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.

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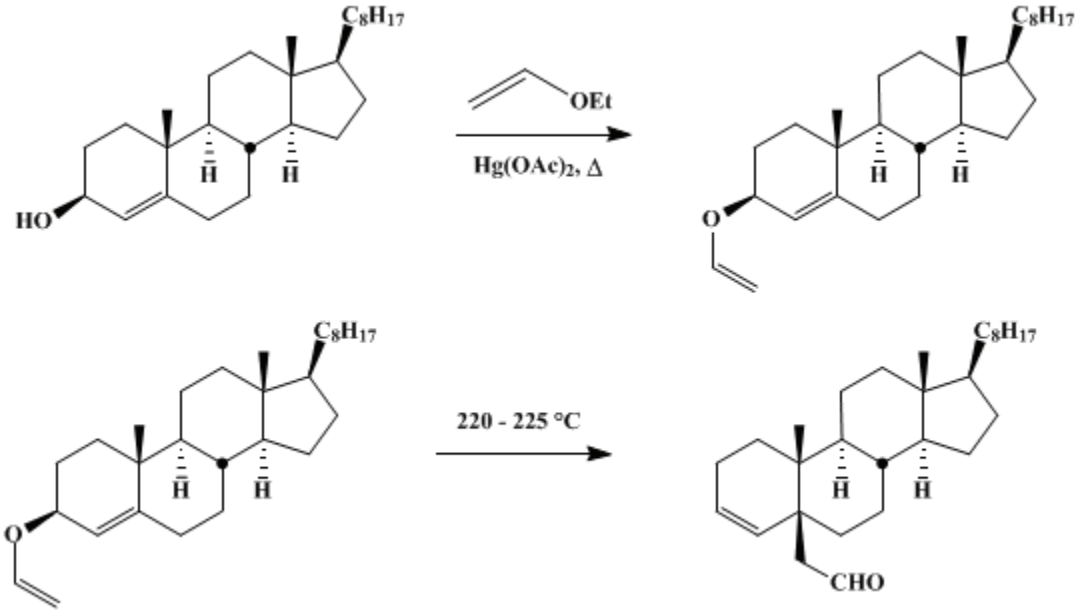
5β-CHOLEST-3-ENE-5-ACETALDEHYDE

[Cholest-3-ene-5-acetaldehyde, (5β)-]



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1. Procedure

A 50-ml., round-bottomed flask equipped with a magnetic stirring bar and a 20-ml. calibration mark (Note 1) is charged with 970 mg. (2.51 mmoles) of cholest-4-en-3β-ol (Note 2). Ethyl vinyl ether is distilled into the flask to the 20-ml. mark (Note 3). The mixture is stirred to effect solution before 820 mg. (2.55 mmoles) of mercury(II) acetate (Note 4) is added to the reaction mixture. The flask is fitted with a reflux condenser connected to a gas-inlet tube and flushed with argon. The reaction mixture is then stirred and heated (Note 5) at reflux under a positive argon pressure for 17 hours. After the solution has cooled to room temperature, 0.062 ml. (1.1 mmoles) of glacial acetic acid (Note 6) is added, and stirring is continued for 3 hours. The reaction mixture is poured into a preshaken mixture of 150 ml. of petroleum ether (Note 7) and 50 ml. of 5% aqueous potassium hydroxide. The aqueous phase is extracted with 50 ml. of petroleum ether, and the combined extracts are washed with three 50-ml. portions of a 20% aqueous sodium chloride, dried over anhydrous sodium carbonate, filtered and evaporated at reduced pressure (Note 8), giving 1.11 g. of an oil which, upon filtration through 5 g. of silica gel (Note 9) with 200 ml. of petroleum ether, affords 0.81 g. of the cholestenyl vinyl ether as a clear, colorless oil. If desired, crystallization of this oil from 10 ml. of acetone will give 0.74 g. (71%) of the vinyl ether as colorless prisms, m.p. 55–56.5° (Note 10).

