Pergamon

Tetrahedron 54 (1998) 11597–11602

TETRAHEDRON

A New Base Promoted Rearrangement of (*E*)-1-Benzyloxy-2,3-Epoxyalkanes

Angelika Thurner[a], Ferenc Faigl[a*], Alessandro Mordini[b*], Anna Bigi[b], Gianna Reginato[b], László Töke[a]

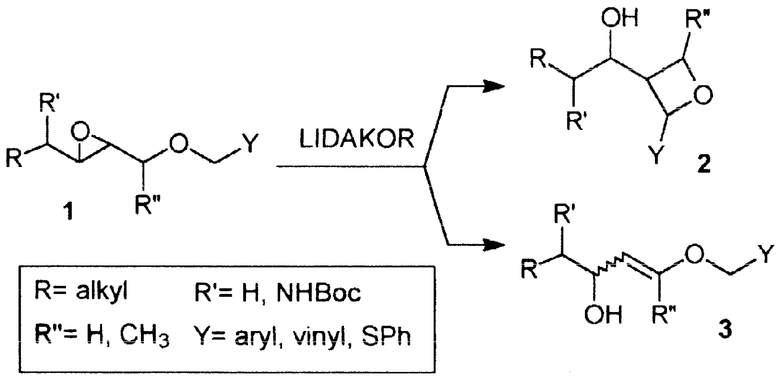
[a] The Research Group of Hungarian Academy of Sciences, Department of Organic Chemical Technology, Technical University of Budapest, Müegyetem rkp. 3, H-1521 Budapest, Hungary; e-mail: faigl.oct@chem.bme.hu

[b] Centro CNR Composti Eterociclici, c/o Dipartimento di Chimica Organica "U. Schiff", via G. Capponi 9, I-50121 Firenze, Italy; e-mail: mordini@cesce.fi.cnr.it

Received 15 April 1998; revised 29 June 1998; accepted 16 July 1998

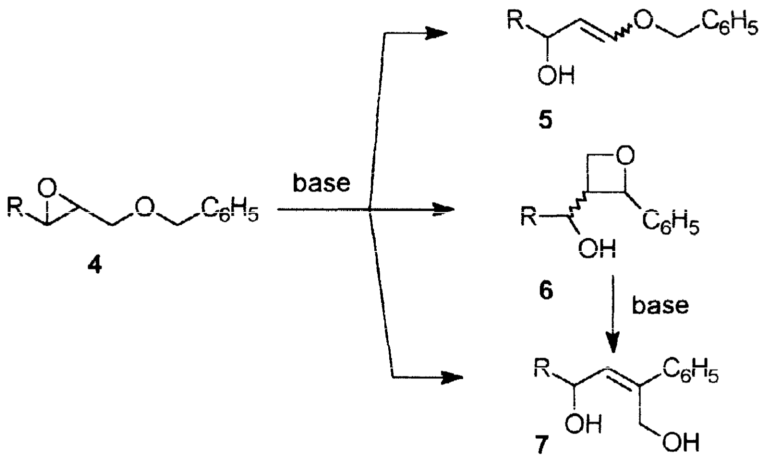
Abstract: (*E*)-1-benzyloxy-2,3-epoxyalkanes (**4**) underwent stereoselective rearrangement in the presence of LIDAKOR reagent and large excess of butyllithium producing (*Z*)-alkendiols (**7**) at ambident temperature. The same reaction serves *anti* oxetanes (**6**) at -75 °C which can also rearrange to **7** when the temperature arises. © 1998 Elsevier Science Ltd. All rights reserved.

We have very recently reported[1-3] about the rearrangement of oxiranyl ethers **1** to hydroxy oxetanes **2**. Primary oxiranyl ethers (**1**, R''= H) when treated with the superbasic[4] mixture butyllithium/ diisopropylamine/ potassium *tert*-butoxide (LIDAKOR[5]), undergo a clean conversion to disubstituted oxetanes (**2**, R''= H) only when Y is an unsubstituted phenyl group,[1] other substituent on the chain bonded to the oxiranyl ring being tolerated.[2] If Y is a *para*-substituted phenyl ring or another kind of activating group, a mixture of the oxetane **2** and of the vinyl ether **3** is obtained with the latter being usually the major product.[1] On the other hand, secondary oxiranyl ethers (**1**, R''= CH_3) are converted into the corresponding trisubstituted oxetanes (**2**, R''= CH_3) no matter which is the nature of group Y.[3] In all cases the rearrangement is highly stereoselective, always leading to the *anti*-stereoisomer as the major if not exclusive product.



