Preparation of 2-(3-Hydroxyalkylthio)benzoxazoles and their Conversion into Thietanes

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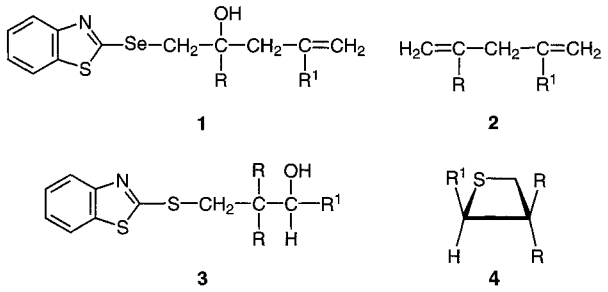
Received 5 August 1997

Abstract: Reaction of primary or secondary 1,3-diols with dibenzoxazol-2-yl disulfide and tributylphosphine or triphenylphosphine selectively gave 2-(3-hydroxyalkylthio)benzoxazoles which, on treatment with KH, were converted into the corresponding thietanes. 2,2-Dibenzylthietane-1-oxide reacted with silylated purines and pyrimidines in the presence of TMSOTf and ZnI_2 to give the corresponding thietane nucleosides in 17-69% yields.

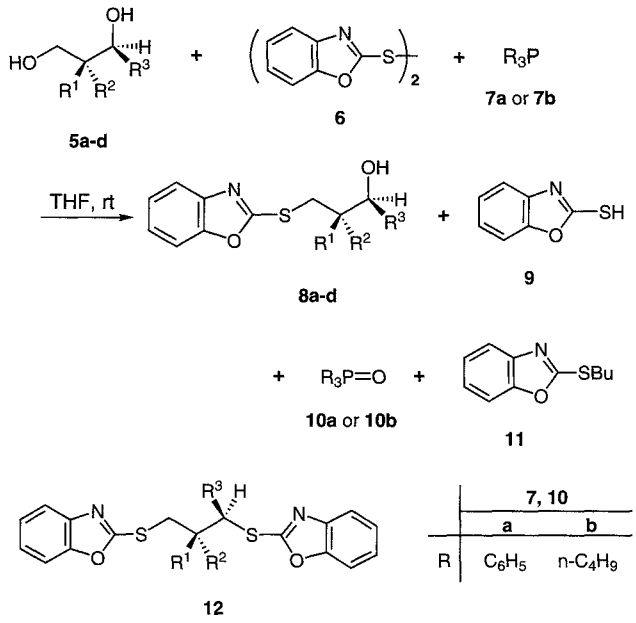
Four-membered heterocycles have attracted much attention due to their potential reactivities and biological activities.[1] Of these heterocycles, however, chemistry and biological activities of thietanes have hardly been elucidated.[2, 3] As part of our project aimed to develop convenient procedures for the activation of alcoholic hydroxyl group,[4] we are interested in the preparation of oxetanes, thietanes and selenetanes. In this communication, we wish to report a novel method for the preparation of thietanes and their conversion into nucleoside analogues. Matsuda and his coworkers recently reported preparation of thietane nucleosides from thietanes.[5]

A previous paper described that the reaction of 2-(2-hydroxy-4-pentenylseleno)benzothiazoles (**1**) with NaH and triphenylphosphine gave 1,4-dienes (**2**) presumably through unstable seleniranes.[6] In view of this results, it would be reasonable to assume that 2-(3-hydroxyalkylthio)benzoxazoles (**3**) could be converted into thietanes (**4**) by treatment with a base (Scheme 1).



Scheme 1

The regioselective introduction of benzoxazolylthio group into the primary position of 1,3-diols could be attained by the reaction with dibenzoxazol-2-yl disulfide (**6**) and tertiary phosphines **7** (Scheme 2).[7] When 1,3-butanediol (**5a**) reacted with **6** and triphenylphosphine (**7a**) at room temperature for 1 h, the primary hydroxyl group selectively entered into the reaction giving 2-(3-hydroxybutylthio)benzoxazole (**8a**) in 58% yield (Table 1, entry 1). When tributylphosphine (**7b**) was used in the place of **7a**, the yield of **8a** was decreased to 37% along with a small amount of 2-(butylthio)benzoxazole (**11**) (entry 2). On the other hand, the reaction of 1-phenyl-1,3-propanediol (**5b**) with **6** and **7a** gave only a trace of **8b** (entry 3), while the yield of **8b** was increased to 38% in the reaction using **7b** (entry 4). The reaction of 2,2-dibenzyl-propane-1,3-diol (**5c**) with **6** and **7a** was sluggish and required reflux to afford **8c** in 72% yield (entry 5). In these reactions, varied amounts of 2-mercaptobenzoxazole (**9**) and triphenylphosphine oxide (**10a**) were obtained. However, no attempt was made to isolate tributylphosphine oxide (**10b**).



