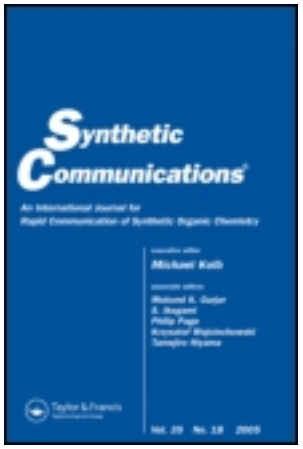

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A FACILE SYNTHESIS OF 1,3-THIAZOLE-4-SULFONYL CHLORIDES

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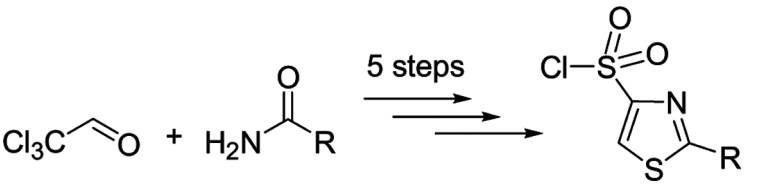
GRAPHICAL ABSTRACT



Abstract *A four-step preparative-scale synthesis of eight 2-alkyl- and arylsubstituted thiazole-4-sulfonyl chlorides from chloralamides is reported. Good yields and easy availability of starting materials are valuable advantages of the procedure that gives access to formerly unattainable building blocks.*

Keywords Chloralamides; sulfonyl chlorides; thiazole

INTRODUCTION

The thiazole structural unit is found in many natural products and synthetic compounds with a broad spectrum of biological activities.[1–3] In this context the development of reliable methods for preparation of building blocks with the thiazole scaffold is of significance in drug discovery and agrochemistry. Integration of the thiazole subunit into biologically potent species is most frequently carried out by acylation of 2-amino-1,3-thiazoles.[3] Alternative methods for introduction of the thiazole fragment include the use of halogenated thiazoles and thiazole acyl- or sulfonyl chlorides.[4] The latter are especially useful synthetic building blocks because a biologically relevant sulfo-group is introduced along with the valuable thiazole fragment. There are many reports on the preparation and the use of diverse thiazole-2- and 5-sulfonyl chlorides in the synthesis of pharmacologically active compounds,[4]

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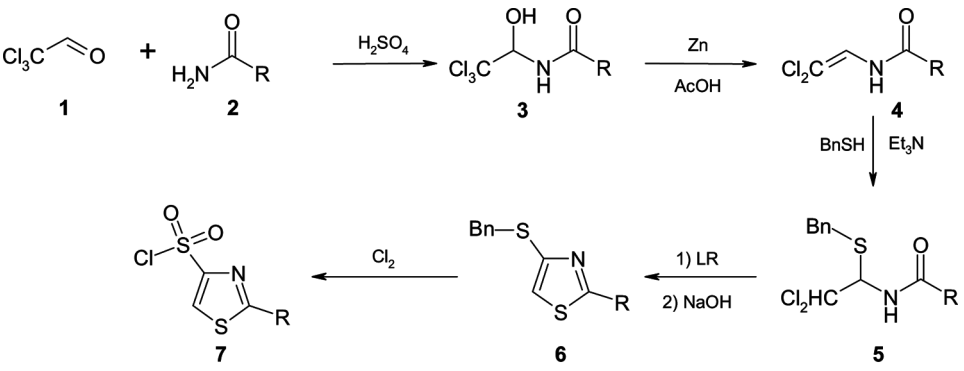
whereas, to our knowledge, there are only two articles describing thiazole-4-sulfonyl chlorides.[5,6] In both reports, the thiazole-4-sulfonyl chlorides were prepared by sulfonylation of 2,5-substituted thiazole derivatives. Presently no suitable procedure allowing a straightforward preparation of parent or monosubstituted thiazole-4-sulfonyl chlorides is available. Given the potential of thiazole sulfonyl chlorides in high-throughput synthesis of screening compounds for early drug discovery programs, it seems important to have access to all of their isomeric forms. In this work, we describe a simple and efficient synthetic route to 2-substituted thiazole-4-sulfonyl chlorides.

