

Highly chemo- and regioselective rearrangement of α,β -epoxy ketones to 1,3-dicarbonyl compounds in 5 mol dm⁻³ lithium perchlorate–diethyl ether medium

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Received (in Cambridge, UK) 12th July 1999, Accepted 13th September 1999

Epoxides from α,β -unsaturated ketones undergo highly chemo- and regioselective rearrangement to 1,3-dicarbonyl compounds in 5 mol dm⁻³ lithium perchlorate–diethyl ether medium by a 1,2-migration of the carbonyl group at ambient conditions.

Introduction

Conversion of an epoxide to a carbonyl compound is a synthetically useful and important transformation.¹ However, the lack of chemo-, regio- and stereoselectivities in the ring-opening/rearrangement steps can limit the use of this reaction in synthetic sequences. Although the most commonly used reagent for this reaction is BF₃, it does not offer any chemo-selectivity.¹ Recently we have reported highly chemo-, regio- and stereoselective conversion of epoxides of simple olefins to carbonyl compounds in 5 mol dm⁻³ lithium perchlorate–diethyl ether (LPDE) medium.² Rearrangement of epoxides from α,β -unsaturated carbonyl compounds offers a convenient method for the synthesis of 1,2- and 1,3-dicarbonyl compounds and spirodiketones.³ Herein, we report highly selective transformation of epoxides from α,β -unsaturated ketones to 1,3-dicarbonyl compounds in 5 mol dm⁻³ lithium perchlorate–diethyl ether medium under mild reaction conditions.

Results and discussion

The epoxide **1** of benzalacetone reacted in 5 mol dm⁻³ LPDE medium at room temperature to give 3-oxo-2-phenylbutanal **2** as the only product in 78% yield after chromatographic purification. However, the epoxide of benzalacetophenone, **3**, failed to undergo any reaction under a variety of conditions listed in Table 1 and the starting material was recovered in all cases. The use of a stronger Lewis acid such as ytterbium triflate in catalytic amount in LPDE resulted in the conversion of epoxide **3** into 2,3-diphenyl-3-oxopropanal **4** as the sole product in 73% yield. Control experiments clearly showed that ytterbium triflate alone in diethyl ether did not cause any reaction in the absence of lithium perchlorate. In sharp contrast, epoxide **5** bearing an electron donating methoxy group in the *para* position underwent rearrangement smoothly to yield the keto aldehyde **6** in good yield within 30 min. Although it is well known in the literature that electron-donating substituents on the phenyl ring accelerate the rearrangement of epoxides from α,β -unsaturated ketones,⁴ the chemoselectivity observed between epoxides **1** and **3** is surprising and such selectivity is not observed when a stronger Lewis acid such as BF₃ is used. The epoxide **7** of mesityl oxide (4-methylpent-3-en-2-one), rearranged to give the keto aldehyde **8** whereas epoxide **9** did not undergo any reaction in this medium. In all these cases the formation of the 1,3-dicarbonyl compounds can be explained by a selective C–O bond cleavage followed by a 1,2-acyl migration mechanism.⁵

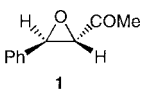
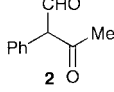
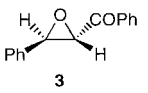
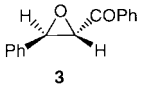
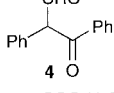
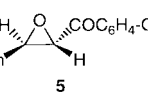
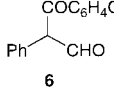
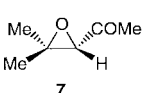
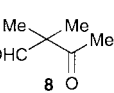
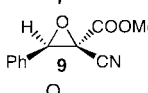
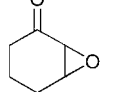
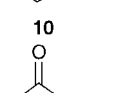
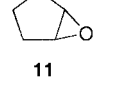
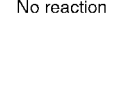
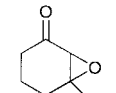
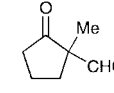
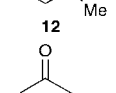
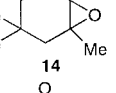
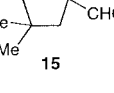
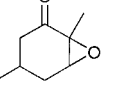
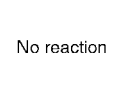
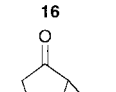
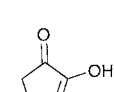
The epoxides from cyclohex-2-enone, **10**, and cyclopent-2-enone, **11**, were both inert and did not undergo any reaction in LPDE medium under a variety of conditions given in Table 1.

