (m, 1H), 3.91 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 170.0, 159.0, 150.9, 133.5, 127.8, 127.1, 116.7, 113.7, 98.7, 55.1, 48.1. ESI-MS: *m/z* 246.76 $[M+H]^+$. Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37; Found: C, 63.34; H, 5.80; N, 11.42.

***N*-Allyl-4-(4-fluorophenyl)thiazol-2-amine** (**3l**): Mp 75–76 °C. IR (KBr) (ν_{max}, cm^{-1}): 3216, 3087, 2968, 2878, 1574, 1489, 1325, 1225. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.77–7.73 (m, 2H), 7.08–7.03 (m, 2H), 6.63 (s, 1H), 6.00–5.87 (m, 1H), 5.57 (s, 1H, NH), 5.37–5.30 (m, 1H), 5.24–5.19 (m, 1H), 3.94 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 170.1, 162.3 (d, $^{1}J_{C\text{-}F}$=245.1 Hz), 150.2, 133.3 (d, $^{4}J_{C\text{-}F}$=3.2 Hz), 131.1, 127.6 (d, $^{3}J_{C\text{-}F}$=8.0 Hz), 116.9, 115.2 (d, $^{2}J_{C\text{-}F}$=21.4 Hz), 100.2, 48.2. ESI-MS: *m/z* 234.85 $[M+H]^+$. Anal. Calcd for $C_{12}H_{11}FN_2S$: C, 61.52; H, 4.73; N, 11.96; Found: C, 61.47; H, 4.79; N, 12.04.

***N*-Allyl-4-(biphenyl-4-yl)thiazol-2-amine** (**3m**): Mp 134–135 °C. IR (KBr) (ν_{max}, cm^{-1}): 3209, 3111, 2969, 2887, 1588, 1410, 1323, 1123. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.86 (d, 2H, J=8.7 Hz), 7.64–7.60 (m, 4H), 7.47–7.41 (m, 2H), 7.37–7.31 (m, 1H), 6.75 (s, 1H), 6.00–5.88 (m, 1H), 5.70 (s, 1H, NH), 5.38–5.30 (m, 1H), 5.24–5.19 (m, 1H), 3.94 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 169.8, 151.0, 140.7, 140.2, 133.9, 133.5, 128.7, 127.2, 127.1, 126.9, 126.4, 117.1, 100.9, 48.4. ESI-MS: *m/z* 293.61 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92; Found: C, 68.01; H, 5.06; N, 9.98.

***N*-Allyl-4-(naphthalen-2-yl)thiazol-2-amine** (**3n**): Mp 120–121 °C. IR (KBr) (ν_{max}, cm^{-1}): 3413, 3196, 3087, 2966, 1580, 1418, 1354, 1290, 1233. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.33 (s, 1H), 7.90–7.80 (m,

4H), 7.50–7.42 (m, 2H), 6.84 (s, 1H), 6.00–5.90 (m, 1H), 5.62 (s, 1H, NH), 5.40–5.21 (m, 2H), 3.98 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 169.8, 151.2, 133.6, 133.4, 132.9, 132.0, 128.3, 128.1, 127.6, 126.2, 125.8, 124.9, 124.0, 117.2, 101.5, 48.3. ESI-MS: *m/z* 266.90 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52; Found: C, 72.10; H, 5.36; N, 10.58.

***N*-Allyl-4-(furan-2-yl)thiazol-2-amine** (**3o**): Mp 81–83 °C (lit.,[17] 104 °C). IR (KBr) (ν_{max}, cm^{-1}): 3443, 3210, 3004, 1548, 1451, 1195, 1073, 1003, 935. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.39 (dd, 1H, J_1=1.8 Hz, J_2=0.6 Hz), 6.78 (s, 1H), 6.63 (dd, 1H, J_1=3.3 Hz, J_2=0.6 Hz), 6.43 (dd, 1H, J_1=3.3 Hz, J_2=1.8 Hz), 5.99–5.86 (m, 1H), 5.61 (s, 1H, NH), 5.37–5.30 (m, 1H), 5.24–5.19 (m, 1H), 3.93 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 170.5, 150.5, 142.8, 141.7, 133.4, 117.1, 111.3, 106.2, 100.3, 48.4; IR (KBr) 3439, 3209, 3006, 1548, 1509, 1452, 1415, 1316, 1196, 1074, 1003 cm^{-1}; ESI-MS: *m/z* 206.69 $[M+H]^+$.

***N*-Allyl-4-(thiophen-2-yl)thiazol-2-amine** (**3p**): Mp 49–50 °C. IR (KBr) (ν_{max}, cm^{-1}): 3410, 3214, 2968, 1542, 1580, 1415, 1356, 1294, 1220. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.33 (dd, 1H, J_1=3.6 Hz, J_2=0.9 Hz), 7.20 (dd, 1H, J_1=5.1 Hz, J_2=0.9 Hz), 7.01 (dd, 1H, J_1=5.1 Hz, J_2=3.6 Hz), 6.59 (s, 1H), 5.98–5.84 (m, 1H), 5.64 (s, 1H, NH), 5.36–5.28 (m, 1H), 5.23–5.18 (m, 1H), 3.88 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 170.0, 145.5, 138.8, 133.2, 127.4, 124.2, 123.3, 116.9, 99.5, 48.2. ESI-MS: *m/z* 222.70 $[M+H]^+$. Anal. Calcd for $C_{10}H_{10}N_2S_2$: C, 54.02; H, 4.53; N, 12.60; Found: C, 53.98; H, 4.56; N, 12.68.

