Methoxylation of Enolizable Steroidal 4-Ene-3-ones using Hypervalent Iodine

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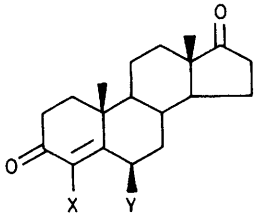
Reaction of androst-4-ene-3,17-dione (**1**) with *o*-iodosylbenzoic acid in methanolic potassium hydroxide gave the methoxylated products, the 4- and 6β-methoxides (**2**) and (**3**), along with the dehydrogenated compound, the 4,6-dienone (**4**).

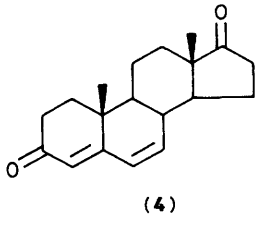
In recent years, it has been reported that hypervalent iodines, iodosylbenzene and *o*-iodosylbenzoic acid, are useful reagents for the conversion of enolizable ketones into α-hydroxydimethylacetals.[1] More recently, α,β-unsaturated ketones, which cannot form anions by α-hydrogen abstraction, have been shown to react with hypervalent iodine, giving the α-hydroxy-β-methoxydimethylacetal derivatives.[2]

We now report on the *o*-iodosylbenzoic acid–MeOH–KOH reaction applied to an enolizable steroidal α,β-unsaturated ketone, androst-4-ene-3,17-dione (**1**).

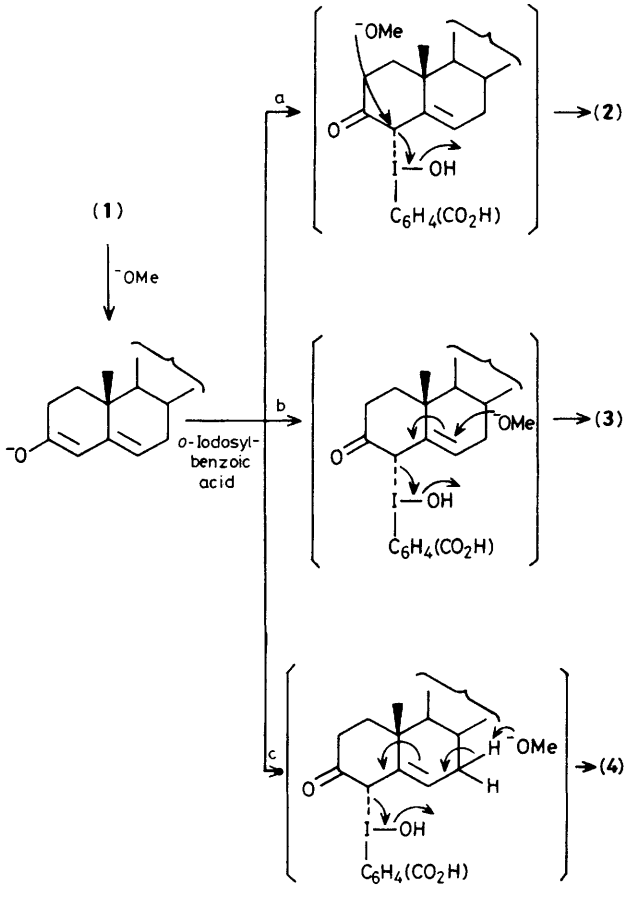
Treatment of the steroid (**1**) with 1.2 equiv. of *o*-iodosylbenzoic acid and 3.3 equiv. of KOH in dry MeOH (70 °C, 1 h, N_2 atmosphere) afforded a mixture of the 4-methoxide (**2**), the 6β-methoxide (**3**), and the dehydrogenated product, 4,6-dienone (**4**). Silica gel column chromatography of the crude product gave a 25% yield of (**2**) [m.p. 135—136 °C (lit.,[3] m.p. 136—138 °C); ^{1}H n.m.r. ($CDCl_3$) δ 0.93 (s, 18-Me), 1.22 (s, 19-Me), 3.60 (s, 4-OMe); $\nu_{max.}$ (KBr) 1740, 1675 cm^{-1}], a 33% yield of (**3**) [m.p. 161—162 °C (lit.,[4] m.p. 164—166 °C); ^{1}H n.m.r. ($CDCl_3$) δ 0.93 (s, 18-Me), 1.32 (s, 19-Me), 3.21 (s, 6β-OMe), 3.72 (m, 6α-H), 5.80 (br s, 4-H); $\nu_{max.}$ (KBr) 1740, 1680 cm^{-1}], and a 20% yield of (**4**) [m.p. 171—172 °C (lit.,[5]



(**1**) X = Y = H
(**2**) X = OMe, Y = H
(**3**) X = H, Y = OMe



(**4**)



Scheme 1

m.p. 170—172 °C); ^{1}H n.m.r. ($CDCl_3$) δ 0.98 (s, 18-Me), 1.16 (s, 19-Me), 5.73 (br s, 4-H), and 6.22 (br s, 6- and 7-H); $\nu_{max.}$ (KBr) 1740, 1660 cm^{-1}]. When the reaction was carried out at room temperature (36 h), similar results were obtained. These products were not isolated in the reaction without KOH and/or the iodosyl compound, but the starting material was quantitatively recovered.

Previous results from the PhIO-dependent alkene epoxidation[6] and the conversion of the 4,5-epoxide of (**1**) into (**2**) on treatment with methanolic sodium hydroxide[3] suggested that (**2**) might be produced *via* the epoxide in this study. However, when the epoxide was subjected to the above reaction with or without the iodosyl compound, (**2**) was not produced. Moreover, similar treatment of the dienone (**4**) gave neither (**2**) nor (**3**). The reaction thus probably proceeds *via* the kinetically-preferred 2,4-dienolate which is allowed to equilibrate in favour of the stable 3,5-isomer[7] owing to the low reactivity of the iodosyl compound (Scheme 1); subsequent electrophilic addition to the C-4 position of the 3,5-isomers through the less hindered α-face gives an adduct. Finally, addition of MeO^- at the C-4 and C-6 positions yields (**2**) with elimination of *o*-iodobenzoic acid followed by isomerization (path a) and (**3**) (path b), respectively. The β-face addition of MeO^- in path b is predicted in view of the steric hindrance of the *o*-iodosylbenzoic acid substituent at C-4α which is bulkier than the C-19 angular methyl. Deprotonation at C-7 with the elimination of the iodo compound affords (**4**) (path c).

The above reaction represents a striking way of functionalizing the C-4 and C-6 positions without affecting the C-17 carbonyl function. The methoxide (**2**) is an obvious precursor for the synthesis of 4-hydroxyandrost-4-ene-3,17-dione, a potent inhibitor of the estrogen synthetase.[3,8]

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