CHEMISTRY LETTERS, pp. 1787-1790, 1993.

Synthesis of 2-Aminomethyloxiranes

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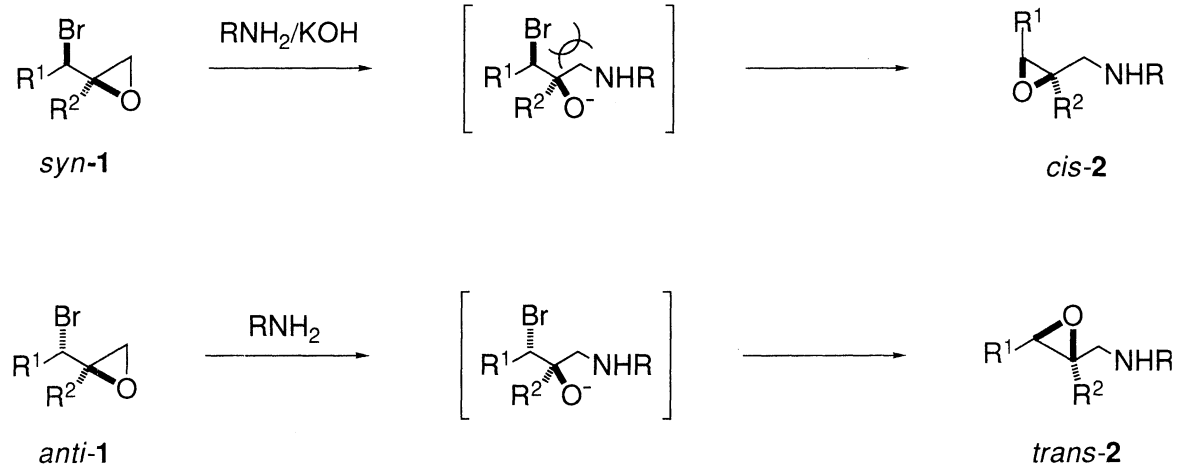
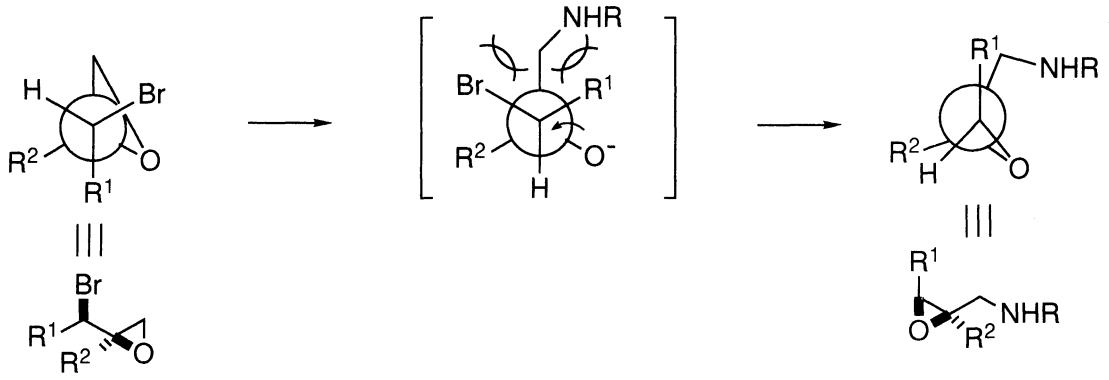
Several 2-aminomethyloxiranes (**2**) have been synthesized in good yields by the reaction of 2-(1-bromoalkyl)oxiranes (**1**) with primary or secondary amines. *cis*-2-Aminomethyloxiranes (**2**) were obtained from *syn*-(2-bromomethyl)oxiranes (**1**) with amines and KOH, and *trans*-2-aminomethyloxiranes (**2**) were obtained from *anti*-(2-bromomethyl)oxiranes (**1**) with amines, respectively, with stereospecific manner.

Functionalized oxiranes have proved to be useful intermediates in organic synthesis.[1] Especially glycidol derivatives are versatile intermediates in the syntheses of natural products and pharmaceuticals.[2] Surprisingly very few synthetic studies have so far been made on 2-aminomethyloxiranes (**2**).[3] We became particularly intrigued with the possibility of using **2** as substrates for regiocontrolled and stereocontrolled synthesis of heterocyclic compounds.

