Preparation of 4-Hydroxy-2-trifluoromethylthiophene: A Novel Bioisostere of α,α,α-Trifluoro-*m*-cresol

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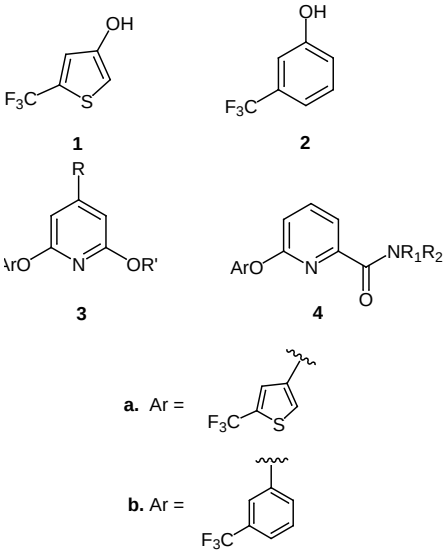
Abstract: A simple and convenient four-step synthesis of 4-hydroxy-2-trifluoromethylthiophene (**1**) a novel bioisostere of α,α,α−trifluoro-*m*-cresol is reported. The key step is the condensation between ethyl 3-methoxy-4,4,4-trifluorocrotonate and methyl thioglycolate to form methyl 3-hydroxy-5-trifluoromethylthiophene-2-carboxylate (**6**). Hydrolysis of the ester followed by decarboxylation furnishes **1**. Multi-hundred gram quantities of **1** have been obtained utilizing the present procedure.

Key words: addition-reactions, cyclizations, thiophenes, Fiesselmann reaction, bioisosteres

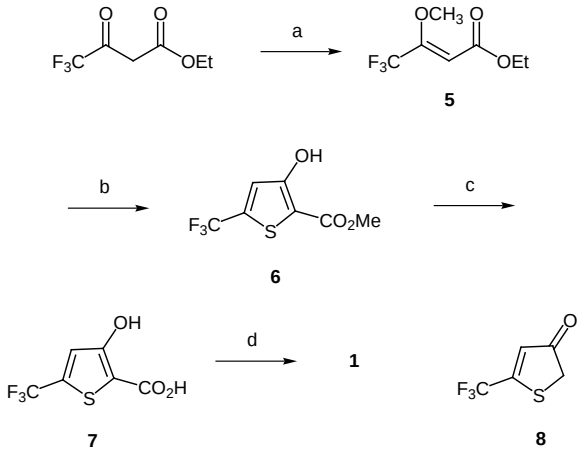


The discovery of novel medicinal and agrochemical agents has been approached in a variety of ways, from random screening to mechanism-based rational design. The concept of bioisosterism has been widely utilized as one such strategy for lead optimization in the discovery of new drugs and agrochemicals.[1-6] Bioisosteres have been described by Burger[1] as "…compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and exhibit similar physical properties." Many examples have been cited in which the replacement of a benzene ring with a ring equivalent bioisostere (e.g., thiophene or pyridine) has led to compounds with similar or improved biological profiles.[3,4,6]

A common structural motif present in a number of commercial as well as experimental herbicides, insecticides and fungicides is the α,α,α-trifluoro-*m*-cresol moiety (**2**). Based on some prior experience with thiophene-based chemistry in another area, we became interested in preparing 4-hydroxy-2-trifluoromethylthiophene (**1**), a putative thiophene bioisostere of α,α,α-trifluoro-*m*-cresol as part of a project directed towards the discovery of novel inhibitors of phytoene desaturase,[7] a key enzyme in the biosynthesis of carotenoids.[8,9] The results of this effort have led to the discovery of several novel classes of herbicides, e.g. **3a**[10] and **4a**,[11] bioisosteres of **3b**[12] and **4b** respectively.[13]

