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Room temperature nucleophilic trifluoromethylthiolation of benzyl bromides with (bpy)Cu(SCF_3)

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ABSTRACT

The nucleophilic trifluoromethylthiolation of benzyl bromides using (bpy)Cu(SCF_3) gave the desired products of benzyl trifluoromethyl sulfides in good to excellent yields. A diverse set of important functional groups including cyano, nitro, ester, alkoxy, halide, and heterocyclic groups can be well tolerated in the protocol.

1. Introduction

The incorporation of fluorine-containing groups into organic molecules is a powerful strategy in the process of drug design.[1] This escalating importance stems from the prevalence of fluorine-containing substituents in many compounds that are of biological, pharmaceutical, agricultural, and materials interest.

Among these substituents, the trifluoromethylthio group ($-SCF_3$) has attracted much attention by virtue of its strong electron-withdrawing effect and high hydrophobicity parameter (π_R=1.44).[2] Accordingly, the synthesis of trifluoromethyl thioether compounds is of great interest to synthetic chemists. A number of synthetic methods exist to accomplish this transformation, e.g., the nucleophilic,[3] electrophilic,[4] and radical[5] trifluoromethylation of disulfides, thiocyanates, thiols, and thiolates with a trifluoromethylation reagent. However, these reactions are generally limited by their need for the preparation of sulfur-precursors, a narrow substrate scope, and a combination of high temperature.

The recent development of transition-metal-catalyzed trifluoromethylthiolation provides a useful methodology for the preparation of aryl trifluoromethyl thioethers in a single step with readily available aryl halides,[6] aryl boronic acids,[7] and arenes.[8] The use of organometallic reagent, i.e., trifluoromethylthiocopper ($CuSCF_3$) is one of the most straightforward methods for the synthesis of trifluoromethylthiolated compounds.[9] Recently, we reported the synthesis of a series of copper(I) trifluoromethylthiolate complexes ligated by bipyridine ligands for nucleophilic trifluoromethylthiolation of aryl halides.[10] These reactions provide a novel and convenience approach for trifluoromethylthiolation of aryl halides.

In view of the likelihood of benzyl substituents acting as rigid lipophilic groups in pharmacophore development,[11] it would be of interest to develop a transformation for the direct introduction of a trifluoromethylthio group at the benzylic position. It is also worthy of note that although a number of methods have been developed for synthesis of aryl trifluoromethyl thioethers, efficient synthetic protocol able to prepare benzyl trifluoromethyl sulfides are still rare. Examples have been reported involving reaction of benzyl thiocyanate and (trifluoromethyl)trimethylsilane[3f] or the reaction of benzyl halides with a trifluoromethyl sulfide anionic salt.[5e,12] However, in all of the cases, only unsubstituted benzyl halides were employed. To date, a general method for synthesis of various aryl-substituted benzyl trifluoromethyl sulfide mediated by transition-metals under mild reaction conditions have not been explored.

As part of our continuing efforts in the development of copper-mediated trifluoromethylation[13] and trifluoromethylthiolation,[10] we herein report a nucleophilic trifluoromethylthiolation of benzyl bromides using (bpy)Cu(SCF_3).

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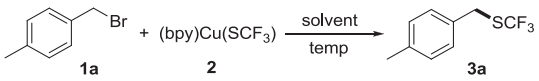
2. Results and discussion

We began the exploration of trifluoromethylthiolation with a model reaction between *p*-methylbenzyl bromide (**1a**) (1.5 equiv) with (bpy)Cu(SCF_3) (**2**) (1 equiv) (Table 1). To our delight this reaction takes place and the desired product benzyl(trifluoromethyl) sulfane (**3a**) was isolated in a moderate 66% after 8 h at 110 °C in toluene (Table 1, entry 1). To enable the efficiency of this transformation, we examined various solvents and temperatures. The reaction performed in THF at 80 °C also resulted in a good yield (75%, entry 2). On the contrary, using CH_2Cl_2, NMP, DMF, and DMSO as solvent at room temperature or 80 °C led to lower product yields (entries 3, 7–9) and the reactions in a protic solvent, such as methanol or ethanol furnished **3a** in low yields (~10%) at 80 °C after 18 h (entries 5 and 6). By using diglyme and CH_3CN as the solvents, the trifluoromethylthiolation proceeded with excellent yields of **3a** at 80 °C (91% and 98%, respectively; entries 4 and 10). Further experiments revealed that a reaction at room temperature in CH_3CN after 12 h to give the desired **3a** in 99% yield (entry 11).

