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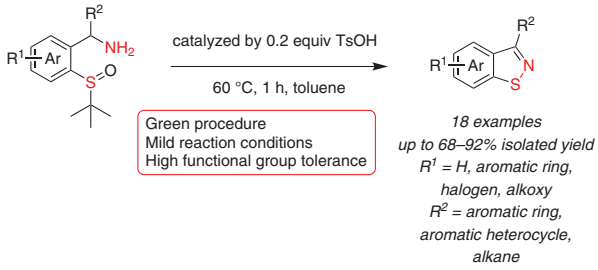
Acid-Catalyzed Synthesis of Aryl[4,5]isothiazoles through a Sulfenic Acid Pathway

Hong Yuan
Zhihua Sun*

College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, 333 Longteng Road, Shanghai 201620, P. R. of China
sungaris@gmail.com



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Abstract A new method to efficiently prepare 3-substituted aryl[4,5]isothiazoles by simply heating the starting materials with a catalytic amount of *p*-toluenesulfonic acid in toluene is reported. This simple procedure is well suitable for a variety of substrates that can tolerate substitution changes in the fusing aromatic ring, as well as at the 3-position. Substituted aryl rings of varying electronic properties and alkyl substitution eventually afford aryl[4,5]isothiazoles in high yields.

Key words 3-substituted aryl[4,5]isothiazoles, *p*-toluenesulfonic acid, fused aromatic rings, catalytic reactions, synthetic methods

The isothiazole moiety can be found in many compounds useful for biomedical research and for medical and agricultural use. For example, as shown in Figure 1, compounds **1**[1] and **2**[2] are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia; compound **3**[3] is a pesticide, and compounds **4**, **5**, and **6** are potent inhibitors of biological targets/pathways.[4] Isothiazoles represent an important class of five-membered sulfur heterocycles that are widely utilized in medicinal chemistry and organic synthesis because of their unique properties: They contain two electronegative heteroatoms in a 1,2-relationship.[5] Therefore, the development of a synthetic method for the construction of isothiazole moieties is of great research interest. Among the reported methods, there are a few that can easily manipulate the substitution at the 3-position of aryl[4,5]isothiazole. McKinnon and Lee reported a condensation method of the oximes of 2-acylthisoanisoles (Scheme 1).[6] Devarie-Baez and Xian described a procedure that proceeds through *S*-nitrosation of *o*-mercaptoacylphenones.[7] We also reported an all-heteroatom Wittig-equivalent procedure that uses *tert*-butyl sulfoxide as the sulfinyl source.[8] In continuing our investigation for the synthesis of 3-substituted aryl[4,5]isothiazoles, here we report a new procedure that avoids the use of NBS as activating reagent.

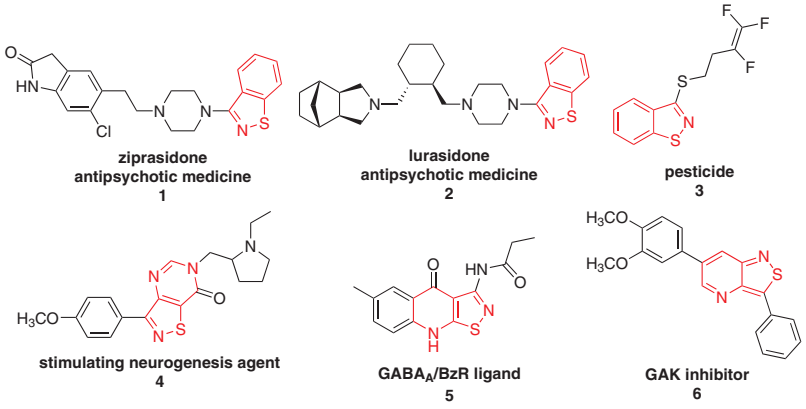

Figure 1 Selected examples of bioactive molecules that contain the isothiazole moiety

