STEREOSELECTIVE SYNTHESIS OF HEXAHYDRO-1,4-THIAZEPIN-3-ONE AND DIHYDRO-1,4-THIAZIN-3-ONE DERIVATIVES

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Abstract - Diastereomerically pure 4-benzyl-7-substituted 6-hydroxy-hexahydro-1,4-thiazepin-3-one and 4-benzyl-1'-hydroxyalkyl-1,4-tetra-hydrothiazin-3-one derivatives are obtained by the reaction of a 2,3-epoxy alkylamine derivative with methyl thioglycolate in good yields. *trans*-Epoxy amine derivatives gave *trans*-thiazepinone derivatives and *anti*-thiazepinone derivatives whilst *cis*-epoxy amines gave *cis*-thiazepinone and *syn*-thiazepinone derivatives. Substituent effects on regioselectivity were also examined with the use of several epoxy amine derivatives.

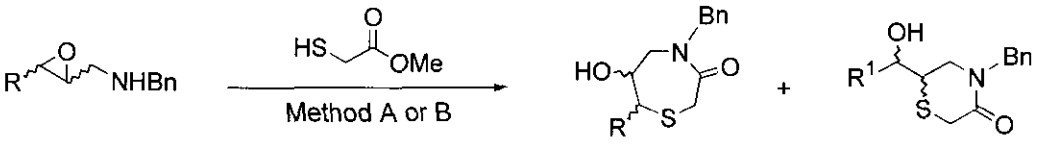
Recently, several synthetic methods for 2,3-epoxy amine derivatives (**1**) have been reported due to their unique structure and synthetic utility.[1,2] As **1** possesses both a nucleophilic amino group and an electrophilic epoxide group, **1** is used for the synthesis of nitrogen-containing heterocycles.[2,3] Previously, we reported the reaction of **1** with several heterocumulens gave nitrogen containing 1,3-heterocycles.[3] In the course of this study, we envisioned that the reaction of **1** with thioglycolate esters would give sulfur- and nitrogen-containing 1,4-hetero-cycles.

As part of a program aimed at developing new epoxy amine transformation, we were interested in the general synthetic methods for 1,4-thio-aza-heterocyclic systems. Since 1,4-thio-aza-heterocycles are interesting as biologically active compounds,[4] 1,4-thiazepinone derivatives are of particular interest as monocyclic analogues of the penicillin antibiotics.[5] Although extensive work has been reported on penicillin antibiotics, the ring formation of 1,4-thiazepine derivative has been little investigated.[6] In this communication we describe a new synthetic method for 4,7-substituted 6-hydroxyhexahydro-1,4-thiazepin-3-one derivatives (**2**) and 1,4-thiazinone derivatives (**3**).

When a solution of **1** with 1.2 equiv. mol of methyl thioglycolate was refluxed in methanol for 12 h (Method A), *cis*-4-benzyl-7-methy-6-hydroxyhexahydro-1,4-thiazepin-3-one (*cis*-**2a**) and (6*R**,1'*R**)-4-benzyl-1'-hydroxymethyl-1,4-tetrahydrothiazin-3-one derivatives (*syn*-**3a**) were

obtained in 54 and 33% yields, respectively (Table 1, Entry 1). Similarly, when the reaction was conducted in the presence of 1.2 equiv. of KOH for 2 h (Method B), **2a** and **3a** were obtained in 48 and 29% yields, respectively (Entry 2). Several derivatives (**1b** and **1c**) which possess propyl and phenyl groups instead of a methyl group were examined, and **2b** and **2c** were obtained predominantly (Entries 3-10). On the other hand, trisubstituted derivatives (**1d** or **1e**) gave only **2d** or **3e** exclusively (Table 2).

As can be seen from Table 1, the reaction of the thiol with epoxides occurred predominantly at the C-3 position and stereospecifically gave the corresponding ring-closed product (**2a**-**2c**) in each case. The reaction has the following two features. (i) The configuration of the epoxide affects the regioselectivity, especially in the case of *cis*-**1c** and *trans*-**1c** (Entries 7-10). The phenyl substituted *trans*-**1c** gave *trans*-**2c** exclusively (Entries 9, 10). On the other hand, *cis*-**1c** gave mixtures of *cis*-**2c** and *syn*-**3c** in a ratio of ca. 6 : 4 (Entries 7, 8). (ii) The presence of KOH in the reaction (Method B) improves the reaction rate but does not affect the regioselectivity.



