EPOXIDATION OF BICYCLIC AND STEROIDAL α,β–UNSATURATED CARBONYL COMPOUNDS BY DIMETHYLDIOXIRANE: KINETICS

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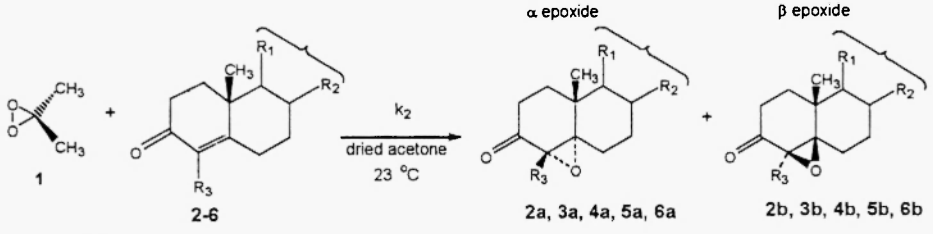
Abstract. Epoxidation of selected bicyclic and steroidal α,β-unsaturated carbonyl compounds by dimethyldioxirane produced only the corresponding epoxides. In all cases, higher α versus β face selectivity for the enone epoxidation was observed. The second order rate constants were obtained at 23 °C.

Introduction

The epoxidation of unsaturated compounds is a straightforward method for the introduction of functionality into organic molecules.[1] Whether generated *in situ*[1b-1d] or isolated[2] in acetone solution, dimethyldioxirane (**1**), has proven to be a very powerful and versatile oxidant. The epoxidation of carbon carbon double bonds using dimethyldioxirane has been established as electrophilic in nature[3] and is considered to occur via a concerted *'spiro'* transition state mechanism.[4] Kinetic data on epoxidation of monocyclic α,β-unsaturated carbonyl compounds by **1** have been carried out.[5] No kinetic data are available for the epoxidation of more complex α,β-unsaturated systems by **1**, however, product studies for the epoxidation of several steroids by **1** have been reported.[6] We report here the results of a kinetic study of the epoxidation of selected bicyclic and steroidal α,β-unsaturated carbonyl compounds by dimethyldioxirane in dried acetone at 23 °C.

Results and Discussions

The epoxidation of (±)-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one, **2**, (S)-(+)-3,4,8,8a-tetrahydro-8a-methylnaphthalen-1,6(2*H*,7*H*)-dione, **3**, (±)-1,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one, **4**, 4-cholesten-3-one, **5**, and 4-pregnene-3,20-dione **6**, (progesterone), with an excess of dimethyldioxirane (Reaction 1) afforded the corresponding α and β epoxides as the sole observable products



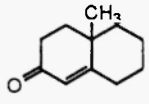
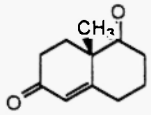
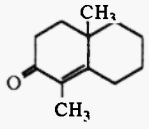
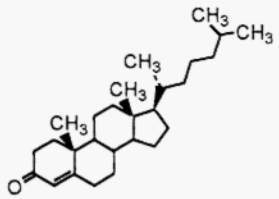
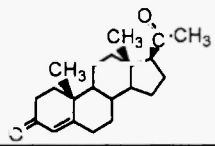
(1)

2, $R_1R_2R_3$= H; **3**, R_1(=O), R_2R_3= H; **4**, R_1R_2= H, R_3= Me; **5**, 4-cholesten-3-one; **6**, progesterone

in high yield (Table 1). The products were characterized by physical and spectroscopic methods and the results are in agreement with literature values.[6-7 9-10]

For the bicyclic systems **2-4**, the ratio of α and β epoxides were found to be roughly 3 to 2, for all cases. For the steroidal compounds **5** and **6**, α/β product ratios of 74:26 and 79:21 were obtained respectively. The facial selectivity results for the enone systems clearly show preference for α side oxygen atom transfer. Presumably the β-side is partially protected due to steric influences of the angular methyl C 8a group. The results for **5** and **6** are in agreement with published data on the steroids.[6]

Table 1. Second order rate constants for the epoxidation of α,β–unsaturated compounds **2-6** by **1** at 23 °C in dried acetone solution.

