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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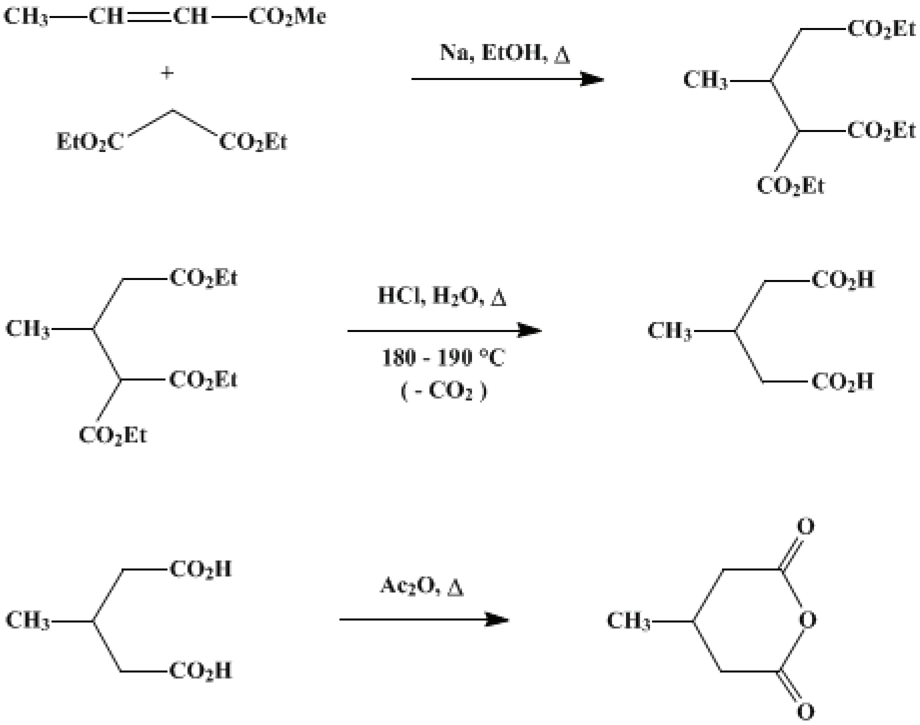
β-METHYLGLUTARIC ANHYDRIDE

[Glutaric anhydride, 3-methyl-]



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1. Procedure

A. *Triethyl 2-methyl-1,1,3-propanetricarboxylate* (not isolated). A 1-l. three-necked flask is fitted with a mechanical stirrer, a reflux condenser protected by a calcium chloride tube, and a 250-ml. dropping funnel. All parts of the apparatus should be scrupulously dry. Three hundred milliliters of anhydrous ethanol (Note 1) is placed in the flask, and 14.1 g. (0.61 g. atom) of clean sodium, cut in pieces as large as will easily pass through a neck of the flask, is added rapidly. The neck of the flask is immediately closed, and the mixture is stirred until all the sodium has dissolved; the cooling bath is removed, and heat is applied if the reaction becomes sluggish at the end.

After all the sodium has dissolved, a mixture of 115 g. (0.72 mole) of diethyl malonate (Note 2) and 60 g. (0.60 mole) of methyl crotonate (Note 2) is added from the separatory funnel. This addition is made as rapidly as is consistent with keeping the exothermic reaction under control. After the exothermic reaction has subsided, the mixture is heated for 1 hour under reflux with stirring. An oil bath is recommended for heating. At the end of the heating period the condenser is changed to a position for distilling, and the temperature of the oil bath is raised sufficiently to distil alcohol fairly rapidly from the stirred mixture. Distillation is continued until most of the alcohol has been distilled. There is left a residue of the sodio derivative of triethyl 2-methyl-1,1,3-propanetricarboxylate (Note 3). If water is added to obtain the free ester, considerable heat is generated and cooling must be adequate to prevent partial hydrolysis of the ester by the alkali liberated. For present purposes there is no advantage in attempting isolation of the ester, and the residue is processed as described below.

B. β-*Methylglutaric anhydride*. The residue described above is cooled in an ice bath during the successive addition of 200 ml. of water and 450 ml. of concentrated hydrochloric acid. The resultant mixture is heated under reflux, with stirring, for 8 hours (Note 4). The condenser is again set for distillation, the bath temperature is raised, and, with continued stirring, water and alcohol are distilled. The bath is finally heated to 180–190° until gas evolution ceases (usually about 1 hour).

