The Effects of Solvents and Acid Catalysts on the Rearrangement of 2-Benzylidenecyclohexanone Oxide

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(Received April 12, 1971)

The rearrangement of 2-benzylidenecyclohexanone oxide (I) to 2-phenylcycloheptane-1,3-dione (II) was carried out in the presence of a Lewis acid or a Brϕnsted acid in various media-liquid sulfur dioxide, benzene, and ether. The only reaction product of I with a Brϕnsted acid in these solvents was the rearranged compound, II. In addition to II, 2-(α-halobenzyl)-2-hydroxycyclohexanone, (III) or (IV), was also obtained in the reaction of I with a Lewis acid in solutions. Drastic solvent effects were observed on the rate and the distribution of products in this reaction; however, no solvent effect was observed when a Brϕnsted acid, which could donate a proton to I, was used as the catalyst. From the variations in the concentrations of the reactant, the intermediate, and the product during the reaction course, the solvent effects upon the reaction pathways were discussed.

In a preceding paper[1] the rearrangement of 2-cyclohexylidenecyclohexanone oxide in the presence of a Lewis acid or Brϕnsted acid in a solvent, cyclohexane or liquid sulfur dioxide, was reported. The yield of the derived spiro [5.6]-dodecane-7,12-dione was discussed on the basis of its dependence on the solvent and the acid catalyst used. The combined use of a Lewis acid as the catalyst and liq. SO_2 as the solvent gave an excellent conversion, as large as a 93% yield of the spiro compound.

Although the rearrangement of α,β-epoxyketones under acidic conditions has been studied comprehensively from the synthetic point of view,[2] only a few studies have been undertaken to clarify the effects of the solvents and the catalysts.[3]

In the present communication, the results of the reaction of 2-benzylidenecyclohexanone oxide with an acidic catalyst in benzene, ether, or liq. SO_2 will be reported. As was reported previously, 2-cyclohexylidenecyclohexanone oxide has a hydrogen atom which can be eliminated as the proton during the reaction. The purpose of the present work is to study the solvent effects and also the role of the Lewis or the Brϕnsted acid on the α,β-epoxyketone rearrangement by selecting another compound, 2-benzylidenecyclohexanone oxide (I), which has no hydrogen atom to be drawn off during the reaction. In the reaction of 2-benzylidenecyclohexanone oxide (I), a procedure[1] similar to that used in the case of cyclohexylidenecyclohexanone oxide was followed.

Results and Discussion

The rearrangement of I was carried out at 20°C in sulfur dioxide, in benzene, and in ether. The reaction proceeds instantaneously in liq. SO_2, while in benzene the reaction is completed within thirty minutes. The reaction product of I with Brϕnsted acids in various solvents consisted only of the rearranged compound, 2-phenylcycloheptane-1,3-dione (II), mp 76.5—78.0°C.

Two products were obtained by the reaction with a Lewis acid, boron trifluoride etherate in benzene or ether. One was the rearranged product (II), while the other was 2-(α-fluorobenzyl)-2-hydroxycyclohexanone (III). The reaction of I with another Lewis acid, antimony pentachloride in benzene or ether, also gave two products, the rearranged compound, II and 2-(α-chlorobenzyl)-2-hydroxycyclohexanone (IV).

In Table 1 the results of experiments under various conditions are listed.

Table 1. Acid-catalyzed reactions of I at 20°C for 30 min

Catalyst	Solvent	Products, %		
		II	III	IV
H_2SO_4	SO_2	90.2	—	—
H_2SO_4	Benzene	90.1	—	—
FSO_3H	SO_2	80.7	—	—
FSO_3H	Benzene	83.2	—	—
$BF_3 \cdot OEt_2$	SO_2	70.3	0	—
$BF_3 \cdot OEt_2$	Benzene	36.1	50.6	—
$SbCl_5$	SO_2	50.0	—	8.7
$SbCl_5$	Benzene	6.7	—	73.9

II: 2-Phenyl-cycloheptane-1,3-dione.
III: 2-(α-Fluorobenzyl)-2-hydroxycyclohexanone.
IV: 2-(α-Chlorobenzyl)-2-hydroxycyclohexanone.

As is indicated in Table 1, when a Brϕnsted acid, H_2SO_4 of FSO_3H, was used, the product was exclusively the rearranged product (II), and the yields in the two solvents, liq.SO_2 and benzene, were almost the same.

However, the use as the catalyst of a Lewis acid, $BF_3 \cdot OEt_2$ or $SbCl_5$, which has no protonic hydrogen to donate, causes a drastic change in the solvent effects, affording a large quantity of III or IV in benzene. A similar trend was also observed when ether was used as the solvent.

