DOI: 10.1002/cjoc.201500905

Nucleophilic Trifluoromethylthiolation of Alkyl Chlorides, Bromides and Tosylates

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A direct nucleophilic trifluoromethylthiolation of alkyl chlorides, bromides and tosylates with $AgSCF_3$ was described. It was found that the presence of nBu$_4$NI or a combination of nBu$_4$NI/nBu$_4$NBr significantly enhanced the reaction rates. The reaction conditions were mild, thus allowing the tolerance of a variety of functional groups.

Keywords trifluoromethylthiolation, nucleophilic, fluorine, alkyl halides

Introduction

Due to its strong electron-withdrawing and high lipophilic nature,[1] the trifluoromethylthio group (CF_3S—) is generally considered by the medicinal chemists as one of the most prominent groups in their isostere-based drug design.[2] Consequently, development of efficient methods for the introduction of trifluoromethylthio group has been the recent focus of pharmaceutical/agrochemical industries, and academic community as well.[3] In this context, in the past several years, we have witnessed an explosive increase in the number of the methodologies for the incorporation of CF_3S group into small molecules that involved the formation of C_{sp}-SCF_3, C_{sp^2}-SCF_3 or C_{sp^3}-SCF_3 bond by employing transition metal catalyzed trifluoromethylthiolation,[4] radical trifluoromethylthiolation[5] or direct trifluoromethylthiolation with an electrophilic trifluoromethylthiolating reagent.[6]

One of the simplest methods for the formation of alkyl-trifluoromethylthioether is the nucleophilic trifluoromethylthiolation of an appropriate electrophile by a nucleophilic trifluoromethylthiolating reagent.[7] For example, direct nucleophilic trifluoromethylthiolation of alkyl halides with $Hg(SCF_3)_2$ was reported by Muetterties as early as 1959.[7a] Yet, with few exceptions,[7e,7g] most of the known nucleophilic trifluoromethylthiolation methods involved the reactions of activated electrophiles such as allylic halides, benzylic halides or α-halo carbonyl compounds. Herein, we reported a nucleophilic trifluoromethylthiolation of unactivated alkyl chlorides, bromides and tosylates using easily available $AgSCF_3$[8] as the nucleophile. The reactions were typically conducted at 80—100 ℃ and a variety of functional groups were compatible.

Experimental

General information

All solvents were purified by standard method. ^{1}H NMR spectra were recorded on a 500 MHz, 400 MHz or 300 MHz. ^{19}F NMR were recorded on a 376 MHz or 282 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker AM400 spectrometer and Agilent 400 or 500 MHz spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0 and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as inter standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash column chromatograph was carried out using 300—400 mesh silica gel at medium pressure. Detection of melting point was conducted on the SGW X-4 microscopic melting point meter.

Materials

All reagents were received from commercial sources. Solvents were freshly dried and degassed according to the purification handbook *Purification of Laboratory Chemicals* before using.

General procedure A for trifluoromethylthiolation of alkyl bromides

A 25 mL Schlenk tube charged with a magnetic bar, alkyl bromides (0.5 mmol), nBu$_4$NI (0.65 mmol, 240.5 mg) and $AgSCF_3$ (0.65 mmol, 135.2 mg) was evacuated under high vacuum and backfilled with argon three times. Fresh distilled acetone (2.0 mL) was then added under argon via syringe. The reaction mixture was stirred at 80 ℃ for 3—24 h, and then cooled to room temperature. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column

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Received December 27, 2015; accepted January 14, 2016; published online March 8, 2016.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201500905 or from the author.

chromatography to give the corresponding products.

General procedure B for trifluoromethylthiolation of alkyl chlorides

A 25 mL Schlenk tube charged with a magnetic bar, alkyl chlorides (0.5 mmol), nBu$_4$NI (1.0 mmol, 370.0 mg), nBu$_4$NBr (1.0 mmol, 322.0 mg) and AgSCF$_3$ (1.0 mmol, 208.0 mg) was evacuated under high vacuum and backfilled with argon three times. Fresh distilled THF (2.0 mL) was then added under argon via syringe. The reaction mixture was stirred at 80 ℃ for 15 h, and then cooled to room temperature. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography to give the corresponding products.

General procedure C for trifluoromethylthiolation of alkyl tosylates

A 25 mL Schlenk tube charged with a magnetic bar, alkyl tosylates (0.5 mmol), nBu$_4$NI (1.0 mmol, 370.0 mg) and AgSCF$_3$ (1.0 mmol, 208.0 mg) was evacuated under high vacuum and backfilled with argon three times. Fresh distilled CH$_3$CN (2.0 mL) was then added under argon via syringe. The reaction mixture was stirred at 100 ℃ for 6 h, and then cooled to room temperature. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography to give the corresponding products.

(3-Phenylpropyl)(trifluoromethyl)thioether (Scheme 2, **2a**)[7g] The general procedure A with (3-bromopropyl) benzene (198 mg, 1.0 mmol), gave 157 mg (72%) of (3-phenylpropyl)(trifluoromethyl) sulfane as a colorless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.40 (m, 2H), 7.34－7.24 (m, 3H), 2.95 (t, J=7.3 Hz, 2H), 2.82 (t, J=7.5 Hz, 2H), 2.11 (m, 2H); ^{19}F NMR (376 MHz, CDCl$_3$) δ: –41.00 (s, 3F); ^{13}C NMR (126 MHz, CDCl$_3$) δ: 140.58, 131.27 (q, J=306.4 Hz), 128.63, 128.51, 126.30, 34.31, 30.70, 29.24. MS (EI) m/z: 220.1; HRMS (EI) m/z: calcd for C$_{10}$H$_{11}$F$_3$S: 220.0534, found 220.0529. IR v: 3065, 3029, 2928, 1497, 1455, 1115, 744, 699 cm^{-1}.

(4-(Naphthalen-2-yloxy)butyl)(trifluoromethyl)-thioether (Scheme 2, **2b**) The general procedure A with 2-(4-bromobutoxy)naphthalene (139 mg, 0.5 mmol), gave 154 mg (99%) of (4-(naphthalen-2-yloxy)butyl) (trifluoromethyl)sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.85－7.80 (m, 3 H), 7.54－7.50 (m, 1H), 7.44－7.40 (m, 1H), 7.26－7.17 (m, 2H), 4.10 (t, J=5.4 Hz, 2H), 3.02 (t, J=6.6 Hz, 2H), 2.01－1.94 (m, 4H); ^{19}F NMR (376 MHz, CDCl$_3$) δ: –40.99 (s, 3F); ^{13}C NMR (126 MHz, CDCl$_3$) δ: 156.82, 134.69, 131.33 (q, J = 305.7 Hz), 129.54, 129.13, 127.78, 126.83, 126.51, 123.76, 118.97, 106.67, 67.05, 29.78, 28.10, 26.50. MS (EI) m/z: 300.1; HRMS (EI): calcd for C$_{15}$H$_{15}$OF$_3$S: 300.0796, found 300.0798. IR v: 3059, 2945, 2877, 1629, 1600, 1509, 1465, 1391, 1260, 1218, 1107, 1051, 840, 753 cm^{-1}.

Ethyl 7-((trifluoromethyl)thio)heptanoate (Scheme 2, **2c**) The general procedure A with ethyl 7-bromoheptanoate (118 mg, 0.5 mmol), gave 118 mg (92%) of ethyl 7-[(trifluoromethyl)thio]heptanoate as a pale yellow liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 4.09 (q, J= 7.1 Hz, 2H), 2.84 (t, J=7.4 Hz, 2H), 2.26 (t, J=7.4 Hz, 2H), 1.70－1.56 (m, 4H), 1.43－1.28 (m, 4H), 1.22 (t, J=7.1 Hz, 3H); ^{19}F NMR (376 MHz, CDCl$_3$) δ: –41.39 (s, 3F); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 173.64, 131.29 (q, J=305.6 Hz), 60.28, 34.22, 29.82, 29.30, 28.51, 28.19, 24.77, 14.27. MS (EI) m/z: 258.1; HRMS (EI): calcd for C$_{10}$H$_{17}$O$_2$F$_3$S: 258.0901, found 258.0903. IR v: 2939, 2861, 1735, 1251, 1119 cm^{-1}.

