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.

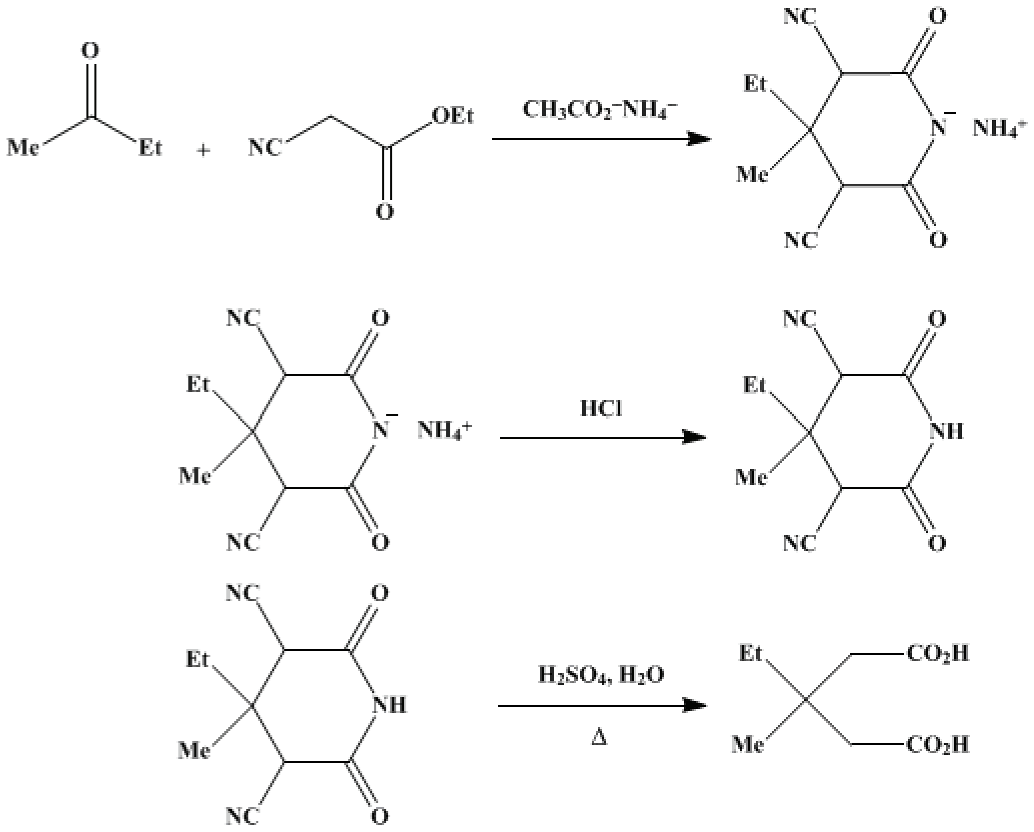
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.036.0028

Organic Syntheses, Coll. Vol. 4, p.441 (1963); Vol. 36, p.28 (1956).

β-ETHYL-β-METHYLGLUTARIC ACID

[Glutaric acid, 3-ethyl-3-methyl-]



Submitted by H. H. Farmer and Norman Rabjohn[1].
Checked by Melvin S. Newman and Robert Harper.

1. Procedure

A. *α,α'-Dicyano-β-ethyl-β-methylglutarimide.* In a 2-l. round-bottomed flask are placed 452 g. (4.0 moles) of ethyl cyanoacetate, 144 g. (2.0 moles) of methyl ethyl ketone, 2 g. of ammonium acetate, and 800 ml. of 95% ethanol which contains 80 g. (4.7 moles) of anhydrous ammonia (Note 1) and (Note 2). The flask is stoppered and placed in a refrigerator.

After about 12 hours, the ammonium salt of the imide which has precipitated is removed by filtration (Note 3), washed on a Büchner funnel with about 200 ml. of ether and air-dried. It is dissolved in the minimum amount (about 800 ml.) of boiling water, and the solution is made acid to Congo red paper with concentrated hydrochloric acid. The free imide precipitates immediately and forms a white slurry which is cooled in an ice bath. The imide is collected on a Büchner funnel and dried at 100° in an oven, or in a vacuum desiccator. The yield is 266–287 g. (65–70%), m.p. 187–191° (Note 4).

