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.

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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.

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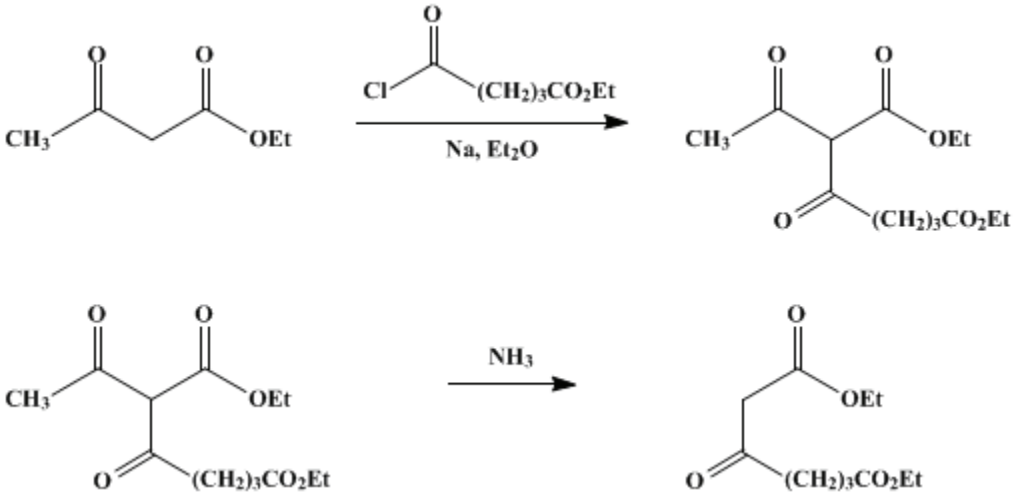
DIETHYL β-KETOPIMELATE

[Pimelic acid, β-oxo-, diethyl ester]



Submitted by Maya Guha and D. Nasipuri[1].
Checked by William G. Dauben and Richard Ellis.

1. Procedure

A. *Diethyl α-acetyl-β-ketopimelate*. In a 2-l. three-necked flask equipped with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser protected with a calcium chloride tube are placed 11.5 g. (0.5 g. atom) of finely powdered sodium (Note 1) and 500 ml. of dry ether. The flask is placed in an ice bath, and 65.0 g. (63.5 ml., 0.5 mole) of freshly distilled ethyl acetoacetate in 150 ml. of dry ether is slowly added from the dropping funnel with stirring (approximate time for addition is 30–40 minutes). The mixture is stirred overnight, then it is cooled in an ice bath, and 89.0 g. (0.5 mole) of γ-carbethoxybutyryl chloride (Note 2) in 200 ml. of dry ether is added gradually over the course of 1 hour. The reaction is first stirred overnight at room temperature, then gently refluxed by heating in a water bath for 30 minutes. The mixture is cooled in an ice bath, and a cold solution of 20 ml. of concentrated sulfuric acid in 300 ml. of water is added cautiously with vigorous stirring. The stirring is continued until two clear layers form when the stirring is stopped. The ethereal layer is separated and the aqueous layer extracted once with 100 ml. of ether. The two organic layers are combined, washed once with water, and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the solvent is removed by heating the ethereal solution on a water bath held at about 50–60°. The residual light-brown liquid is transferred to a 150 ml. Claisen flask and distilled under reduced pressure. The fraction boiling at 142–147°/0.4 mm. or 158–162°/2.5 mm. is collected (Note 3). The yield is 84–91 g. (61–66%), n_D^{28} 1.4649–1.4655.

B. *Diethyl β-ketopimelate*. In a 250-ml. distillation flask fitted with an inlet tube reaching near the bottom of the flask and a soda-lime drying tube on the side-arm is placed a solution of 50 g. (0.18 mole) of diethyl α-acetyl-β-ketopimelate in 75 ml. of dry ether. The solution is cooled by placing the flask in an ice-salt bath, and then a slow stream of ammonia gas is passed through the inlet tube. The solution becomes turbid during the first few minutes and soon becomes clear again. The gas stream is continued for 45–50 minutes, and the yellow liquid is allowed to stand at room temperature overnight with due protection from atmospheric moisture. Most of the ether is then removed by passing a stream of dry air through the solution, and the residue is transferred to a separatory funnel with the aid of 50 ml. of ether. The ethereal solution is washed with three 70-ml. portions of cold 3*N* hydrochloric acid, each extraction being shaken vigorously for 10 minutes. The ethereal layer is set aside, and the acid washings are extracted twice with 50-ml. portions of ether. The combined ethereal extracts are washed once with

water and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the solvent is removed by heating the solution on a water bath. The residue is transferred to a Claisen flask with a short Vigreux column, and the fraction boiling at 130–132°/0.5 mm. or 120–121°/0.2 mm. is collected (Note 4) and (Note 5). The yield is 21–25 g. (50–59%), n_D^{28} 1.4400, $n_D^{31.5}$ 1.4376, $n_D^{36.5}$ 1.4338.

2. Notes

1. Clean pieces of sodium are melted under xylene and powdered by vigorous shaking. When cold, the xylene is decanted and the sodium powder is washed by decantation with a few milliliters of dry ether and then washed into the reaction flask with dry ether.
2. The γ-carbethoxybutyryl chloride (b.p. 100–101°/5–6 mm. or 108–110°/15 mm.) was prepared by the method of Bachmann, Kushner, and Stevenson.[2]
3. The distillate contains mostly C-acyl ester with a little of O-acyl ester. Separation of these two esters by means of a carbonate solution in which only the C-acyl ester is soluble[3,4] is possible. This separation is unnecessary in the present procedure for the O-acyl derivative gives rise to ethyl acetoacetate during decomposition with ammonia. This low-boiling ester is removed during the distillation of diethyl β-ketopimelate.
4. A small fore-run, b.p. 60–80°/5 mm., is collected which gives a positive test with ferric chloride reagent. Presumably this fraction consists mostly of ethyl acetoacetate.
5. The checkers used an 18-in. Vigreux column with a heated jacket and observed a boiling point of 126–128°/2 mm.

3. Discussion

The described method of preparing diethyl β-ketopimelate is a modification of that described by Bouveault[5] and is essentially the same as that reported by Bardhan and Nasipuri.[6] This ester has also been prepared by condensation of γ-carbethoxybutyryl chloride with ethoxymagnesiummalonic ester and cleavage of the resulting acylated malonic ester by β-naphthalenesulfonic acid[7] or by acetic or propionic acids containing a trace of concentrated sulfuric acid.[8]

4. Merits of Preparation

The present method offers a more convenient synthesis with appreciably higher yields of diethyl β-ketopimelate. It is reported to be useful for the preparation of dimethyl β-ketoadipate[3,9] and diethyl β-ketosuberate.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 359

References and Notes

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

Ethoxymagnesiummalonic ester

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

sodium sulfate (7757-82-6)

β-naphthalenesulfonic acid (120-18-3)

sodium (13966-32-0)

ferric chloride (7705-08-0)

xylene (106-42-3)

Ethyl acetoacetate (141-97-9)

Diethyl β-ketopimelate,
Pimelic acid, β-oxo-, diethyl ester (40420-22-2)

γ-carbethoxybutyryl chloride (5205-39-0)

Diethyl α-acetyl-β-ketopimelate (61983-62-8)

dimethyl β-ketoadipate

diethyl β-ketosuberate