1-(4-(3-((Trifluoromethyl)thio)propoxy)phenyl)-ethanone (Scheme 2, **2d**)[9] The general procedure A with 1-[4-(3-bromopropoxy)phenyl]ethanone (128 mg, 0.5 mmol), gave 138 mg (99%) of 1-(4-(3-((trifluoromethyl)thio)propoxy)phenyl)ethanone as a pale yellow liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.90 (d, J=8.2 Hz, 2H), 6.90 (d, J=8.3 Hz, 2H), 4.11 (t, J=5.6 Hz, 2H), 3.08 (t, J=7.1 Hz, 2H), 2.51 (s, 3H), 2.21－2.16 (m, 2H); ^{19}F NMR (376 MHz, CDCl$_3$) δ: –41.17 (s, 3F); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 196.66, 162.48, 131.07 (q, J=307.5 Hz), 130.61, 114.40, 114.13, 65.57, 29.22, 26.56 (q, J=2.1 Hz), 26.30. MS (EI) m/z: 278.1; HRMS (EI): calcd for C$_{12}$H$_{13}$O$_2$F$_3$S: 278.0588, found 278.0591. IR v: 2943, 1678, 1602, 1508, 1392, 1359, 1272, 1255, 1116, 835 cm^{-1}.

2-(4-((Trifluoromethyl)thio)butyl)isoindoline-1,3-dione (Scheme 2, **2e**)[9] The general procedure A with 2-(4-bromobutyl)isoindoline-1,3-dione (140 mg, 0.5 mmol), gave 144 mg (99%) of 2-(4-((trifluoromethyl)-thio)butyl)isoindoline-1,3-dione as a pale yellow liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.79－7.77 (m, 2H), 7.68－7.65 (m, 2H), 3.67 (t, J=6.7 Hz, 2H), 2.89 (t, J=7.0 Hz, 2 H), 1.80－1.69 (m, 4 H); ^{19}F NMR (376 MHz, CDCl$_3$) δ: –41.20 (s, 3F); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.31, 134.02, 132.04, 131.08 (q, J=307.4 Hz), 123.26, 37.06, 29.30 (q, J=2.0 Hz), 27.42, 26.77. MS (EI) m/z: 303.1; HRMS (EI): calcd for C$_{13}$H$_{12}$NO$_2$F$_3$S: 303.0541, found 303.0538. IR v: 2945, 1772, 1712, 1397, 1374, 1119, 1032, 720 cm^{-1}.

4-Methyl-7-(4-((trifluoromethyl)thio)butoxy)-2*H*-chromen-2-one (Scheme 2, **2f**)[9] The general procedure A with 7-(4-bromobutoxy)-4-methyl-2*H*-chromen-2-one (155 mg, 0.5 mmol), gave 123 mg (77%) of 4-methyl-7-(4-((trifluoromethyl)thio)butoxy)-2*H*-chromen-2-one as a pale yellow liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.43 (d, J=8.8 Hz, 1H), 6.79 (dd, J=8.8, 2.4 Hz, 1H), 6.71 (d, J=2.4 Hz, 1H), 6.06 (d, J=1.0 Hz, 1H), 4.00 (t, J=5.5 Hz, 2H), 2.94 (t, J=6.6 Hz, 2H), 2.34 (s, 3H), 1.95－1.84 (m, 4H); ^{19}F NMR (376 MHz, CDCl$_3$) δ: –41.13 (s, 3 F); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 161.76, 161.12, 155.13, 152.56 131.06 (q, J=305.9 Hz), 125.55, 113.54, 112.40, 111.82, 101.24, 67.56, 29.55 (q, J=2.0 Hz), 27.73, 26.22, 18.54. MS (EI) m/z: 332.2; HRMS (EI): calcd for C$_{15}$H$_{15}$O$_3$F$_3$S: 332.0694, found 332.0690. IR v: 2950, 1720, 1615, 1388, 1294, 1119, 1071, 849 cm^{-1}.

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9-(4-((Trifluoromethyl)thio)butyl)-9*H*-carbazole (Scheme 2, **2g**) The general procedure A with 9-(4-bromobutyl)-9*H*-carbazole (155 mg, 0.5 mmol), gave 152 mg (94%) of 9-(4-((trifluoromethyl)thio) butyl)-9*H*-carbazole as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, J=7.7 Hz, 2H), 7.56 (t, J=8.4 Hz, 2H), 7.42 (d, J=8.2 Hz, 2H), 7.34 (t, J=7.2 Hz, 2H), 4.32 (t, J=7.0 Hz, 2H), 2.86 (t, J=7.2 Hz, 2H), 2.02−1.97 (m, 2H), 1.82−1.76 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.98 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 140.32, 131.15 (q, J = 305.9 Hz), 125.84, 122.99, 120.52, 119.10, 108.56, 42.30, 29.59 (q, J=2.0 Hz), 27.84, 27.22. MS (EI) *m*/*z*: 323.2; HRMS (EI): calcd for $C_{17}H_{16}NF_3S$: 323.0956, found 323.0955. IR *v*: 3047, 2943, 2860, 1592, 1484, 1468, 1325, 1122, 752 cm^{-1}.

Dimethyl 2-allyl-2-(2-((trifluoromethyl)thio)ethyl) malonate (Scheme 2, **2h**) The general procedure A with dimethyl 2-allyl-2-(2-bromoethyl)malonate (59 mg, 0.21 mmol), gave 63 mg (99%) of dimethyl 2-allyl-2-(2-((trifluoromethyl)thio)ethyl)malonate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.67−5.58 (m, 1H), 5.14 (d, J=12.4, 2H), 3.73 (s, 6H), 2.85−2.81 (m, 2H), 2.66 (d, J=7.4 Hz, 2H), 2.26−2.22 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.35 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.71, 131.56, 130.89 (q, J= 306.3 Hz), 119.82, 57.20, 52.66, 37.84, 33.44, 24.97 (q, J=2.1 Hz). MS (EI) *m*/*z*: 300.1; HRMS (EI): calcd for $C_{11}H_{15}O_4F_3S$: 300.0643, found 300.0644. IR *v*: 3457, 2956, 1735, 1115, 927, 756 cm^{-1}.

(4-Nitrophenethyl)(trifluoromethyl)thioether (Scheme 2, **2i**) The general procedure A with 1-(2-bromoethyl)-4-nitrobenzene (119 mg, 0.5 mmol), gave 120 mg (96%) of (4-nitrophenethyl) (trifluoromethyl)-sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, J=8.6 Hz, 2H), 7.38 (d, J=8.6 Hz, 2H), 3.18−3.12 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.01 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.16, 146.38, 131.03 (q, J = 308.7 Hz), 129.64, 124.01, 35.77, 30.58 (q, J=1.9 Hz). MS (EI) *m*/*z*: 251.1; HRMS (EI): calcd for $C_9H_8NO_2F_3S$: 251.0228, found 251.0223. IR *v*: 3081, 2945, 2856, 1606, 1521, 1348, 1115, 855, 757 cm^{-1}.

