Oxygen Atom Transfer from Iodylbenzene to Diphenyl Diselenide - A Convenient Method for Dehydrogenation of Steroidal 3-Ketones

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Summary Steroidal 3-ketones are smoothly dehydrogenated in high yield using benzeneseleninic anhydride generated *in situ* by oxygen atom transfer from iodylbenzene, $PhIO_2$, to catalytic amounts of diphenyl diselenide; use of *meta*-iodylbenzoic acid in the above cycle has led to the development of an economical and experimentally convenient method avoiding chromatographic separations and with recovery of the *m*-iodobenzoic acid and the diphenyl diselenide.

WE have previously shown that benzeneseleninic anhydride is a useful stoicheiometric reagent for alcohol oxidation[1] and for dehydrogenation of ketones[2] to give biologically important steroidal cyclohexa-1,4-dien-3-ones. Benzeneselenenic acid or reduced forms of its anhydride generated in the elimination step may, however, give rise to unwanted side reactions.[2] An attractive solution for avoidance of these side reactions is the development of a catalytic cycle[2] for immediate reoxidation of the reduced organoselenium species. Such a process would also considerably reduce the cost of the operation.

We conceived that an efficient oxygen atom transfer from iodylbenzene to diphenyl diselenide should exist and could be the basis of a catalytic process. The results for a variety

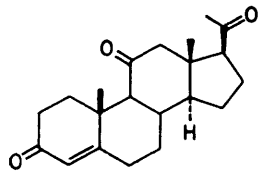
TABLE

Substrate	Time/h	Solvent[a]	Catalyst(s)[a] (equiv.)	Iodylbenzene reagent[a] (equiv.)	% Yield of ring A 1,4-dien-3-one
Cholestan-3-one	24	A	D (0·2)	G (3·3)	84
Cholestan-3β-ol	24	A	D (0·2)	G (3·3)	81
	12	A	D′(0·2)	G (3·3)	77
Androst-4-en-3,17-dione	12	A	D (0·16)	G (3·6)	72
(**1**)	12	A	D (0·18)	G (3·3)	51
Cholestan-3β-ol	20	A	D (0·2)	H (3·3)	74
	3	B	E (0·2)	H (3·3)	88
	2	C	E (0·2)	H (3·3)	79
	16	B	E (0·03)	H (4·16)	73
Spiro[5.5]undec-2-en-3-one	3	B	D (0·1)	H (2·0)	85
	36	B	E (0·02)	H (3·0)	87
Spiro[4.5]dec-7-en-8-one	3	B	D (0·1)	H (2·0)	70
(**5**)	2·5	B	E (0·2)	H (3·2)	86[b]
(**6**)	2·5	B	D (0·14)	H (3·0)	75[c]
(**7**)	3	B	E (0·2)	H (3·3)	84
Cholestan-3-one	3	C	F (0·5)	G (3·0)	58

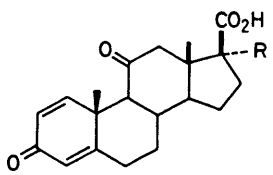
[a] A, Benzene at reflux; B, toluene at reflux; C, chlorobenzene at reflux; D, benzeneseleninic anhydride; D′, benzeneseleninic anhydride + (trace) *p*-$MeC_6H_4SO_2OH$; E, diphenyl diselenide; F, selenium dioxide; G, iodylbenzene; H, *m*-iodylbenzoic acid. [b] M.p. 230—233 °C, $[\alpha]_D$ + 10° (*c* 0·9, $CHCl_3$). [c] M.p. 217—220 °C $[\alpha]_D$ + 1° (*c* 0·9, $CHCl_3$).

of steroidal alcohols and ketones are presented in the Table and confirm this idea. Either diphenyl diselenide or benzeneseleninic anhydride may be used as the organoselenium catalyst. In the absence of the selenium reagent cyclohexadienone formation is not observed and only slow oxidation of the alcohol to the ketone by iodylbenzene occurs. We have also noted that addition of toluene-*p*-sulphonic acid leads to a faster reaction rate. Alcohol oxidation followed by dehydrogenation provides yields which are comparable with or higher than those obtained when the anhydride alone is used.