PII: S0040-4020(98)00684-X

In a further investigation on the stereoselectivity of the process as a function of the base employed and the reaction conditions used, we have found that upon treatment of (*E*)-1-benzyloxy-2,3-epoxyoctane **4a** or (*E*)-1-benzyloxy-2,3-epoxyhexane **4b** with a metal amide in the presence of a large excess of alkyllithium the unsaturated diols **7a** and **7b** are formed, respectively. The influence of the reaction conditions on the product distribution was carefully investigated in the case of **4a**. The results are summarized in the Table.



a: R = C_5H_{11}

b: R= C_3H_7

The diol **7a** is obtained as the unique product (yields are given in the experimental section) when an excess of butyllithium in ethereal solvents is used (entries 3, 5, 13), whereas in hexane even a large excess of base leads to a mixture in which the diol is present in a 80 : 20 ratio together with the oxetane **6a** (entry 9). The rearrangement is also strongly dependent on the temperature. When the reaction mixture is kept at low temperature (-75 °C) after addition of the base, no rearrangement occurs (entries 4, 6, 8, 10) despite the large excess of base. As soon as the temperature is increased to 25 °C, the reaction takes place at an extent which is related to the other conditions as specified above. The diol **7a** is certainly derived from the oxetane **6a** as it has been demonstrated by submitting the latter to treatment with two equivalents of the same organometallic base and recovering again diol **7a** as the sole product.

We obtained the same results with **4b.** The *anti* oxetane **6b** formed when one equivalent of LIDAKOR reagent was used in tetrahydrofuran solution. The diol **7b** was again the sole product from the reaction of **4b** with the LIDAKOR reagent in the presence of a large excess of butyllithium. at 25 °C.

Attempts to extend this isomerization method to the oxiranes **1** where **Y** was *para* methoxy, fluoro, trifluoromethyl or *tert*-butyl substituted phenyl ring or R'' was methyl group instead of hydrogen have failed. Multicomponent reaction mixtures were obtained in all cases. This observation is in accordance with our previous findings[1-3] on the parallel formation of the oxetanes **2** and vinyl ethers **3** in these cases. Furthermore, vinyl ethers (**3**) undergo Wittig type rearrangement in the presence of an excess of strong bases.[1-3]

Table. **Isomerization** of Oxirane **4a** with Bases.

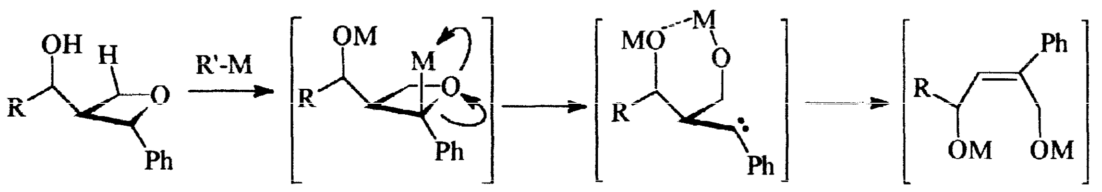
Entry	Amine[a]	Reagent comp.[b]	Solvent, T °C, time	**5** : **6** : **7**	*Z*-**5** : *E*-**5**	*syn*-**6** : *anti*-**6**
1	DIA	1 : 1 : 1	THF, 25 °C, 2h	0 : 100 : 0		0 : 100
2	DIA	1 : 2 : 1	THF, 25 °C, 2h	0 : 100 : 0		0 : 100
3	DIA	1 : 3 : 1	THF, 25 °C, 2h	0 : 0 : 100		
4	DIA	1 : 3 : 1	THF, -75 °C, 2h	0 : 100 : 0		25 : 75
5	DIA	1 : 3 : 1	DEE, 25 °C, 2h	0 : 0 : 100		
6	DIA	1 : 3 : 1	DEE, -75 °C, 2h	0 : 100 : 0		40 : 60
7	DIA	1 : 1 : 1	HEX, 25 °C, 2h	0 : 100 : 0		0 : 100
8	DIA	1 : 3 : 1	HEX, -75 °C, 2h	4 : 96 : 0	100 : 0	30 : 70
9	DIA	1 : 3 : 1	HEX, 25 °C, 2h	0 : 20 : 80		0 : 100
10	DMPM	1 : 2 : 0	THF, -75 °C, 2h	0 : 100 : 0		20 : 80
11	DMPM	1 : 2 : 0	THF, 25 °C, 2h	28 : 72 : 0	52 : 48	26 : 74
12	DMPM	1 : 4 : 0	THF, 25 °C, 1h	0 : 22 : 78		0 : 100
13	DMPM	1 : 8 : 0	THF, 25 °C, 2h	0 : 0 : 100		

[a] DIA= diisopropylamine; DMPM=α,α-dimethyl-2-pyrrolidinemethanol; [b] Reagents composition: amine : butyl-lithium : potassium *tert*-butoxide; [c] THF=tetrahydrofuran, DEE=diethyl ether, HEX=hexane

It is worth noting that, no matter which is the base and the reaction conditions used, diols **7a** and **7b** are always obtained as pure *Z*-isomers as confirmed by several spectroscopic analyses[6] as well as by the preparation and characterization of the di-4-nitrobenzoyl esters (**11a** and **11b**).