It has well been established that fluorohydrins are formed by the reaction of epoxide with boron trifluoride etherate if the experimental conditions are right.[4,5] H.O.House showed that the treatment of I with boron

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[1] M. Nojima, K. Hinoue, and N. Tokura, This Bulletin, **43**, 827 (1970).

[2] R. E. Parker and N. S. Issacs, *Chem. Rev.*, **58**, 737 (1959), and the references cited there.

[3] W. Reusch, D. F. Anderson, and C. K. Johnson, *J. Amer. Chem. Soc.*, **90**, 4988 (1968).

[4] B. N. Blackett, J. M. Coxon, M. P. Hartshorn, and K. E. Richards, *Tetrahedron*, **25**, 4999 (1969).

[5] J. M. Coxon, M. P. Hartshorn, A. J. Lewis, K. E. Richards, and W. H. Swallow, *ibid.*, **25**, 4445 (1969).

trifluoride etherate in ether led to the formation of the fluorohydrin (III).6) The reaction of III with boron trifluoride etherate in ether to produce II was also examined; II was obtained directly from the reaction of I with boron trifluoride etherate in benzene. However, there was no conclusive evidence to indicate whether III was an intermediate in the formation of the carbonyl compound or merely a by-product. We examined the concentrations-time curves for the reactant and three products, I, II, and III, in an effort to decide whether or not III is an intermediate in the formation of 1,3-dione, boron trifluoride etherate being used as the catalyst.

Figure 1 reveals the concentration-time relationship between the constituents of the reaction mixture and the reaction process in the reaction in ether. In this case, only fluorohydrin (III) was formed at the early stage of the reaction; it reached a maximum value of 36%, and then slowly decreased with the reaction time. The yield of 1,3-dione (II) increased with an increase in the reaction time, and after 48 hr the yield reached 74%. These results seems to show that III is the intermediate for the formation of 1,3-dione under these conditions.

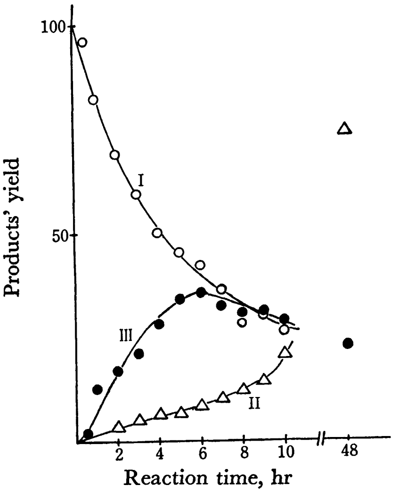


Fig. 1. The reaction of I with $BF_3\cdot OEt_2$ in ether.

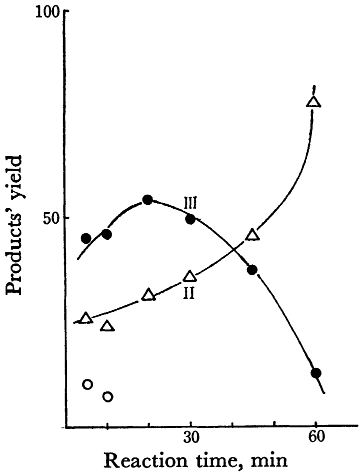
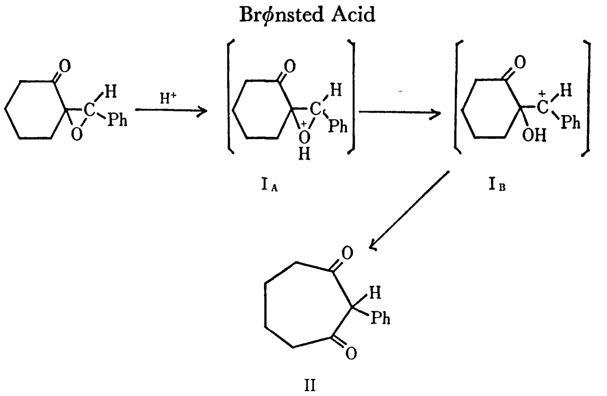


Fig. 2. The reaction of I with $BF_3\cdot OEt_2$ in benzene.

Figure 2 illustrates the behavior of I in a benzene solution. These curves indicate that III is produced at the first stage of the reaction and is then converted to 1,3-dione. However, at the early stage of the reaction periods *ca.* a 20% yield of 1,3-dione was formed; this result indicates that onestep (direct) formation of 1,3-dione may contribute in some degree.

