A New and Efficient Epoxide Ring Opening via Poor Nucleophiles: Indole, *p*-Nitroaniline, Borane and *O*-Trimethylsilylhydroxylamine in Lithium Perchlorate

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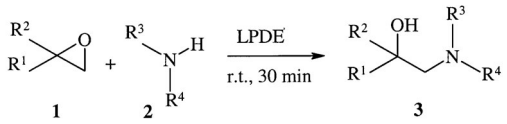
Abstract: Highly regioselective ring opening of 2,3-dimethyloxirane, 2-epoxyphenylether and allyl(2-epoxymethyl) ether are observed through reactions with poor nucleophiles such as indole, borane, *O*-trimethylsilylhydroxylamine, *p*-nitroaniline and sterically hindered *tert*-butylamine in the presence of 5.0 M lithium perchlorate–Et_2O solution. These reactions are fast, convenient, with rather high yields and are carried out at ambient temperatures.

Key words: lithium perchlorate, epoxide, β-amino alcohols

Oxiranes (epoxides) are widely distributed in nature and are of industrial and biochemical interest. In addition, they are becoming a powerful tool in the field of synthetic organic chemistry.[1] Epoxides are efficiently converted into functionalized alcohols by employing nucleophilic ring-opening reactions. However, this reaction, which is usually carried out with a large excess of nucleophiles at elevated temperature with long reaction times and drastic conditions, often fails when poor nucleophiles and/or sterically bulky nucleophiles or epoxides are used.[2] Therefore, there is a significant current interest in the ring opening of epoxides.

β-Amino alcohols constitute an important class of well-known organic compounds that have importance in natural products, medicinal chemistry and other chemical fields.[3] The most practical and widely used method for preparing these compounds is the direct aminolysis of epoxides with an excess of amines or their synthetic equivalents at elevated temperatures.[4] Due to the elevated temperature, these reactions often fail when poorly nucleophilic or sterically bulky amines and in some case low boiling points amines are concerned. These are some significant limitations on the general utility of epoxide aminolysis.[5] To obviate these problems, several useful modifications activator/promoters have been reported: $COCl_2$,[6] fluoro-alcohols as reaction media[7] (benzylic and aliphatic amines do not react under these conditions), $Ti(O\text{-}i\text{-}Pr)_4$,[8] SmI_2 and $SmCl_3$,[9] metal triflates,[10] metal amides,[11] Mg, Li, Pb, Sn, Si (an important drawback of these methods is that epoxides bearing α-hydrogens, frequently undergo rearrangement to produce allyl alcohols and primary amines show no regioselectivity). Good regioselectivity of ring opening by nucleophiles has been observed with $LiClO_4$.[12] However, with this catalyst, deactivated aromatic amines and some sterically hindered amines fail to open up epoxides or require high temperature or pressure. Although a wide choice of promoters is available many are associated with one or other drawback. Hence, there is a need for new versatile methods.

In the course of our investigations toward the development of new reactions promoted by lithium perchlorate in Et_2O (LPDE) solution, we have found that 5.0 M LPDE solutions promote the addition of deactivated *p*-nitroaniline and secondary amines to epoxides under mild experimental conditions (r.t., 30 min).[13] The reaction was highly regioselective as **3** was the only detectable product. The results are summarized in Scheme 1.



1 **2** **3**

	R¹	R²	R³	R⁴	% 3
a	$PhOCH_2$	H	Ph	H	97
b	CH_3	CH_3	Ph	H	98
c	$CH_2{=}CH_2CH_2OCH_2$	H	Ph	H	95
d	$PhOCH_2$	H	*p*-NO_2Ph	H	95
e	CH_3	CH_3	*p*-NO_2Ph	H	95
f	$CH_2{=}CH_2CH_2OCH_2$	H	*p*-NO_2Ph	H	89
g	$PhOCH_2$	H	CH_3CH_2	CH_3CH_2	97
h	CH_3	CH_3	CH_3CH_2	CH_3CH_2	92
i	$CH_2{=}CH_2CH_2OCH_2$	H	CH_3CH_2	CH_3CH_2	95
j	$PhOCH_2$	H	*t*-Bu	H	96
k	CH_3	CH_3	*t*-Bu	H	91
l	$CH_2{=}CH_2CH_2OCH_2$	H	*t*-Bu	H	95

Scheme 1

This encouraging result prompts us to further investigate the use of LPDE solution (5.0 M) as catalyst. We have been investigating the use of hydroxylamine in the synthesis of a range of functionalized β-hydroxyhydroxylamines. In order to prepare the desired compounds, we proposed to ring open functionalized epoxides with *O*-trimethylsilylhydroxylamine. We were surprised to note, that to our knowledge, there are very few examples of the ring opening of epoxides with hydroxylamines, and the

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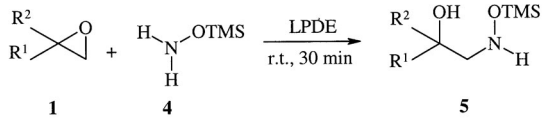
few cases that have been reported are simple *O*-protected glycidol ethers[14] and *N*-alkylhydroxylamines.[15] Accordingly, we have examined the ring opening of epoxides with *O*-tri-methylsilylhydroxylamine and found that the reaction is high yielding and regioselective (Scheme 2).

