

# A Facile One Step Synthesis of Novel Ethyl 2,6-Bis(trifluoromethyl)-4-hydroxypyrimidine-5-carboxylate

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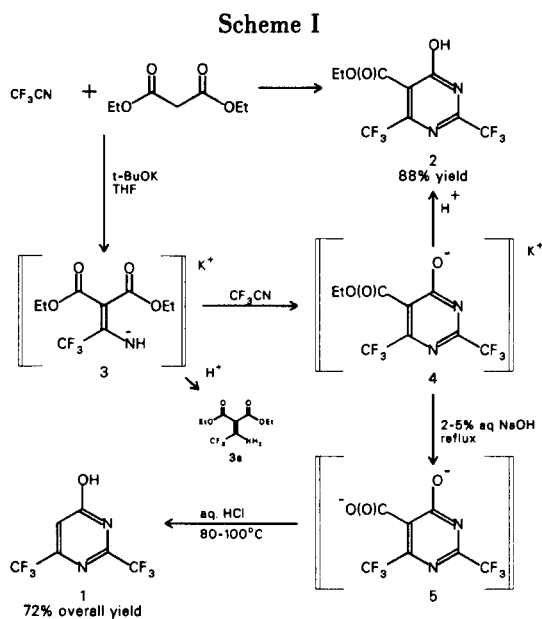
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Trifluoroacetonitrile was condensed with diethyl malonate to give a novel ethyl 2,6-bis(trifluoromethyl)-4-hydroxypyrimidine-5-carboxylate (**2**) in 88% yield. Derivations of **2** are also described.

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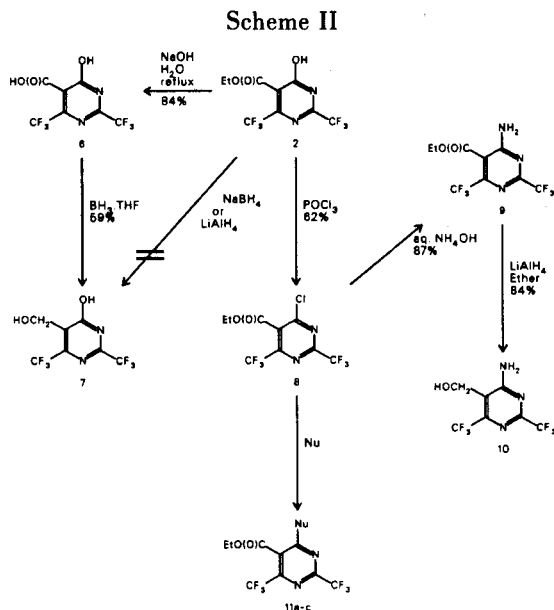
Trifluoromethyl substituted pyrimidines have shown antibacterial activities [1-2]. 2,6-Bis(trifluoromethyl)-4-hydroxypyrimidine (**1**) has been synthesized by the condensation of trifluoroacetamide with ethyl trifluoroacetate [1]. However, the yield was low (15-35%) and was too tedious for a large scale (kilograms) preparation which was required in our biological evaluation.

We have now synthesized **1** conveniently by a one-pot procedure in an overall yield of 72%. The new method is based on a simple one step synthesis of a novel ethyl 2,6-bis(trifluoromethyl)-4-hydroxypyrimidine-5-carboxylate (**2**) as described in Scheme I. Trifluoroacetonitrile is reacted with diethyl malonate in tetrahydrofuran with potassium *t*-butoxide to give a pyrimidine intermediate **4**. An enamine anion **3** [3] is formed prior to the formation of **4**. The ester group of **4** is hydrolyzed to give acid dianion **5**, which when decarboxylated with aqueous hydrochloric acid gives **1** in 72% overall yield (Scheme I). It is noteworthy that alternatively **4** may be treated with acid to give the pyrimidinecarboxylate ester **2**, isolated in 88% yield.



