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A Novel Synthesis of 3-Thietanols by Reactions of 2-(1-Haloalkyl)oxiranes with Monothiocarbamic Acid Salts

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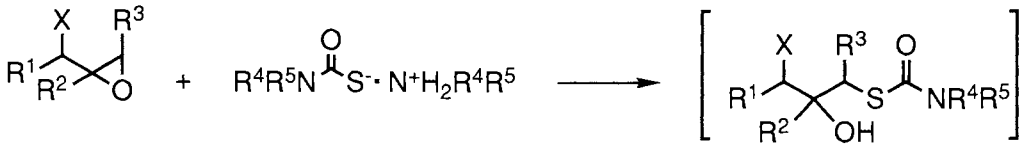
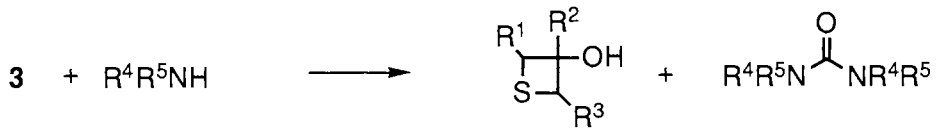
Several 3-thietanol derivatives were synthesized in good yields by stereospecific reactions of 2-(1-haloalkyl)oxiranes with monothiocarbamic acid salts.

Although a large number of studies have been undertaken to prepare small size heterocycles, little attention has been given to effective synthetic methodology for thietanes[1,2] which are expected to have some interesting biological activities.[1-3] Abbott[4] and Dittmer[5] reported synthesis of thietane derivatives using 2-(1-haloalkyl)oxiranes (**1**) and hydrogen sulfide. However, these methods suffer from low yields, since intermolecular reactions took place at the same time with the formation of thietanes. One of the reasons of these intermolecular reactions depends on the formation of sulfide anion moieties.

Carbon oxide sulfide is an analogous C1 compound of carbon dioxide and carbon disulfide. In contrast with the latters, the former possesses polar character. This reagent is readily available and forms monothiocarbamic acid salts (**2**) by the reaction with primary or secondary amines. By the reaction with **1**, these monothiocarbamic acid salts (**2**) would give the thiolcarbamate derivatives (**3**) which could be transformed to 3-thietanols (**4**) by attack of appropriate nucleophiles on the carbonyl groups to give corresponding thiols and then intramolecular cyclization between the thiol moiety and the halogenated carbon. By this procedure, intermolecular reactions could be avoided, because free thiols were not always present in the reaction system and intermolecular reactions would be prevented by the bulky thiocarbamoyl group in the molecule. In this communication, we will present a novel and useful method for synthesis of **4** using of **1** and **2**.



1 **2** **3**



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At first we chose *syn*-2-bromobenzyloxirane (**1a**)[6] as the substrate, and **1a** was treated with several monothiocarbamic acid salts **2**, which are derived from propylamine, isopropylamine, cyclohexylamine,

phenethylamine, diethylamines, *p*-toluidine, and pyrrolidine. In most cases, the reactions smoothly proceeded under the mild conditions to give corresponding **3** in good yields, while the reactions with sterically bulky or insoluble **2** did not give good results. These reactions were markedly retarded in nonpolar solvents. Various reaction conditions of the synthesis of **4a** were tested, and the following conditions has been adopted as the most reasonable one. A solution of **1a** (213 mg, 1.0 mmol) and phenethylaminomonothiocarbamic acid salt **2** (362 mg, 1.2 mmol) was stirred in methanol at room temperature for 5 h. Then, the mixture was diluted with dichloromethane and washed with aqueous HCl (1%). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was used for the subsequent reaction without further purification.[7] Then, the resulting mixture was dissolved in DMSO (5 ml) and treated with phenethylamine (242 mg, 2.0 mmol) at 50 °C for 2 h. The GC analysis revealed the formation of *trans*-2-phenyl-3-thietanol (**4a**, 80%). The reaction mixture was poured into water and extracted with dichloromethane. The extract was dried and evaporated. Pure **4a** was obtained by column chromatography on SiO_2 (benzene). The isolated product was analyzed by IR, ^1H NMR, and ^{13}C NMR. These spectral data agreed completely with those of the authentic sample.[4]

