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Studies in the Rearrangement of Epoxides with Lithium Dialkylamide-Lithium *tert*-Butoxide

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Abstract: Rearrangement of epoxides with lithium diethylamide or lithium diisopropylamide in conjunction with lithium *tert*-butoxide was studied in different solvents. In some cases, an increase in the rate of reaction was observed.

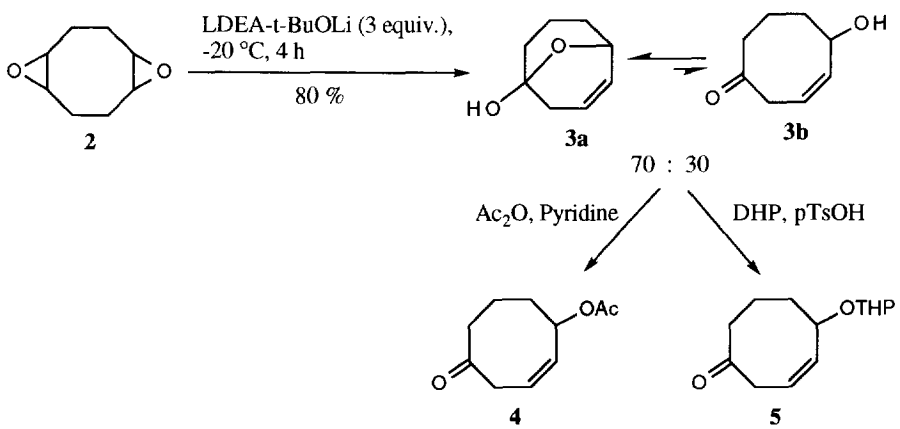
It was Cope and co-workers[1] who first reported the facile base promoted conversion of epoxides to their isomerized products using lithium diethylamide (LDEA)[2] base. Crandall *et. al.*[3] extended the work further to some other epoxides. Rickborn and co-worker[4] did extensive studies on the deprotonation of cyclohexene oxide using lithium monoalkyl and dialkylamide bases derived from primary and secondary amines, respectively. They have shown that allylic alcohols are invariably major products in the reaction. The other minor products are homoallylic alcohol, ketone, and aminoalcohol. The ratio of these products depends very much on the substituents attached to the nitrogen atom of the base used in the reaction. Boeckman[5] observed that n-butyllithium (n-BuLi) itself can deprotonate epoxides at low temperature. This was an important observation since n-BuLi is commonly used for making lithium dialkylamide bases. Apparu and Barrelle[6] have reported that the replacement of normal solvents (THF, ether, benzene) by hexamethylphosphoramide (HMPA) causes a dramatic change in the deprotonation reaction, both in the rate and product distribution. Schlosser and co-workers[7] have used LIDAKOR, a mixed base prepared from lithium diisopropylamide (LDA) and t-BuOK for smooth conversion of epoxides to allylic alcohols. The reagent is quite effective on acyclic substrates as well.[8]

A survey of available literature[9] reveals that the base induced isomerization of epoxides proceeds *via* two major pathways, *viz.* β-elimination and α-elimination. In the former case, a methylene hydrogen adjacent to an epoxide ring is abstracted to give allylic alcohol whereas in the latter process, the epoxide ring hydrogen is abstracted to give a carbonyl group or other isomeric compounds. It has been proved through deuterium-labelling studies that cyclohexene oxide undergoes exclusive *syn* β-elimination in ether, benzene, and HMPA. However, cyclopentene oxide gives 2-cyclopentenol *via* an α-elimination in benzene or in ether solvents but *via* β-elimination in HMPA.[10] The α-elimination process in the conversion of acyclic epoxide to allylic alcohol has been ruled out based on deuterium studies.[1e] Among medium ring epoxides, due to transannular interactions, the bicyclic alcohol is the major or the sole product. This kind of reaction is called transannular cyclization and is thought to proceed *via* α-elimination, followed by C-H insertion to the lithiated epoxide. The importance of Li^+ complexation in nonpolar solvents such as benzene and ether is crucial in the rearrangement of epoxides with

LDA. In HMPA, which is a cation-complexing solvent, the Li^+ complexation is not necessary for β-elimination.[10]

