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# STEREOCONTROLLED SYNTHESIS OF 3-HYDROXY-2,3,4,5-TETRA-HYDRO-1,5-BENZOTHIAZEPINES BY MEANS OF NEIGHBORING GROUP PARTICIPATION

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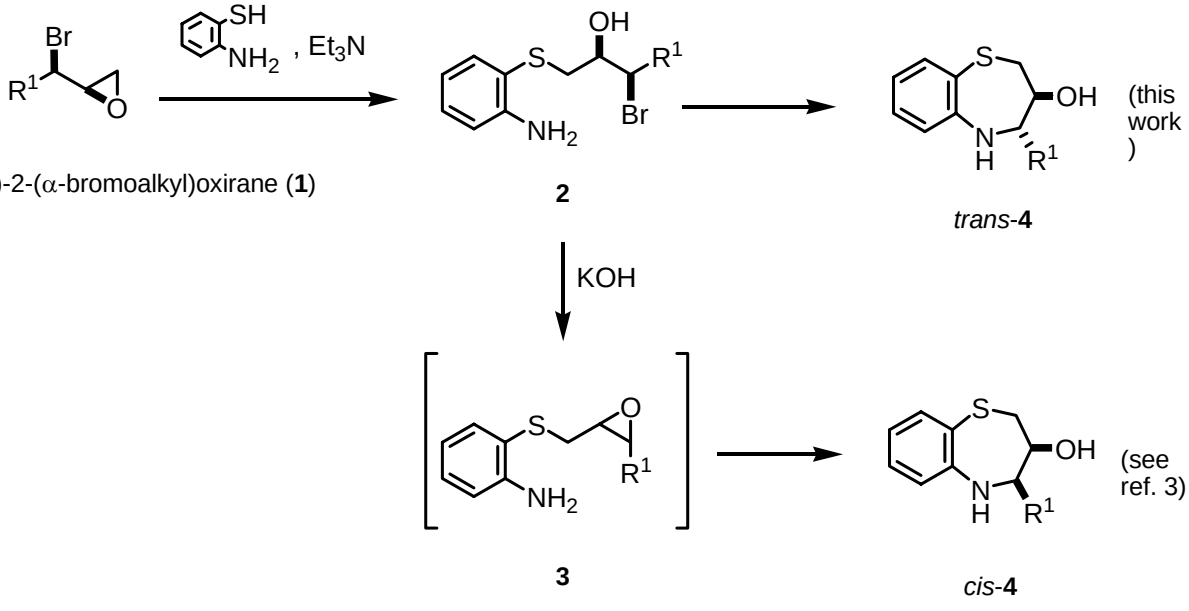
**Abstract**-A novel stereocontrolled synthesis of 3-hydroxy-2,3,4,5-tetrahydro-1,5-Benzothiazepines (**4**) by means of neighboring group participation is described. The influence of solvents, additives, and substituents is also discussed.

Although a considerable number of studies have been made on the neighboring group mechanism,[1] only a few applications have so far been made to stereocontrolled synthesis.[2] Previously, we have reported the stereospecific synthesis of 1,5-benzothiazepines (**4**)[3] by the reaction of 2-(α-bromoalkyl)oxiranes (**1**)[4] with 2-aminothiophenol. The mechanism of this reaction consisted of two sequential $S_N2$ at the bromide-substituted carbon *via* the epoxy intermediate (**3**), each causing an inversion so the net result is retention of configuration. The intriguing possibility exists, if the bromide was substituted by the amino group directly, instead of the neighboring hydroxyl group, the sterochemical outcome will be reversed. Thus, the two diastereoisomers will be available from a single starting substrate (**1**). Here we wish to report preliminary results on the stereocontrolled synthesis of 1,5-benzothiazepines (**4**) by means of the neighboring mechanism.




(*2R*,1'R**)-2-(α-bromoalkyl)oxirane (**1**)

**2**

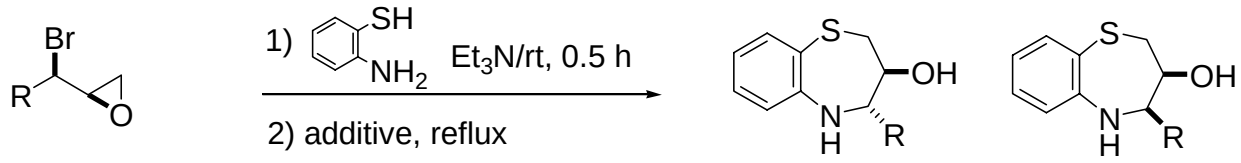
*trans*-**4**

**3**

*cis*-**4**

Table 1 summarizes a set of representative reactions of (*2R*,1'R**)-2-(α-haloalkyl)oxiranes (**1a-c**) with 2-aminothiophenol carried out under respective conditions. The results indicated in brackets reported in ref. 3 are also listed in Table 1. In the previous work, KOH was used for the formation of epoxy intermediate (**3**). On the other hand, in this work the formation of **3** should be prevented. Thus, we chose $Et_3N$ instead of KOH as a weaker base.