Table 1
Optimization of the trifluoromethylthiolation of benzyl bromides[a]



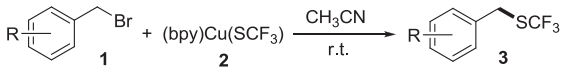
1a **2** **3a**

Entry	Solvent	T (°C)	Time (h)	Yield (%)[b]
1	Toluene	110	8	66
2	THF	80	24	75
3	CH_2Cl_2	rt	24	54
4	Diglyme	80	12	91
5	MeOH	80	18	10
6	EtOH	80	18	10
7	NMP	80	12	61
8	DMF	80	12	39
9	DMSO	80	12	60
10	CH_3CN	80	10	98
11	CH_3CN	rt	12	99

[a] Reaction conditions: **1a** (0.038 mmol), **2** (0.025 mmol), solvent (1.0 mL), under N_2 atmosphere.
[b] Yield were determined by the ^{19}F NMR analysis of the crude reaction mixture with an internal standard.

With the preliminary results in hand, the scope of trifluoromethylthiolation of benzyl bromides was investigated under the optimized conditions, and the results are shown in Table 2.

Table 2
Trifluoromethylthiolation of benzyl bromides by (bpy)Cu(SCF_3)[a]



1 **2** **3**

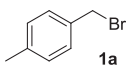
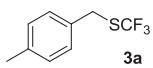
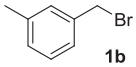
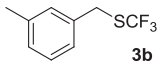
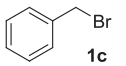
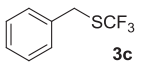
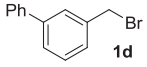
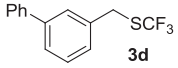
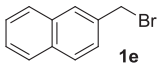
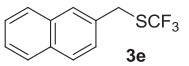
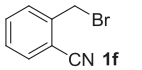
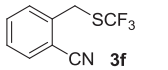
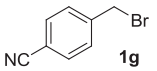
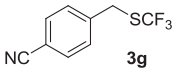
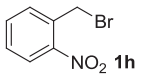
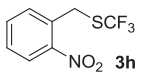
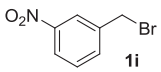
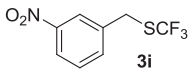
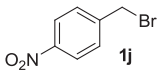
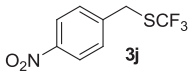
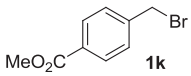
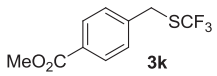
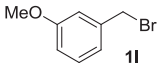
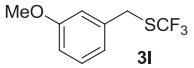
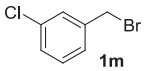
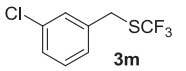
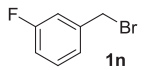
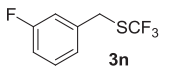
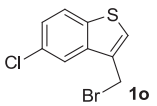
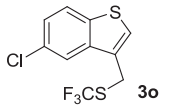
Entry	Benzyl bromides	Product	Yield (%)[b]
1	 **1a**	 **3a**	95
2	 **1b**	 **3b**	96
3	 **1c**	 **3c**	89
4	 **1d**	 **3d**	97

Table 2 (*continued*)

Entry	Benzyl bromides	Product	Yield (%)[b]
5	 **1e**	 **3e**	98
6	 **1f**	 **3f**	96
7	 **1g**	 **3g**	95
8	 **1h**	 **3h**	96
9	 **1i**	 **3i**	96
10	 **1j**	 **3j**	95
11	 **1k**	 **3k**	97
12	 **1l**	 **3l**	91
13	 **1m**	 **3m**	89
14	 **1n**	 **3n**	90
15	 **1o**	 **3o**	97

[a] Reaction conditions: benzyl bromides (0.17 mmol), **2** (0.25 mmol), MeCN (1.0 mL), rt, 8 h.
[b] Isolation yield.

Under these conditions, the reaction proceeded very smoothly and appears to tolerate a wide range of functionalized benzyl bromides, including those containing alkyl, phenyl, cyano, nitro, ester, alkoxy, halide, and heterocyclic groups.

