Organic Syntheses

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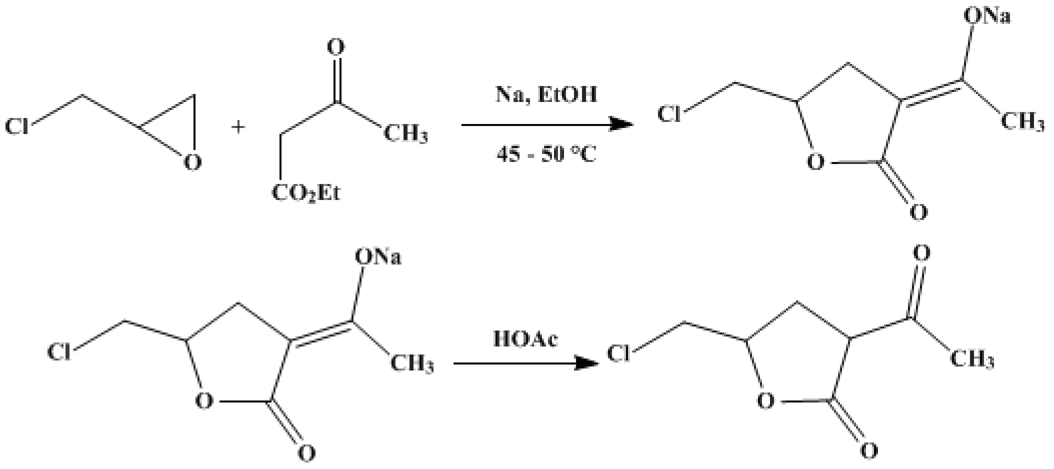
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.031.0001

Organic Syntheses, Coll. Vol. 4, p.10 (1963); Vol. 31, p.1 (1951).

α-ACETYL-δ-CHLORO-γ-VALEROLACTONE

[Valeric acid, 2-acetyl-5-chloro-4-hydroxy-, γ-lactone]



Submitted by G. D. Zuidema, E. van Tamelen, and G. Van Zyl[1].
Checked by William S. Johnson and Herbert I. Hadler.

1. Procedure

A 1-l. three-necked round-bottomed flask is equipped with a sealed stirrer, a thermometer, a dropping funnel, and an efficient condenser, the upper end of which is protected with a calcium chloride drying tube. In this flask 23 g. (1 g. atom) of lustrous sodium (Note 1) is dissolved in 400 ml. of absolute ethanol (Note 2). The sodium is cut into about 25 pieces, and the entire amount is added at one time. It may be necessary to cool the flask in a cold-water bath if the reaction becomes violent. When all the sodium has dissolved, the solution is cooled to 50° and 130 g. (127 ml., 1 mole) of ethyl acetoacetate (Note 3) is added dropwise while the temperature is maintained between 45° and 50°. The resulting solution is cooled to about 35°, and 92.5 g. (78.4 ml., 1 mole) of epichlorohydrin (Note 4) is added dropwise with stirring over a period of 20 minutes. The temperature is then raised to 45° and is kept at 45–50° for 18 hours. The clear red-orange solution is cooled to 15°, and chilled glacial acetic acid (60–65 ml.) is added with stirring until the solution is just acid to litmus; a mush of sodium acetate crystals precipitates. The dropping funnel is replaced by a capillary tube, and the condenser is set for distillation. About three-fourths of the ethanol is removed under reduced pressure while air is bubbled into the mixture through the capillary tube (Note 5). Care is taken that the internal temperature does not exceed 100°.

The mushy residue is shaken with 250–300 ml. of water until the sodium acetate dissolves. The oily layer of lactone is separated, and the aqueous phase is extracted with two 100-ml. portions of ether. The combined oil and ether extracts are washed with 150 ml. of water and dried overnight over anhydrous sodium sulfate. The ether is removed under reduced pressure, and the product is distilled from a modified Claisen flask. The fraction boiling at 160–170°/11 mm. is collected; refractionation yields 107–114 g. (61–64%) of product boiling at 164–168°/11 mm. or 151–156°/8 mm.; n_D^{25} 1.4815–1.4830 (Note 6) and (Note 7).

2. Notes

1. The sodium must be present in an equivalent amount for best results. When 0.2 g. atom of sodium was used, the yield was only 10%.
2. It is necessary to maintain strictly anhydrous conditions in this reaction. The apparatus should be carefully predried and the absolute ethanol freshly prepared either by the diethyl phthalate method[2] or

by the magnesium ethoxide method.[3]

3. Eastman Kodak Company white label quality ethyl acetoacetate (b.p. 78–79°/11 mm.) was used.
4. Epichlorohydrin may be prepared from glycerol-α,γ-dichlorohydrin.[4] It is also commercially available.
5. Unless this precaution is taken, there is considerable bumping due to the presence of the solid sodium acetate in the mixture.
6. The product may become slightly colored upon standing.
7. This reaction is typical of those between the following epoxides and ethyl acetoacetate:

Epoxide	Boiling Point of Product	% Yield of Product
Butadiene monoxide	148–151°/32 mm.	54
Propylene oxide	138–141°/26 mm.	49
Styrene oxide	164–167°/3 mm.	60
Ethyl glycidyl ether	160–163°/14–15 mm.	46
Phenyl glycidyl ether	195–197°/1 mm.	77

3. Discussion

α-Acetyl-δ-chloro-γ-valerolactone has been prepared only by the condensation of epichlorohydrin with ethyl acetoacetate. The preparation described is based on the method of Traube and Lehman.[5]

References and Notes

1. Hope College, Holland, Michigan.
2. Manske, *J. Am. Chem. Soc.*, **53**, 1106 (1931), footnote 9.
3. Lund and Bjerrum, *Ber.*, **64**, 210 (1931). Fieser, *Experiments in Organic Chemistry*, 3rd ed., p. 286, D. C. Heath and Company, Boston, Massachusetts, 1955.
4. *Org. Syntheses Coll. Vol.* **1**, 233 (1941).
5. Traube and Lehman, *Ber.*, **34**, 1980 (1901).

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

glycerol-α,γ-dichlorohydrin

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

sodium acetate (127-09-3)

Epichlorohydrin (106-89-8)

sodium sulfate (7757-82-6)

propylene oxide (75-56-9)

sodium (13966-32-0)

Ethyl acetoacetate (141-97-9)

Styrene oxide (96-09-3)

α-Acetyl-δ-chloro-γ-valerolactone,
Valeric acid, 2-acetyl-5-chloro-4-hydroxy-, γ-lactone (3154-75-4)

Butadiene monoxide (930-22-3)

Ethyl glycidyl ether (4016-11-9)

Phenyl glycidyl ether (122-60-1)

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