Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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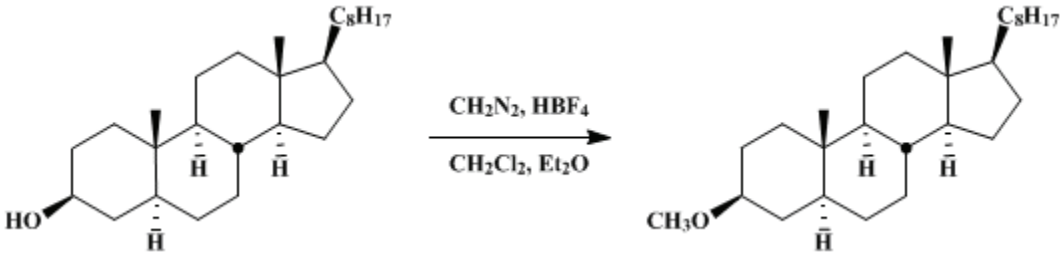
CHOLESTANYL METHYL ETHER

[Cholestane, 3β-methoxy-]



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1. Procedure

To a solution of 0.200 g. (0.515 mmole) of dry dihydrocholesterol (Note 1) in 10 ml. of methylene chloride contained in a 50-ml. Erlenmeyer flask is added 0.3 ml. of a catalyst stock solution containing 0.0016 ml. (0.018 mmole) of concentrated fluoboric acid (Note 2) in 3:1 anhydrous diethyl ether-methylene chloride (Note 3). The solution is swirled, and a 0.45*M* solution of diazomethane (Note 4) in dry methylene chloride is added from a buret (Note 5) at a rate of about 2 ml. per minute. The yellow color of diazomethane disappears rapidly on contact with the reaction mixture and nitrogen is vigorously evolved. When about 3 ml. of diazomethane solution has been added, the reaction becomes sluggish. The yellow color persists for several minutes after the total amount of 3.9 ml. of diazomethane solution (1.76 mmoles) has been added (Note 6). After 1 hour the reaction mixture is filtered to remove a small amount of amorphous polymethylene, which is washed with methylene chloride. The washings are combined with the methylene chloride solution, washed with 5 ml. of saturated aqueous sodium bicarbonate, with three 5-ml. portions of water, and dried over anhydrous sodium sulfate. The solvent is removed on a steam bath in a stream of nitrogen and finally at reduced pressure. The crystalline residue of 0.207 g. (Note 7) is recrystallized in a 10-ml. conical flask from 1 ml. of acetone. When the flask has cooled to room temperature, 0.5 ml. of methanol is added, and the flask is chilled to +2° for 2 hours. The crystals are collected on a tared Hirsch funnel of 40-mm. diameter, washed on the funnel with two 0.5-ml. portions of ice-cold methanol, and dried for 2 hours at 40°/2 mm. The first crop of cholestanyl methyl ether thus obtained forms large colorless glistening plates, m.p. 85.5–86° (Note 8). An additional 0.002 g. of pure methyl ether adheres to the flask and spatula and is collected by washing with acetone. The total first crop material (0.197 g.) represents a 95% yield of methyl ether (Note 9).

2. Notes

1. Satisfactory material of melting point 143–143.5° is prepared as already described,[3] and dried for 2 hours at 110°/2 mm.
2. Commercial 50% fluoboric acid is evaporated at 50–60°/5 mm. to afford a residue of about 11*N* total acidity, which is satisfactory for use as a catalyst.
3. The catalyst stock solution should be freshly prepared by placing 19 ml. of anhydrous diethyl ether in a 25-ml. volumetric flask cooled to 0° and adding 0.133 ml. of concentrated fluoboric acid (Note 2). The volume is made up to 25 ml. with methylene chloride.
4. Diazomethane solution in dry methylene chloride may be prepared from N-nitroso-N-methyl-N'-nitroguanidine by a procedure based on McKay's method.[4] [5] Methylene chloride is substituted for diethyl ether used in the original procedure. A satisfactory solution of diazomethane is obtained, without distilling, by separating the methylene chloride layer from the reaction mixture, drying it for 2 hours over potassium hydroxide pellets, and decanting through a funnel plugged loosely with cotton. The diazomethane solution is kept in a loosely stoppered test tube immersed in a Dewar flask containing Dry Ice during the drying period and prior to use. *All handling of the highly toxic diazomethane should be*