RESULTS AND DISCUSSION

The synthetic route to thiazole-4-sulfonyl chlorides is outlined in Scheme 1. Starting chloralamides **3** were prepared in nearly quantitative yields from chloral **1** and amides **2** by the classical procedure of Jacobsen.[7] The chloralamides were efficiently transformed into *N*-(2,2,-dichlorovinyl)amides **4**.[8] Compounds **4** are known to undergo the addition reaction with alkylamines[9] and thiophenoles.[10] By analogy with the latter procedure, we carried out reactions of **4** with benzyl thiol. Compounds **4** were reactive enough to allow the addition of benzyl thiol under mild basic conditions, giving rise to amidosulfides **5**. Thionation of compounds **5** with 2,4-bis(4-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide (so-called Lawesson reagent)[11] followed by in situ treatment of thioamide intermediates with sodium hydroxide resulted in thiazole-4-benzylsulfides **6**. Notably, the latter reaction step is a completely new approach to functionalized thiazoles.[12] The oxidative cleavage



a R = Me **d** R = 4-$CH_3C_6H_4$ **g** R = 3-BrC_6H_4

b R = Ph **e** R = 4-FC_6H_4 **h** R = 4-BrC_6H_4

c R = 3-$CH_3C_6H_4$ **f** R = 4-ClC_6H_4

Scheme 1. Preparation of 2-substituted thiazole-4-sulfonyl chlorides (LR stands for Lawesson reagent).

of sulfides **6** with chlorine[13] gave rise to corresponding thiazole-4-sulfonyl chlorides in good to excellent yields.

CONCLUSIONS

The described approach allows a straightforward preparation of hitherto unavailable thiazole-4-sulfonyl chlorides bearing 2-alkyl or aryl substituent. The prepared sulfonyl chlorides are promising building blocks for medicinal chemistry and high-throughput synthesis of screening compounds.

EXPERIMENTAL

^{1}H (500-MHz) and ^{13}C (125-MHz) NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer in DMSO-d_6 solution with tetramethylsilane (TMS) as an internal standard. Melting points were measured with a Büchi melting-point apparatus and are uncorrected. Elemental analysis was carried out by the Analytical Laboratory of Institute of Bioorganic Chemistry and Petrochemistry of National Academy of Sciences of Ukraine (NAS). Preparation and characterization of compounds **3a**;[7] **3b, 3d, 3f;**[14] **3c**;[15] **3h**;[16] **4a**;[17] **4b, 4d, 4e**;[14] and **4f**[18] are available from the literature.

Preparation of Compounds 3e and 3g

General procedure. A stirred mixture of amide (0.2 mol), chloral (21.5 mL, 0.22 mol), and concentrated sulfuric acid (1 mL) was heated at 100–110 °C for 1 h. The reaction mixture crystallized upon cooling. The mixture was triturated with deionized water, filtered, washed with a large amount of water, and recrystallized from ethanol.

***N*-(2,2,2-Trichloro-1-hydroxyethyl)-4-fluorobenzamide (3e).** Prepared from 27.8 g of **2e**. Yield 52.7 g (92%). Colorless crystals; mp 130–131 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 6.03$ (d, $^3J_{HH} = 9$ Hz, 1 H, CH), 7.32 (t, $^3J_{HH} = 9$ Hz, 2 H, ArH), 7.87 (b.s., 1 H, NH), 7.98–8.01 (m, 2 H, ArH), 9.17 (d, $^3J_{HH} = 9$ Hz, 1 H, OH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 81.92$, 103.08, 115.61, 115.78, 130.36, 131.12, 131.20, 163.74, 165.73, 166.25. ^{19}F NMR (470 MHz, DMSO-d_6): $\delta = -54.13$. Calcd (%) for $C_9H_7Cl_3FNO_2$: C, 37.73; H, 2.46; Cl, 37.12; N, 4.89. Found: C, 37.66; H, 2.51; Cl, 36.96; N, 4.82.

***N*-(2,2,2-Trichloro-1-hydroxyethyl)-3-bromobenzamide (3g).** Prepared from 40 g of **2g**. Yield 65.3 g (94%). Colorless crystals; mp 145–146 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 6.03$ (d, $^3J_{HH} = 8.5$ Hz, 1 H, CH), 7.46 (t, $^3J_{HH} = 9$ Hz, 1 H, ArH), 7.78 (d, 7.87 $^3J_{HH} = 9$ Hz, 1 H, ArH), 7.90 (m, 2 H, ArH, NH), 8.10 (s, 1 H, ArH), 9.33 (d, $^3J_{HH} = 8.5$ Hz, 1 H, OH). ^{13}C NMR (125 MHz, DMSO-d_6): 81.94, 102.92, 122.04, 127.56, 130.96, 131.02, 135.07, 136.05, 165.92. Calcd. (%) for $C_9H_7BrCl_3NO_2$: C, 31.11; H, 2.03; Br, 23.00; Cl, 30.61; N, 4.03. Found: C, 31.20; H, 2.09; Br, 23.05; Cl, 30.76; N, 3.98.

