



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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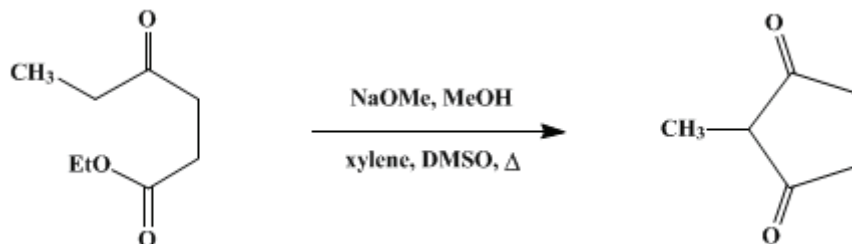
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 6, p.774 (1988); Vol. 58, p.83 (1978).

γ -KETOESTERS TO PREPARE CYCLIC DIKETONES: 2-METHYL-1,3-CYCLOPENTANEDIONE

[1,3-Cyclopentanedione, 2-methyl-]



Submitted by U. Hengartner¹ and Vera Chu.

Checked by William B. Farnham and William A. Sheppard.

1. Procedure

A 3-l., three-necked, round-bottomed flask fitted with a dropping funnel (Note 1), a mechanical stirrer, and a distillation head with a thermometer and efficient Liebig condenser is charged with 1.4 l. of *xylene* (Note 2). The *xylene* is stirred and heated to boiling with a heating mantle, while 179 g. of a solution containing 43 g. (0.80 mole) of *sodium methoxide* in *methyl alcohol* (Note 3) is added over 20 minutes. During this period 450 ml. of solvent is distilled.

After addition is complete, 300 ml. of *xylene* is added and the distillation continued until the vapor temperature rises again to 138°. During that time an additional 250 ml. of distillate is collected, leaving a white suspension to which 18 ml. of *dimethylsulfoxide* is added. A solution of 100 g. (0.633 mole) of *ethyl 4-oxohexanoate* (Note 4) in 200 ml. of *xylene* is then added (Note 1) to the vigorously stirred *sodium methoxide* suspension over 25 minutes, while 900 ml. of distillate is collected continuously, maintaining the vapor temperature at 134–137°. The orange-colored mixture is stirred and heated for an additional 5 minutes, then cooled to room temperature. Addition of 165 ml. of water with vigorous stirring over a 5-minute period (Note 5) gives two clear phases, which are cooled in an ice bath and acidified by adding 82 ml. (0.98 mole) of 12 *N* *hydrochloric acid* with vigorous stirring. After the mixture is stirred at 0° for another 1.5 hours, the crystalline product is collected by suction filtration and carefully washed successively with 100-ml. and 50-ml. portions of ice-cooled *diethyl ether* (Note 6).

The crude product is dissolved in 1 l. of boiling water, and the solution is filtered quickly through a preheated fritted-disk funnel (Note 7). The filtrate is concentrated on a hot plate at atmospheric pressure to a volume of 550–600 ml. and allowed to stand at 0° overnight. The crystals are collected by filtration and dried at 85°, yielding 50.0–50.6 g. (70–71%) of *2-methyl-1,3-cyclopentanedione*, m.p.210–211° (Note 8).

2. Notes

1. A 500-ml. dropping funnel, provided with a calcium sulfate drying tube, was used.
2. Reagent grade *xylene*, b.p. 138–141°, from Fisher Scientific Company, was used.
3. The *sodium methoxide* solution was prepared as follows: 203 g. of *methyl alcohol*, available from Fisher Scientific Company, is placed in a 500-ml., two-necked flask under an inert atmosphere. The flask is equipped with a magnetic stirring bar and a reflux condenser provided with a calcium sulfate drying tube. Freshly cut, clean *sodium* (23 g., 1.0 mole) is added in small pieces at such a rate that reflux is maintained. The mixture is stirred until all the *sodium* has reacted.
4. *Ethyl 4-oxohexanoate* was prepared by the method in *Org. Synth.*, **Coll. Vol. 6**, 615 (1988).
5. The temperature of the mixture is kept at 25–35°.
6. The *ether* washings contain 11 g. of a brown viscous oil containing various condensation products.

