



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.

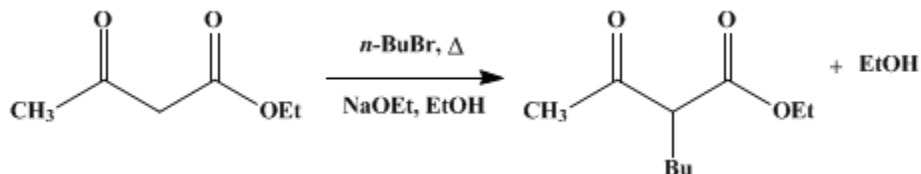
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 1, p.248 (1941); Vol. 7, p.36 (1927).

ETHYL *n*-BUTYLACETOACETATE

[Caproic acid, α -acetyl-, ethyl ester]



Submitted by C. S. Marvel and F. D. Hager.
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1. Procedure

A 5-l. round-bottomed flask, fitted with an efficient mechanical stirrer (Note 1), a reflux condenser, the upper end of which is protected by a calcium chloride tube, and a separatory funnel, is arranged for heating on a steam bath.

In the flask is placed 2.5 l. of absolute alcohol (Note 2), and then there is added gradually 115 g. (5 atoms) of metallic sodium cut into pieces. This requires three to four hours. After all the sodium has dissolved, 650 g. (5 moles) of ethyl acetoacetate (Note 3) is added. The stirrer is started and the solution heated to gentle boiling. To the boiling solution 750 g. (5.47 moles) of *n*-butyl bromide (Note 4) is added over a period of about two hours. The refluxing and stirring are continued until a sample of the solution is neutral to moist litmus paper. The time varies from six to ten hours.

When the reaction is complete, the mixture is cooled, and the solution is decanted from the sodium bromide. The salt is washed with 100 cc. of absolute alcohol, and the washings are added to the main solution. The alcohol (Note 5) is separated from the substituted acetoacetic ester by distilling through a short column from a steam bath. The crude residue after removal of the alcohol weighs about 925 g. It is satisfactory for hydrolysis to give the corresponding ketone (p. 351). If the pure ester is desired, the crude product is distilled under reduced pressure. The yield of product boiling at 112–117°/16 mm. is 642–672 g. (69–72 per cent of the theoretical amount) (Note 6).

2. Notes

1. The stirrer should be efficient in order to prevent bumping due to the settling of the sodium bromide which is formed during the reaction.
2. *Absolute Alcohol.*—The grade of absolute alcohol is important. Alcohol dried with sodium ethoxide (p. 259) is satisfactory. It is more effective to dry alcohol with magnesium methoxide if the presence of methyl alcohol in the absolute alcohol is permissible. This may be done by dissolving 24 g. of magnesium turnings in 200 cc. of absolute methyl alcohol (the reaction is very vigorous) and then adding 3 l. of the ordinary grade of absolute alcohol (about 99.5 per cent). The mixture is refluxed for about five hours and distilled into the flask in which the absolute alcohol is to be used. A like principle has been suggested recently for the preparation of anhydrous alcohols in general. It involves the addition of magnesium and a little iodine to the alcohol which is to be dehydrated.¹
3. The ethyl acetoacetate used in these experiments boiled over a 5° range under reduced pressure. The product prepared as described on p. 235 is satisfactory.
4. The *n*-butyl bromide (p. 28) boiled over a range of three degrees. The excess was used in order to decrease the time necessary to complete the reaction.
5. The alcoholic solution should be protected from moisture, and the alcohol which is recovered by the distillation should be treated with sodium and boiled under a reflux condenser to remove the excess of alkyl halide. After distillation the alcohol may then be used in a subsequent preparation.
6. This reaction is very general and other substituted acetoacetic esters may be obtained in approximately the same yields if this procedure is followed.

3. Discussion

Ethyl *n*-butylacetoacetate can be prepared by the action of *n*-butyl bromide on the sodium salt of ethyl acetoacetate.² The procedure described is the usual one for alkylating ethyl acetoacetate.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 5
- Org. Syn. Coll. Vol. 1, 99
- Org. Syn. Coll. Vol. 1, 119
- Org. Syn. Coll. Vol. 1, 205
- Org. Syn. Coll. Vol. 1, 237
- Org. Syn. Coll. Vol. 1, 238
- Org. Syn. Coll. Vol. 1, 250
- Org. Syn. Coll. Vol. 1, 254
- Org. Syn. Coll. Vol. 1, 258
- Org. Syn. Coll. Vol. 1, 261
- Org. Syn. Coll. Vol. 1, 272
- Org. Syn. Coll. Vol. 1, 296
- Org. Syn. Coll. Vol. 1, 351
- Org. Syn. Coll. Vol. 1, 451
- Org. Syn. Coll. Vol. 1, 528
- Org. Syn. Coll. Vol. 2, 318
- Org. Syn. Coll. Vol. 2, 372
- Org. Syn. Coll. Vol. 3, 16
- Org. Syn. Coll. Vol. 4, 630

References and Notes

1. Lund and Bjerrum, Ber. **64**, 210 (1931).
 2. Tafel and Jürgens, Ber. **42**, 2555 (1909); Ryan and Shannon, Proc. Roy. Irish Acad. **36B**, 322 (1924) [C. A. **19**, 470 (1925)]; Hess and Bappert, Ann. **441**, 153 (1925).
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

acetoacetic ester

acetoacetic esters

sodium salt of ethyl acetoacetate

alcohol (64-17-5)

methyl alcohol (67-56-1)

magnesium,
magnesium turnings (7439-95-4)

n-butyl bromide (109-65-9)

sodium bromide (7647-15-6)

iodine (7553-56-2)

sodium,
metallic sodium (13966-32-0)

sodium ethoxide (141-52-6)

Ethyl acetoacetate (141-97-9)

Caproic acid, α -acetyl-, ethyl ester,
ETHYL n-BUTYLACETOACETATE (1540-29-0)

magnesium methoxide