Preparation of Compounds 4e, 4g, and 4h

General procedure. Zinc dust (13.1 g, 0.2 mol) was gradually added to a stirred suspension of **3** (0.1 mol) in glacial acetic acid (50 mL) over a period of 3 h. During the zinc addition the temperature of the reaction mixture was kept below 40 °C. The reaction mixture was then stirred at room temperature for 24 h. Then the precipitated zinc salt was filtered off and washed with glacial acetic acid. The acetic acid was removed under reduced pressure. The solid residue was triturated with deionized water and recrystallized.

***N*-(2,2-Dichloroethenyl)-3-methylbenzamide (4e).** Prepared from 28.2 g of **3c** and recrystallized from *n*-hexane. Yield 12.6 g (55%). Colorless crystals; mp 57–58°C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.39$ (s, 3 H, CH_3), 7.40–7.43 (m, 3 H, CH, ArH), 7.69–7.73 (m, 2 H, ArH), 10.02 (d, $^3J_{HH} = 9$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.34$, 106.79, 124.14, 125.89, 128.73, 129.13, 132.96, 133.38, 138.19, 165.52. Calcd. (%) for $C_{10}H_9Cl_2NO$: C, 52.20; H, 3.94; Cl, 30.82; N, 6.09. Found: C, 52.12; H, 4.02; Cl, 30.86; N, 6.02.

***N*-(2,2-Dichloroethenyl)-3-bromobenzamide (4g).** Prepared from 34.7 g of **3g** and recrystallized from 2-propanol. Yield 23.6 g (80%). Colorless crystals; mp 92–93 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.41$ (d, $^3J_{HH} = 9$ Hz, 1 H, CH), 7.49 (t, $^3J_{HH} = 7.5$ Hz, 1 H, ArH), 7.82 (d, $^3J_{HH} = 7.5$ Hz, 1 H, ArH), 7.89 (d, $^3J_{HH} = 7.5$ Hz, 1 H, ArH), 10.25 (d, $^3J_{HH} = 9$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 107.51$, 122.00, 124.01, 127.92, 131.03, 131.28, 135.19, 135.45, 164.17. Calcd. (%) for $C_9H_6BrCl_2NO$: C, 36.65; H, 2.05; Br, 27.09; Cl, 24.04; N, 4.75. Found: C, 36.60; H, 2.02; Br, 27.12; Cl, 24.16; N, 4.68.

***N*-(2,2-Dichloroethenyl)-4-bromobenzamide (4h).** Prepared from 34.7 g of **3h** and recrystallized from 2-propanol. Yield 21 g (72%). Colorless crystals; mp 113–114 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.41$ (d, $^3J_{HH} = 9$ Hz, 1 H, CH), 7.73 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH), 7.86 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH), 10.17 (d, $^3J_{HH} = 9$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 107.30$, 124.04, 126.66, 130.83, 131.86, 132.11, 164.67. Calcd. (%) for $C_9H_6BrCl_2FNO$: C, 36.65; H, 2.05; Br, 27.09; Cl, 24.04; N, 4.75. Found: C, 36.58; H, 1.98; Br, 27.16; Cl, 24.16; N, 4.67.

Preparation of Compounds 5

General procedure. Benzylthiol (1.2 mL, 0.01 mol) and triethylamine (1.4 mL, 0.01 mol) were added to a stirred solution of compound **4** (0.01 mol) in 2-propanol (50 mL). The reaction mixture was stirred at room temperature for 48 h. Then the solvent was removed under reduced pressure and the residue was triturated with water, resulting in a crystalline solid. The crude product was purified by recrystallization from either 2-propanol or ethanol.