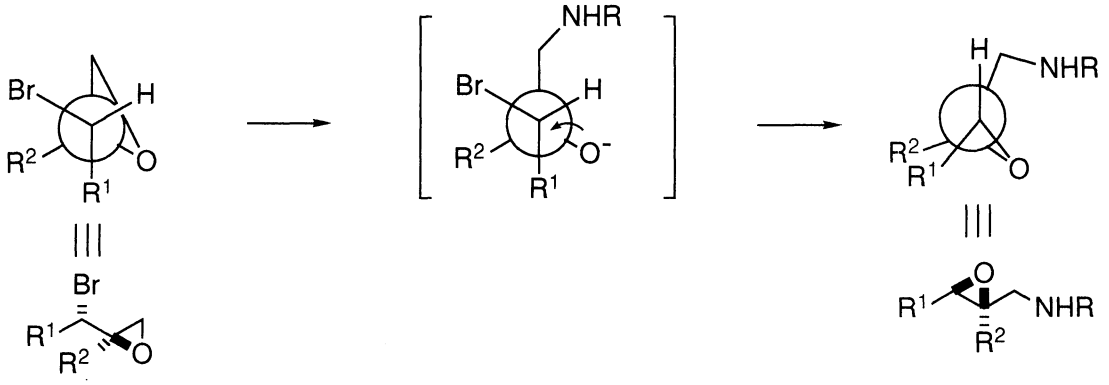
One of the most successful methods for the preparation of the 2-aminomethyloxiranes (**2**) is the reaction of epichlorohydrin with primary amines.[4] In this method, **2** should possess the sterically hindered *N*-substituents to prevent dimerization reactions; no available synthetic methods of *N*-*n*-alkyl substituted **2** were reported. Therefore, we conceived that introduction of alkyl or aryl substituents on the resulting oxirane skeleton of **2** (C-3 position) would prevent the dimerization reaction efficiently. This method of generating **2** described in this paper.



Our initial investigations were carried out on the preparation of *syn*-**1a** derived from *E*-cinnamylalcohol.[5] In a previous paper,[6] we showed that **1a** with 2.4 equiv of primary amines in MeOH was the reaction system for the synthesis of azetidine derivatives. Now we found an efficient synthetic method of **2a**, by treatment of **1a** with 1.2 equiv of amines in the presence 1.2 equiv of KOH (Method A). In this procedure, azetidine formation was not observed. The general applicability of this method was established by treating other substrates (**1b-1f**), and the corresponding 2-aminomethyloxiranes (**2b-2l**) were obtained in reasonable yields. Representative results are summarized in Table 1. Each of the *syn*-**1** and *anti*-**1** were converted to the *cis*-**2** and *trans*-**2**, respectively. In contrast to the *syn*-**1**, however, the reaction of *anti*-**1** with 2.4 equiv of amines (Method B) gave *trans*-**2** without azetidine formation (Entries 4,5,10-12). The significant difference of their reactivities can be rationalized on the basis of their reactive conformers, *syn* and *anti*-**3**, described as below.



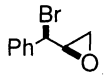
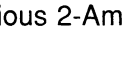
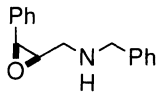
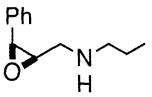
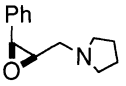
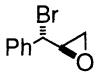
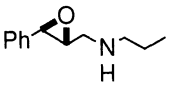
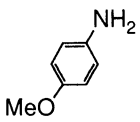
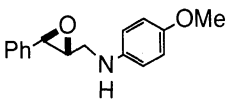
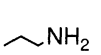
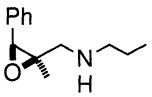
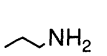
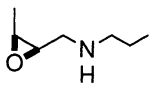
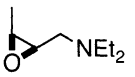
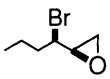
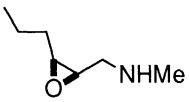
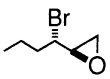
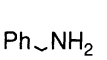
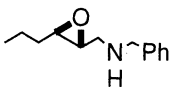
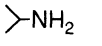
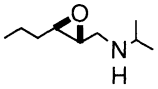
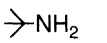
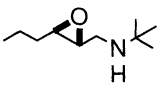
syn-**1** *syn*-**3** *cis*-**2**



anti-**1** *anti*-**3** *trans*-**2**

The intermediate of *syn* -**3** is destabilized by *gauche* interaction of the amino methyl group and both R^1 and the bromine atom. Only in strongly basic conditions, the cyclization can occur *via* the conformer *syn*-**3**, and exclusively *cis*-**2** is formed. On the other hand, *anti*-**3** has the substituents which are in antiperipulanar orientation. Therefore *anti*-**3** is smoothly converted into *trans*-**2**.

