



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.

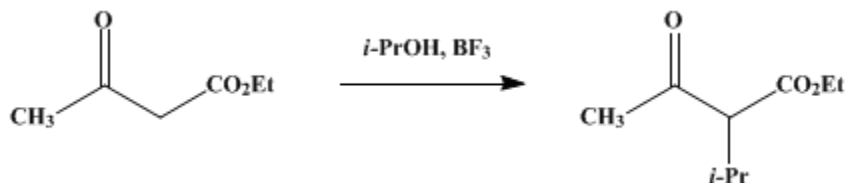
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 3, p.405 (1955); Vol. 27, p.35 (1947).

ETHYL α -ISOPROPYLACETOACETATE

[Isovaleric acid, α -acetyl, ethyl ester]



Submitted by Joe T. Adams, Robert Levine, and Charles R. Hauser.

Checked by H. R. Snyder and John Mirza.

1. Procedure

This reaction should be carried out under a well-ventilated hood (Note 1).

A mixture of 30.0 g. (0.5 mole) of anhydrous **isopropyl alcohol** and 65.0 g. (0.5 mole) of freshly distilled **ethyl acetoacetate** is placed in a 500-ml. round-bottomed three-necked flask equipped with a mercury-sealed stirrer, a gas inlet tube terminating about 1 cm. above the surface of the liquid, a gas outlet tube connected with a calcium chloride drying tube, and a thermometer (Note 2). The gas inlet tube is connected to a source of boron fluorides (Note 3), and an ice bath is applied to the reaction flask; when the temperature of the stirred mixture has fallen to approximately 0° the stream of **boron fluoride** is started and adjusted so that the temperature of the mixture does not exceed 7°. The addition of **boron fluoride** is continued until the mixture is saturated and for 15 minutes thereafter (Note 4). The reaction mixture then is stirred at 28° for 2.5 hours (Note 5), at the end of which period it is poured slowly into a stirred mixture of 130 g. of hydrated **sodium acetate**, 100 ml. of water, and 200 g. of crushed ice. The beaker containing the resulting mixture is allowed to stand in an ice bath for 2 hours with occasional stirring.

The mixture is poured into a 1-l. separatory funnel. The beaker is rinsed with 300 ml. of **ether**, and this portion of solvent is shaken with the mixture in the separatory funnel. The phases are separated, and the aqueous solution is extracted twice with 100-ml. portions of **ether**. The combined **ether** solutions are washed with saturated aqueous bicarbonate solution until **carbon dioxide** no longer forms. The solution is transferred to an Erlenmeyer flask and dried over about 25 g. of anhydrous **sodium sulfate** for 12 hours, after which it is decanted into another Erlenmeyer flask and dried over about 10 g. of Drierite for 6 hours.

A 125-ml. modified Claisen flask is arranged for distillation, but with a dropping funnel fitted in the neck intended for the ebullator tube. Portions of the dried **ether** solution are introduced into the flask through the funnel while the flask is heated on the steam bath for continuous removal of the solvent. After all the **ether** solution and the **ether** washings from the last drying agent have been concentrated, the dropping funnel is replaced by an ebullator tube and distillation under diminished pressure is begun cautiously. Fractions are collected at 60–96°/20 mm. and at 96–98°/20 mm. The first fraction is redistilled to give an additional quantity of material boiling at 96–98°/20 mm. (Note 6). The combined product weighs 52–58 g. (60–67%) (Note 7).

2. Notes

1. Although no definite data are available concerning the toxicity of **boron fluoride**, users should exercise caution and avoid breathing the fumes. The toxic effects of **hydrogen fluoride** and alkali fluorides are well known. **Boron fluoride** reacts with moisture in the air, forming white fumes of fluoboric acid and **boric acid** which cause a choking sensation when breathed.
2. The entire apparatus is dried in an oven at about 100° just before use.
3. Commercial **boron fluoride** from a tank is passed through a saturated solution of boric oxide in

concentrated [sulfuric acid](#).

4. The time required for saturation varies from 1 to 2 hours, depending upon the rate of addition. As the saturation point is approached, the fuming at the end of the exit tube increases rather sharply; the mixture is considered to be saturated when the fuming appears to have become constant.

5. The temperature and time at this point are critical and must be controlled carefully.

6. If the fractionation is conducted with a 30-cm. Vigreux column the redistillation of the fore-run is unnecessary.

7. By the same method [ethyl \$\alpha\$ -cyclohexylacetoacetate](#) (b.p. 146–148°/20 mm.) has been prepared in 34% yield from [cyclohexanol](#) and acetoacetic ester, and [ethyl \$\alpha\$ -*tert*-butylacetoacetate](#) (b.p. 101–102°/20 mm.) in 10–14% yield from [*tert*-butyl alcohol](#) and acetoacetic ester.

3. Discussion

The above procedure is based on that described by Adams, Abramovitch, and Hauser.¹ [Ethyl \$\alpha\$ -isopropylacetoacetate](#) has also been prepared by Hauser and Breslow² by the reaction of [ethyl acetoacetate](#) with [isopropyl ether](#) in the presence of [boron trifluoride](#), by Bischoff³ by the alkylation of the sodium derivative of ethyl acetoacetate with [isopropyl bromide](#), and by Renfrow⁴ by the alkylation of [ethyl acetoacetate](#) with [isopropyl bromide](#) using potassium *tert*-amyloxide as the condensing agent.

References and Notes

1. Adams, Abramovitch, and Hauser, *J. Am. Chem. Soc.*, **65**, 552 (1943).
 2. Hauser and Breslow, *J. Am. Chem. Soc.*, **62**, 2389 (1940).
 3. Bischoff, *Ber.*, **28**, 2620 (1895).
 4. Renfrow, *J. Am. Chem. Soc.*, **66**, 144 (1944).
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Appendix

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

acetoacetic ester

sodium derivative of ethyl acetoacetate

fluoboric acid

Drierite

potassium *tert*-amyloxide

boric oxide

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

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

[sodium acetate](#) (127-09-3)

[Cyclohexanol](#) (108-93-0)

Isopropyl bromide (75-26-3)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

hydrogen fluoride (7664-39-3)

isopropyl alcohol (67-63-0)

Ethyl acetoacetate (141-97-9)

boric acid (10043-35-3)

boron fluoride,
boron trifluoride (7637-07-2)

isopropyl ether (108-20-3)

Ethyl α -isopropylacetoacetate,
Isovaleric acid, α -acetyl, ethyl ester (1522-46-9)

ethyl α -cyclohexylacetoacetate

tert-butyl alcohol (75-65-0)

ethyl α -tert-butylacetoacetate