

Chemo- and Regioselective Conversion of Epoxides to Carbonyl Compounds in 5 M Lithium Perchlorate–Diethyl Ether Medium

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Received October 12, 1995

Epoxides are useful substrates in organic synthesis due to their high reactivity.¹ Conversion of an epoxide to a carbonyl compound is a synthetically useful reaction, and BF₃ and its etherate are the most commonly used reagents for this purpose.² Unless there is a structural or a stereochemical bias, generally multiple products are obtained due to the lack of regioselectivity in the ring opening step. Moreover, lack of chemoselectivity among various substituted epoxides limits the synthetic utility of this reaction in multistep synthesis. In fact, no epoxide has been reported to be insensitive to BF₃.² Lithium and magnesium halides have been used for epoxide ring opening reaction.^{2–4} Recently, chemo and regioselective isomerization of epoxides to carbonyl compounds by a palladium catalyst has been reported.⁵ Lithium perchlorate in refluxing benzene has been reported to be a very useful reagent for the rearrangement of several epoxides as it shows higher product selectivity compared to strong Lewis acids.^{2,3,6} Recently, 5 M lithium perchlorate in diethyl ether (LPDE) has been shown to be an excellent medium for several synthetic transformations, and high chemo-, regio-, and stereoselectivities have been reported.⁷ In our efforts to use this medium for selective synthetic transformations,^{8,9} we have investigated the ring opening reaction of epoxides, and herein we report our results.

Results and Discussion

The results from the rearrangement of various epoxides are summarized in Table 1. Benzylic epoxides from both acyclic and cyclic olefins (**1a**, **1b**, **1k**, and **1n**) rearranged with high regiospecificity to give a single product in each case. The reactions of the oxides of styrene and *trans*-stilbene were highly exothermic, and hence they were carried out either at 0 °C in 5 M LPDE or at rt in 1 M LPDE. It is noteworthy that styrene oxide

(**1a**) gave only phenylacetaldehyde (**2a**), which was stable to the reaction conditions. This product can be directly converted to the corresponding dithioacetal⁸ by adding 1 equiv of 1,2-ethanedithiol in the same medium, thus offering a convenient one-pot conversion of the epoxide to the corresponding dithioacetal. Among the acyclic olefin epoxides, the terminal olefin epoxides **1f–i** did not react in 5 M LPDE medium. However, the di- and trisubstituted epoxides (**1c–e** and **1p**) rearranged smoothly at rt. The bis-epoxide **1e** is an interesting example demonstrating the high chemo- and regioselectivities that can be achieved in 5 M LPDE medium. Thus, **1e** reacted to yield the epoxy ketone **2e** as the only product in which the terminal epoxide remained intact under the reaction conditions. Among the cyclic olefin epoxides, cyclohexene oxide (**11**) was found to be stable in 5 M LPDE medium. However, epoxides with a tertiary oxirane center rearranged readily to give the corresponding ketones without any ring contraction. The case of limonene oxide (**1o**) is noteworthy. When a 1:1 mixture of *cis* and *trans*-limonene oxides was reacted, it was found that only the *trans* diastereomer [1-methyl-*t*-4-(2-propenyl)-*r*-1-cyclohexene oxide] rearranged stereospecifically to give, exclusively, *trans*-dihydrocarvone [*trans*-5-(2-propenyl)-2-methylcyclohexanone] (**2o**) and the *cis* isomer [1-methyl-*c*-4-(2-propenyl)-*r*-1-cyclohexene oxide] remained intact. With strong Lewis acids such as ZnBr₂ and BF₃, no stereoselectivity has been reported for limonene oxide and other structurally related epoxides.^{10,11} Finally, norbornene oxide (**1q**) gave only 2-norbornanone (**2q**), in sharp contrast to the formation of two products in LiClO₄–benzene medium³ arising from the involvement of a nonclassical carbenium ion.

Based on the observed chemo- and regioselectivities and the products of rearrangement, it is inferred that the rearrangement of epoxides in LPDE medium could proceed by the coordination of the lithium ion to the epoxide oxygen followed by the cleavage of a C–O bond to give the most stable carbenium ion and subsequent hydride migration (except in the case of **1b**) to give the observed product. We attribute the observed chemo- and regioselectivities to the mild Lewis acidity of the lithium ion in ether.⁸ The stereoselectivity in the case of limonene oxide (**1o**) can be explained by invoking the rule of diaxial ring opening or the Furst–Plattner rule.¹¹ The *trans*-limonene oxide could undergo antiperiplanar ring opening with ease to give directly a chair conformer of the tertiary carbenium ion where as such a ring opening in the case of the *cis* isomer will initially lead to a twist boat conformer.^{2,11} The small differences in the activation barriers for the ring opening of these two diastereomers is manifested in LPDE medium. Such a highly diastereoselective ring opening is not possible with strong Lewis acids such as BF₃.¹¹ Similarly, the small differences in the activation barriers for the rearrangement of monosubstituted and higher substituted epoxides (as in **1e**) is also exemplified in this medium leading to very high chemoselectivity.

