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.

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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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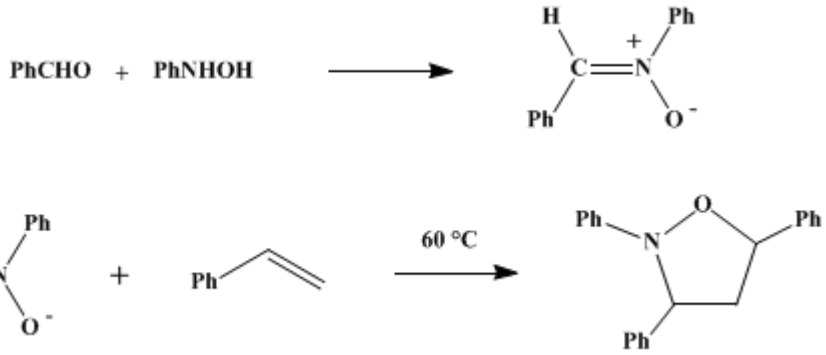
2,3,5-TRIPHENYLISOXAZOLIDINE

[Isoxazolidine, 2,3,5-triphenyl-]



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1. Procedure

A. *N,α-Diphenylnitrone*. A solution of 27.3 g. (0.25 mole) of pure N-phenylhydroxylamine[2] (Note 1) in 50 ml. of ethanol is prepared in a 200-ml. Erlenmeyer flask by swirling a mixture of the two and warming it briefly to 40–60° (Note 2). To the clear, lightly colored solution is added 26.5 g. (25.3 ml., 0.25 mole) of freshly distilled benzaldehyde (exothermic reaction). The flask is stoppered and kept overnight at room temperature in the dark. The colorless needles of N,α-diphenylnitrone are collected on a Büchner funnel and washed once with 20 ml. of ethanol. There is obtained 42–43 g. (85–87%) of product (m.p. 111–113°), which can be further purified by dissolving the crude material in 80 ml. of ethanol and allowing the solution to cool for several hours in the ice box. In this manner there is produced 35–39 g. (71–79%) of pure crystalline nitrone, m.p. 113–114° (Note 3).

B. *2,3,5-Triphenylisoxazolidine*. In a 100-ml. two-necked flask provided with a reflux condenser and a gas-inlet tube are placed 20.0 g. (0.101 mole) of pure N,α-diphenylnitrone and 50 ml. (0.43 mole) of freshly distilled styrene (Note 4). The flask is heated at 60° for 40 hours a slow nitrogen stream. The mixture is then cooled, and most of the excess styrene is removed (Note 5) from the clear orange solution by heating at a bath temperature of 55° (12 mm.). The warm residue is poured into 40 ml. of petroleum ether (40–60°), whereupon the isoxazolidine crystallizes immediately (Note 6). The flask is rinsed twice with 20-ml. portions of petroleum ether, and the washings are combined with the product. The resulting mixture is cooled for 1 hour in the ice box, and the lightly colored crystals are collected on a Büchner funnel and washed with two 20-ml. portions of petroleum ether. The yield of crude air-dried isoxazolidine (m.p. 96–98°) is 28–30 g. (92–99%).

For further purification the product is dissolved in 40 ml. of methylene chloride in a 250-ml. Erlenmeyer flask. The solution is heated to boiling, and 30 ml. of methanol is added (Note 7). When the solution has cooled to room temperature, 70 ml. of methanol is added to complete the crystallization, and the solution is kept in the ice box for 3 hours. The colorless needles are collected by vacuum filtration and washed with two 30-ml. portions of cold methanol. There is obtained 23–25 g. (76–82%) of product which melts at 99–100° (Note 8),(Note 9),(Note 10).

2. Notes

1. The N-phenylhydroxylamine should be free of sodium chloride. This is easily attained by dissolution of the compound in benzene followed by filtration and then addition of petroleum ether to cause rapid crystallization.
2. On prolonged heating, N-phenylhydroxylamine begins to decompose.

