



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](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.

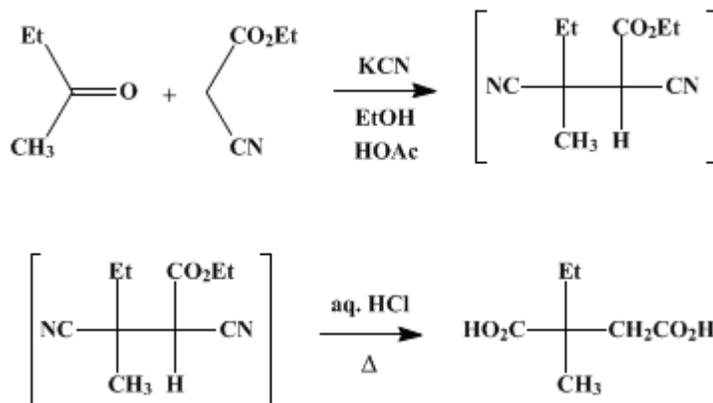
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 5, p.572 (1973); Vol. 44, p.59 (1964).*

## **$\alpha$ -ETHYL- $\alpha$ -METHYLSUCCINIC ACID**

[Succinic acid,  $\alpha$ -ethyl- $\alpha$ -methyl-]



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### 1. Procedure

Potassium cyanide (71.6 g., 1.1 moles, U.S.P.) and 100 ml. of 95% ethanol are placed in a 2-l. round-bottomed flask having a ground joint and arranged with a Hershberg stirrer<sup>2</sup> (Note 1). A solution of 113 g. (106 ml., 1 mole) of ethyl cyanoacetate, 79 g. (98 ml., 1.1 moles) of 2-butanone, and 66 ml. of glacial acetic acid is added to the stirred solution over a period of 1 hour. The mixture is stirred for an additional hour, the stirrer is removed, and the mixture is allowed to stand at room temperature for 7 days (Note 2).

Concentrated hydrochloric acid (500 ml.) is added to the semisolid reaction mixture, a reflux condenser is placed on the flask, and the mixture is heated under vigorous reflux for a period of 4 hours (Note 3). An additional 500 ml. of hydrochloric acid is added, and the boiling under reflux is continued for an additional 4 hours.

The cooled reaction mixture is extracted (Note 4) with four portions of ether (400 ml., 250 ml., 200 ml., 200 ml.) (Note 5) The ether extracts are filtered and combined, and about two-thirds of the ether is distilled. The ethereal solution is transferred to a 500-ml. Erlenmeyer flask, and the remaining ether is removed. The residue (about 160 g.) is dissolved in 200 ml. of 24% hydrochloric acid (1 part water, 2 parts concentrated hydrochloric acid) and the solution distilled until the boiling point reaches 108° (Note 6) The solution is cooled and allowed to stand at 5° for about 20 hours. The product is collected by vacuum filtration and dried in a vacuum desiccator containing both concentrated sulfuric acid and potassium hydroxide pellets. The yield of  $\alpha$ -ethyl- $\alpha$ -methylsuccinic acid is 65–75 g. (41–47%), m.p. 91–97°. Concentration of the mother liquor to 125 ml. gives an additional 8–9 g. of acid, m.p. 85–91° (Note 7).

### 2. Notes

- The reaction can be run in an open flask because only a small amount of gas escapes. See (Note 3). Sodium cyanide can be substituted for potassium cyanide if 2 g. of  $\beta$ -alanine is also employed as a catalyst.
- Heating the reaction for shorter periods gave erratic results. At this point the semisolid mixture can be diluted with 200 ml. of water, extracted with benzene, and the benzene extract fractionally distilled to give ethyl 2,3-dicyano-3-methylpentanoate, b.p. 146.0–147.5° (2.5 mm.),  $n_D^{27}$  1.4429 (highly purified ester has b.p. 138.5–141.5° (2 mm.),  $n_D^{25}$  1.4432). The overall yield of  $\alpha$ -ethyl- $\alpha$ -methylsuccinic acid is

decreased by about 5% when the dicyano intermediate is isolated.