***N*-(1-Benzylsulfanyl-2,2-dichloroethyl)acetamide (5a).** Prepared from 1.54 g of **4a**. Yield 2.25 g (81%). Colorless crystals; mp 108–109 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 1.94$ (s, 3 H, CH_3), 3.83 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 3.91 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 5.41 (dd, $^3J_{HH} = 3$ Hz, $^3J_{HH} = 9.5$ Hz, 1 H,

CH), 6.41 (d, $^3J_{HH} = 3$ Hz, 1 H, CH), 7.25–7.33 (m, 5 H, ArH), 8.71 (d, $^3J_{HH} = 9.5$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 22.78$, 35.12, 60.83, 75.30, 127.57, 128.92, 129.34, 138.23, 170.17. Calcd. (%) for $C_{11}H_{13}Cl_2NOS$: C, 47.49; H, 4.71; Cl, 25.49; N, 5.03; S, 11.53. Found: C, 47.51; H, 4.76; Cl, 25.38; N, 4.96; S, 11.67.

***N*-(1-Benzylsulfanyl-2,2-dichloroethyl)benzamide (5b).** Prepared from 2 g of **4b**. Yield 2.24 g (66%). Colorless crystals; mp 118–120 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.96$ (d, $^3J_{HH} = 13.5$ Hz, 1 H, CH_2), 4.06 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 5.80 (d, $^2J_{HH} = 9$ Hz, 1 H, CH), 6.73 (d, $^2J_{HH} = 9$ Hz, 1 H, CH), 7.27–7.65 (m, 10 H, ArH), 8.23 (d, $J = 9$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 35.52$, 62.06, 75.00, 127.60, 128.28, 128.78, 128.94, 129.39, 132.31, 133.79, 138.14, 167.06. Calcd. (%) for $C_{16}H_{15}Cl_2NOS$: C, 56.48; H, 4.44; Cl, 20.84; N, 4.12; S, 9.42. Found: C, 56.55; H, 4.33; Cl, 20.76; N, 4.09; S, 9.36.

***N*-(1-Benzylsulfanyl-2,2-dichloroethyl)-3-methylbenzamide (5c).** Prepared from 2.30 g of **4c**. Yield 2.90 g (82%). Colorless crystals; mp 87–89 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.38$ (s, 3 H, CH_3), 3.91 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 3.98 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 5.60 (dd, $^3J_{HH} = 4.5$ Hz, $^3J_{HH} = 9$ Hz, 1 H, CH), 6.44 (d, $^3J_{HH} = 4.5$ Hz, 1 H, CH), 7.23–7.71 (m, 9 H, ArH), 9.13 (d, $^3J_{HH} = 9$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.38$, 35.50, 62.03, 74.99, 125.44, 127.58, 128.68, 128.72, 128.93, 129.38, 132.85, 133.75, 138.09, 138.17, 167.12. Calcd. (%) for $C_{17}H_{17}Cl_2NOS$: C, 57.63; H, 4.84; Cl, 20.01; N, 3.95; S, 9.05. Found: C, 57.66; H, 4.82; Cl, 19.96; N, 3.93; S, 9.12.

***N*-(1-Benzylsulfanyl-2,2-dichloroethyl)-4-methylbenzamide (5d).** Prepared from 2.30 g of **4d**. Yield 2.37 g (67%). Colorless crystals; mp 107–108 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.39$ (s, 3 H, CH_3), 3.91 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 3.98 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 5.56 (dd, $^3J_{HH} = 4.5$ Hz, $^3J_{HH} = 9$ Hz, 1 H, CH), 6.28 (d, $^3J_{HH} = 4.5$ Hz, 1 H, CH), 7.21–7.80 (m, 9 H, ArH), 8.96 (d, $^3J_{HH} = 9$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.52$, 35.52, 62.08, 75.01, 127.58, 128.31, 128.93, 129.31, 129.38, 130.96, 138.15, 142.34, 166.86. Calcd. (%) for $C_{17}H_{17}Cl_2NOS$: C, 57.63; H, 4.84; Cl, 20.01; N, 3.95; S, 9.05. Found: C, 57.56; H, 4.90; Cl, 19.99; N, 4.21; S, 9.40.