In order to understand some details of the before mentioned isomerisation reaction we accomplished metallation - deuteration (metallation with an excess of LIDAKOR followed by addition of heavy water) reaction of **6a** at -75 °C in tetrahydrofuran. As it was evident from the ^{1}H-NMR spectrum of the product, we introduced deuterium into the benzylic position, selectively.

On the basis of all the previoulsy described data we think that the oxirane **4** rearranges first to oxetanes and the 2-phenyl-substituted oxetane **6** can be deprotonated with a large excess of base in the benzylic position to give **8** which is probably stable at low temperature. In our case metalation to the less hindered position on the oxetane ring[7] (position 4) may be less favored because of the stabilizing effect of the phenyl group in position 2. As soon as the temperature is raised, an alpha ring opening of the lithiated oxetane **8** occurs leading to a carbene type intermediate **9** followed by an alkyl-1,2-shift to the dialcoholate **10**. Mioskowski and his co-workers has established analogous mechanism in the lithiation reactions of substituted oxiranes.[8, 9] Considering Mioskowski's work[8, 9] some details of the above described process can be explained. The phenyl group probably assists development of the carbene and this also reduces (along with steric effects) the possibility of alkyllithium addition to the carbene. Furthermore, the carbene may not fully form, "the carbene-like intermediate retains its stereochemical integrity"[9] and affects which alkoxide group migrates. The stereochemistry of the product may also be determined and the reaction assisted by chelation between the two alkoxide groups.



6 **8** **9** **10**

The diols having structure **7** are useful intermediates for synthesis of pharmaceutically interesting compounds. In order to better understand and exploit this unprecedented rearrangement, we are going to further investigate the process using a variety of oxiranes and oxetanes in different reactions conditions.

EXPERIMENTAL SECTION

Generalities. Regarding standard laboratory practice and formalities, see related articles.[1, 10] ^{1}H-NMR spectra were recorded of samples dissolved in deuterochloroform at 200, 250 or 500 MHz and ^{13}C-NMR spectra were recorded at 125 MHz. α,α-Dimethyl-2-pyrrolidinemethanol,[11] (*E*)-2,3-epoxyoctane-1-ol,[12] (*E*)-epoxyhexane-1-ol[12] and the benzyl ethers (**4a**[1] and **4b**) were prepared according to already reported procedures.

(*E*)-1-(Benzyloxy)-2,3-epoxyhexane 4b: 60 %, ^{1}H-NMR: 7.35-7,22 (5H, m), 4.56 (2H, dd, *J* 18.0,12.0, AB system), 3.70 (1H, dd, *J* 11.5, 3.5), 3.45 (1H, dd, *J* 11.5, 5.5), 2.93 (1H, m), 2.82 (1H, m), 1.6-1.3 (4H, m), 0.95 (3H, t, *J* 6.8). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69 %; H, 8.79 %. Found: C, 75.74 %; H, 8.81 %.

LIDAKOR induced isomerization. Typical working procedure.

A solution of potassium *tert*-butoxide (0.18 g, 1.6 mmol) in THF (3 ml) was cooled to -78 °C. Then diisopropylamine (0.16 g, 1.6 mmol) and a solution of butyllithium in hexane (3.14 ml; 4.8 mmol) were added and the mixture stirred for 30 min. After the addition of (*E*)-1-benzyloxy-2,3-epoxyoctane **4a** (0.38 g, 1.6 mmol) the reaction mixture was stirred for 2 h at the desired temperature before being diluted with diethyl ether (10 ml) and treated with a saturated aqueous solution of NH_4Cl (10 ml). The aqueous phase was then extracted with ether (3 x 10 ml) and the organic solution washed with brine (10 ml) and dried. After removal of the solvent we got either a mixture of (*Z,E*)-3-hydroxy-1-benzyloxy-1-octene **5a** and 2-phenyl-3-(1-hydroxyalkyl)oxetane **6a**[1] (65 %) or the pure **6a** (70 %) or 2-phenyl-2-nonen-1,4-diol **7a** (55 %), respectively (for special conditions see the Table). The products were purified by column chromatography (hexane:ethyl acetate 2:1).