**Table 1**. Synthesis of 1,5-Benzothiazepines (**4**) by the Reaction of α-Haloalkyloxirane (**1**) with 2-Aminothiophenol




(*2R*,1'R**)-**1a-c** *trans*-**4a-c** *cis*-**4a-c**

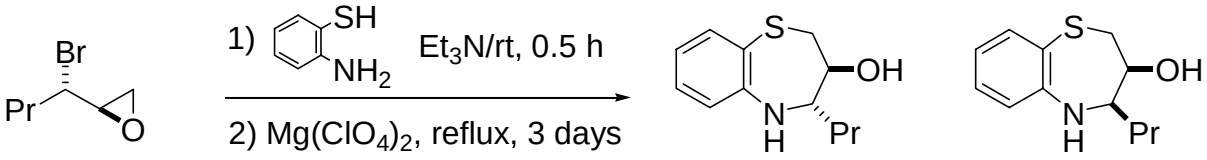
| Entry | Substrate R | Solvent | Additive (5 eq.) | Time days | Yield of **4**[a] % | Ratio of **4**[b] *trans/cis* |
|---|---|---|---|---|---|---|
| 1 | Me (**1a**) | MeOH | none | 5 h | 78 (**4a**) | 22/78 |
| 2 | Me (**1a**) | DMSO | none | 1 | 76 (**4a**) | 51/49 |
| 3 | Me (**1a**) | dioxane | NaI | 7 | 85 (**4a**) | 61/39 |
| 4 | Me (**1a**) | dioxane | $Mg(ClO_4)_2$ | 4 | 85 (**4a**) | 82/18 |
| 5 | Me (**1a**) | dioxane | $LiClO_4$ | 7 | 93 (**4a**) | 63/37 |
| 6 | Me (**1a**) | $^t$BuOH | none | 7 | 92 (**4a**) | 80/20 |
| 7 | Me (**1a**) | $^t$BuOH | $Mg(ClO_4)_2$ | 1 | 76 (**4a**) | 85 /15 |
| | ( Me (**1a**) | MeOH | KOH (1 eq.) | 1 | 87 (**4a**) | 2 />98 )[c] |
| 8 | Pr (**1b**) | $^t$BuOH | none | 4 | 95 (**4b**) | 88/12 |
| 9 | Pr (**1b**) | $^t$BuOH | $Mg(ClO_4)_2$ | 3 | 92 (**4b**) | 87/13 |
| | ( Pr (**1b**) | MeOH | KOH (1 eq.) | 2 | 78 (**4b**) | 2 />98 )[c] |
| 10 | Ph (**1c**) | $^t$BuOH | none | 1 | 66 (**4c**) | >98/ 2 |
| 11 | Ph (**1c**) | $^t$BuOH | $Mg(ClO_4)_2$ | 1 | 79 (**4c**) | >98/ 2 |
| | ( Ph(**1c**) | MeOH | KOH (1 eq.) | 4 h | 63 (**4c**) | 2 />98 )[c] |

[a]Isolated yields as diastereomeric mixture except for **4c**. [b]Ratio was determined by $^1$H NMR, [c]Yields and ratios indicated in brackets are the results on using KOH as base in MeOH at rt reported in ref. 3.

