Selective Isomerization of 1,2-Epoxyalkanes to Aldehydes with Lithium Dialkylamides

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Reaction of a variety of 1,2-epoxyalkanes with 2.5 equiv. of bulky metal amide—lithium 2,2,6,6-tetramethylpiperidide—affords the corresponding aldehydes exclusively in high yields; this is the first example of base-promoted isomerization of monosubstituted epoxides to aldehydes.

Treatment of monosubstituted epoxide **1a** with lithium 2,2,6,6-tetramethylpiperidide (LiTMP, 2.5 equiv.) in THF at 20 °C results in smooth formation of aldehyde **2a** in 83% yield [eqn. (1)].

The reactions of epoxides with a variety of metal amides have been extensively studied.[1] In fact, the base-promoted isomerization of epoxides to allylic alcohols[2] is well known as an excellent method which has been widely used in organic synthesis. However, as far as we know, there is no efficient procedure in the literature on the rearrangement of monosubstituted epoxides to aldehydes.[1,3]

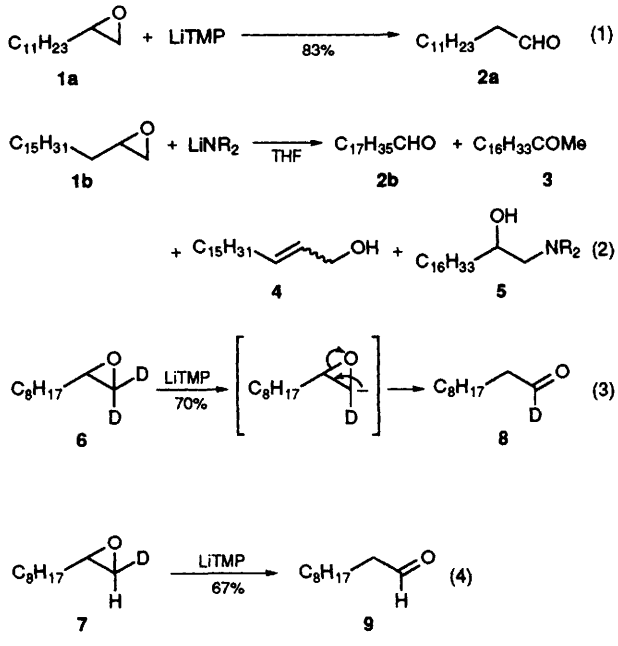


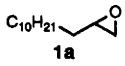
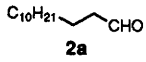
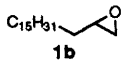
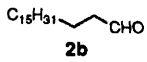
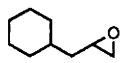
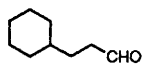
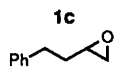
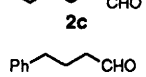
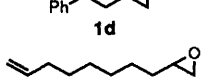
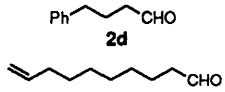
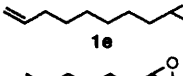
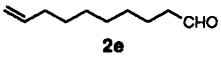
Table 1 summarizes the results obtained for the reaction of various 1,2-epoxyalkanes. The characteristic features of the results are as follows: (1) all reactions resulted in high yields without contamination of any ketones; (2) existence of phenyl group or double bond in the epoxide had no effect on the course of the reaction (entries 4 and 5); (3) diepoxide **1f** was also successfully converted to the corresponding dialdehyde **2f** by use of 5 equiv. of LiTMP (entry 6). The present method is an operationally simple and useful aldehyde synthesis starting from monosubstituted epoxides (or terminal olefins).

Findings in the study of the reaction of 1,2-epoxyoctadecane **1b** with various lithium dialkylamides are summarized in Table 2. For this process, at least four pathways could exist: (1) rearrangement to aldehyde **2b**; (2) rearrangement to ketone **3**; (3) rearrangement to allylic alcohol **4**; (4) direct nucleophilic substitution with amide to produce amino alcohol **5** [eqn. (2)].[4]

It was previously determined that lithium dimethylamide gives the amino alcohol **5** (R = Me) predominantly (entry 1).[5] With bulkier bases (R = Pr^i and c-Hex), rearrangement to aldehyde **2b** is the preferred reaction (entries 4 and 5). Among these lithium dialkylamides, LiTMP was found to be unique for exclusive aldehyde formation (entry 8). Use of 2.5 equiv. of the base is the most appropriate to obtain high yields (entries 6–9). In marked contrast to this, another sterically hindered lithium bis(trimethylsilyl)amide resulted in exclusive formation of the amino alcohol **5** (R = H, entry 10).