***N*-(1-Benzylsulfanyl-2,2-dichloroethyl)-4-fluorobenzamide (5e).** Prepared from 2.34 g of **4e**. Yield 3.33 g (93%). Colorless crystals; mp 92–93 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.92$ (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 3.98 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 5.59 (dd, $^3J_{HH} = 5$ Hz, $^3J_{HH} = 9$ Hz, 1 H, CH), 6.45 (d, $J = 5$ Hz, 1 H, CH), 7.24-7.98 (m, 9 H, ArH), 9.23 (d, $J = 9$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 35.52$, 62.11, 74.99, 115.64, 115.81, 127.58, 128.92, 129.37, 130.22, 131.00, 131.08, 138.13, 163.72, 165.70, 166.00. ^{19}F NMR (470 MHz, DMSO-d_6): $\delta = -54.18$. Calcd. (%) for $C_{16}H_{14}Cl_2FNOS$: C, 53.64; H, 3.94; Cl, 19.79; N, 3.91; S, 8.95. Found: C, 53.72; H, 4.02; Cl, 19.73; N, 3.82; S, 8.79.

***N*-(1-Benzylsulfanyl-2,2-dichloroethyl)-4-chlorobenzamide (5f).** Prepared from 2.50 g of **4f**. Yield 2.92 g (78%). Colorless crystals; mp 114–115 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.92$ (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 4.02 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 5.73 (dd, $^3J_{HH} = 2.5$ Hz, $^3J_{HH} = 9$ Hz, 1 H, CH), 5.95

(d, $^3J_{HH} = 2.5$ Hz, 1 H, CH), 6.59 (d, $^3J_{HH} = 9$ Hz, 1 H, NH), 7.23-7.70 (m, 9 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 35.54$, 62.11, 74.96, 127.59, 128.86, 128.92, 129.37, 130.24, 132.50, 137.16, 138.10, 166.08. Calcd. (%) for $C_{16}H_{14}Cl_3NOS$: C, 51.29; H, 3.77; Cl, 28.38; N, 3.74; S, 8.56. Found: C, 51.23; H, 3.72; Cl, 28.42; N, 3.69; S, 8.73.

***N*-(1-Benzylsulfanyl-2,2-dichloroethyl)-3-bromobenzamide (5g).** Prepared from 2.95 g of **4g**. Yield 4.02 g (96%). Colorless crystals; mp 81–83 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.99$ (m, 2 H, CH_2), 5.61 (m, 1 H, CH), 6.42 (d, $^3J_{HH} = 5$ Hz, 1 H, CH), 7.25–7.88 (m, 8 H, ArH) 8.04 (s, 1 H, ArH), 9.23 (s, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 35.50$, 62.10, 74.93, 122.03, 127.50, 127.58, 128.92, 129.36, 130.87, 131.03, 135.00, 135.88, 138.14, 165.63. Calcd. (%) for $C_{16}H_{14}BrCl_2NOS$: C, 45.85; H, 3.37; Br, 19.09; Cl, 16.92; N, 3.34; S, 7.65. Found: C, 45.88; H, 3.44; Br, 19.03; Cl, 17.12; N, 3.28; S, 7.73.

***N*-(1-Benzylsulfanyl-2,2-dichloroethyl)-4-bromobenzamide (5h).** Prepared from 2.95 g of **4h**. Yield 3.56 g (85%). Colorless crystals; mp 120–121 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.93$ (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 3.99 (d, $^2J_{HH} = 13.5$ Hz, 1 H, CH_2), 5.59 (dd, $^3J_{HH} = 5$ Hz, $^3J_{HH} = 9$ Hz, 1 H, CH), 6.46 (d, $^3J_{HH} = 5$ Hz, 1 H, CH), 7.23–7.37 (m, 5 H, ArH) 7.72 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH), 7.83 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH), 9.31 (d, $^3J_{HH} = 9$ Hz, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 35.55$, 62.12, 74.95, 126.10, 127.59, 128.92, 129.36, 130.40, 131.80, 132.90, 138.10, 166.21. Calcd. (%) for $C_{16}H_{14}BrCl_2NOS$: C, 45.85; H, 3.37; Br, 19.09; Cl, 16.92; N, 3.34; S, 7.65. Found: C, 45.74; H, 3.41; Br, 19.12; Cl, 17.03; N, 3.26; S, 7.71.

Preparation of Compounds 6

General procedure. Lawesson reagent (2.22 g, 5.5 mmol) was added to a stirred solution of compound **5** (5 mmol) in 1,4-dioxane (30 mL). The reaction mixture was refluxed for 8 h, and then the solvent was removed under reduced pressure. The residue was triturated with 10% aqueous NaOH, adjusting to pH 9. The raw product was filtered, dried, and recrystallized from 2-propanol. Liquid products were extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated, and the product was purified by distillation in vacuo for **6a**.

