NOTES

SYNTHESIS OF 4-TRIFLUOROMETHYLPHTHALIC ACID

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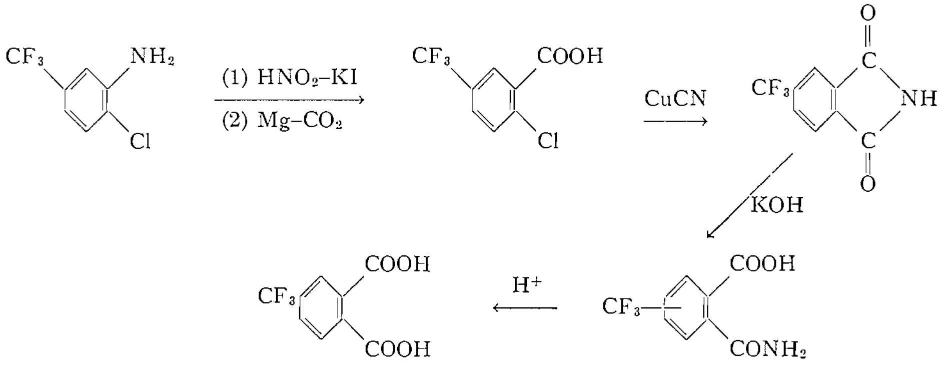
During a study of reactions of phthalic acids, it became necessary to prepare 4-trifluoromethylphthalic acid (I). This compound, not previously described, proved to be unexpectedly difficult to prepare; most of the standard methods either failed entirely or gave, at some stage in the reaction sequence, such low yields as to be unsuitable for preparative purposes. In this paper, we describe a convenient synthesis of this compound.

The synthetic scheme is outlined below and proceeds from the commercially available 3-amino-4-chlorobenzotrifluoride.

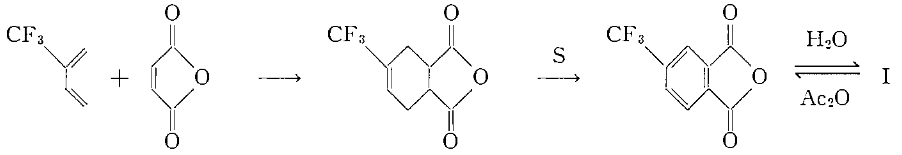


I

Reaction of 2-chloro-5-trifluoromethylbenzoic acid with cuprous cyanide gave 4-trifluoromethylphthalimide (70% yield) rather than the expected 2-cyano-5-trifluoromethylbenzoic acid.

4-Trifluoromethylphthalimide, on being stirred with base, gave the phthalamic acid, which, on being warmed with dilute acid, gave I. The hydrolysis of the imide can be carried out without isolation of the phthalamic acid; in this way, I is obtained in 90% yield.

Another far less satisfactory route to I involved the Diels–Alder reaction. Dehydrogenation of the adduct (II) was accomplished in 30% yield by heating it with sulphur at 230 to 250° C.



II

Adduct II could not be aromatized using chloranil, bromine, or palladium-on-carbon in refluxing quinoline or dimethylformamide. 4-Trifluoromethylphthalic anhydride, surprisingly, was a very fluid liquid; on being heated with water it was reconverted to the acid (I).

This route to I was not suitable on a preparative scale because of the difficulty of obtaining 2-trifluoromethylbutadiene; this difficulty has been observed by others (1, 2).

Some of the other methods that were investigated, unsuccessfully, for the synthesis of I were via diazotization of 3-nitro-4-aminobenzotrifluoride and 3,4-diaminobenzotrifluoride (in attempts to prepare the corresponding nitriles), via oxidation of 5- or 6-trifluoromethyl isatins,[1] via a Rosenmund–vonBraun reaction on 2-nitro-3-chlorobenzotrifluoride,[2] and via reaction of 4-carboxyphthalic ester and anhydride with sulphur tetrafluoride.

