

# Convenient Approaches to 4-Trifluoromethylpyridine

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## Abstract:

A number of approaches to the synthesis of 2-chloro- and 2,6-dichloro-4-trifluoromethylpyridine are described. The first method for 2-chloro- and 2,6-dichloro-4-trifluoromethylpyridine is based on commercially available ethyl trifluoroacetate. An alternative access to 2,6-dichloro-4-trifluoromethyl pyridine uses trifluoroacetaldehyde as starting material. 2-Chloro-4-trifluoromethylpyridine is prepared from ethyl(trifluoroacetylvinyl)-ether in two steps.

## Introduction

Many trifluoromethylated pyridines, or their derivatives, have shown remarkable biological activity, and they have been widely used in a variety of fields ranging from medicinal to agricultural applications.<sup>1</sup> 2-Chloro- or 2,6-dichloro-4-trifluoromethylated pyridines are versatile intermediates in the synthesis of biologically active trifluoromethyl-containing compounds.<sup>2</sup> Only a few approaches to the preparation of trifluoromethylated pyridines have been developed.<sup>3</sup> General procedures reported for the synthesis of chloro-trifluoromethyl pyridine are: (1) by reaction of methylpyridines with chlorine and HF,<sup>3a</sup> (2) reaction of trichloromethylpyridines with HF in the presence of an antimony catalyst,<sup>3c</sup> or (3) Reaction of pyridine carboxylic acids with MoF<sub>6</sub> at high temperature and pressure.<sup>3d</sup> An alternative method involves directly introducing a trifluoromethyl group into pyridine by utilizing CF<sub>3</sub>I or CF<sub>3</sub>Cl.<sup>4</sup> However, these methods have some drawbacks such as high

temperature, high pressure, use of toxic and corrosive hydrogen fluoride, low reactivity, low selectivity, limited scope and formation of by-products. More convenient and effective synthetic methods to prepare the trifluoromethylated pyridine are increasingly required. The use of easily available trifluoromethylated building blocks has often been found to be the best choice rather than those direct methods. Thus, we devised and improved several convenient synthetic methodologies for 2-chloro- and 2,6-dichloro-4-trifluoromethylpyridine from commercially available building blocks under mild conditions.

## Results and Discussion

The first approach to 2-chloro-4-trifluoromethyl-pyridine (**7**) and 2,6-dichloro-4-trifluoromethylpyridine (**10**) starts with the commercially available ethyl trifluoroacetate (**1**), which was based on the suitable use of the dialdehyde **4** as a key intermediate (Scheme 1). Ethyl trifluoroacetate (**1**) was reacted with allylmagnesium bromide to form 4-hydroxy-4-trifluoromethyl-1,6-heptadiene (**3**) in 92% yield.<sup>5</sup> Ozonolysis of diene **3** and subsequent addition of Me<sub>2</sub>S afforded dialdehyde **4**, which was cyclized in ammonia-saturated methanol solution to yield 4-trifluoromethylpyridine (**5**). Oxidation of pyridine **5** with *m*-CPBA produced *N*-oxide **6**. Chlorination of *N*-oxide **6** with thionyl chloride under reflux gave the desired 2-chloro-4-trifluoromethylpyridine **7** in 62% yield. Dialdehyde **4** was further converted into diacid **8** by oxidation with 30% hydrogen peroxide in formic acid under reflux. Heating the diacid **8** with urea at 200 °C gave pyridinediol **9**.<sup>6</sup> Chlorination of pyridinediol **9** with phosphorus oxychloride under reflux afforded 2,6-dichloro-4-trifluoromethylpyridine **10** in 30% yield.

