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A New Route to 16-Methylene-17-ketosteroids

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A NEW ROUTE TO 16-METHYLENE-17-KETOSTEROIDS

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ABSTRACT: A new, high-yield preparation of 16-methylene-17-ketosteroids by the methylenation of trimethylsilyl enol ethers is described.

16-Methylene-17-ketosteroids are important targets and intermediates in the synthesis of modified steroids. They can be prepared by Mannich condensation of 17-ketosteroids followed by β-elimination of the 16-dialkylamino group[1,2] or via the 16-hydroxymethyl-17-ketone as demonstrated earlier[3]. In both methods a careful purification of the product is needed, possibly by column chromatography. In the present paper we report the

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preparation and methylenation of 17-silyl enol ethers to afford very pure 16-methylene-17-ketosteroids in excellent overall yields.

J.L. Gras described the direct α-methylenation of simple cyclic ketones by a suitable choice of special Mannich reagents (s-trioxane and N-methylanilinium trifluoroacetate)[4]. Other highly reactive Mannich reagents are also known. In connection with the possible Mannich intermediate aminomethyl carbonium ion[5], modified Mannich reactions were developed in which various immonium salts (preformed Mannich salts) are used[6]. α-Methylene ketones can be obtained from these Mannich bases only via pyrolysis or after quaternization. In the steroidal series A. Ahond and coworkers prepared Mannich bases among others from 17-ketones with N,N-dimethylmethyleneammonium trifluoroacetate[7]. S.J. deSolms performed the α-methylenation of simple benzyl aryl ketones in a mixture of N,N,N',N'-tetramethyldiaminomethane (TMDM) and acetic anhydride[8]. The reagent in this case too is probably the in situ formed immonium salt.

We have studied the possibilities of methylenation of 17-ketosteroids on the basis of the above experience. We chose estrone methyl ether (1a), dehydroepiandrosterone acetate (1b) and epiandrosterone (1c) as model compounds. The steroidal 17-ketones of low reactivity failed to react with s-trioxane and N-methylanilinium trifluoroacetate. Using TMDM and Ac_2O as reagents in an aprotic solvent, we could transform the present

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17-ketosteroids directly only under quite drastic conditions. The desired α-methylene compounds were obtained in moderate yield with a tenfold excess of reagent in dioxane after refluxing for 4 hours. We then prepared the silyl enol ethers from these steroidal ketones in order to transpolarize the C-16 position so that it could be substituted by electrophiles.

17-Ketosteroids cannot be efficiently converted into the corresponding trimethylsilyl enol ethers by the classical House method (chlorotrimethylsilane-triethylamine-dimethylformamide)[9]; therefore, instead of chlorotrimethylsilane we used the more reactive bromotrimethylsilane, generated in situ by the Iqbal procedure (NaBr-chlorotrimethylsilane)[10]. By modifying the reaction conditions (higher concentration and excess of reagent, slightly elevated temperature), we isolated the silyl enol ethers in nearly quantitative yields. The products were sufficiently pure for the next reaction step. Preparation via the lithium enolate (lithium diisopropylamide, chlorotrimethylsilane) afforded a slightly poorer yield.

Finally, when 17-silyloxy-3-methoxy-1,3,5(10),16-estratetraene (2a), 17-silyloxy-3β-acetoxy-5,16-androstadiene (2b) and 3β,17-disilyloxy-5α-androst-16-ene (2c) were stirred at room temperature with a fivefold excess of TMDM and Ac_2O in dioxane or tetrahydrofuran, the corresponding 16-methylene-17-ketosteroids were obtained in very high yields and high purity. The TMDM/Ac_2O reagent has not previously been applied for the alkenylation of silyl enol ethers.

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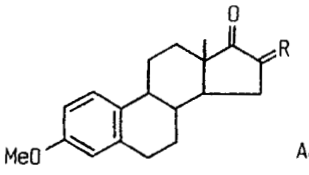

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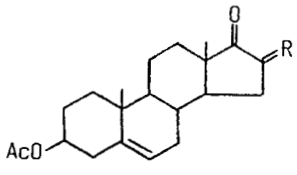
3: R=CH_2 3a



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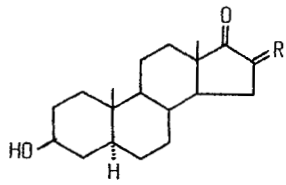

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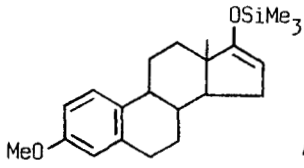