Recent interest in the base induced isomerization of epoxides has been due to the need for an asymmetric version of the reaction. From our laboratory, we have made a significant contribution to this area.[11] However, there is a need for more work. The task has become difficult due to uncertainty about the structure of lithium dialkylamide bases. It is known in the literature that lithium dialkylamides exist as aggregates of dimer, tetramer, or higher oligomers.[12-14] The degree as well as the nature of the aggregation or association depends upon the structure of the amine and the solvent used for its preparation. Though, for simplicity, the monomeric structure of lithium dialkylamide is usually shown, the actual reactive species may be any of the forms or a combination of all. Moreover, the lithium alkoxide generated during the reaction may also be involved in the aggregation process. In order to see the effect of lithium alkoxide on the base induced rearrangement of epoxides, we report here our results on lithium dialkylamide-t-BuOLi induced isomerisation of epoxides.

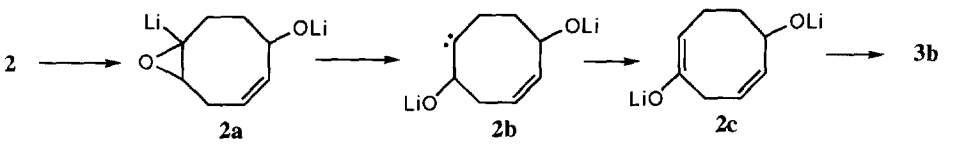
A variety of epoxides were synthesized from the corresponding olefins. The deprotonation reaction was carried out in THF and the results are summarized in table 1. It is clear from the table that there is some effect of t-BuOLi on the deprotonation reaction. It was observed that the combination of t-BuOLi and LDEA enhanced the isolated yield of 2-cyclohexen-1-ol **1** in the deprotonation reaction of cyclohexene oxide (entry 2). The preliminary study was quite encouraging, so the reactions were extended to other epoxides. The effect of t-BuOLi in the deprotonation of cyclooctadiene diepoxide **2** is the most obvious (table 1; entries 4 vs 5 and 7 vs 8). LDEA at lower temperature (-20 °C) did not produce even trace amounts of products **3** (table 1; entry 6). However, the reaction took place efficiently with LDEA in conjunction with t-BuOLi under the same conditions (Scheme I). As was the case with the earlier substrate, t-BuOLi alone was not a strong enough base to cause reaction.



Scheme I

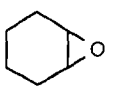
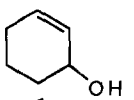
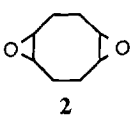
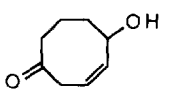
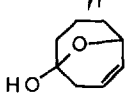
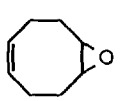
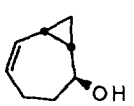
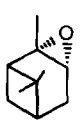
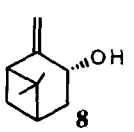
As shown in Scheme I, the reaction of the diepoxide **2** with 3 equivalents of LDEA-t-BuOLi provided **3** (80 % yield) which existed as an equilibrium mixture of a lactol **3a** and a keto-form **3b** in the ratio of 70:30. If the stoichiometry of the base system is 1.5 equivalent, the isolated yield is reduced to 70% (Table 1; Entry 8). The structure of the product **3** was also confirmed by derivatization to its corresponding acetate **4** and THP ether

5. The formation of **3b** is unique and it can be explained if one epoxide ring undergoes deprotonation *via* β-hydrogen elimination and the another epoxide cleaves *via* α-hydrogen elimination[15] to give a species **2a** followed by hydrogen insertion to a carbene **2b** (Scheme II). We are unable to explain the regiospecific α-elimination of hydrogen to provide the species **2a**.



Scheme II

Table 1: LDA-t-BuOLi and LDEA-t-BuOLi Induced Rearrangement of Epoxides.