Scheme 2 (For R^1, R^2, R^3, see Table 1)

Table 1. Reaction of 1,3-diols **5** with **6** and **7** in THF at room temperature for 1 h

Entry	Substituents of **5** and **8**			Reactants		Products	
	R^1	R^2	R^3	**5**	**7**	**8**:%	**11**:%
1	H	H	CH_3	**5a**	Ph_3P	**8a**: 58	
2	H	H	CH_3	**5a**	Bu_3P	**8a**: 37	15
3	H	H	Ph	**5b**	Ph_3P	**8b**: trace[1]	
4	H	H	Ph	**5b**	Bu_3P	**8b**: 38	4
5	Bn	Bn	H	**5c**	Ph_3P	**8c**: 72[2]	
6	H	Et	Ph	*anti*-**5d**	Ph_3P	*anti*-**8d**: 74	
7	H	Et	Ph	*anti*-**5d**	Bu_3P	*anti*-**8d**: 62	8
8	Et	H	Ph	*syn*-**5d**	Ph_3P	*syn*-**8d**: nd[1,3]	
9	Et	H	Ph	*syn*-**5d**	Bu_3P	*syn*-**8d**: 65	10
10	CH_3	H	Ph	*syn*-**5e**	Ph_3P	*syn*-**8e**: complex mixture	
11	CH_3	H	Ph	*syn*-**5e**	Bu_3P	*syn*-**8e**: 54	5

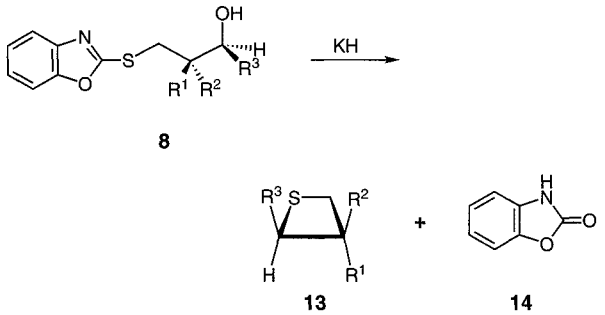
1) A complex mixture of products was formed. 2) The reaction was carried out at room temperature for 1.5 h and then under reflux for 12 h. 3) Even when the reaction was carried out at –34 °C → –4 °C for 1 h, a complex mixture of products again formed

Next, *anti*-2-ethyl-1-phenyl-1,3-propanediol (*anti*-**5d**) was allowed to react with **6** in the presence of **7a** or **7b** at room temperature for 1h to give *anti*-2-(2-ethyl-3-hydroxy-3-phenylpropylthio)benzoxazole(*anti*-**8d**) in 74% or 62% yield, respectively (Table 1, entries 6 and 7). On the other hand, reaction of *syn*-**5d** with **6** and **7a** resulted in the formation of a complex mixture of products in which no *syn*-**8d** could be detected (Table 1, entry 8). However, *syn*-**8d** was obtained in 65% yield when *syn*-**5d** reacted with **6** and **7b** at room temperature (Table 1, entry 9).

Although the yields of the desired **8** were not necessarily high, neither the formation of bis(benzoxazolyl) derivatives **12** nor recovery of the starting alcohol could be detected in all the cases examined.

Compound **8** thus prepared was subjected to cyclization by the use of KH (Scheme 3). When a 0.22 M solution of **8b** in THF was treated with 1.5 molar amount of KH at room temperature for 1 h, the expected thietane **13b** and benzoxazol-2-one (**14**) were obtained in 32% and 81% yields, respectively (Table 2; entry 1). The inconsistency in the yields of **13b** and **14** suggested that a competitive intermolecular displacement took place. Thus, the concentration of **8b** was lowered to 0.07 M, where the yield of **13b** was increased to 42% (Table 2; entry 2). When the amount of KH was increased to 3.0 molar, practically same result was obtained (Table 2, entry 3: standard conditions). Under the same conditions, **8c** gave **13c** in 60% yield (Table 2, entry 4).

Under standard conditions, *syn*-**8d** and *syn*-**8e** reacted smoothly with KH to afford single thietanes which was tentatively assigned to be *trans*-isomers (*trans*-**13d** and *trans*-**13e**: Table 2; entries 5 and 7). In contrast, no thietane **13** could be obtained in the reaction of *anti*-**8d** with KH (Table 2; entry 6).

