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Synthesis of 2-(Benzylthio)-4-(trifluoromethyl)thiazole-5-carboxylates Using *S*-Benzylisothiouronium Halides as Thiol Equivalents

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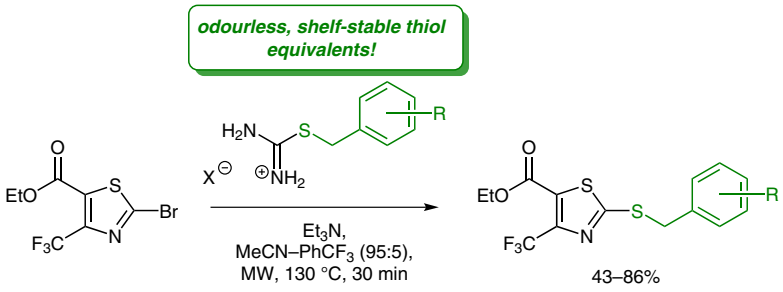

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Abstract *S*-Benzylisothiouronium halides are used as shelf-stable, odorless thiol equivalents. The method developed is used to access 2-(benzylthio)-4-(trifluoromethyl)thiazole carboxyl building blocks. Using the latent trifluoromethyl substituent the reactions could be monitored using ^{19}F NMR spectroscopy.

Key words thioether, isothiouronium halide, ^{19}F NMR spectroscopy, nucleophilic aromatic substitution, thiazole

The 4-(trifluoromethyl)-5-carboxyl-substituted thiazole ring is a common component in compounds exhibiting antifungal and insecticidal activity.[1] However, there are limited examples in the literature in which the 2-position of these substituted thiazole rings contains an *S*-alkylthioether.[2] For example, 2-ethylthiothiazole (**1**, Figure 1)[2c] and the succinate dehydrogenase inhibitor, 2-methylthiothiazole (**3**, pI_{50} = 6.32 μM),[1c] were synthesized using the respective alkylthiolate reagents. The notoriously pungent odor and toxicity associated with alkylthiolates is a possible deterrent for the investigation of thioethers during synthetic campaigns.

Despite the utility of benzyl substituents in medicinal chemistry, there are no benzylthioethers like compound **2** reported. To the best of our knowledge, the only benzyl-like compound is sulfone **4** (Figure 1), which was patented as part of a series of herbicidal compounds.[2a] In this case the sulfone was introduced by nucleophilic aromatic substitution (S_NAr) reaction with the corresponding sodium sulfinate.

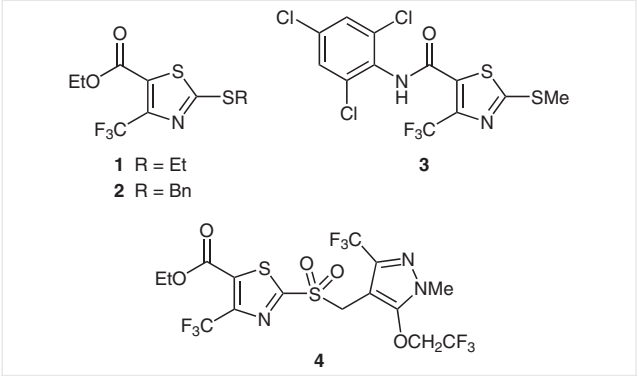
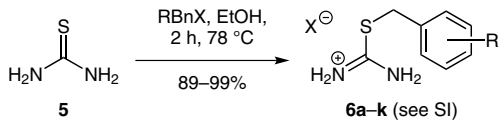


Figure 1 Examples of thiazoles bearing 2-alkylthioethers; compound **2** is the focus of this study

A method that allows access to simple 2-benzylthiol analogues, such as **2** (Figure 1), in a manner suited to analogue generation is reported. In addition, this method does not require the synthesis or handling of malodorous and toxic benzylthiols. The requisite thiol reagents are generated in situ by base-mediated decomposition of *S*-benzylisothiouronium salts. There has been renewed interest in this approach in recent years in synthesizing symmetrical[3] or nonsymmetrical thioethers; through basic decomposition[2a,4] or in copper-[5] and palladium-mediated processes.[6] Analogous methodology has also been extended to Michael addition protocols[7] as well as the synthesis of thioesters.[8]

