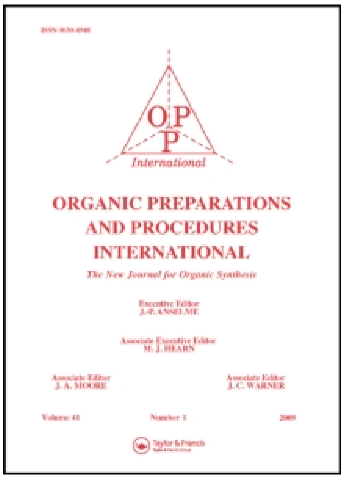

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THE PREPARATION OF Δ² STEROIDS. AN IMPROVED PROCEDURE

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THE PREPARATION OF Δ^2 STEROIDS. AN IMPROVED PROCEDURE

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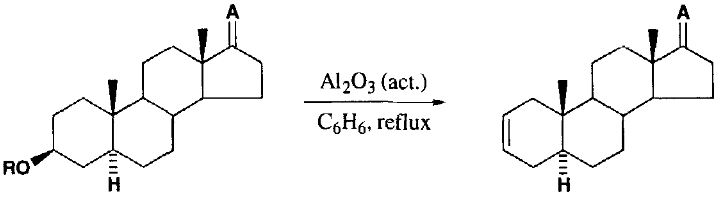
The conversion of steroidal alcohols into olefins is important in steroid synthesis. The simple and straightforward preparation of unsaturated Δ^2-steroids appears to be the acid-catalyzed elimination of water from the readily available 3β-alcohols. Solid-supported acids have been described as effective catalysts in the dehydration of olefins.[1] However, the reaction of **1c** with $CuSO_4$ supported on SiO_2[2] gave a low yield of **2a**. Similarly, the reaction of **1c** with *p*-TsOH supported on SiO_2 carried out in boiling benzene[3] gave **2a** with the yield varying from 6-54%, depending on the catalyst preparation and the reaction time. In the course of the transformation of steroid tosylates and mesylates adsorbed on alumina, elimination was found as a competitive process to epimerization and hydrolysis.[4] The highest yield (70%) of the olefin **2a** was reported[4] for the reaction in which the tosylate **1c** was adsorbed on the column of alumina (ratio 100:1) for 18 hrs.



1

a) R = Tos, A = H, β-C_8H_{17}
b) R = Tos, A = O
c) R = H, A = H, β-C_8H_{17}

2

a) A = H, β-C_8H_{17}
b) A = O

We now report a modified procedure in which 5α-cholest-2-ene **2a** is prepared from 5α-cholestan-3β-ol tosylate **1a** in yield greater than 80%. The procedure is efficient, simple, cheaper than the original one and requires short reaction time. The results are summarized in the Table.

TABLE. Reaction of 5α-Cholestan-3β-ol tosylate **1a** on Al_2O_3

Method	Al_2O_3	Ratio Al_2O_3 to substrate	Solvent	Temp. (°C)	Time (hr)	Yield (%)
B	unact.	100:1	hexane	r.t.	48	42
B	unact.	100:1	PhH	r.t.	48	59
B	act.	30:1	PhH	r.t.	24	69
A	act.	100:1	PhH	r.t.	24	73
C	unact.	10:1	PhH	reflux	3.5	59
C	act.	10:1	PhH	reflux	2	83
C	act.	4:1	PhH	reflux	2	43

The best yield of **2a** is obtained when the tosylate **1a** is adsorbed from benzene solution on activated alumina in 10:1 ratio and the mixture is refluxed for 2 hrs. The ^{1}H NMR spectrum of the crude reaction product was consistent with the presence of Δ^2 olefin exclusively; no other product, such as Δ^3 olefin, was detected. The yield of **2a** was the same on milligram as well as on several gram scale. Under similar reaction conditions (Al_2O_3/substrate 10:1, benzene, 4 hr reflux), 3β-tosyloxy-5α-androstan-17-one[5] is transformed to 5α-androst-2-en-17-one (**2b**)[6] in 84% yield. The elimination reaction was further examined by using tosylates of Δ^5 unsaturated sterols as substrates. In these cases the pure 3,5-dienes were formed, albeit the yield of the product extracted from alumina (Al_2O_3/substrate 5:1, r. time 1 hr) dropped to 60-70%. For example, β-sitosteryl tosylate[7] afforded the stigmasta-3,5-diene[8] in 66% yield, while cholesteryl tosylate[9] gave cholesta-3,5-diene[10] in 60% yield. When A/B *cis* steroid, methyl 3α-tosyloxycholan-24-oate[11] was treated under similar conditions (method C, r. time 0.5 hr), the olefinic product was formed in only 40% yield (as a mixture of Δ^2 and Δ^3 olefin[12] in the ratio 2:3, as estimated from ^{1}H-NMR spectrum of the olefinic fraction) along with 3α-alcohol (26%). 17β-Tosyloxyandrost-4-en-3-one[13] gave (method C, 20 hrs) a mixture of olefins (53%) consisting of the expected androsta-4,16-dien-3-one[13,14] and two 18-methyl migrated olefins (^{1}H NMR evidence).

In conclusion, efficient and regioselective elimination occurs in the case of 3β-tosyloxy-5α-steroids.

EXPERIMENTAL SECTION

All products were analysed by ^{1}H-NMR [Varian Gemini 300 VT (300 MHz) and Tesla BS-587A (80 MHz)], UV (in the case of dienes; Shimadzu UV-160) and TLC (Merck No 5554) for purity and they were compared with authentic samples

Activation of Alumina. - Aluminum oxide (Woelm, neutral) was heated in the oven at 500° for 5 hrs and stored in desiccator over P_2O_5.

Elimination Procedures. Method A. The substrate was adsorbed on the column of alumina from the solvent and left for a specified period of time and then the product was eluted with the same solvent.

Method B. A solution of the substrate in the solvent was poured into a round bottomed flask containing alumina and the solvent was removed under reduced pressure. The mixture was left for 24 hrs and the product was isolated by washing the adsorbent with the solvent.

Method C. The substrate dissolved in small amount of the solvent was added to a mixture of benzene and alumina at reflux. The stirred mixture was then refluxed for further 2-4 hrs; the alumina was filtered off, washed with solvent and the combined extracts were evaporated to give the pure olefin.

Preparation of Olefins. Typical Procedure (Method C). - To a mixture of activated Woelm alumina (100 g) and sodium dried benzene (300 mL) heated under reflux , was added dropwise a solution of the tosylate **1a** (10.1 g) in benzene (20 mL) and the resulting mixture is refluxed for further 2 hrs. The alumina is filtered off, washed with small portion of benzene and the combined filtrates are evaporated to give chromatographically pure olefin **2a** (5.804 g, 83% yield), mp. 68-69.5°, lit.[15] mp.

69-70°. Its ^{1}H-NMR spectrum[16] was identical with that of an authentic sample.

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