Simplified Preparation of 16-Dehydropregnenolone Acetate

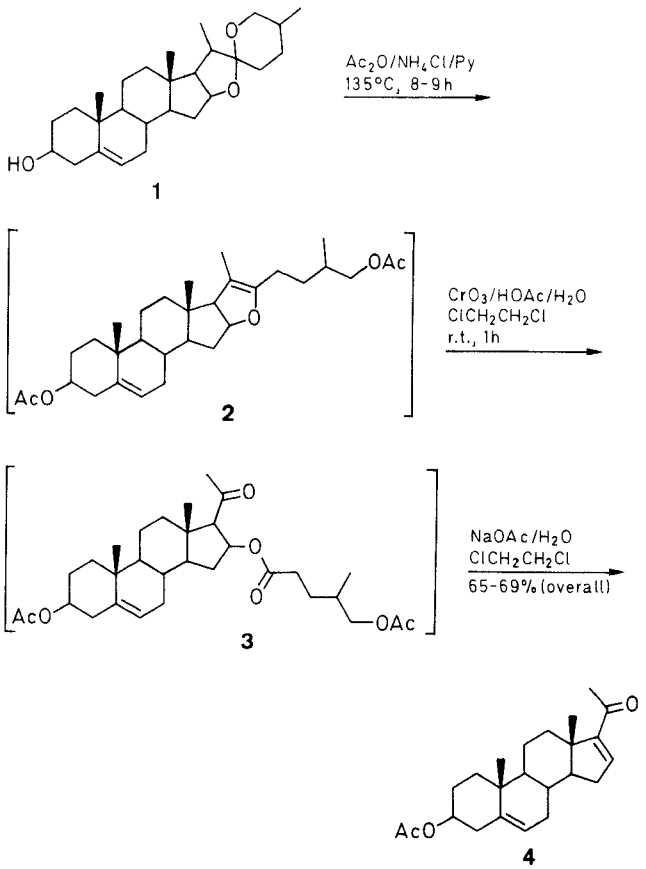
I. V. Mićović,*[a] M. D. Ivanović,[b] D. M. Piatak[c]

[a] Faculty of Chemistry, University of Belgrade, POB 550, 11001 Belgrade, Yugoslavia
[b] Institute of Organic Chemistry, Biochemistry and Instrumental Analysis, IHTM, Njegoševa 12, 11000 Belgrade, Yugoslavia
[c] Department of Chemsistry, Northern Illinois University, DeKalb, IL 60115, USA

A simplified, one-pot preparation of 16-dehydropregnenolone acetate (**4**) from diosgenin (**1**) using normal pressure and a much reduced temperature compared to known procedure was developed in an overall yield varied from 65 to 69%. The method lends itself very well to industrial scale methodology.

As the central intermediate in the synthesis of various steroid hormones, 16-dehydropregnenolone acetate (3β-acetyloxypregna-5,16-dien-20-one, **4**) is best prepared from the naturally, occuring diosgenin (**1**). This conversion was first achieved by Marker and co-workers,[1-3] who discovered that the spiroketal ring system could be opened with acetic anhydride under autoclave conditions. Oxidation of the resultant pseudodiosgenin (**2**), followed by hydrolysis of diozon (**3**) eventually afforded the desired 16-dehydropregnenolone (**4**). The key step in the synthesis involving acetolysis of diosgenin (**1**) to pseudodisogenin (**2**) can be performed uncatalysed under elevated pressure[1-4] or acid-catalyzed without pressure.[5-8] Among the catalysts examined were hydrochloric acid, *p*-toluenesulfonic acid, acetyl chloride, aluminum chloride, and octanoic acid. However, pyridine/acetyl chloride or pyridinium hydrochloride were found to be far superior.[7,8] Ammonium chloride was also tested but proved inferior to pyridine.[8]

We now wish to report that an equimolar combination of ammonium chloride/pyridine is a far more effective catalyst for this initial transformation step. First of all, the ring opening can be accomplished at 135 °C compared to the 200 °C and autoclave conditions first used.[1-3] Although pyridine/acetyl chloride or anhydrous pyridinium hydrochloride do not require elevated pressures, our reagent represents a less complex combination in terms of simplicity of use and expense. More significantly, the reagent does not interfere with the subsequent oxidation step on the same solution permitting use of a single flask for both reactions. Overall yields varied from 65.0 to 69.0% (Table) comparable to those obtained with other methods.