An alternative route to 2,6-dichloro-4-trifluoromethylpyridine is outlined in Scheme 2. It has been reported that condensation of trifluoroacetaldehyde with 2 mol of cyanoacetamide and subsequent hydrolysis and decarboxylation afforded the diacid **11**.<sup>7</sup> Diacid **11** was dehydrated to give cyclic anhydride **12**. Amination of cyclic anhydride **12** led to the monoamide of glutaric acid, which on dehydration gave the glutarimide **14**.<sup>8</sup> Treatment of the glutarimide **14** with phosphorus pentachloride and phosphorus oxychloride gave the 2,6-dichloropyridine **10** in 65% yield.<sup>9</sup>

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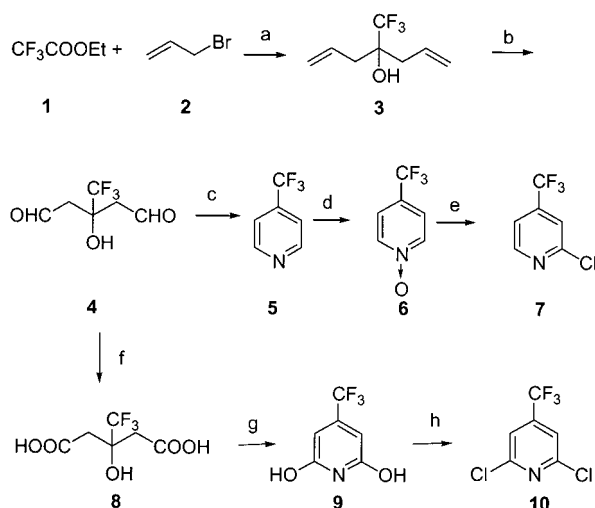
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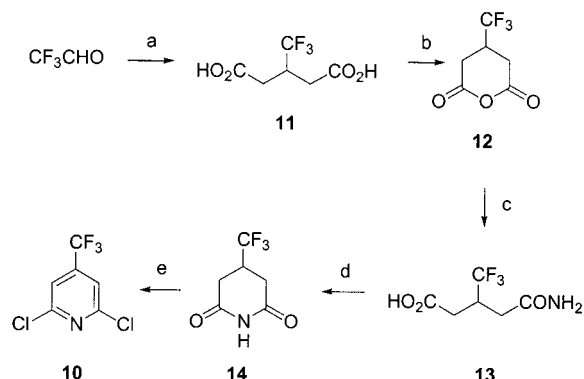
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### Scheme 1<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) Mg, THF, 50 °C, 3 h, 92%; (b) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, -78 °C, 24 h, 90%; (c) NH<sub>3</sub>/MeOH, reflux, 24 h, 70%; (d) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 10 h, 73%; (e) SOCl<sub>2</sub>, reflux, 3 h, 62%; (f) 30% H<sub>2</sub>O<sub>2</sub>, HCOOH, 70 °C, 10 h, 75%; (g) NH<sub>2</sub>CONH<sub>2</sub>, 200 °C, 8 h, 32%; (h) POCl<sub>3</sub>, reflux, 10 h, 30%.

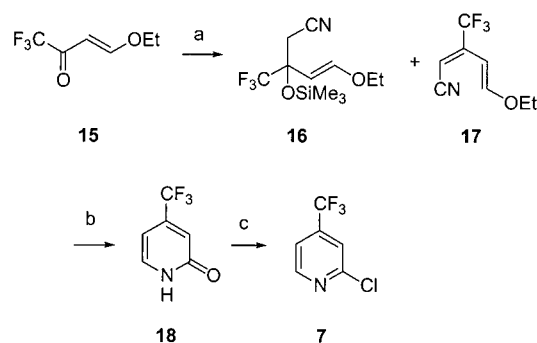
### Scheme 2<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) Cyanacetamide, EtOH, piperidine, reflux, then 20% HCl, reflux; (b) Ac<sub>2</sub>O, reflux; (c) NH<sub>3</sub>·H<sub>2</sub>O, rt; (d) 220–230 °C, 1.5 h, 30%; (e) POCl<sub>3</sub>, PCl<sub>5</sub>, reflux, 10 h, 65%.