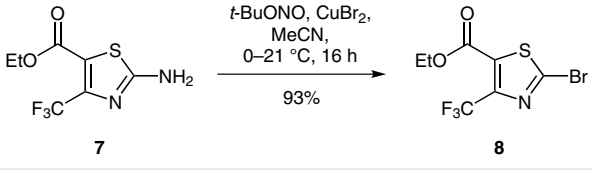
Herein, the *S*-benzylisothiouronium halides were generated from thiourea and the appropriate benzyl halide. A key practical advantage of this approach is that the number of commercially available benzyl halides greatly exceeds the number of benzyl thiols. Furthermore, the isothiouronium halides are indefinitely stable at ambient temperature, are nonhygroscopic, and have no vapor pressure or odor that is typically associated with thiol reagents.

As illustrated in Scheme 1, the synthesis of isothiouronium halide salts **6a**–**k** was achieved by heating the benzyl halide with an equimolar amount of thiourea in EtOH at 78 °C. After removal of the solvent, the products were easily isolated by trituration (Et_2O) in excellent yields (89–99%, Scheme 1; see the Supporting Information for full details).



Scheme 1 Formation of *S*-benzylisothiouronium salts

Using Sandmeyer chemistry, 2-bromothiazole **8** (Scheme 2) was synthesized from the 2-amino thiazole **7** which is commercially available or readily synthesized from ethyl 2-chloro-3-oxo-4,4,4-trifluorobutyrate and thiourea. The 2-aminothiazole **7** was treated with *t*-BuONO (1.5 equiv) in the presence of $CuBr_2$ (0.8 equiv) at 0 °C for one hour then at 21 °C overnight to afford, after extractive workup, **8** in 93% yield.



Scheme 2 Synthesis of 2-bromothiazole

When an equimolar amount of 2-bromothiazole **8**, *S*-benzylisothiouronium bromide (**6a**), and Et_3N (1:1:1 ratio) were heated in MeCN (Table 1, entry 1) at 82 °C for 12 hours, it was found that the isothiouronium was consumed and that there was evidence of the desired benzylarylthioether **2** (δ_H = 4.49 ppm for SCH_2Ph) in the crude ^1H NMR spectrum. An additional singlet was present in the ^1H NMR spectrum at δ_H = 3.60 ppm, which can be attributed to the formation of dibenzylsulfide as a byproduct.

In an effort to circumvent this byproduct formation, a mixture of **8**/**6a**/Et_3N (1:2:2) was used (Table 1, entry 2). The ^1H NMR spectrum of the crude reaction mixture indicated that more of the desired product had formed though some of the bromide **8** still remained. It appeared that the byproduct formation was occurring at a similar rate as the desired reaction. Unfortunately, it was not possible to separate the bromide **8** from the benzylthioether **2** by conventional chromatographic techniques. As such, the reaction conditions had to be refined to ensure that starting material was consistently consumed. Pleasingly, when **8**/**6a**/Et_3N in a 1:2:4 ratio was used (Table 1, entry 3), the starting material was completely consumed within 48 hours (as per ^1H NMR spectrum) and the desired benzylthioether **2** was isolated in 76% yield after purification by column chromatography.

The reaction time was significantly reduced when the reaction was heated using microwave irradiation; after two hours at 100 °C, benzylthioether **2** was obtained in 83% yield (Table 1, entry 4). A similar result (78% yield) was obtained using EtOH in place of MeCN as the solvent (Table 1, entry 5). The reaction also worked well at higher temperatures (110–130 °C, Table 1, entries 6–8) with decreasing reaction times (90–30 min), wherein yields were maintained within the range of 75 to 82%.