4-Benzylsulfanyl-2-methyl-1,3-thiazole (6a). Prepared from 13.91 g of **5a**. Yield 8.63 g (78%). Colorless liquid; bp 146–148 °C (5 mbar). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.59$ (s, 3 H, CH_3), 4.04 (s, 2 H, CH_2), 7.20–7.33 (m, 5 H, ArH), 7.44 (s, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.71$, 43.25, 127.50, 128.47, 128.55, 129.00, 137.17, 148.06, 170.21. Calcd. (%) for $C_{11}H_{11}NS_2$: C, 59.69; H, 5.07; N, 6.33; S, 28.97. Found: C, 59.71; H, 5.07; N, 6.27; S, 29.03.

4-Benzylsulfanyl-2-phenyl-1,3-thiazole (6b). Prepared from 1.70 g of **5b**. Yield 1.12 g (79%). Colorless crystals; mp 54–55 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.08$ (s, 2 H, CH_2), 7.21–7.84 (m, 10 H, ArH), 7.61 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 42.37$, 126.50, 127.87, 128.91, 129.49, 129.75, 131.06, 133.29, 137.67, 148.95, 170.56. Calcd. (%) for $C_{16}H_{13}NS_2$: C, 67.81; H, 4.62; N, 4.94; S, 22.63. Found: C, 67.61; H, 4.72; N, 5.33; S, 22.28.

4-Benzylsulfanyl-2-(3-methylphenyl)-1,3-thiazole (6c). Prepared from 1.77 g of **5c**. Yield 1.15 g (77%). Yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.36$ (s, 3 H, CH_3), 4.13 (s, 2 H, CH_2), 7.24–7.32 (m, 6 H, ArH), 7.36 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.64 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.68 (s, 1 H, ArH), 7.70 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.36$, 42.43, 123.75, 126.91, 127.85, 128.89, 129.28, 129.46, 129.59, 131.71, 133.29, 137.66, 139.10, 148.90, 170.75. Calcd. (%) for $C_{17}H_{15}NS_2$: C, 68.65; H, 5.08; N, 4.71; S, 21.56. Found: C, 68.61; H, 5.10; N, 4.67; S, 21.60.

4-Benzylsulfanyl-2-(4-methylphenyl)-1,3-thiazole (6d). Prepared from 1.77 g of **5d**. Yield 1.31 g (88%). Colorless crystals; mp 84–85 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.36$ (s, 3 H, CH_3), 4.07 (s, 2 H, CH_2), 7.21–7.78 (m, 9 H, ArH), 7.95 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.46$, 42.38, 126.44, 127.85, 128.90, 129.09, 129.48, 130.28, 130.74, 137.71, 141.01, 148.89, 170.77. Calcd. (%) for $C_{17}H_{15}NS_2$: C, 68.65; H, 5.08; N, 4.71; S, 21.56. Found: C, 68.66; H, 5.11; N, 4.69; S, 21.63.

4-Benzylsulfanyl-2-(4-fluorophenyl)-1,3-thiazole (6e). Prepared from 1.79 g of **5e**. Yield 1.07 g (71%). Colorless crystals; mp 85–87 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.14$ (s, 2 H, CH_2), 7.24–7.92 (m, 9 H, ArH), 7.70 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 42.34$, 116.74, 116.91, 127.88, 127.88, 128.79, 128.92, 129.48, 129.93, 129.96, 137.66, 148.95, 162.86, 164.84, 169.34. ^{19}F NMR (470 MHz, DMSO-d_6): $\delta = -55.69$. Calcd. (%) for $C_{16}H_{12}FNS_2$: C, 63.76; H, 4.01; N, 4.65; S, 21.28. Found: C, 63.67; H, 3.98; N, 4.57; S, 21.34.

4-Benzylsulfanyl-2-(4-chlorophenyl)-1,3-thiazole (6f). Prepared from 1.87 g of **5f**. Yield 1.06 g (67%). Colorless crystals; mp 99–100 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.40$ (s, 2 H, CH_2), 7.21–7.42 (m, 5H, ArH), 7.41 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH), 7.58 (s, 1 H, ArH), 7.81 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 42.30$, 127.89, 128.14, 128.92, 129.48, 129.83, 130.44, 132.05, 135.64, 137.61, 148.94, 169.04. Calcd. (%) for $C_{16}H_{12}ClNS_2$: C, 60.46; H, 3.81; Cl, 11.15; N, 4.41; S, 20.17. Found: C, 60.51; H, 3.86; Cl, 11.28; N, 4.36; S, 20.19.

