Generation and Reaction of 2,4-Dienolate Ions from Δ^4-3-Keto-steroids with Lithium Hexamethyldisilazane

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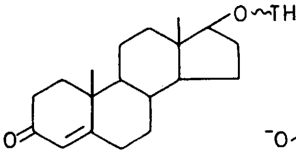
Summary Reaction of Δ^4-3-keto-steroids with lithium hexamethyldisilazane yields 2,4-dienolate ions which can be methylated at C-2 or trapped as 2,4-dienolsilyl ethers.

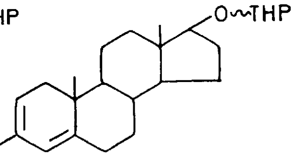
PROLONGED reaction of Δ^4-3-keto-steroids with potassium t-butoxide in t-butyl alcohol and methyl iodide yields, through alkylation of the thermodynamically more stable 3,5-enolate anion, 4,4-dimethyl-Δ^5-3-keto-steroids.[1] We report on the rapid transformation of the Δ^4-3-keto-system of testosterone 17-tetrahydropyranyl ether (**1**) to the kinetically controlled $\Delta^{2,4}$-homoannular dienolate ion (**3**) with lithium hexamethyldisilazane[2] (**2**) in tetrahydrofuran solution. The ion (**3**) is an important synthetic intermediate for effecting steroid transformations.

Reaction of (**3**) with t-butyldimethylchlorosilane[3] and subsequent aqueous work-up of an ether–tetrahydrofuran solution gave, in over 90% yield (u.v.), the hitherto unknown ring A homoannular 2,4-dienol silyl ether (**4**). Analytically pure material was obtained by crystallization from acetone, m.p. 124—128°; λ_{max} (ether) 278 nm (ϵ 3800); λ_{max} (Nujol) 6·0 [$C{=}C(OSiMe_2Bu^t){-}C{=}C$], 8·0, and 11·8 μm (Si–C); τ ($CDCl_3$) 4·73 (4-H), 5·4 (2-H), 9·03 (19-Me), 9·10 (9H, O–Si–CMe_3), 9·23 (18-Me), 9·9 (6H, $OSiMe_2$). Crystalline (**4**) can be stored in the cold under an inert atmosphere for extended periods. Mild acidic or basic conditions readily regenerate the parent 3-keto-Δ^4-system. In contrast, acid-catalysed enol ether formation from Δ^4-3-keto-steroids yields the thermodynamically more stable 3,5-enol ether.[4]

Alkylation of (**3**) with methyl iodide in hexamethylphosphoric triamide afforded a 80% conversion (n.m.r., t.l.c.) into a mixture of the 2α- and 2β-methylated epimers. Sodium methoxide catalysed equilibration to the stable 2α-epimer, acid-catalysed removal of the C-17-tetrahydropyranyl (THP) ether, and crystallization from acetone–hexane yields directly 2α-methyltestosterone (**5**), m.p. 155—

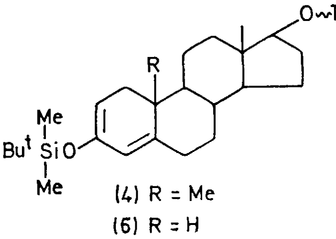


(1)

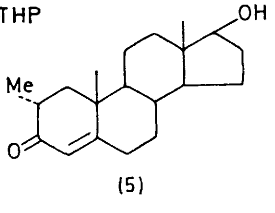


(3)

$LiN(SiMe_3)_2$
(2)



(4) R = Me
(6) R = H



(5)

157° (lit. 155—157°), which has been previously prepared in a multistep sequence by methylation of the 2-ethoxyoxalate derivatives of testosterone.[5]

In a similar manner, 19-nortestosterone 17-tetrahydropyranyl ether and (**2**) produced the kinetically controlled 2,4-dienolate ion, which was trapped by silylation with t-butyldimethylchlorosilane to give the 2,4-silylenol ether (**6**). The appearance of 2 vinyl protons *at* τ 4·6 *and* 5·35 in the n.m.r. spectrum rules out the alternative linearly conjugated homoannular 3,5(10)-dienol silyl ether.

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