(*Z*)-3-hydroxy-1-benzyloxy-1-octene (*Z*)-5a[1, 12]: ^{1}H-NMR: 7.38 (5H, m); 6.10 (1H, d, *J* 5.6); 4.82 (2H, s); 4.68-4.46 (2H, m); 2.20 (1H, bs); 1.68-1.44 (2H, m); 1.29 (6H, m); 0.88 (3H, t, *J* 6.2). ^{13}C-NMR: 145.85; 136.65; 128.53; 127.79; 127.39; 110.99; 70.75; 66.41; 37.93; 31.37; 25.32; 22.46; 14.01. Anal. Calcd for $C_{15}H_{22}O_2$: C 76.88 %; H 9.46 %. Found: C 76.54 %; H 9.50 %.

(*E*)-3-hydroxy-1-benzyloxy-1-octene (*E*)-5a[1, 12]: ^{1}H-NMR: 7.38 (5H, m); 6.57 (1H, d, *J* 12.8); 4.95 (1H, dd, *J* 12.8, 8.4); 4.76 (2H, s); 4.04 (1H, m); 2.20 (1H, bs); 1.68-1.44 (2H, m); 1.29 (6H, m); 0.88 (3H, t, *J* 6.2). ^{13}C-NMR: 148.44; 135.94; 128.06; 127.55; 127.50; 108.10; 74.10; 70.76; 37.93; 31.37; 25.32; 22.46; 14.01. Anal. Calcd for $C_{15}H_{22}O_2$: C 76.88 %; H 9.46 %. Found: C 76.68 %; H 9.41 %.

(*Z*)-2-Phenyl-2-nonen-1,4-diol 7a: 55 %, ^{1}H-NMR: 7.5-7.2 (5H, m); 5.85 (1H, d, *J* 8.0); 4.65 (1H, d, *J* 12.0); 4.57 (1H, m); 4.46 (1H, d, *J* 12.0); 3.62 (2H, bs); 1.8-1.2 (8H, m); 0.87 (3H, t, *J* 6.6). ^{13}C-NMR: 141.45; 140.64; 134.40; 128.54; 126.46; 128.00; 68.23; 60.30; 37.57; 31.81; 25.16; 22.64; 14.10. Anal. Calcd for $C_{15}H_{22}O_2$: C 76.88 %; H 9.46 %. Found: C 76.69 %; H 9.42 %.

(*Z*)-2-Phenyl-2-nonen-1,4-diol di-4-nitrobenzoyl ester 11a: ^{1}H-NMR: 8.3-8.0 (8H, m); 7.5-7.2 (5H, m); 6.05 (2H, s); 5.63 (1H, d, *J* 12.0); 5.39 (1H, d, *J* 12.0); 1.5-1.1 (8H, m); 0.85 (3H, t, *J* 6.6). IR: 1720 ($\nu_{C=O}$); 1525 (ν_{NO}); 1353 (ν_{NO}). Anal. Calcd for: $C_{29}H_{28}N_2O_8$: C 65.41 %; H 5.30 %. Found: C 65.34 %; H 5.34 %.

3-(1-Hydroxybutyl)-2-phenyloxetane 6b: 60 %, ^{1}H-NMR: 7.5-7.2 (5H, m), 5.50 (1H, d, *J* 6.8), 4.68 (2H, d, *J* 7.8), 4.0-3.9 (1H, m), 2.90 (1H, m), 1.98 (1H, br s), 1.5-1.2 (4H, m), 0.87 (3H, t, *J* 6.6). Anal. Calcd for $C_{13}H_{18}O_2$: C 75.69 %; H 8.79 %. Found: C 75.62 %; H 8.74 %.

(*Z*)-2-Phenyl-2-hepten-1,4-diol 7b 64 %, ^{1}H-NMR: 7.5-7.2 (5H, m); 5.82 (1H, d, *J* 8.5); 4.63 (1H, d, *J* 12.0); 4.55 (1H, m); 4.38 (1H, d, *J* 12.0); 3.68 (2H, br. s); 1.7-1.1 (4H, m); 0.90 (3H, t, *J* 7.5). Anal. Calcd for $C_{13}H_{18}O_2$: C 75.69 %; H 8.79 %. Found: C 75.73 %; H 8.84 %.

(*Z*)-2-Phenyl-2-hepten-1,4-diol di-4-nitrobenzoyl ester 11b: ^{1}H-NMR: 8.4-8.0 (8H, m); 7.5-7.2 (5H, m); 6.03 (2H, s); 5.62 (1H, d, *J* 12.5); 5.39 (1H, d, *J* 12.0); 1.5-1.1 (8H, m); 0.85 (3H, t, *J* 6.6). Anal. Calcd for: $C_{27}H_{24}N_2O_8$: C 64.28 %; H 4.80 %. Found: C 64.32 %; H 4.74 %.

Acknowledgements: This work was done in the frame of a joint research project between CNR (Italy) and MTA (Hungary, project No. 03/7.) which are gratefully acknowledged. Further financial support by CNR-Rome and by the National Research Foundation of Hungary, Budapest (OTKA grant T-014397) is much appreciated.

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