Ethyl(trifluoroacetylvinyl)ether **15** is a versatile synthon for convenient introduction of trifluoromethyl group into heterocyclic compounds.<sup>10</sup> There are several reports on the use of alkyl(trifluoroacetylvinyl)ethers to synthesize 6-trifluoromethylated pyridines.<sup>11</sup> We have found that chloroacetonitrile reacts with **15** in tetrahydrofuran as solvent, in the presence of zinc powder and trimethylchlorosilane, to produce the  $\beta$ -trimethylsilyloxynitrile **16** accompanied by the elimination product **17**. The mixture of **16** and **17** was heated at reflux in concentrated HCl to give 4-trifluoromethyl-2-pyridone **18** in one pot. We suggest that the mechanism of heterocyclization involves Reformatsky reaction to give intermediate **16**, which undergoes elimination to give

### Scheme 3<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) ClCH<sub>2</sub>CN, Zn, TMSiCl, THF, 3 h; (b) concd HCl, reflux, 74%; (c) POCl<sub>3</sub>, 3 h, 60%.

**17** and further cyclization by nucleophilic substitution to afford 4-trifluoromethyl pyridone **18**. Chlorination of the pyridone **18** resulted in the desired product **7** in good yield (Scheme 3).

In conclusion, we have demonstrated a number of novel and convenient routes to 2-chloro- or 2,6-dichloro-4-trifluoromethylpyridine, which can be readily obtained in multi-hundred gram quantities. These methods are superior to the other methods with respect to: ease of preparation, commercial availability of the starting materials, milder conditions, high selectivity, and high yield.

### Experimental Section

All melting points were measured with a WRS-1A digital melting point apparatus, without correction. IR spectra were determined with a Shimadzu IR-440 spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker AM-300 instrument. The chemical shifts are expressed in ppm, and coupling constants are given in Hz. Low-resolution MS spectra were obtained on a VG-Quattro or HP-5969A spectrometer, and high-resolution MS spectra were recorded on a Finnigan MAT-95 spectrometer. Elemental analyses were carried out on a Heraeus Rapid-CHNO instrument. Column chromatography was performed on silica gel H (10–40  $\mu$ m). Reagents purchased commercially were used without further purification. Solvents were dried using standard procedures.

**4-Hydroxy-4-(trifluoromethyl)-1,6-heptadiene (3).** A mixture of allyl bromide **2** (14.5 g, 120 mmol) and ethyl trifluoroacetate **1** (7.1 g, 50 mmol) was added dropwise to a stirred solution of magnesium (2.9 g, 120 mmol) in anhydrous THF (50 mL) under N<sub>2</sub>. The reaction mixture was heated at 50 °C for 3 h. The reaction was quenched with saturated NH<sub>4</sub>Cl. The product was extracted from the aqueous layer with ethyl acetate and washed with brine. The combined organic extracts were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude product was distilled in vacuo to give a colorless oil **3** (8.31 g, 92%); bp 37–39 °C (10 mmHg).<sup>5</sup> <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  2.2 (s, CF<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  5.84 (m, 2H), 5.22 (m, 4H), 2.47 (m, 4H). IR (KBr)  $\nu_{\max}$  3463, 2984, 1643, 1179, 1150 (CF<sub>3</sub>) cm<sup>-1</sup>. MS (EI)  $m/z$  180 (M<sup>+</sup>, 1), 163 (M<sup>+</sup> – OH, 11), 91 (47), 69 (CF<sub>3</sub>, 90), 41 (100). Anal. Calcd for C<sub>8</sub>H<sub>11</sub>F<sub>3</sub>O: C, 53.33; H, 6.11. Found: C, 53.40; H, 6.22.

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**3-Hydroxy-3-trifluoromethyl-1,5-pentanedialdehyde (4).** **3** (8.31 g, 46 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and MeOH and cooled to -78 °C. Oxygen-containing ozone was passed through the solution. After 48 h, ozone was no longer absorbed, and the excess ozone was purged with nitrogen. The mixture was allowed to warm to room temperature. Dimethyl sulfide was added and the mixture stirred at room temperature for 2 h. The solvent and methyl sulfide were removed in vacuo to afford the crude product **4** (7.6 g, 90%) which was used directly in the next reaction without purification.