(4-(4-Methoxyphenoxy)butyl)(trifluoromethyl) thioether (Scheme 2, **2j**)[9] The general procedure A with 1-(4-bromobutoxy)-4-methoxybenzene (129 mg, 0.5 mmol), gave 105 mg (74%) of (4-(4-methoxyphenoxy) butyl)(trifluoromethyl)sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.85 (s, 4H), 3.95 (t, J=5.4 Hz, 2H), 3.78 (s, 3H), 2.98 (t, J=6.7 Hz, 2H), 1.93−1.87 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.15 (s, 3F); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.02, 153.08, 131.27 (q, J=281.6 Hz), 115.51, 114.76, 67.73, 55.74, 29.77 (q, J=2.0 Hz), 28.26, 26.49. MS (EI) *m*/*z*: 280.1; HRMS (EI): calcd for $C_{12}H_{15}O_2F_3S$: 280.0745, found 280.0743. IR *v*: 2950, 2871, 1508, 1469, 1232, 1118, 1040, 825, 734 cm^{-1}.

Ethyl 4-(4-((trifluoromethyl)thio)butoxy)benzoate (Scheme 2, **2k**)[9] The general procedure A with ethyl 4-(4-bromobutoxy)benzoate (150 mg, 0.5 mmol), gave 149 mg (92%) of ethyl 4-(4-((trifluoromethyl)thio)butoxy)benzoate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=8.9 Hz, 2H), 6.87 (d, J=8.9 Hz, 2H), 4.33 (q, J=7.1 Hz, 2H), 4.00 (t, J=5.4 Hz, 2H), 2.95 (t, J=6.5 Hz, 2H), 1.90−1.89 (m, 4H), 1.36 (t, J=7.1 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.19 (s, 3F); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 166.35, 162.55, 131.59, 131.19 (q, J = 307.7 Hz), 123.11, 114.02, 67.23, 60.67, 29.68, 27.95, 26.36, 14.39. MS (EI) *m*/*z*: 322.2; HRMS (EI): calcd for $C_{14}H_{17}O_3F_3S$: 322.0851, found 322.0848. IR *v*: 2952, 1712, 1607, 1510, 1278, 1254, 1115, 771 cm^{-1}.

1-(1*H*-Pyrrol-1-yl)-2-((trifluoromethyl)thio)propan-1-one (Scheme 2, **2l**) The general procedure A with 2-bromo-1-(1*H*-pyrrol-1-yl)propan-1-one (80 mg, 0.4 mmol), nBu$_4$NI (222 mg, 0.6 mmol), $AgSCF_3$ (125 mg, 0.6 mmol), gave 81 mg (90%) of 1-(1*H*-pyrrol-1-yl)-2-((trifluoromethyl)thio)propan-1-one as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.11 (s, 1H), 7.18−7.16 (m, 1H), 7.04−7.03 (m, 1H), 6.36−6.33 (m, 1H), 4.68 (q, J=7.1 Hz, 1H), 1.70 (d, J=7.1 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.60 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 186.41, 130.70 (q, J= 307.0 Hz), 128.84, 127.27, 117.98, 111.40, 44.09 19.94. MS (EI) *m*/*z*: 222.9; HRMS (EI): calcd for $C_8H_8NOF_3S$: 223.0279, found 223.0277. IR *v*: 3299, 2984, 2936, 1636, 1544, 1451, 1403, 1115, 1049, 1009, 910, 756 cm^{-1}.

Phenyl 2-((trifluoromethyl)thio)propanoate (Scheme 2, **2m**) The general procedure A with phenyl 2-bromopropanoate (91.2 mg, 0.4 mmol), nBu$_4$NI (222 mg, 0.6 mmol), $AgSCF_3$ (125 mg, 0.6 mmol), gave 75 mg (75%) of phenyl 2-((trifluoromethyl)thio) propanoate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (t, J=7.8 Hz, 2H), 7.27 (t, J=7.4 Hz, 1H), 7.12 (d, J=7.7 Hz, 2H), 4.16 (q, J=7.3 Hz, 1H), 1.74 (d, J=7.3 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.35 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.89, 150.55, 130.24 (q, J = 308.6 Hz), 129.71, 126.48, 121.19, 41.57 (q, J=1.7 Hz), 18.14. MS (EI) *m*/*z*: 250.1; HRMS (EI): calcd for $C_{10}H_9O_2F_3S$: 250.0275, found 250.0274. IR *v*: 1766, 1593, 1493, 1454, 1322, 1232, 1195, 1164, 1115, 1076, 757, 688 cm^{-1}.

***N*,*N*-Diethyl-2-((trifluoromethyl)thio)propanamide** (Scheme 2, **2n**) The general procedure A with 2-bromo-*N*,*N*-diethylpropanamide (104 mg, 0.5 mmol), gave 101 mg (88%) of *N*,*N*-diethyl-2-((trifluoromethyl)-thio)propanamide as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.19 (q, J=6.8 Hz, 1H), 3.42−3.30 (m, 4H), 1.63 (d, J=6.8 Hz, 3H), 1.23 (t, J=7.1 Hz, 3H), 1.11 (t, J=7.1 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.90 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.50, 131.01 (q, J=306.8 Hz), 42.51, 40.93, 40.54, 20.48, 14.63, 12.64. MS (EI) *m*/*z*: 229.1; HRMS (EI): calcd for $C_8H_{14}NOF_3S$: 229.0784, found 229.0743. IR *v*: 2976, 2933, 1651, 1513, 1461, 1432, 1263, 1135, 1120, 1062, 792 cm^{-1}.

1-(4-Fluorophenyl)-2-((trifluoromethyl)thio)propan-1-one (Scheme 2, **2o**) The general procedure A with 2-bromo-1-(4-fluorophenyl)propan-1-one (115 mg, 0.5 mmol), gave 105 mg (83%) of 1-(4-fluorophenyl)-2-((trifluoromethyl)thio)propan-1-one as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08−8.04 (m, 2H), 7.18−7.14 (m, 2H), 5.24 (q, J=6.6 Hz, 1H), 1.90 (d, J=6.6 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −39.85 (s, 3F), −103.09 (m, 1F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 194.82, 166.43 (d, J=256.9 Hz), 131.64 (d, J=9.5 Hz), 130.82 (q, J=308.4 Hz), 130.58 (d, J=3.0 Hz), 116.38 (d, J=22.1 Hz), 44.33, 19.76. MS (EI) m/z: 251.9; HMRS (EI): calcd for $C_{10}H_8OF_4S$: 252.0232, found 252.0230. IR v: 3353, 3075, 2936, 2876, 1686, 1599, 1508, 1452, 1410, 1315, 1205, 1239, 1115, 975, 849, 819, 756, 591 cm^{-1}.

1-(4-Bromophenyl)-2-((trifluoromethyl)thio)propan-1-one (Scheme 2, **2p**)[7i] The general procedure A with 2-bromo-1-(4-bromophenyl)propan-1-one (145 mg, 0.5 mmol), gave 109 mg (70%) of 1-(4-bromophenyl)-2-((trifluoromethyl)thio)propan-1-one as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, J=8.8 Hz, 2H), 7.65 (J=8.8 Hz, 2H), 4.89 (q, J=7.1 Hz, 1H), 1.71 (d, J=7.1 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −39.75 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.23, 132.79, 132.35, 130.61 (q, J = 308.5 Hz), 130.16, 129.45, 44.14, 19.47. MS (EI) m/z: 312, 314; HRMS (EI): calcd for $C_{10}H_8OF_3SBr$: 311.9431, found 311.9429. IR v: 2936, 1687, 1585, 1566, 1485, 1452, 1398, 1380, 1317, 1296, 1241, 1203, 1118, 1072, 1011, 972, 952, 840, 769, 756, 471 cm^{-1}.

1-(4-Chlorophenyl)-2-((trifluoromethyl)thio)propan-1-one (Scheme 2, **2q**) The general procedure A with 2-bromo-1-(4-chlorophenyl)propan-1-one (123 mg, 0.5 mmol), gave 98 mg (73%) of 1-(4-chlorophenyl)-2-((trifluoromethyl)thio)propan-1-one as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J=8.6 Hz, 2H), 7.63 (d, J=8.6 Hz, 2H), 5.22 (q, J=6.6 Hz, 1H), 1.90 (d, J=6.6 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −39.79 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.17, 140.38, 132.51, 130.77 (q, J=308.4 Hz), 130.25, 129.49, 44.31, 19.64. MS (EI) m/z: 268.0; HRMS (EI): calcd for $C_{10}H_8OF_3SCl$: 267.9936, found 267.9940. IR v: 2934, 1686, 1590, 1319, 1119, 842 cm^{-1}.