However, the corresponding β -methyl derivatives **12** and **17** reacted in LPDE at room temperature. In the case of epoxide **12**, rearrangement accompanied by ring contraction resulted in the formation of the keto aldehyde **13** whereas epoxide **17** yielded the α -hydroxy ketone **18** as the sole product. Similarly, isophorone oxide **14** underwent ring contraction to give **15** as the only product. In the case of **16**, an α -methyl-substituted derivative, no reaction occurred under various conditions employed. In the case of epoxide **19** rearrangement resulted in ring enlargement to yield the diketone **20**. The bicyclic epoxide **21** yielded the α -hydroxy enone **22**. Both the epoxides **19** and **21** rearranged only in the presence of Yb(OTf)₃ in LPDE.

Mechanism

Spectroscopic evidences strongly suggest that lithium ion in LPDE medium is a weak Lewis acid, its Lewis acidity being moderated by the coordination of the ether oxygen to the lithium ion.⁶ The high selectivities observed in organic transformations carried out in LPDE medium is attributed to the mild Lewis acidity of the lithium ion.⁷ Earlier we had reported chemo-, regio- and stereoselective conversion of simple epoxides to carbonyl compounds and we attributed the observed selectivities to the mild Lewis acidity of the lithium ion in LPDE medium.² The epoxide ring-opening/rearrangement reaction in LPDE medium could proceed by the tentative mechanism shown in Scheme 1. The lithium ion coordinates to the epoxide oxygen and the carbonyl oxygen, resulting in weakening of the epoxide C–O bond followed by regio-selective cleavage of the C–O bond to give the most stable carbenium ion (Scheme 1). This explains why only β -substituted epoxides undergo rearrangement because only then can a stable tertiary carbenium ion be formed. The migration of the acyl group to the carbenium ion center leads to the formation of the 1,3-dicarbonyl compound as the product of rearrangement. Attempts to trap any carbenium ion intermediates that could be formed during the ring-opening step using a silyl enol ether as a nucleophile failed. For example, the rearrangement of epoxide **5** in the presence of 1-(trimethylsilyloxy)cyclohexene yielded only the rearranged product although retardation of the rate of the reaction was observed in the presence of the silyl enol ether. Whereas in the absence of the silyl enol ether the rearrangement of **5** was complete within 30 min, in the presence of the same the reaction was complete only after 36 h, under otherwise identical conditions. Similarly the rearrangement of epoxide **14** in LPDE in the presence of 1-(trimethylsilyloxy)cyclohexene also yielded only the keto aldehyde **15** and there is no evidence for the formation of any trapping product from the silyl enol ether. However, in the presence of the enol ether the

Table 1 Rearrangement of α,β -epoxy ketones in LPDE

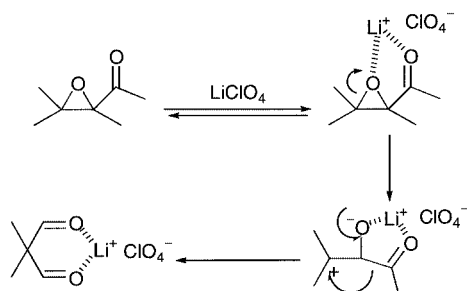
Epoxide	Product	Ref.	Conditions ^a	Yield (%)
		9	A, 30 min	78
	No reaction		A–D, 2 days	
		10	E, 20 h	73
		10, 11	A, 30 min	75
		12	A, 21 h	53
	No reaction		A, C, 2 days	
	No reaction		A–E, 2 days	
	No reaction		A–E, 2 days	
		9, 13	A, 21 h	68
		14	A, 21 h	69
	No reaction		A–E, 2 days	
		13, 15	A, 6 h	74
		13	E, 20 h	70
		16	E, 21 h	65