3. The compound is light-sensitive and should be kept in a brown container.
4. The styrene should be redistilled and stabilized with 0.1% hydroquinone just prior to use; otherwise the final product will be contaminated with polystyrene. The checkers used approximately 60 ml. (0.52 mole) of styrene.
5. The checkers found that, if all the styrene is removed, the product may become too viscous to pour.
6. By this method the formation of a thick crustaceous material, which is difficult to pulverize or wash, is avoided.
7. In this way the boiling solution is kept clear.
8. From the mother liquor a second diastereoisomer can be isolated (m.p. 78.5–79.5°) in about 10% yield by fractional crystallization.
9. In an analogous manner several other isoxazolidines can be prepared. From the reaction of N,α-diphenylnitrone with 1,1-diphenylethylene, 2,3,5,5-tetraphenylisoxazolidine is obtained. As above, 10.0 g. (50.7 mmoles) of diphenylnitrone is heated under a nitrogen atmosphere for 24 hours at 85° with 15.3 g. (15.0 ml., 85.0 mmole) of 1,1-diphenylethylene.[3] The excess olefin is removed at 105–130° (bath temperature) under high vacuum (0.005 mm.). The yellow-gold viscous residue is dissolved by warming it in a mixture of 15 ml. of methylene chloride and 30 ml. of methanol; on cooling, crystallization commences. After 2 hours another 10 ml. of methanol is added, and the mixture is cooled overnight in the ice box. The colorless crystals are collected on a Büchner funnel and washed twice with 20-ml. portions of methanol. The yield of air-dried product (m.p. 113–115°) is 14–16 g. (73–84%). The compound can be further purified by adding methanol (30 ml.) to a boiling solution in methylene chloride (15 ml.). After the solution has cooled to room temperature, another 10 ml. of methanol is added; the mixture is kept in the ice box for several hours and then filtered. The pure compound melts at 115–116°, yield 13–15 g. (68–79%).
10. The preparation of the oily ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate provides another example of this reaction. As in the procedure described with styrene, 10.0 g. (50.7 mmoles) of N,α-diphenylnitrone is heated under nitrogen for 24 hours at 90–100° with 35.0 g. (38.0 ml., 307 mmoles) of ethyl crotonate. The excess olefin, b.p. 45° (12 mm.) is removed on the water pump, and the red-orange residue, while still warm, is transferred to a 50-ml. Claisen flask using acetone as a rinse. After removal of the solvent, 13–14 g. (82–88%) of the isoxazolidine is obtained as an orange oil by high-vacuum distillation at 163–173° (0.003 mm.). Redistillation of this material yields 2–3 g. of fore-run and a purer product obtained as a yellow oil, b.p. 165–170° (0.003 mm.), n^{20}D 1.5602–1.5612.

3. Discussion

N,α-Diphenylnitrone was first obtained by Bamberger[4] from N-phenylhydroxylamine and benzaldehyde. The procedure described above is analogous to that of Wheeler and Gore.[5]

2,3,5-Triphenylisoxazolidine, 2,3,5,5-tetraphenylisoxazolidine, and ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate have been prepared only by this method.[6]

4. Merits of the Preparation

The procedure described illustrates the use of 1,3-dipolar addition[7] of nitrones to olefins for the preparation of isoxazolidines. The preparations of 2,3,5,5-tetraphenylisoxazolidine and ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate, as described in (Note 9) and (Note 10), respectively, indicate the versatility of the method.

References and Notes

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4. E. Bamberger, *Ber.*, **27**, 1548 (1894).
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6. H. Hauck, Dissertation, Universität München, 1963.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

polystyrene

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

hydroquinone (123-31-9)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

acetone (67-64-1)

N-Phenylhydroxylamine (100-65-2)

1,1-Diphenylethylene (530-48-3)

methylene chloride (75-09-2)

styrene (100-42-5)

ethyl crotonate (623-70-1)

2,3,5-Triphenylisoxazolidine,
Isoxazolidine, 2,3,5-triphenyl- (13787-96-7)

N,α-Diphenylnitrone (1137-96-8)

2,3,5,5-tetraphenylisoxazolidine (25116-92-1)

diphenylnitrone (59862-61-2)

ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate (19744-10-6)