Up to this point, the reaction progress was first monitored postreaction by ^1H NMR spectroscopy after removal of the reaction solvent. This approach was necessitated due to coincidental R_f values for the 2-bromothiazole **8** and thioether **2**, and whilst this is a specific case, an alternative method of monitoring the substitution reaction was sought.

Due to the presence of the 4-trifluoromethyl substituent on **8**, it was possible to monitor the reaction using ^{19}F NMR spectroscopy. By adding an internal standard ($PhCF_3$) to the solvent system it is possible to monitor the small, yet observable, difference in chemical shift ($\Delta\delta$ = 0.05 ppm) between **8** (δ_F = –61.88 ppm) and **2** (δ_F = –61.93 ppm). Using a mixture of MeCN–$PhCF_3$ (95:5) the standard peak was only ca. twofold that of the starting material and the reaction could be monitored by dissolving 1–2 drops of the reaction mixture into $CDCl_3$ before acquiring the ^{19}F NMR spectrum. Using the mixed solvent system and heating at 120 °C for 60 minutes, compound **2** was obtained in 83% yield (Table 1, entry 9) and is comparable to using MeCN (82%, Table 1, entry 7). A similar result was obtained when heating at 130 °C for 30 minutes. Using MeCN–$PhCF_3$, thioether **2** was obtained in 80% (Table 1, entry 10) which compares favorably to MeCN alone (75%, Table 1, entry 8).

Full characterization of benzylthioether **2** was complicated by coincidental peaks in the ^{13}C NMR spectrum from C-5 of the thiazole and a C–H of the phenyl ring. Compound **2** was isolated as a clear oil in all instances, however, in one circumstance the oil solidified on standing to give clear prisms that were suitable for X-ray structural analysis (Figure 2). The X-ray crystal structure clearly shows the presence of the thioether at the 2-position of the thiazole ring.[9]

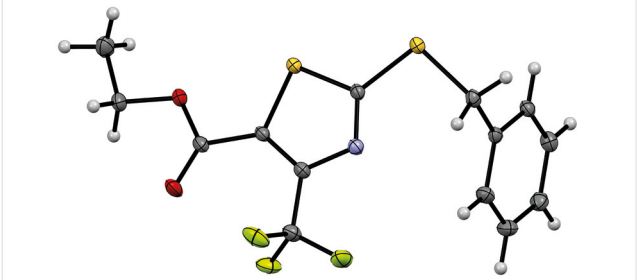
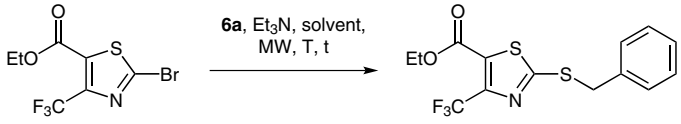


Figure 2 ORTEP drawing of **2** (CCDC 1055990); thermal ellipsoids are at the 30% probability level

Table 1 Optimization of the Benzylthioether Formation from **8**[a]