4-Benzylsulfanyl-2-(3-bromophenyl)-1,3-thiazole (6g). Prepared from 2.09 g of **5g**. Yield 1.41 g (78%). Colorless crystals; mp 53–54 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = ^{1}H NMR (DMSO-d_6): $\delta = 4.17$ (s, 2 H, CH_2), 7.25–7.31 (m, 5 H, ArH), 7.46 (t, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.69 (d, $^3J_{HH} = 8.5$ Hz, 1 H, ArH), 7.76 (s, 1 H, ArH), 7.84 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.02 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 42.27$, 122.99, 125.65, 127.91, 128.58, 128.94, 129.49, 130.97, 131.95, 133.64, 135.24, 137.58, 148.88, 168.35. Calcd. (%) for $C_{16}H_{12}BrNS_2$: C, 53.04; H, 3.34; Br, 22.05; N, 3.87; S, 17.70. Found: C, 53.03; H, 3.37; Br, 22.07; N, 3.85; S, 17.72.

4-Benzylsulfanyl-2-(4-bromophenyl)-1,3-thiazole (6h). Prepared from 2.09 g of **5h**. Yield 1.37 g (76%). Colorless crystals; mp 101–102 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = ^{1}H NMR (DMSO-d_6): $\delta = 4.16$ (s, 2 H, CH_2), 7.27–7.32 (m, 5 H, ArH), 7.70 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH), 7.74 (s, 1 H, ArH), 7.80 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 42.28$,

123.68, 128.53, 128.93, 129.49, 130.95, 131.44, 133.05, 135.28, 137.59, 148.90, 168.49. Calcd. (%) for $C_{16}H_{12}BrNS_2$: C, 53.04; H, 3.34; Br, 22.05; N, 3.87; S, 17.70. Found: C, 53.13; H, 3.27; Br, 22.08; N, 3.81; S, 17.63.

Preparation of 1,3-Thiazole-4-sulfonyl Chlorides (7)

General procedure. Compound **6** (5 mmol) was dissolved in a mixture of glacial acetic acid (50 mL) and deionized water (5 mL). The chlorine was bubbled slowly into the stirred reaction mixture at a temperature below 20 °C for 30 min. Then the reaction mixture was poured onto ice. The precipitated crude product was filtered, washed with water, dried in vacuum, and recrystallized from n-hexanes. In the case of liquid products, the crude product was extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated, and the product was purified by distillation in vacuo for **7a.**

2-Methyl-1,3-thiazole-4-sulfonyl chloride (7a). Prepared from 7.96 g of **6a**. Yield 2.37 g (24%). Colorless liquid; bp 75–80 °C (5 mbar). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.85$ (s, 3 H, CH_3), 8.31 (s, 1 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.86$, 126.83, 150.01, 171.54. Calcd. (%) for $C_4H_4ClNO_2S_2$: C, 24.31; H, 2.04; Cl, 17.94; N, 7.09; S, 32.44. Found: C, 24.27; H, 2.09; Cl, 18.02; N, 7.06; S, 32.38.

2-Phenyl-1,3-thiazole-4-sulfonyl chloride (7b). Prepared from 1.42 g of **6b**. Yield 0.86 g (66%). Colorless crystals; mp 89–90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.50$–8.00 (m, 5 H, ArH), 8.46 (s, 1 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 127.36$, 129.52, 131.61, 132.72, 139.23, 149.68, 176.71. Calcd. (%) for $C_9H_6ClNO_2S_2$: C, 41.62; H, 2.33; Cl, 13.65; N, 5.39; S, 24.69. Found: C, 41.58; H, 2.38; Cl, 13.70; N, 5.36; S, 24.76.