Derivatives of pyrimidine **2** were also investigated (Scheme II). Compound **2** was converted to the 4-chloro

derivative **8** which when reacted with ammonia gives an 4-amino derivative **9**. The carboethoxy group of **9** was reduced by lithium aluminum hydride to give a hydroxymethyl derivative **10**. It is noteworthy that the mono-trifluoromethyl analog of **10**, 4-amino-5-hydroxymethyl-2-trifluoromethylpyrimidine has been reported as a potent anti-bacteria agent [5]. Attempted reduction of the carboethoxy group of **2** did not give the desired hydroxymethylpyrimidine **7**; with sodium borohydride only starting material is recovered while lithium aluminum hydride treatment gives a complex mixture. Since carboxylic acids can be reduced selectively by borane-tetrahydrofuran [4], **2** was hydrolyzed to give the pyrimidine carboxylic acid **6** which was then reduced by this reagent to afford the hydroxymethylpyrimidine **7** in 59% yield. The chloro group of pyrimidine **8** is readily replaced with a variety of nucleophiles. For example, **8** was reacted with the anion of diethyl malonate, 4-chlorophenol, and 4-chlorobenzethiol to yield the corresponding products **11a-c** as shown in Table I.



There are several reported syntheses of pyrimidines by the condensation of perhaloacetonitrile. Burger [2] reported the reaction of trifluoroacetonitrile with enamine

Table I

	Nu	Reaction Condition	m.p.	Yield
<b>11a</b>	-CH(C(O)OEt) <sub>2</sub>	CH <sub>2</sub> C(O)OEt <sub>2</sub> , NaOH, Cyclohexane	84-85°	83%
<b>11b</b>	-O-Ph-4-Cl	HO-Ph-4-Cl, K <sub>2</sub> CO <sub>3</sub> , toluene, reflux	111-112°	88%
<b>11c</b>	-S-Ph-4-Cl	HS-Ph-4-Cl, K <sub>2</sub> CO <sub>3</sub> , toluene, reflux	91-93°	96%

and ynamine to give 4-alkyl-2,6-bis(trifluoromethyl)pyrimidines and 4-amino-2,6-bis(trifluoromethyl)pyrimidine respectively. Benzoylacetonitrile was reacted with trichloroacetonitrile in the presence of sodium to give an enamine which was further reacted with trichloroacetonitrile to give 4-phenyl-2,6-bis(trichloromethyl)-5-pyrimidinocarbonitrile [6]. Reaction of trifluoroacetonitrile with diethyl malonate to give enamine **3a** was reported [3]. However, further reaction of **3a** with trifluoroacetonitrile to give **2** has not been reported in the literature.

#### EXPERIMENTAL

Melting points are uncorrected. The nmr and fmr spectra were obtained on a Varian EM-360 spectrometer. The cmr spectra were recorded on a JEOL FX-100 spectrometer. Signals are reported in parts per million downfield from tetramethylsilane. Infrared spectra were obtained on a Perkin-Elmer Model 727B infrared spectrophotometer. Mass spectra were obtained on a Finnigan Mat CH7A mass spectrometer. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