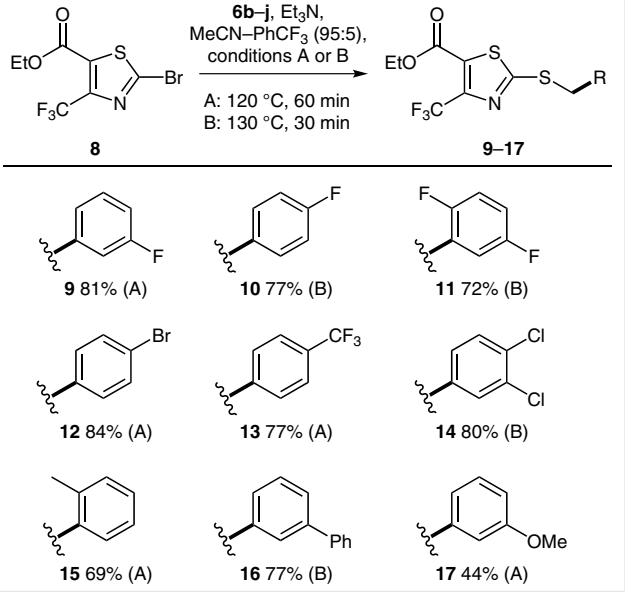
8 δ_F –61.88 ppm **2** δ_F –61.93 ppm

Entry	**6a** (equiv)	Et_3N (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	1.0	1.0	MeCN	82[b]	12	n.d.[c]
2	2.1	2.0	MeCN	82[b]	48	n.d.[c]
3	2.0	4.0	MeCN	82[b]	48	76[d]
4	2.0	4.0	MeCN	100	2	83
5	2.0	4.0	EtOH	100	2	78
6	2.0	4.0	MeCN	110	1.5	79
7	2.0	4.0	MeCN	120	1	82
8	2.0	4.0	MeCN	130	0.5	75
9	2.0	4.0	MeCN–$PhCF_3$ (95:5)	120	1	83
10	2.0	4.0	MeCN–$PhCF_3$ (95:5)	130	0.5	80

[a] Reactions were performed using **8** (0.50 mmol) in solvent (5 mL).
[b] Conventional reflux.
[c] n.d. = not determined: **6a** was consumed before **8**.
[d] Bn_2S was isolated from this reaction.

Interestingly, the distance between the bivalent oxygen of the ester and the sulfur atom of the thiazole was found to be 2.82 Å (sum of van der Waals radius 3.32 Å) and the dihedral angle for S–C–C–O was almost coplanar at 6.90°. These measurements indicate a potential n→σ* interaction which could be influencing the conformation of the ester substituent.[10]

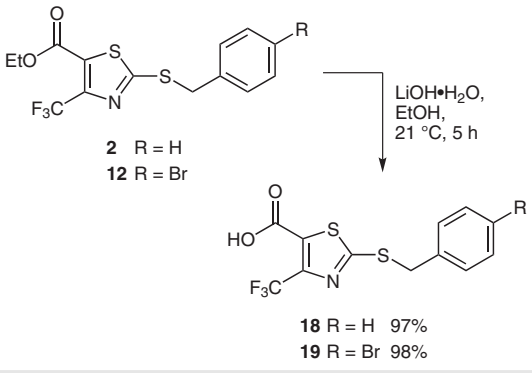
With confirmation of the successful reaction and establishment of a method, substituted benzyl derivatives were investigated (Scheme 3). Using the aforementioned protocol, benzylthioethers bearing 3-fluoro (**9**) and 4-fluoro substituents (**10**) were isolated in yields of 81 and 77%, respectively. Similarly, the 4-bromo and 4-trifluoromethyl analogues (**12**[11] and **13**) were obtained in 84 and 77%, respectively. When the 3,4-dichloro-substituted salt was used, compound **14** was isolated in 80% yield. The 2,5-difluorobenzylthioether **11** was obtained in a slightly reduced yield of 72%. A lower yield (69%) was also obtained with the 2-methyl derivative **15**, suggesting that a substituent in the 2-position of the phenyl ring may encumber the reaction slightly. When the 3-phenyl substituent was present the reaction also proceeded smoothly to give the biphenyl **16** in 77% yield. When a 3-methoxy substituent was present, the corresponding thioether **17** was isolated in a lower yield (44%) than previous examples. This poorer result is attributed to complications in the isolation of **17** that are due to the formation of bis(3-methoxybenzyl)sulfide, which exhibited an R_f value similar to **17**.



Scheme 3 Synthesis of substituted benzylthioether thiazoles

Ester hydrolysis of **2** and **12** was achieved using $LiOH·H_2O$ (5.0 equiv) in EtOH at ambient temperature for five hours (Scheme 4). Carboxylic acids **18** and **19** were obtained in high yields (97 and 98%, respectively) using an extractive workup. As high conversions could be achieved during the S_NAr step, which can be monitored by ^{19}F NMR spectroscopy, as well as excellent yields for hydrolysis, we reasoned

that we could telescope both reaction steps. This has the advantage of obtaining the carboxylic acid handle and avoiding chromatographic purification.



