Steroid A-Ring Aromatisation of C-Ring Substituted 1,4-dien-3-ones

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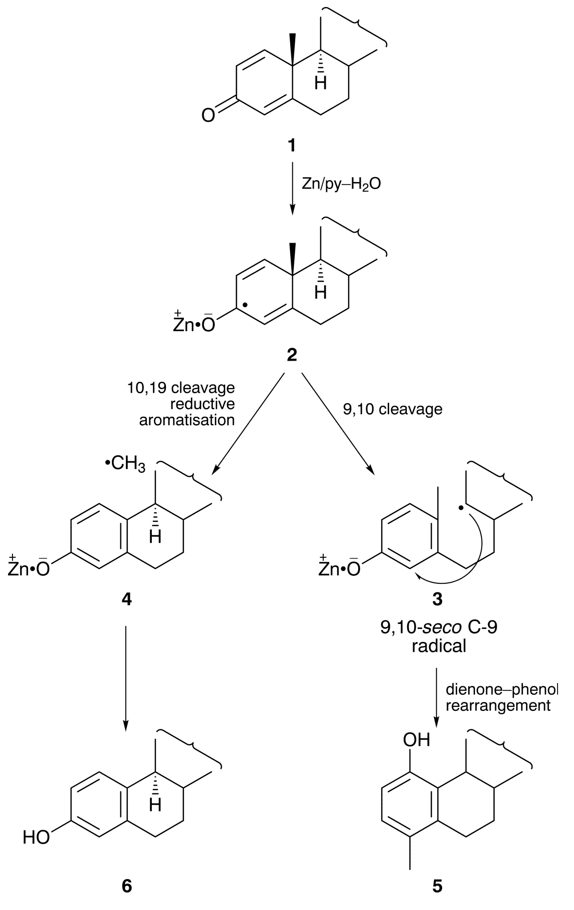
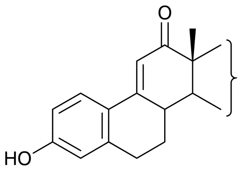
A number of A-ring steroidal 1,4-dien-3-ones **7**, **8**, **9** and **10** have been aromatised in zinc/pyridine–water; the products depend upon the position and type of C-ring substituents and provide new evidence in support of a radical anion mechanism.

Aromatisation of steroidal $\Delta^{1,4}$-dien-3-ones **1** is well known and includes (Lewis) acid-catalysed dienone-phenol rearrangements in which the 19-carbon is retained and demethylations (reductive aromatisation) involving reaction with lithium and biphenyl or zinc.[1] The reactions with zinc are thought to involve a single electron addition leading *via* the radical anion **2** and either a 9,10-*seco*-C-9 radical **3** or loss of a methyl radical **4** (Scheme 1) to the *para*-phenol **5** or the 3-hydroxy compound **6** respectively. However, it has been suggested that in certain cases zinc may act as a Lewis acid.[2]



Scheme 1

In the course of a study directed to the synthesis of C-ring substituted A-ring aromatic steroids,[3] we have examined the aromatisation of $\Delta^{1,4}$-dien-3-ones **7**, **8**, **9** and **10** with zinc in pyridine containing water and have to report new evidence in support of the radical anion mechanism (Table 1).



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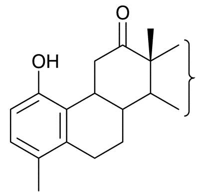

