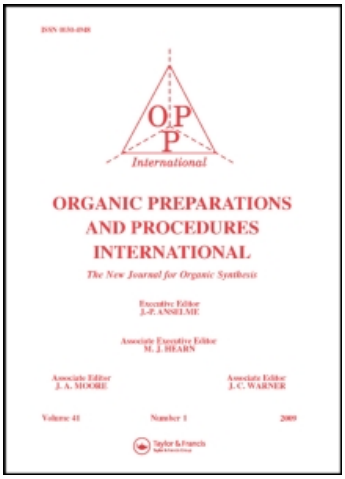

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVENIENT SYNTHESIS OF 5-TRIFLUOROMETHYLSALICYLIC ACID

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To cite this Article Alexander, Jose(1986) 'A CONVENIENT SYNTHESIS OF 5-TRIFLUOROMETHYLSALICYLIC ACID', Organic Preparations and Procedures International, 18: 3, 213 — 215
To link to this Article: DOI: 10.1080/00304948609458143
URL: http://dx.doi.org/10.1080/00304948609458143

A CONVENIENT SYNTHESIS OF 5-TRIFLUOROMETHYLSALICYLIC ACID

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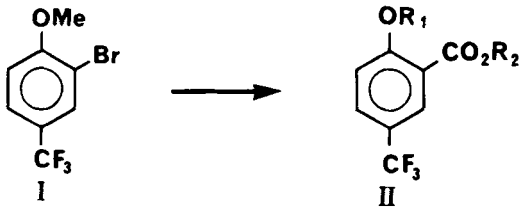
In connection with our interest in certain salicylic acid analogs that act as absorption promoters[1] of poorly absorbed drugs from the gastrointestinal tract, we needed hitherto unreported 5-trifluoromethylsalicylic acid,[2] which has been synthesized by the method described in this communication.

2-Bromo-4-trifluoromethylphenol[3] obtained by bromination of the commercially available 4-trifluoromethylphenol in carbon tetrachloride at ice bath temperature, was methylated with dimethyl sulfate and potassium carbonate in acetone. Acylation of the lithio derivative derived from the methyl ether I with methyl chloroformate gave a very poor yield (12.5%) of



a) R_1 = Me, R_2 = Me
b) R_1 = Me, R_2 = H
c) R_1 = H, R_2 = H

the methyl ester IIa, the major product being 2,2'-dimethoxy-5,5'-ditrifluoromethylbenzophenone (mp. 163-164°) formed from further condensation of the initially formed IIa with the lithio derivative. However, quantitative carboxylation of the lithio derivative to IIb was achieved by reaction with dry carbon dioxide. Iodotrimethylsilane failed to cleave

the methyl ether function. Treatment of IIb with aluminum chloride in refluxing chloroform resulted in demethylation accompanied by hydrolysis of the trifluoro methyl group to form 4-hydroxy-1,3-benzenedicarboxylic acid.[4] The methyl ether group could be cleanly cleaved by pyridine hydrochloride to furnish the required 5-trifluoromethylsalicylic acid in excellent yield. It proved to be an effective absorption promoter.[2]

EXPERIMENTAL

2-Bromo-4-trifluoromethylanisole (I) was prepared from 2-bromotrifluoromethylphenol[3] (14.3 g, 59.3 mmol), dimethyl sulfate (7.84 g, 62.2 mmol) and potassium carbonate (8.6 g, 62.3 mmol) in refluxing acetone. Filtration of an ethereal solution of the crude product through a column of basic alumina (60 g) yielded 14.8 g (98%) of pure I as a colorless oil. IR (film): 1618, 1512, 1412, 1345, 1280, 1180, 1124 cm^{-1}; ^1H NMR($CDCl_3$): δ 3.95 (s, OMe), 6.91 (d, J = 9 Hz, H-6), 7.5 (dd, J = 9 and 2 Hz, H-5), 7.78 (d, J = 2 Hz, H-3).

Anal. Calcd. for $C_8H_6BrF_3O$: C, 37.64; H, 2.35

Found: C, 37.58; H, 2.39

2-Methoxy-5-trifluoromethylbenzoic Acid (IIb).- To a solution of I (7.26 g, 28.4 mmol) in dry tetrahydrofuran (50 ml) and hexane (10 ml) cooled to -100 to -110° under a positive pressure of dry nitrogen, 19 ml of 1.5 M n-butyllithium was slowly introduced through a rubber septum. The reaction mixture was allowed to warm up to -80° during 0.5 hr. Carbon dioxide gas dried by dispersing through sulfuric acid and over Drierite was bubbled into the reaction mixture which was maintained at -75°. After 0.5 hr, the reaction mixture was brought to room temperature and the solvent was evaporated. The residue was dissolved in water and the aqueous solution was washed with ether. The aqueous layer was acidified and extracted with ether. The ether extract was washed, dried (Na_2SO_4) and evaporated to

furnish practically pure IIb (6.05 g, 97%) as an off-white solid. An analytical sample was prepared by crystallization from chloroform-hexane, mp. 106.5 - 107.5°. IR (KBr):3300-2650, 1715, 1333, 1278, 1248, 1188, 1095, 1018, 825 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.1 (s, OMe), 7.15 (d, J = 9 Hz, H-3), 7.78 (dd, J = 9 and 2 Hz, H-4), 8.36 (d, J = 2 Hz, H-6) and 10.66 (s, CO_2H); MS, m/e 220 (M^+), 203, 191, 173.

Anal. Calcd. for $C_9H_7F_3O_3$: C, 49.09; H, 3.20; F, 25.89

Found: C, 49.36; H, 3.41; F, 25.99

2-Hydroxy-5-trifluoromethylbenzoic Acid (IIc).- The above methoxy acid (3.0 g) was heated at 195° with freshly distilled pyridine hydrochloride (30 g) for 35 min with stirring. The reaction mixture was cooled, diluted with 3N hydrochloric acid (50 ml) and extracted with ether. The ethereal extract was washed with 3N hydrochloric acid and water and dried (Na_2SO_4). The ether was evaporated to yield the practically pure phenolic acid (2.76 g) as a white crystalline solid. Crystallization from light petrol gave analytically pure IIc (2.4 g, 85%), mp. 150-151°. IR (KBr):3300-2500, 1680, 1642, 1595 cm^{-1}; ^1H NMR ($CDCl_3$-DMSO-d_6): δ 7.01 (d, J = 9 Hz, H-3), 7.63 (dd, J = 9 and 2 Hz, H-4), 8.13 (d, J = 2 Hz, H-6), 11.4 (br s, CO_2H, OH); MS, m/e 206(M^+), 187, 160, 132.

Anal. Calcd. for $C_8H_5F_3O_3$: C, 46.60; H, 2.42; F, 27.66

Found: C, 46.48; H, 2.51; F, 27.92

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