Scheme 4 Carboxylic acid synthesis

The microwave reaction of 3-methoxybenzylisothiouronium chloride (**6j**) and 2-bromothiazole **8** was repeated. The solvent was removed from the reaction mixture and the crude material was reconstituted in EtOH and treated with LiOH·H_2O for five hours (Scheme 5). The carboxylic acid was isolated in 43% yield after extractive workup, which was comparable to the isolated ester with an extra step and without isolation of the intermediate. The analogous procedure was then performed using 4-methoxybenzylisothiouronium chloride (**6k**) to give the corresponding carboxylic acid **21** in 76% yield.

As EtOH could be used as the solvent for both the S_NAr (Table 1, entry 5) and the hydrolysis reactions (Scheme 4), we envisaged that the use of EtOH–$PhCF_3$ (95:5) as the solvent system would facilitate a one-pot process. After the completion of the thioether formation using **6k** and **8** at 130 °C for 30 minutes (Scheme 5), LiOH·H_2O was added to the flask and stirring was continued for 6.5 hours. The carboxylic acid was isolated from an extractive workup in 78% yield in a one-pot procedure.

Through the use of odorless, shelf-stable *S*-benzylisothiouronium salts as masked thiol reagents, a methodology has been developed for the synthesis of 2-(benzylthio)-4-(trifluoromethyl)-1,3-thiazole-5-carboxyl building blocks. The method described is exemplified by a series of analogues that are synthesized in typically high yields (ca. 80%). The method is extendable to a two-step, one-pot process to include the hydrolysis of the ethyl ester. It is likely that this approach can be exploited for other heterocyclic systems as a means of generating benzylthioether analogues.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380748.

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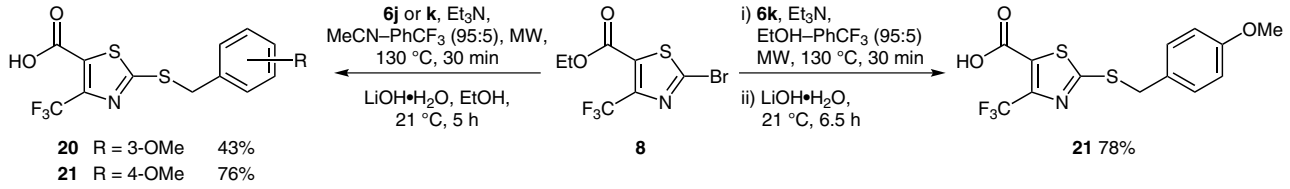

Scheme 5 One-pot sequential nucleophilic aromatic substitution and hydrolysis.

(9) The crystal structure for compound **2** has been deposited at the Cambridge Crystallographic Data Centre. CCDC 1055009 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(11) **Example Procedure: Ethyl 2-[(4-Bromobenzyl)thio]-4-(trifluoromethyl)thiazole-5-carboxylate (12)**

A mixture of 2-bromothiazole **8** (152 mg, 0.50 mmol), Et_3N (0.28 mL, 2.0 mmol, 4.0 equiv), and **6e** (326 mg, 1.00 mmol, 2.0 equiv) in MeCN–$PhCF_3$ (5 mL, Table 1) was heated at 120 °C for 60 min using MW irradiation. The reaction mixture was diluted using MeOH and concentrated onto SiO_2 and then purified by column chromatography using CH_2Cl_2–petroleum spirits (1:3 to 1:1) to give **12** (178 mg, 84%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.44 (m, 2 H), 7.31–7.28 (m, 2 H), 4.43 (s, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 158.5, 145.7 (q, $^2J_{CF}$ = 37.9 Hz), 134.6, 131.8, 130.9, 129.3, 122.0, 119.5 (q, $^1J_{CF}$ = 271.1 Hz), 62.6, 37.2, 13.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –61.93 (s). ESI-HRMS: *m/z* calcd for $C_{14}H_{11}{}^{79}BrF_3NO_2S_2$ [M + H$^+$]: 425.9439; found: 425.9446.