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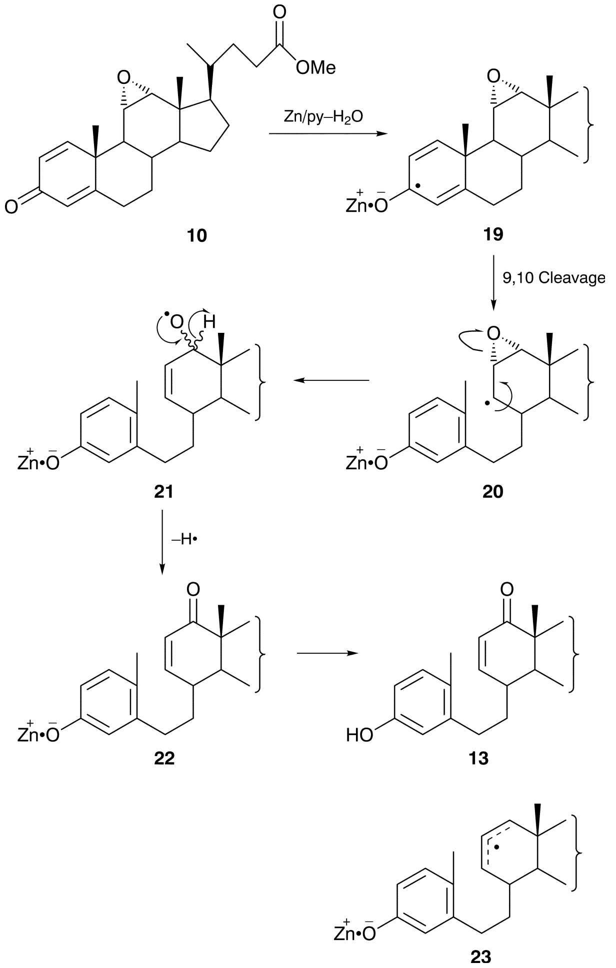

Scheme 2

Reaction of $\Delta^{1,4,9(11)}$-triene-3,12-dione **7** with zinc/pyridine–water as previously reported[11] gave a high yield of the A-ring aromatic-$\Delta^{9(11)}$-12-ketone **11** whereas the $\Delta^{1,4}$-diene-3,12-dione **8** gave largely the *para*-phenol **12**, the product of the dienone–phenol rearrangement (Table 1). Treatment of **9** with zinc under the usual conditions gave a complex mixture (Table 1). Although it was apparent from the ^{1}H NMR spectrum of the crude product that aromatisation had occurred, it was not possible to satisfactorily purify the components of the mixture. Similar

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Table 1 Aromatisation of $\Delta^{1,4}$-dien-3-ones with zinc in pyridine–water[a]

Starting 1,4-dien-3-one	Product	Yield (%)	Reaction type
$\Delta^{9,11}$-12-one **7**	**11**[11]	90	10-methyl expulsion
12-ketone **8**	**12**	86	dienone–phenol rearrangement
Δ^{11} **9**	intractable mixture	—	—
11α,12α-epoxide **10**	**13**	97	9,10-fission

[a] *Reaction conditions*: Zn/pyridine–water, reflux, 18 h.

treatment of the 11α,12α-epoxide **10** gave the 9,10-*seco*-$\Delta^{9,11}$-*seco*-12-ketone **13**.

All of the results are best explained by the intermediacy of the radical anion **2** or its equivalent. As reported before, loss of the methyl is facilitated by a $\Delta^{9,11}$ double bond hence the high yield of the enone **11** from **7**.[1] The products from **8, 9** and **10** all arise from the C-9 radical **3** or its equivalent and, in the case of the 11α,12α-epoxide **10**, the reaction is particularly efficient owing to the trapping of the C-9 radical **20** by the epoxide followed by expulsion of a hydrogen radical by allylically activated β-cleavage of the oxyl radical **21** (Scheme 2).

The failure of the $\Delta^{1,4,11}$-trien-3-one **9** to give a single product was expected since the reaction would proceed through the C-9 allylic radical **23**. It is unlikely that Lewis-acid catalysis is involved in the epoxide reaction since treatment of 11α,12α-epoxide **10** with $BF_3{\cdot}Et_2O$ in diethyl ether or $SnCl_4$ in dichloromethane gave complex mixtures.

Techniques used: IR, ^{1}H and ^{13}C NMR, HRMS

Schemes: 4

References: 13

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