Trifluoromethylation of Heterocycles
in Water at Room Temperature

James C. Fennwelald, Bruce H. Lipshutz*

Department of Chemistry & Biochemistry
University of California, Santa Barbara, CA 93106
PHONE: 805-893-2521
FAX: 805-893-8265
E MAIL: lipshutz@chem.ucsb.edu
WWW: http://www.chem.ucsb.edu/~lipshutzgroup/

Supporting Information

I. General Information S2
II. Standard Procedures S2-7
   i. Surfactant screening S2-3
   ii. Surfactant strength screening S3
   iii. Peroxide screening S4
   iv. Metal additives S4-5
   v. Portion wise addition S5
   vi. Representative procedure S6
   vii. Recycling study S6
   viii. Surfactant solutions S7
III. Compound data S7-10
IV. References S10-11
V. $^1$H and $^{13}$C NMR S11-24
Experimental

I. General Information

The water used in this study was HPLC grade and was degassed prior to use by bubbling a flow of argon through the mixture for several hours. All commercially available reagents were used without further purification unless otherwise stated. The surfactant TPGS-750-M is commercially available from Sigma-Aldrich but can be synthesized through a previously published procedure. Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). The developed chromatogram was analyzed by UV lamp (254 nm) and/or aqueous potassium permanganate (KMnO₄), and developed by applying heat with a heat gun. Flash chromatography was performed in glass columns using Silica Flash® P60 (SiliCycle, 40-63 µm). ′H and ′³C spectra were recorded at 23 °C on a Varian UNITY INOVA 500 MHz. Chemical shifts in ′H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ′³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.23 ppm) on the δ scale. GC/MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column a HP-5MS cross-linked 5% phenylmethyl- polysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min.

II. Standard Procedures

i. Procedure for surfactant screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1 x 5mm) with septum was added 2 wt % surfactant ([0.5], 0.2 mL, Table 1), 4-γ-butylpyridine (0.10 mmol, 15 uL), and sodium trifluoromethanesulfinate (0.30 mmol, 47 mg) and the mixture was then cooled to ~ 5 °C. Then via syringe 70 wt % TBHP (0.50 mmol, 68 uL) was added. The mixture was allowed to stir at rt (~ 23 °C) for 24 h, quenched with saturated NaHCO₃ (1 mL), and then extracted with EtOAc (1 mL). The percent conversion was determined by GC.
Table 1: Impact of the surfactant for the conversion of 1 to 2

<table>
<thead>
<tr>
<th>entry</th>
<th>surfactant(^a)</th>
<th>conversion ((%))(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TPGS-750-M(^1,2)</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>PTS-600 (^3,5)</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>Cremophor</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>Triton X 100</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>Brij-30</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>TPGS-1000</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>PQS(^6)</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>17</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: substrate (0.1 mmol); NaSO\(_2\)CF\(_3\) (3 equiv); TBHP (5 equiv); surfactant:water (2% w/w), \(^b\) % conversion, by GC.

ii. Loading of surfactant screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1x5mm) with septum was added TPGS-750-M ([0.5], 0.2 mL, Table 2), 4-t-butylpyridine (0.10 mmol, 15 uL), and sodium trifluoromethanesulfinate (0.30 mmol, 47 mg), and the mixture was then cooled to ~ 5 °C. Then via syringe 70 wt % TBHP (0.50 mmol, 68 uL) was added. The mixture was allowed to stir at rt (~ 23 °C) for 24 h, quenched with saturated NaHCO\(_3\) (1 mL), and then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Table 2: Impact of the weight percent of TPGS-750-M for the conversion of 1 to 2

<table>
<thead>
<tr>
<th>entry</th>
<th>weight (%)</th>
<th>conversion ((%))(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: Substrate (0.1 mmol); NaSO\(_2\)CF\(_3\) (3 equiv.); TBHP (5 equiv.); TPGS-750-M:Water (2% w/w), \(^b\) % conversion, by GC.
iii. Peroxide screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) and a septum was added 2 wt % TPGS-750-M (0.5 mmol, 0.2 mL), 4-t-butylpyridine (0.10 mmol, 15 µL), and sodium trifluoromethanesulfinate (0.30 mmol, 47 mg), and the mixture was then cooled to ~ 5 °C. The peroxide (Table 3) was then added dropwise for liquid reagents, while for solids it was added slowly: 70 wt % TBHP (0.50 mmol, 68 µL), 80% CHP (0.5 mmol, 94 µL), benzoyl peroxide (0.5 mmol, 121 mg), and 30% hydrogen peroxide (0.5 mmol, 40 µL). The mixture was allowed to stir at rt (~ 23 °C) for 24 h, and then quenched with saturated NaHCO₃ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. The crude material was passed through a bed a silica gel with 20% EtOAc:hex.