2-((Trifluoromethyl)thio)-3,4-dihydronaphthalen-1(2*H*)-one (Scheme 2, **2r**) The general procedure A with 2-bromo-3,4-dihydronaphthalen-1(2*H*)-one (112 mg, 0.5 mmol), gave 80 mg (65%) of 2-((trifluoromethyl)thio)-3,4-dihydronaphthalen-1(2*H*)-one as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (dd, J=7.9, 1.0 Hz, 1H), 7.53 (td, J=7.5, 1.4 Hz, 1H), 7.38−7.30 (m, 1H), 7.27 (d, J=7.9 Hz, 1H), 4.36 (dd, J=10.9, 4.4 Hz, 1H), 3.17−3.06 (m, 2H), 2.75−2.63 (m, 1H), 2.47−2.31 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −38.73 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.17, 142.97, 134.31, 131.10, 130.77 (q, J=308.2 Hz), 128.77, 128.17, 127.18, 51.76, 31.23, 28.18. MS (EI) m/z: 245.9; HRMS (EI): calcd for $C_{11}H_9OF_3S$: 246.0326, found 246.0330. IR v: 2937, 1687, 1599, 1486, 1456, 1434, 1354, 1312, 1276, 1224, 1116, 1025, 1006, 949, 895, 816, 795, 757, 741, 619, 471 cm^{-1}.

6-((Trifluoromethyl)thio)hexyl cyclohexane carboxylate (Scheme 4, **3b**) The general procedure B with 6-chlorohexyl cyclohexanecarboxylate (98.4 mg, 0.4 mmol), gave 119 mg (95%) of 6-((trifluoromethyl)thio)hexyl cyclohexanecarboxylate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.02 (t, J=6.3 Hz, 2H), 2.84 (t, J=7.2 Hz, 2H), 2.28−2.21 (m, 1H), 1.86 (d, J=12.7 Hz, 2H), 1.70−1.58 (m, 7H), 1.45−1.31 (m, 6H), 1.26−1.16 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −41.60 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.13, 131.16 (q, J=305.7 Hz), 63.85, 43.24, 29.71 (q, J=2.0 Hz), 29.27, 29.03, 28.44, 28.06, 25.75, 25.43, 25.34. MS (EI) m/z: 312.1; HRMS (EI): calcd for $C_{14}H_{23}O_2F_3S$: 312.1371, found 312.1374. IR v: 2935, 2858, 1731, 1452, 1117, 756 cm^{-1}.

6-((Trifluoromethyl)thio)hexyl benzoate (Scheme 4, **3c**) The general procedure B with 6-chlorohexyl benzoate (96 mg, 0.4 mmol), gave 146 mg (95%) of 6-((trifluoromethyl)thio)hexyl benzoate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04−8.01 (m, 2H), 7.56−7.51 (m, 1H), 7.44−7.39 (m, 2H), 4.30 (t, J=6.5 Hz, 2H), 2.86 (t, J=7.4 Hz, 2H), 1.79−1.68 (m, 4H), 1.51−1.42 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −41.34 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.60, 132.85, 130.88 (q, J = 306.8 Hz), 130.44, 129.52, 128.33, 64.75, 29.75, 29.30, 28.54, 28.12, 25.48. MS (EI) m/z: 306.1; HRMS (EI): calcd for $C_{14}H_{17}O_2F_3S$: 306.0901, found 306.0899. IR v: 2940, 2816, 1720, 1602, 1585, 1491, 1452, 1275, 1116 cm^{-1}.

6-((Trifluoromethyl)thio)hexyl 2-phenylacetate (Scheme 4, **3d**) The general procedure B with 6-chlorohexyl 2-phenylacetate (101 mg, 0.4 mmol), gave 118 mg (92%) of 6-((trifluoromethyl)thio)hexyl 2-phenylacetate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35−7.25 (m, 5H), 4.09 (t, J=6.6 Hz, 2H), 3.62 (s, 2H), 2.84 (t, J=7.4 Hz, 2H), 1.66−1.59 (m, 4H), 1.43−1.30 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −42.36 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.55, 134.18, 131.21 (q, J=306.8 Hz), 129.24, 128.55, 127.07, 64.99, 41.82, 29.71, 29.29, 28.35, 28.00, 25.45. MS (EI) m/z: 320.2, HRMS (EI): calcd for $C_{15}H_{19}O_2F_3S$: 320.1058, found 320.1063. IR v: 2940, 2861, 1735, 1497, 1455, 1115, 723 cm^{-1}.

2-((6-((Trifluoromethyl)thio)hexyl)oxy)tetrahydro-2*H*-pyran (Scheme 4, **3e**) The general procedure B with 2-(6-chlorohexyloxy)tetrahydro-2*H*-pyran (88 mg, 0.4 mmol), gave 130 mg (91%) of 2-((6-((trifluoromethyl)thio)hexyl)oxy)tetrahydro-2H-pyran as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.57 (m, 1H), 3.87−3.81 (m, 1H), 3.74−3.69 (m, 1H), 3.50−3.45 (m, 1H), 3.39−3.33 (m, 1H), 2.85 (t, J=7.4 Hz, 2H), 1.79−1.77 (m, 1H), 1.70−1.64 (m, 3H), 1.58−1.48 (m, 6H), 1.41−1.36 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −41.38 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$)

δ: 131.17 (q, J=305.6 Hz), 98.80, 67.23, 62.21, 30.70, 29.69, 29.44, 29.29, 28.23, 25.60, 25.44, 19.59. MS (EI) m/z: 285.1 (M–H); HRMS (EI): calcd for $C_{12}H_{20}O_2F_3S$ (M-H): 285.1136, found 285.1135. IR v: 2940, 2862, 1455, 1352, 1119, 1078, 1034, 869 cm^{-1}.

(2-(4-Fluorophenoxy)ethyl)(trifluoromethyl)thioether (Scheme 4, **3f**) The general procedure B with 1-(2-chloroethoxy)-4-fluorobenzene (87 mg, 0.5 mmol), gave 100 mg (83%) of (2-(4-fluorophenoxy)ethyl) (trifluoromethyl)sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10−6.93 (m, 2H), 6.94−6.80 (m, 2H), 4.18 (t, J=6.4 Hz, 2H), 3.25 (t, J=6.4 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.98 (s, 3F), –122.99 (s, 1F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.84 (q, J=239.3 Hz), 154.36 (d, J=2.1 Hz), 131.08 (q, J=306.2 Hz), 116.14 (d, J=23.2 Hz), 115.96 (d, J=8.1 Hz), 67.48, 29.13. MS (EI) m/z: 240.1; HRMS (EI): calcd for $C_9H_8OF_4S$: 240.0232, found 240.0229. IR v: 2945, 1507, 1496, 1248, 1222, 1116, 1030, 829 cm^{-1}.

(2-(4-Bromophenoxy)ethyl)(trifluoromethyl)thioether (Scheme 4, **3g**) The general procedure B with 1-bromo-4-(2-chloroethoxy)benzene (117 mg, 0.5 mmol), gave 102 mg (68%) of (2-(4-bromophenoxy)-ethyl)(trifluoromethyl)sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, J=9.0 Hz, 2H), 6.79 (d, J=9.0 Hz, 2H), 4.19 (t, J=6.4 Hz, 2H), 3.26 (t, J=6.4 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.98 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.33, 132.55, 131.03 (q, J=307.4 Hz), 116.55, 113.84, 66.85, 29.02 (q, J=2.1 Hz). MS (EI) m/z: 300.0; HRMS (EI): calcd for $C_9H_8OF_3SBr$: 299.9431, found 299.9435. IR v: 2939, 2881, 1592, 1580, 1489, 1466, 1299, 1243, 1115, 1072, 1029, 822 cm^{-1}.

