Acid-Catalyzed Oxidation of Oxiranes with Dimethyl Sulfoxide Giving α-Hydroxy Ketones

Tadakazu TSUJI
Department of Chemistry, Japan Women's University, Mejirodai, Bunkyo-ku, Tokyo 112
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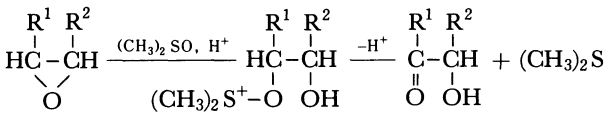
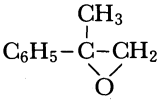
Synopsis. The reaction of various oxiranes with dimethyl sulfoxide in the presence of Molecular Sieve 4A and acid afforded the corresponding α-hydroxy ketones. The molecular sieve was found to accelerate the reaction.

It has previously been reported that the boron trifluoride induced dimethyl sulfoxide (DMSO) oxidation of some oxiranes gave α-hydroxy ketones.[1] Subsequently, the proposed intermediacy of (2-hydroxyalkoxy)sulfonium salts has been prepared by Swern and co-workers as a stable form by the treatment of oxiranes with excess DMSO in the presence of an equimolar amount of acid (i.e., CF_3CO_2H, HBF_4, and CH_3SO_3H).[2,3] However, they reported that the thermolysis of the intermediate alkoxysulfonium salt from 1,2-epoxycyclohexane gave a complex mixture without giving any predominant products.[3] They also described that the reaction of the salts from 2-phenyloxirane and 2,3-dimethyloxirane in DMSO-d_6 at 100 °C for 1 h resulted in an exclusive formation of phenylethanal and 2-butanone, respectively.[2,3] We found that the treatment of a DMSO solution of 2-phenyloxirane (**1a**) at 100 °C in the presence of a catalytic amount of alkoxysulfonium salt (**2a**), which was generated in situ from DMSO, **1a** and CF_3CO_2H, gave the expected 2-hydroxy-1-phenylethanone (**3a**). This finding led us to investigate the reactions of oxiranes with DMSO and acid giving α-hydroxy ketones via the alkoxysulfonium salts. The present paper deals with reactions of the various types of oxiranes with DMSO in the presence of an appropriate acid as catalyst.



1 **2** **3**

	R^1	R^2
a	C_6H_5	H
b	C_6H_5	C_6H_5
c	C_2H_5	H
d	C_6H_{13}	H
e	CH_3	CH_3
f	-(CH_2)-	
g	-$(CH_2)_{10}$-	



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Results and Discussion

The acid-catalyzed DMSO oxidation of 2-phenyloxirane (**1a**) in the presence of molecular sieve was examined in a ^1H NMR sealed tube. The solution of **1a** (0.5 mmol) in DMSO or DMSO-d_6 (2.5 mmol) showed the NMR signals which are assignable to the starting material. Upon the addition of CF_3CO_2H (0.025 mmol) and Molecular Sieve 4A (20 mg) at room temperature, three signal sets appeared: a methylene doublet at δ 3.90 and a methine triplet at δ 5.70 along with a pair of singlet of two nonequivalent *S*-methyl groups at δ 3.35 and 3.50. The new spectral sets observed are consistent with those of the reported (2-hydroxyalkoxy)sulfonium salt **2a**.[3] The molar ratio of **1a** : **2a** was calculated to be about 25 : 1, by a comparison of the signal magnitude of methylene protons of **1a** (δ 2.80 and 3.15) with that of *S*-methyl protons of **2a**. Upon heating the mixture at 100 °C, the signals of oxirane ring protons gradually disappeared and were replaced by three sets of signals: a singlet at δ 4.98 and two multiplets at δ 7.33—7.75 and 7.91—8.71. By a comparison with the spectrum of authentic sample **3a**,[1] the singlet and two multiplets could be assigned to the methylene and aromatic protons of **3a**. The simultaneous appearance of the other additional sets of signals, two multiplets at δ 3.0—3.8 and 4.4—4.8, and a singlet at δ 7.1, were observed. These are assigned to the methylene, methine, and aromatic proton signals[4] of the polymer of **1a** (**4**), which was isolated from the mixture after work-up. In addition, the formation of dimethyl sulfide was found in the NMR spectra (δ 2.00, singlet). No formation of 1,2-diol nor aldehyde was observed in a reaction mixture by NMR and GC-MS analysis, but a trace amount of the dimer of **1a** was detected by GC-MS. The dimer was assumed to be in a mixture of 2,5-diphenyl-1,4-dioxane and 2-benzyl-4-phenyl-1,3-dioxolane by NMR.[5] The relation between the used amount of CF_3CO_2H and the yields of **3a** and **4** in this reaction (100 °C, 7 and 14 h with molecular sieve) was examined, and the results are shown in Table 1. The yields of both compounds were calculated by an integration of their methylene signals using the aromatic proton signals as an internal standard. As shown in the table, the yield of **3a** reached its maximum value, 68.5% in a concentration of 0.05 equimolar amount of acid (Run 3). The yield of polymer **4** was 28.3% in this run. The use of a large amount of acid resulted in a decrease in the formation of **3a**. However, a longer time was required for completion at a lower content of CF_3CO_2H amount. In one run using 0.05 equivalent of CF_3CO_2H without a molecular sieve (Run 4), the reaction rate was slower than that in the presence of a molecular sieve (Run 3).