3. During the reflux period, gases are continuously evolved; these apparently are [hydrogen chloride](#), [carbon dioxide](#), [ethyl acetate](#), and possibly [ethyl chloride](#). The reaction should be run in a hood, or the gases should be trapped.<sup>3</sup>

4. If no layer separates on addition of the [ether](#), add 200 ml. of water.

5. This extraction, designed to remove organic acids from inorganic salts, may also be effected with a lighter-than-water Kutscher-Stuedel extractor.<sup>4</sup>

6. The distillate consists of low-boiling solvents.

7. The acid can be purified further by dissolving 50 g. of it in 100 ml. of [benzene](#). The solution is filtered, diluted with 100 ml. of [hexane](#), and cooled to 5°. The yield of acid is 45.0 g., m.p. 97–102° (lit.<sup>5</sup> m.p. 101–102°).

### 3. Discussion

The one-step condensation to convert [2-butanone](#), [ethyl cyanoacetate](#), and [hydrocyanic acid](#) to [ethyl 2,3-dicyano-3-methylpentanoate](#) is a modification of the procedure described by Smith and Horowitz<sup>5</sup> in which [pyridine acetate](#) was employed as the catalyst. Higson and Thorpe<sup>6</sup> employed a two-step procedure in which [butanone](#) was converted to its cyanohydrin, which in turn was condensed with [ethyl cyanoacetate](#).

$\alpha$ -Ethyl- $\alpha$ -methylsuccinic acid also has been prepared by the [sulfuric acid](#) hydrolysis of [ethyl  \$\alpha\$ -ethyl- \$\alpha\$ -methyl- \$\beta\$ -carbethoxysuccinate](#),<sup>7</sup> the action of 80% [sulfuric acid](#) on [1-ethoxy-3-ethyl-3-methyl-1,2-cyclopropanedioic acid](#),<sup>8</sup> and the dichromate oxidation of  [\$\beta\$ -ethyl- \$\beta\$ -methylbutyrolactone](#).<sup>9</sup>

### 4. Merits of the Preparation

This procedure illustrates a process which should be general for many  $\alpha,\alpha$ -disubstituted succinic acids. It is more convenient than those previously employed because the reaction sequence is carried out in one step.

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### References and Notes

1. Department of Chemistry, DePaul University, Chicago, Illinois.
2. *Org. Syntheses*, Coll. Vol. 2, 116 (1943).
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4. L. C. Craig and D. Craig, in A. Weissberger, "Technique of Organic Chemistry," Vol. III, Part I, 2nd Ed., Interscience Publishers, New York (1956), p. 230. *Org. Syntheses*, Coll. Vol. 3, 539 (1955).
5. P. A. S. Smith and J. P. Horowitz, *J. Am. Chem. Soc.*, **71**, 3418 (1949).
6. A. Higson and J. F. Thorpe, *J. Chem. Soc.*, **89**, 1467 (1906).
7. K. Auwers and R. Fritzweiler, *Ann.*, **298**, 166 (1897).
8. B. Singh and J. F. Thorpe, *J. Chem. Soc.*, **123**, 113 (1923).
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### Appendix

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

[ethanol](#) (64-17-5)

[sulfuric acid](#) (7664-93-9)

hydrogen chloride,  
hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium cyanide (143-33-9)

hydrocyanic acid (74-90-8)

potassium cyanide (151-50-8)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

Ethyl cyanoacetate (105-56-6)

$\beta$ -Alanine (107-95-9)

butanone,  
2-butanone (78-93-3)

hexane (110-54-3)

ethyl chloride (75-00-3)

$\alpha$ -Ethyl- $\alpha$ -methylsuccinic acid,  
Succinic acid,  $\alpha$ -ethyl- $\alpha$ -methyl- (631-31-2)

ethyl 2,3-dicyano-3-methylpentanoate

pyridine acetate

ethyl  $\alpha$ -ethyl- $\alpha$ -methyl- $\beta$ -carbethoxysuccinate

1-ethoxy-3-ethyl-3-methyl-1,2-cyclopropanedioic acid

$\beta$ -ethyl- $\beta$ -methylbutyrolactone