Herein we report on the facile preparation of the hitherto unknown 4-hydroxy-2-trifluoromethylthiophene, which can be readily obtained in multi-hundred gram quantities. It was initially envisioned that the thiophene ring could be prepared from the condensation between an alkyl trifluorotetrolate and an alkyl thioglycolate in a fashion analogous to that reported by Fiesselmann.[14,15] As an alternative to a trifluorotetrolate ester,[16,17] however, we reasoned that a 3-alkoxy-4,4,4-trifluorocrotonate ester should serve as a suitable tetrolate synthon. Ethyl 3-methoxy-4,4,4-trifluorocrotonate (**5**)[18,19] could serve this purpose and be prepared from readily available ethyl 4,4,4-trifluoroacetoacetate. The strongly electron withdrawing nature of the trifluoromethyl group allows for the exclusive O-alkylation of the β-keto ester. Thus, treatment of ethyl 4,4,4-trifluoroacetoacetate with Cs_2CO_3 and methyl *p*-toluenesulfonate afforded crotonate **5** in 60% yield after distillation (Scheme). Cyclocondensation of **5** with methyl thioglycolate in methanolic KOH occurs smoothly at room temperature to give methyl 3-hydroxy-5-trifluoromethylthiophene-2-carboxylate (**6**)[20] in 63% yield after distillation. Saponification afforded the acid **7** in 65% yield. Compound **7** readily undergoes thermal decarboxylation upon heating the solid to 100 °C in the absence of solvent. Distillation of the resulting crude product affords the title compound **1** in 82% yield as a colorless to pale yellow liquid. On standing at room temperature, **1** takes on a light to medium green appearance without apparent loss of quality. Compound **1** has been demonstrated to exist predominantly in the enol form as indicated by IR, ^1H and ^{13}C NMR spectra. In $CDCl_3$, the enol **1**/keto **8** ratio is 8.5:1 while in DMSO-d_6 only the enol tautomer is observed

within the limits of detection. The chemical reactivity of **1** in many cases is similar to that of α,α,α-trifluoro-*m*-cresol.[10,11]



Reagents and conditions: a, Cs_2CO_3/DMF/MeOTs, r.t.−70 °C, 60%; b, methyl thioglycolate, MeOH/KOH, 63%; c, NaOH/MeOH−H_2O, reflux, 65%; d, 100 °C (neat), 82%.

Scheme

In summary, we report the first synthesis of **1**, a thiophene bioisostere of α,α,α-trifluoro-*m*-cresol, in four steps from readily available ethyl 4,4,4-trifluoroacetoacetate and methyl thioglycolate. The above sequence is amenable to large-scale synthesis. Over one kg of **1** has been obtained without purification of the intermediates in 35−40% overall yield. Compound **1** should offer the potential for further utility in both medicinal and agrochemical pursuits.

All reactions were carried out under an atmosphere of N_2 or Ar. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. DMF was stored over 4 Å sieves. Organic layers from aqueous extractions were dried over $MgSO_4$ or Na_2SO_4 and concentrated in vacuo. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 400 or Varian Unity 300 spectrometers in $CDCl_3$ or DMSO-d_6. Coupling constants *J* are given in Hz and unless otherwise indicated represent proton-proton coupling. IR spectra were recorded on a Perkin−Elmer 1600 FTIR. Mass spectra were obtained on a Finnegan MAT TSQ 700 or MAT 9005 mass spectrometer using chemical ionization techniques.

Ethyl 4,4,4-Trifluoro-3-methoxycrotonate (5)

To a mechanically stirred solution of ethyl 4,4,4-trifluoroacetoacetate (444 g, 2.41 mol) in DMF (2.40 L) was added Cs_2CO_3 (785 g, 2.41 mol). The reaction mixture was heated to 70 °C. A solution of methyl-*p*-toluenesulfonate (494 g, 2.65 mol) in DMF (890 mL) was then added dropwise during 1.5 h and the reaction mixture was stirred for an additional hour. After cooling to r.t., the reaction mixture was diluted with H_2O (4.5 L) and extracted with Et_2O (4 × 1 L). The Et_2O extracts were combined, washed successively with H_2O (3 × 1 L), and saturated brine (1 L) and then dried and concentrated to an oil. Fractional distillation through a Vigreux column [40−48 °C, 9 mm (Lit.[19] bp 90−100 °C, 120 mm)] afforded 285 g (60%) of pure product.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.75 (s, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 4.01 (s, 3H), 1.28 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 154.0 (q, $^2J_{CF}$ = 33 Hz), 119.8 (q, $^1J_{CF}$ = 277 Hz), 101.9 (q, $^3J_{CF}$ = 3.7 Hz), 62.6, 61.1, 14.2.

