Supporting Information

Copper-mediated oxidative trifluoromethylthiolation of potassium aryltrifluoroborates with elemental sulfur and Ruppert-Prakash reagent

By
Srinivas Reddy Dubbaka*, Azmi Reddy Atthunuri§, Koraboina Chandra Prakash§, Prabhu Rangabashyam, Satyanarayana Gadde, and Rajesh Kothandaraman

Department of Medicinal Chemistry, Albany Molecular Research Singapore Research Centre, Pte. Ltd., 61 Science Park Road, #05-01, Galen, Science Park II, Singapore-117525

TABLE OF CONTENTS
I. General information……………………………………………………………………...S2
II. Reagents’ commercial source information table……………………………………..S2
III. Optimization conditions for trifluoromethylthiolation of potassium aryltrifluoroborate …………………………………………………………………………………S3-S4
IV. General procedure……………………………………………………………………....S5
V. Spectral data of Aryl-SCF₃ compounds…….………………………………………S6-S12
VI. References……………………………………………………………………………...S13
EXPERIMENTAL

I General information: $^1$H and $^{19}$F NMR Spectra were recorded on a Bruker 400 MHz or 300 MHz in the solvents indicated; chemical shifts are reported in units (ppm) by assigning CDCl$_3$ resonance in the $^1$H spectrum as 7.26 ppm. $^{19}$F NMR chemical shifts were determined relative to CFCl$_3$ as internal standard and are measured proton decoupled. All coupling constants ($J$ values) were reported in Hertz (Hz). GC-MS spectra were measured on Shimadzu GCMS-QP2010S. Column chromatography was performed on silica gel 200-300 mesh on CombiFlash®. If not specially mentioned, all the solvents and reagents were used as purchased from Sigma-Aldrich, Combi-Blocks, Matrix and Oakwood and without further purification.

II Reagents’ commercial sources: Reactants (boronic acids or trifluoroborates) were purchased from Combi-Blocks, Tokyo chemical industry (TCI) Japan, Frontier Scientific and Aldrich and used without purification. Commercial sources for other relevant reagents are shown below.

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Commercial source</th>
<th>CAS no</th>
<th>Product no</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuSCN</td>
<td>Strem</td>
<td>1111-67-7</td>
<td>93-2964</td>
</tr>
<tr>
<td>CF$_3$SiMe$_3$ (Ruppert-Prakash reagent)</td>
<td>Oakwood</td>
<td>81290-20-2</td>
<td>007685</td>
</tr>
<tr>
<td>Ag$_2$CO$_3$</td>
<td>Aldrich</td>
<td>534-16-7</td>
<td>179647</td>
</tr>
<tr>
<td>Sulfur</td>
<td>Aldrich</td>
<td>7704-34-9</td>
<td>84683</td>
</tr>
<tr>
<td>K$_3$PO$_4$</td>
<td>Aldrich</td>
<td>7778-53-2</td>
<td>P5629</td>
</tr>
</tbody>
</table>
III Optimization conditions for trifluoromethylthiolation of potassium aryltrifluoroborate

Table S1. Identifying optimal additives of potassium aryltrifluoroborates for trifluoromethylthiolation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>%Yield (4a)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOH•H₂O</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Na₂CO₃</td>
<td>40</td>
</tr>
<tr>
<td>3c</td>
<td>Cs₂CO₃</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>NaHCO₃</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>KH₂PO₄</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>NaOAc</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>Et₃N</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>pyridine</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>NaF</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>KF</td>
<td>28</td>
</tr>
<tr>
<td>11</td>
<td>AgF</td>
<td>49</td>
</tr>
</tbody>
</table>

²Reaction conditions: 1a (1.0 equiv, 0.10 mmol), CuSCN (1.0 equiv), CuSCN (1.0 equiv), 1,10-phenthroline (Phen, 2.0 equiv), S₈ (8.0 equiv), Ag₂CO₃ (2.0 equiv), additive (2.0 equiv), 4Å M.S (20 mg), TMSCF₃ (5.0 equiv), DMF, 70 °C, 20 h. bYield determined by ¹⁹F NMR with 4-fluorobenzonitrile as an internal standard added after the reaction.
Table S2. Identifying optimal solvent of potassium aryltrifluoroboroates for trifluoromethylthiolation