The reaction was then applied to several other haloalkyloxiranes (**1b-m**), and the results are shown in Table 1. Various 3-thietanol derivatives (**4b-h**) were obtained in reasonable yields.[8] These reactions were conducted in a stereoselective and stereospecific manner. In Entries 3 and 4, the steric interference between the methyl group (R^2) and the thiocarbamoyl group in the intermediates **3** may reduce the yields of **4b**. The oxiranes (**1a-f,1h,1i,1l,1m**) derived from *trans*-allylalcohol gave *trans*-thietanol (**4a,4b,4d,4e,4g,4h**) selectively (Entries 1-6, 8, 9, 12, and 13). On the other hand, a reaction of *anti*-**1a** (R^1=Ph R^2=R^3=H, not listed) derived from *cis*-cinnamyl alcohol gave no thietanol derivatives.[9] In order to synthesize *cis*-3-thietanol derivatives (**4**), **1g** was treated by a similar procedure as described above (Entry 7).

In contrast with the cases of phenyl substituted oxiranes **1a,1b,1d-i** (Entries 1,2,5-9), alkyl or nonsubstituted oxiranes **1j-m** (Entries 10-13) were not converted into the corresponding thietanols (**4f-h**) in practical yields. In order to obtain the alkyl substituted **4** in good yields, thiocarbamate derivatives **3** were converted into their *p*-nitrobenzoates (**5**) before treatment with amines. Reactions of **5** with phenethylamine in DMSO at 50 °C gave **6** in good yields (Table 2).

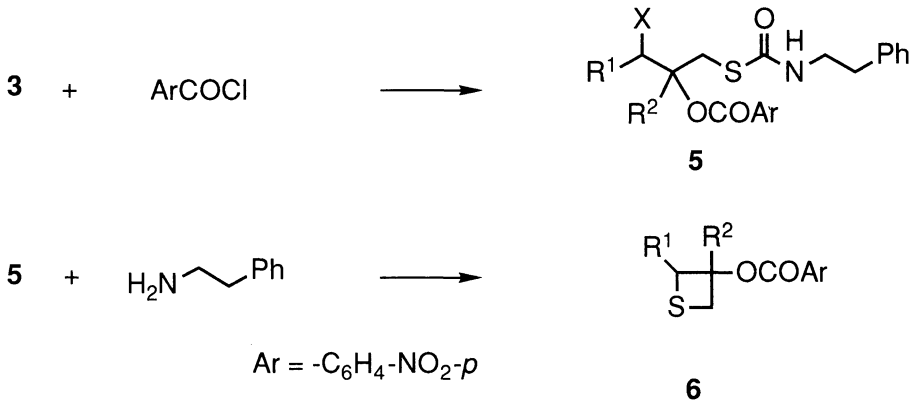
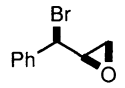
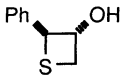
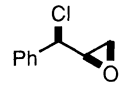
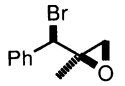
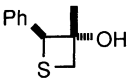
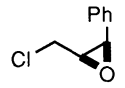
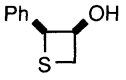
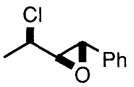
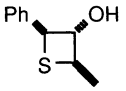
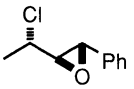
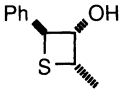
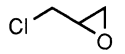
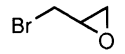
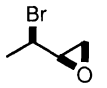
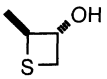
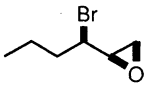
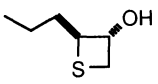


Table 1. Reactions of 2-(1-haloalkyl)oxiranes (**1**) with phenethylaminomonothiocarbamic acid salt (**2**)

Entry	2-(1-Haloalkyl)oxirane		Time/h[a]	Product		Yield/%[a]
1		**1a**	0.5		**4a**	80
2		**1b**	2		**4a**	66[b]
3		**1c**	0.5		**4b**	13[b]
4		**1d**	1		**4b**	34[b]
5		**1e**	0.5		**4a**	53
6		**1f**	1		**4a**	79
7		**1g**	1		**4c**	66
8		**1h**	1		**4d**	79[b]
9		**1i**	1		**4e**	84[b]
10		**1j**	1		**4f**	33
11		**1k**	0.5		**4f**	36
12		**1l**	0.5		**4g**	37
13		**1m**	0.5		**4h**	43

a) Cyclization step: DMSO-phenethylamine system. Yields based on **1** were determined by GC.

b) Yields based on **1** were determined by ^{1}H NMR (300 MHz).

