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

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PHENYLACETIC ACID (MOSHER'S ACID)**

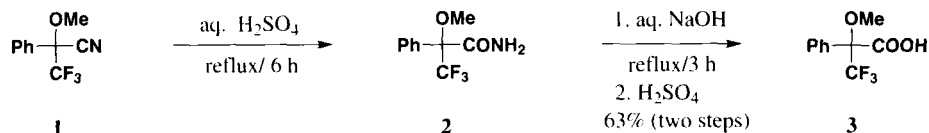
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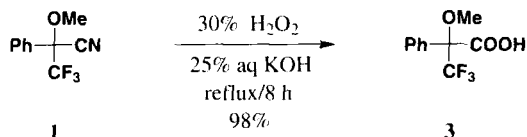
Mosher's acid, α -methoxy- α -(trifluoromethyl)phenylacetic acid (MTPA), is a valuable and useful reagent used for the determination of the enantiomeric purity and the absolute configuration of alcohols and amines, among other things.^{1,2} During the course of an investigation into the use of chiral 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 hydrolysis⁴ 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

¹H 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. H₂SO₄, 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 NaHSO₃ (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. $^1\text{H NMR}$ (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 $\text{C}_{10}\text{H}_9\text{F}_3\text{O}_3$: C, 51.29; H, 3.87. Found: C, 51.42; H, 3.95

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