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.

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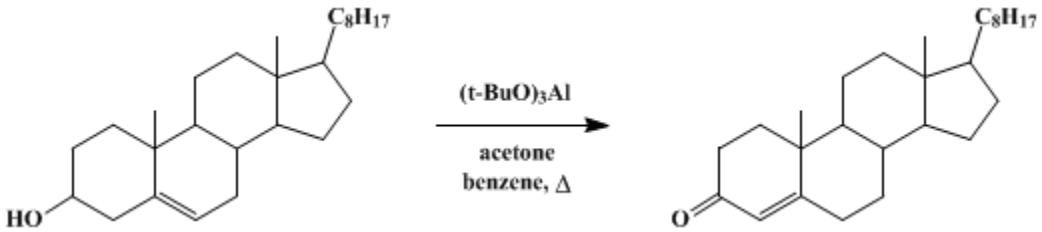
CHOLESTENONE



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1. Procedure

A carefully dried 5-l. round-bottomed flask equipped with a reflux condenser carrying a calcium chloride tube is charged with 100 g. of cholesterol (Note 1), 750 ml. of acetone (Note 2), and 1 l. of benzene (Note 3). A boiling tube is introduced to prevent bumping (Note 4), and the mixture is heated to boiling in an oil bath which is maintained at 75–85° during the reaction. A solution of 80 g. of aluminum *tert*-butoxide (p. 48) in 500 ml. of dry benzene is added in one portion to the boiling solution. The mixture turns cloudy and in 10–15 minutes develops a yellow color. Gentle boiling is continued at a bath temperature of 75–85° for a total of 8 hours. The mixture is then cooled, treated with 200 ml. of water and then 500 ml. of 10% sulfuric acid, shaken vigorously, and transferred to a 5-l. separatory funnel. The mixture is diluted with 1.5 l. of water and shaken for several minutes, after which the yellow aqueous layer is drawn off into a second separatory funnel and shaken out with a small amount of benzene (Note 5). The combined benzene extracts are washed thoroughly with water and dried by filtration through a layer of sodium sulfate; the solvent is evaporated, the last traces being removed by heating the residue at 60° at the water pump vacuum. The oily yellow residue solidifies when it is cooled in an ice-salt bath and scratched. For crystallization the material is dissolved in a mixture of 70 ml. of acetone and 100 ml. of methanol; the solution is allowed to cool very slowly and is seeded, for otherwise the product tends to separate as an oil. After the bulk of the material has crystallized, the mixture is allowed to stand for 1 day at 0°; the product is then collected, washed with 100 ml. of ice-cold methanol, and dried in vacuum at room temperature. The yield of almost colorless cholestenone, m.p. 77–79°, is 70–81 g. (70–81%). Recrystallization by the same method gives material melting at 78.5–80.5° with 90% recovery (Note 6) and (Note 7).

2. Notes

1. The material should be dried to constant weight at 80–100° in vacuum. Commercial cholesterol, m.p. 146–148.5°, gives satisfactory results; the yield is raised 5–10% by using cholesterol that has been purified by regeneration from the dibromide.
2. The acetone is distilled once from permanganate and twice from freshly fused potassium hydroxide.
3. The benzene is distilled over sodium.
4. If boiling stones are employed, fresh ones must be added at intervals; the boiling tube promotes smooth boiling at the bath temperature specified.
5. The troublesome emulsions sometimes encountered are easily broken by filtration from a trace of suspended solid.
6. For recovery of material in the mother liquors, the solutions are subjected to steam distillation to remove solvents and condensation products from the acetone. The process is continued until the distillate is odorless (1–2 hours), and the residual oil is dried by heating it under reduced pressure on the steam bath. From a solution in acetone-methanol (20 ml. and 50 ml., respectively) there is obtained after some manipulation (slow cooling, scratching) 3.3 g. of crude cholestenone, m.p. 72–80° (cloudy melt).
7. The yield is reduced by about 5% by halving the amounts of acetone and benzene specified and using only 50 g. of aluminum *tert*-butoxide.

3. Discussion

Cholestenone has been prepared by oxidation of cholesterol dibromide with chromic acid[1,2] or potassium permanganate[3] and subsequent debromination; by dehydrogenation of cholesterol over copper oxide;[4,5] and by the method described above.[6,7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 192
- Org. Syn. Coll. Vol. 4, 195

References and Notes

1. Windaus, *Ber.*, **39**, 518 (1906).
2. Bretschneider and Ajtai, *Monatsh.*, **74**, 57 (1943).
3. Schoenheimer, *J. Biol. Chem.*, **110**, 461 (1935).
4. Diels and Abderhalden, *Ber.*, **37**, 3099 (1904).
5. Diels, Gädke, and Körding, *Ann.*, **459**, 21 (1927).
6. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).
7. Brit. pat. 487,360 [*C. A.*, **33**, 323 (1939)].

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

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

potassium permanganate (7722-64-7)

sodium sulfate (7757-82-6)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

chromic acid (7738-94-5)

copper oxide (1317-38-0)

Cholesterol (57-88-5)

Cholestenone

acetone-methanol (590-90-9)

Cholesterol dibromide (1857-80-3)

ALUMINUM tert-BUTOXIDE