



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.

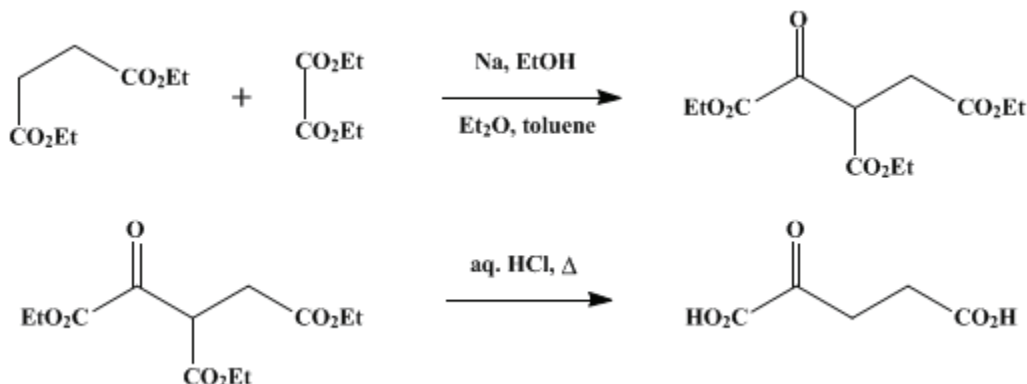
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries 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.*

*Organic Syntheses, Coll. Vol. 5, p.687 (1973); Vol. 44, p.67 (1964).*

## **$\alpha$ -KETOGLUTARIC ACID**

[Glutaric acid, 2-oxo-]



Submitted by E. M. Bottorff and L. L. Moore<sup>1</sup>.

Checked by William G. Dauben and Robert M. Coates.

### 1. Procedure

A. *Triethyl oxalylsuccinate*. In a 2-l. three-necked flask equipped with a sealed stirrer and a reflux condenser bearing a calcium chloride drying tube is placed 356 ml. (276 g., 6.00 moles) of anhydrous ethanol (Note 1). Sodium (23 g., 1.0 g. atom) is added in small portions at a rate sufficient to keep the ethanol boiling. External heating is required to dissolve the last portions of the metal. After all the sodium has dissolved, the excess ethanol is removed by distillation at atmospheric pressure; as the mixture becomes pasty, dry toluene is added in sufficient amounts to permit stirring and to prevent splattering of the salt. Distillation and addition of toluene is continued until all the ethanol is removed and the contents of the flask reach a temperature of 105° (Note 2). The sodium ethoxide slurry is cooled to room temperature and 650 ml. of anhydrous ether is added, followed by 146 g. (1.00 mole) of diethyl oxalate. To the yellow solution there is added 174 g. (1.00 mole) of diethyl succinate, and the mixture is allowed to stand at room temperature for at least 12 hours.

The mixture is hydrolyzed by the addition of 500 ml. of water with stirring. The layers are separated, the ether layer is washed with 150 ml. of water, and the ether layer is discarded. The combined aqueous layers are acidified with 100 ml. of 12*N* hydrochloric acid, and the layers are separated. The aqueous layer is extracted with three 150-ml. portions of ether, which are added to the oily layer. The ethereal solution is dried over anhydrous magnesium sulfate, and the ether is removed by evaporation under water-pump pressure at a bath temperature of 35–45°. Triethyl oxalylsuccinate, a yellow oil weighing 235–250 g. (86–91%), remains in the flask (Note 3).

B.  *$\alpha$ -Ketoglutaric acid*. A mixture of 225 g. (0.82 mole) of triethyl oxalylsuccinate, 330 ml. of 12*N* hydrochloric acid, and 660 ml. of water is heated under reflux for 4 hours, and the mixture is distilled to dryness under reduced pressure at a bath temperature of 60–70° (Note 4). The liquid residue, which solidifies readily on standing, is warmed with 200 ml. of nitroethane on a steam bath until it is in solution. The warm solution is filtered, the funnel is washed with 40 ml. of nitroethane, and the filtrate is stirred at 0–10° for 5 hours.  $\alpha$ -Ketoglutaric acid is separated by filtration and dried at 90° under reduced pressure for 4 hours. It is obtained as a tan solid; weight 88–99 g. (73–83%); m.p. 103–110° (Note 5).

### 2. Notes

1. Commercial absolute ethanol is dried by heating with sodium and diethyl succinate and is then distilled directly into the reaction flask.

2. If the [toluene](#) method to remove all the [ethanol](#) is not used, the yield is lower by 5–10%.
3. [Triethyl oxalylsuccinate](#) begins to decompose at 84° at 760 mm. It cannot be distilled without decomposition even at a pressure of 1 mm.
4. The color of the [α-ketoglutaric acid](#) is darker if the pot temperature goes much above 90° during the evaporation and recrystallization.
5. The product is pure enough for most purposes. Further recrystallization from [nitroethane](#) does not improve the melting point.

### 3. Discussion

The present procedure is a modification of one reported in an earlier volume of *Organic Syntheses*.<sup>2</sup> The methods used to prepare [triethyl oxalylsuccinate](#) and [α-ketoglutaric acid](#) are summarized in that volume.

### 4. Merits of the Preparation

The advantages of this procedure over the earlier version are the use of [sodium ethoxide](#) instead of [potassium ethoxide](#) and better reproducibility.

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### References and Notes

1. Organic Chemical Development, Eli Lilly and Company, Indianapolis, Indiana.
  2. L. Friedman and E. Kosower, *Org. Syntheses*, Coll. Vol. **3**, 510 (1955).
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### Appendix

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

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

[hydrochloric acid](#) (7647-01-0)

[ether](#) (60-29-7)

[toluene](#) (108-88-3)

[sodium](#) (13966-32-0)

[sodium ethoxide](#) (141-52-6)

[magnesium sulfate](#) (7487-88-9)

[potassium ethoxide](#) (917-58-8)

[α-Ketoglutaric acid](#),  
[Glutaric acid, 2-oxo-](#) (328-50-7)

[Diethyl succinate](#) (123-25-1)

[diethyl oxalate](#) (95-92-1)

nitroethane (79-24-3)

Triethyl oxalysuccinate