EXPERIMENTAL[3]

3-Iodo-4-chlorobenzotrifluoride

Two 22-liter three-necked round-bottom flasks equipped with an efficient stirrer, addition funnel, and thermometer were charged with 2 liters of concentrated sulphuric acid in 4 liters of water. To this hot solution was added rapidly 616.5 g (3 moles, 95% pure) of 3-amino-4-chlorobenzotrifluoride,[4] after which the solution was slowly cooled to 0–5° C with vigorous stirring. The suspension of the white sulphate salt was then diazotized with a solution of 207 g of sodium nitrite (3 moles) in 840 ml of water. After this addition was completed, there was added 549 g (3.3 moles) of potassium iodide in 815 ml of water over a period of 25 minutes. The brown oily mixture was then heated to 50° C for 1 hour, cooled in an ice water bath, and extracted with three 5 liter portions of ether. The ether extracts were washed with an aqueous solution of sodium thiosulphate, then water, and finally dried over anhydrous magnesium sulphate. The ether solution was filtered and concentrated, and the reddish-colored residue was distilled at 58–60° C (0.5 mm) to give 1620 g (83.5%) of a pink-colored liquid. Anal. Calc. for $C_7H_3ClF_3I$: C, 27.44; H, 0.98. Found: C, 27.37; H, 0.96.

2-Chloro-5-trifluoromethylbenzoic Acid

A 22-liter three-necked round-bottom flask equipped with an efficient stirrer, condenser, gas inlet tube, thermometer, and addition funnel was charged with 150 g (6.25 moles) of magnesium and 2 liters of ether. This solution was kept under a nitrogen atmosphere, as, with vigorous stirring, the solution was heated to reflux, at which time a few drops of ethylene bromide and 1620 g of 3-iodo-4-chlorobenzotrifluoride in 9400 ml of ether was added over a period of 2 hours. The mixture was refluxed and stirred vigorously for another 2 hours, and 1 ml of ethylene bromide was added after each hour. The mixture was cooled to −20° C in a dry ice – acetone bath and 800 g (18.2 moles) of dry carbon dioxide was bubbled into it over a period of 90 minutes. After it was allowed to stand overnight at room temperature, the reaction mixture was hydrolyzed at 0° C with 3 liters of cold 10% hydrochloric acid and was then extracted with three 2-liter portions of ether, and the ethereal solutions extracted with three 2-liter portions of a 10% potassium carbonate solution. The aqueous solution was treated with a small amount of charcoal and the solution filtered. Acidification of the filtrate with concentrated hydrochloric acid gave 663 g (49.5%) of an off-white material which was recrystallized from benzene–petroleum ether, m.p. 91–92° C. Anal. Calc. for $C_8H_4ClF_3O_2$: C, 42.78; H, 1.80. Found: C, 42.91; H, 1.89.

4-Trifluoromethylphthalimide

A mixture of 50 g (0.223 mole) 2-chloro-5-trifluoromethylbenzoic acid, and 30 g (0.335 mole) cuprous cyanide in 80 ml dimethylformamide was heated at reflux, with stirring, for 45 minutes. The resulting dark suspension was cooled slightly, and a solution containing 75 g of ferric chloride and 25 ml of concentrated hydrochloric acid in 125 ml of water was added over a period of 5 minutes. The mixture was then heated at 65° C for 15 minutes, chilled, diluted with 50 ml of ice water, and filtered. The dark brown solid was triturated with 5% sodium bicarbonate and filtered, giving 46.5 g of 4-trifluoromethylphthalimide, m.p. 164–166° C. A small sample recrystallized from benzene melted at 168.5–169.5° C. Anal. Calc. for $C_9H_4F_3NO_2$: C, 50.25; H, 1.87; N, 6.51. Found: C, 50.35; H, 1.85; N, 6.74.

4- (or 5)-Trifluoromethylphthalamic Acid

A suspension of 0.5 g 4-trifluoromethylphthalimide in 2.5 ml of 25% potassium hydroxide was stirred for 4 hours; then sufficient water was added to dissolve all the solid. The solution was cooled and acidified. The resulting waxy white solid was recrystallized from a mixture of isopropanol and hexane, m.p. 154–155° C. Anal. calc. for $C_9H_6F_3NO_3$: C, 46.36; H, 2.59. Found: C, 46.38; H, 2.94.