The structure of 16-dehydropregnenolone acetate (**4**) prepared was confirmed by mixed melting point determination and by comparison of its IR and ^{1}H-NMR spectral data with those of an authentic specimen.

Melting points were obtained with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter on 0.2 M $CHCl_3$ solutions. Reactions were monitored by TLC on silica gel HF_{254} (Stahl) using 9:1, 8.5:1.5, petroleum ether (bp 40–60 °C)/acetone (9:1, 8.5:1,5, 8:2) as eluents.

Table. Summary of 16-Dehydropregnenolone Acetate Preparation

Diosogenin (**1**) (in g)[a]	First Crop Recovered[b]				Second Crop			Third Crop		
	Amount (g)	Yield (%)	mp (°C)	$[\alpha]_D^{20}$	Amount (g)	Yield (%)	mp (°C)	Amount (g)	Yield (%)	mp (°C)
210.00	105.60	58.5	171	−40.7	11.3	6.3	169	6.89	3.82	164
210.00	102.80	56.9	173	−39.4	9.2	5.1	168	5.10	2.82	166
21.00	9.50	52.6	172	−40.3	1.45	8.0	168			
21.00	9.04	50.1	170	−39.3	1.50	8.3	169			
21.00	8.90	49.3	169	−41.2	1.42	7.9	168			
21.00	9.10	50.4	171	−38.3	1.56	8.6	168			
21.00	8.84	49.0	173	−37.7	1.35	7.5	168			
21.00	9.15	50.7	169	−40.2	1.40	7.8	169			

[a] Reactions at the 21.0 g level were performed with a 2:1 molar ratios of pyridine and NH_4Cl to diosgenin (**1**).
[b] $[\alpha]_D^{20}$ were measured in $CHCl_3$ ($c = 0.2$).

16-Dehydropregnenolone Acetate (4):
A mixture of pyridine (40 mL, 0.50 mol) and NH_4Cl (26.0 g, 0.50 mol) is added at once to a stirred suspension of diosgenin (**1**; 210.0 g, 0.50 mol). The mixture is heated to 125–135 °C and kept at that temperature until TLC indicates the reaction to be complete (usually 8–9 h). HOAc (400 mL), 1,2-dichloroethane (400 mL), and water (54 mL) are then added, and the mixture is cooled to 0 °C. A solution of CrO_3 (88.2 g, 0.882 mol) in water (124 mL) and HOAc (42 mL) precooled to 0 °C is added dropwise, while the temperature is kept at 7–10 °C. When 90% (200 mL) of the solution has been added, cooling is discontinued. After the remaining portion has been added, the mixture is stirred for 1 h at r.t. A solution of NaCl (100 g) in water (1.5 L) and MeOH (16 mL) is then introduced and the stirring is continued for an additional hour. The keto ester **3** is extracted with 1,2-dichloroethane (1 × 450 mL and 3 × 60 mL), and the combined extracts are washed with water (2 × 500 mL) to remove the residual chromium salts. Solid NaOAc · 3 H_2O (70 g, 0.51 mol) is added to the organic phase and the solvent is distilled off azeotropically to remove the water (4–6 h). The cooled residue is carefully treated with water (2 L) to produce a solid product, which is collected by filtration. The product is washed thoroughly with water until the filtrate is completely colorless. (To achieve complete removal of the residual chromium salts it may require a similar washing after 1 d). Crystallization from MeOH (400 mL) affords pure 16-dehydropregnenolone acetate (**4**); yield: 117.1–123.8 g (65.0–69.0%); mp 167–172 °C (Lit.[1–4] mp 172–175 °C); $[\alpha]_D^{20}$ – 37.7° to – 41.2° (c = 0.2, $CHCl_3$), [(Lit.[5] $[\alpha]_D^{20}$ – 39.5° (c = 1% in $CHCl_3$)]. (See Table for a summary of this and other data. Additional material may be secured by combining the mother liquors from several reactions).

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