Meanwhile, the correlation between the amount of DMSO (2—9 equivalents) and the yield of **3a** was examined in the presence of a molecular sieve and 0.05 equivalent of CF_3CO_2H at 100 °C for 7 h. As a result, it was found that the use of a 5 equivalent amount of DMSO is optimum to yield **3a**.

Subsequently, the catalytic efficacy of other acids

Table 1. Reaction of 2-Phenyloxirane (**1a**) with DMSO in the Presence of CF_3CO_2H[a)]

Run	CF_3CO_2H/equiv	React. time/h	Products and yields/%[b)]		
			3a	**4**	**1a**
1	0.03	7	18.5	7.6	72.3
2	0.04	7	50.8	19.6	27.1
3	0.05	7	68.5	28.3	0
4[c)]	0.05	7	49.1	20.3	27.5
5	0.1	7	53	43.4	0
6	0.15	7	36.8	60	0
7	0.03	14	35.5	14.3	46.9
8	0.04	14	70.5	27	0

a) Reaction of **1a** (0.5 mmol) was conducted with DMSO (5 equiv) in the presence of CF_3CO_2H at 100 °C. All runs except Run 4 was carried out in the presence of Molecular Sieve 4A (20 mg). b) Determined by ^1H NMR. c) Molecular Sieve 4A was not added.

Table 2. Acid-Catalyzed Oxidation of Oxiranes with DMSO

Run	Compd., mmol	Acid, mmol	DMSO/ mmol	Mol. Sieve 4A/g	React. time/h	α-Hydroxy ketone (Isolated yield/%)	Other products (Isolated yield/%)
1	**1a**, 100	CF_3CO_2H, 5	500	4	20	**3a**(62.1)	Polymer **4**(8.4), **1a**(1.1)
2	**1b**, 100	CF_3CO_2H, 10	500	4	9	**3b**(57.2)	1,2-Diphenylethanone (7.9), Dimer of **1b**[a)] (trace)
3	**1b**, 100	CF_3CO_2H, 10	500	0	9	**3b**(49.3)	1,2-Diphenylethanone (7.1), Dimer of **1b** (trace), **1b**(6.6)
4	**1c**, 30	$HBF_4.Me_2O$, 1.5	150	0.75	10	**3c**(51.4)	
5	**1d**, 50	$HBF_4.Me_2O$, 2	250	1.25	14	**3d**(74.6)	**1d**(10.9)
6	**1e**, 30	$HBF_4.Me_2O$, 1.5	150	0.75	10	**3e**(44.4)	
7	**1f**, 50	$HBF_4.Me_2O$, 2	250	1.25	5	**3f**(88)[b)]	Cyclohexanone(0.8)
8	**1g**, 33	$HBF_4.Me_2O$, 1.65	165	0.825	9	**3g**(19.9)	Cyclododecanone(50)
9	**1h**, 50	CF_3CO_2H, 1	250	1.25	10	—	2-Phenylpropanal(44)

a) Detected by GC-MS.[6)] b) A mixture of monomer and dimer.[1)]

were examined by the NMR technique. A reaction of **1a** with DMSO in the presence of either $HBF_4 \cdot Me_2O$ (0.05 equivalent) or CH_3SO_3H (0.1 equivalent) at 100 °C for 10 h gave **3a** in modest yield, 30.1 and 25.2%, respectively.

The preparative experiment was carried out by the reaction of oxiranes with 5 equivalent DMSO in the presence of Molecular Sieve 4A and a catalytic amount of acid at 100 °C. The reaction conditions and results are given in Table 2. When Runs 2 and 3 were compared, it seemed likely that the use of a molecular sieve promotes the reaction of *trans*-2,3-diphenyloxirane (**1b**). The similar effect of a molecular sieve is demonstrated in Table 1, in a reaction of 2-phenyloxirane (**1a**). Thus, the other runs in Table 2 were performed in the presence of a molecular sieve. Compounds **3a** and **3b** were synthesized by the use of CF_3CO_2H as acid, while the preparation of other α-hydroxy ketones, **3c**—**3g**, were accomplished by the use of 0.04—0.05 equivalents of $HBF_4 \cdot Me_2O$, but not by CF_3CO_2H and CH_3SO_3H. No formation of isomeric 2-hydroxy aldehyde was observed in the oxidation of **1c** or **1d**. The reaction of 1,2-epoxycyclododecane (**1g**) gave a mixture of 2-hydroxycyclododecanone (**3g**) and cyclododecanone in yields of 19.9 and 50%, respectively. The modest yield of **3g** may be due to the steric hindrance of a bulky cycloalkyl group against the attack of DMSO on the oxonium salt of **1g**. 2-Methyl-2-phenyloxirane (**1h**) afforded 2-phenylpropanal exclusively in 44% yield. The GC-MS analysis of the crude product suggested the presence of a trace amount of 2-hydroxy aldehyde.