1-(4-(2-((Trifluoromethyl)thio)ethoxy)phenyl)ethanone (Scheme 4, **3h**) The general procedure B with 1-(4-(2-chloroethoxy)phenyl)ethanone (99 mg, 0.5 mmol), gave 123 mg (93%) of 1-(4-(2-((trifluoromethyl) thio)ethoxy)phenyl)ethanone as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, J=8.9 Hz, 2H), 6.91 (d, J=8.8 Hz, 2H), 4.26 (t, J=6.3 Hz, 2H), 3.27 (t, J=6.4 Hz, 2H), 2.54 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.99 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 196.70, 161.86, 130.95, 130.86 (q, J=307.5 Hz), 130.66, 114.19, 66.56, 28.79, 26.37. MS (EI) m/z: 264.1; HRMS (EI): calcd for $C_{11}H_{11}O_2F_3S$: 264.0432, found 264.0433. IR v: 3003, 1678, 1600, 1508, 1150, 1111, 1017, 829 cm^{-1}.

6-((Trifluoromethyl)thio)hexyl cinnamate (Scheme 4, **3i**). The general procedure B with 6-chlorohexyl cinnamate (106 mg, 0.4 mmol), gave 115 mg (86%) of 6-((trifluoromethyl)thio)hexyl cinnamate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=16.0 Hz, 1 H), 7.53−7.51 (m, 2H), 7.38−7.37 (m, 3H), 6.44 (d, J=16.0 Hz, 1H), 4.20 (t, J=6.6 Hz, 2H), 2.88 (t, J=7.4 Hz, 2H), 1.79−1.63 (m, 4H), 1.51−1.38 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.22 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.97, 144.68, 134.45, 131.22 (q, J = 303.8 Hz), 130.25, 128.88, 128.05, 118.17, 64.32, 29.72, 29.31, 28.53, 28.12, 25.42. MS (EI) m/z: 332.2; HRMS (EI): calcd for $C_{16}H_{19}O_2F_3S$: 332.1058, found 332.1056. IR v: 2940, 2860, 1713, 1638, 1327, 1311, 1202, 1119, 768 cm^{-1}.

6-((Trifluoromethyl)thio)hexyl furan-2-carboxylate (Scheme 4, **3j**) The general procedure B with 6-chlorohexyl furan-2-carboxylate (115 mg, 0.5 mmol), gave 137 mg (92%) of 6-((trifluoromethyl)thio)hexyl furan-2-carboxylate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67−7.50 (m, 1H), 7.15 (d, J=3.5 Hz, 1H), 6.58−6.15 (m, 1H), 4.28 (t, J=6.4 Hz, 2H), 2.86 (t, J=7.3 Hz, 2H), 1.76−1.67 (m, 4H), 1.54−1.43 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.97 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.76, 146.21, 144.80, 131.16 (q, J=305.7 Hz), 117.75, 111.77, 64.69, 29.70, 29.26, 28.47, 28.06, 25.33. MS (EI) m/z: 296.1; HRMS (EI): calcd for $C_{12}H_{15}O_3F_3S$: 296.0694, found 296.0692. IR v: 3445, 2942, 2862, 1728, 1581, 1298, 1118, 764 cm^{-1}.

6-((Trifluoromethyl)thio)hexyl thiophene-2-carboxylate (Scheme 4, **3k**) The general procedure B with 6-chlorohexyl thiophene-2-carboxylate (112 mg, 0.5 mmol), gave 158 mg (91%) of 6-((trifluoromethyl)-thio)hexyl thiophene-2-carboxylate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (dd, J=3.7, 0.8 Hz, 1H), 7.53 (dd, J=5.0, 0.8 Hz, 1H), 7.08 (dd, J=4.7, 3.9 Hz, 1H), 4.27 (t, J=6.6 Hz, 2H), 2.86 (t, J=7.4 Hz, 2H), 1.89−1.61 (m, 4H), 1.52−1.38 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.34 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.54, 133.97, 133.30, 132.24, 131.17 (q, J=306.9 Hz), 127.72, 64.92, 29.75, 29.30, 28.49, 28.10, 25.41. MS (EI) m/z: 312.1; HRMS (EI): calcd for $C_{12}H_{15}O_2F_3S_2$: 312.0466, found 312.0464. IR v: 2940, 2861, 1710, 1526, 1420, 1281, 1262, 1116, 752 cm^{-1}.

6-((Trifluoromethyl)thio)hexyl picolinate (Scheme 4, **3l**) The general procedure B with 6-chlorohexyl picolinate (97 mg, 0.4 mmol), gave 104 mg (85%) of 6-((trifluoromethyl)thio)hexyl picolinate as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74−8.73 (m, 1H), 8.11−8.08 (m, 1H), 7.81 (td, J=7.7, 1.7 Hz, 1H), 7.45 (ddd, J=7.6, 4.7, 1.2 Hz, 1H), 4.39 (t, J=6.8 Hz, 2H), 2.85 (t, J=7.4 Hz, 2H), 1.83−1.77 (m, 2H), 1.70−1.69 (m, 2H), 1.46−1.43 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –42.00 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.23, 149.88, 148.20, 136.95, 131.14 (q, J=305.7 Hz), 126.81, 125.07, 65.68, 29.70, 29.25, 28.45, 28.08, 25.33. MS (EI) m/z: 307; HRMS (EI): calcd for $C_{13}H_{16}NO_2F_3S$: 307.0854; found 307.0857. IR v: 2940, 2861, 1740, 1720, 1306, 1292, 1119, 747 cm^{-1}.

Dodecyl(trifluoromethyl)thioether (Scheme 5, **4a**)[10] The general procedure C with dodecyl 4-methylbenzene sulfonate (170 mg, 0.5 mmol), gave 104 mg (77%) of dodecyl(trifluoromethyl)sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.88 (t, J=7.5 Hz, 2H), 1.72−1.64 (m, 2H), 1.40−1.27 (m, 18H), 0.89 (t, J=6.8 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.41 (s, 3F); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 131.41

(q, J=305.6 Hz), 32.11, 30.06 (q, J=1.9 Hz), 29.81, 29.73, 29.60, 29.54, 29.15, 28.71, 22.87, 14.25. MS (EI) *m*/*z*: 269.3; HRMS (EI): calcd for $C_{13}H_{24}F_3S$ (M–H): 269.1553, found 269.1555. IR *v*: 2926, 2855, 1467, 1153, 1118 cm^{-1}.

Dec-9-en-1-yl(trifluoromethyl)thioether (Scheme 5, **4b**) The general procedure C with dodec-11-enyl 4-methylbenzenesulfonate (169 mg, 0.5 mmol), gave 111 mg (93%) of dec-9-en-1-yl(trifluoromethyl)sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.81 (ddt, J=16.9, 10.2, 6.7 Hz, 1H), 5.03−4.92 (m, 2H), 2.88 (t, J=7.5 Hz, 2H), 2.08−2.02 (m, 2H), 1.73−1.66 (m, 2H), 1.44−1.28 (m, 10H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.36 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.04, 131.22 (q, J=305.6 Hz), 114.16, 33.77, 29.84 (q, J=1.9 Hz), 29.39, 29.24, 28.99, 28.91, 28.86, 28.49. MS (DART POS) *m*/*z*: 241.1 (M+H); HRMS (DART POS): calcd for $C_{11}H_{20}F_3S$ (M+H): 241.1238, found 241.1232. IR *v*: 3078, 2977, 2928, 2856, 1641, 1465, 1153, 1117, 910 cm^{-1}.