The reaction of electron-neutral benzyl bromides **1a**–**d** and 2-naphthylmethyl bromide **1e** with **2** furnished the respective benzyl trifluoromethyl sulfides **3a**–**e** in excellent yields (89–98%; entries 1–5). Facile transformations of bromides **1f**–**k** containing electron-withdrawing groups on the aromatic ring gave the corresponding trifluoromethylthiolated products in excellent yields again (95–97%; entries 6–11). Substrates bearing electron-donating groups, such as 3-methoxybenzyl bromide **1l** also afforded the desired product **3l** in a good yield (91%, entry 12). It is noteworthy that a chloro- and fluoro-substituent on the aromatic ring of the benzyl bromides were tolerated under reaction conditions and afforded the products in 89% and 90% yields, respectively (entries 13 and 14). The heterocyclic functional groups were also compatible with the reaction conditions and produced the desired product in 97% yield (entry 15).

The high efficiency of the trifluoromethylthiolation described above prompted us to extend the application to more complex organic molecules. 4-Bromomethyl-7-methoxycoumarin (**1p**), one of coumarin derivatives, was chosen to evaluate the late-stage

trifluoromethylthiolation of biologically active molecules.[14] Under identical conditions as described in Table 2, the reaction of **1p** with **2** led to the isolation of 4-trifluoroethylthio-7-methoxycoumarin (**3p**) in 98% yield (Eq. 1).

(1)

3. Conclusions

In summary, we have successfully employed a copper reagent for nucleophilic trifluoromethylthiolation of benzyl bromides. This reaction provides an efficient and convenient access to benzyl trifluoromethyl sulfides. Cyano, nitro, ester, alkoxy, halide, and heterocyclic functional groups were compatible with the reaction conditions. Further investigations of related trifluoromethylthiolation are in progress.

4. Experimental

4.1. General experimental

^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded using Bruker AVIII 400 or AVIII 500 spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as the external standard and low field is positive. Coupling constants (J) are reported in Hertz (Hz). The residual solvent peak was used as an internal reference: ^{1}H NMR (chloroform δ 7.26) and ^{13}C NMR (chloroform δ 77.0). The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. (bpy)Cu(SCF_3) was prepared according to the published procedures.[10] Other reagents were received from commercial sources. Solvents were freshly dried and degassed according to *the purification handbook Purification of Laboratory Chemicals* prior to use. Column chromatography purifications were performed by flash chromatography using Merck silica gel 60.

4.2. General procedure for trifluoromethylthiolation of benzyl bromides with (bpy)Cu(SCF_3)

Benzyl bromide **1** (0.17 mmol), [(bpy)Cu(SCF_3)] (80 mg, 0.25 mmol, 1.5 equiv), and CH_3CN (1.0 mL) were added to a reaction tube equipped with a stir bar. The mixture was stirred at room temperature for 8–24 h until the reaction was judged complete by TLC analysis. The reaction mixture was filtered through a pad of Celite. The filtrate was added water (3×10 mL) at 0 °C. The resulting mixture was extracted with Et_2O (3×15 mL), and the combined organic layers was washed with water, and then dried over $MgSO_4$. The solvent was removed to give the desired product **3** without further purification.

*4.2.1. (4-Methylbenzyl)(trifluoromethyl)sulfane (**3a**).* Following the general procedure and workup, **3a** was isolated as an orange-red oil (33 mg, 95% yield). R_f (25% EtOAc/hexane) 0.38. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J=8.0 Hz, 2H), 7.06 (d, J=8.0 Hz, 2H), 4.00 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 130.8, 129.6 (q, J=306.9 Hz), 128.5, 127.8, 33.0 (q, J=2.4 Hz), 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.66 (s). IR (KBr): 2927, 2857, 1515, 1441, 1258, 1146, 1116, 817, 756 cm^{-1}. GC–MS m/z 206 (M^+). HRMS (EI) calcd for $C_9H_9SF_3$: 206.0377; Found: 206.0378.