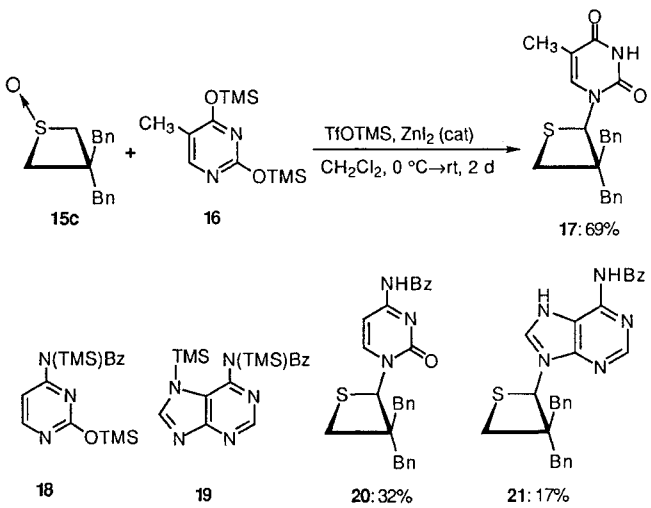


Scheme 3 (For R^1, R^2, R^3, see Table 2)

Table 2. Preparation of thietanes by the reaction of **8** with KH

Entry	Substituents of **8** and **13**			Reactants		Time/h	Products	
	R^1	R^2	R^3	**8** (M)[1]	KH^2		**13**: %	**14**: %
1	H	H	Ph	**8b** (0.22)	1.5	1	**13b**: 32	81
2	H	H	Ph	**8b** (0.07)	1.5	3	**13b**: 42	87
3	H	H	Ph	**8b** (0.07)	3.0	3	**13b**: 44	85
4	Bn	Bn	H	**8c** (0.07)	3.0	4	**13c**: 60	95
5	Et	H	Ph	*syn*-**8d** (0.07)	3.0	3	*trans*-**13d**: 72	98
6	H	Et	Ph	*anti*-**8d** (0.07)	3.0	3	*cis*-**13d**: nd[3]	26
7	Me	H	Ph	*syn*-**8e** (0.07)	3.0	3	*trans*-**13e**: 52	89

1) Concentration of 8 (M). 2) Molar amount used. 3) Not detected. A complex mixture of products was formed.



Scheme 4

Next, the coupling of thietane with nucleoside bases was examined by the use of Pummerer reaction.[5, 8] Thus, thietane **13c** was converted into the corresponding sulfoxide **15c** (91% yield) by the reaction with MCPBA (1 equiv.) in CH_2Cl_2 at 0 °C for 1 h. The reaction of **15c** with silylated thymine **16** in the presence of ZnI_2 in CH_2Cl_2 at 0 °C to room temperature for 2 days gave the expected thietanylthymine **17** in 69% yield (Scheme 4). When silylated N^4-benzoylcytosine **18** and N^6-benzoyladenine **19** reacted with **15c** under the same conditions, the corresponding thietane nucleosides **20** and **21** were obtained in 32% and 17% yields, respectively.

The work described in this paper makes thietanes readily available and suggests a number of interesting possibilities for further work.

The preparation of 3,3-dibenzylthietane (13c)

A solution of **8c** (1.3 g, 3.3 mmol) in THF (13 ml) was added to KH (1.2 g, 10 mmol) in THF (35 ml) at room tempereture with vigorous stirring. After stirring for 4 h, the mixture was quenched with aqueous saturated NH_4Cl, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by TLC (hexane/EtOAc = 6/1) to afford **13c** (0.51 g, 60 %) as a colorless solid: ^{1}H-NMR (270 MHz, $CDCl_3$);2.95 (4H, s), 3.00-3.25 (4H, brs), 7.18-7.36 (10H, m).

Acknowledgments

This work was supported in part by a grant from the Research Institute of Aoyama Gakuin University.

References and notes

1) For the preparation of four-membered heterocycles, see for example, Ghosez, L.; Marchand-Brynaert, J. "Formation of Four-membered Heterocycles," in "Comprehensive Organic Synthesis," ed-in-chief, Trost, B. M.; Fleming, I.; vol. ed, Paquette, L. A. Pergamon Press; New York, 1991; Vol. 5, Chapter 22, pp 85-122, and refs therein.

2) For the preparation of thietanes, see for example, a) Gay,J.; Scherowsky, G. *Syn. Commun.* **1995**, *25*, 2665-2672. b) Block, E.; Wang, M. D. "Thietanes and Thietes," in "Comprehensive Heterocyclic Chemistry II," ed-in-chief, Katritzky, A. R.; Rees, C. A.; Screven, E. F. V.; vol. ed, Padwa, A. Pergamon Press, New York, 1996; Vol. 1B, Chapter 1. 24, pp 773-821, and refs therein.

3) Oxetanes having nucleoside bases have recently attracted attention; see for example; a) Niitsuma, S.; Kato, K.; Takita, T. *Tetrahedron Lett.* **1987**, *28*, 3967-3970. b) Niitsuma, S.; Kato, K.;Takita, T. *Tetrahedron Lett.* **1987**, 28, 4713-4714. c) Daniel, W. N.; James, B. K. *J. Am. Chem. Soc.* **1988**, *110*, 2717-2718, and refs therein.

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7) For related reactions, see, a) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *17*, 1409-1412. b) Shibata, K.; Mitsunobu, O. *Chem. Lett.* **1993**, 549-552.

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