In liquid sulfur dioxide the following results were obtained. At 20°C only the rearranged product (II) was formed. To explain these results, two mechanisms seem to be plausible. One is that, as the reaction rate of III is rapid in liquid sulfur dioxide, II is obtained as the sole product, although III is produced as the short-lived intermediate. The other possible explanation for these results is the one-step formation of II from I. To distinguish between the above two pathways, we carried out a reaction at −70°C. Under these reaction conditions we could not detect the formation of III, the only product being II at any reaction period. These results seem to show that the reaction of I with Boron trifluoride etherate in liquid sulfur dioxide proceeds directly to form 1,3-dione.

From these data, Scheme I may be taken to illustrate the probable reaction process. When Brønsted acid is used as the catalyst, I is attacked by a proton to form the intermediate, I_B, after the ring opening, and the migration of the acyl group may subsequently produce 1,3-dione, (II). Since the nucleophilicities of HSO_4^- and FSO_3^- in liq.SO_2 are very small, the intramolecular reaction (rearrangement) must occur predominantly.



Scheme I

Contrary to the above results, however, halohydrins were formed by the intermolecular epoxide cleavage reaction when Lewis acid was used as the catalyst in ether or benzene. Thus, the reaction pathways with boron trifluoride etherate are greatly dependent on the differences in the solvents. These results may indicate that the reaction rate is slowed down by the decrease in the electrophilicity of the catalyst for the formation of the cordinated complex and that the ionization necessary for the formation of 1,3-dione may be inhibited; the alternative reaction leading to fluorohydrin can then be operative, as is shown in Scheme II.

The fluorohydrin formed in an ether solution seems to arise through a cationic intermediate, I_A' (Scheme II), in which the carbon-oxygen bond is, for the most

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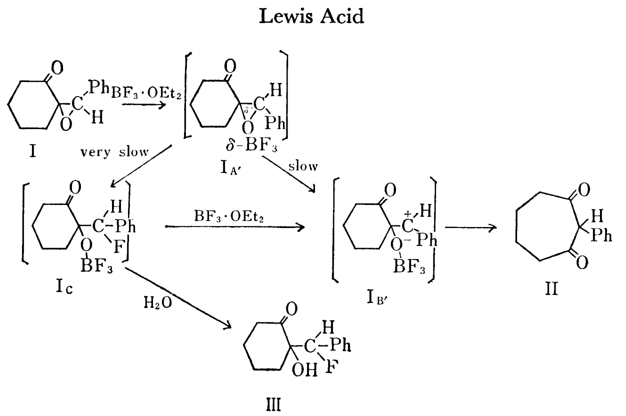
6) H. O. House and D. J. Reif, *J. Amer. Chem. Soc.*, **77**, 6525 (1955).



Scheme II

part, maintained. The opening of the epoxide ring of I in benzene seems to involve a transition state of a greater ionic character than the reaction in ether. It seems likely that the rearrangement of the intermediate, I_B', to form II is accelerated by the stabilization of the intermediate due to the solvation of the counter anion by liquid sulfur dioxide. When benzene or ether is used as the solvent, however, there is little means to stabilize the transition state and the displacement to form III seems to be competitive.

To examine further the reactivity of the reactant in this rearrangement, 2-*p*-chloro (IV) and 2-*p*-methyl derivatives (VI) of benzylidenecyclohexanone oxide were prepared and subjected to the same reaction. The reaction was carried out as has been described above, and the same procedure was used to separate the products.

In liquid sulfur dioxide, both the compounds gave over 90% yields of rearranged products, V and VII, when boron trifluoride etherate was used as the catalyst. In benzene, the same catalyst gave 94.7% of V; however, VI (*p*-chlorobenzylidenecyclohexanone oxide) gave 57.7% of the rearranged product, VII, and 28.3% of a fluorohydrine, VIII.

Thus, the electrodonative *p*-methyl group may facilitate the formation and stabilization of a carbonium ion of such a type as I_B' in Scheme II, which is a prime requisite for the rearrangement.

Experimental

Materials. The liquid SO_2 was dehydrated with H_2SO_4 and P_2O_5 successively and distilled. The benzene and ether were purified by ordinary methods.

Apparatus. The IR spectra were run on an EPIS2-type Hitachi IR Spectrometer. The NMR spectra were obtained with a Japan Electron Optics Spectrometer, JNM3H-60.

The mass spectra were recorded on a Hitachi RMU-6E single focusing instrument.

2-Benzylidenecyclohexanone Oxide (I). 2-Benzylidenecyclohexanone oxide was prepared by the method of House.[6] From 30.0 g of 2-benzylidenecyclohexanone and 60 m*l* of a 30% hydrogen peroxide solution, 10.0 g (32.6% yield, based on 2-benzylidenecyclohexanone) of 2-benzylidenecyclohexanone oxide was obtained; mp 124.5—125.0°C (lit,[6] mp 124.5—125.0°C).

