SYNTHESIS OF 3-HYDROXY-2,3,4,5-TETRAHYDRO-1,5-BENZOTHIAZEPINES†

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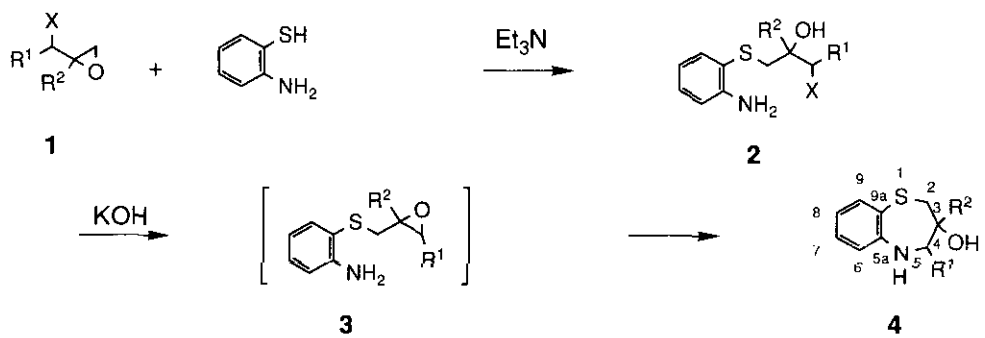
Abstract - New general synthetic methods of benzothiazepine derivatives were studied. Treatment of 2-(1-haloalkyl)oxiranes (**1**) with 2-aminothiophenol in the presence of a base provides a variety of benzothiazepine derivatives (**4**) in excellent yields. The reaction is assumed to proceed through cyclization of an oxirane intermediate (**3**).

In contrast to the synthesis of 1,5-benzothiazepine-4-one skeleton,[1-3] which has been actively explored as biologically active compounds,[4] relatively little attention has been given thus far to general synthetic methods of 1,5-benzothiazepine ring system.[5] We now wish to report that the reaction of 2-aminothiophenol with various 2-(1-haloalkyl)oxiranes (**1**)[6] provides *cis* and *trans* isomers of 1,5-benzothiazepines (**4**). The stereochemical outcome of these reactions depends on the configuration of the starting **1**.



In our first attempt we carried the above reaction in the presence of KOH. As the typical example, the reaction of epichlorohydrine (**1a**) with 1 equivalent of 2-aminothiophenol and KOH in MeOH gave **4a** only 42 % yield together with oily by-products. Treatment of **1a** with triethylamine afforded the precursor (**2**) as a pale yellow oil in 98 % yield. Subsequent treatment of the precursor (**2**) with KOH gave **4a** in 90 % yield. The synthetic utility of this reaction was further exemplified by one-pot procedure. Thus, the oxiranes (**1**) were derived at first to the precursors (**2**) with 2-aminothiophenol using triethylamine. Then, KOH was added to a stirred reaction mixture at room temperature. The cyclization of the precursors (**2**) were completed in a few hours. Some of the results are listed in Table 1.[7] Alkyl or aryl substituents can be introduced at positions 3 (R^1) and 4 (R^2) by properly choosing starting 2-(1-haloalkyl)oxiranes (**1**).

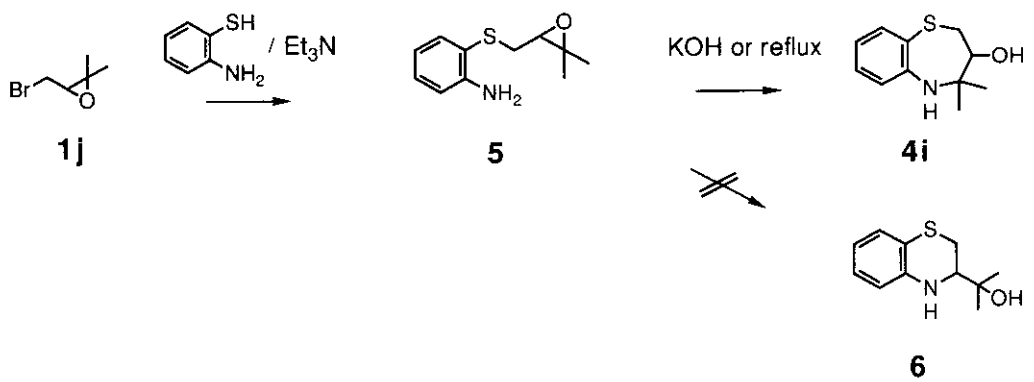
Table 1. Synthesis of benzothiazepines

Substrate					Product		
	Config.	R^1	R^2	X		Config.	Yield/%[a]
1a	-	H	H	Cl	**4a**	-	90
1b	-	H	H	Br	**4a**	-	87
1c	-	H	Me	Br	**4b**	-	72
1d	*syn*	Me	H	Br	**4c**	*cis*	87
1e	*syn*	Pr	H	Br	**4d**	*cis*	78
1f	*anti*	Pr	H	Br	**4e**	*trans*	59
1g	*syn*	Ph	H	Br	**4f**	*cis*	63
1h	*anti*	Ph	H	Br	**4g**	*trans*	51
1i	*syn*	Ph	Me	Br	**4h**	*cis*	85

a) Yields of pure isolated products.