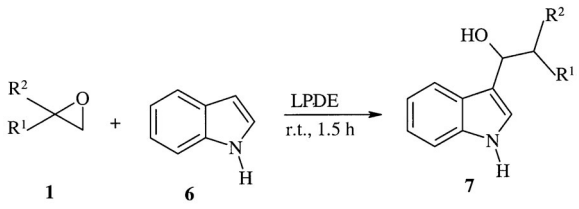


1 4 5

	R1	R2	% 5
a	$PhOCH_2$	H	96
b	CH_3	CH_3	92
c	CH_2=$CH_2CH_2OCH_2$	H	98

Scheme 2

In order to extend the scope of effectiveness of the above-mentioned new ring opening, reactions between indole and epoxides were studied and it was found that the corresponding indolyl derivatives were obtained. It is interesting to note that the procedures for the indole ring-opening reaction can be catalyzed by high pressure (10 kbar) or by the use of SiO_2 and $InBr_3$.[16] Several examples of Friedel–Crafts (F–C) reactions between indole and epoxides using the novel 5.0 M LPDE catalyst are shown in Scheme 3. In all cases, the desired tryptophol derivatives (which are of interest as synthetic intermediates toward antibiotics such as indolmycin)[17] were obtained in good yields.



1 6 7

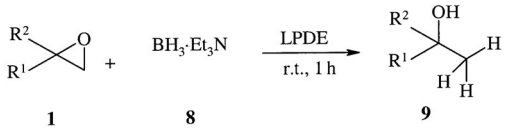
	R1	R2	% 7
a	$PhOCH_2$	H	65[1]
b	CH_3	CH_3	52
c	CH_2=$CH_2CH_2OCH_2$	H	67

[1]Compared to the result obtained at high pressure 10 kbar, SiO_2, 63 °C, 3 days; 29% yield.[16a]

Scheme 3

To explore the generality and scope of the LPDE catalyzed ring opening of epoxides, the reaction was examined with a borane–Et_3N complex (Scheme 4). In all cases, the reactions proceeded cleanly, and the desirable secondary alcohols were obtained in good yields.

In conclusion, the discovery of the LPDE (5.0 M) solution catalyzed method for the ring opening of epoxides with amines, *O*-silylatedhydroxylamine, indole and $BH_3{\cdot}Et_3N$ complex to give, under mild conditions and in fair yields, the corresponding ring opening products (β-amino alcohols, β-hydroxyhydroxylamines, tryptophol and alcohols derivatives, respectively). Further synthetic applications of the reaction are now in progress in our laboratory.



1 8 9

	R1	R2	% 9
a	$PhOCH_2$	H	90
b	CH_3	CH_3	85
c	CH_2=$CH_2CH_2OCH_2$	H	76
d	$(CH_3)_2CHOCH_2$	H	77

Scheme 4

All reactions were carried out under Ar. ^1H and ^{13}C NMR spectra were recorded at 90 Mhz and 22.5 MHz on JEOL EX-90A spectrometers, respectively. The chemical shifts are reported in ppm (δ) relative to Me_4Si in $CDCl_3$. IR spectra were recorded on a Perkin Elmer Model 1600 spectrophotometer. Mass spectra were recorded on a Shimadzu IR-460 spectrometer or on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Heraus CHN-O-Rapid analyzer. The experimental data were in agreement with the calculated values.

Typical Experimental Procedure

To a mixture of epoxide (2 mmol) in 5 M LPDE (4 mL) was added nucleophile (2.2 mmol) at r.t. The mixture was stirred for 30 min and then water was added and the product was extracted with CH_2Cl_2. The organic phase was collected, dried (Na_2SO_4) and evaporated to afford the crude product. The product was purified by flash chromatography (hexane–EtOAc). ^1H NMR, ^{13}C NMR, IR and MS spectra were entirely consistent with the assigned structures.

3b

^1H NMR (90 MHz, $CDCl_3$): δ = 7.2 (m, 2 H), 6.6 (m, 3 H), 3.2 (br s, 2 H), 3.0 (s 2 H), 1.2 (s, 6 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 146.66 (C), 129.16 (CH), 118.49 (CH), 117.47 (CH), 115.07 (CH), 113.07 (CH), 70.64 (C), 54.88 (CH_2), 27.40 (CH_3).

3e

^1H NMR (90 MHz, $CDCl_3$): δ = 8 (m, 2 H), 6.5 (m, 2 H), 3.6 (br s, 2 H), 3.2 (s, 2 H), 1.3 (s, 6 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 154.04 (C), 137.42 (C), 116.39 (CH), 112.16 (CH), 70.32 (C), 50.66 (CH_2), 27.44 (CH_3).

3h

^1H NMR (90 MHz, $CDCl_3$): δ = 3.4 (br s, 1 H), 2.7 (q, 4 H), 2.4 (s, 2 H), 1.2 (s, 6 H), 1.0 (t, 6 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 68.69 (C), 64.62 (CH_2), 49.02 (CH_2), 28.01 (CH_3), 12.21 (CH_3).

3k

^1H NMR (90 MHz, $CDCl_3$): δ = 3.7 (br s, 1 H), 3.3 (br s, 1 H), 2.4 (s, 2 H), 1.1 (s, 6 H), 1.0 (s, 9 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 68.20 (C), 52.60 (CH_2), 50.24 (C), 29.03 (CH_3), 27.19 (CH_3).

5b

^{1}H NMR (90 MHz, $CDCl_3$): δ = 5.5 (br s, 1 H), 3.8 (br s, 1 H), 2.8 (s, 2 H), 1.2 (s, 6 H), 0.2 (s, 9 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 71.05 (C), 63.44 (CH_2), 27.44 (CH_3), –0.1 (CH_3).

7a

Comparison of the spectroscopic data to those reported in ref.[17]

9a

^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.4 (m, 2 H), 7.0 (m, 3 H), 4.2 (m, 1 H), 3.9 (d, 2 H), 2.5 (br s, 1 H), 1.3 (d, 3 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 159.53 (C), 130.31 (CH), 121.89 (CH), 115.28 (CH), 73.76 (CH_2), 66.76 (CH), 19.01 (CH_3).

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