*4.2.2. (3-Methylbenzyl)(trifluoromethyl)sulfane (**3b**).* Following the general procedure and workup, **3b** was isolated as an orange-red oil (34 mg, 96% yield). R_f (25% EtOAc/hexane) 0.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.03 (m, 4H), 4.01 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 134.8, 129.6, 128.7 (d, J=3.6 Hz), 127.6 (q, J=307.3 Hz), 125.9, 34.2 (q, J=2.4 Hz), 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.72 (s). IR (KBr): 2957, 2924, 2854, 1689, 1609, 1451, 1377, 1261, 1114, 1029, 911, 870, 799, 740, 693 cm^{-1}. GC–MS m/z 206 (M^+). HRMS (EI) calcd for $C_9H_9SF_3$: 206.0377; Found: 206.0378.

*4.2.3. Benzyl(trifluoromethyl)sulfane (**3c**).*[12c] Following the general procedure and workup, **3c** was isolated as an orange-red oil (29 mg, 89% yield). R_f (25% EtOAc/hexane) 0.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.20 (m, 5H), 4.04 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.0, 128.0, 127.8, 126.9, 33.2 (q, J=2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.65 (s). IR (KBr): 2961, 2925, 2854, 1512, 1456, 1377, 1261, 1104, 1023, 869, 802, 755, 698 cm^{-1}. GC–MS m/z 192 (M^+).

*4.2.4. (Biphenyl-3-ylmethyl)(trifluoromethyl)sulfane (**3d**).* Following the general procedure and workup, **3d** was isolated as a white solid (44 mg, 97% yield): mp 58–60 °C. R_f (4% Et_2O/pentane) 0.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.40 (m, 4H), 7.37–7.20 (m, 5H), 4.07 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 139.5, 134.4, 129.62 (q, J=307.0 Hz), 128.2, 127.8, 126.7, 126.5, 126.1, 125.8, 33.2 (q, J=2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.52 (s). IR (KBr): 3062, 3034, 2958, 2926, 1600, 1480, 1405, 1146, 1114, 1052, 757, 734, 698 cm^{-1}. GC–MS m/z 268 (M^+). HRMS (EI) calcd for $C_{14}H_{11}SF_3$: 268.0534; Found: 268.0532.

*4.2.5. (Naphthalen-2-ylmethyl)(trifluoromethyl)sulfane (**3e**).* Following the general procedure and workup, **3e** was isolated as an orange-red oil (40 mg, 98% yield). R_f (4% Et_2O/pentane) 0.43. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.68 (m, 4H), 7.40–7.34 (m, 3H), 4.18 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.2, 131.8, 131.3, 131.1, 129.6 (q, J=307.1 Hz), 128.1, 127.7, 126.8, 126.7 (d, J=3.0 Hz), 125.4 (d, J=2.3 Hz), 125.3, 33.5 (q, J=2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.46 (s). IR (KBr): 3058, 2925, 2855, 1599, 1509, 1439, 1364, 1212, 1107, 954, 867, 827, 753, 476 cm^{-1}. GC–MS m/z 242 (M^+). HRMS (EI) calcd for $C_{12}H_9SF_3$: 242.0377; Found: 242.0379.

*4.2.6. 2-((Trifluoromethylthio)methyl)benzonitrile (**3f**).* Following th e general procedure and workup, **3f** was isolated as an orange-red oil (35 mg, 96% yield). R_f (10% Et_2O/pentane) 0.28. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J=7.7 Hz, 1H), 7.53 (t, J=7.7 Hz, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.36 (t, J=7.7 Hz, 1H), 4.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 132.2, 132.1, 129.3 (q, J=307.4 Hz), 129.2–129.1 (m), 127.6, 115.8, 111.6, 31.3 (q, J=2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.22 (s). IR (KBr): 2958, 2926, 2854, 2228, 1600, 1488, 1451, 1259, 1153, 1113, 958, 869, 757, 678 cm^{-1}. GC–MS m/z 217 (M^+). HRMS (EI) calcd for $C_9H_6SF_3N$: 217.0173; Found: 217.0174.

*4.2.7. 4-((Trifluoromethylthio)methyl)benzonitrile (**3g**).* Following the general procedure and workup, **3g** was isolated as an orange-red oil (35 mg, 95% yield). R_f (10% Et_2O/pentane) 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J=8.3 Hz, 2H), 7.38 (d, J=8.3 Hz, 2H), 4.05 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 131.6, 129.3 (q, J=307.3 Hz), 128.6, 117.3, 111.0, 32.8 (q, J=2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.34 (s). IR (KBr): 2961, 2926, 2853, 2231, 1609, 1504, 1415, 1148, 1116, 1021, 827, 757, 550 cm^{-1}. GC–MS m/z 217 (M^+). HRMS (EI) calcd for $C_9H_6SF_3N$: 217.0173; Found: 217.0175.

