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Functionalisations of estrone benzyl ether at the 11 and 12 positions

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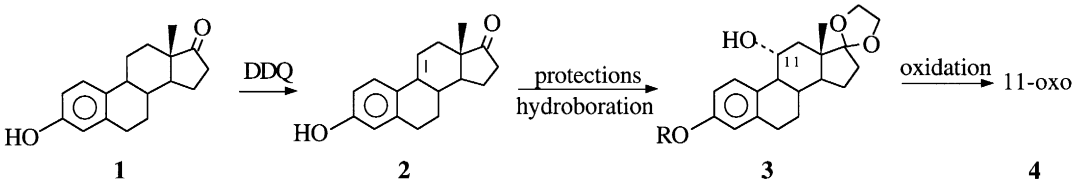
Abstract

The prior protection of estrone as estrone benzyl ether (EBE) facilitated the 9,11 dehydrogenation by DDQ, which is a key step for the 11 functionalisation. The oxidation of estrone benzyl ether by an excess of DDQ in dioxane containing a small amount of methanol allowed for an unusual 12 functionalisation with a methoxy group.

The estradiol derivatives substituted at the 11β position may present an interesting biological potential.[1,2] A protected 11-oxoestrone may be a key compound for the preparation of such estradiols, and a common way to obtain this estrone is described below (Scheme 1).



1 **2** **3** **4**

Scheme 1.

The first step of the synthesis is an oxidation of estrone **1** by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). This reaction requires a large volume of solvent (150 to 270 ml of methanol per g of estrone) and, usually, a tedious work-up.[3–7] The same oxidation reaction has been described in the case of estrone methyl ether[8] but a methoxy group is not that easy to cleave. Curiously, the oxidation of estrone benzyl ether (EBE), which presents a labile protecting group,[9] has never been described. We found that the oxidation of EBE became regioselective in a mixture of dioxane and methanol (17 ml of solvent per g of EBE) and the work-up was made very easy. Moreover, the oxidation of EBE with an excess of DDQ in dioxane containing 5 to 20% of methanol allowed for the further functionalisation at the 12 position by an oxidative nucleophilic substitution.

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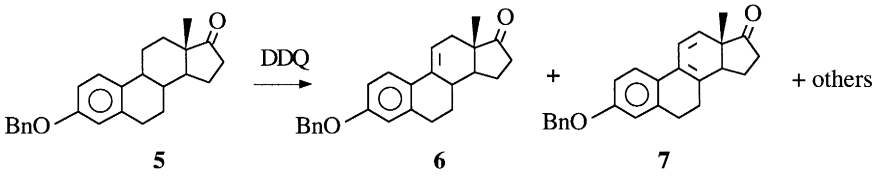
EBE **5** was oxidised by 1 to 1.5 equivalents of DDQ, at room temperature in various solvents (Scheme 2).



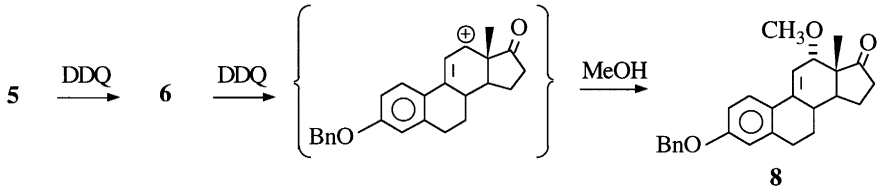
Scheme 2.

Mixtures of unreacted EBE, 9,11-dehydrocompound **6** and diene **7** (formed by further oxidation of **6**[10]) were obtained in aprotic solvents like dioxane, THF or acetonitrile for reaction times of 3 to 5 h. These solvents were, therefore, inadequate for the preparation of **6**. The oxidation in methanol occurred more slowly (the reaction was still not achieved after 3 days) and without formation of the diene. A mixture of dioxane and methanol (1:1, v:v) was used to obtain the regiospecific formation of **6**:

1.88 g DDQ (1.5 equiv.) was added to a solution of 2 g EBE in 32 ml of a dioxane:methanol mixture (1:1) and the medium stirred for 20 h at room temperature. The solvents were then evaporated and dichloromethane added. The resulting suspension was filtered on neutral alumina (10 g) and washed with dichloromethane. The crude product obtained after evaporation of the solvent was crystallised in ether to give 1.2 g of a pink solid (m.p.=135°C), with a 60% yield. ^{1}H NMR (ppm) in $CDCl_3$: 7.55 (d, J_{12}=8.7 Hz, H-1), 6.81 (dd, J_{24}=2.7 Hz, H-2), 6.72 (d, H-4), 6.16 (m, H-11), 5.07 (s, CH_2-Ph), 0.95 (s, CH_3-18).

The protected 11-oxoestrone (**4**, R=Bn) can be prepared as previously described[7] with two modifications: the protection of the 17-keto group required *p*-toluenesulfonic acid as a catalyst (1% by weight) and a longer reaction time than for dehydroestrone (14 h reflux versus 2.5 h). The hydroboration step to generate the alcohol **3** (R=Bn) required only 1 equiv. of a borane–methyl sulfide complex.

When EBE reacted with an excess of DDQ (2 to 2.5 equiv.) in dioxane containing 2 to 20% methanol, at room temperature for 20 h, the following reaction was observed, **8** being the major product (Scheme 3).



Scheme 3.

Compound **8** was probably formed by the reaction of methanol with a carbocation resulting from a hydride abstraction from **6** by DDQ. The synthesis of the methoxy compound **8** was best achieved as follows:

2.4 g DDQ (1.5 equiv.) was added to a solution of 2.5 g of 9,11-dehydro EBE (**6**) in 150 ml dioxane containing 6 ml methanol and stirred for 1 h at room temperature. The solvents were evaporated and dichloromethane added. The resulting suspension was filtered on neutral alumina and washed with dichloromethane. The crude product obtained after the evaporation of the solvent was crystallised in methanol to give 2 g of a solid (m.p.=150°C), with a 73.5% yield. ^{1}H NMR (ppm) in $CDCl_3$: 7.6 (d, J_{12}=8.6 Hz, H-1), 6.83 (dd, J_{24}=2.7 Hz, H-2), 6.72 (d, H-4), 6.35 (d, J_{11-12}=5.2 Hz, H-11), 5.08 (s, CH_2–Ph), 3.83 (d, H-12), 3.47 (s, OMe), 0.88 (s, CH_3–18).

An NOE experiment was performed on compound **8** in order to determine its configuration at the 12 position. The strong interaction observed between the CH3–18 and the H-12 indicated a 12α configuration for the methoxy group.

The debenzylation of compound **8** was achieved by hydrogenolysis on Pd/C,[11] this reaction being accompanied by a hydrogenation of the 9,11 double bond.

Work is in progress to obtain other functionalisations at the 12 position by using other nucleophiles.

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