Tetrahedron Letters, Vol. 33, No. 48, pp. 7399-7402, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Direct Transformation of Steroidal Ethers into Ketones by Dimethyldioxirane

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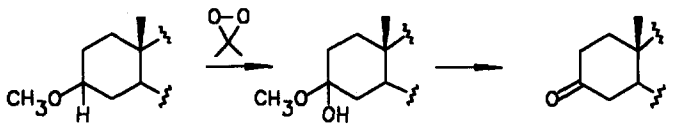
Abstract: Treatment of the methyl- and benzyl ethers of 3-hydroxy steroids with a solution of dimethyldioxirane resulted in the formation of the corresponding ketones in high yield.

Dioxiranes, a new class of oxidants, received much attention in recent literature due to the versatility of these reagents as well as the extremely mild conditions required for reactions.[1,2] Dimethyldioxirane, the most commonly used dioxirane, oxidizes alkenes to epoxides, sulfides to sulfoxides and sulfones, amines to hydroxylamines or nitro compounds, alcohols to ketones and saturated hydrocarbons to hydroxylated compounds.[1] Hitherto, however, no reference has been made to the reaction of dimethyldioxirane with ethers.

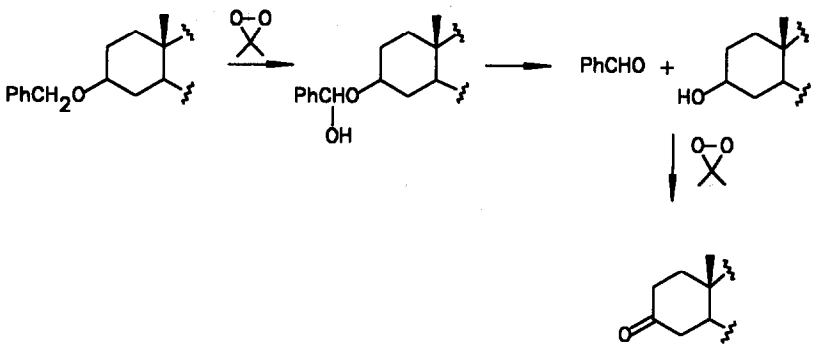
In an investigation of the oxyfunctionalization of steroids by dimethyldioxirane, we treated a number of steroid methyl- and benzyl ethers with dimethyldioxirane (See Table). Ethers **1a** - **8a** afforded the corresponding ketones **1b** - **8b** in high yield. In the reaction with the methyl ethers, the ketones were the only products detected, and the mechanism is most likely similar to that proposed for the oxidation of alcohols to ketones,[3,4] *i.e.* insertion of oxygen into the tertiary C-H bond, and decomposition of the corresponding hemiketal to the ketone (Scheme 1).



SCHEME 1

In the reaction with the benzyl ethers, intermediate products, which were identified as the corresponding 3-hydroxy steroids, could be detected by t.l.c. The initial oxygen insertion by dimethyldioxirane therefore occurs at the more electron rich benzylic C-H bond to form a hemiketal, which decomposes to benzaldehyde and the hydroxy steroid. Further oxidation of the alcohol yielded the keto steroid (Scheme 2). This result is

consistent with the observation that insertion of oxygen into C-H bonds is strongly affected by the electrophilic nature of the C-H bond, electron rich bonds being more reactive.[5,6] A similar reaction was observed between benzyl ethers and ozone.[7]

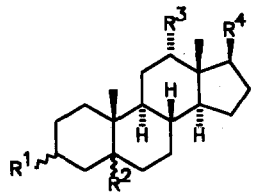


SCHEME 2

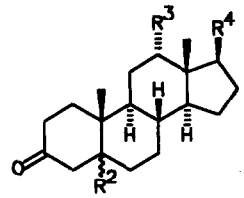
This new reaction of dimethyldioxirane raises the question of the reactivity of different functional groups towards this reagent. It was recently shown that treatment of 5β-steroids with dimethyldioxirane resulted in the formation of 5β-hydroxy steroids.[8] The formation of the corresponding 5β-derivatives was not observed for **1a** and **2a** under the reaction conditions used here, and the transformation of ethers to ketones can therefore be accomplished without the concomitant oxidation of unactivated C-H bonds. The oxidation of 3-*O*-benzylpregnenolone (**9b**) with 2 equivalents of dimethyldioxirane afforded a mixture of products **9c**, **9d** and **9e**. The presence of **9c** indicated that epoxidation preceded oxidation of the benzyl ether. However, the formation of **9d** and **9e**, products also obtained in the oxidation of pregnenolone (**9a**) by dimethyldioxirane,[5] was observed before all the starting material was consumed and it is, therefore, evident that although the epoxidation of the double bond is faster than the oxidation of the benzyl ether, the difference in the reactivity is not pronounced enough to allow the quantitative transformation to the epoxide.