Entry	Compound	Epoxide α : β	k_2 ($M^{-1}s^{-1}$)	k_{rel}
2		3 : 2	$3.1 \pm 0.5 \times 10^{-3}$	1.0
3		59 : 41	$7.5 \pm 0.2 \times 10^{-4}$	0.24
4		60 : 40	$7.1 \pm 0.5 \times 10^{-2}$	23
5		74 : 26 3 : 1[(a)]	$5.8 \pm 0.3 \times 10^{-3}$	1.9
6		79 : 21 4 : 1[(a)]	$3.5 \pm 0.3 \times 10^{-3}$	1.1

[(a)] At 20 °C, taken from ref. 6

Kinetics studies for the epoxidation of compounds **2-6** by **1** were carried out using UV techniques at 23 °C in dried acetone under pseudo-first order conditions with the enones in excess. Due to interference from the substrate, the decrease in absorbance after addition of **1** was monitored at 370 nm rather than at

the usual wavelength (330 nm). In all cases, excellent linear pseudofirst order plots were obtained. The rate constants (k_2's) are the average of at least three independent experiments. The kinetics results are listed in Table 1.

The second order rate constant for the epoxidation of a model compound, 3-methyl-2-cyclohexene-1-one was reported[5] to be 2.0 x 10^{-3} M^{-1} s^{-1}. For the bicyclic enone **2**, the value of k_2 obtained was found to be 3.1 x 10^{-3} M^{-1} s^{-1}, while for steroids **5**, and **6** values of 5.8 x 10^{-3} M^{-1} s^{-1} and 3.5 x 10^{-3} M^{-1} s^{-1} were obtained, respectively. Thus, there are only minor differences between the k_2 values for epoxidation of the monocyclic model compound and those of the bicyclic compounds **2,3** and steroids **5,6**. For simple alkene epoxidation by **1**, steric effects within a series have been shown[1b] to be dominant for the calculation of relative rate constants. The prediction of relative reactivity for α,β–unsaturated systems is more complex. Due to the locked conformation and the similarity of the "groups" in the β positions, one might expect the approach of **1** to the double bond to encounter very similar steric influences. Thus, the similarity of the k_2 values is not unexpected.

The k_2 value for epoxidation of compound **3** was found to be smaller than that for compound **2** by a factor of 4. This can be ascribed to an electronic effect since the structures differ only by the formal addition of a carbonyl at C-8. Addition of an electron withdrawing group is expected to slow electrophilic epoxidation. The rate constant for epoxidation of compound **4** was found to be 7.1 x 10^{-2} M^{-1} s^{-1}, which is roughly 23-fold greater than those for enones **2** and **6**. This is also consistent with electrophilic epoxidation. However, the magnitude of the effect is much larger than that that has been reported[5] for simple substituent effects in monosubstituted cyclic enone systems. The additional methyl group apparently enhances the electron density of the double bond on compound **4** more than expected.[8]

Nucleophilic oxidation (alkaline hydrogen peroxide) of the parent bicyclic enone of **2**, 4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one has been reported[9] to afford only the β epoxide. Kuene and Nelson reported the β epoxide as the major product of epoxidation of compound **2** using 4 N NaOH and 30% H_2O_2 at 0 °C.[9a] Epoxidation of steroid **6** using *t*-butyl hydroperoxide and LiOH has also been reported to afford only the β epoxide.[9b] Electrophilic epoxidation of steroid **6** using *m*-CPBA led to the formation of a large mixture of products; the enol lactone is the major product (57%) followed by α/β-epoxy-lactones with only traces of α/β epoxides.[10] The electrophilic epoxidation of compounds **2-6** employing excess dimethyldioxirane, **1**, yielded only α/β epoxides under mild conditions with no observable side products.

In summary, fused polycyclic α,β-unsaturated carbonyl systems undergo electrophilic epoxidation by dimethyldioxirane with k_2 values similar to those of monocyclic α,β-unsaturated model compounds solely affording α and β epoxides in high yield. The k_2 values are roughly 10^{*3} lower than those for alkene epoxidation.[3a,4a] In contrast to nucleophilic processes, the epoxidation of compounds **2-6** by dimethyldioxirane affords the α epoxide as the major product in each case without unwanted side reactions.

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11. Compound **2** was prepared by Robinson annulation as described by F.E. Ziegler and K.J. Hwang, *J. Org. Chem.* **48**, 3349 (1983). Compound 4 was prepared according to the published methodology by C.C. Lang'at, R.A. Watt, I. Toth and J.D. Phillipson, *Tetrahedron* **54**, 6857 (1998). Compounds **3**, **5** and **6** were commercially available (Aldrich).

12. The determination of the facial selectivity of epoxidation of enones **2-6** by **1** was carried out by ^{1}HNMR spectroscopy after reaction of 3 equiv of **1** with the enone at 24 °C for 48 to 72 hours. The diastereoisomeric ratios were measured by integration of the chemical shifts corresponding to the methine H, C4-H, or C4-Me and the angular C8a-Me of the reaction mixtures for compounds **2-6**. The results were confirmed by GC/MS analysis.

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