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A facile and efficient one-pot synthesis of thiirans by the reaction of benzoxazolyl β-ketosulfides with $NaBH_4$/NaOH

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Abstract

Convenient and efficient procedures for thiirans have been developed via a one-pot reaction of benzoxazolyl β-ketosulfides with $NaBH_4$ and NaOH in MeOH and THF. The reaction is considered to proceed via the spiro intermediate by the *ipso*-addition of β-hydroxygroup, which is formed by the $NaBH_4$ reduction of β-keto group, to 2-position of benzoxazole group.

Keywords: Thiirans; One-pot synthesis; β-Ketosulfides; Benzoxazole

Organosulfur compounds are useful and important in organic synthesis. It is known that thiirans are the simplest sulfur containing heterocycles, and they are important building blocks in the field of polymer, pharmaceutical, pesticide, and herbicide industries.[1] Many methods for the preparation of thiirans are reported. The most general synthetic method is the conversion of oxirans to thiirans with several sulfurated reagents such as thiourea,[2] KSCN,[3] NH_4CN,[4] and phosphine sulfides.[4] Thiirans are also synthesized from α-haloketones,[5] 2-mercaptoalkanols,[6] aldehydes, and ketones.[7] However, some of these methods resulted in low yields, and sometimes required harsh reaction conditions, long reaction time, and the aid of expensive metal catalysts. The formation of polymeric product is also seen as by product.

Recently, we reported that the thermolysis of benzothiazolyl β-hydroxysulfides afforded the corresponding olefins efficiently. The thermolysis is found to proceed via a spiro intermediate to afford thiirans, which are successively decomposed to olefins by desulfurization at high temperature.[8] To obtain thiirans in good yields without desulfurization, the milder and more efficient reaction conditions were required. However, we could not find the good result in the reaction of benzothiazolyl β-hydroxysulfides. After extensive work using other heterocyclic systems, we have found a facile and efficient one-pot procedure. Herein, we report the reactions of benzoxazolyl β-ketosulfides with $NaBH_4$ and NaOH in MeOH and THF.

The reactions of β-ketosulfides bearing several heteroaromatics, such as benzothiazole, benzoxazole, benzimidazole, and 5-(1-phenyl)-1,2,3,4-tetrazole, with $NaBH_4$ and NaOH were studied at rt. The results are summarized in Table 1. In the case of benzothiazolyl β-ketosulfide **1**, only thiiran **5b** was obtained in a trace yield with the formation of the reduction product, namely, benzothiazolyl β-hydroxysulfides (entry 1) after 30 min. When an excess base was added and the reaction was continued for prolonged reaction time, thiiran **5b** was not obtained at all, but an undesired polymerized product was formed, probably via nucleophilic ring opening reaction of thiiran (Scheme 1). In contrast, the reaction of benzoxazolyl β-ketosulfide **2b** with $NaBH_4$/NaOH was found to proceed very rapidly to afford the corresponding thiiran **5b** in a high yield as a sole product (entry 2). In comparison with benzothiazolyl

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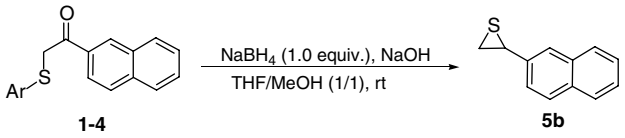
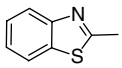
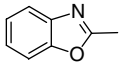
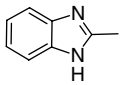
Table 1
Reactions of β-ketosulfides bearing several heteroaromatics **1**–**4** with base



1-4 **5b**

Entry	Ar		NaOH (equiv)	Time	Yield (%)
1		**1**	1.0 1.5	30 min 6 h	Trace —[a]
2		**2b**	1.0	5 min	88[b]
3		**3**	2.0	6 h	0[c]
4		**4**	2.0	6 h	0[c]

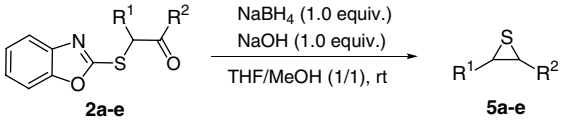
[a] Complex mixture was obtained.
[b] An isolated yield (not optimized).
[c] Only β-hydroxysulfides were obtained quantitatively.

