



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.

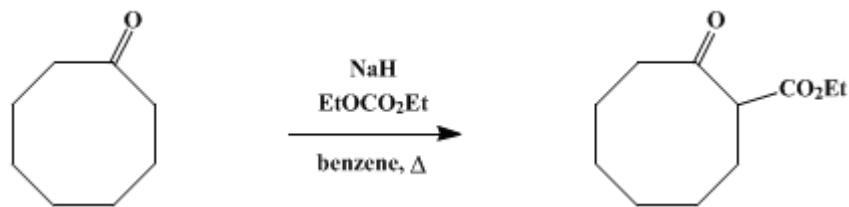
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 5, p.198 (1973); Vol. 47, p.20 (1967).

2-CARBETHOXYCYCLOOCTANONE

[2-Oxocyclooctanecarboxylic acid, ethyl ester]



Submitted by A. Paul Krapcho, Joseph Diamanti, Charles Cayen, and Richard Bingham¹.
Checked by William G. Dauben and Charles Dale Poulter.

1. Procedure

A 2-l. two-necked, round-bottomed flask equipped with a magnetic stirrer (Note 1) is fitted with a 250-ml. pressure-equalizing constant-rate dropping funnel and a condenser, the top of which is connected to a mercury trap to prevent the entrance of air during the reaction and for the detection of gas evolution. The dropping funnel is removed, and 35 g. (0.85 mole) of sodium hydride dispersed in mineral oil is added (Note 2). The mineral oil is removed by washing the dispersion four times with 100-ml. portions of benzene (Note 3). The benzene is removed with a pipet after the sodium hydride is allowed to settle (Note 4).

After most of the mineral oil has been removed, 400 ml. of benzene is added to the sodium hydride, followed by 71 g. (0.6 mole) of diethyl carbonate (Note 5). This mixture is heated to reflux, and a solution of 38 g. (0.3 mole) of cyclooctanone (Note 6) in 100 ml. of benzene is added dropwise from the dropping funnel over a period of 3–4 hours. After the addition is complete, this mixture is allowed to reflux until the evolution of hydrogen ceases (15–20 minutes).

When the reaction mixture has cooled to room temperature, 60 ml. of glacial acetic acid is added dropwise, and a heavy, pasty solid separates. Ice-cold water (about 200 ml.) is added dropwise, and the stirring is continued until all the solid material has gone into solution (Note 7). The benzene layer is separated, and the aqueous layer is extracted three times using 100-ml. portions of benzene. The combined benzene extracts are washed three times with 100-ml. portions of cold water. The benzene is removed by distillation at atmospheric pressure, and the excess diethyl carbonate is removed under water-pump pressure with gentle heating. The residual material is transferred to a 100-ml. distillation flask, and the fraction boiling at 85–87° (0.1 mm.) is collected. The yield of 2-carbethoxycyclooctanone is 54–56 g. (91–94%), n_D^{25} 1.4795–1.4800.

2. Notes

1. The checkers found that the agitation of the reaction mixture required later in this reaction is better achieved by use of a sealed mechanical stirrer.
2. The sodium hydride was obtained as a 58.6% dispersion in mineral oil from Metal Hydrides, Inc., Beverly, Massachusetts.
3. The benzene (Fisher certified reagent, thiophene free) was dried over potassium hydroxide and distilled from sodium metal.
4. By this procedure about 80–85% of the mineral oil was removed. Because some sodium hydride is lost in the pipetting procedure, an excess is initially employed.
5. The product supplied by Matheson, Coleman and Bell was used as received. Lower yields were obtained when a molar equivalent of diethyl carbonate was utilized, possibly because of self-condensation of the ketone.
6. The cyclooctanone was obtained from the Aldrich Chemical Co. and was utilized as received.
7. At this point the aqueous layer should be acidic, or more acetic acid should be added.

3. Discussion

The reaction of [cyclooctanone](#) with [diethyl oxalate](#), followed by decarbonylation of the resulting glyoxylate, has been reported to yield 32% of [2-carbomethoxycyclooctanone](#).² The reaction of [cyclooctanone](#) with [sodium amide](#) in [ether](#), followed by the addition of [diethyl carbonate](#), provided the product in 70% yield.³

The preparation of several medium- and large-sized 2-carbomethoxycycloalkanones has been accomplished by treatment of the cycloalkanone with sodium triphenylmethyl, followed by carbonation with dry ice, and esterification with [diazomethane](#).⁴ The yields are good but the procedure is laborious. The synthesis of [2-carbomethoxycyclooctanone](#) via the Dieckmann cyclization of [dimethyl azelate](#) with [sodium hydride](#) yields 48% of this product when the procedure is carried out over a 9-day period.⁵

4. Merits of the Preparation

The reaction described is of general synthetic utility for the preparation of a variety of cyclic β -keto esters from the corresponding ketones. Using this procedure the 2-carbomethoxycycloalkanones have been prepared from [cyclononanone](#), [cyclodecanone](#), and [cyclododecanone](#) in yields of 85%, 95%, and 90%, respectively. The procedure is simpler and gives much higher yields than other synthetic routes to these systems.

This procedure has been patterned after the method by which the carbomethoxy group is introduced into a few alicyclic ketones⁶ and several cyclic ketones. [Cyclohexanone](#) has been reported to yield 50% of [2-carbomethoxycyclohexanone](#) when treated with [sodium hydride](#) and [diethyl carbonate](#) using [ether](#) as the solvent.⁷ The preparation of [2-carbomethoxycycloheptanone](#) using [potassium *t*-butoxide](#) and [diethyl carbonate](#) in [benzene](#) has been reported in 40% yield.⁸ Jacob and Dev report an 80% yield of the latter compound using [sodium hydride](#) as the base.⁹

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 5, 221](#)

References and Notes

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

sodium triphenylmethyl

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

hydrogen (1333-74-0)

Cyclohexanone (108-94-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Thiophene (110-02-1)

Diazomethane (334-88-3)

sodium amide (7782-92-5)

2-carbethoxycyclohexanone (1655-07-8)

diethyl carbonate (105-58-8)

sodium hydride (7646-69-7)

diethyl oxalate (95-92-1)

Cyclodecanone (1502-06-3)

cyclononane (3350-30-9)

2-Carbethoxycyclooctanone,
2-Oxocyclooctanecarboxylic acid, ethyl ester (4017-56-5)

Cyclooctanone (502-49-8)

2-carbomethoxycyclooctanone

dimethyl azelate (1732-10-1)

cyclododecanone (830-13-7)

2-carbethoxycycloheptanone (774-05-0)

potassium t-butoxide (865-47-4)