#### 2,6-Bis(trifluoromethyl)-4-hydroxypyrimidine (1)

To a suspension of 71.47 g (0.637 mole) of anhydrous potassium *t*-butoxide in 400 ml of tetrahydrofuran was added dropwise 100 g (0.624 mole) of diethyl malonate in 50 ml of tetrahydrofuran under an atmosphere of nitrogen. The temperature rose to 60° and the mixture became white muddy. The additional funnel was removed and replaced with a gas inlet. Trifluoroacetonitrile was passed in slowly with vigorous stirring. Periodically, a small sample of the acidified reaction mixture was analyzed by gas chromatography. Compound **3** was formed during the reaction as evidenced by comparison of a gas chromatograph analysis with an authentic sample. At the end of 6 hours, 190 g of trifluoroacetonitrile had been passed into the solution affording only one major product. The light brown, slightly cloudy solution was allowed to cool to room temperature, diluted with 600 ml of water, and washed with methylene chloride. The methylene chloride layer was extracted with 300 ml of water [7]. To the combined aqueous solution was added 80 ml of 50% aqueous sodium hydroxide and the mixture refluxed for 2 hours, from which 300 ml of water was distilled over and discarded. Concentrated hydrochloric acid (300 ml) was added to the resulting clear light yellow aqueous solution. This was followed by heating. When the temperature reached 80° the external heating was stopped and to the solution a stream of hydrogen chloride was slowly passed in. Gas evolution was observed. When gas evolution subsided, the solution was refluxed by external heating with hydrogen chloride passed in continuously for 30 minutes. The introduction of hydrogen chloride gas was then stopped and the product collected by steam distillation. After cooling in an ice bath, the crystallized distillate was filtered to give 103.5 g (72% yield) of a white solid as **1**, mp 119-121° (lit [1] 117-118°); ir (Nujol): 1690 (s), 1630 (s) cm<sup>-1</sup>; nmr (deuteriochloroform): δ 7.12 (s, 1H), 10.0 (s, 1H); cmr (perdeuterioacetone): 400 MHz, δ 175.47 (C<sub>6</sub>, s), 161.10 (q, J = 37.6 Hz,

CF<sub>3</sub>-C), 160.85 (q, J = 38.0 Hz, CF<sub>3</sub>-C), 125.42 (q, J = 274.3 Hz, CF<sub>3</sub>), 123.9 (q, J = 276.1 Hz, CF<sub>3</sub>), 113.64 (q, J = 11.4 Hz, C<sub>5</sub>).

#### Ethyl 2,6-Bis(trifluoromethyl)-4-hydroxypyrimidine-5-carboxylate (2)

To a suspension of 14.03 g (0.125 mole) of anhydrous potassium *t*-butoxide in 150 ml of tetrahydrofuran was added dropwise 20 g (0.125 mole) of diethyl malonate in 20 ml of tetrahydrofuran under an atmosphere of nitrogen. The temperature rose to 60° and the mixture became white muddy. The additional funnel was removed and replaced with a gas inlet. Trifluoroacetonitrile was passed in slowly with vigorous stirring. Periodically, a sample of the acidified reaction mixture was monitored by gas chromatography. At the end of 2 hours, 73 g of trifluoroacetonitrile has been passed into the solution and only one major product identified. The light brown slightly cloudy solution was allowed to cool down to room temperature, diluted with 400 ml of water, and washed with ether (4 x 100 ml). The aqueous layer was acidified by adding 100 ml of concentrated hydrochloric acid and extracted with ether. The ether layer was washed with water, brine, and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporator and the residual solid was dried under vacuum to give 33.4 g of a white solid as **2** (88% yield), mp 131-132°; ir (Nujol): 1750 (s), 1670 (s) cm<sup>-1</sup>; nmr (deuteriochloroform): δ 8.2 (b, 1H), 4.46 (q, 2H), 1.40 (t, 3H); cmr (perdeuterioacetone): δ 163.99 (s, C<sub>4</sub>), 159.43 (s, C(O)O), 152.17 (q, J = 39.6 Hz, C-CF<sub>3</sub>), 148.77 (q, J = 35.9 Hz, C-CF<sub>3</sub>), 117.98 (q, J = 275.5 Hz, CF<sub>3</sub>), 115.64 (s, C-C(O)O), 116.23 (q, J = 275.5 Hz, CF<sub>3</sub>), 60.57 (s, CH<sub>2</sub>), 11.07 (s, CH<sub>3</sub>); ms: (m/e) 304 (M<sup>+</sup>, 1.57), 285 (5.63), 277 (22.31), 276 (10.44), 28 (100.00).

*Anal.* Calcd. for C<sub>8</sub>H<sub>6</sub>F<sub>6</sub>N<sub>2</sub>O<sub>5</sub>: C, 35.54; H, 1.99; N, 9.21. Found: C, 35.58; H, 2.01; N, 9.16.