done in an efficiently exhausted hood. Attention is called to other precautions;[6] see also pp. 16–17.
Rigorous drying and exclusion of moisture are not necessary. The concentration of diazomethane solutions is determined by analysis,[6] using about 0.12 g. of benzoic acid per milliliter of solution and assuming a concentration of about 0.8*M* as in McKay's method.[5] Solutions approximately 0.45*M* are obtained by appropriate dilution.
5. Burets with ground-glass stopcocks should not be used, as leaking is caused by polymethylene formed preferentially on the ground surfaces. A buret such as "Ultramax F and P," having a stopcock of plastic material, is satisfactory. The buret should be filled immediately before commencement of the reaction to keep the diazomethane solution cool and thus to minimize polymerization. The technique used is very similar to that of a titration, and a number of methylations of prepared batches can be quickly performed with one filling of the buret.
6. Addition of a drop of catalyst stock solution after addition of diazomethane solution is complete causes rapid disappearance of the yellow color. The yield is not affected.
7. The crude reaction product is slightly yellow and has a very faint ammoniacal odor. It may be dissolved in acetone; on slow evaporation to dryness, the solution leaves large glistening transparent plates of good-quality cholestanyl methyl ether, m.p. 83–85°.
8. All melting points are corrected for stem exposure. Reported[7] melting point 83°.
9. The mother liquor may be evaporated to dryness and the slightly colored residue recrystallized in a 3-ml. conical flask from 6 drops of 1:1 acetone-methanol. The resulting large plates are easily transferred to a small Hirsch funnel and washed with 5 drops of methanol. This second crop of colorless methyl ether amounts to 0.010 g., m.p. 78.5–79.5°.

3. Discussion

Cholestanyl methyl ether has been prepared by catalytic hydrogenation of cholesteryl methyl ether[7,8] and of cholest-4-en-3-one in methanolic hydrobromic acid,[8] and by methylation of cholestanol with methyl iodide in the presence of "activated" silver oxide and sodium hydroxide.[9] The reported[10] formation of cholestanyl methyl ether from *epi*cholestanol in 96% yield by refluxing with "molecular" potassium in benzene and subsequent treatment with methyl iodide stands unconfirmed.[11] Methanolysis of *epi*cholestanyl tosylate afforded a 23% yield of cholestanyl methyl ether.[12] The procedure described here,[13] with slight changes in the molar proportions of the reactants, also gave a 98% yield of *epi*cholestanyl methyl ether from *epi*cholestanol, and a 95% yield of cholesteryl methyl ether from cholesterol.

4. Merits of Preparation

The present procedure is illustrative of the utility of the general method for preparation of methyl ethers from diazomethane and alcohols with fluoboric acid as catalyst.[13]

References and Notes

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

fluoboric acid

polymethylene

epicholestanol

epicholestanyl methyl ether

epicholestanyl tosylate

Benzene (71-43-2)

methanol (67-56-1)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

silver oxide (20667-12-3)

HYDROBROMIC ACID (10035-10-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

acetone (67-64-1)

potassium hydroxide pellets (1310-58-3)

potassium (7440-09-7)

Methyl iodide (74-88-4)

methylene chloride (75-09-2)

Dihydrocholesterol,
cholestanol (80-97-7)

Cholesterol (57-88-5)

Diazomethane (334-88-3)

acetone-methanol (590-90-9)

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

N-nitroso-N-methyl-N'-nitroguanidine (674-81-7)

Cholestanyl methyl ether (1981-90-4)

Cholestane, 3β-methoxy-

diethyl ether-methylene chloride

cholesteryl methyl ether