Table 3. Peroxide screening for the conversion of 1 to 2

<table>
<thead>
<tr>
<th>entry</th>
<th>peroxide</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBHP</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>CHP</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>Bz₂O₂</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>H₂O₂</td>
<td>0</td>
</tr>
</tbody>
</table>

*a Conditions: Substrate (0.1 mmol); NaSO₂CF₃ (3 equiv); peroxide (5 equiv); TPGS-750-M:Water (2% w/w)*

iv. Metal additives

To a 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) with a septum was added 2 wt % TPGS-750-M (0.5, 0.3 mL), annulated pyridine 3 or substituted indole 4 (0.15 mmol), sodium trifluoromethanesulfinate (0.45 mmol, 70 mg), and one of various metal salts (10 mol %) and associated ligands (1 equiv; Table 4). The mixture was then cooled to ~ 5 °C. To this mixture was then added 70 wt % TBHP (0.75 mmol, 103 µL) dropwise. After stirring at rt (~ 23 °C) for 24 h, the mixture was then quenched with saturated NaHCO₃ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with 20% EtOAc:hex provided the trifluoromethylated product.
Table 4. Effects of metal salts of the annulated pyridine 3 and substituted indole 4

<table>
<thead>
<tr>
<th>entry</th>
<th>metal</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>73</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl$_2$</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl$_2$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CuI</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>CuOAc</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>CuBr·SMe$_2$</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>NiCl$_2$</td>
<td>42</td>
<td>Nd</td>
</tr>
<tr>
<td>8</td>
<td>Ni$_2$(PPh$_3$)$_2$</td>
<td>47</td>
<td>Nd</td>
</tr>
<tr>
<td>9</td>
<td>Ni(COD)$_2$</td>
<td>45</td>
<td>Nd</td>
</tr>
</tbody>
</table>

*a Conditions: substrate (0.15 mmol); metal salts (10 mol %) NaSO$_2$CF$_3$ (3 equiv); TBHP (5 equiv); TPGS-750-M:water (2% w/w), $^b$ TMEDA (1 equiv), $^c$ 1,10-Phen (1 equiv), $^d$ Not Determined.

v. Portionwise addition of TBHP

To a 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) with a septum was added 2 wt % TPGS-750-M ([0.5], 0.5 mL), and caffeine (0.25 mmol). The sodium trifluoromethanesulfinate (0.75 mmol, 117 mg), and TBHP (70 wt % TBHP; 1.25 mmol, 171 uL) were then added in three equal portions each hour over three hours. The mixture was allowed to stir at rt (~ 23 °C) for 48 h, then quenched with saturated NaHCO$_3$ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with 20% EtOAc:hex provided the trifluoromethylated caffeine analog 6 in 81% yield as a white crystalline solid.
vi. Representative Procedure

To a 5 mL round bottom flask with a PTFE stir bar (1 x 5 mm) with a septum was added 2 wt % TPGS-750-M ([0.5], 2.0 mL), the heterocycle (1.00 mmol), and sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and the mixture was then cooled to ~ 5 °C and stirred for 2-3 min. Then added 70 wt % TBHP (5.00 mmol, 690 uL) dropwise, and the mixture allowed to stir at rt (~ 23 °C) until complete as judged by TLC. It was then quenched with saturated NaHCO₃ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with 20% EtOAc:hex provided the desired trifluoromethylated analog.

