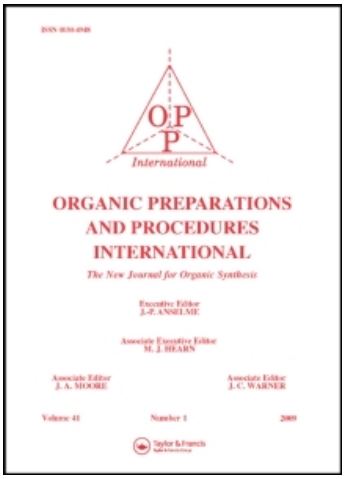

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A SIMPLIFIED, ONE STEP SYNTHESIS OF CHOLEST-5-EN-3-ONE

Edward J. Parish[a]; Sarawanee Chitrokorn[a]
[a] Department of Chemistry, Auburn University, Auburn, Alabama

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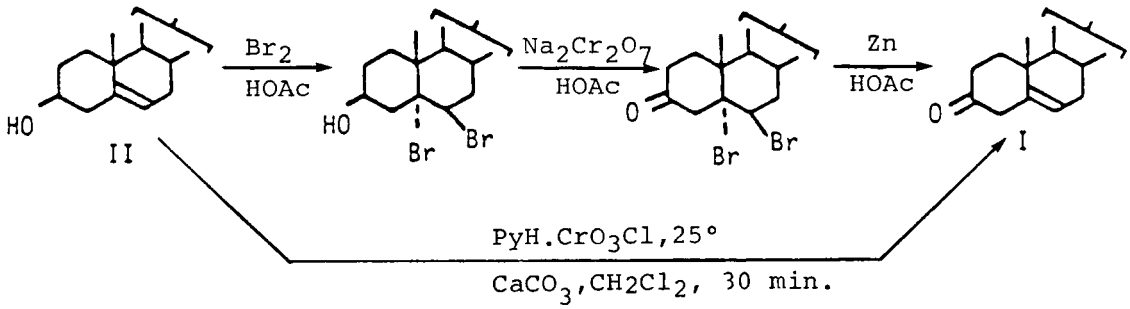
A SIMPLIFIED, ONE STEP SYNTHESIS OF CHOLEST-5-EN-3-ONE

Submitted by Edward J. Parish* and Sarawanee Chitrokorn
(05/23/83)
Department of Chemistry
Auburn University
Auburn University, Alabama 36849

Cholest-5-en-3-one(I) is a key intermediate in the preparation of a variety of steroids derived from cholesterol(II).[1] Also, Δ^5-steroidal olefins are among the most common naturally occurring steroids and the preservation of the Δ^5 double bond is an important synthetic consideration. Literature procedures for the preparation of I are inconvenient and require a multi-step synthesis.[2,3]



We now report a rapid and convenient one-step preparation of I utilizing commercial cholesterol(II) as a starting material. This synthesis employs the versatile oxidant pyridinium chlorochromate[10,11] (a slightly acidic reagent), buffered with anhydrous $CaCO_3$, for the described conversion. The $CaCO_3$ allows the reaction to proceed without significant isomerization of the Δ^5 double bond, both during the course of the reaction and subsequent aqueous work-up. The resulting reaction product

is purified by recrystallization to give an excellent yield of I.

EXPERIMENTAL

Melting points were determined with an Electrothermal capillary apparatus and are uncorrected. Infrared spectra (KBr pellet) were recorded by using a Perkin-Elmer Model 580 spectrometer. Proton NMR spectra ($CDCl_3$ solvent) were obtained with a Varian EM-390 spectrometer using Me_4Si as an internal standard. Proton chemical shifts for the C-18 and C-19 angular methyl resonances were calculated by the method of Zurcher.[6] Ultraviolet spectra (ethanol solution) were recorded with a Cary 17 spectrometer. Mass spectral analyses were conducted using a DuPont 491 mass spectrometer. Thin layer chromatography (TLC) was carried out on plates of silica gel G (Analtech, Newark, DE) using visualization of the components after spraying with molybdic acid.[7] Solvent systems for TLC analyses were: 10% ether in toluene; 10% ethyl acetate in toluene; 35% ethyl acetate in chloroform. Authentic I was prepared by the method of Fieser.[1] Commercial cholesterol(II) was obtained from Sigma Chemical Co. and was recrystallized three times from acetone-water. Pyridinium chlorochromate was obtained from Aldrich Chemical Co.

Cholest-5-en-3-one(I).- Anhydrous $CaCO_3$ powder (2.0 g, 19.98 mmole) was added to a solution of cholesterol (II, 1.85 g, 4.79 mmol) in CH_2Cl_2 (160 ml). Pyridinium chlorochromate (3.5 g, 16.24 mmole) was added and the mixture stirred for 30 min. under nitrogen at room temperature (25°C). A saturated NaCl solution was then added, and the mixture was thoroughly extracted with ether. The resulting extracts were filtered through anhyd. $MgSO_4$ and evaporated to dryness under reduced pressure to give a residue (TLC analysis indicated a product of approximately 98% purity; 10% ether-toluene) which was recrystallized from acetone-water to yield I (1.67 g, 91%): mp. 125-127°, lit.[2,3] 117-125°, 126-127°; IR ν_{max} identical with authentic sample (C=O, 1725 cm^{-1}); ^1H NMR: δ 0.73 (s, 3H, C-18-CH_3; calc. 0.73), 1.24 (s, 3H, C-19-CH_3; calc. 1.25), 5.37 (m, 1H, C-6-H); MS identical with authentic sample: 384(M;

100%), 369(m-CH_3; 28%), 271 (m-side chain; 19%), 229 (55%); UV absorption at 242 nm indicated product contained less than 1% of the conjugated ketone. TLC analysis in three solvent systems indicated a product of greater than 99% purity (identical mobility with authentic sample).

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