B. *β-Ethyl-β-methylglutaric acid.* A mixture of 280 g. (1.36 moles) of α,α'-dicyano-β-ethyl-β-methylglutarimide (Note 5) and 1.35 l. of 65% (by weight) sulfuric acid is heated under reflux in a 5-l. round-bottomed flask for 8–10 hours (Note 6). The mixture is allowed to cool, and the precipitate is removed by filtration on a sintered glass (or other suitable type) filter. The crude β-ethyl-β-methylglutaric acid is recrystallized from water (Note 7). The yield of product is 174–191 g. (73–80%), m.p. 78–80°.

2. Notes

1. The ethyl cyanoacetate and methyl ethyl ketone were Eastman Kodak Company white label grade chemicals and were used without further purification. Commercial absolute ethanol was found to give a slightly better yield of the ammonium salt of the imide.
2. It is convenient to pass gaseous ammonia into the ethanol. It is advisable to carry out the preparation and manipulation of the ammonia solution in a hood.
3. The mother liquor is returned to the refrigerator and a second and a third crop of crystals may be collected after 24 and 48 hours. The first crop of crystals usually comprises 95% of the total yield.
4. In taking the melting point of this compound there was still some solid remaining at 200°. The crude imide is satisfactory for conversion to β-ethyl-β-methylglutaric acid and need not be dried before hydrolysis.
5. Although the ammonium salt of the imide may be hydrolyzed to the acid, the free imide appears to give better results.
6. The large flask is used because considerable foaming occurs during the first 2–3 hours of reaction.
7. A ratio of 3 ml. of water to 1 g. of acid gives satisfactory results. The use of activated carbon during the recrystallization is recommended.

3. Discussion

α,α'-Dicyano-β-ethyl-β-methylglutarimide apparently has been prepared only from the condensation of methyl ethyl ketone, ethyl cyanoacetate, and ammonia.[2,3,4,5,6]

β-Ethyl-β-methylglutaric acid has been prepared by the acid hydrolysis of α,α'-dicyano-β-ethyl-β-methylglutarimide,[2,3,4,5,6] 3-cyano-4-ethyl-6-imino-2-keto-4-methylpiperidine-5-carboxamide or the diimide of β-ethyl-β-methylpropane-α,α,α',α'-tetracarboxylic acid;[7] by the oxidation of β-ethyl-β-methyl-δ-valerolactone with chromic acid;[8] and by the reaction of sodium hypobromite on 1,4-dimethyl-1-ethyl-3,5-cyclohexanedione.[9]

The present procedure is essentially that of Guareschi[2] as detailed by Vogel.[4]

References and Notes

1. University of Missouri, Columbia, Missouri.
2. Guareschi, *Atti. accad. sci. Torino*, **36**, 443 (1900–1901) [*Chem. Zentr.*, **1901**, **I**, 821].
3. Kon and Thorpe, *J. Chem. Soc.*, **115**, 686 (1919).
4. Vogel, *J. Chem. Soc.*, **1934**, 1758.
5. Benica and Wilson, *J. Am. Pharm. Assoc.*, **39**, 451 (1950).
6. Lukes and Ferles, *Collection Czechoslov. Chem. Communs.*, **16**, 252; *Chem. listy*, **45**, 386 (1951) [*C. A.*, **47**, 5870 (1953)].
7. Thole and Thorpe, *J. Chem. Soc.*, **99**, 422 (1911).
8. Sircar, *J. Chem. Soc.*, **1928**, 898.
9. Becker and Thorpe, *J. Chem. Soc.*, **121**, 1303 (1922).

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

diimide of β-ethyl-β-methylpropane-α,α,α',α'-tetracarboxylic acid

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium acetate (631-61-8)

carbon (7782-42-5)

chromic acid (7738-94-5)

Ethyl cyanoacetate (105-56-6)

sodium hypobromite

methyl ethyl ketone (78-93-3)

β-Ethyl-β-methylglutaric acid,
Glutaric acid, 3-ethyl-3-methyl- (5345-01-7)

3-cyano-4-ethyl-6-imino-2-keto-4-methylpiperidine-5-carboxamide

β-ethyl-β-methyl-δ-valerolactone

1,4-dimethyl-1-ethyl-3,5-cyclohexanedione

α,α'-Dicyano-β-ethyl-β-methylglutarimide