Note: An additional water wash may be necessary to remove oxidized surfactant (vitamin E and MPEG)

Note: Highly crystalline solids must be ground to a fine powder (mortar and pestle) thereby forming a uniform suspension in the aqueous medium prior to introduction of reagents. Slow addition of the TBHP is also necessary. Failure to do so causes clumping, and/or rapid release of sulfur dioxide and ultimately quenching of the CF₃ radical to form fluoroform (CHF₃)⁷.

vii. Recycling study

To a 5 mL round bottom flask with a PTFE stir bar (1 x 5 mm) with a septum was added 2 wt % TPGS-750-M ([0.5], 2.0 mL), 4-tert-butylpyridine (1.0 mmol, 148 uL), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg) then cooled to ~ 5 °C. Then added 70 wt % TBHP (5.00 mmol, 690 uL) dropwise (~100 uL/min) and the mixture was allowed to stir at rt (~ 23 °C for 24 h, and then extracted with EtOAc (1 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with 20% EtOAc:hex provided the trifluoromethylated 4-tert-butyl pyridine analog 2. The aqueous reaction medium was then subjected to a subsequent identical reaction, and the cycle repeated four more times, as summarized in Table 5.

Table 5. Recycling of the aqueous reaction mixture for the conversion of 1 to 2.⁸

<table>
<thead>
<tr>
<th>entry</th>
<th>cycle</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>2ᵇ</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>3ᵇ</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>4ᵇ</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>5ᵇ</td>
<td>62</td>
</tr>
</tbody>
</table>

⁸ Conditions: substrate (1 mmol); NaSO₂CF₃ (3 equiv); TBHP (5 equiv); TPGS-750-M:water (2% w/w), b Extracted with EtOAc; aqueous medium used for next reaction.
viii. Surfactant solution preparation

The water used in this study was HPLC grade and was degassed prior to use by bubbling a flow of argon through the mixture for several hours. Then each solution was prepared by weight percent for the desired surfactant concentration with degassed HPLC grade water and subjected to an additional sparging with argon for an hour. All surfactants were stored under an argon atmosphere prior to use. Surfactants PTS and TPGS-750-M are both commercially available from Sigma-Aldrich but can be synthesized through a previously published procedure.

III. Compound Data

\[ \text{4-}t\text{-Butyl-2-trifluoromethylpyridine (2).} \]

The representative procedure was followed using 4-\(t\)-butylpyridine (1.0 mmol, 148 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). Reaction was complete after 15 h by TLC. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex. (\(R_f = 0.55, 20\% \text{ EtOAc:hex}\)) to yield 161 mg, 79% of faint yellow liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.63 (d, \(J = 5.19\) Hz, 1H), 7.66 (s, 1H), 7.47 (d, \(J = 5.19\) Hz, 1H), 1.35 (s, 9H). GC/MS m/z: 203.09. Compound data match that previously reported.

\[ \text{2-(Trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (3-C2) and 3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (3-C3).} \]

The representative procedure was followed using 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (1.0 mmol, 156 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete after 43 h by TLC. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex to yield 394 mg, 73%, (1:3.8 3-C2:3-C3) of faint yellow liquid. Data for (3-C2) (105 mg), (\(R_f = 0.60, 20\% \text{ EtOAc:hex}\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.51 (d, \(J = 7.68\) Hz, 1H) 7.38 (d, \(J = 7.70\) Hz, 1H), 3.14 – 3.08 (m, 2H), 2.88 – 2.81 (m, 2H), 1.95 – 1.86 (m, 2H), 1.79 – 1.64 (m, 4H), GC/MS m/z: 215.1. Data for (3-C3) (289 mg), (\(R_f = 0.55, 20\% \text{ EtOAc:hex}\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.41 (d, \(J = 5.20\) Hz, 1H), 7.33 (d, \(J = 5.19\) Hz, 1H), 3.21 – 3.11 (m, 2H), 2.98 – 2.90 (m, 2H), 1.92 – 1.83 (m, 2H), 1.74 – 1.62 (m,
4H). GC/MS m/z: 215.09. Compound data match that previously reported. Note: Minor region-isomer impurities observed in 1H NMR.

