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Practical synthesis of α-(trifluoromethyl)phenylacetic acid

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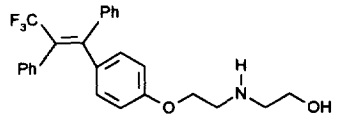
Abstract

α-(Trifluoromethyl)phenylacetic acid (**1**) was synthesized in good overall yield starting from the cyanohydrin of α,α,α-trifluoroacetophenone, via hydrogenolysis of α-mesyloxy-α-(trifluoromethyl)phenylacetamide or ethyl α-mesyloxy-α-(trifluoromethyl)phenylacetate followed by acidic hydrolysis.

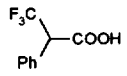
Keywords: α-(Trifluoromethyl)phenylacetic acid derivatives; Mesylates; Catalytic hydrogenation; NMR spectroscopy; IR spectroscopy

1. Introduction

In connection with the synthesis of panomifene (GYKI-13504, EGIS-5650) [1], a mammary-tumour inhibiting antiestrogen, a practical procedure for the large-scale synthesis of α-(trifluoromethyl)phenylacetic acid (**1**) was sought.



panomifene



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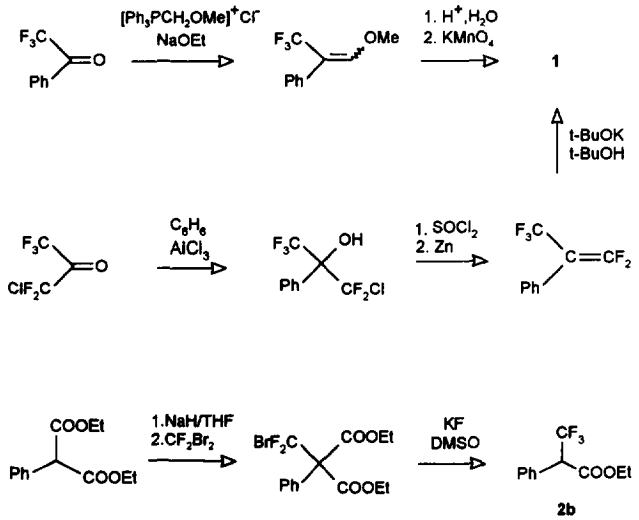
The reported failure in reducing the easily available α-hydroxy-α-(trifluoromethyl)phenylacetic acid to acid **1** with iodine, water and red phosphorus [2] was confirmed by our own attempts.

The methods available in the literature for the synthesis of compound **1** and its derivatives are rather cumbersome and suffer from low yields, and hence did not meet our requirements (Scheme 1). The first procedure is based on the Wittig reaction of α,α,α-trifluoroacetophenone and methoxymethylenetriphenylphosphonium chloride. Hydrolysis of the resulting enol ether affords the corresponding aldehyde which is oxidized to give the required acid [2]. Another method relies on the Friedel–Crafts reaction of chloropentafluoroacetone with benzene followed by a multistep reaction sequence [3] leading to the desired product. The ester of our target compound (**2b**) was prepared by alkylation of diethyl phenylmalonate with dibromodifluoromethane and subsequent bromide–fluoride exchange accompanied by deethoxycarbonylation [4].



Scheme 1.

2. Results and discussion

We report here a new and efficient synthesis for α-(trifluoromethyl)phenylacetic acid from cheap and readily available starting materials. The procedure works equally well on a larger scale.

We have overcome the difficulty associated with the failure of reducing the α-hydroxy function of α-hydroxy-α-(trifluoromethyl)phenylacetic acid derivatives. Inspiration came

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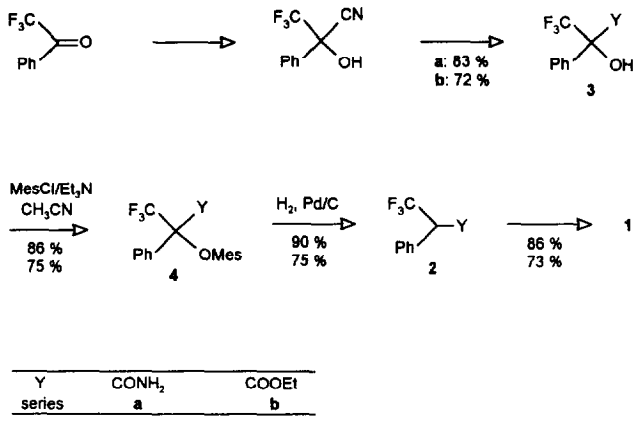

Scheme 2.

from the fact that the tosylate of 2,2,2-trifluoro-1-phenylethanol had been transformed to 2,2,2-trifluoro-1-phenylethane by hydrogenolysis in the presence of a palladium/charcoal catalyst [5].