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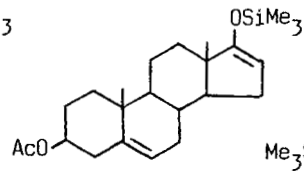

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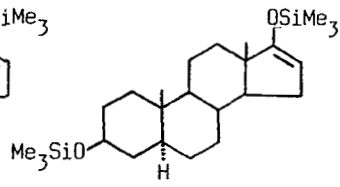

2c

Table: 17-Silyl enol ethers and 16-methylene-17-ketones

cpd	yield % (crude)	m.p. °C (recryst.)	$[\alpha]_D$ ($CHCl_3$, c=1)	^{1}H-NMR ($CDCl_3$) δ (ppm)
2a	94	84-85	+96	0.21(s, 9H), 0.85(s, 3H) 3.78(s, 3H), 4.52(m, 1H) 6.64-7.26(m, 3H)
2b	97	138-139	-42	0.20(s, 9H), 0.85(s, 3H) 1.05(s, 3H), 2,04(s, 3H) 4,49(m, 1H), 4,60(m, 1H) 5.39(m, 1H)
2c	92	147-149	+38	0.11(s, 9H), 0.19(s, 9H) 0.81(s, 3H), 0.82(s, 3H) 3.54(m, 1H), 4.47(m, 1H)
3a	95	124-125	+121	0.93(s, 3H), 3.78(s, 3H) 5.41(m, 1H), 6.10(m, 1H) 6.64-7.26(m, 3H)
3b	95	159-161	-57	0.92(s, 3H), 1.06(s, 3H) 2.04(s, 3H), 4.60(m, 1H) 5.38(m, 1H), 5.41(m, 1H) 6.07(m, 1H)
3c	92	158-160	+40	0.85(s, 3H), 0.89(s, 3H) 3.60(m, 1H), 5.36(m, 1H) 6.05(m, 1H)

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Tentatively, we also examined the following reactions: the transformation of these silyl enol ethers in the classical Mannich reaction and with N-methylanilinium trifluoroacetate and s-trioxane. In the first case we observed the desired α-methylene product only in low yield, and in the latter reaction only the cleavage of the silyl enol ether bonding was detected.

In conclusion, the method is suitable for the synthesis of 16-methylene-17-ketosteroids under mild conditions in higher yields than provided by the known procedures. Note may be made of the high purity of the products, which makes further purification, e.g. by column chromatography unnecessary.

EXPERIMENTAL

Melting points (Kofler block) are uncorrected. Thin-layer chromatograms: Kieselgel G layers (Merck 5554). The specific rotations were measured with a Polamat-A polarimeter, the concentration being c=1 in chloroform. The ^{1}H-NMR spectra were obtained in $CDCl_3$ solution with a Bruker Spectrospin AC-200 FT NMR instrument (200 MHz); chemical shifts are given in δ values, with TMS as internal standard.

GENERAL PROCEDURES

A. Preparation of trimethylsilyl enol ethers from 17-ketones

A stirred solution of 3.5 equiv. of anhydrous NaBr in dry dimethylformamide (ca 0.1 mol/130 ml) was treated dropwise with 3.5 equiv. of chlorotrimethylsilane. The mixture was stirred for

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0.5 h at room temperature under N_2. Crystalline 1 (1 equiv.) and 3.5 equiv. of dry triethylamine were added and the mixture was stirred at 60-70°C under N_2 for 5 h. The yellow suspension obtained was then poured into cold saturated aqueous $NaHCO_3$ solution. The precipitate was filtered off, washed with water, dried and dissolved in diethyl ether, and the solution was filtered through a silica gel pad (ca 3 g/1 g steroid, 230-400 mesh). The solution was evaporated and the solid crystalline residue was converted without further purification. (In the case of compound 1c, 5 equiv. each of NaBr, TMSCl and Et_3N were used and silylation of the 3β-OH group also took place.)

B. Preparation of 16-methylene-17-ketones from silyl enol ethers

To a stirred solution of crude 2 in dry 1,4-dioxane or tetrahydrofuran (1 mmol/2 ml), 5 equiv. of N,N,N',N'-tetramethyldiaminomethane[11] and then 7.5 equiv. of acetic anhydride were added dropwise at 0°C. The solution was stirred at room temperature for 3 days and next poured into ice/water to precipitate the semicrystalline pure product. (In the case of compound 2c, the 3β-trimethylsilyloxy group was finally hydrolyzed in situ with methanolic potassium carbonate for 2 h to afford 3c.)

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