Entry	Epoxide	Product	Base System[a]	Solvent	Conditions	Yield[b](%)
1.		 **1**	LDEA	THF	0 °C, 6 h	50
2.			LDEA-t-BuOLi	THF	0 °C, 6 h	79
3.			t-BuOLi	THF	0 °C, 6 h	00
4.	 **2**	 **3a** (33%)	LDA	THF	0 °C, 2 h	40
5.			LDA-t-BuOLi	THF	0 °C, 2 h	70
6.			LDEA	THF	-20 °C, 2 h	00
7.			LDEA	THF	0 °C, 2 h	10
8.			LDEA-t-BuOLi	THF	-20 °C, 2 h	70
9.		 **3b** (66%)	t-BuOLi	THF	0 °C, 2 h	00
10.	 **6**	 **7**	LDEA	THF-HMPA (1:1)	-20 °C, 30 min	95
11.			LDEA-t-BuOLi	THF-HMPA (1:1)	-20 °C, 30 min	95
12.		 **8**	LDEA	THF	reflux, 6 h	52
13.			LDEA-t-BuOLi	THF	reflux, 6 h	74

[a]1.5 equivalent of the base has been used in all the entries. [b]The reported yield is isolated ones.

It has been reported[3a] that an epoxide **6**, on deprotonation with LDEA in THF, gave a mixture of allylic and homoallylic alcohols in 2:1 ratio. However, if the reaction was done in neat HMPA, a bicyclic alcohol **7** was the major product.[6] In order to see the effect of t-BuOLi, we studied the reaction in its presence in different ratios of solvents and concluded that THF: HMPA (1:1) is the best combination for obtaining product **7** (Table 1; Entries 10, 11). Although t-BuOLi did not show any rate acceleration in this reaction, the present condition is more convenient to synthesize the bicyclic compound **7**. A marginal effect of rate acceleration is seen in the rearrangement of α-pinene oxide (Entry 12 & 13). In view of the nonavailability of any solid proof, we refrain from commenting about the exact species involved in the base induced rearrangement of epoxides in the presence of t-BuOLi. But, we do predict that t-BuOLi may be an aid in breaking aggregation of the bases.

In conclusion, we have studied the effect of t-BuOLi in the rearrangement of epoxides with LDA and LDEA. We have shown that there is an appreciable increase in the isolated yield of the product. The drawback with the method was that it did not show any effect on acyclic epoxides. The application of the idea to an asymmetric version of the deprotonation reaction is in progress and will be reported in due course.

EXPERIMENTALS

^{1}H NMR spectra were recorded on Jeol and Brucker, as mentioned in the experimental, using TMS as internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. IR spectra were recorded on Perkin-Elmer 580 and 1320 spectrometers.

Routine monitoring of reactions was performed using silica gel-G obtained from Acme. All the chromatographic separations were done by using silica gel (Acme's, 60-120 mesh). Petroleum ether used was of boiling range 60-80 °C. Reactions, which needed anhydrous conditions, were run under an atmosphere of dry nitrogen or argon using flame-dried glasswares. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl under nitogen. Hexamethylphosphoroic amide (HMPA) was distilled over CaH_2 at reduced pressure. t-BuOH was dried over sodium metal by refluxing for a few hours followed by distillation. The organic layer was washed with brine and stored over *anhydrous* Na_2SO_4 for 30 min before use. Evaporation of solvents was performed at reduced pressure, using a Büchi rotary evaporator.

General Procedure for Deprotonation of Epoxides by the Base System (LDA-t-BuOLi or LDEA-t-BuOLi): Diethylamine or diisopropylamine (1.7 mmol) and t-BuOH (1.5 mmol) were taken in an appropriate solvent (5 mL). n-BuLi (1.5 M in hexanes, 3.0 mmol) was added at -20 °C or at 0 °C (as mentioned in Table 1). After 15 min. an epoxide (1 mmol) was added at the same temperature and the reaction mixture was further stirred. It was diluted with ether and washed with water and brine. The organic layer was dried over *anhydrous* Na_2SO_4. The solvent was removed on a rotary evaporator and the crude was purified over silica gel column chromatography to get the pure product (Table 1).

2-Cyclohexen-1-ol 1[11]: R_f 0.45 (EtOAc in petroleum ether, 1:4); IR (film): 3350, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.60 (m, 2H), 1.75 (m, 1H), 1.85 (s, 1H, -OH), 1.90 (m, 1H), 2.0 (m, 2H), 4.2 (s, 1H), 5.76 (m, 1H), 5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ18.9, 25.0, 32.0, 65.4, 129.9, 130.4.