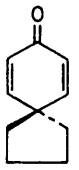
The dehydrogenation of cholestan-3β-ol, which was performed on a 1 g scale with only 0·03 equiv. of diphenyl diselenide, is particularly striking. The low yield in the oxidation of compound (**1**) is the result of further oxidation of the progesterone side chain leading to the acid (**2**) {methyl ester, m.p. 179—181 °C, $[\alpha]_D$ + 205° (*c* 0·85, $CHCl_3$)} and hydroxy-acid (**3**), previously characterised as its methyl ester.[3]



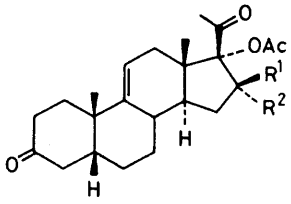
(1)



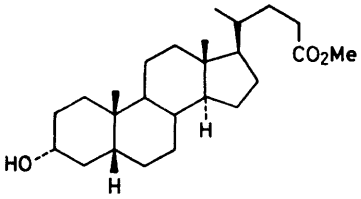
(2) R = H
(3) R = OH



(4)



(5) R^1 = Me, R^2 = H
(6) R^1 = H, R^2 = Me



(7)

In contrast with a literature report,[4] we find that formation of the spiro[4.5]decadienone (**4**) can be smoothly accomplished (77%) by use of a stoicheiometric amount of benzeneseleninic anhydride. The catalytic method can also be successfully applied in this case, without rearrangement, to non-spiro-derivatives.

We have also noted, in the case of compounds (**5**) and (**6**), that protection of the 17α-hydroxy-group as the acetate is necessary in order to avoid complex side reactions. The regeneration of selenium dioxide by this method should also be applicable to allylic oxidation reactions.

From the practical standpoint, replacement of iodylbenzene by *m*-iodylbenzoic acid led to the development of an experimentally convenient method, not only for isolation of the steroidal product, but also for separation and recovery of *m*-iodobenzoic acid and diphenyl diselenide without chromatography. This is illustrated by a typical experimental procedure for the oxidation of ketone (**5**).

m-Iodylbenzoic acid (720 mg) and diphenyl diselenide (52 mg) were heated under reflux in dry toluene (20 ml) until the yellow colour of the diselenide disappeared (15 min). The steroidal acetate (**5**) (300 mg) was added and heating was continued for a further 2·5 h. After cooling, the reaction mixture was thoroughly extracted with saturated sodium hydrogen carbonate solution and the organic phase was washed with water and dried. Removal of solvent and recrystallisation from acetone–hexane gave the required steroidal dienone (255 mg) (86%), m.p. 230—233 °C, $[\alpha]_D^{19}$ + 10° (*c* 0·9, $CHCl_3$). The combined aqueous extracts were reduced by treatment at room temperature with a saturated solution of sodium dithionite (excess) for 1 h. The aqueous phase was oxidized by a stream of air for 1 h to destroy the excess of dithionite. Recovered diphenyl diselenide (47 mg) (90%) was obtained by extraction with toluene. Acidification with dilute sulphuric acid gave precipitated *m*-iodobenzoic acid which was filtered off, washed with water, and dried (550 mg) (86%).

Although iodylbenzenes are normally prepared *via* iodobenzene dichlorides,[5] we have found that iodobenzenes can be oxidised directly to iodylbenzenes in high yield using the inexpensive Stevens[6] reagent in acetic acid. Iodylbenzene and *m*-iodylbenzoic acid are said to be explosive.[5] This is not correct. This type of compound undergoes deflagration at about 230 °C, more than 100 °C above the temperature used for our catalytic dehydrogenation.

Although it is inert to saturated ketones, we consider that *m*-iodylbenzoic acid and its congeners are, *per se*, interesting selective oxidants for organic chemistry.[7]

(*Received, 22nd June* 1981; *Com.* 721.)

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