Treatment of methyl tetra-*O*-acetyl-α-D-glucopyranoside with dimethyldioxirane did not yield any products. In this substrate the anomeric C-H bond is more sterically hindered and this is most likely the reason for the low reactivity. The unreactivity of a double bond towards reaction with dimethyldioxirane due to steric hindrance was also observed by Maynard *et al.*[9] It is clear that the intermediate in the reaction where oxygen is inserted into a C-H bond by dimethyldioxirane, as is the case for the epoxidation of a double bond, must be bulky, and that the reaction is slowed down in cases where steric hindrance exists.

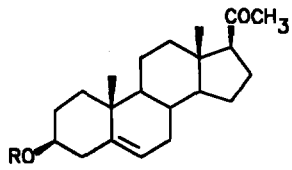
We also observed that, analogous to oxidation of 3-hydroxy steroids,[3] the rate of oxidation of the equatorial ether **4a** was slower than that of the axial ether **3a** by a factor of *ca.* 1.5.[10] The greater steric constraints of the axial C-H as compared to the equatorial C-H may account for the difference in the reaction rate of these two substrates. No difference in the reaction rate of the axial and equatorial benzyl ethers **5a** and



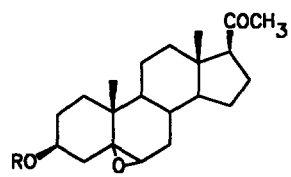
1a-8a



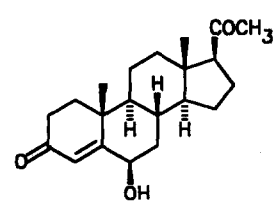
1b-8b



9a: R=H
9b: R=CH_2Ph



9c: R=CH_2Ph
9d: R=H



9e

Table. Oxidation of Steroidal Ethers.[11]

Substrate					Reaction Conditions*	Product	Isolated Yield(%)
	R^1	R^2	R^3	R^4			
1a:	α-OCH_3	β-H	OAc	$CH(CH_3)$-$(CH_2)_2$-CO_2CH_3	1.1 eq.	**1b**	79
1a					1.75 eq.	**1b**	95
2a:	α-OCH_3	β-H	H	$CH(CH_3)$-$(CH_2)_3$-$CH(CH_3)_2$	1.1 eq.	**2b**	57
3a:	α-OCH_3	α-H	H	$CH(CH_3)$-$(CH_2)_3$-$CH(CH_3)_2$	2 eq.	**3b**	75
4a:	β-OCH_3	α-H	H	$CH(CH_3)$-$(CH_2)_3$-$CH(CH_3)_2$	2 eq.	**4b**	78
5a:	α-OCH_2Ph	α-H	H	$CH(CH_3)$-$(CH_2)_3$-$CH(CH_3)_2$	2 eq.	**5b**	88
6a:	β-OCH_2Ph	α-H	H	$CH(CH_3)$-$(CH_2)_3$-$CH(CH_3)_2$	3 eq.	**6b**	91
7a:	β-OCH_3	α-H	H	$COCH_3$	2 eq.	**7b**	95
8a:	β-OCH_2Ph	α-H	H	$COCH_3$	2 eq	**8b.**	82
9b					2 eq.	**9c**	37
						9d	30
						9e	16

* The substrate was dissolved in 1.1 eq. of dimethyldioxirane in acetone and the reaction mixture stirred at room temperature for 18 h. If the reaction was not completed another equivalent of dimethyldioxirane was added and the mixture stirred for another 18h. The quantities required to force the reactions to completion are indicated in the Table.

6a could be detected. This observation corroborated the mechanism proposed for the oxidation of the benzyl ethers, because oxygen insertion in the benzylic C-H bond in the rate- determining step will not experience a substantial difference in steric hindrance for the α- and β-isomers.

Considering the high yields obtainable and the mild reaction conditions required, this method should be a valuable addition to the limited number of reactions[7,12] available for the direct conversion of ethers to ketones.

ACKNOWLEDGEMENTS: We gratefully acknowledge the financial support of the Foundation for Research Development.

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10. A mixture of equimolar quantities of **3a** and **4a** was treated with 0.45 mole eq. of dimethyldioxirane for 8 h. The ratio of **3a**:**4a** in the resulting mixture was determined by ^{1}H n.m.r. spectroscopy.

11. All products gave satisfactory analytical and spectroscopic data. The products were mostly known compounds, and ^{13}C NMR data are in agreement with literature values: Blunt, J.W.; Stothers, J.B. *Org. Magn. Reson.*, **1977**, *9*, 439-464.

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(Received in UK 20 July 1992)