2-Trifluoromethyl melatonin (4). The representative procedure was followed using melatonin (1.0 mmol, 232 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). Reaction was complete as judged by TLC in 44 h. Crude product was purified by passage through a bed a silica gel with EtOAc (Rf = 0.70, 100% EtOAc) to yield 192 mg, 64% of off white solid; 1H NMR (500 MHz, CDCl3) δ 9.97 (s, 1H), 7.54 (d, J = 9.04 Hz, 1H), 7.06 (d, J = 9.06 Hz, 1H), 5.72 (t, J = 5.36 Hz, 1H), 3.89 (s, 3H), 3.47 (m, 2H), 1.95 (s, 3H). GC/MS m/z: 300.11. Compound data match that previously reported.

1-(5-(Trifluoromethyl)-1H-pyrrol-2-yl)ethan-1-one (5). The representative procedure was followed using 1-(1H-pyrrol-2-yl)ethan-1-one (1.0 mmol, 109 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 28 h. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (Rf = 0.45, 20% EtOAc:hex) to yield 110 mg, 62% of an off white solid; 1H NMR (500 MHz, CDCl3) δ 9.79 (brs, 1H), 6.87 (s, 1H), 6.61 (s, 1H), 2.48 (s, 3H). GC/MS m/z: 177.04. Compound data match that previously reported. Note: Minor regio-isomer impurities observed in 1H NMR.

Trifluoromethylated caffeine (6). The representative procedure was followed using caffeine (1.0 mmol, 194 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 23 h. The crude product was purified by passed through a bed a silica gel with 20% EtOAc:hex (Rf = 0.25, 20% EtOAc:hex) to yield 222 mg, 84% of white crystalline solid; 1H NMR (500 MHz, CDCl3) δ 4.16
(s, 3H), 3.58 (s, 3H), 3.40 (s, 3H). GC/MS m/z: 264.08. Compound data match that previously reported. 7

2-Trifluoromethyl-4-cyano-pyridine (7-C2) and 3-trifluoromethyl-4-cyano-pyridine (7-C3). The representative procedure was followed using 4-cyano-pyridine (1.0 mmol, 104 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 44 h. The crude product was purified by passage through a bed of silica gel with 20% EtOAc:hex to yield 97 mg, 55% (1.6:1 7-C2:7-C3) of a colorless oil. Data for 7-C2 (61 mg), (Rf = 0.50, 20% EtOAc:Hex); 1H NMR (500 MHz, CDCl3) δ 8.95 (d, J = 4.93 Hz, 1H), 7.92 (s, 1H), 7.76 (d, J = 4.92 Hz, 1H). GC/MS m/z: 172.02; Data for (7-C3) (35 mg), (Rf = 0.30, 20% EtOAc:hex); 1H NMR (500 MHz, CDCl3) δ 9.11 (s, 1H), 9.03 (d, J = 4.93 Hz, 1H), 7.74 (d, J = 4.94 Hz, 1H). GC/MS m/z: 172.02. Compound data match that previously reported. 7 Note: Minor regio-isomer impurities observed in 1H NMR.

Methyl 5-(trifluoromethyl)pyrazine-2-carboxylate (8). The representative procedure was followed using methyl pyrazine-2-carboxylate (1.0 mmol, 138 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 51 h. The crude product was purified through a bed of silica gel with 20% EtOAc:hex (Rf = 0.35, 20% EtOAc:hex) to yield 112 mg, 54%, as an off white solid; 1H NMR (500 MHz, CDCl3) δ 9.40 (s, 1H), 9.07 (s, 1H), 4.10 (s, 3H). GC/MS m/z: 206.03. Compound data match that previously reported. 7

5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (9). The representative procedure was followed using 1,3,4-thiadiazol-2-amine (1.0 mmol, 101 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 38 h. The crude product was purified through a bed of silica gel with 50% EtOAc:hex (Rf = 0.73,
75% EtOAc:hex) to yield 73 mg, 43%, as an off white solid; $^1$H NMR (500 MHz, MeOD) $\delta$ 4.88 (s, 2H), GC/MS m/z: 169.12. Compound data match that previously reported. $^7$

![Image 10](image)

**4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidine (10).** The representative procedure was followed using 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (1.0 mmol, 154 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 52 h. The crude product by passed through a bed a silica gel with 40% EtOAc:hex (Rf = 0.70, 50% EtOAc:hex) to yield 73 mg, 47%, as an off white solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.67 (br s, 1H), 8.81 (s, 1H), 7.09 (s, 1H). GC/MS m/z: 221.54. Compound data match that previously reported. $^7$