*4.2.8. (2-Nitrobenzyl)(trifluoromethyl)sulfane (**3h**).* Following the ge neral procedure and workup, **3h** was isolated as an orange-red oil

(38 mg, 96% yield). R_f (4% Et_2O/pentane) 0.20. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J=8.0 Hz, 1H), 7.60–7.51 (m, 1H), 7.44 (t, J=8.0 Hz, 2H), 4.33 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 132.9, 131.6, 131.2 (d, J=1.0 Hz), 129.8 (q, J=307.1 Hz), 128.3, 124.7, 31.1 (q, J=2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.40 (s). IR (KBr): 2961, 2925, 2853, 1612, 1529, 1345, 1261, 1112, 788, 707 cm^{-1}. GC–MS m/z 237 (M^+). HRMS (EI) calcd for $C_8H_6SF_3NO_2$: 237.0071; Found: 237.0078.

*4.2.9. (3-Nitrobenzyl)(trifluoromethyl)sulfane (**3i**).* Following the general procedure and workup, **3i** was isolated as an orange-red oil (38 mg, 96% yield). R_f (5% Et_2O/pentane) 0.25. ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (t, J=1.8 Hz, 1H), 8.12–8.09 (m, 1H), 7.63 (d, J=7.7 Hz, 1H), 7.48 (t, J=3.8 Hz, 1H), 4.13 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 136.7, 133.8, 129.2 (q, J=307.3 Hz), 128.9, 122.7, 122.0, 32.4 (q, J=2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.30 (s). IR (KBr): 2960, 2926, 2854, 1532, 1353, 1317, 1260, 1150, 1113, 906, 862, 811, 756, 719, 680 cm^{-1}. GC–MS m/z 237 (M^+). HRMS (EI) calcd for $C_8H_6SF_3NO_2$: 237.0071; Found: 237.0073.

*4.2.10. (4-Nitrobenzyl)(trifluoromethyl)sulfane (**3j**).* Following the general procedure and workup, **3j** was isolated as an orange-red oil (38 mg, 95% yield). R_f (5% Et_2O/pentane) 0.23. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J=8.5 Hz, 2H), 7.54 (d, J=8.5 Hz, 2H), 4.18 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 141.9, 129.2 (q, J=307.4 Hz), 128.7, 123.0, 32.5 (q, J=2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.31 (s). IR (KBr): 2960, 2927, 2856, 1711, 1608, 1524, 1494, 1348, 1148, 1115, 1016, 859, 802, 756, 708 cm^{-1}. GC–MS m/z 237 (M^+). HRMS (EI) calcd for $C_8H_6SF_3NO_2$: 237.0071; Found: 237.0072.

*4.2.11. Methyl 4-((trifluoromethylthio)methyl)benzoate (**3k**).* Following the general procedure and workup, **3k** was isolated as an orange-red oil (41 mg, 97% yield). R_f (10% Et_2O/pentane) 0.33. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J=8.1 Hz, 2H), 7.34 (d, J=8.1 Hz, 2H), 4.06 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 139.4, 129.4 (q, J=307.1 Hz), 129.1, 128.8, 127.8, 51.1, 32.9 (q, J=2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.51 (s). IR (KBr): 2956, 2928, 2852, 1724, 1613, 1437, 1415, 1284, 1181, 1112, 1020, 798, 756, 713 cm^{-1}. GC–MS m/z 250 (M^+). HRMS (EI) calcd for $C_{10}H_9SF_3O_2$: 250.0275; Found: 250.0276.

*4.2.12. (3-Methoxybenzyl)(trifluoromethyl)sulfane (**3l**).* Following the general procedure and workup, **3l** was isolated as an orange-red oil (34 mg, 91% yield). R_f (pentane) 0.24. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J=7.9 Hz, 1H), 6.93–6.83 (m, 3H), 4.09 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 136.4, 130.6 (q, J=306.9 Hz), 129.9, 121.1, 114.4, 113.5, 55.2, 34.2 (q, J=2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.67 (s). IR (KBr): 2963, 2838, 1602, 1492, 1456, 1299, 1267, 1114, 1049, 919, 873, 791, 757, 737, 709, 690 cm^{-1}. GC–MS m/z 222 (M^+). HRMS (EI) calcd for $C_9H_9SF_3O$: 222.0326; Found: 222.0327.

