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AN IMPROVED SYNTHESIS OF α-METHOXY-α-(TRWLUOROMETHYL)-PHENYLACETIC ACID (MOSHER'S ACID

Keith R. Buszek [a] & Nagaaki Sato [a]

[a] Department of Chemistty, Kansas State University, 111 Willard Hall, Manhattan, KS, 66506-3701, USA

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AN IMPROVED SYNTHESIS OF α-METHOXY-α-(TRIFLUOROMETHYL)-PHENYLACETIC ACID (MOSHER'S ACID)

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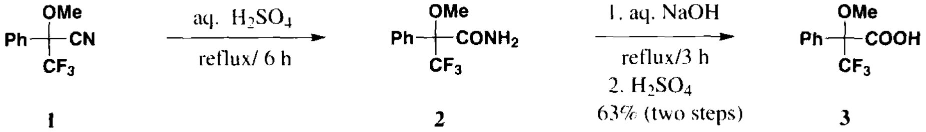
Keith R. Buszek* and Nagaaki Sato

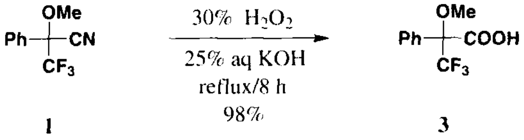
Department of Chemistry, 111 Willard Hall
Kansas State University, Manhattan, KS 66506-3701, USA

Mosher's acid, α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), is a valuable and useful reagent used for the determination of the enantiomeric purity and the absolute configuration of alcohols and amines, among other things.[1,2] During the course of an investigation into the use of chiral solvents for enantioselective organic and inorganic transformations, we required substantial quantities of the title compound. We now report an effective modification to the original synthesis for the preparation of MTPA.

The Mosher synthesis requires the hydrolysis of the nitrile **1** under strongly acidic conditions to afford the amide **2** (not isolated), which was further subjected to base-induced hydrolysis, and is reported to give after acidification, the desired carboxylic acid **3** in 63% overall yield. In our hands, however, the yield was typically between 30-40%, and never exceeded 50%.



Our modification of this sequence gives in a one-pot procedure the desired carboxylic acid in nearly quantitative yield.[3] Basic hydrogen peroxide hydrolysis[4] of the nitrile under reflux followed by acidification and extraction with chloroform consistently gave the corresponding acid in 97-99% after distillation. This new procedure offers a practical and convenient improvement for the preparation of Mosher's acid.



EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Varian Unity Plus 400-MHz spectrometer operating at 399.886 MHz in the indicated solvents. Elemental analyses were performed by Galbraith Laboratories, Inc. Thin layer chromatography (TLC) was carried out using E. Merck silica gel (60 F 254) plates of 0.25 mm thickness. Visualization was accomplished with short wavelength ultraviolet light, and stained with anisaldehyde dip reagent (prepared from 1350 mL abs EtOH, 50 mL conc. H_2SO_4, 15 mL glacial acetic acid, and 37 mL anisaldehyde). All solvents and reagents were obtained from either Aldrich Chemical Co., Inc. or Fisher Scientific and used without further purification.

α-Methoxy-α-(trifluoromethyl)phenylacetic Acid (3).- To a vigorously stirred suspension of nitrile **1** (47.8 g, 0.222 mol) in aqueous potassium hydroxide (480 mL, 25% w/w) at room temperature was added dropwise 30% aqueous hydrogen peroxide (96 mL, 0.47 mol). The reaction mixture was slowly heated to reflux and maintained at that temperature for 8 hrs. After cooling to room temperature, the mixture was cautiously acidified with conc. aqueous HCl (200 mL, 2.4 mol), and extracted with chloroform (5 x 200 mL). The combined organic extracts were washed with saturated aqueous $NaHSO_3$ (3 x 100 mL or until a negligible hydrogen peroxide concentration remains as determined by the EM

Science Merckoquant Peroxide Test strip), dried over $MgSO_4$, filtered and concentrated. The residue was distilled through a short-path apparatus to give the pure carboxylic acid **3** (51.0 g, 98%) as a colorless liquid, bp 105-110° (1 mmHg) which solidified as a low melting solid, mp 44-45°. The crude material was sufficiently pure and could be used without distillation in the subsequent resolution step. ^{1}H NMR ($CDCl_3$): δ 11.65 (1 H, s), 7.62-7.45 (5 H, m), 3.58 (3 H, s); IR (neat) 3500-2700, 1695 cm^{-1}. *Anal.* Calcd for $C_{10}H_9F_3O_3$: C, 51.29; H, 3.87. Found: C, 51.42; H, 3.95

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