α-Hydroxy-α-(trifluoromethyl)phenylacetamide (**3a**) was prepared from α,α,α-trifluoroacetophenone cyanohydrin as described in the literature [6]. The same starting compound was converted into the corresponding ethyl ester (**3b**) under conventional conditions. Reaction of compounds **3** with mesyl chloride in acetonitrile afforded mesylates **4** in 75%–86% yield [1]. Hydrogenolysis of the mesylates has been accomplished by catalytic hydrogenation in the presence of palladium/charcoal to give the acetamide **2a** and the ester **2b**. Acidic hydrolysis of amide **2a** provided the desired product **1** in 46% overall yield based on α,α,α-trifluoroacetophenone. Similarly, ester **2b** afforded the carboxylic acid **1** in 25% overall yield (see Scheme 2).

3. Experimental details

The IR spectra were recorded on an Aspect 2000 computer-controlled Bruker IFS-113v vacuum optic FT spectrometer, using KBr pellets for solids or liquid films. The ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-250 FT spectrometer at 250.13 and 62.89 MHz, respectively, using the 2H signal of the solvent as the lock and TMS as internal standard. All boiling and melting points are uncorrected.

3.1. α-Hydroxy-α-(trifluoromethyl)phenylacetamide (3a)

Compound **3a** was prepared as described in the literature [6].

3.2. Ethyl α-hydroxy-α-(trifluoromethyl)phenylacetate (3b)

α-Hydroxy-α-(trifluoromethyl)phenylacetonitrile [6] (25.0 g, 0.124 mol) was dissolved in ethanol. Concentrated sulphuric acid (13 ml) was added and the mixture refluxed. After about 15 h the reaction was complete (TLC, eluent: hexane/EtOAc, 9:1). The resulting mixture was poured into ice-water (80 ml) and extracted with diethyl ether (2×40 ml). The combined organic phases were washed with 0.5 N sodium hydrogen carbonate solution (2×40 ml) and water (40 ml), dried over magnesium sulphate and evaporated. The resulting oil was purified by distillation under reduced pressure (b.p. 81–86 °C/1.2 mmHg, lit. value [8] b.p. 138 °C/0.5 mmHg) to give **3b** (22.1 g, 72%) as a colourless oil.

IR (film) (cm^{-1}): 3483; 1740. ^1H NMR ($CDCl_3+D_2O$) δ: 7.80 (2H, m); 7.42 (3H, m); 4.43 (1H, dq, J=10.7, 7.2 Hz); 4.36 (1H, dq, J=10.7, 7.1 Hz); 1.35 (3H, t, J=7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6) δ: 168.2, 134.7, 129.7, 128.7, 126.7, 124.1 (q, $^1J_{CF}$=286 Hz); 78.7 (q, $^2J_{CF}$=29 Hz); 62.6; 14.0 ppm.

3.3. α-Mesyloxy-α-(trifluoromethyl)phenylacetamide (4a)

To a cold (−20 °C), stirred solution of α-hydroxy-α-(trifluoromethyl)phenylacetamide [6] (**3a**, 21.9 g, 0.100 mol) and triethylamine (55.6 ml, 40.4 g, 0.400 mol) in acetonitrile (200 ml), mesyl chloride (31.1 ml, 45.8 g, 0.400 mol) was added dropwise. After 15 min, the mixture was poured into ice-water (800 ml) and extracted with chloroform (3×250 ml). The organic fractions were washed with water (200 ml), dried over magnesium sulphate and evaporated. The residue was recrystallized from a mixture of 2-propanol (50 ml) and water (200 ml) to give **4a** (25.6 g, 86%), m.p. 120–121 °C (ethyl acetate/hexane).

IR (KBr) (cm^{-1}): 3420; 3184; 1719. ^1H NMR ($CDCl_3$) δ: 7.68 (2H, m); 7.50 (3H, m); 6.29 (2H, bs); 3.23 (3H, s) ppm. ^{13}C NMR (DMSO-d_6) δ: 165.3, 131.6, 130.4, 128.6, 127.6, 122.3 (q, $^1J_{CF}$=286 Hz); 86.4 (q, $^2J_{CF}$=29 Hz); 41.0 ppm. Analysis: Calc. for $C_{10}H_{10}F_3NO_4S$ (297.26): C, 40.41; H, 3.39; N, 4.71; S, 10.79%. Found: C, 40.55; H, 3.46; N, 4.78; S, 11.08%.

3.4. Ethyl α-mesyloxy-α-(trifluoromethyl)phenylacetate (4b)

This compound was prepared analogously to **4a**, starting from ethyl α-hydroxy-α-(trifluoromethyl)phenylacetate (**3b**, 19.9 g, 0.080 mol). The resulting crude oil was purified by distillation under reduced pressure (b.p. 126–129 °C/0.03 mmHg) to give **4b** (19.6 g, 75%) as a colourless oil.

IR (film) (cm^{-1}): 1762. ^1H NMR ($CDCl_3$) δ: 7.60 (2H, m); 7.47 (3H, m); 4.42 (2H, q, J=7.1 Hz); 3.27 (3H, s); 1.35 (3H, t, J=7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 163.7, 130.7, 130.3, 128.6, 126.5, 121.5 (q, $^1J_{CF}$=286 Hz); 86.3 (q, $^2J_{CF}$=30 Hz); 63.6; 40.8; 13.6 ppm. Analysis: Calc. for $C_{12}H_{13}F_3O_5S$ (326.30): C, 44.17; H, 4.02; S, 9.83%. Found: C, 43.88; H, 3.86; S, 9.81%.