*4.2.13. (3-Chlorobenzyl)(trifluoromethyl)sulfane (**3m**).* Following the general procedure and workup, **3m** was isolated as an orange-red oil (34 mg, 89% yield). R_f (4% EtOAc/hexane) 0.31. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.14 (m, 4H), 3.99 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3, 132.8, 128.6 (q, J=307.1 Hz), 128.2, 127.1, 126.4, 125.2, 31.8 (q, J=2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.55 (s). IR (KBr): 2957, 2926, 2855, 1648, 1600, 1515, 1464, 1377, 1261, 1116, 880, 803, 756 cm^{-1}. GC–MS m/z 226 (M^+). HRMS (EI) calcd for $C_8H_6SF_3$: 225.9831; Found: 225.9836.

*4.2.14. (3-Fluorobenzyl)(trifluoromethyl)sulfane (**3n**).*[15] Following the general procedure and workup, **3n** was isolated as an orange-red oil (32 mg, 90% yield). R_f (25% EtOAc/hexane) 0.28. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–6.93 (m, 4H), 4.02 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 137.6 (dd, J=7.7, 1.0 Hz), 130.4 (d, J=8.4 Hz), 128.9 (q, J=307.6 Hz), 124.5 (d, J=2.8 Hz), 115.8 (d, J=22.2 Hz), 115.0 (d, J=21.2 Hz), 33.7 (q, J=2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.57 (s), −112.33 (s). IR (KBr): 2960, 2926, 2855, 1731, 1616, 1527, 1489, 1449, 1347, 1114, 946, 802, 749, 693 cm^{-1}. GC–MS m/z 210 (M^+). HRMS (EI) calcd for $C_8H_6SF_4$: 210.0126; Found: 210.0127.

*4.2.15. 5-Chloro-3-((trifluoromethylthio)methyl)benzo[b]thiophene (**3o**).* Following the general procedure and workup, **3o** was isolated as an orange-red oil (47 mg, 97% yield). R_f (2% Et_2O/pentane) 0.25. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=8.4 Hz, 2H), 7.39 (s, 1H), 7.27 (dd, J=8.4, 1.5 Hz, 1H), 4.24 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 137.5, 129.9, 129.4 (q, J=307.2 Hz), 127.4, 126.8 (d, J=0.6 Hz), 124.3, 123.0, 120.2, 26.3 (q, J=2.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.56 (s). IR (KBr): 2958, 2926, 2854, 1588, 1518, 1423, 1259, 1112, 1078, 862, 835, 795, 757 cm^{-1}. GC–MS m/z 282 (M^+). HRMS (EI) calcd for $C_{10}H_6S_2F_3Cl$: 281.9552; Found: 281.9555.

*4.2.16. 4-Trifluoroethylthio-7-methoxycoumarin (**3p**).* Following the general procedure and workup, **3p** was isolated as a bright yellow solid (46 mg, 98% yield): mp 109–111 °C. R_f (50% Et_2O/hexane) 0.35. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J=8.6 Hz, 2H), 7.16–6.62 (m, 2H), 6.37 (s, 1H), 4.16 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 159.4, 154.7, 147.7, 129.0 (q, J=307.5 Hz), 124.5, 123.9, 111.9 (d, J=50.0 Hz), 109.9, 100.3, 54.8, 29.0 (q, J=2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.41 (s). IR (KBr): 2942, 1716, 1608, 1557, 1516, 1460, 1448, 1425, 1398, 1379, 1350, 1291, 1270, 1209, 1171, 1155, 1135, 1124, 1104, 1057, 1023, 989, 901, 865, 847, 822, 760, 721, 703 cm^{-1}. GC–MS m/z 290 (M^+). HRMS (EI) calcd for $C_{12}H_9F_3O_3S$: 290.0224; Found: 290.0227.

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Supplementary data

Copies of NMR spectra for all products. Supplementary data related to this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.073.

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