(2-(4-Fluorophenoxy)ethyl)(trifluoromethyl)thioether (Scheme 5, **4c**) The general procedure C with 4-fluorophenethyl 4-methylbenzenesulfonate (147 mg, 0.5 mmol), gave 106 mg (95%) of (2-(4-fluorophenoxy) ethyl) (trifluoromethyl)sulfane as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19−7.16 (m, 2H), 7.02 (m, 2H), 3.11 (t, J=7.5 Hz, 2H), 2.98 (t, J=7.5 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.05 (s, 3F), –115.95 (m, 1F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.02 (d , J=245.1 Hz), 134.71 (d, J=3.3 Hz), 131.27 (q, J=307.2 Hz), 130.19 (d, J=8.0 Hz), 115.68 (d, J=21.4 Hz), 35.32, 31.44. MS (EI) *m*/*z*: 224.1; HRMS (EI): calcd for $C_9H_8F_4S$: 224.0283, found 224.0280. IR *v*: 2931, 1602, 1510, 1227, 1159, 1112, 824, 757 cm^{-1}.

(4-Bromophenethyl)(trifluoromethyl)thioether (Scheme 5, **4d**) The general procedure C with 4-bromophenethyl 4-methylbenzenesulfonate (177 mg, 0.5 mmol), gave 136 mg (96%) of (4-bromophenethyl)-(trifluoromethyl)sulfane as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (d, J=8.1 Hz, 2H), 7.09 (d, J=8.1 Hz, 2H), 3.11 (t, J=7.5 Hz, 2H), 2.96 (t, J=7.6 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.99 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.92, 131.94, 131.20 (q, J=307.3 Hz), 130.42, 120.97, 35.50, 31.09 (q, J=1.9 Hz). MS (EI) *m*/*z*: 284.0; HRMS (EI): calcd for $C_9H_8F_3SBr$: 283.9482, found 283.9481. IR *v*: 2927, 1488, 1114, 1073, 1012, 802, 756 cm^{-1}.

(4-Methylphenethyl)(trifluoromethyl)thioether (Scheme 5, **4e**) The general procedure C with 4-methylphenethyl 4-methylbenzenesulfonate (145 mg, 0.5 mmol), gave 86 mg (78%) of (4-methylphenethyl)-(trifluoromethyl)sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, J=7.8 Hz, 2H), 7.12 (d, J=7.5 Hz, 2H), 3.14 (t, J=7.6 Hz, 2H), 2.98 (t, J=7.6 Hz, 2H), 2.37 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.40 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.66, 136.01, 131.36 (q, J=305.9 Hz), 129.53, 128.54, 35.68, 31.48 (q, J=1.7 Hz), 21.15. MS (EI) *m*/*z*: 220.1; HRMS (EI): calcd for $C_{10}H_{11}F_3S$: 220.0534, found 220.0529. IR *v*: 3023, 2926, 1516, 1451, 1115, 806, 756 cm^{-1}.

4-(2-((Trifluoromethyl)thio)ethyl)benzonitrile (Scheme 5, **4f**) The general procedure C with 4-cyanophenethyl 4-methylbenzenesulfonate (151 mg, 0.5 mmol), gave 83 mg (71%) of 4-(2-((trifluoromethyl) thio)ethyl)benzonitrile as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, J=7.9 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 3.14 (t, J=7.2 Hz, 2H), 3.06 (t, J=7.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.00 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.27, 132.61, 131.08 (q, J=307.2 Hz), 129.55, 118.77, 111.10, 36.05, 30.61 (q, J=1.9 Hz). MS (EI) *m*/*z*: 231.1; HRMS (EI): calcd for $C_{10}H_8NF_3S$: 231.0330, found 231.0329. IR *v*: 2940, 2229, 1609, 1506, 1417, 1115, 822 cm^{-1}.

(4-Methoxyphenethyl)(trifluoromethyl)thioether (Scheme 5, **4g**) The general procedure C with 4-methoxyphenethyl 4-methylbenzenesulfonate (153 mg, 0.5 mmol), gave 110 mg (93%) of (4-methoxyphenethyl)-(trifluoromethyl)sulfane as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, J=8.3 Hz, 2H), 6.88 (d, J=8.4 Hz, 2H), 3.81 (s, 3H), 3.11 (t, J=7.7 Hz, 2H), 2.95 (t, J=7.5 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.38 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.62, 131.25 (q, J=306.9 Hz), 131.00, 129.54, 114.12, 55.23, 35.10, 31.51 (q, J=1.7 Hz). MS (EI) *m*/*z*: 236.1; HRMS (EI): calcd for $C_{10}H_{11}OF_3S$: 236.0483, found 236.0488. IR *v*: 3005, 2938, 2837, 1612, 1514, 1466, 1250, 1178, 1108, 1037, 822 cm^{-1}.

(2-Iodobenzyl)(trifluoromethyl)thioether (Scheme 5, **4h**) The general procedure C with 2-iodobenzyl 4-methylbenzenesulfonate (116 mg, 0.3 mmol), gave 87 mg (95%) of (2-iodobenzyl)(trifluoromethyl)sulfane as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, J=7.9 Hz, 1H), 7.41 (d, J=7.5 Hz, 1H), 7.34 (t, J=7.5 Hz, 1H), 7.00 (t, J=7.6 Hz, 1H), 4.22 (s, 2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.30 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 140.07, 138.33, 130.76 (q, J=308.5 Hz), 130.42, 129.86, 128.85, 100.40, 39.74 (q, J=2.4 Hz). MS (EI) *m*/*z*: 318.0, HRMS (EI): calcd for $C_8H_6F_3SI$: 317.9187, found 317.9184. IR *v*: 3061, 1585, 1566, 1465, 1438, 1150, 1115, 1014, 756, 727 cm^{-1}.

(2-(Naphthalen-2-yl)ethyl)(trifluoromethyl)thioether (Scheme 5, **4i**) The general procedure C with 2-(naphthalen-2-yl)ethyl 4-methylbenzenesulfonate (130 mg, 0.4 mmol), gave 80 mg (78%) of (2-(naphthalen-2-yl)ethyl)(trifluoromethyl)sulfane as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, J=8.2 Hz, 1H), 7.91 (d, J=7.5 Hz, 1H), 7.80 (d, J=8.1 Hz, 1H), 7.60−7.50 (m, 2H), 7.45 (t, J=7.5 Hz, 1H), 7.38 (d, J=6.7 Hz, 1H), 3.49 (t, J=8.0 Hz, 2H), 3.26 (t, J=7.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –40.82 (s, 3F); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 135.08, 134.10, 131.55, 131.37 (q, J = 306.8 Hz), 129.16, 127.94, 126.87, 126.57, 125.94, 125.68, 123.09, 33.65, 30.59 (q, J=1.8 Hz). MS (EI) *m*/*z*: 256.1; HRMS (EI): calcd for $C_{13}H_{11}F_3S$: 256.0534, found 256.0538. IR *v*: 061, 2947,

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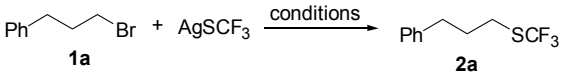
1598, 1511, 1117, 779 cm^{-1}.

2-(2-((Trifluoromethyl)thio)ethyl)isoindoline-1,3-dione (Scheme 5, **4j**) The general procedure C with 2-(1,3-dioxoisoindolin-2-yl)ethyl 4-methylbenzene sulfonate (103 mg, 0.3 mmol), gave 34 mg (41%) of 2-(2-((trifluoromethyl)thio) ethyl)isoindoline-1,3-dione as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87—7.84 (m, 2H), 7.75—7.72 (m, 2H), 3.99 (t, J=7.0 Hz, 2H), 3.20 (t, J=7.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –41.05 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.94, 134.37, 131.93, 130.78 (q, J=307.8 Hz), 123.63, 37.48, 27.97 (q, J=1.9 Hz). MS (EI) m/z: 275.1; HRMS (EI): calcd for $C_{11}H_8NO_2F_3S$: 275.0228, found 275.0231. IR ν: 3476, 3063, 2947, 1775, 1719, 1615, 1468, 1439, 1333, 1115, 1007, 865, 715 cm^{-1}.