\[
\text{MeO-} \text{BF}_3K + S_8 + \text{TMSCF}_3 \xrightarrow{\text{CuSCN (1.0 equiv)}} \text{MeO-} \text{-SCF}_3
\]

| Entry | Additives     | % Yield (4a)\(|^b|) |
|-------|---------------|-----------------------|
| 1     | THF           | 10                    |
| 2     | Toluene       | 35                    |
| 3\(^c\) | CH$_2$Cl$_2$  | 0                     |
| 4     | Acetone       | 1                     |
| 5     | DMF           | 80                    |
| 6     | DMA           | 40                    |
| 7     | DMSO          | 20                    |
| 8     | water         | 0                     |
| 9     | DME           | 20                    |
| 10    | THF/H$_2$O    | 9                     |
| 11    | iPrOAc        | 28                    |
| 12    | EtOAc         | 38                    |
| 13    | DMF/toluene (1/1) | 82                |

\(^a\)Reaction conditions: 1a (1.0 equiv, 0.10 mmol), CuSCN (1.0 equiv), 1,10-phentroline (Phen, 2.0 equiv), S$_8$ (8.0 equiv), Ag$_2$CO$_3$ (2.0 equiv), K$_3$PO$_4$ (2.0 equiv), 4Å M.S. (20 mg), Solvent, 70 °C, 20 h. \(^b\)Yield determined by $^{19}$F NMR with 4-fluorobenzonitrile as an internal standard added after the reaction
IV General procedure for the copper-mediated trifluoromethylthiolation of potassium aryl and heteroaryltrifluoroborates with S$_8$ and TMSCF$_3$ (Table 3).

Trifluoroborate (0.20 mmol, 1.0 equiv), CuSCN (24.3 mg, 0.20 mmol, 1.0 equiv), 1,10-phenthroline (72.0 mg, 0.4 mmol, 2.0 equiv), S$_8$ (410 mg, 1.6 mmol, 8.0 equiv), Ag$_2$CO$_3$ (110 mg, 0.4 mmol, 2.0 equiv) were weighed into a 20 mL tube. 4Å powdered molecular sieves (50 mg) and K$_3$PO$_4$ (84.9 mg, 0.5 mmol, 2.5 equiv) were quickly added to the tube under N$_2$ atmosphere. Anhydrous DMF (2.5 mL), toluene (2.5 mL) and followed by TMSCF$_3$ (150 µL, 1.0 mmol, 5.0 equiv) were added to the reaction mixture under nitrogen atmosphere. The reaction vessel was sealed with a cap and the mixture was stirred at 70 ºC for 20 h. The resulting mixture was cooled to room temperature. For the compounds reported with isolated yields (4a, 4b, 4c, 4d, 4e, 4f, 4g, 4j, 4k, 4n, 4o, and 4p) the reaction mixture was filtered through Celite and washed with EtOAc (20 mL). The combined solutions were washed with brine. The organic phase was dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified Combiflash with hexanes/EtOAc to afford the desired compounds.

The low yielding products (4h, 4i, 4l, 4m, 4q and 4r) were not isolated and their yields were determined only by $^{19}$F NMR of the reaction mixture. For the compounds reported with $^{19}$F NMR yields, 4-fluorobenzonitrile (0.20 mmol) was added as reference to the reaction mixture, which was stirred for 5 min, and then diluted with EtOAc (5 mL) and brine (5 mL). The layers were separated and an organic aliquot was withdrawn for the $^{19}$F NMR measurement in CDCl$_3$. 
V  Spectral data of Aryl-SCF$_3$ compounds (Table 3) (Note: Same spectral data placed in the paper):

1-Methoxy-4-[(trifluoromethyl)thio]benzene (4a).$^1$

Compound 4a was isolated in 70% yield (29.1 mg). $^1$H NMR (CDCl$_3$, 400 MHz): δ ppm 7.57 (d, $J = 8.6$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 3.83 (s, 3H); $^{19}$F NMR (CDCl$_3$, 376 MHz) δ ppm −44.40 (s, 3F); GC–MS m/z 208 (M$^+$). The $^{19}$F NMR spectral data correspond to previously reported data.