**4-Trifluoromethyl-pyridine (5).** **4** (7.6 g, 41.3 mmol) was added to the saturated ammonia-methanol solution (100 mL). The mixture was refluxed for 24 h. The solvent was evaporated in vacuo, and the residue was purified with column chromatography to give **5** (4.25 g, 70%).<sup>3a</sup> <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ -13 (s). MS (EI) *m/z* 147 (M<sup>+</sup>, 3.5), 127 (10), 97 (22), 78 (19), 57 (100).

**4-Trifluoromethyl-1-oxo-pyridine (6).** A solution of **5** (4.25 g, 28.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added *m*-CPBA (9.36 g, 57.8 mmol), and the mixture was stirred at ambient temperature for 10 h, diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with saturated sodium sulfite, 2N NaOH, and saturated NaCl. It was dried over NaSO<sub>4</sub> and then concentrated in vacuo. The residue was purified by column chromatography on silica gel to give product **6** (3.42 g, 73%). <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ -13 (s). MS (EI): *m/z* 163 (M<sup>+</sup>, 100), 147 (M<sup>+</sup> - O, 7), 144 (M<sup>+</sup> - F, 18), 139 (20), 69 (10).

**3-Hydroxy-3-trifluoromethyl-1,5-pentanedicarboxylic Acid (8).** To **4** (6 g, 33 mmol) was added 30% hydrogen peroxide (11.4 mL) and 98% formic acid (23 mL). The reaction mixture was refluxed overnight. The formic acid was evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford **8** (5.3 g, 75%): mp 100–102 °C (lit.<sup>5</sup> mp 102–105 °C). <sup>19</sup>F NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 5.0 (s, CF<sub>3</sub>). <sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 3.11–2.91 (m, 4H). <sup>13</sup>C NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 207.5, 127.23 (q, *J* = 285 Hz), 73.7 (q, *J* = 28.5 Hz), 37.15. IR (KBr) *ν*<sub>max</sub> 3436, 3065, 1741, 1691, 1168 cm<sup>-1</sup>. MS (EI) *m/z* 217 (M<sup>+</sup> + 1, 21), 199 (M<sup>+</sup> - OH, 50), 181 (69), 129 (63), 69 (CF<sub>3</sub>, 90), 42 (100).

**4-Trifluoromethyl-2,6-pyridinediol (9).** **8** (3.4 g, 15.7 mmol) and urea (1.25 g, 20.8 mmol) was heated at 185 °C until no more ammonia was evolved. The mixture was dissolved in ethyl acetate and washed with brine dried over NaSO<sub>4</sub> and then concentrated in vacuo. The residue was purified by column chromatography on silica gel to give product **9** (0.9 g, 32%). <sup>19</sup>F NMR (CD<sub>3</sub>OD) δ -13 (s). MS (EI) *m/z* 179 (M<sup>+</sup>, 19), 160 (4), 151 (13), 136 (100), 67 (66).

**4-Trifluoromethyl-2,6-piperidinedione (14).** A mixture of trifluoroacetaldehyde (1.96 g, 20 mmol) and cyanoacetamide (2.8 g, 40 mmol) were refluxed in ethanol (15 mL) with piperidine as a catalyst for 10 h. Then the ethanol was removed. Hydrochloric acid (20%, 20 mL) was added. The reaction mixture was refluxed for 6 h, diluted with ethyl ether, washed with brine, dried over NaSO<sub>4</sub>, and then concentrated in vacuo to obtain crude product **11**. A mixture