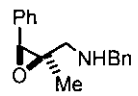
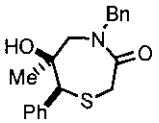
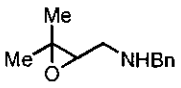
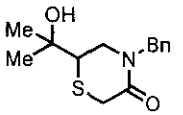
1 **2** **3**

Table 1. Reaction of 2,3-epoxy amine with methyl thioglycolate

Entry	Substrate	Method (h)[a]	Isolated Yields (%) of **2**, **3**	
1	*cis*-**1a**, R = Me	A (12)	*cis*-**2a** (54),	*syn*-**3a** (33)
2		B (2)	*cis*-**2a** (48),	*syn*-**3a** (29)
3	*cis*-**1b**, R = Pr	A (12)	*cis*-**2b** (49),	*syn*-**3b** (21)
4		B (2)	*cis*-**2b** (38),	*syn*-**3b** (24)
5	*trans*-**1b**, R = Pr	A (12)	*trans*-**2b** (52),	*anti*-**3b** (18)
6		B (2)	*trans*-**2b** (47),	*anti*-**3b** (8)
7	*cis*-**1c**, R = Ph	A (24)	*cis*-**2c** (37),	*syn*-**3c** (26)
8		B (2)	*cis*-**2c** (49),	*syn*-**3c** (33)
9	*trans*-**1c**, R = Ph	A (24)	*trans*-**2c** (68),	*anti*-**3c** (0)
10		B (2)	*trans*-**2c** (81),	*anti*-**3c** (0)

a) See text.

Table 2. Reaction of trisubstituted 2,3-epoxy amine with methyl thioglycolate

Substrate	Method (h)[a]	Isolated Yield (%)	Substrate	Method (h)[a]	Isolated Yield (%)
					
cis-**1d**	B (2)	*cis*-**2d** (58)	**1e**	A (48) B (2)	**3e** (45) **3e** (71)

a) See Text.

The structures of these compounds are elucidated on the basis of their NMR, MS, and IR data.[8] The regiochemistry of the reaction can be unequivocally determined by ^{1}H NMR data. For example, ^{1}H NMR spectra of the thiazepinone derivatives (**2c**) show a doublet at 4.27 ppm (J_{vicnal} = 1.5 Hz) due to the benzylic proton, whereas those of the thiazinone derivatives (**3c**) show it at 4.59 ppm (J_{vicnal} = 5.1 Hz). The ^{13}C NMR spectrum of **2c** and **3c** was also in agreement with the suggested structure. The stereochemistry of these products was also confirmed by comparing their ^{1}H NMR and NOESY spectra.

A typical procedure for the reaction of **1** with methyl thioglycolate is as follows. A mixture of *cis*-*N*-benzyl-2,3-epoxybutylamine (**1a**) (177 mg, 1.0 mmol) and methyl tioglycolate (127 mg, 1.2 mmol) in methanol (2.5 mL) was refluxed for 12 h. After cooling, the mixture was poured into H_2O (*ca.* 30 mL), and the solid products were filtered and dried *in vacuo*. The solid was recrystallized from toluene to give 135 mg (54%) of pure *cis*-**2a** as a single diastereomer (mp 175-176 °C). The filtrate was extracted with chloroform (15 mL X 3). The organic phases were dried (Na_2SO_4) and concentrated. The residue was distilled by use of Kugelrohr apparatus to give 84 mg (33%) of pure *syn*-**3a** as a colorless liquid (bp 200-210 °C/0.08 mmHg). (Method A: Table 1, Entry 1).

Production of diastereomerically pure 2,3-epoxy amine derivatives employing our previously reported method is relatively easy.[3] Therefore, our protocol demonstrates a convenient single-step synthesis of diastereomerically pure 1,4-thio-aza heterocyclic systems.

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8. Compound *cis*-**2c**: mp 225-226 °C (chloroform); IR (KBr) 3320, 1610 cm^{-1}; ^1H NMR (DMSO-d_6, 50 °C) δ 3.19 (1H, d, J = 13.8 Hz), 3.38 (1H, dd, J = 15.6, 6.9 Hz) 3.77 (1H, d, J = 15.6 Hz), 3.87 (1H, d, J = 13.8 Hz), 3.94 (1H, td, J = 6.9, 2.1 Hz), 4.06 (1H, d, J = 15.0 Hz), 4.27 (1H, d, J = 2.1 Hz), 4.81 (1H, d, J = 6.9 Hz), 5.23 (1H, d, J = 15.0 Hz), 7.2-7.4 (10H, m); ^{13}C NMR (DMSO-d_6, 50 °C) δ 34.24, 51.57, 52.10, 54.95, 67.26, 126.84, 127.07, 127.47, 127.87, 128.26, 128.39, 138.01, 139.92, 171.13; MS (70 eV, rel. intensity) 314 (M^++1, 23), 313 (M^+, 100), 91 (43). Compound *syn*-**3c**: mp 157-159 °C (toluene); IR (KBr) 3320, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (1H, d, J = 15.0 Hz), 3.36 (3H, m) 3.49 (1H, d, J = 15.0 Hz), 4.33 (1H, d, J = 14.7 Hz), 4.59 (1H, d, J = 5.1 Hz), 4.80 (1H, d, J = 14.7 Hz), 7.1-7.2 (4H, m), 7.2-7.3 (6H, m); ^{13}C NMR ($CDCl_3$) δ 28.73, 49.17, 49.37, 50.49, 74.22, 126.11, 127.69, 128.12, 128.38, 128.64, 128.68, 136.58, 140.40, 167.91.

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