Results and Discussion

In 1972, Yagupolskii reported that $AgSCF_3$ can react with activated electrophile 2-bromo-1-phenylethanone to give α-trifluoromethylthiolated ketone in good yield.[7c] Yet, low conversion was observed when other non-activated electrophiles were subjected. $AgSCF_3$ which could be easily prepared from AgF and CS_2 is air,[8] moisture and light insensitive, representing an ideal nucleophilic trifluoromethylthiolating reagent. We reason that the low reactivity of $AgSCF_3$ is likely due to the covalent bond nature of the Ag—S bond in $AgSCF_3$. Thus, if we can make a more ionic trifluoromethylthio intermediate by the addition of an additive, the reactivity of $AgSCF_3$ could be significantly increased. With these in mind, we first examined the nucleophilic trifluoromethylthiolation of (3-bromopropyl)benzene **1a** with $AgSCF_3$ in the presence of different additive. A quick screening revealed that nBu$_4$NI[4a] was superior to copper salts. The formation of alkyl-trifluoromethylthioether **2a** was observed in 84% yield when 1.0 equivalent of nBu$_4$NI was used, while less than 2% of the corresponding products were detected when CuCl, CuBr or CuI was added (Scheme 1, Entries 1—5). To probe if the cation is important for the increased reactivity, we studied the reaction using NaI as the additive, yet, the reaction occurred in less than 2% conversion. These results indicated that upon addition of nBu$_4$NI, it is likely a more reactive nBu$_4$NSCF$_3$ was formed and reacted immediately with electrophile to give the desired trifluoromethylthiolated compound. After identifying the effective additive, we then further studied the effects of the temperature and the solvents on the conversion of the reactions. These studies suggest that the reaction conducted at 80 ℃ proceeded to full conversion after 3 h, while the reactions were much slower if the reactions were conducted below 60 ℃ (Scheme 1, Entries 7—9). Likewise, these studies also disclosed that reactions in polar non-protic solvents gave higher yields (Scheme 1, Entries 10—15). Since acetone is much easy for workup, we chose acetone for further substrate scope investigation. Interestingly, the yield of the product could be further improved to 97% when 1.3 equivalents of $AgSCF_3$ and nBu_4NI were used (Scheme 1, Entry 16).

Scheme 1 Trifluoromethylthiolation of alkyl bromide in the presence of different additives[a]



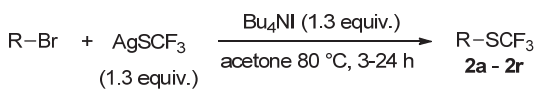
Entry	Additive	Solvent	Temp/℃	Time/h	Yield[b]/%
1	none	DMF	80	2	—
2	CuI	DMF	80	2	—
3	CuCl	DMF	80	2	—
4	CuBr	DMF	80	2	—
5	Bu_4NI	DMF	80	2	84
6	NaI	DMF	80	2	—
7	Bu_4NI	DMF	60	2	58
8	Bu_4NI	DMF	40	2	26
9	Bu_4NI	DMF	r.t.	2	14
10	Bu_4NI	DMSO	80	3	46
11	Bu_4NI	THF	80	3	67
12	Bu_4NI	Acetone	80	3	79
13	Bu_4NI	CH_3CN	80	3	63
14	Bu_4NI	NMP	80	3	74
15	Bu_4NI	DMAc	80	3	58
16[c]	Bu_4NI	Acetone	80	3	97

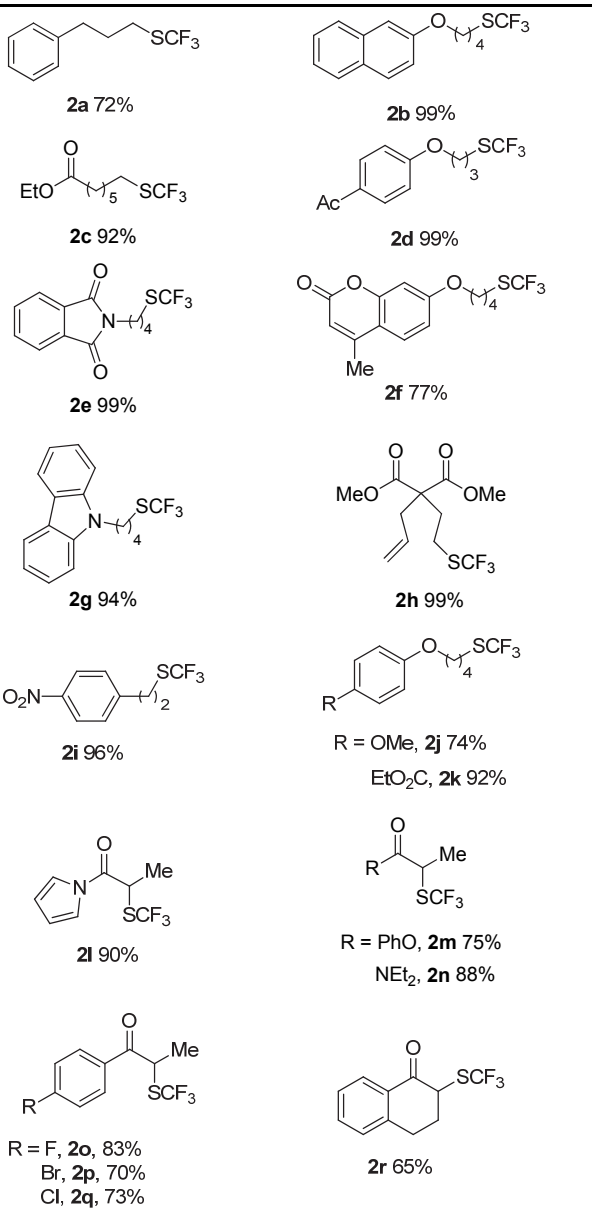
[a] Reaction conditions: alkylbromide (0.05 mmol), $AgSCF_3$ (0.05 mmol), solvent (1.0 mL), additive (0.05 mmol). [b] Yields were determined by ^{19}F NMR analysis using $PhCF_3$ as internal standard. [c] nBu$_4$NI (0.065 mmol), $AgSCF_3$ (0.065 mmol).

The optimized conditions were applied to a variety of readily available alkyl bromides, the results were summarized in Scheme 2. In general, the reactions of a variety of primary alkyl bromides gave rise to the corresponding trifluoromethylthiolated products in high yields (Scheme 2, **2a**—**2k**). Reactions of secondary alkyl bromides were much more difficult. Nevertheless, activated secondary alkyl bromides successfully reacted to give the trifluoromethylthiolated products in 65%—90% yields (Scheme 2, **2l**—**2r**). A variety of functional groups such as ester, enolizable ketone, amide, and halogens were compatible with the mild reaction conditions.