of **11** (4 g, 20 mmol) and acetic anhydride (15 mL) was refluxed for 14 h. The excess acetic anhydride was removed in vacuo. Then ammonia water (30 mL) was added and the mixture stirred at room temperature overnight. The aqueous layers were extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were washed with 1 N HCl (75 mL) and brine (2 × 50 mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give a crude reaction mixture which was used directly in the next reaction without purification. The crude product was heated at 220–230 °C until water no longer distilled. The reaction mixture was cooled to ambient temperature and dissolved in water (10 mL). The solution was boiled for 30 min with about 0.5 g of charcoal. The charcoal was removed by filtration. The dry residue was crystallized from 95% ethanol to give product **14** (1.1 g, 30%): mp 136–138 °C. <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -3.4 (d, *J* = 6.6 Hz). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.60 (brs, 1H), 2.85–3.03 (m, 4H), 2.62–2.7 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 169.2, 125.6 (q, *J* = 276.7 Hz), 35.1 (q, *J* = 29.8 Hz), 30.6. IR (KBr) *ν* 3202, 3098, 1698, 1130. MS (EI) *m/z* 181 (M<sup>+</sup>, 12), 138 (23), 69 (8), 42 (100). HRMS (EI) calcd for C<sub>5</sub>H<sub>5</sub>F<sub>3</sub>O 138.02925. Found 138.02948.

**2,6-Dichloro-4-trifluoromethyl-pyridine (10).** Method 1: A mixture of **9** (1.79 g, 10 mmol) and phosphorus oxychloride (10 mL) was heated to reflux for 10 h. The excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was poured onto ice water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The organic phase was washed with saturated NaHCO<sub>3</sub> (10 mL) and brine (15 mL). After drying (Na<sub>2</sub>SO<sub>4</sub>), concentration in vacuo afforded a residue that was purified by flash chromatography to give the desired **10** (0.65 g, 30%) as a colorless oil.<sup>3a</sup> Method 2: A mixture of **14** (5.43 g, 30 mmol) and phosphorus oxychloride (30 mL) was heated to reflux for 8 h. The excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was poured onto ice water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 mL). The organic phase was washed with saturated NaHCO<sub>3</sub> (30 mL) and brine (30 mL). After drying (Na<sub>2</sub>SO<sub>4</sub>), concentration in vacuo afforded a residue that was purified by flash chromatography to give **10** (4.2 g, 65%). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -13 (s). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40 (s, 1H). MS (EI) *m/z* 215 (M<sup>+</sup>, 10), 217 (6), 196 (6), 180 (100), 182 (32), 160 (29), 144 (8), 110 (15).

**5-Ethoxy-3-trimethylsilyloxy-3-trifluoromethyl-4-pentenenitrile (16) and 5-Ethoxy-3-trifluoro-methyl-2,4-pentadienenitrile (17).** Trimethylchlorosilane (5.3 mL, 30 mmol) was added to the suspension of zinc powder (2 g, 30 mmol) in anhydrous THF (30 mL) under N<sub>2</sub>. After stirring for 0.5 h, a solution of chloroacetonitrile (1.27 mL, 20 mmol) and ethyl (trifluoroacetylvinyl)ether (1.68 g, 10 mmol) in anhydrous THF (15 mL) was added dropwise slowly to keep the temperature at 40 °C. After stirring at room temperature for 1.5 h, 2 N HCl (5 mL) was added to adjust pH 3. The mixture was poured onto ice water. The product was extracted with EtOAc (3 × 50 mL), and the combined extracts were washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to dryness to

give a crude reaction mixture of **16** (5.1 g, 61%) and **17** (1.4 g, 25%), which were separated by column chromatography (petroleum ether/EtOAc, 5:1). **16**:  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3 (s).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.51 (d,  $J = 12.8$  Hz, 1H), 4.65 (d,  $J = 12.8$  Hz, 1H), 3.59 (m, 2H), 2.60 (q,  $J = 16.67$  Hz, 2H), 1.09 (t,  $J = 9.93$  Hz, 3H), 0.00 (s, 9H). MS (EI)  $m/z$  282 ( $\text{M}^+ + 1$ , 1), 241 (62), 212 (10), 197 (42), 142 ((8), 99 (100). Anal. Calcd for  $\text{C}_{11}\text{H}_{18}\text{F}_3\text{NO}_2\text{Si}$ : C, 46.96; H, 6.45; N, 4.98. Found: C, 46.68; H, 6.69; N, 5.31. **17**:  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -13 (s).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.26 (d,  $J = 12.92$  Hz, 1H), 5.91 (d,  $J = 12.93$  Hz, 1H), 5.47 (s, 1H), 4.02 (q,  $J = 7.06$  Hz, 2H), 1.37 (t,  $J = 6.94$  Hz, 3H). MS (EI)  $m/z$  191 ( $\text{M}^+$ , 32), 136 (100), 103 (56), 73 (65). Anal. Calcd for  $\text{C}_8\text{H}_8\text{F}_3\text{NO}$ : C, 50.27; H, 4.22; N, 7.33. Found: C, 50.42; H, 4.19; N, 7.51.