Initial studies were conducted with (*2R*,1'R**)-2-(α-bromoethyl)oxirane (**1a**). A mixture of **1a,**

2-aminothiophenol (1.2 equiv.), and $Et_3N$ (1.2 equiv.) was stirred in MeOH at room temperature for 0.5 h, and the bromohydrin intermediate (**2**) was formed by this procedure. Then, the reaction mixture was subjected to reflux for 5 h. After completion (*vide* TLC), the solvent was evaporated and the residue was extracted with toluene (15 mL × 3) After usual work-up, the products were separated by column chromatography on silica gel (hexane/AcOEt=1/3). The 1,5-benzothiazepine (**4**) was obtained as a diastereomeric mixture. The ratio of *trans*-**4a** and *cis*-**4a** was determined by the integration of $^1$H NMR. Unfortunately, reaction under these conditions was found to give poor stereoselectivity. The desired *trans*-**4a** was formed as a minor diastereoisomer (*trans*-**4a**/*cis*-**4a**=22/78 ). The major diastereoisomer (*cis*-**4a**) was presumably formed *via* the epoxy intermediate (**3**) (Entry 1). In the case of DMSO, the ratio of the desired *trans*-**4a** was slightly increased (*trans*-**4a**/*cis*-**4a**=51/49, Entry 2). Using $^t$BuOH, *cis*-**4a** was obtained dominantly (*trans*-**4a**/*cis*-**4a**=80/20, Entry 6). The addition of $Mg(ClO_4)_2$ (5 equiv) to the reaction mixture slightly improved the diastereomeric ratio (*trans*-**4a**/*cis*-**4a**=85/15 ) as shown in Entry 7. This may be attributed to the fact that $Mg(ClO_4)_2$ increases the ionic strength of the solution (this is called the salt effect[5]). Several salts (NaI, $LiClO_4$, $Mg(ClO_4)_2$) were screened for their ability to allow direct substitution by an amino group (Entries 3,4,5). By far, the superior salt for this purpose was found to be $Mg(ClO_4)_2$, which afforded *trans*-**4c** selectively. Similar results were obtained for (*2R*,1'R**)-2-(α-bromobutyl)oxirane (**1b**) (Entries 8, 9). Surprisingly, in the case of (*2R*,1'R**)-2-(α-bromobenzyl)oxirane (**1c**), stereochemistry was perfectly controlled. No diastereomeric isomer *cis*-**4c** was detected (Entries 10, 11).

We found this process was also applicable for the diastereoisomeric substrate (*2R*,1'S**)-**1d**. According to the same reaction procedure, a mixture of *trans*-**4b** and *cis*-**4b** was obtained in 94% yield (*trans*-**4b**/*cis*-**4b** = 24/76). Compared with the result of Entry 9, the stereochemical outcome was cleanly reversed.




(*2R*,1'S**)-**1d**

*trans*-**4b**

*cis*-**4b**

Yield 94%

24 : 76

The stereoselectivity for the formation of *trans*-**4** can be explained by the steric influence of the substituent $R^1$. The order of stereoselectivity is **1c** ($R^1$=Ph) > **1b** ($R^1$=Pr) > **1a** ($R^1$=Me) > **1d** ($R^1$=Pr). Thus, the substituent effect for the stereoselectivity can be attributed to the steric hindrance preventing the formation of epoxy intermediate (**3**). In the cases of **1a** and **1b**, a small amount of *cis*-epoxy intermediate (**3a, 3b**) will be formed. Similaly, diastereoisomeric substrate (**1d**) will proceed *via* thermodynamically preferable *trans*-epoxy intermediate (**3**). Thus, in the case of **1d,** the ratio of the desired *cis*-**4b** was less selective.

In summary, we have shown a new stereocontrolled synthesis of 1,5-benzothiazepines (**4**). A combination of this procedure and the previous work allowed us to obtain both diastereoisomers from a single starting substrate (**1**). We believe that this is a unique example of practical application to stereocontrolled synthesis by means of neighboring group participation. Applications to the synthesis of other heterocyclic systems are under investigation.

## REFERENCES AND NOTES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6. A typical procedure is as follows: (*trans*-3-hydroxy-4-methyl-2,3,4,-tetrahydro-1,5-benzothiazepine (**4b**)): A solution of (*2R*,1'R**)-2-(α-bromoethyl)oxirane (138 mg, 1.0 mmol), 2-aminothiophenol (150 mg, 1.2 mmol), and tryethylamine (101 mg, 1.0 mmol) in *t*-BuOH (5.0 mL) was stirred for 0.5 h at room temperature. The reaction was monitored by TLC analysis. $Mg(ClO_4)_2$ (530 mg, 5.0 mmol) and *t*-BuOH (50 mL) were added, the reaction refluxed for further 1 day, After usual work-up, the crude products were purified by silica gel chromatography (hexane/ethylacetate =3/1 as eluent). The diastereomeric ratio of the 1,5-benzothiazepines (**4**) was determined by $^1H$ NMR spectral analysis.