#### 2,6-Bis(trifluoromethyl)-4-hydroxypyrimidine-5-carboxylic Acid (6)

A sample of **2** (8.86 g, 0.0291 mole) in 2% aqueous sodium hydroxide (100 ml) was refluxed for 1 hour. After cooling it was quenched with 6 *N* aqueous hydrochloric acid and extracted with ethyl acetate to give 8.33 g of a white solid (mp 220-223°). The resulting white solid was recrystallized from toluene (450 ml) to give 6.75 g of a white powder as **6** (84% yield): mp 226-228°; ir (Nujol): 1730 (s), 1680 (s) cm<sup>-1</sup>; nmr (perdeuterioacetone): δ 11.7 (s); cmr (perdeuterioacetone): δ 167.34 (s, C<sub>4</sub>), 163.34 (s, C(O)O), 155.09 (q, J = 38.1 Hz, C-CF<sub>3</sub>), 151.43 (q, J = 36.6 Hz, C-CF<sub>3</sub>), 121.06 (q, 274.7 Hz, CF<sub>3</sub>), 119.02 (s, C-C(O)O), 119.28 (q, J = 275.5 Hz, CF<sub>3</sub>); ms: (m/e) 276 (M<sup>+</sup>, 31.78), 258 (21.37), 232 (32.52), 230 (39.00), 19 (100).

*Anal.* Calcd. for C<sub>7</sub>H<sub>2</sub>F<sub>6</sub>N<sub>2</sub>O<sub>5</sub>: C, 30.45; H, 0.73; N, 10.15. Found: C, 30.43; H, 0.73; N, 10.17.

#### 2,6-Bis(trifluoromethyl)-5-hydroxymethyl-4-hydroxypyrimidine (7)

To a solution of **6** (10 g, 0.036 mole) in tetrahydrofuran (30 ml) at 0° was added dropwise a solution of 1 *M* borane-tetrahydrofuran complex (72 ml, 0.0724 mole). The resulting clear solution was stirred at room temperature overnight. It was then quenched with water carefully to destroy the excess borane. The tetrahydrofuran was evaporated and the residual aqueous solution washed with ether (discarded) and then acidified with concentrated hydrochloric acid. It was then extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and evaporated to give a colorless glass. This was Kugelrohr distilled at 120°/1 mm-Hg to give 5.6 g (59% yield) of a colorless glass as **7**, ir (Nujol): 3300 (br s), 1680 (s) cm<sup>-1</sup>; nmr (deuteriochloroform): δ 4.9 (s, CH<sub>2</sub>, 2H), 6.3 (br, 2H); cmr (deuteriochloroform): δ 165.45 (s, C<sub>4</sub>), 149.98 (q, J = 35.7 Hz, C-CF<sub>3</sub>), 148.17 (q, J = 40.29 Hz, C-CF<sub>3</sub>), 127.85 (s, C<sub>5</sub>), 120.4 (q, J = 277.0 Hz, CF<sub>3</sub>), 119.71 (q, J = 277.0 Hz, CF<sub>3</sub>), 55.66 (q, J = 2.9 Hz, CH<sub>2</sub>).

*Anal.* Calcd. for C<sub>7</sub>H<sub>4</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub>: C, 32.07; H, 1.54; N, 10.68. Found: C, 31.85; H, 1.58; N, 10.58.

#### Ethyl 2,6-Bis(trifluoromethyl)-4-chloropyrimidine-5-carboxylate (8)

A mixture of 28.63 g (0.094 mole) of **2** and 400 ml of phosphorus oxychloride was refluxed under an atmosphere of nitrogen for 30 hours. The excess phosphorus oxychloride was evaporated under reduced pressure. The residual light brown oil was quenched with ice-water. After half of an

