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OXIDATION OF α-METHYLBENZYL ALCOHOLS BY DIMETHYLDIOXIRANE

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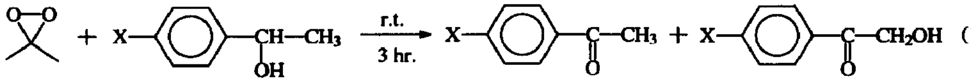
Abstract: Dimethyldioxirane converts *p*-substituted α-methylbenzyl alcohols to the corresponding acetophenones in excellent yield with α-hydroxyacetophenones as the minor products; the oxidation shows a ρ of -1.57, PKIE of 3.55, KIE of 1.09 for OD and activation parameters with a large, negative $\Delta S^{\ddagger}$ term.

Dimethyldioxirane, **1**, has been shown[1,2] to be an important and versatile oxidizing agent; efficiently transferring oxygen atoms to a wide assortment of organic substrates[3]. The oxidation of different substrates can be carried out under extremely mild conditions with the yield of corresponding oxidation products usually high. The oxidation of C-H bonds of saturated hydrocarbons[4,5,6] and phenyl substituted hydrocarbons[5,7,8] by dimethyldioxirane has been documented. In addition, the conversion of secondary alcohols to carbonyl compounds has been accomplished with methyl(trifluoromethyl)dioxirane[9].We report here a study of the oxidation of a series of *p*-substituted α-methylbenzyl alcohols **2a-g** by dimethyldioxirane in acetone.



(1)

1 excess

2a X=OMe; **b** X=Me; **c** X=H; **d** X=F; **e** X=Cl; **f** X=Br; **g** X=CN

3a-g 97 %

4a-g 2-3 %

The reaction of 0.1 M dimethyldioxirane , **1**, (1.5 equivalents, 3 hrs) in acetone with a series of *p*-substituted α-methylbenzyl alcohols **2a-g** (rxn 1) produced the corresponding acetophenones **3a-g** in excellent yield (97 %). α-Hydroxyacetophenones **4a-g** were found as the minor products (2 - 3 %). Treatment of acetophenone with excess **1** under the reaction condition did not yield α-hydroxyacetophenone. Use of a 1 : 1 ratio of reactants in rxn 1 resulted in lowered product yields and recovery of unreacted starting materials (~ 30 %). Product yields for reactions carried out in the dark and under nitrogen atmosphere were unaffected except in the case of the slower oxidations (**2e-g**). For the compounds with electron - withdrawing groups and without excess 1, slightly lower yields were obtained. The major products **3a-g** were isolated and identified by comparison of NMR spectra and GC/MS data with those of authentic samples. For oxidation of α-methylbenzyl alcohol **2c**, the minor product **4c** was isolated and the structure proven by comparison with the authentic compound[10,11]. The reminder were identified using GC/MS data. The product yields are listed in Table 1.

Kinetic studies of rxn 1 were carried out in dried acetone with at least a 10-fold excess of dimethyldioxirane at various temperatures. The reactions were proven to be of the second order overall. The second order rate constants (k_2) obtained from UV data under pseudo first order conditions are shown in Table 1. Excellent correlations were obtained in all cases. The rate constants for oxidation of *p*-substituted α-methylbenzylalcohols **2a-f** were measured every 5 °C (range: 20-40 °C). Employing the Arrhenius method, activation energies (Ea) were obtained and the enthalpies of activation ($\Delta H^{\ddagger}$), entropies of activation ($\Delta S^{\ddagger}$) and free energies of activation ($\Delta G^{\ddagger}$) were calculated at 25 °C (Table 1). The addition of water did not result in a measurable increase in rate in contrast to the effect observed on the epoxidation of unsaturated carbonyl compounds[13] and alkenes [14] by **1**. Changes in solvent from acetone to acetone/CH_2Cl_2 and acetone/$CHCl_3$ in volume ratio 1 : 1 did not affect the magnitude of the rate constants. Significant solvent effects have been observed[6] for CH oxidation of alkanes by **1**.

Table 1: Products yields[a], second order rate constants (k_2)[b] and activation parameters for the oxidation of p-substituted α-methylbenzyl alcohols by dimethyldioxirane in acetone at 25 °C.

Alcohol	yield[a] 3 %	yield[a] 4 %	$k_2 \times 10^2$ [b] $mol^{-1}s^{-1}$	Ea kcal mol^{-1}	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta S^{\ddagger}$ eu	$\Delta G^{\ddagger}$ kcal mol^{-1}
2a	97	3	3.56±0.08	8.7±0.4	8.1	-38	19.5±0.4
2b	97	2	2.89±0.06	9.2±0.3	8.7	-37	19.6±0.3
2c	98	2	2.24±0.06	12.2±0.4	11.6	-28	19.7±0.4
2d	97	2	1.85±0.04	10.1±0.4	9.6	-35	19.9±0.4
2e	97	3	1.59±0.04	10.2±0.4	9.4	-35	20.0±0.4
2f	96	3	1.51±0.04	10.5±0.4	9.9	-34	20.0±0.4
2g	97	2	0.76±0.04	-	-	-	-

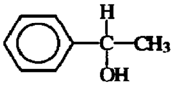
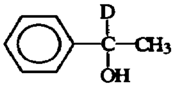
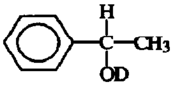
a) 1.5 to 1 ratio of dimethyldioxirane to alcohol; b) Pseudo first order conditions at 25 °C.