**4-Trifluoromethyl-2(1H)-pyridinone (18)**. Trimethylchlorosilane (5.3 mL, 30 mmol) was added to the solution of zinc powder (2 g, 30 mmol) in anhydrous THF (30 mL) under  $\text{N}_2$ . After stirring for 0.5 h, a solution of chloroacetonitrile (1.27 mL, 20 mmol) and ethyl(trifluoroacetylvinyl)ether (1.68 g, 10 mmol) in anhydrous THF (15 mL) was added dropwise slowly to keep the temperature at 40 °C. The mixture was refluxed for 2 h. After the mixture was cooled to room temperature, concentrated HCl (5 mL) was added. The mixture was refluxed for 1 h, then cooled to room temperature, and poured onto ice water. The product was extracted with EtOAc (3  $\times$  50 mL), and the combined extracts were washed with brine. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated to dryness to give the residue that could be used in the next reaction without further purification. The residue was purified by column chromatography to afford **18** (1.2 g, 74%).<sup>12</sup>  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -13 (s).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.49 (dd,  $J = 1.6$ ,

6.9 Hz, 1H), 6.78 (d,  $J = 0.85$  Hz, 1H), 7.75 (d,  $J = 7.0$  Hz, 1H). IR (KBr)  $\nu_{\text{max}}$  3151 (N-H), 2851, 1664 (C=O), 1621, 1072 ( $\text{CF}_3$ )  $\text{cm}^{-1}$ . MS (EI)  $m/z$  163 ( $\text{M}^+$ , 100), 144 ( $\text{M}^+ - \text{F}$ , 12), 135 (83), 116 (99), 85 (25), 69 ( $\text{CF}_3$ , 15), 57 (15), 43 (15).

**2-Chloro-4-trifluoromethyl-pyridine (7)**. Method 1: A mixture of **6** (1.5 g, 15.8 mmol) and thionyl chloride (20 mL) was stirred and heated slowly to reflux over a period of 1.5 h. The solution was then heated under reflux for 1 h. After evaporation of the excess thionyl chloride, the residue was poured onto ice water and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  50 mL). The organic phase was washed with saturated  $\text{NaHCO}_3$  (20 mL) and brine (30 mL). After drying ( $\text{Na}_2\text{SO}_4$ ), concentration in vacuo afforded a residue that was purified by flash chromatography to give the desired **7** (1.8 g, 62%) as a colorless oil.<sup>3a</sup> Method 2: A mixture of **18** (3 g, 18.4 mmol) and phosphorus oxychloride (30 mL) was heated to reflux for 3 h. The excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was poured onto ice water and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  50 mL). The organic phase was washed with saturated  $\text{NaHCO}_3$  (20 mL) and brine (30 mL). After drying ( $\text{Na}_2\text{SO}_4$ ), concentration in vacuo afforded a residue that was purified by flash chromatography to give the desired **7** (2.0 g, 60%) as a colorless oil.  $^{19}\text{F}$  NMR -13 (s,  $\text{CF}_3$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.61 (d,  $J = 5.13$  Hz, 1H), 7.58 (s, 1H), 7.47 (d,  $J = 5.08$  Hz, 1H). IR (KBr)  $\nu_{\text{max}}$  1450, 1334, 1146  $\text{cm}^{-1}$ . MS (EI)  $m/z$  181 ( $\text{M}^+$ , 3.58), 146 ( $\text{M}^+ - \text{Cl}$ , 100), 69 ( $\text{CF}_3$ , 54), 126 (25).

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