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.

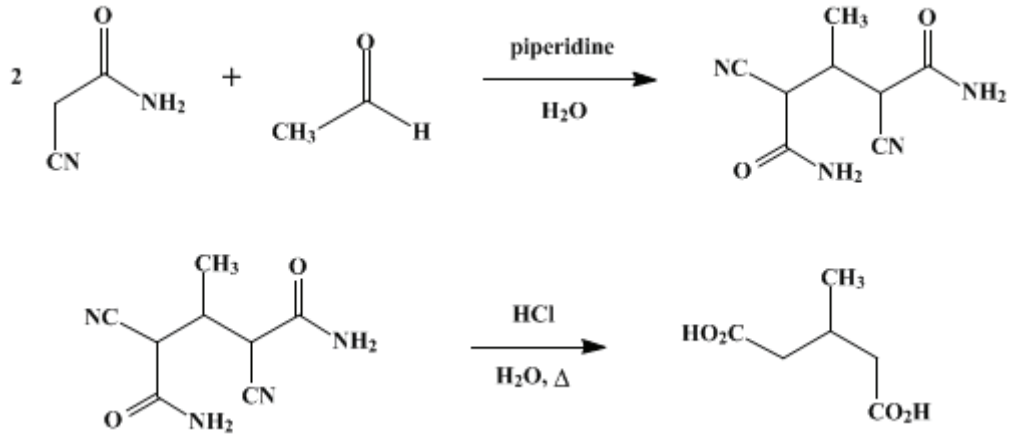
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.023.0060

Organic Syntheses, Coll. Vol. 3, p.591 (1955); Vol. 23, p.60 (1943).

β-METHYLGLUTARIC ACID

[Glutaric acid, β-methyl-]



Submitted by Robert E. Kent and S. M. McElvain.
Checked by Lee Irvin Smith and G. A. Boyack.

1. Procedure

A. α,α'-*Dicyano-β-methylglutaramide*. In a 6-l. flask, 520 g. (6.2 moles) of recrystallized cyanoacetamide (Note 1) is dissolved in 3.4 l. of water, and the solution is cooled to 10° and filtered if it is not clear (Note 2). While the flask is shaken constantly, 137.5 g. (3.1 moles) of freshly distilled acetaldehyde and 20 ml. of piperidine are added *successively* to the solution. After the mixture has stood at room temperature for 2 hours, the flask is transferred to an ice-salt bath and the mixture is partially frozen. During this operation, the flask should be shaken frequently. After 30 minutes, α,α'-dicyano-β-methylglutaramide begins to deposit, and when the precipitation is complete (about 1 hour), the mixture is allowed to come to room temperature in order to melt the ice that is present. The precipitate is then filtered with suction and washed thoroughly with cold distilled water. The yield is 420–425 g. (71%) of a white, powdery solid which melts at 152–157° (Note 3).

B. β-*Methylglutaric acid.* In a 5-l. flask are placed 400 g. of the amide and 1 l. of concentrated hydrochloric acid; the mixture is warmed on a steam bath until solution is complete, after which it is diluted with 1 l. of water and refluxed for 8 hours. The amber-colored solution is saturated with sodium chloride and extracted with five 600-ml. portions of ether. The combined ether extracts are dried for 1 hour over phosphorus pentoxide, and the solvent is removed by distillation. The residue, crude β-methylglutaric acid, weighs 238–240 g. (80%) and melts at 79–82° with previous softening. This product is recrystallized from about 250 ml. of 10% hydrochloric acid. The recovery is about 90% (Note 4), and the purified product melts at 85–86°.

2. Notes

1. Ammonia exerts a hindering effect on this condensation, and the yield is greatly reduced when crude cyanoacetamide is used.
2. At 10°, cyanoacetamide sometimes crystallizes. The mixture should not be filtered until it is certain that the precipitate contains no cyanoacetamide. Any cyanoacetamide that separates redissolves quickly after the acetaldehyde and piperidine have been added.
3. This amide is insoluble in the usual solvents, but it may be further purified, if desired, by trituration with dilute hydrochloric acid, followed by washing with hot absolute ethanol. It then melts sharply at 160–161°.
4. The checkers used one-tenth of the specified amounts of reagents. They obtained, in two runs, the

following average yields of products: crude α,α'-dicyano-β-methylglutaramide, m.p. 152–157°, 75%; crude β-methylglutaric acid, m.p. 79–82°, 78%; purified β-methylglutaric acid, m.p. 84–85°, 80% (recovery). In the second run, however, the yields (except for the recovery in the recrystallization) were slightly higher than those given for the larger runs.

3. Discussion

The above method is adapted from the procedure of Day and Thorpe.[1] β-Methylglutaric acid has been prepared by hydrolysis of β-methylglutaronitrile;[2] by condensation of crotonic ester with ethyl sodiocyanoacetate,[3] and with sodiomalonic ester;[4,5] and by condensation of acetaldehyde with malonic ester.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 630

References and Notes

1. Day and Thorpe, *J. Chem. Soc.*, **117**, 1465 (1920).
2. Blaise and Gault, *Bull. soc. chim. France*, (4) **1**, 88 (1907).
3. Howles, Thorpe, and Udall, *J. Chem. Soc.*, **77**, 948 (1900); Darbishire and Thorpe, *J. Chem. Soc.*, **87**, 1716 (1905).
4. Hunsdiecker, *Ber.*, **75B**, 1199 (1942).
5. Auwers, Kobner, and Meyenberg, *Ber.*, **24**, 2887 (1891).
6. Knoevenagel, *Ber.*, **31**, 2585 (1899).

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

sodiomalonic ester

Malonic Ester

ethanol (64-17-5)

acetaldehyde (75-07-0)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium chloride (7647-14-5)

piperidine (110-89-4)

CYANOACETAMIDE (107-91-5)

β-Methylglutaric acid,
Glutaric acid, β-methyl- (626-51-7)

β-methylglutaronitrile

ethyl sodiocyanoacetate

phosphorus pentoxide (1314-56-3)

α,α'-Dicyano-β-methylglutaramide