7. A small amount of insoluble, tarry material is removed by this filtration. Preheating the funnel is necessary, since the product crystallizes easily on cooling. Dark-colored impurities in crude 2-methyl-1,3-cyclopentanedione can be removed by recrystallization from methanol.

8. 2-Methyl-1,3-cyclopentanedione, [*Org. Synth.*, **Coll. Vol. 5**, 747 (1973)] m.p. 210–212°, exists in the enol form in solution. It has the following spectral properties: UV (0.1 N HCl) nm. max. (ϵ): 252 (19,000); ^1H NMR (dimethyl sulfoxide- d_6) δ (multiplicity, number of protons, assignment): 1.51 (s, 3H, CH_3), 2.39 (s, 4H, 2CH_2).

3. Discussion

2-Methyl-1,3-cyclopentanedione is a key intermediate in the total synthesis of steroids.² A number of methods have been described for its preparation, among them the condensation of succinic acid with propionyl chloride,³ and that of succinic anhydride with 2-buten-2-ol acetate,⁴ both in the presence of aluminum chloride. It has also been obtained from 3-methylcyclopentane-1,2,4-trione by catalytic hydrogenation⁵ and Wolff–Kishner reduction.⁶ The base-promoted cyclization of ethyl 4-oxohexanoate and diethyl propionylsuccinate with tertiary alkoxides was first reported by Bucourt.⁷ The present cyclization process provides an experimentally simple route to 2-methyl-1,3-cyclopentanedione. Using the same procedure, ethyl 4-oxohexanoate has been cyclized to give 2-ethyl-1,3-cyclopentanedione in 46% yield.

This preparation is referenced from:

- *Org. Syn. Coll. Vol. 6*, 615
- *Org. Syn. Coll. Vol. 7*, 363
- *Org. Syn. Coll. Vol. 8*, 578
- *Org. Syn. Coll. Vol. 9*, 570

References and Notes

1. Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.
2. For leading references, see R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, "Total Synthesis of Steroids," Academic Press, New York, 1974.
3. H. Schick, G. Lehmann, and G. Hilgetag, *Chem. Ber.*, **102**, 3238 (1969).
4. V. J. Grenda, G. W. Lindberg, N. L. Wendler, and S. H. Pines, *J. Org. Chem.*, **32**, 1236 (1967).
5. M. Orchin and L. W. Butz, *J. Am. Chem. Soc.*, **65**, 2296 (1943).
6. J. P. John, S. Swaminathan, and P. S. Venkataramani, *Org. Synth.*, **Coll. Vol. 5**, 747 (1973).
7. R. Bucourt, A. Pierdet, G. Costerousse, and E. Toromanoff, *Bull. Soc. Chim. Fr.*, 645 (1965).

Appendix

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

hydrochloric acid (7647-01-0)

methyl alcohol,
methanol (67-56-1)

ether,
diethyl ether (60-29-7)

Succinic acid (110-15-6)

sodium methoxide (124-41-4)

aluminum chloride (3495-54-3)

sodium (13966-32-0)

xylene (106-42-3)

Succinic anhydride (108-30-5)

propionyl chloride (79-03-8)

dimethylsulfoxide (67-68-5)

1,3-Cyclopentanedione, 2-methyl-,
2-Methyl-1,3-cyclopentanedione (765-69-5)

3-methylcyclopentane-1,2,4-trione (4505-54-8)

Ethyl 4-oxohexanoate (3249-33-0)

2-buten-2-ol acetate

Diethyl propionylsuccinate (4117-76-4)

2-ethyl-1,3-cyclopentanedione (823-36-9)