hour, the oil solidified and was extracted with ether. The ether solution was washed successively with 2% aqueous sodium hydroxide, water, and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 18.13 g of a cream color solid which was purified by sublimation at 70°/2 mm Hg to give 16.5 g (62% yield) of white cubic crystals as **8**, mp 40.5-42°; ir (Nujol): 1750 (s), 1570 (s)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  4.58 (q,  $\text{CH}_2$ , 2H), 1.24 (t,  $\text{CH}_3$ , 3H); cmr (deuteriochloroform):  $\delta$  162.33 (s,  $\text{C}_4$ ), 160.96 (s, C(O)O), 156.82 (q, J = 40.3 Hz, C-CF<sub>3</sub>), 154.23 (q, J = 38.1 Hz, C-CF<sub>3</sub>), 134.75 (s, C<sub>5</sub>), 119.36 (q, J = 276.9 Hz, CF<sub>3</sub>), 118.21 (q, J = 276.2 Hz, CF<sub>3</sub>), 64.25 (s, CH<sub>2</sub>), 13.77 (s, CH<sub>3</sub>).

Anal. Calcd. for C<sub>8</sub>H<sub>5</sub>Cl<sub>3</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub>: C, 33.51; H, 1.56; N, 8.68; Cl, 10.99. Found: C, 33.51; H, 1.55; N, 8.69; Cl, 11.19.

#### Ethyl 4-Amino-2,6-bis(trifluoromethyl)pyrimidine-5-carboxylate (**9**).

To a stirred solution of 5 g (0.0155 mole) of **8** in 25 ml of absolute ethanol was added 9 ml of concentrated aqueous ammonium hydroxide (28-30%). The solution became hot and turned yellow. The reaction was complete as evidenced by thin layer chromatographic analysis (silica gel, 5% ethyl acetate in cyclohexane). The solvent was partially removed to give a white solid which was extracted with ether. The ether solution was then washed with water and dried over anhydrous magnesium sulfate. After the solvent was removed under reduced pressure, a 4.5 g sample of a white solid was obtained. This was recrystallized from 30 ml of hot cyclohexane to give 4.15 g (87% yield) of **9** as white crystals, mp 93-94°; ir (Nujol): 3425 (s), 3410 (s), 2990 (s), 1710 (s), 1640 (s)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  7.20 (br s, NH, 2H), 4.50 (q,  $\text{CH}_2$ , 2H), 1.42 (t,  $\text{CH}_3$ , 3H); cmr (deuteriochloroform):  $\delta$  164.54 (s, C(O)O), 163.69 (s, C<sub>4</sub>), 156.98 (q, J = 37.3 Hz, C-CF<sub>3</sub>), 155.27 (q, J = 36.6 Hz, C-CF<sub>3</sub>), 120.23 (q, J = 276.2 Hz, CF<sub>3</sub>), 118.81 (q, J = 276.8 Hz, CF<sub>3</sub>), 107.35 (s, C<sub>5</sub>), 63.47 (s, CH<sub>2</sub>), 13.57 (s, CH<sub>3</sub>).

Anal. Calcd. for C<sub>9</sub>H<sub>7</sub>F<sub>6</sub>N<sub>3</sub>O<sub>2</sub>: C, 35.66; H, 2.33; N, 13.86. Found: C, 35.54; H, 2.33; N, 13.81.

#### 4-Amino-2,6-bis(trifluoromethyl)-5-hydroxymethylpyrimidine (**10**).

To a suspension of lithium aluminum hydride (1.49 g, 0.039 mole) in anhydrous ether (300 ml) was added in one hour a solution of **9** (7 g, 0.0231 mole) in anhydrous ether (150 ml). The mixture was refluxed for 80 minutes. After cooling in an ice-bath, the reaction mixture was quenched dropwise with water and filtered. The filter cake was washed with ether. The combined ether solution was evaporated to give 5.11 g of a light yellow solid as **10** (84% yield), mp 151-153°. This material was further purified by liquid chromatography (silica gel, 40% ethyl acetate in cyclohexane), mp 156-157°; ir (Nujol): 3420 (s), 3320 (s), 3200 (s), 1650 (s), 1590 (s)  $\text{cm}^{-1}$ ; nmr (perdeuterioacetone):  $\delta$  6.8 (br), 4.4 (s, CH<sub>2</sub>); fmr (perdeuterioacetone):  $\delta$  -68.77 (s, 6-CF<sub>3</sub>), -71.73 (s, 2-CF<sub>3</sub>).

