



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.

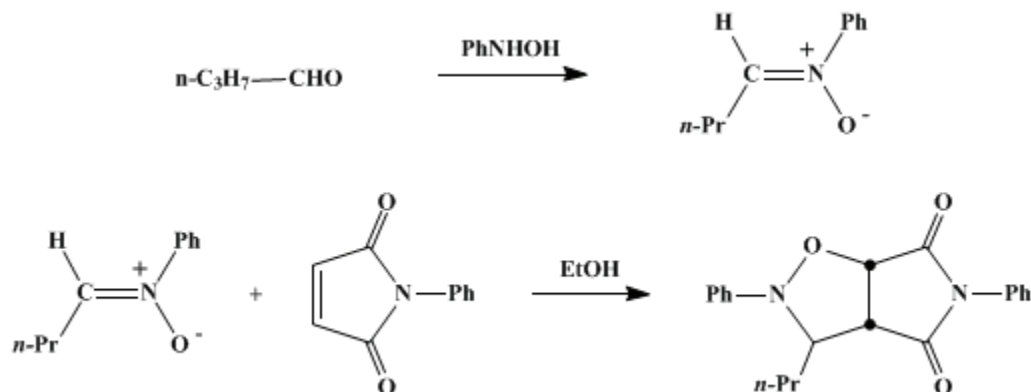
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

Organic Syntheses, Coll. Vol. 5, p.957 (1973); Vol. 46, p.96 (1966).

2-PHENYL-3-*n*-PROPYLISOXAZOLIDINE-4,5-*cis*-DICARBOXYLIC ACID N-PHENYLIMIDE



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 Checked by Robert Eliason, Wayland E. Noland, and William E. Parham.

1. Procedure

N-Phenylhydroxylamine (11 g., 0.10 mole)² (Note 1) and N-phenylmaleimide (17.4 g., 0.10 mole)³ are suspended in 40 ml. of ethanol contained in a 200-ml. Erlenmeyer flask. To the mixture is added immediately (Note 2) 8.98 g. (11.2 ml., 0.124 mole) of freshly distilled *n*-butylaldehyde. An exothermic reaction ensues, and the mixture spontaneously heats to the boiling point. A clear slightly yellow solution results which, upon cooling, deposits an almost colorless crystalline cake. The mixture is allowed to stand in the ice box for 1 day; it is then filtered through a Büchner funnel, and the crystals are washed twice with 25-ml. portions of ice-cold ethanol. The yield of air-dried product, m.p. 99–101°, is 31–32 g. (92–95%). For further purification the crude material is dissolved in 60 ml. of boiling ethanol on the steam bath, and the resulting solution is allowed to cool slowly to room temperature. If crystallization does not spontaneously begin in 5–10 minutes, it can then be induced by seeding. After being kept for 5 hours in the refrigerator, the solution is filtered and the colorless crystals are washed twice with 20-ml. portions of cold ethanol. The dried product weighs 29–30 g. An additional recrystallization of the air-dried product from 60 ml. of ethanol gives 26–27 g. (77–80%) of the pure isoxazolidine, m.p. 106.5–107.5°.

2. Notes

1. The phenylhydroxylamine should be free of sodium chloride. This can be easily removed by dissolution of the substance in benzene followed by filtration, and then addition of petroleum ether to precipitate the pure compound.
2. The checkers observed, in two runs, that when *n*-butylaldehyde is added after 10–15 minutes, the reaction is only mildly exothermic, and the white precipitate that forms does not dissolve. The infrared spectrum of the white crystalline product (19–20 g., m.p. 181–184° dec.) suggests that it may be the adduct of phenylhydroxylamine and N-phenylmaleimide formed by addition of the N-H bond of the amine to the olefinic bond of the imide; however, the structure of the product was not further examined.

3. Discussion

The preparation of 2-phenyl-3-*n*-propylisoxazolidine-4,5-*cis*-dicarboxylic acid N-phenylimide from *n*-butylaldehyde, N-phenylhydroxylamine, and N-phenylmaleimide is new and is described by Hauck.⁴ The intermediate, C-(*n*-propyl)-N-phenylnitrone, is an unstable compound and is difficult to purify. The procedure described avoids the isolation of the nitrone by adding it *in situ* to a suitable dipolarophile.

4. Merits of the Preparation

The present procedure serves as a model for the generation and use *in situ* of unstable nitrones in 1,3-dipolar cycloaddition reactions.

References and Notes

1. Institut für Organische Chemie der Universität München, München, Germany.
 2. O. Kamm, *Org. Syntheses*, Coll. Vol. **1**, 445 (1941).
 3. M. P. Cava, A. A. Deana, K. Muth, and M. J. Mitchell, *this volume*, p. 944.
 4. H. Hauck, Dissertation, Universität München, 1963.
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

2-PHENYL-3-n-PROPYLISOXAZOLIDINE-4,5-cis-DICARBOXYLIC ACID N-PHENYLIMIDE

ethanol (64-17-5)

Benzene (71-43-2)

sodium chloride (7647-14-5)

n-butyraldehyde (123-72-8)

Phenylhydroxylamine,
N-Phenylhydroxylamine (100-65-2)

N-Phenylmaleimide (941-69-5)

C-(n-propyl)-N-phenylnitrone