The stirrer is removed, 125 ml. of technical acetic anhydride is added to the residue, and, after thorough mixing, the mixture is heated on a steam bath for 1 hour. The condenser protected by a calcium chloride tube is left attached, and the other necks of the flask are closed. At the end of the heating period salt is removed from the cooled reaction mixture by filtering it with suction, using a filter aid mat, into a 250-ml. Claisen flask. The reaction vessel and filter are washed with a few milliliters of acetic acid.

The combined filtrate and washings are distilled at reduced pressure, using a water pump, until all acetic acid and acetic anhydride have been removed. An oil pump is then connected, and the distillation is continued. β-Methylglutaric anhydride is collected at 118–122°/3.5 mm. The yield of semisolid anhydride (Note 5) is 46–58 g. (60–76%) (Note 6).

2. Notes

1. Commercial absolute ethanol from a freshly opened bottle is often satisfactory; otherwise it can be dried by treatment with sodium,[2] sodium ethoxide and diethyl phthalate,[3] magnesium methoxide,[4] or aluminum *tert*-butoxide.[5]
2. Because commercial diethyl malonate is likely to contain small amounts of water and acid, it should be distilled from a Claisen flask at reduced pressure before use. The material used should be collected over a two- or three-degree range. The boiling point of malonic ester is 98°/20 mm.
Commercial methyl crotonate is rather impure and should be distilled at atmospheric pressure through a simple Vigreux or packed column which is 40–60 cm. in length. The fraction used should be collected over a two-degree range, and 70–85% of material boiling in such a range may usually be obtained from the commercial product. The boiling point is 117–118°.
3. Because of transesterification, the ester is principally the triethyl ester.
4. Sometimes the mixture becomes homogeneous after 3–5 hours, and heating can be stopped. At other times oily material remains even after 8 hours, but nothing is gained by further heating.
5. Pure β-methylglutaric anhydride melts at 46°.[6] The β-methylglutaric anhydride obtained in this preparation varies in its appearance at 25° from an almost completely crystalline mass to a mixture of about one-third solid and two-thirds liquid. However, the submitter has found that product of either appearance can be converted to methyl hydrogen β-methylglutarate in 80–85% yield. Further purification is troublesome, and the product of the present procedure is pure enough for most purposes.
6. The submitter has obtained yields of 85–90%.

3. Discussion

β-Methylglutaric anhydride is obtained from the acid, which has been prepared by condensation of acetaldehyde with cyanoacetamide[7,8] or by the oxidation of 3-methyl-1,3-cyclohexanedione with periodic acid.[9] The present method, which is a simplification of that published by Ställberg-Stenhagen,[10] gives a higher yield and is much better adapted to the preparation of large quantities.

References and Notes

1. University of California, Berkeley, California.
2. *Org. Syntheses Coll. Vol.* **1**, 259 (1941).
3. *Org. Syntheses Coll. Vol.* **2**, 155 (1943).
4. *Org. Syntheses Coll. Vol.* **1**, 249 (1941).
5. *Org. Syntheses Coll. Vol.* **3**, 672 (1955).
6. Darbishire and Thorpe, *J. Chem. Soc.*, **87**, 1717 (1905).
7. Day and Thorpe, *J. Chem. Soc.*, **117**, 1465 (1920).
8. *Org. Syntheses Coll. Vol.* **3**, 591 (1955).
9. Wolfrom and Bobbitt, *J. Am. Chem. Soc.*, **78**, 2489 (1956).
10. Ställberg-Stenhagen, *Arkiv Kemi Mineral. Geol.*, **25A**, No. 10 (1947) [*C. A.*, **42**, 5851 (1948)].

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

3-methyl-1,3-cyclohexanedione

sodio derivative of triethyl 2-methyl-1,1,3-propanetricarboxylate

ethanol (64-17-5)

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

acetic anhydride (108-24-7)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

CYANOACETAMIDE (107-91-5)

diethyl malonate (105-53-3)

magnesium methoxide

diethyl phthalate (84-66-2)

periodic acid

β-Methylglutaric anhydride,
Glutaric anhydride, 3-methyl- (4166-53-4)

methyl crotonate (623-43-8)

Triethyl 2-methyl-1,1,3-propanetricarboxylate

methyl hydrogen β-methylglutarate

ALUMINUM tert-BUTOXIDE