^a Reaction conditions: A: 5 mol dm⁻³ LPDE, rt; B: 5 mol dm⁻³ LPDE, 60 °C; C: 5 mol dm⁻³ LPNM, rt; D: 5 mol dm⁻³, LPNM, 60 °C; E: 5 mol dm⁻³ LPDE, 10% Yb(OTf)₃, rt.

rearrangement of **14** was complete only after several days. The retardation in the rate could be due to the competitive binding of lithium ion by the silyl enol ether thereby reducing the

effective concentration of the lithium ion. That the rate of the rearrangement is highly dependent on the lithium ion concentration is clearly demonstrated by carrying out the reaction

under various lithium perchlorate concentrations. Reducing the concentration of the lithium perchlorate from 5 mol dm⁻³ to 2.5 mol dm⁻³ caused a dramatic decrease in the rates of these reactions. For example, the rearrangement of epoxide **5** was complete within 30 min in 5 mol dm⁻³ LPDE whereas in 2.5 mol dm⁻³ LPDE it took 36 h for completion. Similarly the rearrangement of epoxide **14** was complete only after 55 h in 2.5 mol dm⁻³ LPDE solution whereas the reaction was complete within 21 h in 5 mol dm⁻³ LPDE. This type of concentration effect on the rate has also been observed earlier in the dithioacetalization of aldehydes and acetals, a Michael reaction of enol ethers in LPDE medium.⁷



Scheme 1 Mechanism for the rearrangement of epoxides in LPDE medium.

Conclusions

Epoxides derived from cyclic and acyclic α,β -unsaturated carbonyl compounds underwent highly chemo- and regioselective rearrangement to yield 1,3-dicarbonyl compounds in 5 mol dm⁻³ LPDE medium. The high selectivities observed in the rearrangement of epoxide are attributed to the mild Lewis acidity of lithium ion in this medium. Addition of silyl enol ether affected only the rate of the reaction and did not alter the course of the rearrangement reactions.

Experimental

Materials

Preparation of 5 mol dm⁻³ LPDE and lithium perchlorate in nitromethane (LPNM) and the instrumentation used have been described earlier.⁷ The epoxides were prepared according to the following general procedure.⁸ To a solution of the α,β -unsaturated ketone (20 mmol) in methanol (140 cm³) cooled to 0 °C was added a 30% aqueous solution of H₂O₂ (110 mmol). To this stirred mixture was added a 10% aqueous solution of NaOH (5 cm³) and the mixture was stirred for an additional 1–2 h at 0 °C. The reaction mixture was diluted with CH₂Cl₂ (250 cm³), and the organic layer was separated, washed with saturated brine (50 cm³), dried over anhydrous Na₂SO₄ and then concentrated under vacuum to afford the crude epoxides, which were further purified by either recrystallization or by vacuum distillation. All the epoxides are literature known compounds and in the present study they were characterized by IR, high-resolution (400 MHz) ¹H and ¹³C NMR, and mass spectroscopic data.

General procedure for the rearrangement of epoxides

A solution of an epoxide (2 mmol) in 5 mol dm⁻³ LPDE (2 cm³) was stirred at room temperature under N₂ atmosphere until its complete disappearance as indicated by TLC. The reaction mixture was diluted with CH₂Cl₂ (30 cm³) and washed with water. The organic layer was dried over anhydrous Na₂SO₄ and the solvent was removed to obtain the crude product, which was purified by column chromatography over silica gel. The products are literature known compounds and they were characterized in the present study by IR, high-resolution (400 MHz) ¹H and ¹³C NMR, and mass spectroscopic data. The literature references are given in Table 1.

Acknowledgements

Financial support from CSIR, New Delhi, in the form of a Senior Research Fellowship (J. E. N) and a Sponsored Research Project (S. S.) is gratefully acknowledged. We thank the Regional Sophisticated Instrumentation Centre, IIT, Madras, for the high-resolution NMR and mass spectral data.

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