On the basis of elemental analysis, ir, nmr, and mass spectral data, compounds (**4a-4h**) were confirmed to be benzothiazepine derivatives. Shift correlation by long-range chemical shift correlation spectrum ("LR-HETCOR") of **4** shows couplings of the carbons at positions 5a and 9a with the protons at positions 4 and 2, respectively. Compounds (**4c-4h**) were obtained in

diastereomerically pure form. The stereochemistry at C-4 and C-3 was confirmed by analysis of NOESY spectrum and vicinal coupling constants. For example, the NOESY spectrum of *cis* isomers showed the nOe between 3-R^2 (H or Me) and 4-H, but no nOe for *trans* isomers. Further, the large difference in the $J_{3,4}$ are observed. The *cis* isomers showed $J_{3,4}$ = 0~0.9 Hz and the *trans* isomers showed $J_{3,4}$ = 8.7~9.0 Hz. It is noteworthy that the reaction proceeded stereospecific manner, (i.e., *syn* **1** give *cis* **4** and *anti* **1** give *trans* **4**). These results strongly suggest the reaction proceeded *via* the oxirane intermediates (**3**). While we were not able to observe the intermediates (**3**)during the preparation of **4**, an analogous intermediate (**5**) was obtained upon reaction of 3,3-dimethyl-2-bromomethyloxirane (**1j**) with aminothiophenol in the presence of triethylamine, in which the initial nucleophilic substitution was occurred at the bromomethyl group. Moreover, when **1j** was stirred with KOH in MeOH at room temperature or reflux in toluene without bases, benzothiazepine (**4i**) was obtained in 62 or 72 % yield, respectively. In the former cyclization conditions, it took 4 days[8] for completion of the reaction. This may be caused by steric hindrance around the oxirane ring of **5** owing to its dimethyl group. In this reaction, we anticipated that formation of *exo*-6 cyclization porduct (**6**). While, the ^{1}H nmr spectrum of the product exhibits large coupling constant of 12.3 Hz for the OH and the methin proton, indicates that the product is not **6**, but **4i**.



1j **5** **4i** **6**

In conclusion, the general synthesis of 1,5-benzothiazepine has been established with good yields in one-pot procedure.

REFERENCES AND NOTES

† Dedicated to Professor Edward C. Taylor on the occasion of his 70 th birthday.

1 O. Miyata, T. Shinada, I. Ninomiya, and T. Naito, *Tetrahedron Lett.*, 1991, **32**, 3519.

2 S. Y. Dike, D. H. Ner, and A. Kumar, *Synlett,* **1991,** 443.

3 V. Ambrogi and G. Grandolini, *Synthesis* , **1987**, 724.

4 H. Kugita, H, Inoue, M. Ikezaki, M. Konda, and S. Takeo, *Chem. Pharm. Bull.,* 1971, **19**, 595.

5 M. Morimoto, H. Kohno, and K. Yasuda, *Heterocycles*, 1990, **30**, 471.

6 2-(1-Haloalkyl)oxiranes (**1c-i**) were prepared according to the literature. **1c**: E. P. Adams, F. P. Doyle, D. L.Hatt, D. O. Holland, W. H. Hunter, K. R. L. Mansford, J. H. C. Nayler, and A. Queen, *J. Chem. Soc.*, **1960**, 2649; **1d**: H. Tucker, *J. Org. Chem.*, 1979, **44**, 2943; **1e** And **1f** were obtained from *trans*- and *cis*-2-hexenyl alcohol by an analogous method of **1d**; **1g-i**: M. Yoshida, T. Hide, M. Ohshima, H. Sasaki, and T. Toda, *Heterocycles*, 1992, **33**, 507; **1j**: S. Winstein and L. Goodman, *J. Am. Chem. Soc.*, 1954, **76**, 4373.

7 Spectral and analytical data of representative product are as follows: ***cis*-3-Hydroxy-4-methyl-2,3,4,5-tetrahydro-1,5-benzothiazepine (4b).** mp 90-91 °C. ^{1}H Nmr ($CDCl_3$) δ 1.37 (3H, d, *J*=6.9 Hz), 2.77 (1H, dd, *J*=14.4, 1.8 Hz), 2.93 (1H, dd, *J*=14.4, 5.4 Hz), 2.98 (1H, qt, *J*=6.9, 0.6 Hz), 3.06 (1H, br s), 3.53 (1H, d, *J*=12.0 Hz), 3.81(1H, m), 6.86 (1H, td, *J*=7.5, 1.2 Hz), 6.89 (1H, td, *J*=7.5, 1.2 Hz), 7.13 (1H, td, *J*=7.5, 1.2 Hz), 7.46 (1H, dd, *J*=7.5, 1.2 Hz). ^{13}C Nmr ($CDCl_3$) δ 20.68, 39.73, 57.41, 69.38, 121.10, 122.30, 126.76, 128.42, 133.01, 151.04. Ir (KBr) 3460, 3320, 1580, 1470 cm^{-1}. Ms m/z (rel. intensity) : 195 (M^+, 57.3), 151 (41.1), 136 (100). Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.50; H, 6.71; N, 7.17. Found : C, 61.39; H, 7.00; N, 7.00.

8 In the first series of experiments, the cyclization reactions were completed within a few hours, but **4d** took 24 h owing to the steric hindrance of the propyl group. In the case of **4i**, it took longer reaction period.

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