Experimental Section

Materials. Preparation of 5 M LPDE medium has been described previously.⁸ The epoxides were prepared from the

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

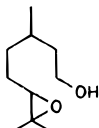
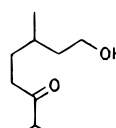
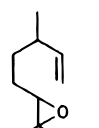
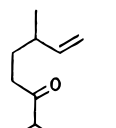
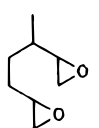
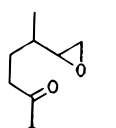


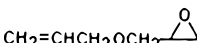
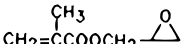





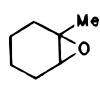

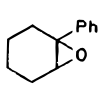

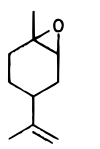
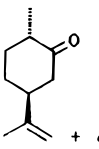
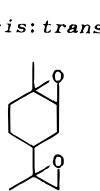
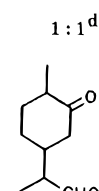


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Table 1. Epoxide to Carbonyl Rearrangement in 5 M LPDE

| | epoxide (1) | product (2) | duration | yield (%) | Ref |
|---|---|---|----------|-----------------|-------|
| a |  | PhCH ₂ CHO | 10 min | 85 | 3 |
| b |  | Ph ₂ CHCHO | 15 min | 60 | 14 |
| c |  |  | 4 h | 79 | 15 |
| d |  |  | 4 h | 82 ^b | 12,16 |
| e |  |  | 4 h | 70 ^b | 16 |
| f |  | no reaction | 24 h | 0 | 17 |
| g |  | no reaction | 24 h | 0 | 17 |
| h |  | no reaction | 24 h | 0 | |
| i |  | no reaction | 24 h | 0 | |
| j |  |  | 10 min | 78 | 18 |
| k |  |  | 10 min | 75 | 19 |
| l |  | no reaction | 24 h | 0 | 4 |
| m |  |  | 2 h | 83 | 4 |
| n |  |  | 45 min | 73 | 11 |
| o |  |  | 5 h | 90 ^c | 10,20 |
| | <i>cis:trans</i> 1:1 ^d | 1:1 ^d | | | |
| p |  |  | 4 h | 70 ^b | 21 |
| q |  |  | 1 h | 70 | 22 |

^a Isolated yield after purification. ^b Mixture of diastereomers. ^c Isolated yield based on unrecovered epoxide. ^d From the 400 MHz ¹H-NMR peak integration.

corresponding olefins using *m*-CPBA in CH₂Cl₂,¹² purified by column chromatography over silica gel, and characterized by IR, ¹H- and ¹³C-NMR, and mass spectral data, which were compared with the literature values. Epoxides **1h-i** were commercial samples.

General Procedure for the Epoxide Rearrangement in LPDE. In a typical experiment 0.01 mol of the epoxide was added to an ice-cold 5 M LPDE solution (2 mL) kept under N₂ atmosphere. In the case of **1a, b, j, k, n**, the reactions were carried out in the ice bath. In all the other cases the mixture was warmed to rt and stirred for the duration indicated in Table 1. The reactions were followed by TLC and GC analysis. After aqueous workup the products were purified either by preparative TLC or by column chromatography. The unreacted *cis*-limonene oxide (*cis*-**1o**) and *trans*-dihydrocarvone (**2o**) were separated by preparative GC. The products were characterized by IR, ¹H and ¹³C-NMR, and mass spectral data, which were compared with the literature values, and also by preparing the semicarbazone derivative. **2o** was identified by IR, NMR,¹³ and mass spectral data and also by preparing the semicarbazone derivative; mp

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187 °C (lit. 189–190 °C).¹⁰ An authentic sample of **2e** was obtained by the epoxidation of **2d**.

Acknowledgment. We gratefully acknowledge the Regional Sophisticated Instrumentation Centre, IIT, Madras, for NMR and mass spectral data. We thank Prof. K. K. Balasubramanian for valuable suggestions and discussions. We (R.S and V.G.S) thank CSIR, New Delhi, for Research Fellowships.

JO951839D

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