



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.

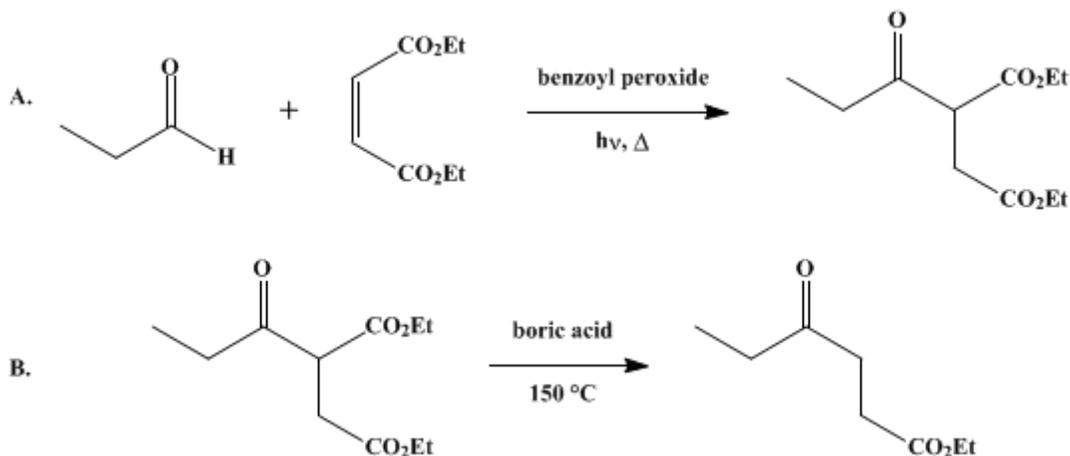
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.615 (1988); Vol. 58, p.79 (1978).

γ -KETOESTERS FROM ALDEHYDES VIA DIETHYL ACYLSUCCINATES: ETHYL 4-OXOHEXOATE

[Hexanoic acid, 4-oxo-, ethyl ester]



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1. Procedure

A. *Diethyl propionylsuccinate* (**1**). A solution of 412 g. (2.40 mole) of *diethyl maleate* (Note 1), 278 g. (4.79 mole) of freshly distilled *propionaldehyde* (Note 2), and 1.2 g. (0.0048 mole) of *benzoyl peroxide* in a normal, 2-l. Pyrex flask is heated under reflux while undergoing irradiation with a UV lamp (Note 3). The initial reflux temperature is 60°. After 2 hours another 1.2 g. of *benzoyl peroxide* is added. Strong reflux and irradiation are maintained throughout the entire reaction period. After 18 hours of reflux, the internal pot temperature reaches 68°, at which point the last 1.2 g. of *benzoyl peroxide* is added. The reaction is continued for a total of 30 hours, at which time the pot temperature reaches 74.5°. The reflux condenser is then replaced with a distillation head, and the excess *propionaldehyde* (119 g.) is distilled under atmospheric pressure, b.p. 48–49°. *Succinate 1* is distilled under reduced pressure. The main fraction, b.p. 145–151.5° (15–16 mm), provides 417–449 g. (75–81%) of product having sufficient purity for use in the next step (Note 4).

B. *Ethyl 4-oxohexanoate* (**2**). A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and Claisen condenser connected to a gas-measuring device (Note 5) is charged with 276 g. (1.20 mole) of *succinate 1* and 74.1 g. (1.20 mole) of *boric acid* (Note 6). The initially heterogeneous mixture is stirred and immersed in a 150° oil bath. Within 1 hour 36 g. of distillate (mainly *ethanol*) and approximately 2.3 l. of gas collect. As the temperature is raised to 170°, the rate of *carbon dioxide* evolution increases, a total of 24.9 l. of gas being collected after 1.5 hours. At this time gas evolution has almost ceased, and the reaction mixture has a clear, light-yellow appearance. The contents of the flask are cooled to room temperature, poured onto 1.5 l. of ice, and extracted with three 500-ml. portions of *toluene*. The combined organic layers are dried over anhydrous *magnesium sulfate*, and the solvent is removed under reduced pressure. The product is distilled through a 10-cm. Vigreux column, yielding 156–162 g. (82–85%) of *ethyl 4-oxohexanoate*, b.p. 109–112° (18 mm.). GC analysis indicates the material to be 99.2% pure (Note 7).