***N*,4-Diphenylthiazol-2-amine** (**3q**): Mp 137–138 °C (lit.,[19] 135–136 °C). IR (KBr) (ν_{max}, cm^{-1}): 3448, 3228, 2951, 1605, 1583, 1467, 1423, 1310. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.87–7.83 (m, 2H), 7.68 (s, 1H), 7.43–7.28 (m, 7H), 7.09–7.03 (m, 1H), 6.83 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 165.0, 151.2, 140.3, 134.5, 129.3, 128.6, 127.8, 126.1, 122.9, 118.3, 101.6. ESI-MS: *m/z* 252.82 $[M+H]^+$.

4-(4-Methoxyphenyl)-*N*-phenylthiazol-2-amine (**3r**): Mp 139–141 °C (lit.,[19] 138–139 °C). IR (KBr) (ν_{max}, cm^{-1}): 3448, 3348, 1601, 1555, 1474, 1238, 743, 685. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.78 (d, 2H, *J*=9.0 Hz), 7.38–7.34 (m, 4H), 7.08–7.04 (m, 1H), 6.92 (d, 2H, *J*=9.0 Hz), 6.68 (s, 1H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 164.7, 159.4, 151.0, 140.4, 129.3, 127.5, 127.4, 122.8, 118.2, 113.9, 99.9, 55.2. ESI-MS: *m/z* 282.93 $[M+H]^+$.

4-(4-Fluorophenyl)-*N*-phenylthiazol-2-amine (**3s**): Mp 132–133 °C (lit.,[19] 110–111 °C). IR (KBr) (ν_{max}, cm^{-1}): 3436, 1604, 1560, 1489, 1412, 1307, 1225, 837, 741, 688. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.84–7.79 (m, 2H), 7.65 (s, 1H, NH), 7.37–7.34 (m, 4H), 7.10–7.04 (m, 3H), 6.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 165.3, 162.5 (d, $^1J_{C\text{-}F}$=245.6 Hz), 150.2, 140.2, 130.7 (d, $^4J_{C\text{-}F}$=3.2 Hz), 129.3, 127.8 (d, $^3J_{C\text{-}F}$=8.1 Hz), 123.1, 118.4, 115.4 (d, $^2J_{C\text{-}F}$=21.5 Hz), 101.1. ESI-MS: *m/z* 270.91 $[M+H]^+$.

***N*-(Naphthalen-2-yl)-4-phenylthiazol-2-amine** (**3t**): Mp 125–126 °C IR (KBr) (ν_{max}, cm^{-1}): 3393, 3182, 3119, 3055, 2932, 1591, 1552, 1502, 1338, 1278, 1173, 1068; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.91–7.88 (m, 3H), 7.78–7.73 (m, 3H), 7.47–7.25 (m, 6H), 6.87 (s, 1H), NH not observed. ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.56 (s, 1H, NH), 8.54 (s, 1H), 8.02 (d, 2H, *J*=7.3 Hz), 7.90–7.82 (m, 3H), 7.66–7.62 (m,

1H), 7.51–7.35 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 164.7, 151.2, 137.7, 134.5, 134.1, 129.9, 129.3, 128.7, 128.0, 127.6, 127.1, 126.7, 126.2, 124.5, 119.4, 113.4, 101.9. ESI-MS: *m/z* 303.86 $[M+H]^+$. Anal. Calcd for $C_{19}H_{14}N_2S$: C, 75.47; H, 4.67; N, 9.26; Found: C, 75.41; H, 4.52; N, 9.30.

4-(4-Fluorophenyl)-*N*-(naphthalen-2-yl)thiazol-2-amine (**3u**): Mp 149–150 ^{o}C IR (KBr) (ν_{max}, cm^{-1}): 3441, 3059, 2939, 1575, 1494, 1437, 1312, 1223, 1154, 1062. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.95–7.78 (m, 6H), 7.49–7.35 (m, 3H), 7.14–7.07 (m, 2H), 6.80 (s, 1H), NH not observed. ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.54 (s, 1H, NH), 8.51 (s, 1H), 8.06–8.01 (m, 2H), 7.89–7.82 (m, 3H), 7.72–7.27 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 164.5, 162.6 (d, $^1J_{C\text{-}F}$=245.8 Hz), 150.1, 137.5, 134.1, 130.6 (d, $^4J_{C\text{-}F}$=3.2 Hz), 130.0, 129.4, 127.8 (d, $^3J_{C\text{-}F}$=8.1 Hz), 127.7, 127.1, 126.8, 124.7, 119.4, 115.6 (d, $^2J_{C\text{-}F}$=21.5 Hz), 113.5, 101.5. ESI-MS: *m/z* 320.99 $[M+H]^+$. Anal. Calcd for $C_{19}H_{13}FN_2S$: C, 71.23; H, 4.09; N, 8.74; Found: C, 71.19; H, 4.14; N, 8.80.

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