[1] Tosylation of compound **3a** in pyridine at 25 °C resulted in the formation of the dehydration product α-tosyloxy-α-(trifluoromethyl)phenylacetonitrile (identical to a sample obtained by Kanagasabapathy et al. [7]).

3.5. α-(Trifluoromethyl)phenylacetamide (2a)

A solution of α-mesyloxy-α-(trifluoromethyl)-phenylacetamide (**4a**, 26.1 g, 0.087 mol) in methanol (300 ml) was hydrogenated in the presence of 10% palladium on charcoal (2.6 g), at 25 °C under 6 bar hydrogen for 5 h. The catalyst was removed by filtration, the filtrate evaporated and the residue crystallized from a mixture of methanol (20 ml) and water (60 ml) to give **2a** (16.1 g, 90%), m.p. 108–109 °C (methanol/water).

IR (KBr) (cm^{-1}): 3455; 3331; 1678. ^1H NMR ($CDCl_3$) δ: 7.48–7.38 (5H, m); 6.15 (1H, bs); 5.76 (1H, bs); 4.21 (1H, q, $J_{HF}=8.9$ Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 168.0, 130.4, 129.3, 128.8, 128.6, 124.1 (q, $^1J_{CF}=280$ Hz); 54.8 (q, $^2J_{CF}=29$ Hz) ppm. Analysis: Calc. for $C_9H_8F_3NO$ (203.17): C, 53.21; H, 3.97; N, 6.89%. Found: C, 53.12; H, 3.85; N, 6.94%.

3.6. Ethyl α-(trifluoromethyl)phenylacetate (2b)

This compound was prepared analogously to **2a**, starting from ethyl α-mesyloxy-α-(trifluoromethyl)phenylacetate (**4b**, 8.7 g, 0.027 mol). After removal of the catalyst, the solution was evaporated. The residue was dissolved in chloroform, extracted with water (3×15 ml), dried over magnesium sulphate and evaporated. The resulting oil was purified by distillation under reduced pressure (b.p. 77–80 °C/2.0 mmHg, lit. value b.p. 62 °C/0.3 mmHg [4]) to give **2b** (4.6 g, 75%) as a colourless oil.

IR (film) (cm^{-1}): 1750. ^1H NMR ($CDCl_3$) δ: 7.50–7.35 (5H, m); 4.31 (1H, q, $J_{HF}=8.6$ Hz); 4.26 (1H, dq, $J=10.8$, 7.2 Hz); 4.18 (1H, dq, $J=10.8$, 7.1 Hz); 1.24 (3H, t, $J=7.2$ Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 166.1, 129.4, 129.2, 128.9, 123.7 (q, $^1J_{CF}=280$ Hz); 62.0, 55.5 (q, $^2J_{CF}=29$ Hz); 13.8 ppm.

3.7. α-(Trifluoromethyl)phenylacetic acid (1)

Method a

A stirred mixture of α-(trifluoromethyl)phenylacetamide (**2a**, 25.9 g, 0.127 mol) and 50% aqueous sulphuric acid solution (260 ml) was heated at 120 °C for 1 h. It was poured into ice-water (180 ml) and extracted with chloroform (3×100 ml). The combined organic phases were washed with water (2×60 ml), dried over magnesium sulphate and evaporated. The residue was recrystallized from hexane to give **1** (22.3 g, 86%) as colourless crystals, m.p. 78–79 °C (hexane) (lit. value m.p. 77–78 °C [2]).

IR (KBr) (cm^{-1}): 3045; 1724. ^1H NMR ($CDCl_3$) δ: 10.76 (1H, bs); 7.50–7.40 (5H, m); 4.35 (1H, q, $J_{HF}=8.4$ Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 172.6 (q, $^3J_{CF}=3$ Hz); 129.7, 129.6, 129.2, 128.7, 123.5 (q, $^1J_{CF}=280$ Hz); 55.4 (q, $^2J_{CF}=30$ Hz) ppm.

Method b

A mixture of ethyl α-(trifluoromethyl)phenylacetate (**2b**, 18.8 g, 0.081 mol), concentrated hydrochloric acid (90 ml) and dioxane (180 ml) was refluxed for 30 h. Dichloromethane (50 ml) was added and the phases separated. The aqueous phase was extracted with dichloromethane (2×50 ml). The combined organic phases were extracted with 1 N sodium hydrogen carbonate solution (2×100 ml). The combined aqueous layers were acidified to pH 1 with 2 N hydrogen chloride solution and extracted with dichloromethane (3×50 ml). The combined organic phases were evaporated and the residue crystallized from hexane to give **1** (12.1 g, 73%), which was identical to that obtained according to Method a.

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