Specific A Ring Functionalization of Cholestanol by a Metal–Oxygen Complex

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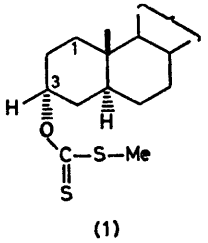
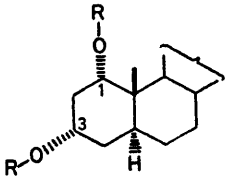
Summary Cholestane-1α,3α-diyl diacetate is obtained in good yield by a one-step regio- and stereo-specific functionalization of *O*-cholestan-3α-yl *S*-methyl dithiocarbonate; this reaction involves activation of the 1α CH bond by a transient iron–oxygen complex.

METAL complex-induced C–H bond activation, a key-step for hydrocarbon functionalization, is of fundamental and commercial importance.[1,2] In order to mimic hydroxylase models and to overcome the difficulty of bringing the C–H bond to be activated in close proximity to the active site our approach was based on the strategy of the Barton reaction[3] and the template effect.[4] It seemed plausible that an active organometallic oxygenated intermediate generated at C-3 on the α side of a steroid would interact specifically with the axial C–H bonds of the A ring. For this purpose we have chosen the electron-rich *S*-alkyl xanthates, which have been shown to complex readily with metal carbonyls,[5,6] for their capability to co-ordinate transition-metals cations known to give rise to dioxygen complexes leading to peroxide species.[7]



(1)



(2) R = Ac
(3) R = H

In a typical experiment a solution of cholestan-3α-yl xanthate (**1**) (1 mmol) and $Fe(ClO_4)_2$ (1 mmol) in acetic acid was heated at 120 °C for 1 h with oxygen bubbling. After work-up and chromatographic separation on silica plates cholestane-1α,3α-diyl diacetate (**2**) was obtained as the more polar fraction (34% yield), m.p. 129—130 °C, α_D + 55° (lit.[8] m.p. 105 °C; α_D + 54°). The structure of (**2**) was confirmed by ^1H n.m.r. spectroscopy (2 OAc s at δ 2·06 and 2·03 and *eq.* β-1-H and β-3-H m at δ 4·88, with $W_{\frac{1}{2}}$ 7 Hz[9]) and by $LiAlH_4$ reduction which afforded the diol (**3**) m.p. 210—212 °C, α_D + 29° (lit.[8] m.p. 210 °C, α_D + 25°). In addition to the diacetate (**2**), cholestenes (mixture of Δ^2 and Δ^3) and cholestan-3-yl acetate (α and β in *ca.* 1 : 1 ratio) were also obtained. Addition to the mixture of 10^{-3} mol of Fe^{III} reduced the amount of olefins and increased the yield of the diacetate (**2**) to 45%; in contrast, addition of hydroquinone gave a lower amount of (**2**) (5%). When oxygen was rigorously excluded no diacetate was obtained, the xanthate (**1**) giving a mixture of cholestenes almost entirely. In the absence of Fe^{II}, the xanthate (**1**) was recovered unchanged after several hours in refluxing acetic acid under oxygen.

These results are in agreement with complexation of the metal cation on the soft sulphur ligand and show that functionalization at C-1 is carried out by an iron–oxygen intermediate. The metal-complexed xanthate also behaves as a leaving group, this competitive reaction being responsible for the observed elimination and substitution at C-3.

Other Group 8 transition metals have been tried without success for functionalization of C-1. Surprisingly, no 3,5-diacetate was detected; similar results have been reported with simple alkanes which show a poor reactivity of tertiary CH bonds.[10] Thus, our system seems to behave differently from others in giving a strongly polarized

peroxide form leading preferentially to hydroxylation of tertiary CH bonds.[11] However, analogy can be made with the mode of action of cytochrome P_{450},[12] the xanthate group acting as an electron donor. Activation of the C–H bond can occur in a concerted way *via* an oxygen transfer followed by acetylation. In that case the rate-controlling step may not involve C–H bond rupture but, instead, formation of a complex between the C–H bond and iron as proposed by Tanaka.[13] There are, of course, plausible alternatives such as the intervention of an oxenoid complex;[14] the mechanism will be discussed in more detail elsewhere.

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