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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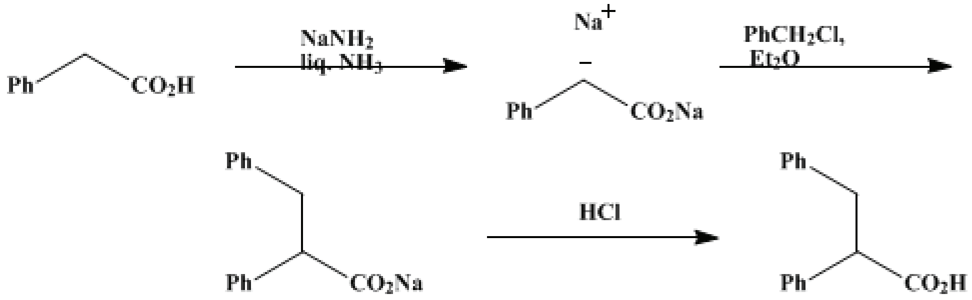
α,β-DIPHENYLPROPIONIC ACID

[Propionic acid, 2,3-diphenyl-]



Submitted by Charles R. Hauser and W. R. Dunnavant[1].
Checked by Virgil Boekelheide and P. Warrick.

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A solution of sodium amide (0.226 mole) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with a condenser, a ball-sealed mechanical stirrer, and a dropping funnel. Commercial anhydrous liquid ammonia (500 ml.) is introduced from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of sodium. After the appearance of a blue color, a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut sodium until 5.2 g. has been added. After all the sodium has been converted to the amide (Note 1), 14.2 g. (0.104 mole) of phenylacetic acid (Note 2) is added and the dark-green suspension is stirred for 15 minutes. To the green suspension is added rapidly 13.2 g. (0.104 mole) of benzyl chloride (Note 3) in 25 ml. of anhydrous ether, and the mixture is then stirred for 1 hour. The mixture is then evaporated to near dryness on a steam bath, 200 ml. of ether added, and evaporation to dryness effected. Another 200 ml. of ether is added, followed by evaporation to dryness. The resulting solid is then dissolved in 300 ml. of water and washed with three 200-ml. portions of ether. The aqueous solution is filtered through a layer of Celite to remove the slight brown coloration, and the filtrate is acidified with hydrochloric acid. A colorless oil forms which, when cooled for a few minutes in an ice bath, becomes a white crystalline solid. This is collected by filtration and washed with three 100-ml. portions of hot water (Note 4) and dried. The yield of crude α,β-diphenylpropionic acid, m.p. 92.0–93.5°, is 19.85 g. (84.5–88%). The crude solid is recrystallized from 60 ml. of petroleum ether (60–90°) to yield 18.80 g. (80–84%) (Note 5) of α,β-diphenylpropionic acid, m.p. 95.5–96.5° (Note 6) and (Note 7).

2. Notes

1. Conversion is indicated by the disappearance of any blue color. This generally requires about 20 minutes.
2. Phenylacetic acid as supplied by the Eastman Kodak Company was used without purification.
3. Eastman Kodak Company "Practical Grade" benzyl chloride was distilled before use, the fraction with b.p. 63–64°/12 mm. being used.
4. The hot water effectively removes unreacted phenylacetic acid, m.p. 76.7°, the presence of which hinders the purification of the product. The water should be hot but not boiling, since α,β-diphenylpropionic acid has some solubility in boiling water and may be recrystallized from water.
5. An identical preparation using potassium amide instead of sodium amide gave α,β-diphenylpropionic acid in 57% yield.
6. Miller and Rohde[2] report that α,β-diphenylpropionic acid exists in three crystalline modifications

melting at 82°, 88–89°, and 95–96°. Although the product obtained by the submitters melted at 95.5–96.5°, corresponding to the high-melting form, the sample obtained by the checkers melted sharply at 88–89° corresponding to the crystalline form of intermediate melting point.

7. Under comparable conditions the corresponding alkylations of phenylacetic acid with α-phenylethyl chloride and benzhydryl chloride have been effected to form α,β-diphenylbutyric acid and α,β,β-triphenylpropionic acid in yields of 74% and 51%, respectively.[3]

3. Discussion

This procedure is an adaption of one described by Hauser and Chambers.[3] Previous preparations include the benzylation of diethyl phenylmalonate followed by hydrolysis,[4] the benzylation of phenylacetonitrile followed by hydrolysis,[5,6] the benzylation of phenylacetic acid through the Ivanov reagent,[7] and the reduction of α-phenylcinnamic acid using sodium amalgam.[2]

The present procedure illustrates the use of dianions for alkylation and gives α,β-diphenylpropionic acid more conveniently and in better yield than previous preparations.

The alkylation of ethyl phenylacetate is also described in this volume (see p. 559). The submitters of this alternative procedure reported that it gave an 85% yield of ethyl α,β-diphenylpropionate.

References and Notes

1. Department of Chemistry, Duke University, Durham, North Carolina. Work supported by the Office of Ordnance Research.
2. W. v. Miller and G. Rohde, *Ber.*, **25**, 2017 (1892).
3. C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956).
4. W. Wislicenus and K. Goldstein, *Ber.*, **28**, 818 (1895).
5. A. Meyer, *Ber.*, **21**, 1311 (1888).
6. C. R. Hauser and W. R. Brasen, *J. Am. Chem. Soc.*, **78**, 494 (1956).
7. T. Cohen and G. F. Wright, *J. Org. Chem.*, **18**, 432 (1953).

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

petroleum ether

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium (13966-32-0)

benzyl chloride (100-44-7)

phenylacetonitrile (140-29-4)

Phenylacetic acid (103-82-2)

Ethyl phenylacetate (101-97-3)

diethyl phenylmalonate (83-13-6)

sodium amide (7782-92-5)

potassium amide

ferric nitrate hydrate

α-Phenylcinnamic acid (3368-16-9)

benzhydryl chloride (90-99-3)

α,β,β-Triphenylpropionic acid (53663-24-4)

α-phenylethyl chloride (672-65-1)

α,β-DIPHENYLPROPIONIC ACID,
Propionic acid, 2,3-diphenyl- (3333-15-1)

α,β-diphenylbutyric acid

ethyl α,β-diphenylpropionate