Alkyl chlorides are generally less reactive than alkyl bromides. Not surprisingly, reaction of 1-chlorododecane with 1.0 equivalent of $AgSCF_3$ in the presence of 1.0 equivalent of nBu$_4$NI in acetone at 100 ℃ generated the corresponding trifluoromethylthiolated product in less than 5% yield (Scheme 3, Entry 1). When THF was used as the solvent, the yield was improved to 28%, while reactions in other polar solvents such as DMF, DMSO, DMA, CH_3CN were much less effective (Scheme 3, Entries 2—6). To our delight, the yield was improved to 43% when a combination of 1.3 equivalents of nBu$_4$NI and 1.3 equivalents of $PhEt_3NI$ was

Scheme 2 Scope for trifluoromethylthiolation of alkyl bromides in the presence of nBu$_4$NI[a]

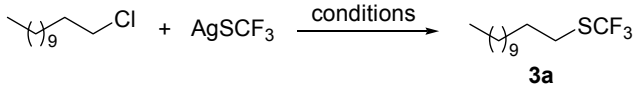




[a] Reaction conditions: alkylbromides (0.5 mmol), AgSCF$_3$ (0.65 mmol), nBu$_4$NI (0.65 mmol), acetone (2.0 mL), 80 ℃, 3—24 h, isolated yields.

used (Scheme 3, Entry 7). The yields could be further increased to 90% when the reaction was conducted when a combination of 2.0 equivalents of AgSCF$_3$, 2.0 equivalents of nBu$_4$NI and 2.0 equivalents of PhEt$_3$NI was used at 80 ℃ for 10 h, as determined by ^{19}F NMR spectroscopy with PhCF$_3$ as an internal standard (Scheme 3, Entry 8). However, GC/MS analysis of the product after column chromatography purification indicated that an inseparable mixture of trifluoromethylthiododecane and iododododecane was formed in the reaction. Interestingly, by replacing PhEt$_3$NI with a cheaper tertiary amine salt nBu$_4$NBr, the halogenated side product was not observed any more (Scheme 3, Entry 9).

Scheme 3 Trifluoromethylthiolation of alkyl chloride in the presence of different additive[a]



Entry	Additive	Solvent	Temp/℃	Time/h	Yield[b]/%
1	Bu$_4$NI	Acetone	100	4	4
2	Bu$_4$NI	DMF	100	4	＜1
3	Bu$_4$NI	THF	100	4	28
4	Bu$_4$NI	CH$_3$CN	100	4	7
5	Bu$_4$NI	DMAc	100	4	3
6	Bu$_4$NI	DMSO	100	4	＜1
7[c]	Bu$_4$NI/PhEt$_3$NI	THF	100	4	43
8[d]	Bu$_4$NI/PhEt$_3$NI	THF	80	10	90
9[e]	Bu$_4$NI/nBu$_4$NBr	THF	80	15	95

[a] Reaction conditions: alkyl-Cl (0.05 mmol), AgSCF$_3$ (0.065 mmol), solvent (1.0 mL), nBu$_4$NI (0.065 mmol). [b] The yield was determined by ^{19}F NMR analysis using PhCF$_3$ as internal standard. [c] PhEt$_3$NI (0.065 mmol) as another additive. [d] nBu$_4$NI (0.10 mmol), PhEt$_3$NI (0.10 mmol), AgSCF$_3$ (0.10 mmol). [e] nBu$_4$NI (0.10 mmol), nBu$_4$NBr (0.10 mmol), AgSCF$_3$ (0.10 mmol).

Under the optimized reaction conditions, a variety of primary alkyl chlorides were allowed to react with AgSCF$_3$ to give the corresponding trifluoromethylthiolated products in good to excellent yields. Again, many functional groups were compatible with the reaction conditions.

Alkyl alcohols are abundant, cheap commodities that are easily available. Very recently, Rueping and Qing independently reported two trifluoromethylthiolating methods that direct conversion of alkyl alcohols to trifluoromethylthioalkyl ethers.[11,12] The reaction was proposed to proceed through nucleophilic trifluoromethylthiolation of an in situ formed sulfonyl ester. In light of these findings, we wondered whether isolable alkyl tosylates can be directly converted to trifluoromethylthioalkyl ethers. A quick screening of the reaction conditions indicated that reaction of alkyl tosylates with AgSCF$_3$ occurred smoothly after 6 h at 100 ℃ to give the corresponding trifluoromethylthiolated compounds in good yields when the reactions were conducted in the presence of 2.0 equivalents of nBu$_4$NI in CH$_3$CN. Under these conditions, a variety of alkyl tosylates could be converted to alkyl trifluoromethylthioethers in good to excellent yields (Scheme 5). Likewise, secondary alkyl tosylates were unable to be trifluoromethylthiolated under these reaction conditions.

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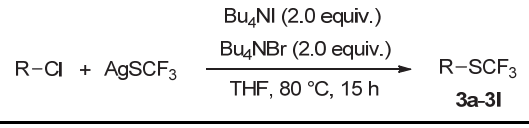
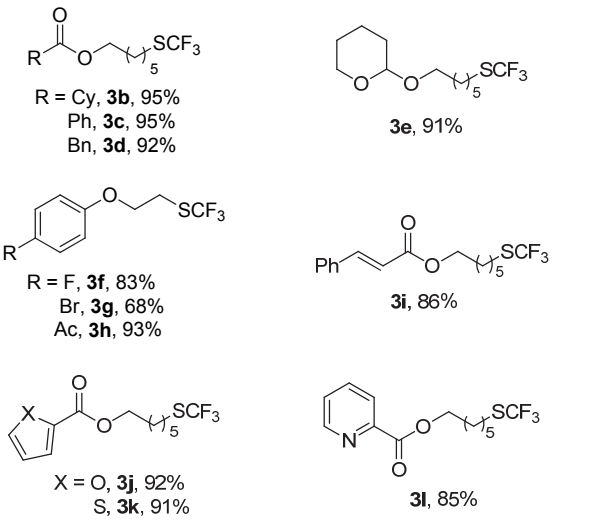
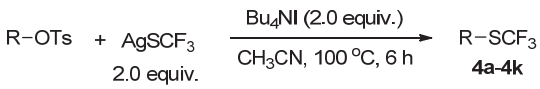
Scheme 4 Scope for trifluoromethylthiolation of alkyl chlorides in the presence of nBu$_4$NI/nBu$_4$NBr[a]

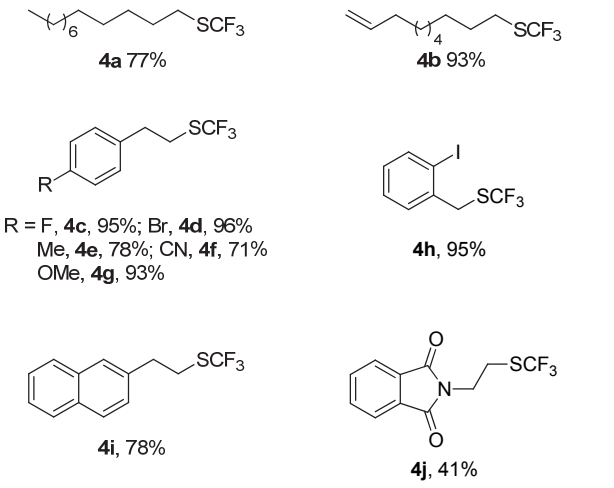




[a] Reaction conditions: alkyl chlorides (0.5 mmol), $AgSCF_3$ (1.0 mmol), nBu$_4$NI (1.0 mmol), nBu$_4$NBr (1.0 mmol), THF (2.0 mL), 80 ℃, 15 h, isolated yields.

Scheme 5 Scope for trifluoromethylthiolation of alkyl tosylates in the presence of nBu$_4$NI[a]





[a] Reaction conditions: alkyl tosylates (0.5 mmol), $AgSCF_3$ (1.0 mmol), nBu$_4$NI (1.0 mmol), CH_3CN (2.0 mL), 100 ℃, 6 h, isolated yield.

Conclusions

In summary, we have developed a new approach for direct nucleophilic trifluoromethylthiolation of alkyl chlorides, bromides and tosylates. The addition of nBu$_4$NI could significantly promote the trifluoromethylthiolation reaction. It is likely that the in situ formed nBu$_4$NSCF$_3$ is more ionic than $AgSCF_3$, thus giving rise to fast nucleophilic substitution reactions. Attempts to convert unactivated secondary alcohols to the corresponding trifluoromethylthioethers are undergoing currently in our laboratory and will be reported in the near future.

Acknowledgement

The authors thank the financial support from the National Basic Research Program of China (No. 2012CB821600), the National Natural Science Foundation of China (No. 21372247/21421002) and SIOC.

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