Anal. Calcd. for C<sub>7</sub>H<sub>5</sub>F<sub>6</sub>N<sub>3</sub>O<sub>2</sub>: C, 32.20; H, 1.93; N, 16.09; F, 43.66. Found: C, 32.38; H, 1.94; N, 16.11; F, 43.55.

#### Diethyl 2-[2,6-Bis(trifluoromethyl)-5-ethoxycarbonyl-4-pyrimidinyl]-propanedioate (**11a**).

To a vigorously stirred solution of 5 g (0.0155 mole) of **8** and 5 g (0.031 mole) of diethyl malonate in 20 ml of cyclohexane was added slowly 3.5 ml of 50% aqueous sodium hydroxide, after which the solution became warm and cloudy. A water bath was used to control the exothermic reaction, so the temperature would not exceed 35°. The resulting viscous orange mass was further aggravated by shaking. The mixture contained a major product with no detectable amount of starting material, as evidenced by thin layer chromatographic analysis (silica gel, 10% ethyl acetate in cyclohexane). The cyclohexane layer was decanted off and the residue dissolved in water. The aqueous layer was washed with cyclohexane and then neutralized with glacial acetic acid. The resulting milky suspension was extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, concentrated under reduced pressure to give 9 g of a white-orange solid. This material was recrystallized from aqueous ethanol to give 5.72 g (83% yield) of pale yellow-white crystals as **11a**, mp 84-85°; ir (Nujol): 1735 (s)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  5.22 (s, 1H), 4.4 (m, 6H), 1.35 (m, 9H); cmr

(deuteriochloroform):  $\delta$  165.03 (s, C<sub>4</sub>), 164.83 (s, C(O)O), 162.75 (s, C(O)O), 156.50 (q, J = 38.8 Hz, C-CF<sub>3</sub>), 154.50 (q, J = 38.1 Hz, C-CF<sub>3</sub>), 126.77 (s, C<sub>5</sub>), 119.84 (q, J = 276.95 Hz, CF<sub>3</sub>), 118.68 (q, J = 276.21 Hz, CF<sub>3</sub>), 64.06 (s, CH<sub>2</sub>), 62.95 (s, CH<sub>2</sub>), 58.61 (s, CH), 13.92 (s, CH<sub>3</sub>), 13.71 (s, CH<sub>3</sub>); ms: (m/e) 446 (M<sup>+</sup>, 3.10), 374 (31.52), 373 (21.25), 355 (23.98).

Anal. Calcd. for C<sub>16</sub>H<sub>16</sub>F<sub>6</sub>N<sub>2</sub>O<sub>6</sub>: C, 43.06; H, 3.61; N, 6.28. Found: C, 43.01; H, 3.64; N, 6.19.