2. Notes

1. *Diethyl maleate*, practical grade, available from Eastman Organic Chemicals, was used without further purification.

2. [Propionaldehyde](#) was obtained from Aldrich Chemical Company, Inc., and must be distilled before use.
3. The checkers used a 275-W. General Electric sunlamp. The submitters used a 140-W. Hanovia Ultraviolet Quartz lamp of a type no longer available.
4. The [succinate 1](#) has the following ^1H NMR spectra (CDCl_3), δ (multiplicity, number of protons, assignment): 1.0–1.45 (m, 9H, 3CH_3), 2.6–3.5 (m, 4H, 2CH_2), 3.9–4.4 (m, 5H, $2\text{OCH}_2\text{CH}_3$ and CH).
5. As a gas-measuring device, the submitters used an inverted, calibrated, 10-l. bottle, filled with saturated [sodium chloride](#), resting in an enamel bucket big enough to hold the volume to be displaced. The checkers used a gas meter. However, the rate of gas evolution can be estimated by using a simple gas bubbler.
6. Reagent grade [boric acid](#), available from Aldrich Chemical Company, Inc., was used.
7. GC analysis was performed on a Hewlett-Packard Model 5720 with dual flame detector; column 1.85 m. \times 0.313 cm. outer diameter, stainless steel; 10% UCW-98 on Diatoport 5, programmed at 30° per minute from 50– 250° . The purity was calculated by an area comparison. Ester **2** has the following ^1H NMR spectrum (CDCl_3), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 1.05 (t, $J = 7$, 3H, CH_3), 1.2 (t, $J = 7$, 3H, CH_3), 2.4–2.9 (m, 6H, 3CH_2), 4.2 (q, $J = 7$, 2H, OCH_2CH_3).

3. Discussion

γ -Ketoesters, notably 5-substituted ethyl levulinate, have been prepared *via* radical addition of aldehydes to [diethyl maleate](#) to give acylated diethyl succinates.² These intermediates in turn had to be saponified,² decarboxylated,² and reesterified to give the corresponding 4-oxocarboxylates. A more direct method³ utilizes the free radical addition of [butyraldehyde](#) to [methyl acrylate](#), but the reported yield is low (11%).

The present method⁴ is simple, versatile, and efficient in contrast to earlier methods, which were multistep or preparatively unsatisfactory. Various 5-substituted 4-oxocarboxylates can be prepared by this procedure.⁴

γ -Ketoesters, in general, and [levulinic acid](#) or esters, in particular, have extensive utility.⁵ For example, they can serve as central intermediates for γ -butyrolactones,⁶ 1,4-diols,⁷ thiophenes,⁸ pyrrolidones,⁹ and 2-alkyl-1,3-cyclopentanediones.¹⁰

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 6, 774](#)
- [Org. Syn. Coll. Vol. 6, 799](#)

References and Notes

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(Registry Number)

ethanol (64-17-5)

sodium chloride (7647-14-5)

Propionaldehyde (123-38-6)

carbon dioxide (124-38-9)

toluene (108-88-3)

butyraldehyde (123-72-8)

diethyl maleate (141-05-9)

LEVULINIC ACID (123-76-2)

boric acid (10043-35-3)

benzoyl peroxide (94-36-0)

methyl acrylate (96-33-3)

magnesium sulfate (7487-88-9)

succinate

Ethyl 4-oxohexanoate,
Hexanoic acid, 4-oxo-, ethyl ester (3249-33-0)

Diethyl propionylsuccinate (4117-76-4)