1-Butoxy-4-[(trifluoromethyl)thio]benzene (4b).$^2$

Compound 4b was isolated in 60% yield (30.0 mg). $^1$H NMR (CDCl$_3$, 400 MHz): δ ppm 7.54 (d, $J = 6.6$ Hz, 2H), 6.91 (d, $J = 6.8$ Hz, 2H), 3.98 (t, $J = 6.5$ Hz, 2H), 1.81–1.74 (m, 2H), 1.52–1.47 (m, 2H), 0.98 (t, $J = 6.7$ Hz, 3H); $^{19}$F NMR (CDCl$_3$, 376 MHz) δ ppm −43.94 (s, 3F); GC–MS m/z 250 (M$^+$). These spectroscopic data correspond to previously reported data.
1-(Benzyloxy)-4-[(trifluoromethyl)thio]benzene (4c).³

Compound 4c was isolated in 68% yield (38.6 mg). ¹H NMR (CDCl₃, 400 MHz): δ ppm 7.57 (d, J = 9.0 Hz, 2H), 7.41–7.38 (m, 5H), 7.00 (d, J = 8.8 Hz, 2H), 5.09 (s, 2H); ¹⁹F NMR (CDCl₃, 376 MHz) δ ppm –43.83 (s, 3F); GC–MS m/z 284 (M⁺). These spectroscopic data correspond to previously reported data.

1-Methyl-4-[(trifluoromethyl)thio]benzene (4d).¹

Compound 4d was isolated in 55% yield (21.2 mg). ¹H NMR (CDCl₃, 400 MHz): δ ppm 7.53 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 2.39 (s, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ ppm –43.67 (s, 3F); GC–MS m/z 192 (M⁺). The ¹⁹F NMR spectral data correspond to previously reported data.

4-[(Trifluoromethyl)thio]biphenyl (4e).³

Compound 4e was isolated in 72% yield (36.6 mg). ¹H NMR (CDCl₃, 400 MHz): δ ppm 7.72 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.61–7.57 (m, 2H), 7.47 (t, J =
7.5 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H); \(^{19}\text{F} \text{NMR (CDCl}_3, 376 \text{ MHz}) \delta \text{ ppm } -43.45 \text{ (s, 3F); GC–MS } m/z \text{ 254 (M}^+\text{). These spectroscopic data correspond to previously reported data.}

\text{1-[(Trifluoromethyl)thio]naphthalene (4f).}^3

\begin{center}
\text{SCF}_3
\end{center}

\text{4f}

Compound 4f was isolated in 50\% yield (22.8 mg). \(^1\text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ ppm 8.53 (d, } J = 8.5 \text{ Hz, 1H), 7.96 (t, } J = 8.4 \text{ Hz, 2H), 7.87 (d, } J = 8.0 \text{ Hz, 1H), 7.63 (t, } J = 7.6 \text{ Hz, 1H), 7.55 (t, } J = 7.3 \text{ Hz, 1H), 7.47 (t, } J = 7.7 \text{ Hz, 1H); } ^{19}\text{F NMR (CDCl}_3, 376 \text{ MHz) } \delta \text{ ppm } -42.19 \text{ (s, 3F); GC–MS } m/z \text{ 228 (M}^+\text{). These spectroscopic data correspond to previously reported data.}

\text{1-Chloro-4-[(trifluoromethyl)thio]benzene (4g).}^1

\begin{center}
\text{SCF}_3
\end{center}

\text{Cl}

\text{4g}

Compound 4g was isolated in 40\% yield (16.9 mg). \(^1\text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ ppm 7.59 (d, } J = 8.4 \text{ Hz, 2H), 7.40 (d, } J = 8.5 \text{ Hz, 2H); } ^{19}\text{F NMR (CDCl}_3, 376 \text{ MHz) } \delta \text{ ppm } -43.31 \text{ (s, 3F); GC–MS } m/z \text{ 212 (M}^+\text{). These spectroscopic data correspond to previously reported data.}

\text{1-Methoxy-3-[(trifluoromethyl)thio]benzene (4h).}^4
The yield (40%) of 4h was determined by $^{19}$F NMR. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ ppm –43.13 (s, 3F); GC–MS m/z 208 (M$^+$$^*$). These spectroscopic data correspond to previously reported data.

1-Methy-3-[(trifluoromethyl)thio]benzene (4i).$^5$

Compound 4i was isolated in 50% yield (19.2 mg). $^1$H NMR (CDCl$_3$, 400 MHz): δ ppm 7.48–7.28 (m, 2H), 7.22–7.01 (m, 2H), 2.38 (s, 3H); $^{19}$F NMR (CDCl$_3$, 376 MHz) δ ppm –42.71 (s, 3F); GC–MS m/z 192 (M$^+$$^*$). NMR spectral data correspond to previously reported data.

