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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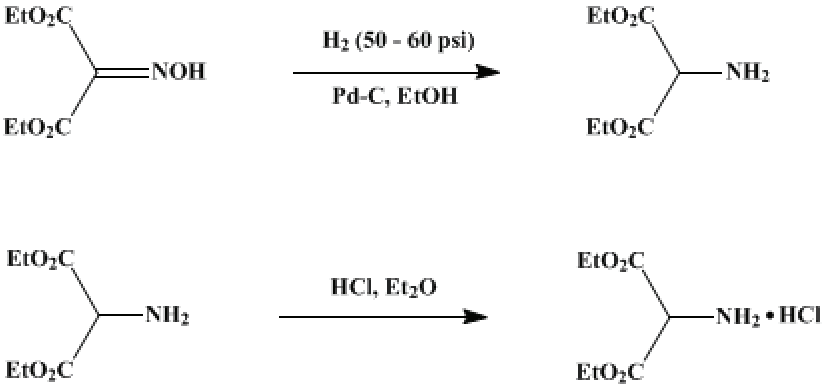
DIETHYL AMINOMALONATE HYDROCHLORIDE

[Malonic acid, amino-, diethyl ester, hydrochloride]



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Checked by John C. Sheehan and Robert W. Parsons, Jr..

1. Procedure

A. *Diethyl aminomalonate*. An ethereal solution (about 150 ml.) of diethyl isonitrosomalonate prepared from 50 g. of diethyl malonate (Note 1) is washed with 80-ml. portions of 1% sodium bicarbonate solution until the final washing has a distinct yellow color (Note 2). The ethereal solution is dried over 40 g. of anhydrous sodium sulfate in a refrigerator overnight and then filtered into a tared round-bottomed flask. The solvent is removed under reduced pressure at a temperature below 30° (water bath). The weight of the residue in one case was 59.6 g. Assuming complete conversion of the 0.312 mole of diethyl malonate to diethyl isonitrosomalonate, a 0.1-mole aliquot (19.1 g.) of the residue is placed in a 500-ml. reduction bottle provided for the Parr Hydrogenator (Note 3). To this is added 100 ml. of absolute alcohol and 3 g. of 10% palladium-on-charcoal catalyst (Note 4). The bottle is placed in a hydrogenator, and the system is flushed three or four times with hydrogen. With the initial reading on the pressure gauge at 50–60 lb., the bottle is shaken until no further drop in pressure is observed (about 15 minutes).

The catalyst is removed by filtration, using an absolute alcohol wash, and the clear filtrate is concentrated under reduced pressure at a temperature below 50° (water bath). As diethyl aminomalonate is not so stable as its salts, the crude product is converted directly to diethyl aminomalonate hydrochloride (Note 5).

B. *Diethyl aminomalonate hydrochloride*. The crude diethyl aminomalonate is diluted with 80 ml. of dry ether and filtered to remove a small amount of white solid. The filtrate is collected in a 250-ml. Erlenmeyer flask and cooled in an ice bath. Dry hydrogen chloride is passed just over the solution while it is being stirred mechanically (Note 6). The fine white crystals which precipitate are collected by suction filtration and washed three times with a total of 60 ml. of dry ether (Note 7). The filtrate and washings are treated again with hydrogen chloride, and a second crop of diethyl aminomalonate hydrochloride is collected and washed as before. This process is repeated until no further precipitation results from passing hydrogen chloride into the solution. A total of 16.5–17.4 g. (78–82% yield based on diethyl malonate) of diethyl aminomalonate hydrochloride, m.p. 162–163°, is obtained. Recrystallization from alcohol-ether affords a purer product, 164–165°.

2. Notes

1. It is convient to use the ether solution of diethyl isonitrosomalonate described by Zambito and Howe.[2]
2. About six washings are required. It may be necessary to add a total of 50 ml. of ether during the first

three washings and 20 ml. during the final washing to facilitate breaking of the interphase emulsions. In each case, after partial separation of phases has occurred, ether is added and the separatory funnel is swirled gently until the interphase clears. The washing process requires about 1.5 hours.

3. As diethyl isonitrosomalonate may decompose with explosive violence on heating, further purification by distillation is not recommended.

According to the submitters, reductions using as much as 0.3 mole of diethyl isonitrosomalonate were carried out.

4. The checkers used 10% palladium-on-charcoal catalyst obtained from Baker and Company, Inc., 113 Astor Street, Newark, New Jersey.

5. According to the submitters, diethyl aminomalonate may be purified by distillation, b.p. 116–118°/12 mm. or 122–123°/16 mm.; $n_{\mathrm{D}}^{16} = 1.4353$; $d_{14}^{16} = 1.100$.

6. Hydrogen chloride is dried by passage through a train of two gas washing bottles containing concentrated sulfuric acid. A 10-mm. tube through which the hydrogen chloride is passed is placed just over the stirring liquid, instead of under the surface, to prevent clogging of the tube by the bulky precipitate which is formed.

The checkers found magnetic stirring satisfactory. More ether may have to be added to prevent the heavy slurry from stopping the stirrer.

7. A medium-porosity sintered-glass funnel was used by the checkers.

3. Discussion

Diethyl isonitrosomalonate has been reduced catalytically, over palladium on charcoal,[3] Raney nickel,[4] and chemically by aluminum amalgam[5] or hydrogen sulfide.[6]

4. Use of Diethyl Aminomalonate Hydrochloride

Diethyl aminomalonate is a useful intermediate, lending itself to N-acylation;[3,7] the N-acyl derivatives may be alkylated by procedures as established for syntheses via malonic ester.

References and Notes

1. Medical College of Virginia, Richmond, Virginia.
2. See p. 373, this volume.
3. H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944).
4. C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 341 (1939).
5. R. Locquin and V. Cherchez, *Compt. Rend.*, **186**, 1360 (1926).
6. T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 352 (1914).
7. J. H. R. Beaujon and W. H. Hartung, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 578 (1952); G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.*, **79**, 5203 (1957).

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

palladium-on-charcoal

palladium on charcoal

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

hydrogen sulfide (7783-06-4)

sodium sulfate (7757-82-6)

aluminum (7429-90-5)

Raney nickel (7440-02-0)

diethyl malonate (105-53-3)

diethyl isonitrosomalonate (6829-41-0)

diethyl aminomalonate (6829-40-9)

Diethyl aminomalonate hydrochloride,
Malonic acid, amino-, diethyl ester, hydrochloride (13433-00-6)