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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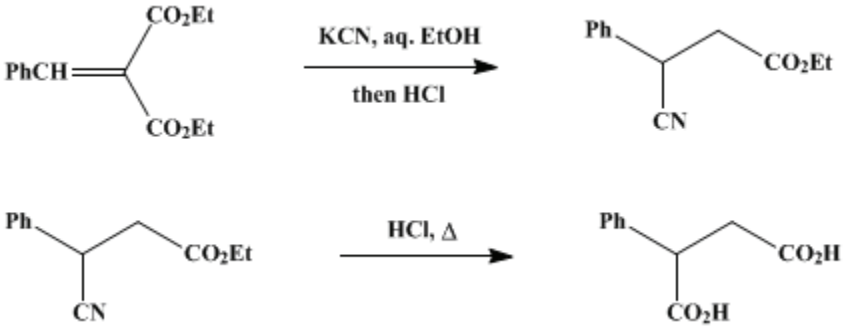
PHENYLSUCCINIC ACID

[Succinic acid, phenyl-]



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1. Procedure

Caution! This preparation should be conducted in a well-ventilated hood to avoid exposure to hydrogen cyanide.

A. *Ethyl β-phenyl-β-cyanopropionate.* In a 5-l. round-bottomed three-necked flask suspended in an oil bath and fitted with a mechanical stirrer, a reflux condenser, and a 250-ml. dropping funnel is placed a solution of 200 g. (0.81 mole) of diethyl benzalmalonate[2] in 2 l. of absolute ethanol. The stirrer is started, and a solution of 56 g. (0.86 mole) of potassium cyanide in 100 ml. of water is added rapidly from the separatory funnel; a small amount of the potassium cyanide precipitates. The temperature of the oil bath is raised to 70° and maintained at 65–75° for 18 hours.

The mixture is cooled to 15°, and the precipitated potassium bicarbonate is collected on a Büchner funnel. The solid (weight 70–72 g.) is washed on the funnel with 100 ml. of 95% ethanol. The combined filtrate and wash liquor is transferred to a 5-l. round-bottomed flask and made slightly acid *(Caution! (Note 1))* with dilute hydrochloric acid (about 15–20 ml. of the 10% acid is required). The solution is then concentrated under reduced pressure to a semi-solid residue (Note 1). The cooled residue is shaken with a mixture of 300 ml. of water and 500 ml. of ether. The material dissolves completely; the water layer is separated and washed with 200 ml. of ether. The ether solutions are combined, dried over 20 g. of calcium chloride, filtered into a 2-l. round-bottomed flask equipped with a glass joint, and concentrated by distillation (heating on a steam bath). The crude ethyl β-phenyl-β-cyanopropionate remains as a clear red oil weighing 130–140 g. It is sufficiently pure for use in the next step (Note 2).

B. *Phenylsuccinic acid.* To the crude ester obtained above is added 500 ml. of concentrated hydrochloric acid (sp. gr. 1.19). The flask is fitted to a condenser (Note 3), and the mixture is heated under reflux for 18 hours (Note 4). At the end of this time only a small amount of red oil remains (Note 5). The mixture is cooled, and the nearly solid cake which forms is broken up and collected on a glass filter cloth (Note 5). The crude tan-colored phenylsuccinic acid is washed with 300 ml. of cold water and dried at 60°. It then weighs 105–110 g. (67–70%) and melts at 163–164° (Note 6) and (Note 7).

2. Notes

1. Since hydrogen cyanide may be liberated during the acidification and the subsequent concentration, both operations should be carried out in a well-ventilated hood.
2. The pure ester can be obtained by distillation under reduced pressure (b.p. 161–164°/8 mm.).
3. Glass-jointed equipment is required in this step. The flask with a glass joint was used in the preceding

operation only to avoid the necessity of transferring the product after the evaporation.
4. Hydrogen chloride is evolved during the first part of the refluxing; it may be disposed of by absorption in water in a gas trap.[3]
5. The red, oily impurity usually distributes itself as a film on the surface of the liquid and as a lump at the bottom of the flask. It solidifies on cooling and is most conveniently removed as a solid; the thin crust on the surface is lifted with a spatula, and the lump at the bottom of the flask is left undisturbed when the product is collected on the filter.
6. The pure acid can be obtained by recrystallization from water. For each 10 g. of acid about 300 ml. of water and 0.5 g. of Norit are required. The recovery is 85–90% of pure white acid melting at 165.5–166°.
7. The checkers found the product at this stage to be of sufficient purity for conversion to phenylsuccinic anhydride.

3. Discussion

Preparative methods for phenylsuccinic acid have been listed in an earlier volume.[4] More recent procedures have been based on the hydrolysis of ethyl α-phenyl-β-cyanopropionate,[5] tetraethyl 1-phenyl-1,1,2,2-ethanetetracarboxylate,[6] diethyl (α-phenyl-β-nitroethyl) malonate,[7] and ethyl[8] or methyl 2,3-dicyano-3-phenylpropionate.[9]

The procedure given above is more economical of time and materials than that previously published.[4] Applications of the present method, due originally to Bredt and Kallen,[10] have been published.[11,12]

References and Notes

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5. Wideqvist, *Arkiv Kemi, Mineral. Geol.*, **26A**, No. 16 (1948) [*C. A.*, **43**, 2167 (1949)].
6. Hsing and Li, *J. Am. Chem. Soc.*, **71**, 774 (1949).
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8. Sen and Bagchi, *J. Org. Chem.*, **20**, 845 (1955).
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10. Bredt and Kallen, *Ann.*, **293**, 344 (1896).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrogen chloride,
hydrochloric acid (7647-01-0)

ether (60-29-7)

hydrogen cyanide (74-90-8)

potassium cyanide (151-50-8)

Norit (7782-42-5)

Phenylsuccinic acid,
Succinic acid, phenyl- (635-51-8)

diethyl benzalmalonate (5292-53-5)

potassium bicarbonate (298-14-6)

Ethyl β-phenyl-β-cyanopropionate (14025-83-3)

phenylsuccinic anhydride (1131-15-3)

ethyl α-phenyl-β-cyanopropionate

tetraethyl 1-phenyl-1,1,2,2-ethanetetracarboxylate

diethyl (α-phenyl-β-nitroethyl) malonate