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[1] *The oximino acetanilides could not be cyclized to the isatins as claimed by P. M. Maginnity and C. A. Gaulin. J. Am. Chem. Soc. 73, 3579 (1951).*

[2] *On mixture with potassium cyanide in dimethyl formamide there was no reaction. When sodium cyanide was used the reaction was almost explosively exothermic, but no product could be isolated.*

[3] *All melting points are corrected. Analyses were carried out by Miss Margaret Carroll and her staff of these laboratories.*

[4] *Aldrich Chemical Company.*

4-Trifluoromethylphthalic Acid

(a) From 4-Trifluoromethylphthalimide

A suspension of 1 g 4-trifluoromethylphthalimide in 5 ml of 25% potassium hydroxide was stirred for 10 hours, then the solution was made strongly acidic with concentrated hydrochloric acid. The solution was heated at reflux for 1 hour, filtered, then chilled, giving 0.9 g of a glistening waxy solid. Recrystallization from water gave the 4-trifluoromethylphthalic acid as a partial hydrate. Anal. calc. for $C_9H_5F_3O_4.3/4\ H_2O$: C, 43.83; H, 2.64. Found: C, 43.84; H, 2.38.

Prolonged drying at 100° C *in vacuo* did not remove the water. The melting point varied with the rate of heating and temperature at which the sample was placed in the melting point bath (phthalic acid shows the same behavior). After recrystallization from benzene, the sample analyzed the anhydrous form, and melted smoothly at melting point 169–170° C. The infrared was identical with that of a sample prepared via the Diels–Alder reaction, described below. Anal. calc. for $C_9H_5F_3O_4$: C, 46.17; H, 2.15. Found: C, 45.76; H, 2.50.

(b) Via Diels–Alder Reaction

A solution of 5 g (0.041 mole) 2-trifluoromethylbutadiene(2) and 4 g (0.041 mole) maleic anhydride in benzene was placed in a sealed bottle and kept at room temperature for 2 hours, then heated at 100° C for 8 hours. The solution was cooled and diluted with hexane. The precipitated 4-trifluoromethyltetrahydrophthalic anhydride was filtered (8 g) and recrystallized from benzene–hexane, m.p. 107–107.5° C (lit. (1) m.p. 107°).

The anhydride (5 g, 0.0228 mole) and 2 g sulphur were heated to 240° C in an oil bath, and maintained at 240–250° C for 3 hours. On cooling, the unreacted sulphur separated. Isopropyl ether was added and the sulphur was filtered off. The filtrate, on evaporation, left 4-trifluoromethylphthalic anhydride as a fluid oil. The oil was boiled with water until it all dissolved (approx. 15 minutes), then the solution was concentrated *in vacuo* leaving 5 g of a viscous oil. This was taken up in a large volume of benzene, then the solution was concentrated to 10 ml and cooled. The product separated as a white solid, m.p. 165–167° C. When a sample of the acid was refluxed with acetic anhydride for 1 hour, then concentrated, it was reconverted to the liquid anhydride.

ACKNOWLEDGMENT

We are indebted to Dr. Dale W. Blackburn and Mr. Gerald E. Jaffe for assistance in preparing some of the intermediates used in this work.

1. A. L. HENNE and P. E. HINKAMP. J. Am. Chem. Soc. **76**, 5147 (1954).
2. P. TARRANT and R. E. TAYLOR. J. Org. Chem. **24**, 1888 (1959).

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DIRECT CONVERSION OF AROMATIC NITRILES INTO PHTHALIMIDINES AND UREAS USING DICOBALT OCTACARBONYL*

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This note summarizes the principal results (shown in Table I) of a study on the direct carbonylation of benzonitrile, *m*-tolunitrile, and phenylacetonitrile. In 1959 Murahashi and Horiie (1) reported that benzonitrile was reduced with a 1:1 molar mixture of carbon monoxide and hydrogen in the presence of dicobalt octacarbonyl to yield amines. When the mole ratio of substrate to hydrogen was about 1:1 in the presence of a large excess of carbon monoxide, Rosenthal and Gervay (2) found that a cyclized product, namely, N-benzylphthalimidine, was produced in low yield.

The yield of N-benzylphthalimidine was increased about threefold by the concomitant

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