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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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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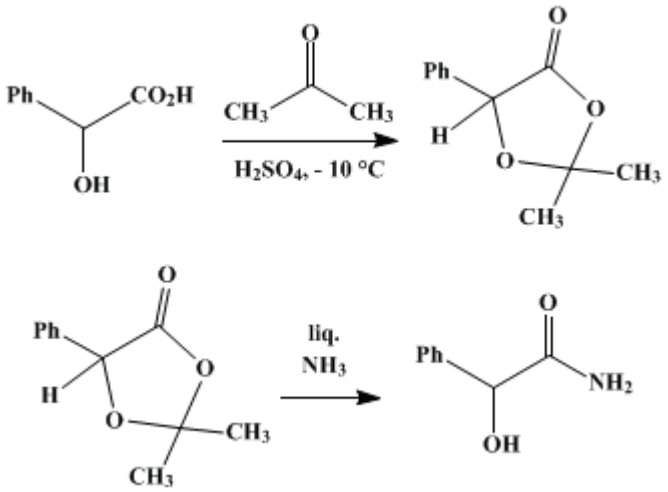
MANDELAMIDE



Submitted by L. F. Audrieth and M. Sveda.
Checked by Homer Adkins and William H. Bateman.

1. Procedure

One hundred and forty-six grams (0.96 mole) of mandelic acid is dissolved in 440 ml. (6.2 moles) of acetone, and the resulting solution is placed in a 2-l. three-necked flask fitted with an efficient stirrer, a dropping funnel, and a thermometer. The reaction flask is placed in an ice-salt bath, and 98 g. of concentrated sulfuric acid (sp. gr. 1.84) is added through the dropping funnel at such a rate that the temperature does not exceed −10°. The reaction mixture is then poured into an ice-cold solution of sodium carbonate containing 200 g. of the anhydrous salt in 1800 ml. of water. The mandelic acid-acetone condensation product precipitates from the solution. The curdy product is washed by grinding with ice water (200 ml.) and is then filtered and dried over calcium chloride under reduced pressure. The crude product weighs 181 g. (Note 1).

The mandelic acid-acetone condensation product is added in small portions to about 1.8 l. of liquid ammonia (Note 2) contained in two silvered 1-l. Dewar flasks. Each flask is fitted with a stopper containing a capillary tube to serve as an ammonia outlet. The ammonolysis is allowed to proceed overnight, after which the contents of the flasks are poured into open beakers to facilitate rapid evaporation of the liquid ammonia.

After the ammonia has been removed to a point where a pulverulent mass remains, the product is treated with 475 ml. of hot absolute ethanol and the resulting solution is filtered through a hot funnel to remove insoluble impurities. The filtrate is cooled in an ice bath to give about 90 g. of glistening white crystals of mandelamide melting at 132° (62% based upon the mandelic acid) (Note 3) and (Note 4).

2. Notes

1. The crude product contains varying quantities of sodium carbonate and sodium sulfate, which are difficult to remove. These impurities are insoluble in liquid ammonia; consequently the crude compound can be ammonolyzed without further purification. The mandelic acid-acetone condensation product may be purified by recrystallization from absolute ethanol; it then melts at 45°.
2. The solubility of the mandelic acid-acetone condensation compound in liquid ammonia at its boiling point is approximately 10 g. per 100 ml.
3. Additional quantities of mandelamide may be obtained by concentrating the ethanolic mother liquor carefully.
4. This method is generally applicable to the preparation of the amides of α-hydroxy acids.

3. Discussion

Mandelamide has been prepared by treating the ethyl ester with concentrated aqueous ammonia,[1,2] and a saturated ethanolic solution of ammonia has been used to effect ammonolysis of the methyl ester.[3] Esters of mandelic acid were treated with liquid ammonia at its boiling point;[4] this procedure was improved by use of ammonia at superatmospheric pressures and higher temperatures.[5] The procedure described in this synthesis was first used by Ôeda.[6]

References and Notes

1. Beyer, *J, prakt. Chem.*, (2) **31**, 390 (1885).
2. Einhorn and Feibelmann, *Ann.*, **361**, 145 (1908).
3. McKenzie and Wren, *J. Chem. Soc.*, **93**, 311 (1908).
4. Glattfeld and MacMillan, *J. Am. Chem. Soc.*, **58**, 898 (1936).
5. Kleinberg and Audrieth, *J. Org. Chem.*, **3**, 312 (1938).
6. Ôeda, *Bull. Chem. Soc. Japan*, **11**, 385 (1936).

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

ethanolic solution of ammonia

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

ammonia (7664-41-7)

Mandelic acid (90-64-2)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

acetone (67-64-1)

Mandelamide (4410-31-5)

mandelic acid-acetone