Electron withdrawing groups in the para position decreased the rate of oxidation while electron releasing group increased the rate of oxidation (rxn 1). A Hammett plot of the second order rate constants for oxidation of *p*-substituted α-methylbenzyl alcohols by **1** showed an excellent LFER against σ (ρ value -1.57±0.04 at 25 °C with a correlation coefficient 0.999).

Derivatives of **2c** in which the α-hydrogen (**2c'**) or the hydroxy proton (**2c"**) have been replaced by deuterium were prepared. Product studies showed no unexpected variations. Oxidation of **2c'** resulted in a relative increase in the yield of **4c**. Kinetic studies (Table 2) carried out as before yielded kinetic isotope effects of 3.55

(k_H/k_D) and 1.09 (k_{OH}/k_{OD}). For oxygen atom insertion into carbon-hydrogen bonds of hydrocarbons by dimethyldioxirane[4] and for oxidation of cyclohexanol by methyl(trifluoromethyl)dioxirane[9] primary kinetic isotope effects of k_H/k_D=4.97 and k_H/k_D=1.6 respectively were found. For oxidation of benzyl alcohols by nitrous acid[15], the kinetic isotope effect was determined to be ~3, while that for oxidation of 2-propanol by chromic acid[16] was 7. Secondary deuterium isotope effects have been measured for epoxidation of deuteriodihydropyrans by dimethyldioxirane[17].

Table 2. Deuterium isotope effects for oxidation of acetophenone by dimethyldioxirane in acetone at 25 °C.

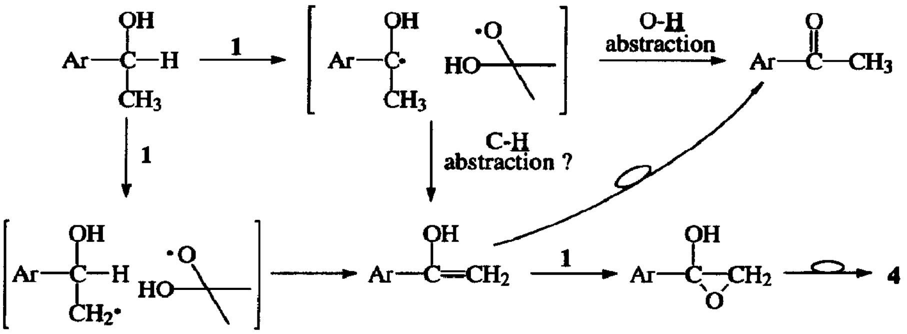
	Alcohol	$k_2 \times 10^2$ $mol^{-1}s^{-1}$ [a]	k_H/k_D	Product yields[b]	
				3c	**4c**
2c		2.24±0.06	-	73%	2%
2c'		0.63±0.02	3.55	70%	3.5%
2c"		2.05±0.06	1.09	70%	2%

a) Pseudo first order conditions; b) 1 to 1 ratio of dioxirane to alcohol

The major products of oxidation of *p*-substituted α-methylbenzyl alcohols (**2a-g**) by **1** were the corresponding acetophenones (**3a-g**) in high yield. This is in agreement with the previously reported oxidation of **2c** by methyl(trifluoromethyl)dioxirane in 98 % yield (reaction time: 20 min.). The minor products α-hydroxyacetophenones (**4a-g**), have not been reported. **4a-g** are direct oxidation products of **2a-g** since they are not formed by oxidation of **3a-g** with **1** in control experiments. The ρ value of -1.57 at 25 °C is higher than those reported in the literature for oxidation of this type of alcohol by chromic acid [16] (ρ =-1.16) or by $S_2O_8^{2-}$ - Cu^{II} (ρ=-0.27)[18a] and comparable to that for oxidation of benzyl alcohols by nitrous acid[15] (ρ=-1.7) (Yukawa-Tsuno method). The observed primary deuterium isotope effect (k_H/k_D=3.55) is comparable with a that (k_H/k_D=4.97) for the oxidation of hydrocarbons by dimethyldioxirane[4]. The k_{OH}/k_{OD} value of 1.09 could represent a large secondary effect or extremely small primary effect[18b].The $\Delta G^{\ddagger}$ values were essentially constant for series of α-methylbenzyl alcohols with large negative $\Delta S^{\ddagger}$ terms. No solvation effects were observed for rxn 1.

Our earlier mechanistic work[19] on formal CH insertion of **1** with benzaldehydes was indicative of hydrogen-atom abstraction by the 1,3-dioxyl diradical of **1**. CH insertion studies on more difficult to abstract positions[4,5,6,7,8] have been interpreted to be consistent with a concerted insertion process. For secondary alcohol oxidation, this would yield the ketone hydrate as the initial product. The characteristics determined for rxn 1 suggest a hydrogen-atom abstraction route although the concerted insertion can not be ruled out. A cage-radical process as shown in Scheme 1 would be consistent with the data. The direct formation of the minor product as well as the increased yield of **4c** noted for oxidation of **2c'** requires CH abstraction from the methyl group. This should lead to caged radicals which could result in a second abstraction to yield the enol. Secondary epoxidation by 1 of the enol would lead to the minor product. This mechanism requires that the second hydrogen-atom abstraction for the caged radical pair is rapid on the molecular time scale.

Scheme 1



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