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.

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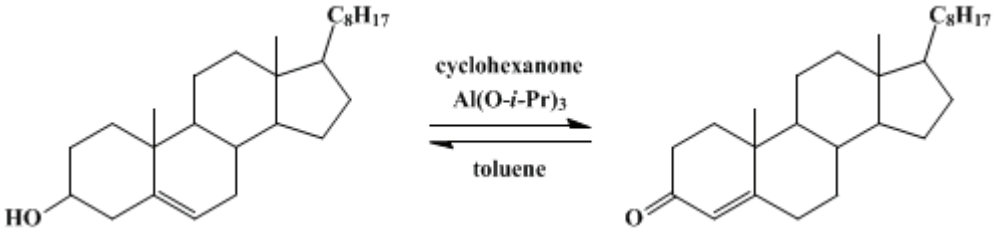
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.035.0039

Organic Syntheses, Coll. Vol. 4, p.192 (1963); Vol. 35, p.39 (1955).

Δ⁴-CHOLESTEN-3-ONE

[Cholest-4-en-3-one]



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1. Procedure

To a 5-l. three-necked flask, equipped with a sealed mechanical stirrer, a dropping funnel, and a take-off reflux condenser, are added 2 l. of sulfur-free toluene and two boiling chips. The openings of the dropping funnel and the condenser are protected by drying tubes containing Drierite. A portion (200 ml.) of the toluene is distilled from the flask (take-off cock open) in order to dry the system by azeotropic distillation; then 100 g. (0.26 mole) of cholesterol and 500 ml. of cyclohexanone (Note 1) are added to the flask. After an additional 50 ml. of toluene has been distilled, a solution of 28 g. (0.14 mole) of aluminum isopropoxide (Note 2) in 400 ml. of dry toluene (Note 3) is added dropwise over a period of approximately 30 minutes. During this time toluene is distilled at a rate slightly greater than the rate of addition of catalyst solution, so that when the addition is complete about 600 ml. of toluene has distilled. An additional 300 ml. of toluene is distilled, and the murky orange-colored reaction mixture is then allowed to cool to room temperature.

Four hundred milliliters of a saturated aqueous solution of potassium-sodium tartrate (Note 4) is added to the mixture, and the organic layer becomes clear and orange. The stirrer assembly is removed, and the mixture is steam-distilled until about 6 l. of distillate has been collected. The residual mixture is cooled and extracted successively with one 300-ml. portion and two 100-ml. portions of chloroform. The combined extracts are washed with two 100-ml. portions of water and dried over anhydrous magnesium sulfate. The chloroform is removed by distillation on the steam bath at reduced pressure (water aspirator). The residual viscous amber oil (Note 5) is dissolved by heating in 150 ml. of methanol. When the solution has cooled to about 40°, seeds of cholestenone are added, and the flask is wrapped with a small towel to ensure slow cooling (Note 6). After the bulk of the material has crystallized, which requires several hours, the mixture is stored at 0° overnight (Note 7). The product is collected by suction filtration, washed with 40–50 ml. of methanol previously cooled in an ice-salt bath, then dried at reduced pressure, first at room temperature and finally at 60°. The yield of light-cream-colored Δ⁴-cholesten-3-one is 81–93 g. (81–93%), m.p. 76–79°. Recrystallization from methanol gives material melting at 79.5–80.5° in 90% recovery (Note 8).

2. Notes

1. Commercial cholesterol, m.p. 146–149°, is satisfactory if dried at reduced pressure at 100° for 48 hours. The cyclohexanone is simply distilled before use, b.p. 153–155°.
2. Directions for the preparation of aluminum isopropoxide are given by Young, Hartung, and Crossley.[2] This compound is also commercially available. Turbidity of the catalyst solution is to be expected and is not detrimental.
3. Toluene is dried satisfactorily by distilling about 20% of it and using the residue, which is cooled with protection from moisture.
4. Either Rochelle or Seignette salt is satisfactory. The tartrate ion serves to keep the aluminum ion in solution.

5. Prolonged heating is not necessary, since the chloroform remaining with the residual oil does not hamper the crystallization.
6. Seed crystals may be obtained by transferring a few drops of the solution to a small test tube, then cooling and scratching.
Ordinarily the cholestenone will separate as an oil from a solution saturated much above 50°. In this event, rather than working with larger volumes of methanol, small portions of chloroform may be added to the solution to lower the saturation temperature to a point at which seed crystals do not turn to oil. The best yield of good crystalline product is realized by inducing crystallization at the highest possible temperature in order to obtain a large initial crop of crystals. A second crop is difficult if not impossible to obtain by direct crystallization.
The towel should be placed around the flask only after crystallization, rather than oil formation, is assured. The towel is carefully removed occasionally during the first hour to ascertain whether oil is forming on top of the crystals. If so, the solution is warmed slightly in order to redissolve the oil but not the crystals. The product is quite impure if it first separates as an oil which later crystallizes.
7. If initial crystallization is not induced at 40° or above, a further period of cooling in an ice-salt bath is necessary to obtain the best yield.
8. In order to avoid large volumes, it is recommended that 700 ml. of methanol be employed to recrystallize 90 g. of cholestenone and that either chloroform or acetone be used to increase the solubility of the cholestenone to the required amount.

3. Discussion

The methods of preparation of Δ^4-cholesten-3-one have been summarized in an earlier volume.[3] In addition, it has been obtained by the deacetylation of 3-acetoxy-3,5-cholestadiene.[4] The present modification is less laborious than the earlier[3] method.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 195
- Org. Syn. Coll. Vol. 6, 293
- Org. Syn. Coll. Vol. 6, 762

References and Notes

1. University of California, Berkeley, California.
2. Young, Hartung, and Crossley, *J. Am. Chem. Soc.*, **58**, 100 (1936).
3. *Org. Syntheses Coll. Vol.* **3**, 207 (1955).
4. Dory, Geri, Szabó, and Oposzky, *Med. Prom. S.S.S.R.*, **13**, No. 10, 14 (1959) [*C. A.*, **54**, 12192 (1960)].

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

Δ^4-Cholesten-3-one

methanol (67-56-1)

chloroform (67-66-3)

Cyclohexanone (108-94-1)

acetone (67-64-1)

toluene (108-88-3)

aluminum isopropoxide

magnesium sulfate (7487-88-9)

Cholesterol (57-88-5)

Cholestenone

Cholest-4-en-3-one (601-57-0)

potassium-sodium tartrate

3-acetoxy-3,5-cholestadiene