Table 1. Preparation of Various 2-Aminomethyloxiranes

Entry	Substrate	Amine	Product	Method[a]	Yield / %[b]
1	 *syn*-**1a**		 *cis*-**2a**	A	58; 46[c]
2	*syn*-**1a**		 *cis*-**2b**	A	48; 37[c]
3	*syn*-**1a**		 *cis*-**2c**	A	65
4	 *anti*-**1b**		 *trans*-**2d**	B	69
5	*anti*-**1b**		 *trans*-**2e**	B	47[c]
6	 *syn*-**1c**		 *cis*-**2f**	A	74; 67[c]
7	 *syn*-**1d**		 *cis*-**2g**	A	74; 55[c]
8	*syn*-**1d**	Et_2NH	 *cis*-**2h**	A	58
9	 *syn*-**1e**	$MeNH_2$	 *cis*-**2i**	A	71; 14[c]
10	 *anti*-**1f**		 *trans*-**2j**	B	71
11	*anti*-**1f**		 *trans*-**2k**	B	78; 51[c]
12	*anti*-**1f**		 *trans*-**2l**	B	60

a) See the text. b) Yields were determined by ^1H NMR. c) Isolated yield.

These products (**2**) are stable at room temperature, and able even to be distilled. However, 2-aminomethyloxiranes (**2**) containing less hindered alkyl groups, such as *N*-methyl derivative (**2i**), causes polymerization during vacuum distillation (Entry 9). So, the lower isolated yield of **2i** may arise from decreased steric hindrance around the amino group of **2i**.

A typical procedure is described as follows. A mixture of **1a** (6.39 g, 30 mmol), benzylamine (3.85 g, 36 mmol), and aqueous solution (5 ml) of KOH (2.34 g, 36 mmol) in *t*-BuOH (75 ml) was stirred at room temperature for 48 h. After usual work up procedure, the oily product was chromatographed on silica gel and distilled under vacuum to afford **2a** as colorless oil; yield: 3.17 g (46 %) (Method A). In the case of *anti*-**1**, the reaction was conducted with 2.4 equiv of benzylamine without KOH (Method B). When secondary amines were used, *N,N*-disubsituted aminomethyloxirane derivatives (**2c** and **2h**) were obtained in good yields (Entries 3 and 8).

References

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2) A review on glycidol, see: R. M. Hanson, *Chem. Rev.*, **91**, 437 (1991).

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6) T. Toda, M. Karikomi, M. Ohshima, and M. Yoshida, *Heterocycles*, **33**, 511 (1992).

7) Spectral data of a representative product are as follows: *cis*-2-(*N*-propylaminomethyl)-3-phenyloxirane (**2b**) bp 109-111 °C/ 3 mmHg, ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, t, *J*=7.5 Hz, CH_3), 1.39 (2H sex, *J*=7.5 Hz, CH_2Me), 2.48 (2H, t, *J*=7.5 Hz, CH_2Et), 2.53 (1H, dd, *J*=13.8, 6.3 Hz, $CHCH_2N$), 2.58 (1H, dd, *J*=13.8, 5.4 Hz, $CHCH_2N$), 3.38 (1H, *J*=6.3, 5.4, 3.9 Hz, PhCHCH), 4.12 (1H, d, *J*=3.9 Hz, PhCH), 7.3-7.4 (5H, m, *Ph*); ^{13}C NMR ($CDCl_3$) δ 11.42 (CH_3), 22.93 (CH_2Me), 46.87 ($CHCH_2N$), 51.58 (NCH_2Et), 56.69 (PhCH), 58.31 ($PhCHCH_2$), 126.12 (*Ph*), 127.51 (*Ph*), 127.97 (*Ph*), 135.10 (*Ph*); IR (neat) 3300, 1450 cm^{-1}.

(Received June 28, 1993)