Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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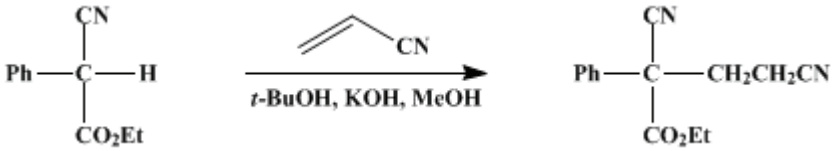
Organic Syntheses, Coll. Vol. 4, p.776 (1963); Vol. 30, p.80 (1950).

α-PHENYL-α-CARBETHOXYGLUTARONITRILE

[Butyric acid, 2,4-dicyano-2-phenyl-, ethyl ester]



Submitted by E. C. Horning and A. F. Finelli[1].
Checked by William S. Johnson and H. Wynberg.

1. Procedure

In a 500-ml. three-necked flask equipped with a stirrer, a dropping funnel, and a thermometer is placed a solution of 57.0 g. (0.30 mole) of ethyl phenylcyanoacetate (p. 461) in 80 ml. of *tert*-butyl alcohol. The solution is heated to 40°, and with stirring the dropwise addition of a solution of 33.0 g. (0.62 mole) of acrylonitrile (Note 1) in 30 ml. of *tert*-butyl alcohol is started. After the addition of about 10–15 drops, 1.0 ml. of a 30% solution of potassium hydroxide in methanol is added, and the temperature is maintained at 40–45° by occasional external cooling while the remaining solution is added slowly. When about one-half of the acrylonitrile has been added, an additional 1.0 ml. of the potassium hydroxide solution is added to ensure the presence of a basic catalyst throughout the reaction. When the addition is completed (after about 30 minutes) and the temperature is no longer maintained above 40° by the exothermic reaction (another 30 minutes), the mixture is heated with a hot-water bath to keep the temperature at 40–45° for 1 hour.

The solution is diluted with 250 ml. of water and acidified with 30–40 ml. of 10% hydrochloric acid. The product is separated after the addition of 100 ml. of ether, and the aqueous solution is extracted with two 50-ml. portions of ether. The combined extracts are washed with 50 ml. of water and dried over anhydrous magnesium sulfate. The ether is distilled at atmospheric pressure, and the residue is distilled under reduced pressure through a short (15-cm.) Vigreux column. After a fore-run of a few grams, the product is collected at 157–167° /0.5–1 mm. (Note 2). The yield is 50–61 g. (69–83%).

2. Notes

1. The acrylonitrile should be distilled before use. Acrylonitrile vapors are toxic, and the distillation as well as the subsequent reaction should be carried out in a hood.
2. Other observed boiling points are 165–167° /1 mm., 195–200° /6 mm. The product is a colorless, viscous oil, n_D^{25} 1.5100–1.5103.

3. Discussion

α-Phenyl-α-carbethoxyglutaronitrile has been prepared by the reaction of ethyl α-cyanophenylacetate with β-chloropropionitrile in the presence of sodium amide.[2] The present procedure has been published,[3] and it follows the general method described by Bruson[4] for the cyanoethylation of arylacetonitriles.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 790

References and Notes

1. University of Pennsylvania, Philadelphia, Pennsylvania.
2. Bergel, Morrison, and Rinderknecht (to Hoffmann-La Roche, Inc.), U. S. pat. 2,446,803 [*C. A.*, **43**, 695 (1949)].
3. Horning and Finelli, *J. Am. Chem. Soc.*, **71**, 3204 (1949).
4. Bruson and Riener, *J. Am. Chem. Soc.*, **65**, 25 (1943).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

potassium hydroxide (1310-58-3)

magnesium sulfate (7487-88-9)

sodium amide (7782-92-5)

acrylonitrile (107-13-1)

β-chloropropionitrile (542-76-7)

tert-butyl alcohol (75-65-0)

Ethyl phenylcyanoacetate,
ethyl α-cyanophenylacetate (4553-07-5)

α-Phenyl-α-carbethoxyglutaronitrile,
Butyric acid, 2,4-dicyano-2-phenyl-, ethyl ester (53555-70-7)