#### Ethyl 4-(4-Chlorophenoxy)-2,6-bis(trifluoromethyl)pyrimidine-5-carboxylate (**11b**).

A mixture of **8** (5 g, 0.0155 mole), *p*-chlorophenol (2 g, 0.0155 mole), and anhydrous potassium carbonate (2.14 g, 0.0155 mole) in toluene (30 ml) was refluxed overnight. It was then quenched with water and the aqueous layer extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and concentrated to give 5.99 g of a light yellow-white solid, mp 100-110°. This material was recrystallized from 65 ml of 90% aqueous ethanol to give 5.65 g of white needles as **11b** (88% yield), mp 111-112°; ir (Nujol): 1880 (w), 1730 (s)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  7.50 (d, J = 9 Hz, 2H, Ph-3-H), 7.08 (d, J = 9 Hz, 2H, Ph-2-H), 4.55 (d, J = 8 Hz, 2H, CH<sub>2</sub>), 1.48 (t, J = 8 Hz, 3H, CH<sub>3</sub>); cmr (deuteriochloroform):  $\delta$  167.98 (s, C<sub>4</sub>), 161.19 (s, C(O)O), 156.51 (q, J = 39.6 Hz, C-CF<sub>3</sub>), 153.92 (q, J = 37.36 Hz, C-CF<sub>3</sub>), 149.7 (s, (Ph)C<sub>1</sub>-O), 132.5 (s, (Ph)C<sub>4</sub>-Cl), 130.01 (s, (Ph)C<sub>2</sub>), 122.64 (s, (Ph)C<sub>3</sub>), 119.71 (q, J = 276.9 Hz, CF<sub>3</sub>), 118.27 (q, J = 276.2 Hz, CF<sub>3</sub>), 63.70 (s, CH<sub>2</sub>), 13.83 (s, CH<sub>3</sub>); ms: (m/e) 415 (M<sup>+</sup>, 0.1), 413 (0.20), 260 (12.49), 259 (12.68), 243 (71.3), 69 (95.3), 28 (100).

Anal. Calcd. for C<sub>15</sub>H<sub>9</sub>ClF<sub>6</sub>N<sub>2</sub>O<sub>3</sub>: C, 43.44; H, 2.19; N, 6.76. Found: C, 43.34; H, 2.32; N, 6.72.

#### Ethyl 4-(4-Chlorophenylthio)-2,6-bis(trifluoromethyl)pyrimidine-5-carboxylate (**11c**).

A mixture of **8** (5 g, 0.0155 mole), *p*-chlorobenzenethiol (2.35 g, 0.0613 mole), and anhydrous potassium carbonate (2.14 g, 0.0155 mole) in 30 ml of toluene was refluxed for 20 hours. The resulting mixture was quenched with water and extracted with ether. The ether layer was washed with water, 5% aqueous sodium hydroxide, water, then dried over anhydrous magnesium sulfate. A light yellow-white solid (7.51 g) remained after the solvent has been removed under vacuum. This material was recrystallized from aqueous ethanol to give 6.42 g of white needles as **11c** (96% yield), mp 91-93°; ir (Nujol): 1890 (w), 1730 (s), 1570 (m)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  7.50 (Ph, 4H, s), 4.56 (q, J = 7 Hz, 2H, CH<sub>2</sub>), 1.50 (t, J = 7 Hz, 3H, CH<sub>3</sub>); cmr (deuteriochloroform):  $\delta$  173.65 (s, C<sub>4</sub>), 162.39 (s, C(O)O), 155.67 (q, J = 38.8 Hz, C-CF<sub>3</sub>), 151.6 (q, J = 36.23 Hz, C-CF<sub>3</sub>), 137.27 (s, (Ph)C<sub>4</sub>-Cl), 136.77 (s, (Ph)C<sub>2</sub>), 129.87 (s, (Ph)C<sub>3</sub>), 129.28 (s, (Ph)C<sub>1</sub>-S), 123.75 (s, C<sub>5</sub>), 119.86 (q, J = 276.9 Hz, CF<sub>3</sub>), 118.44 (q, J = 276.2 Hz, CF<sub>3</sub>), 63.84 (s, CH<sub>2</sub>), 13.65 (s, CH<sub>3</sub>); ms: (m/e) 432 (M<sup>+</sup>, 10.61), 431 (6.53), 430 (42.86), 403 (5.64), 402 (4.94), 401 (12.52), 360 (8.37), 359 (7.63), 358 (26.36), 357 (1.16), 291 (7.32), 289 (26.93), 108 (57.91), 69 (100).

Anal. Calcd. for C<sub>15</sub>H<sub>9</sub>ClF<sub>6</sub>N<sub>2</sub>O<sub>2</sub>S: C, 41.82; H, 2.11; N, 6.50. Found: C, 41.74; H, 2.14; N, 6.56.

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- [7] At this stage, the resulting aqueous solution contains **4** as the major product, which may be acidified and isolated at **2**.