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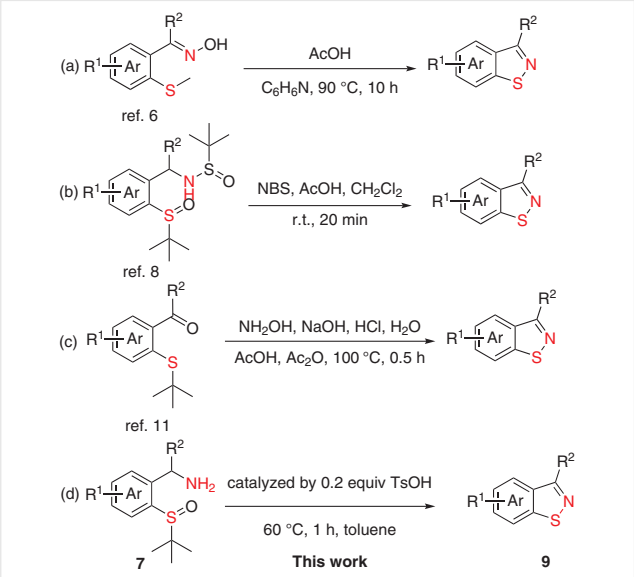
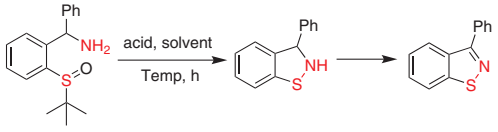


Scheme 1 Methods for the synthesis of aryl[4,5]isothiazoles

In our previous NBS-based procedure we used two equivalents of NBS to activate *tert*-butyl sulfoxide to form a reactive sulfinyl bromide.[9] However, we also noticed that thermolysis of *tert*-butyl sulfoxide could lead to sulfenic acid that can act as an electrophile.[10] Zhang et al. described a procedure that proceeds by *tert*-butyl suifide.[11] We therefore reasoned that the thermolysis procedure may allow us to find conditions that avoid the use of NBS for activation, and allow direct formation of the N–S bond to form the isothiazole ring by using amine as the nucleophile. To test this idea, we performed a model reaction under different heating conditions and the results are shown in Table 1.

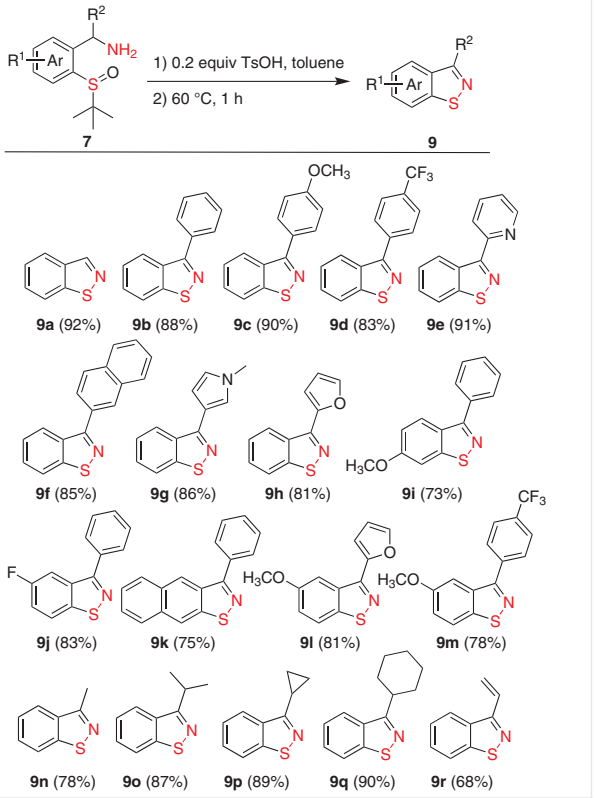
The transformation of **7b** to **9b** was then optimized with regard to reagent ratio, acid used, and solvent. The results are summarized in Table 1. Thermolysis without acid provided the desired product but the reaction time was long (10 h, entry 1). Use of varying amounts of acetic acid and heating in toluene at high temperatures allowed to effectively obtain the desired product in good yields (about 82%) with reduced reaction time; lower temperatures were not useful conditions (entries 2–5). Changing the acid from acetic acid to tosylic acid led to better results with lower tem-