β-hydroxysulfides, the very high reactivity of benzoxazolyl derivative **2b-1** to provide the corresponding thiiran will be explained by the more polar nature of N=C bond in benzoxazole ring, resulting in the acceleration of the formation of spiro intermediate **2b-3**. The plausible formation pathway to **5b** is illustrated in Scheme 1. First, **2b** was reduced by $NaBH_4$ to afford hydroxysulfides **2b-1**, and then, the *ipso* addition of hydroxy group to 2-position of benzoxazole proceeded smoothly by ^-OH catalysis to form spiro intermediate (**2b-2** to **2b-3**). Successively, the spiro intermediate **2b-3** afforded the corresponding thiiran **5b** concertedly or via the thiol anion **2b-4**. The isolation of **5b** is easily performed by silica gel flash column chromatography after concentration. In cases of β-ketosulfides **3** and **4** bearing other heteroaryl groups, such as benzimidazole and 5-(1-phenyl)-1,2,3,4-tetrazole, the corresponding reduction products, namely benzimidazolyl or 5-(1-phenyl)-1,2,3,4-tetrazolyl β-hydroxysulfides, were formed quantitatively, instead of **5b** (entries 3 and 4). Probably, in these cases the formation of spiro intermediates by the *ipso* addition of β-hydroxy group will be retarded greatly both electronically and sterically.

To study the scope and limitations, β-ketosulfides bearing benzoxazole having several substituents at α- and/or β-positions **2a**–**e** were prepared and their reactions under the same conditions were carried out. The results are summarized in Table 2. All reactions are found to afford the corresponding thiiran **5a**–**e** in good to excellent yields within a short time. Interestingly, in the cases of **2c**–**e**, cis–trans selectivity for the formation of thiirans **5c**–**e** was observed (entries 3–5). The configuration and ratio of *cis*-**5c**–**d** and *trans*-**5c**–**d** were determined by comparing with those of the reported ^1H NMR spectra.[9]

In summary, we have found a new and versatile synthetic procedure[10] for substituted thiirans using benzoxazolyl β-ketosulfides. A variety of benzoxazolyl β-ketosulfides are obtained easily from 2-mercaptobenzoxazole and β-haloketones without any toxic and expensive reagents. Namely, the reaction of **2a**–**e** with $NaBH_4$ and NaOH in MeOH/THF

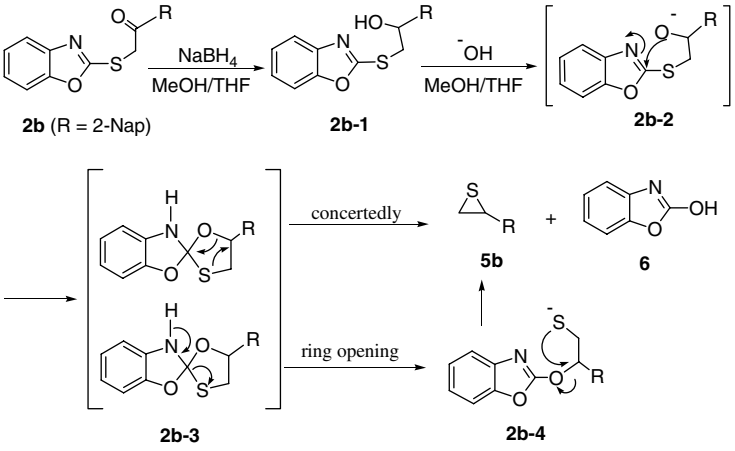
Table 2
Thiiran formation from the reaction of α- and/or β-substituted benzoxazolyl β-ketosulfides



2a-e **5a-e**

Entry	R^1	R^2		Time (min)	Yield[a] (%)	Ratio (cis:trans)[b]
1	H	Ph	**2a**	5	74	—
2	H	2-Nap	**2b**	5	88	—
3	Me	Ph	**2c**	10	76	2.0:1.0
4	Ph	Ph	**2d**	10	94	6.0:1.0
5	*p*-Tol	*p*-Tol	**2e**	10	90	7.0:1.0

[a] Isolated yields (not optimized).
[b] Estimated by ^1H NMR.



Scheme 1. Probable mechanism for the reaction of β-ketosulfide **2b** with $NaBH_4$/NaOH.

solution afforded corresponding thiiran **5a**–**e** in high yields by one-pot procedure. The isolation of thiirans is quite easily attained without loss by the simple extraction with CH_2Cl_2, followed by the silica gel flash chromatography.

References and notes

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10. A typical thiiran procedure for **5d**:[9] To a solution of NaOH (0.50 mmol) and $NaBH_4$ (0.50 mmol) in 2.0 mL of anhydrous MeOH was added **2d** in 2.0 mL of anhydrous THF with stirring at rt under N_2. After 10 min, the reaction mixture was quenched by the addition of water and extracted with 5.0 mL of CH_2Cl_2. The organic layer was washed with brine and water and dried over anhydrous $MgSO_4$. The purification was made by flash chromatography on silica gel to afford thiiran **5d** in 90% yield.