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Regioselective Titanium-mediated Ring Openings of 2,3-Epoxy Alcohols with Dialkylamine Hydrohalides

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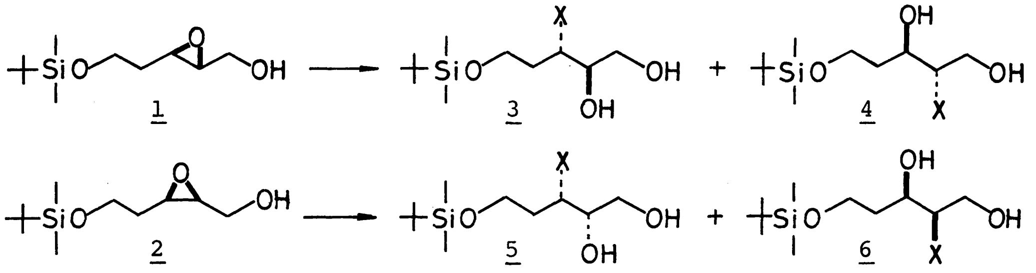
Titanium-mediated ring openings of 2,3-epoxy-1-ols at the 3-position have been performed more efficiently with use of dialkylamine hydrohalides as sources of halide nucleophiles.

Since Sharpless asymmetric epoxidation[1)] has been established extensively, regioselective ring openings of 2,3-epoxy alcohols with nucleophiles have been utilized frequently in the course of asymmetric syntheses of natural products.[2)] Recently, two groups have reported that selective openings of 2,3-epoxy alcohols with halides (Cl^- or Br^-) at the 3-position are effected by use of ammonium halides in the presence of $Ti(O\text{-}\underline{i}\text{-}Pr)_4$[3)] or zeolite-CaY.[4)] However, the more efficient conditions with higher regioselectivity and chemical yield have been still required for the multi-step syntheses of halogen-containing natural products. We describe herein that dialkylamine hydrohalides are much more effective for titanium-mediated ring openings of both trans- and cis-2,3-epoxy-1-ols at the 3-position.

A general procedure is as follows: $Ti(O\text{-}\underline{i}\text{-}Pr)_4$ (0.3 mmol) and halide nucleophile (0.6 mmol) were stirred in CH_2Cl_2 (4 ml) under argon at 23 °C for at least 30 min, until the solution became clear. A solution of epoxy alcohol (0.2 mmol) in CH_2Cl_2 (1 ml) was added and the solution was stirred at 23 °C for 12 h. The reaction was quenched with satd Na_2SO_4 solution (2 ml). We compared the effect of various nucleophiles on the reactions with trans-(**1**) or cis-2,3-epoxy-1-ols (**2**). Our results are summarized in Table 1. The data indicate that, when dialkylamine hydrohalides were used, the ring openings proceeded in satisfactory practical yields and with higher selective nucleophilic attack of halides on the 3-position. It is emphasized that (i) diethylamine hydrohalides ($Et_2NH{\cdot}HX$) are most efficient for the openings at the 3-position in both cases of **1** and **2** (runs 2,3,15, and 16); (ii) $Et_2NH{\cdot}HCl$ is superior to $Et_3N{\cdot}HCl$, which has been reported recently to be the best chloride nucleophile for the corresponding opening of cis-2,3-epoxy alcohol[5)] (compare run 3 with run 10); (iii) $Me_2NH{\cdot}HCl$ (run 4) and cyclic secondary amine hydrochlorides (runs 6 and 7) are available as well, and (iv) tetraalkylammonium halides are inert to the epoxide rings (runs 12 and 19). These results suggest that dialkylamine hydrohalide might exist as some complex with $Ti(O\text{-}\underline{i}\text{-}Pr)_4$, not as a naked halide during the reaction course, though the mechanistic detail remains to be solved.

We believe that the new reaction conditions gained in this work will be applied effectively to the syntheses of halogen-containing marine natural products.

Table 1. Ring openings of 2,3-epoxy alcohols (1 or 2) with halide-nucleophiles$^{a)}$



Run	Starting epoxide	Nucleophile	X	Yield/% 3+4	Yield/% 5+6	Ratio of products$^{b)}$ 3 : 4	Ratio of products$^{b)}$ 5 : 6
1	1	$EtNH_2$·HCl	Cl	78		78 : 22	
2	1	Et_2NH·HCl	Cl	87		91 : 9	
3	2	Et_2NH·HCl	Cl		93		89 : 11
4	1	Me_2NH·HCl	Cl	80		90 : 10	
5	1	i-Pr_2NH·HCl	Cl	75 (83)$^{c)}$		83 : 17	
6	1	Pyrrolidine·HCl	Cl	78		90 : 10	
7	1	Piperidine·HCl	Cl	71		90 : 10	
8	1	2,2,6,6-Tetramethylpiperidine·HCl	Cl	86		85 : 15	
9	1	Et_3N·HCl	Cl	89		81 : 19	
10	2	Et_3N·HCl	Cl		79		75 : 25
11	1	$NH_4Cl^{d)}$	Cl	63 (74)$^{c)}$		64 : 36	
12	1	Et_4NCl	Cl	0		——	
13	1	Pyridine·HCl	Cl	73		77 : 23	
14	1	$EtNH_2$·HBr	Br	77		76 : 24	
15	1	Et_2NH·HBr	Br	87		90 : 10	
16	2	Et_2NH·HBr	Br		94		88 : 12
17	1	Et_3N·HBr	Br	83		80 : 20	
18	1	NH_4Br	Br	72 (78)$^{c)}$		69 : 31	
19	1	Bu_4NBr	Br	0		——	

a) All reactions were performed with the molar ratio (1 : 1.5 : 3) of starting epoxide, Ti(O-i-Pr)$_4$, and halide-nucleophile in CH_2Cl_2 at 23 °C for 12 h, unless otherwise stated. b) Ratios were determined by ^1H NMR analyses of the products. c) The value in parenthesis denotes the yield based on the recovered starting material. d) The reaction was performed for 40 h.

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