



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.

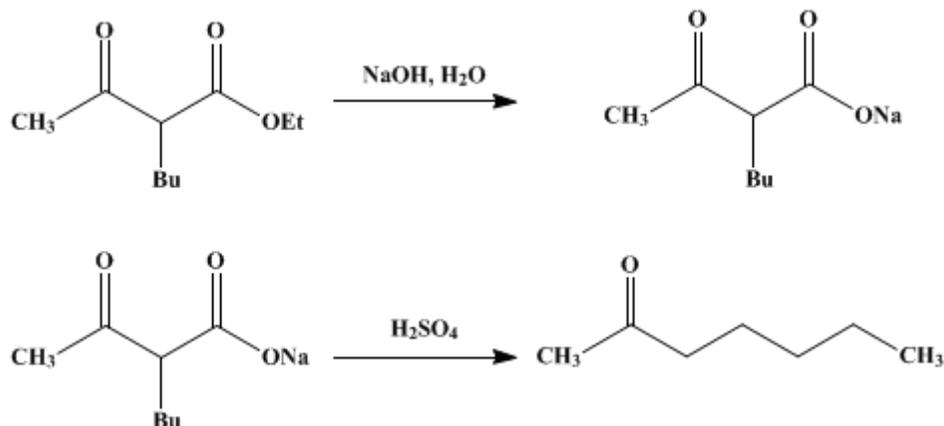
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 1, p.351 (1941); Vol. 7, p.60 (1927).

METHYL *n*-AMYL KETONE

[2-Heptanone]



Submitted by John R. Johnson and F. D. Hager.
 Checked by Frank C. Whitmore and W. F. Singleton.

1. Procedure

In a 12-l. round-bottomed flask, fitted with an efficient mechanical stirrer, is placed 5 l. of a 5 per cent solution of sodium hydroxide (6.25 moles). To this is added the crude ethyl *n*-butylacetoacetate (about 925 g.) obtained (p. 248) from 5 moles of ethyl acetoacetate. The mixture is stirred at room temperature for four hours, during which time the monosubstituted acetoacetic ester is completely saponified and passes into solution. The mixture is then allowed to stand until the unsaponified material separates completely as an oily layer. The aqueous layer is separated (Note 1) and transferred to a flask provided with a stopper fitted with a separatory funnel and a large bent glass tube leading to a condenser set for distillation.

Through the separatory funnel is added slowly 500 cc. of 50 per cent (sp. gr. 1.40) sulfuric acid (3.6 moles), which is somewhat more than the amount required to neutralize the alkali (6.25 moles) used in the saponification of the ester. When the evolution of carbon dioxide ceases to be vigorous, the reaction mixture is heated slowly to boiling, and from one-third to one-half of the total volume is distilled. The distillate is made alkaline with solid sodium hydroxide (Note 2) and redistilled until 80–90 per cent has been collected.

In the distillate the ketone layer is separated from the water, and the latter is distilled until one-third has been collected. The ketone layer in this distillate is separated, and the water layer is again distilled. This procedure is repeated as long as any considerable amount of ketone is obtained in the distillate (Note 3). The combined ketone fraction is washed four times with one-third its volume of a concentrated solution of calcium chloride (sp. gr. 1.3 or greater) to remove alcohol (Note 4), then dried over 50 g. of solid calcium chloride, filtered, and distilled. The yield of methyl *n*-amyl ketone boiling at 148–151°/750 mm. is 300–350 g. (52–61 per cent of the theoretical amount, based upon the original ethyl acetoacetate) (Note 5).

2. Notes

1. The insoluble layer is usually quite small in amount and may be discarded. On distillation it yields but a small amount of ketone and monosubstituted ester, along with considerable high-boiling material, presumably the disubstituted ester, which was present in the crude ethyl *n*-butylacetoacetate.
2. The distillate is rendered alkaline to remove any acids formed by the acid decomposition of the substituted acetoacetic ester or unreacted ethyl acetoacetate.

3. With [methyl *n*-amyl ketone](#) this process was repeated three times after the first separation. In the case of higher ketones, fewer separations are required; with the simpler ketones a greater number is advisable, on account of their solubility in water.

4. With the lower-molecular-weight ketones it is advantageous to distil the [calcium chloride](#) solution to recover the dissolved ketone. This is carried out exactly as described for the separation from the water. With [methyl *n*-amyl ketone](#) the loss is slight if a sufficiently concentrated solution of [calcium chloride](#) is employed.

5. Other ketones may be prepared by the same general procedure. Based upon the [ethyl acetoacetate](#) used, the following yields were obtained:

[Methyl *n*-butyl ketone \(hexanone-2\)](#) b.p. 126–128°, 50 per cent.

[Methyl *iso*-butyl ketone \(4-methylpentanone-2\)](#) b.p. 115–119°, 20 per cent.

[Methyl \$\beta\$ -methylbutyl ketone \(4-methylhexanone-2\)](#) b.p. 139–142°, 30 per cent.

The lower yields are due in some cases to the difficulty of isolating the products, and, in the last two, to the less complete reaction between the secondary alkyl bromide and the sodium derivative of ethyl acetoacetate.

3. Discussion

[Methyl *n*-amyl ketone](#) can be prepared by the hydration of [heptene-1](#) and of [heptene-2](#);¹ by heating [*n*-amylpropionic acid](#) with [potassium hydroxide](#);² by the oxidation of [methyl-*n*-amylcarbinol](#);³ and by the ketone decomposition of [ethyl *n*-butylacetoacetate](#)⁴ which is adapted from that used by Michael and Wolgast⁵ for [ethyl ethylacetoacetate](#).

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 1, 248](#)
- [Org. Syn. Coll. Vol. 2, 317](#)

References and Notes

1. Béhal, *Ann. chim. phys.* (6) **15**, 270 (1888); Desgrez, *ibid.* (7) **3**, 228, 234 (1894); Thomas, Campbell, and Hennion, *J. Am. Chem. Soc.* **60**, 719 (1938).
2. Moureu and Delange, *Bull. soc. chim.* (3) **29**, 674 (1903).
3. Schorlemmer, *Ann.* **161**, 279 (1872).
4. Drake and Riemenschneider, *J. Am. Chem. Soc.* **52**, 5005 (1930). This method reports slightly improved yields over those obtained in the procedure described. The hydrolysis was effected by a large excess of potassium hydroxide and refluxing at 105° for five hours. Dehn and Jackson, *ibid.* **55**, 4285 (1933). This method using phosphoric acid is reported to give yields of 95 per cent.
5. Michael and Wolgast, *Ber.* **42**, 3177 (1909).

Appendix

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

monosubstituted acetoacetic ester

sodium derivative of ethyl acetoacetate

[calcium chloride](#) (10043-52-4)

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

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

Ethyl acetoacetate (141-97-9)

ETHYL n-BUTYLACETOACETATE (1540-29-0)

2-Heptanone,
METHYL n-AMYL KETONE (110-43-0)

hexanone-2,
Methyl n-butyl ketone (591-78-6)

4-methylpentanone-2,
Methyl iso-butyl ketone (108-10-1)

Methyl β -methylbutyl ketone,
4-Methylhexanone-2

heptine-1 (628-71-7)

heptine-2

ethyl ethylacetoacetate (607-97-6)

methyl-n-amylcarbinol (543-49-7)

n-amylpropionic acid (5663-96-7)