Table 2. Reactions of *p*-nitrobenzoate derivatives (**5**) with phenethylamine

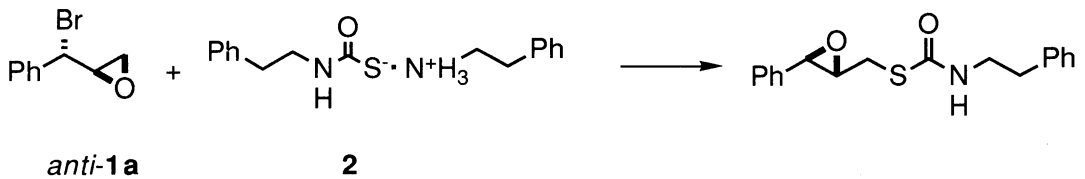
Entry	*p*-Nitrobenzoate (**5**)			Time/min[a]	Yield of **6**/%[b]
	R^1	R^2	X		
1	H	H	Br	30	91
2	H	Me	Br	20	87
3	Ph	H	Br	30	83

a) Cyclization step: DMSO-phenethylamine system. b) Isolated yield.

In conclusion, we have succeeded in the efficient synthesis of several 3-thietanols (**4**) by the novel reaction of **1** with monothiocarbamic acid salts (**2**) under the mild conditions. The efficient cyclization reaction by use of **1** described here strongly depends on the substituents of the substrates. This reaction now has been extended to a facile and widely applicable method for the preparation of **4**. Further examination of this reaction using various kinds of **1** are in progress in our laboratory.

References

1) A review on synthesis of thietane, see: M. Sander, *Chem. Rev.*, **66**, 341 (1966).
2) E. Block, "Comprehensive Heterocyclic Chemistry," ed by A. R. Katritzky, C. W. Rees, and K. W. Lwowski, Pergamon Press, Oxford (1984), Vol. 7, pp. 403-447.
3) A. P. Kozikowski and A. H. Fauq, *Synlett*, **1991**, 783 .
4) F. S. Abbott and K. Haya, *Can. J. Chem.*, **56**, 71 (1977).
5) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961).
6) M. Yoshida, T. Hide, M. Ohshima, H. Sasaki, and T. Toda, *Heterocycles*, **33**, 507 (1992).
7) The ^{1}H NMR spectrum of the residue shows the presence of **3** in 75% yield.
8) All new compounds **4** given in Table 1 were characterized by NMR, IR, and MS. As the typical example, *trans*-2-propyl-3-hydroxythietane (**4h**): IR(neat) 3350 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 0.92 (3H, t, *J*=7.2 Hz, CH_2CH_3), 1.35 (2H, m, CH_2Me), 1.61 (1H, m, CH_2Et), 1.88 (1H, m, CH_2Et), 2.19 (1H, d, *J*=7.8 Hz, O*H*), 3.11 (1H, t, *J*=8.4 Hz, SCH_2), 3.17 (1H, dt, *J*=8.4, 8.1 Hz, SCH_2), 3.71 (1H, td, *J*=8.4, 5.4 Hz, PrC*H*S), 4.40 (1H, tdd, *J*=8.4, 8.1, 7.8 Hz, C*H*OH); ^{13}C NMR($CDCl_3$) δ 13.7 (CH_3), 20.2 (CH_2Me), 34.3 (SCH_2), 37.9 (CH_2Et), 56.3 (SCHPr), 73.6 (CHOH); MS(20 eV) m/z 132 (M^+).
9) The reaction of *anti*-2-bromobenzyloxirane (**1a**) with monothiocarbamic acid salt (**2**) at room temperature gave an oxirane derivative in 48% yield.



anti-**1a** **2**

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