Table 1 Exploration of Optimal Conditions for a Model Reaction[a]



Entry	Acid	Solvent[b]	Reagent ratio (**7b**/acid)	Temp (°C)/time (h)	Yield of **9b** or (**8**) (%)[c]
1	AcOH	toluene	1.0/0	90/10	81
2	AcOH	toluene	1.0/0.2	60/12	42 (40)
3	AcOH	toluene	1.0/0.2	90/6	83
4	AcOH	toluene	1.0/1.5	90/6	82
5	AcOH	toluene	1.0/0.2	35/2	0 (0)
6	TsOH	toluene	1.0/0.2	35/2	0 (25)
7	TsOH	toluene	1.0/0.2	60/1	88
8	TsOH	toluene	1.0/0.2	90/2	78
9	TFA	toluene	1.0/0.2	60/1	30 (12)
10	benzoic acid	toluene	1.0/0.2	60/1	33 (47)
11	H_2SO_4	toluene	1.0/0.2	60/1	28 (4)
12	TsOH	CH_2Cl_2	1.0/0.2	40/2	23 (6)
13	TsOH	THF	1.0/0.2	60/1	47 (2)
14	TsOH	CH_3CN	1.0/0.2	60/1	33 (4)
15	TsOH	EtOH	1.0/0.2	60/1	39 (16)
16	TsOH	DMF	1.0/0.2	60/1	62 (2)

[a] Reaction conditions: To a solution of **7b** (1 mmol) in solvent (3 mL) was added acid (0.2 mmol) in solvent (2 mL) at different temperatures. The mixture was stirred under those conditions for another 1 h.
[b] Purified solvent.
[c] Isolated yield.

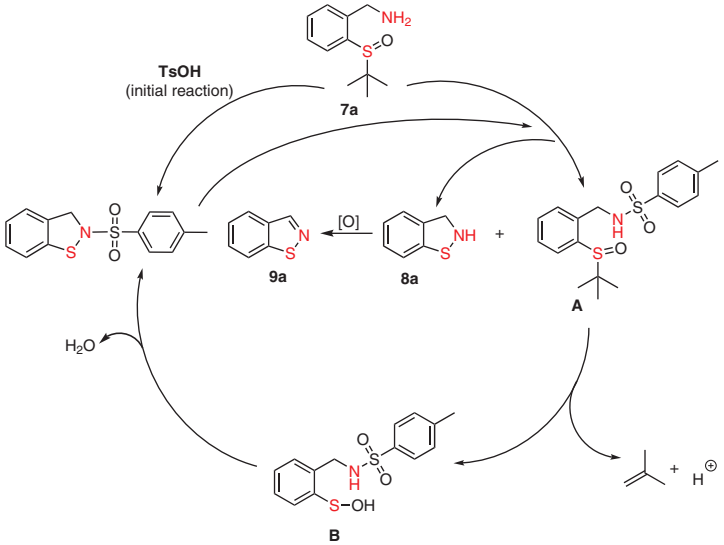


Scheme 2 Results with expanded substrate scope

peratures and short reaction times (entries 6–8, best conditions in entry 7). Other acids in the toluene solvent system were not so effective (entries 9–11). Use of other solvents in combination with TsOH gave lower yields (entries 12–16 with use of CH_2Cl_2, THF, CH_3CN, EtOH, or DMF). Therefore, one hour of heating at 60 °C in toluene with 0.2 equivalents of tosylic acid was chosen as the standard conditions for further investigation. It was notable that product **8** can be isolated as well during the above investigations at various conditions except those that gave more than 80% of the final product **9b**.