Deprotonation of cyclooctadiene diepoxide 3: This was carried out following the general procedure. The product (80 % yield) was an inseparable mixture of lactol **3a** and keto-form **3b** (ratio 3:1): R_f 0.35 (EtOAc

in petroleum ether, 1:5); UV ($CHCl_3$) λ 276, 240 nm; FTIR ($CHCl_3$): 3400, 1703, 1650, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ2.1 (m, 4H), 2.55 (m, 3.7 H), 3.10 (dd, J = 18, 4.5 Hz, 0.15 H), 3.20 (dd, J = 18, 4.5 Hz, 0.15 H), 3.8 (s, 1H, OH), 4.58 (bs, 1H), 5.6 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.2, 37.1, 38.1, 44.2, 70.0 (keto-form) 75.5 (lactol-form) 106.6 (lactol-form), 125.1 (lactol-form), 126.4 (keto-form), 127.1 (keto-form), 127.3 (lactol-form), 212.5 (keto-form). MS (CI, m/z): 140 (M^+, base peak), 85, 57. Anal. calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57; Found: C, 68.26; H, 8.64.

5-Acetoxy-3-cycloocten-1-one 4: The compound **3** (180 mg, 1.28 mmol) was treated with Ac_2O (240 μL, 2.6 mmol) and pyridine (207 μL, 2.6 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left at rt overnight. It was diluted with ether, washed with water and brine. Purification over silica gel gave pure acetate **4** (170 mg, 70% yield): R_f 0.50 (EtOAc in petroleum ether, 1:5); UV ($CHCl_3$) λ 288, 239 nm; FTIR (nujol): 1735, 1703, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ2.03 (s, 3H), 2.06 (m, 1H), 2.12 (m, 1H), 2.3 (m, 2H), 2.45 (m, 1H), 2.6 (m, 1H), 3.13 (dd, J = 18, 4.5 Hz, 1H), 3.2 (dd. J = 18, 4.5 Hz, 1H), 4.93 (m, 1H), 5.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ21.0, 28.7, 30.4, 38.1, 44.2, 71.9, 126.2, 126.8, 170.0, 211.6; MS (Fab, m/z): 183 (M^++ 1), 123 (base peak), 95. Anal. calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69; Found: C, 66.14; H, 7.76.

5-Tetrahydropyranyloxy-3-cycloocten-1-one 5: The compound **3** (120 mg, 0.86 mmol) was treated with dihydropyran (117 μL, 1.28 mmol) and a catalytic amount of p-TSA.H_2O in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was left at rt for 8 h. It was diluted with ether, washed with water and brine. Purification over silica gel gave pure THP ether **5** (135 mg, 60% yield): R_f 0.60 (EtOAc in petroleum ether, 1:5); IR (film): 1700 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ1.5 (m, 6H), 1.6 - 2.8 (m, 6H), 3.1 (m, 2H), 3.2 - 4.1 (m, 3H), 4.8 (m, 1H), 5.8 (m, 2H). Anal. calcd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.92; Found: C, 69.58; H, 9.02.

Bicyclo[5.1.0]octene-5-ol-2-endo 7[6] (Table 1; Entry 11) Yield 95%; R_f 0.26 (EtOAc in petroleum ether, 1:9); IR (film): 3340, 1025 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ0.26 - 2.2 (m, 8H), 2.3 (s, 1H, OH), 4.0 - 4.5 (m, 1H), 5.3 - 6.0 (m, 2H).

Bicyclo[3.3.1]heptan-3-ol, 6,6-dimethyl-2-methylene-(1α, 3α, 5α) 8[3d] (Table 1; Entry 13): Yield 74%; R_f 0.40 (EtOAc in petroleum ether, 1:9); IR (film): 3370, 1640, 890 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ0.65 (s, 3H), 1.28 (s, 3H), 1.6 - 2.6 (m, 7H), 4.4 (d, J = 7 Hz, 1H), 4.80 (s, 1H), 5.0 (s, 1H).

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