Alternatively, the crude vinyl ether (0.81 g.) is transferred with petroleum ether into a 50-ml., round-bottomed flask fitted with a long gas-inlet tube. After the petroleum ether is removed at reduced pressure (Note 8), the flask is filled with argon and heated (Note 11) under a positive argon pressure at 220–225° for 5 hours; little or no bubbling should occur. After cooling, the oil is chromatographed on 75 g. of silica gel using 10% diethyl ether in petroleum ether as the elution solvent (Note 7), (Note 9), (Note 12). The first 175 ml. of eluant contains side products and is discarded; elution with another 175 ml. of the solvent gives 0.45–0.55 g. (50–53% overall yield from cholest-4-en-3β-ol) of 5β-cholest-3-ene-5-acetaldehyde as white prisms, m.p. 66.5–68° (Note 10).

2. Notes

1. This flask must be cleaned with hot chromic acid solution and then, along with *all* other glassware used in this preparation, soaked in a base solution, rinsed with distilled water, and over dried. Thermal rearrangement of the intermediate vinyl ether in a new (untreated) flask resulted in elimination.
2. Cholest-4-en-3β-ol can be prepared by the procedure of Burgstahler and Nordin.[2] A melting point below 130° indicates that the material is contaminated with some of the 3α-hydroxy isomer. The material used above melted at 130.5–131° (from ethanol).
3. Eastman practical grade ethyl vinyl ether was dried over anhydrous sodium carbonate, distilled (b.p. 36°) from sodium wire, and then redistilled from calcium hydride (b.p. 36°) into the reaction flask after a 5-ml. forerun is discarded.
4. Matheson, Coleman and Bell mercury(II) acetate was partially dissolved in hot absolute ethano containing 0.02% glacial acetic acid ((Note 6)) and filtered by suction. The filtrate was cooled, and the white plates of mercury(II) acetate were collected by suction filtration and stored under vacuum.
5. An oil bath at 50–55° was found to be satisfactory.
6. DuPont 99.7% acetic acid was used without purification.
7. Baker petroleum ether (b.p. 30–60°) was used.
8. The solvent was removed by rotary evaporation followed by vacuum (0.01 mm.) drying for 1 hour.
9. Merck silica gel (0.05–0.2 mm., 70–325 mesh ASTM) was used. The filtration column (1.4 × 7 cm.) is prepared in the same way as one used for chromatography, only one (200-ml.) fraction is collected. Use of alumina for the filtration gives variable results.
10. Burgstahler and Nordin report the melting point for the vinyl ether as 56–57°, and for the aldehyde, 66–69°.[2]
11. A Kügelrohr oven was used.
12. Mallinckrodt anhydrous ether was used. The chromatography column was 2.7 × 27 cm.

3. Discussion

The Claisen rearrangement[3] has been adapted in recent years to provide a viable synthetic sequence for the preparation of functional groups other than aldehydes and ketones. Ester[4] and amide[5] syntheses have been reported which proceed through the Claisen intermediate (**A**). The Claisen rearrangement has also been used to generate *trans*-trisubstituted double bonds stereoselectively,[4,6,7,8,9] angularly-functionalized derivatives,[10] substituted cyclohexenes,[11] acids,[12] and furans.[7]

R = —H, —Alkyl —Aryl —OR′, —NR_2', —$OSiR_3'$,

A

The procedure given above is an excellent example of the utilization of the Claisen rearrangement to generate an angularly functionalized steroid. The vinyl ether and aldehyde were originally prepared by Burgstahler and Nordin.[2] This procedure combines variations employed by Ireland and co-workers and, in addition, introduces the use of silica gel for the purification of the vinyl ether, thereby improving the reproducibility of the procedure.

References and Notes

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

petroleum ether

ethanol (64-17-5)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

mercury(II) acetate (1600-27-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

chromic acid (7738-94-5)

ethyl vinyl ether (109-92-2)

argon (7440-37-1)

calcium hydride (7789-78-8)

5β-Cholest-3-ene-5-acetaldehyde,
Cholest-3-ene-5-acetaldehyde, (5β)- (56101-55-4)

cholest-4-en-3β-ol

cholestenyl vinyl ether

vinyl ether (109-93-3)

ethano