Using the standard conditions, we tested our protocol with a range of substrates. The results are summarized in Scheme 2.[12,13] The first example was the formation of the parent benzoisothiazole and 92% isolated yield was obtained. The next seven examples contain different aromatic rings at the 3-position, and all produced excellent isolated yields (81–91%, products **9b–h**). It seems that both electron-withdrawing and -donating groups at the 3-aryl substitution were well tolerated. The next five examples explored the substitution on the fused aromatic ring, and its combination with an electron-rich 3-aryl (furan) or a 3-phenyl with an electron-withdrawing group (CF_3). Again, good isolated yields were obtained in those cases (73–83%, products **9i–m**). Additionally, 3-alkyl- or alkenyl-substituted examples were studied, and our method still produced very good isolated yields (68–90%, **9n–r**).

A tentative mechanism has been proposed (as Scheme 3 shows). The reaction proceeds through initial reaction of **7a** with 0.2 equivalents of *p*-toluenesulfonic acid to afford complex **C**. Then, sulfonamide exchange might occur with substrate **7a** to generate **8a** and complex **A** (conformed by ^{1}H NMR spectroscopy). Complex **A** converts into complex **B** (confirmed by LCMS-IT-TOF, HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}NO_3S_2H$: 310.0537; found: 310.0532) through the loss of a stable *tert*-butyl cation which in turn produces gaseous isobutene and one proton. Furthermore,



Scheme 3 Proposed reaction pathway

the above complex **B** releases of one molecule of water to afford complex **C**. Then, molecular aromatization of **8a** forms **9a** and complex **C** can be recycled.

In summary, using an acid-catalyzed thermolysis procedure, we identified a new method to efficiently prepare 3-substituted aryl[4,5]isothiazoles by simply heating the starting materials with a catalytic amount of *p*-toluenesulfonic acid in toluene without using NBS. This simple procedure is well suitable for a variety of substrates that can tolerate substitution changes in the fusing aromatic ring, as well as at the 3-position with substituted aryl rings of varying electronic properties and alkyl substitutions. Especially, this is the first time we have found that sulfenic acid can be formed from sulfoxide under the catalysis of *p*-toluenesulfonic acid and relatively mild conditions. Further intramolecular ring closure products can be synthesized easily. The "green" aspect of this procedure will make it a good supplement to existing methodologies.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690201.