2-p-*Methylbenzylidenecyclohexanone Oxide (IV).* 2-*p*-Methylbenzylidenecyclohexanone was prepared by the condensation of 2-*p*-methylbenzaldehyde with cyclohexanone, using sodium hydroxide as the catalyst. IV was obtained by the reaction of 2-*p*-methylbenzylidenecyclohexanone with 30% H_2O_2 according to the directions of House.[6] Mp 117°C (recryst. from *n*-hexane), IR(KBr), 1710 cm^{-1}; NMR($CDCl_3$), τ, 6.0(1H), 2.85(4H), 7.65(3H). Found: C, 77.52; H, 7.50%. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46%

2-p-*Chlorobenzylidenecyclohexanone Oxide (VI).* VI was prepared by the condensation of 2-*p*-chlorobenzaldehyde and cyclohexanone, followed by epoxidation. Mp 116.0—116.5 (rec. from *n*-hexane), IR(KBr), 1710 cm^{-1}; NMR ($CDCl_3$), τ, 6.0(1H), 2.69(4H). Found: C, 66.05; H, 5.53%. Calcd for $C_{13}H_{13}O_2Cl$: C, 65.95; H, 5.54%.

The General Procedure of the Reaction of I with the Acid Catalyst. To 200 mg of I and 10 m*l* of a solvent, we added 0.1 m*l* of the acid catalyst, after which the mixture was allowed to react at 20°C for 30 min. The reaction mixture was cooled, diluted with water, and extracted three times with ether. The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. The light yellow solid remaining after the evaporation of the solvent was analyzed by NMR spectroscopy. The relative integrals at the τ values 6.05 (I), 5.20 (II), 4.25 (III), and 4.6 (IV), were used to estimate the constituents in the products.

The Measurement of the Concentration-Time Relationship of the Reactant and of the Products in the Rearrangement. The Reaction with Boron Trifluoride Etherate as the Catalyst. To 2.0 g of I and 200 m*l* of the solvent, we added 2.0 m*l* of boron trifluoride etherate, after which the mixture was allowed to react at 20°C. A 10-m*l* aliquot was withdrawn periodically and diluted with water. Then it was worked up as has been described previously, and the relative ratios of the components were calculated from the relative integrals of the NMR spectra as has been described above.

Identification of the Reaction products. Reaction Products of I with Boron Trifluoride Etherate in Benzene. I(2.0 g), 1 m*l* of freshly-distilled boron trifluoride etherate, and 100 m*l* of benzene were maintained at 20°C for 30 min and then worked up as in the previous case. The residue after the removal of the solvent was chromatographed on 50 g of silica gel. After elution with five 50-m*l* portions of petroleum ether, elution with ten 50-m*l* portions of benzene gave 0.6 g (yield%) of a solid, which was then recrystallized from *n*-hexane. 2-Phenylcycloheptane-1,3-dione, (II); mp 76.5—78.0°C (lit,[6] mp 76.5—78.0°C). Mass; *m/e*, 202, Calcd for $C_{13}H_{14}O_2$, 202. NMR($CDCl_3$); τ, 2.73(5H singlet), 5.20(1H, singlet), 5.20(1H singlet), 7.40 and 8.00(8H multiplet). The physical data were also identical with those in the literature.[6]

Elution with ten 50-m*l* portions of benzene gave 1.2 g (yield%) of a solid, which was then recrystallized from *n*-hexane; 2-(α-fluorobenzyl)-2-hydroxycyclohexanone, (III), mp. 129—130°C (lit,[6] mp 129.5—130°C). IR(KBr), 1720, 3460 cm^{-1}; NMR($CDCl_3$), τ, 2.70(5H singlet), 4.25(1H, J: 40.2 Hz), 5.90(1H, singlet), 7.4 and 8.2(multiplet); Mass, *m/e*, 222, Calcd for $C_{13}H_{15}O_2F$, 222.

Reaction Products with Antimony Pentachloride in Benzene. The products was treated as above. Elution gave 1,3-dione (II) and a product, a white crystalline solid, (IV). IV was recrystallized from *n*-hexane and identified as 2-(α-chlorobenzyl)-2-hydroxycylcohexanone (IV); mp 103.5—105.0°C; IR (KBr) 1710, 3460 cm^{-1}; NMR ($CDCl_3$); τ, 4.6 (1H), 5.3(1H singlet); Mass, *m/e*, 238, Calcd for $C_{13}H_{15}O_2Cl$, 238.

The authors wish to thank the Seitetsu Kagaku K.K. for its donation of liquid sulfur dioxide. The present work was made possible by the support of the Scientific Research Fund of the Ministry of Education.