![Image 11](image)

**3-(Trifluoromethyl)quinolone (11).** The representative procedure was followed using quinoline (1.0 mmol, 129 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was stopped after 36 h (no additional conversion passed this point). The crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (Rf = 0.25, 20% EtOAc:hex) to yield 140 mg of product and starting material. The yield was determined by NMR to be 71%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.09 (d, $J$ = 4.15 Hz, 1H), 8.24 (d, $J$ = 8.30 Hz, 1H), 8.10 (d, $J$ = 7.27 Hz, 1H), 8.04 (d, $J$ = 8.28 Hz, 1H), 7.61 (t, $J$ = 7.32 Hz, 1H), 7.52 (m, 1H). GC/MS m/z: 197.16. Compound data match that previously reported. $^8$ Quinoline proton chemical shifts are dependent upon concentration. $^9$

![Image 12](image)

**2-($p$-Tolyl)-6-(trifluoromethyl)pyridine (12).** The representative procedure was followed using 2-($p$-tolyl)pyridine (1.0 mmol, 169 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 18 h. The crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (Rf = 0.35, 10% EtOAc:hex) to yield 161 mg, 68%, as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.97
(d, J = 8.13 Hz, 2H), 7.89 (d, J = 4.61 Hz, 2H), 7.57 (t, J = 3.89 Hz, 1H), 7.30 (d, J = 8.05 Hz, 2H), 2.42 (s, 3H). GC/MS m/z: 237.08. Compound data match that previously reported.10

1-Methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde (13). The representative procedure was followed using 1-methyl-1H-indole-2-carbaldehyde (1.0 mmol, 159 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The crude product was isolated by passage through a bed silica gel with 20% EtOAc:hex (R f = 0.55, 10% EtOAc:hex) to yield 96 mg, 42%, of an off white solid; 1H NMR (500 MHz, CDCl 3 ) δ 10.30 (s, 1H), 7.91 (d, J = 8.32 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.32 (ddd, J = 1.22, 6.66, 8.08 Hz, 1H), 4.15 (s, 3H). 13C NMR (500 MHz, CDCl 3 ) δ 182.62, 154.30, 131.87, 130.72, 127.49, 122.96, 121.88, 110.78, 96.12, 92.77, 32.49. HREIMS calcd for C 11 H 8 F 3 NO: 227.0558. Found: 227.0560

phenyl(6-(trifluoromethyl)pyridin-3-yl)methanone (14). The representative procedure was followed using phenyl(pyridin-3-yl)methanone (1.0 mmol, 183 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The crude product was isolated by passage through a bed silica gel with 15% EtOAc:hex (R f = 0.35, 20% EtOAc:hex) to yield 166 mg, 66%, of a clear solid; 1H NMR (500 MHz, CDCl 3 ) δ 8.73 (d, J = 1.97 Hz, 1H), 8.19 (d, J = 8.22 Hz, 2H), 8.13 (dd, J = 0.96, 7.85 Hz, 1H), 7.94 (m, 1H), 7.75 (d, J = 8.15 Hz, 2H), 7.53 (m, 1H). GC/MS m/z: 251.23. Compound data match that previously reported.8

IV. References

1. Aldrich catalog number. 763918.
5. A. c. n. 698717.

V. $^1$H and $^{13}$C NMR Spectra

4-tert Butyl-2-trifluoromethyl pyridine (2)

Proton NMR (CDCl$_3$)
2-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (3-C2)

Proton NMR (CDCl₃)
3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (3-C3)

Proton NMR (CDCl₃)
2-trifluoromethyl melatonin (4)

Proton NMR (CDCl₃)
1-(5-(trifluoromethyl)-1H-pyrrol-2-yl)ethan-1-one (5)

Proton NMR (CDCl₃)
Trifluoromethylated caffeine (6)

Proton NMR (CDCl₃)
2-trifluoromethyl-4-cyano-pyridine (7-C2)