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(12) To a solution of **7** (1 equiv) in toluene (3 mL) TsOH (0.2 equiv) in toluene (2 mL) was added. The mixture was stirred at 60 °C for 1 h. Then the reaction mixture was cooled to room temperature and concentrated. The residue was loaded on a silica gel using petroleum ether/ethyl acetate (20:1) to afford the desired product **9**.
(13) **Characterization data of new compounds**
(2-Methyl-propane-2-sulfinyl)-benzylamine (7a): eluent CH_2Cl_2/MeOH (10:1, v/v), yellow oil; yield: 645 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.79 (m, 1 H), 7.50–7.38 (m, 3 H), 4.18 (d, *J* = 14.5 Hz, 1 H), 3.74 (d, *J* = 14.5 Hz, 1 H), 1.72 (s, 2 H), 1.16 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 142.9, 138.0, 131.5, 128.1, 127.3, 126.4, 57.4, 42.7, 23.0.
[2-(*tert*-Butylsulfinyl)phenyl](4-trifluoromethylphenyl)-methanamine (7d): eluent PE/EtOAc (1:9, v/v), colorless oil; yield: 255 mg (72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.84 (m, 1 H), 7.65–7.62 (m, 1 H), 7.60–7.53 (m, 4 H), 7.50–7.42 (m, 2 H), 5.82 (s, 1 H), 1.82 (s, 2 H), 1.31 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 147.0, 145.6, 138.6, 131.9, 129.7, 129.4, 128.0, 127.3, 125.3 (q, *J* = 3.7 Hz), 122.7, 57.5, 53.9, 23.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.42 (s). HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NF_3SH$: 356.4072; found: 356.4069.
[2-(*tert*-Butylsulfinyl)phenyl](1-methyl-1*H*-pyrrol-2-yl)methanamine (7g): eluent PE/EtOAc (1:9, v/v), purple red oil; yield: 230 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 1 H), 7.53–7.46 (m, 3 H), 6.55–6.54 (m, 1 H), 6.07–6.02 (m, 2 H), 5.62 (s, 1 H), 3.52 (s, 3 H), 1.93 (s, 2 H), 1.32 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 144.2, 138.0, 136.1, 131.7, 127.7, 127.4, 126.4, 123.0, 106.7 (d, *J* = 2.2 Hz), 57.0, 48.2, 34.3, 23.4. HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{22}N_2OSNa$: 313.1345; found: 313.1341.
[2-(*tert*-Butylsulfinyl)-4-methoxyphenyl](phenyl)methanamine (7i): eluent PE/EtOAc (1:9, v/v), white solid; yield: 236 mg (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.56 (m, 1 H), 7.44 (t, *J* = 8.1 Hz, 1 H), 7.37 (d, *J* = 7.9 Hz, 2 H), 7.29–7.26 (m, 2 H), 7.19 (d, *J* = 7.3 Hz, 1 H), 6.97 (d, *J* = 7.9 Hz, 1 H), 5.57 (s, 1 H), 3.62 (s, 3 H), 2.27 (s, 3 H), 1.33 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 157.7, 144.3, 139.8, 133.5, 128.6, 128.3, 127.9, 127.6, 126.3 (d, *J* = 8.5 Hz), 125.9 (d, *J* = 19.4 Hz), 118.6, 114.8, 57.3, 55.7, 53.6, 23.3. HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{23}NO_2SNa$: 340.1342; found: 340.1340.
[2-(*tert*-Butylsulfinyl)-5-methoxyphenyl](furan-2-yl)methanamine (7l): eluent PE/EtOAc (1:9, v/v), white solid; yield: 265 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.8 Hz, 1 H), 7.33 (d, *J* = 2.6 Hz, 1 H), 7.16–7.15 (m, 1 H), 6.70–6.97 (m, 1 H), 6.27–6.26 (m, 1 H), 6.03 (d, *J* = 3.2 Hz, 1 H), 3.84 (s, 3 H), 3.17 (s, 2 H), 2.01 (s, 1 H), 1.25 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 162.3, 156.2, 144.4, 142.2, 128.7, 128.5, 113.8, 112.4, 110.3, 106.5, 56.9, 55.5, 49.2, 23.1. HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{21}NO_3SNa$: 330.1134; found: 330.1133.
[2-(*tert*-Butylsulfinyl)-5-methoxyphenyl](4-trifluoro-methyl-phenyl)methanamine (7m): eluent PE/EtOAc (1:9, v/v), colorless oil; yield: 288 mg (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.8 Hz, 1 H), 7.61–7.54 (m, 4 H), 7.17 (d, *J* = 2.6 Hz, 1 H), 6.98–6.95 (m, 1 H), 5.81 (s, 1 H), 3.83 (s, 3 H), 1.94 (s, 2 H), 1.29 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 162.5, 158.3, 147.0, 138.8, 134.8, 128.9, 125.8 (q, *J* = 3.8 Hz), 120.7, 119.3, 104.8, 55.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.49 (s). HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{22}F_3NO_2SNa$: 408.1216; found: 408.1214.
1-[2-(2-Methyl-propane-2-sulfinyl)-phenyl]-allylamine (7r): eluent PE/EtOAc (1:9, v/v), colorless liquid; yield: 226 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.78 (m, 1 H), 7.53–7.51 (m, 1 H), 7.48–7.45 (m, 1 H), 7.44–7.37 (m, 1 H), 5.96–5.88 (m, 1 H), 5.17 (d, *J* = 17.1 Hz, 1 H), 5.06–5.03 (m, 2 H), 1.74 (s, 2 H), 1.22 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 144.3, 141.2, 137.5, 131.6, 127.5, 126.4 (d, *J* = 19.7 Hz), 114.2, 56.9, 53.2, 23.1. HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}NOSNa$: 260.1080; found: 260.1076.
3-Naphthalen-2-yl-benzo[*d*]isothiazole (9f): eluent PE/EtOAc (20:1, v/v), colorless oil; yield: 132 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 8.32 (d, *J* = 8.2 Hz, 1 H), 8.06 (d, *J* = 7.7 Hz, 3 H), 8.02–7.92 (m, 2 H), 7.60 (m, 3 H), 7.53 (m, 1 H). ^{13}C{^{1}H}