At present, two reaction pathways are plausible: (1) abstraction of the C-1 proton of monosubstituted epoxide and epoxide opening to form aldehyde enolate; (2) abstraction of the C-2 proton of the epoxide and α-elimination to form carbene followed by C-1 hydride shift.[6] To elucidate the reaction mechanism, we chose deuterium-labelled epoxides **6** and **7** as substrates, which are readily prepared from dec-1-yne according to Sharpless's procedure.[7]† Treatment of the 1,1-dideuteriated epoxide **6** with 2.5 equiv. of LiTMP in THF

Table 1 Isomerization of various monosubstituted epoxides **1a–1f** to aldehydes **2a–2f** with LiTMP[a]

Entry	Epoxide	Product	Yield (%)[b]
1	 **1a**	 **2a**	83
2	 **1b**	 **2b**	79
3	 **1c**	 **2c**	77
4	 **1d**	 **2d**	75
5	 **1e**	 **2e**	78
6[c]	 **1f**	 **2f**	71

[a] Unless otherwise specified, the reaction was carried out using epoxide (**1**, 1 equiv.) and LiTMP (2.5 equiv.) in THF at 20 °C for 12 h. [b] Isolated yield. [c] 5 equiv. of LiTMP was used.

Table 2 Reaction of **1b** with various lithium dialkylamides[a]

Entry	$LiNR_2$ (equiv.)	Products [Yield (%)][b] 2b	3	4	5
1	$LiNMe_2$ (2.5)	0	0	0	77
2	$LiNEt_2$ (2.5)	<1	0	0	83
3[c]	LDA (1)	27	4	2	24
4	LDA (2.5)	46	0	0	26
5	$LiN(c\text{-Hex})_2$ (2.5)	63	0	0	17
6[d]	LiTMP (1)	42	0	0	<1
7	LiTMP (2)	72	0	0	<1
8	LiTMP (2.5)	79	0	0	<1
9	LiTMP (5)	80	0	0	<1
10	$LiN(TMS)_2$ (2.5)	0	0	<1	63[e]

[a] The reaction was carried out using epoxide **1b** (1 equiv.) and lithium dialkylamide in THF at 20 °C for 12 h. [b] Isolated yield. [c] The starting material **1b** was recovered in 44% yield. [d] The starting material **1b** was recovered in 41% yield. [e] Desilylated amino alcohol **5** (R = H) was obtained after hydrolysis with 4 mol dm^{-3} HCl.

at 20 °C for 12 h provided 1-deuteriodecanal **8** in 70% yield indicating the occurrence of the C-1 proton abstraction [eqn. (3)]. Furthermore, *trans*-proton (or deuteron) at the C-1 position was found to selectively react with LiTMP by reaction of *trans*-1-deuterioepoxide **7** [eqn. (4)].

The following procedure is representative. To a solution of 2,2,6,6-tetramethylpiperidine (2.5 mmol) in THF (5 ml) was added dropwise a solution of n-butyllithium in hexane (1.6 mol dm^{-3}, 2.5 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min, a solution of 1,2-epoxyoctadecane (**1b**, 1 mmol) in THF (1 ml) was added at 20 °C and the reaction mixture was stirred for another 12 h at this temperature. The reaction mixture was treated with a saturated aqueous NH_4Cl solution at 20 °C, extracted with diethyl ether, dried ($MgSO_4$), and finally purified by column chromatography on silica gel to afford octadecanal (**2b**, 79% yield).‡

Financial support from the Ministry of Education, Science and Culture of the Japanese Government is gratefully acknowledged.

Received, 15th June 1994; Com. 4/03629H

Footnotes

† 1,1-Dideuterio-1,2-epoxydecane **6** was synthesized from dec-1-yne by a three-step sequence: (*i*) deuteriation with $BuLi/D_2O$ (>99% yield), (*ii*) hydroalumination with Bu^i_2AlH and subsequent hydrolysis with D_2O (60% yield), (*iii*) epoxidation with MCPBA in CH_2Cl_2 (60% yield). *trans*-1-Deuterio-1,2-epoxydecane **7** was also obtained from dec-1-yne by hydroalumination–deuteriolysis (76% yield) described above and subsequent epoxidation with MCPBA (92% yield).

‡ TLC R_f 0.53 (1 : 5 ethyl acetate–hexane); IR (neat) 2915, 2849, 1713, 1472, 1412, 1393, 897, 718, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* 6.6 Hz, CH_3), 1.18–1.39 (m, 28 H, 14 CH_2), 1.63 (m, 2 H, CH_2), 2.42 (t, 2 H, *J* 7.4 Hz, CH_2), 9.77 (s, 1 H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.1, 22.7, 29.2, 29.3 (2 C), 29.4 (3 C), 29.7 (6 C), 31.9, 43.9, 202.9.

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