Swern and co-workers have reported that a treatment of the intermediate salt **2a** from 2-phenyloxirane **1a** with a base gave **3a**, but other salts prepared from other oxiranes decomposed by the action of base to a mixture of simple ketones, 1,2-diols or other products without giving α-hydroxy ketones.[3)] In contrast, various α-hydroxy ketones were now obtained by the acid-catalyzed oxidation of oxiranes via salts **2**.

The present method for the preparation of α-hydroxy ketones has synthetic utility. The reaction pathway involving the formation of (2-hydroxyalkoxy)sulfonium salts **2** and the elimination of dimethyl sulfide from **2** giving **3** are under way.

Experimental

^1H NMR spectra were obtained using a JEOL JNM-PMX 60 spectrometer (60 MHz). TMS was used as an internal

standard. GC-MS was performed on a JEOL JMX-DX 300 spectrometer at 70 eV.

NMR Monitoring Experiment for Oxidation of 2-Phenyloxirane (1a) with DMSO. Compound **1a** (0.5 mmol), DMSO-d_6 or DMSO (2.5 mmol) containing DSS as an NMR internal standard, Molecular Sieve 4A (20 mg) and CF_3CO_2H (0.025 mmol) were introduced into NMR tube in this order. The tube was sealed after the atmosphere was displaced by CO_2, and the NMR spectrum was then measured. The molar ratios of the reactants and yields of the products were calculated by integrating the NMR signals using the aromatic signals as an internal standard.

General Procedure for Preparation of α-Hydroxy Ketones by DMSO Oxidation of Oxiranes. Oxirane, anhydrous DMSO, Molecular Sieve 4A (beads size) and acid were placed in a sealed tube, and a stream of dry CO_2 was passed through the apparatus in order to displace the air. The vessel was sealed and the reaction mixture was heated at 100 °C. After completion of the reaction, the reaction mixture was poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution and the aqueous solution were separately evaporated in vacuum. The residues were purified by recrystallization or distillation in vacuo. The products were identified by comparisons with authentic samples (mp, IR and /or ^{1}H NMR spectra).

2-Hydroxy-1-phenylethanone (3a): Bp 105—110 °C/7 mmHg (1 mmHg≈133.322 Pa); mp 74—75 °C (lit,[2] 75 °C); IR (KBr) 3400 (OH) and 1690 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ=4.98 (2H, s, CH_2), 7.33—7.75 (2H, m, arom) and 7.91—8.71 (3H, m, arom).

***dl*-2-Hydroxy-1,2-diphenylethanone (3b):** Mp 130—131 °C (lit,[7] 129 °C); ^{1}H NMR ($CDCl_3$) δ=3.46 (1H, s, OH), 6.15 (1H, s, CH) and 7.23—8.05 (10H, m, arom); CI-MS M^++1, 213.

1-Hydroxy-2-butanone (3c): Bp 110—113 °C/100 mmHg (lit,[8] 79—80 °C/30 mmHg); IR (KBr) 3400 (OH) and 1710 cm^{-1} (C=O); EI-MS M^+, 88.

1-Hydroxy-2-octanone (3d): Oil; bp 74—78 °C/6 mmHg (lit,[9] 70—76 °C/6 mmHg); IR (KBr) 3400 (OH) and 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=0.93 (3H, d, CH_3), 1.32—2.33 (8H, m, CH_2), 2.67 (2H, t, CH_2CO), and 4.22 (2H, s, CH_2OH); CI-MS M^++1, 145.

2-Hydroxybutanone (3e): Oil; bp 98-105 °C/100 mmHg (lit,[10] 148 °C); IR (KBr) 3420 (OH) and 1710 cm^{-1} (C=O); CI-MS M^++1, 89.

2-Hydroxycyclohexanone (3f): Bp 82—85 °C/13 mmHg (lit,[1] 83—85 °C/13 mm); Compound **3f** was readily dimerized to 1,4-dioxane derivative.[1]

2-Hydroxycyclododecanone (3g): Bp 114—116 °C/6 mmHg; mp 75—77 °C (lit,[11] 78—79 °C); ^{1}H NMR ($CDCl_3$) δ=1.38—2.25 (18H, m, -$(CH_2)_9$-), 2.83 (2H, m, CH_2CO) and 4.42 (1H, s, CH); CI-MS M^++1, 198.

Cyclododecanone: Bp 73—81 °C/8 mmHg; mp 60—61 °C (lit,[12] 60.7 °C); CI-MS M^++1, 183.

2-Phenylpropanal: Bp 125—128 °C/96 mmHg (lit,[13] 202—205 °C).

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