NMR (101 MHz, $CDCl_3$): δ = 164.3, 153.7, 134.0, 133.7, 133.3, 132.7, 128.6 (d, *J* = 3.2 Hz), 128.2, 127.8, 127.5, 126.9, 126.6, 126.2, 125.0 (d, *J* = 18.6 Hz), 120.0. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{11}NSH$: 262.0685; found: 262.0683.

3-(1-Methyl-1*H*-pyrrol-3-yl)-benzo[*d*]isothiazole (9g): eluent PE/EtOAc (20:1, v/v), colorless oil; yield: 127 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.3 Hz, 1 H), 7.98 (d, *J* = 8.1 Hz, 1 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 7.52–7.46 (m, 1 H), 6.87 (s, 1 H), 6.80–6.74 (m, 1 H), 6.36–6.26 (m, 1 H), 3.98 (s, 3 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.1, 160.6, 153.4, 133.8, 130.0, 127.9, 127.5, 125.0, 124.9, 120.0, 114.3, 55.4. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}N_2SH$: 215.0634; found: 215.0637.

3-Furan-2-yl-benzo[*d*]isothiazole (9h): eluent PE/EtOAc (20:1, v/v), yellow oil; yield: 118 mg (81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68–8.61 (m, 1 H), 8.02–7.93 (m, 1 H), 7.72–7.64 (m, 1 H), 7.55 (m, 2 H), 7.22 (m, 1 H), 6.64 (m, 1 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 153.9, 153.2, 150.7, 143.3, 132.8, 127.7, 125.3, 125.2, 119.7, 111.8, 110.4. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_7NOSH$: 202.0322; found: 202.0321.

6-Methoxy-3-phenyl-benzo[*d*]isothiazole (9i): eluent PE/EtOAc (20:1, v/v), light yellow oil; yield: 111 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.66 (m, 2 H), 7.57–7.49 (m, 2 H), 7.46 (m, 3 H), 6.80 (d, *J* = 7.1 Hz, 1 H), 3.81 (s, 3 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 129.6, 129.3, 128.8, 128.5, 127.3, 112.0, 104.9, 55.2, 29.7. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}NOSH$: 242.0637; found: 242.0634.

3-Furan-2-yl-5-methoxy-benzo[*d*]isothiazole (9l): eluent PE/EtOAc (20:1, v/v), colorless oil; yield: 122 mg (81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 2.3 Hz, 1 H), 7.82 (d, *J* = 8.9 Hz, 1 H), 7.67 (d, *J* = 1.1 Hz, 1 H), 7.24 (m, 1 H), 7.18 (m, 1 H), 6.64 (m, 1 H), 3.98 (s, 3 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 158.2, 153.3, 150.9, 146.5, 143.1, 134.0, 120.3, 119.3, 111.8, 110.2, 105.7, 55.7. HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_9NO_2SNa$: 254.0246; found: 254.0245.

5-Methoxy-3-(4-trifluoromethyl-phenyl)-benzo[*d*]isothiazole (9m): eluent PE/EtOAc (20:1, v/v), yellow oil; yield: 125 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.1 Hz, 2 H), 7.90 (d, *J* = 8.9 Hz, 1 H), 7.84 (d, *J* = 8.2 Hz, 2 H), 7.50 (d, *J* = 2.2 Hz, 1 H), 7.28 (m, 1 H), 3.91 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 162.0, 158.3, 147.0, 138.8, 134.8, 128.9, 125.3 (q, *J* = 3.8 Hz), 120.7, 119.3, 104.8, 55.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −62.64 (s). HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{10}F_3NOSNa$: 332.0327; found: 332.0325.