Proton NMR (CDCl₃)
3-trifluoromethyl-4-cyano-pyridine (7-C3)

Proton NMR (CDCl₃)
methyl 5-(trifluoromethyl)pyrazine-2-carboxylate (8)

Proton NMR (CDCl₃)
5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (9)

Proton NMR (MeOD)
4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidine (10)

Proton NMR (CDCl₃)
3-(trifluoromethyl)quinolone (11)

Proton NMR (CDCl₃)
2-(p-tolyl)-6-(trifluoromethyl)pyridine (12)

Proton NMR (CDCl₃)
1-methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde (13)

Proton NMR (CDCl₃)
Carbon NMR (CDCl₃)
**Elemental Composition Report**

**Sineal Mass Analysis**

Tolerance = 3.0 mDa / DBE: min = -1.5, max = 200.0

Element prediction: Off

**Monoisotopic Mass, Odd and Even Electron ions**

941 formulae evaluated with 27 results within limits (all results up to 1000) for each mass

Elements Used:
C: 0-100  H: 0-200  N: 0-10  O: 0-10  F: 0-5

**Mass** | **Calc. Mass** | **mDa** | **PPM** | **DBE** | **i-FIT** | **formula**
---|---|---|---|---|---|
227.0560 | 227.0558 | 0.2 | 0.0 | 1.0 | 26.5 | C11H8O4F3
227.0564 | 227.0556 | 0.4 | 1.0 | 11.0 | 39.3 | C6H6N7O4
227.0565 | 227.0556 | 0.4 | 1.0 | 11.0 | 39.3 | C6H7N4O4
227.0565 | 227.0556 | 0.4 | 1.0 | 11.0 | 39.3 | C6H7N4O4
227.0554 | 227.0545 | -0.5 | -3.0 | 3.5 | 189.9 | C5H5N10O2F2
227.0554 | 227.0545 | -0.5 | -3.0 | 3.5 | 189.9 | C5H5N10O2F2
227.0554 | 227.0545 | -0.5 | -3.0 | 3.5 | 189.9 | C5H5N10O2F2
227.0554 | 227.0545 | -0.5 | -3.0 | 3.5 | 189.9 | C5H5N10O2F2
227.0557 | 227.0549 | -1.0 | -2.0 | 3.5 | 310.4 | C9H8N4O4F2
227.0556 | 227.0548 | -0.7 | -2.0 | 3.5 | 310.4 | C9H8N4O4F2
227.0554 | 227.0547 | 0.7 | 1.5 | 2.0 | 217.1 | C5H5N7F3
227.0559 | 227.0552 | 0.9 | 1.7 | 2.0 | 217.1 | C5H5N7F3
227.0559 | 227.0552 | 0.9 | 1.7 | 2.0 | 217.1 | C5H5N7F3
227.0554 | 227.0547 | 0.7 | 1.5 | 2.0 | 217.1 | C5H5N7F3
227.0544 | 227.0537 | 1.7 | 7.5 | 4.0 | 1181.0 | C4H5N7F4
227.0542 | 227.0535 | 1.8 | 7.9 | 4.0 | 1181.0 | C4H5N7F4
227.0542 | 227.0535 | 1.8 | 7.9 | 4.0 | 1181.0 | C4H5N7F4
227.0578 | 227.0570 | -1.8 | -7.9 | 3.0 | 1291.6 | C3H7N7O3F2
227.0580 | 227.0572 | -2.0 | -8.0 | 4.5 | 205.2 | C8H8N4O3F3
227.0540 | 227.0532 | 2.0 | 8.0 | 2.5 | 1368.3 | C3H8N6O5F
227.0581 | 227.0573 | -2.1 | -9.2 | -1.0 | 1273.0 | C5H10N5O3F5
227.0582 | 227.0573 | -2.2 | -9.7 | 10.0 | 119.5 | C13H9N3O3
227.0531 | 227.0523 | 3.9 | 12.8 | 2.5 | 455.5 | C8H10O4F3
227.0590 | 227.0580 | -3.0 | -13.2 | -1.0 | 2689.1 | H8N7O4F3
phenyl(6-(trifluoromethyl)pyridin-3-yl)methanone (14)

Proton NMR (CDCl₃)