2-(3-Methylphenyl)-1,3-thiazole-4-sulfonyl chloride (7c). Prepared from 1.49 g of **6c**. Yield 0.81 g (59%). Colorless crystals; mp 74–75 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.46$ (s, 3 H, CH_3), 7.42 (m, 2 H, ArH), 7.79 (d, $^3J_{HH} = 8$ Hz, Hz, 2 H, ArH), 7.83 (s, 1 H, ArH), 8.46 (s, 1 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.34$, 124.59, 127.85, 129.40, 131.54, 133.56, 139.06, 139.51, 149.62, 177.01. Calcd. (%) for $C_{10}H_8ClNO_2S_2$: C, 43.87; H, 2.95; Cl, 12.95; N, 5.12; S, 23.42. Found: C, 43.89; H, 2.98; Cl, 12.92; N, 5.13; S, 23.45.

2-(4-Methylphenyl)-1,3-thiazole-4-sulfonyl chloride (7d). Prepared from 1.49 g of **6d**. Yield 1.08 g (79%). Colorless crystals; mp 104–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3 H, CH_3), 7.33 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH), 7.88 (d, $^3J_{HH} = 8.5$ Hz, 2 H, ArH), 8.45 (s, 1 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.69$, 127.31, 129.02, 130.19, 138.64, 143.64, 149.69, 176.97. Calcd. (%) for $C_{10}H_8ClNO_2S_2$: C, 43.87; H, 2.95; Cl, 12.95; N, 5.12; S, 23.42. Found: C, 43.91; H, 2.87; Cl, 12.91; N, 5.03; S, 23.49.

2-(4-Fluorophenyl)-1,3-thiazole-4-sulfonyl chloride (7e). Prepared from 1.51 g of **6e**. Yield 0.94 g (68%). Colorless crystals; mp 81–82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.21$–8.04 (m, 4 H, ArH), 8.46 (s, 1 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 116.74$, 116.92, 128.01, 129.62, 139.30, 149.65, 164.39, 166.42, 175.28. ^{19}F NMR (470 MHz, DMSO-d_6): $\delta = -52.04$. Calcd. (%) for

$C_9H_5ClFNO_2S_2$: C, 38.92; H, 1.80; Cl, 12.77; N, 5.04; S, 23.09. Found: C, 38.87; H, 1.86; Cl, 12.72; N, 5.04; S, 23.11.

2-(4-Chlorophenyl)-1,3-thiazole-4-sulfonyl chloride (7f). Prepared from 1.59 g of **6f**. Yield 0.98 g (67%). Colorless crystals; mp 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (d, $^3J_{HH}$ = 8.5 Hz, 2 H, ArH), 7.95 (d, $^3J_{HH}$ = 8.5 Hz, 2 H, ArH), 8.47 (s, 1 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 128.52, 129.84, 130.05, 139.04, 139.52, 149.66, 175.15. Calcd. (%) for $C_9H_5Cl_2NO_2S_2$: C, 36.75; H, 1.71; Cl, 24.10; N, 4.76; S, 21.80. Found: C, 36.71; H, 1.75; Cl, 24.12; N, 4.69; S, 21.75.

2-(3-Bromophenyl)-1,3-thiazole-4-sulfonyl chloride (7g). Prepared from 1.81 g of **6g**. Yield 1.2 g (71%). Colorless crystals; mp 95–96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (t, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.72 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.92 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 8.20 (s, 1H, ArH), 8.49 (s, 1H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 123.63, 125.88, 130.13, 130.96, 133.33, 135.48, 139.94, 149.57, 174.56. Calcd. (%) for $C_9H_5BrClNO_2S_2$: C, 31.92; H, 1.49; Br, 23.60; Cl, 10.47; N, 4.14; S, 18.94. Found: C, 31.90; H, 1.50; Br, 23.58; Cl, 10.49; N, 4.12; S, 18.91.

2-(4-Bromophenyl)-1,3-thiazole-4-sulfonyl chloride (7h). Prepared from 1.81 g of **6h**. Yield 1.42 g (84%). Colorless crystals; mp 117–119 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, $^3J_{HH}$ = 8.5 Hz, 2 H, ArH), 7.88 (d, $^3J_{HH}$ = 8.5 Hz, 2 H, ArH), 8.46 (s, 1 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 127.51, 128.62, 130.50, 132.81, 139.57, 149.66, 175.23. Calcd. (%) for $C_9H_5BrClNO_2S_2$: C, 31.92; H, 1.49; Br, 23.60; Cl, 10.47; N, 4.14; S, 18.94. Found: C, 31.87; H, 1.52; Br, 23.64; Cl, 10.42; N, 4.08; S, 18.87.

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