Methyl 3-Hydroxy-5-trifluoromethyl-2-thiophenecarboxylate (6)

A magnetically stirred solution of **5** (525 g, 2.65 mol) and methyl thioglycolate (281 g, 2.65 mol) in absolute MeOH (4 L) was cooled to 5 °C. A solution of methanolic KOH (1 M, 3.2 L) was then added over 1 h. After a small exotherm (< 30 °C), the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then poured over a stirred mixture of ice (5 kg), H_2O (5.2 L) and concd H_2SO_4 (250 mL). After stirring for 15 min, the mixture was extracted with EtOAc (3 × 2.5 L) and the combined extracts were washed with sat. $NaHCO_3$ (2 × 2 L). The $NaHCO_3$ washings were back-extracted with EtOAc (2 L). The combined organic layers were washed with sat. brine (2 × 2 L), dried and then concentrated to afford an oil containing a small amount of insolubles. The material was stirred in hexanes, filtered to remove the insolubles, and then concentrated to an oil. Fractional distillation (60−62 °C, 2.5 mm) through a Vigreux column (30 cm) afforded 378 g (63%) of **6**.[20]

^1H NMR (300 MHz, $CDCl_3$): δ = 9.48 (br s, 1H), 7.06 (s, 1H), 3.92 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 162.7, 135.5 (q, $^2J_{CF}$ = 40 Hz), 121.8 (q, $^1J_{CF}$ = 270 Hz), 120.5 (q, $^3J_{CF}$ = 3.5 Hz), 106.7, 52.5.

3-Hydroxy-5-trifluoromethyl-2-thiophenecarboxylic Acid (7)

To a stirred solution of NaOH (168 g, 4.21 mol) in H_2O (2.1 L) was added a solution of **6** (238 g, 1.05 mol) in MeOH (2.1 L). After the initial exotherm, the reaction mixture was heated at reflux until hydrolysis was complete (approx. 3 h) and then cooled to r.t. The reaction mixture was concentrated to about half volume and cooled to about 5 °C. Acidification to pH 1 with concd HCl (350 mL) resulted in a suspension. After stirring the suspension for 30 min at 5 °C, the solid was collected by filtration, washed with H_2O (3 × 1 L) and dried to afford 145 g (65%) of free acid **7** as a white solid, mp > 100 °C (dec.).

^1H NMR (400 MHz, DMSO-d_6): δ = 11.7 (br s, 2 H), 7.30 (s, 1H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 164.3, 159.9, 132.7 (q, $^2J_{CF}$ = 38.4 Hz), 122.4 (q, $^1J_{CF}$ = 269.6 Hz), 123.4 (q, $^3J_{CF}$ = 3.5 Hz), 110.4.

MS: *m/z* (%) = 211 ($M-H^-$) (100).

Anal. Calcd for $C_6H_3F_3O_3S$: C, 33.97; H, 1.42; S, 15.12. Found: C, 33.91; H, 1.46, S, 15.09.

4-Hydroxy-2-trifluoromethylthiophene (1)

Compound **7** (180 g, 849 mmol) was slowly heated under Ar. Rapid evolution of gas was observed at 90 °C. Heating was continued for an additional 3.5 h to complete the decarboxylation. The resulting oil was vacuum distilled (70−74 °C, 4 mm) through a Vigreux column (6 in.) to obtain 118 g (82%) of a pale yellow liquid.

IR (neat): ν = 3700−2900, 1696, 1570, 1465, 1415, 1297 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$), enol (major): δ = 7.06 (m, 1H), 6.52 (d, *J* = 1.7 Hz), 6.01 (br s, 1H).

^1H NMR (400 MHz, $CDCl_3$), keto (minor): δ = 6.60 (br s, 1H), 3.90 (br s, 2H).

^{13}C NMR (75.6 MHz, $CDCl_3$), enol (major): δ = 152.1, 130.3 (q, $^2J_{CF}$ = 26.2 Hz), 122.3 (q, $^1J_{CF}$ = 268.7 Hz), 121.0 (q, $^3J_{CF}$ = 3.8 Hz), 104.9.

^{13}C NMR (75.6 MHz, $CDCl_3$), keto (minor, partial): δ = 124.1, 41.7.

MS: *m/z* (%) = 168 (M^+) (100).

Anal. Calcd for $C_5H_3F_3OS$: C, 35.72; H, 1.80; S, 19.07. Found: C, 35.83; H, 1.85, S, 19.00.

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