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.

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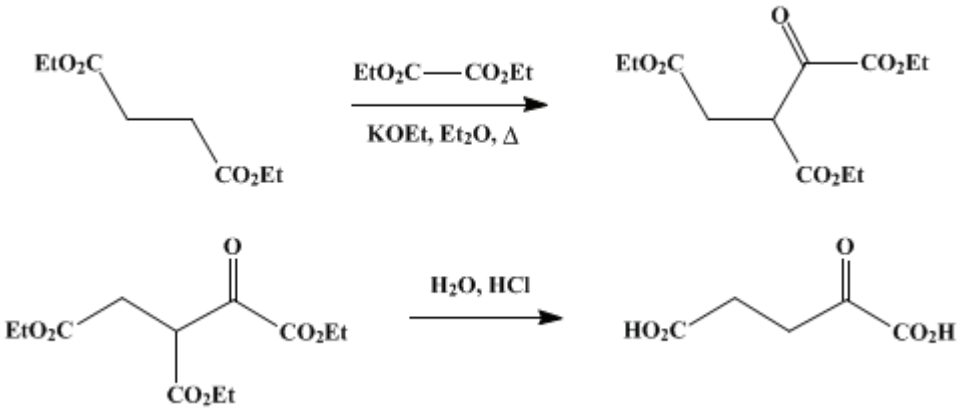
α-KETOGLUTARIC ACID

[Glutaric acid, α-oxo-]



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Checked by Reynold C. Fuson and Elliott N. Marvell.

1. Procedure

A. *Ethyl oxalylsuccinate*. Potassium (39.5 g., 1 gram atom) is cut into pieces under xylene (Note 1) in a wide evaporating dish. The xylene is poured off, and the metal is washed with three 50-ml. portions of absolute ether. The potassium is then transferred quickly to a 2-l. three-necked flask containing 650 ml. of anhydrous ether and fitted with a reflux condenser, a mercury-sealed mechanical stirrer (Note 2), and a dropping funnel containing 150 ml. of anhydrous ethanol. The ethanol is added over a period of about 1.5 hours; stirring is unnecessary. After most of the ethanol has been added, the flask is heated on a water bath to ensure complete solution of the potassium. This usually takes from 3 to 4 hours. After the reaction is completed, the flask is cooled to room temperature, and 146 g. (1 mole) of ethyl oxalate is added rapidly through the dropping funnel, with stirring, to the solution of potassium ethoxide in ether. A yellow color develops at this point. The stirring is continued for an additional 10 minutes. Then 174 g. (1 mole) of ethyl succinate is added rapidly, with vigorous stirring (Note 3). After a few minutes, the potassium salt crystallizes, making further stirring impracticable. It is collected on a filter and washed with ether until the salt is colorless.

The salt is dissolved in 270 ml. of water, and 100 ml. of concentrated hydrochloric acid is added. The ethyl oxalylsuccinate separates as an oil and rises to the surface. It is removed by extracting the mixture with 100-ml. portions of ether until the aqueous solution is almost colorless. The extracts are dried over sodium sulfate, and the ether is distilled under reduced pressure. The ethyl oxalylsuccinate remains in the flask as a yellow oil. The yield is 225–227 g. (82–83%) (Note 4).

B. α-*Ketoglutaric acid*. The ester obtained by the foregoing procedure is mixed with 600 ml. of concentrated hydrochloric acid and left overnight. The mixture is concentrated by distillation (Note 5) until the temperature of the liquid reaches 140°. It is poured into an evaporating dish and allowed to cool. The solid mass, weighing 110–112 g., is then pulverized. The yield of α-ketoglutaric acid is 92–93% of the theoretical for the last step, or 75–77% based upon diethyl succinate. The light-tan product, obtained as described above, is suitable for most purposes, but a purer acid, m.p. 109–110° (cor.), may be obtained by recrystallization from an acetone-benzene mixture.

2. Notes

1. All containers must be absolutely dry, and anhydrous xylene must be used. Important! Destroy with anhydrous ethanol all potassium remaining in the xylene and waste ether.

2. The stirrer is not necessary until the ethyl oxalate is added. The submitters found the use of a nitrogen atmosphere to be unnecessary.
3. The ethyl oxalate was redistilled, and the fraction boiling at 106–107°/25 mm. was used. The ethyl succinate was c.p. material obtained from Eimer and Amend and was used without further purification.
4. For further purification, the product can be distilled at about 115°/1 mm.
5. This should be done in a hood, or a trap should be used to remove the hydrochloric acid.
The submitters wish to thank Mr. Andrew Streitweiser for his invaluable assistance.

3. Discussion

Ethyl oxalylsuccinate has been prepared by the condensation of ethyl oxalate with ethyl succinate in the presence of sodium ethoxide[1] or of potassium ethoxide.[2] [3] The method described above is somewhat more convenient, and has given a higher yield of a better product, than one based upon sodium ethoxide, submitted by A. E. Martell and R. M. Herbst.

α-Ketoglutaric acid has been prepared by the hydrolysis of ethyl oxalylsuccinate with concentrated hydrochloric acid;[4] by the distillation of ethyl oxalylsuccinate with concentrated hydrochloric acid;[5] by treating α,β-dibromoglutaric acid with 2 *N* sodium carbonate solution;[6] by treatment of ethyl α-bromoglutaconate with alkalies;[7] and by treating ethyl α,α'-dibromoglutarate with alcoholic potash.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 687

References and Notes

1. Wislicenus, *Ber.*, **22**, 885 (1889); *Ann.*, **285**, 1 (1895).
2. Wislicenus, *Ber.*, **44**, 1567 (1911);
3. Kögl, Halberstadt, and Barendregt, *Rec. trav. chim.*, **68**, 387 (1949).
4. Blaise and Gault, *Compt. rend.*, **147**, 199 (1908); Gabriel, *Ber.*, **42**, 655 (1909).
5. Blaise and Gault, *Bull. Soc. chim. France*, **9**, 455 (1911).
6. Ingold, *J. Chem. Soc.*, **119**, 2014 (1921).
7. Ingold, *J. Chem. Soc.*, **119**, 2019 (1921).
8. Ingold, *J. Chem. Soc.*, **119**, 326 (1921).

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

alcoholic potash

acetone-benzene

ethyl α,α'-dibromoglutarate

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

ethyl succinate

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium ethoxide (141-52-6)

potassium (7440-09-7)

xylene (106-42-3)

Ethyl oxalate

potassium ethoxide (917-58-8)

α-Ketoglutaric acid,
Glutaric acid, α-oxo- (328-50-7)

Ethyl oxalylsuccinate

Diethyl succinate (123-25-1)

α,β-dibromoglutaric acid

ethyl α-bromoglutaconate