1-Isopropyl-3-[(trifluoromethyl)thio]benzene (4j).$^6$

Compound 4j was isolated in 65% yield (28.6 mg). $^1$H NMR (CDCl$_3$, 400 MHz): δ ppm 7.49–7.30 (m, 2H), 7.24–7.07 (m, 2H), 2.91 (sept, $J = 8.0$ Hz, 1H), 1.24 (d, $J = 8.0$ Hz, 6H); $^{19}$F NMR (CDCl$_3$, 376 MHz) δ ppm –42.71 (s, 3F); GC–MS m/z 220 (M$^+$$^*$). NMR spectral data correspond to previously reported data.
3-[(Trifluoromethyl)thio]biphenyl (4k).³

![Structure of 4k](image)

Compound 4k was isolated in 72% yield (36.6 mg). ¹H NMR (CDCl₃, 400 MHz): δ ppm 7.90 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.66–7.58 (m, 3H), 7.53–7.38 (m, 4H); ¹⁹F NMR (CDCl₃, 376 MHz) δ ppm –43.00 (s, 3F); GC–MS m/z 254 (M⁺). These spectroscopic data correspond to previously reported data.

3-[(Trifluoromethyl)thio]acetophenone (4l).⁵ᵇ

![Structure of 4l](image)

The yield (15%) of 4l was determined by ¹⁹F NMR. ¹⁹F NMR (CDCl₃, 376 MHz) δ ppm –42.50; GC–MS m/z 220 (M⁺). The ¹⁹F NMR spectral data correspond to previously reported data.

1-Methoxy-2-[(trifluoromethyl)thio]benzene (4m).⁴

![Structure of 4m](image)
The yield (35%) of 4m was determined by $^{19}$F NMR. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ ppm –42.40 (s, 3F); GC–MS m/z 208 (M$^+$). The $^{19}$F NMR spectral data correspond to previously reported data.

1-Methy-2-[(trifluoromethyl)thio]benzene (4n).\(^1\)

![Structure of 4n](image)

Compound 4n was isolated in 55% yield (21.2 mg). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ ppm 7.65 (d, $J = 7.8$ Hz, 1H), 7.41–7.30 (m, 2H), 7.24 (d, $J = 7.4$ Hz, 1H), 2.54 (s, 3H); $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ ppm –42.89 (s, 3F); GC–MS m/z 192 (M$^+$). These spectroscopic data correspond to previously reported data.

1-Methoxy-2-methyl-4-[(trifluoromethyl)thio]benzene (4o).\(^7\)

![Structure of 4o](image)

Compound 4o was isolated in 62% yield (27.5 mg). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ ppm 7.65 (dd, $J = 8.6$, 2.2 Hz, 1H), 7.40 (brd, $J = 2.2$ Hz, 1H), 6.83 (d, $J = 8.5$ Hz, 1H), 3.86 (s, 3H), 2.22 (s, 3H); $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ ppm –43.88 (s, 3F); GC–MS m/z 222 (M$^+$). These spectroscopic data correspond to previously reported data.

1-Methoxy-2-chloro-4-[(trifluoromethyl)thio]benzene (4p).\(^8\)
Compound 4p was isolated in 70% yield (33.9 mg). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ ppm 7.67 (d, $J = 2.2$ Hz, 1H), 7.53 (dd, $J = 8.6$, 2.2 Hz, 1H), 6.95 (d, $J = 8.6$ Hz, 1H), 3.94 (s, 3H); $^{19}$F NMR (CDCl$_3$, 376 M Hz) $\delta$ ppm −43.56 (s, 3F); GC–MS $m/z$ 242 ($M^+$). These spectroscopic data correspond to previously reported data.

4-[(Trifluoromethyl)thio]pyridine (4q).$^1$

The yield (33%) of 4q was determined by $^{19}$F NMR. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ ppm −40.45; GC–MS $m/z$ 179 ($M^+$). The $^{19}$F NMR spectral data correspond to previously reported data.

2-Methoxy-3-[(trifluoromethyl)thio]pyridine (4r).$^2$

The yield (26%) of 4r was determined by $^{19}$F NMR. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ ppm −43.88; GC–MS $m/z$ 209 ($M^+$). The $^{19}$F NMR spectral data correspond to previously reported data.
VI References


