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2-Benzothiazolyl Phenacyl Sulfoxide, a New Precursor for 2-Oxo-2-phenylethanethial

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ABSTRACT: *Previously, a facile formation of a thioaldehyde by the thermolysis of a heteroaryl phenacyl sulfoxide was confirmed by the detection of a cycloadduct with 2,3-dimethyl-1,3-butadiene. The usefulness of benzothiazolyl phenacyl sulfoxide as a precursor for 2-oxo-2-phenylethanethial was studied under the same conditions in the presence of various dienes and anthracene. In all cases, the Diels-Alder cycloadducts were formed in moderate to good yields, and the addition of triethylamine as external base was revealed to be effective for carrying out the thermolysis under milder reaction conditions and for the improvement of yields.* Heteroatom Chem 10: 363–367, 1999

INTRODUCTION

Thioaldehydes are well known to be important and useful reagents to afford dihydrothiapyran derivatives through [4 + 2] cycloaddition reactions with 1,3-dienes [1]. Therefore, in spite of their instability and tendency to polymerize, studies of these species have been actively pursued. For example, Vedejs and co-workers reported that the photolysis of a phenacyl sulfide in the presence of various dienes afforded the Diels-Alder cycloadducts [2]. They also reported intramolecular trapping [3], the synthesis of azocine derivatives [4], and diastereoselectivity in the reaction of cyclopentadiene with a thioaldehyde formed under the same condition [5]. As other methods for the generation of thioaldehydes, the elimination of sulfenyl compounds, such as thiosulfinate [6], sulfenyl chloride [7], thiophthalimide [8], sodium thiosulfinate *S*-ester [9], and thiosulfonate derivatives [10], is known.

Recently, we reported that the thermal reaction of heteroaryl phenacyl sulfoxides, with the heterocyclic rings being derived from benzothiazole, pyridine *N*-oxide, pyrimidine, and pyridine, in the presence of 2,3-dimethyl-1,3-butadiene afforded 6-benzoyl-5,6-dihydro-3,4-dimethyl-2*H*-thiapyran **(3)** [11]. This product is considered to be formed by the Diels-Alder reaction of the butadiene with the thioaldehyde formed initially.

In this article, in order to demonstrate the usefulness of 2-benzothiazolyl phenacyl sulfoxide as a precursor of 2-oxo-2-phenylethanethial, we report the formation of the [4 + 2] cycloadducts and their stereochemistry by the thermal reaction of 2-benzothiazolyl phenacyl sulfoxide **(1)** in the presence of various dienes.

RESULTS AND DISCUSSION

The results of the thermal reaction of 2-benzothiazolyl phenacyl sulfoxide **(1)** in the presence of dienes, such as *trans,trans*-1,4-diphenyl-1,3-butadiene, 2-methyl-1,3-butadiene, cyclopentadiene, 1,3-cyclohexadiene, and anthracene, in dioxane are summarized in Table 1 [12].

The thermolytic reaction of phenacyl sulfoxide **1**

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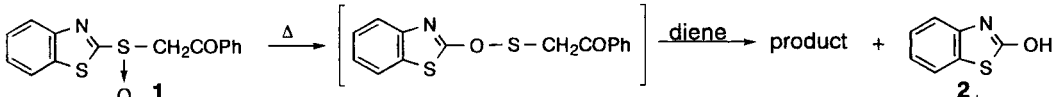
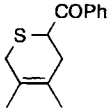
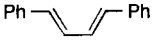
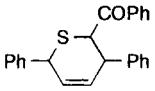
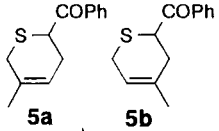
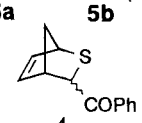
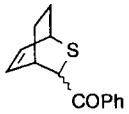
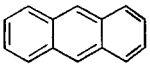
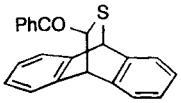
TABLE 1 Thermolytic Reaction of Benzothiazolyl Phenacyl Sulfoxide in the Presence of Various Dienes in Dioxane



Entry	Diene	Equiv.	Condition[a]	Time (h)	Product		Yield% Product[b]	Yield% 2
1		10.0	A	24		**3**	73	83
2		1.5	A	24		**3**	90	98
3		5.0	A	24		**4**	45	72
4		10.0	A	24		**5a, 5b**	68 (2:1)[c]	85
5		10.0	B	6		**5a, 5b**	83 (3.5:1)[c]	83
6		10.0	A	12		**6**	42 (*exo* only)	52
7		10.0	B	1.2		**6**	78 (1:1)[d]	77
8		10.0	A	24		**7**	73 (1:10)[d]	83
9		10.0	B	4		**7**	75 (1:10)[d]	98
10		5.0	A	24		**8**	100	99

[a]A: 100°C, in the absence of base. B: 70°C, in the presence of 1.5 equiv. of Et_3N.
[b]Isolated yield.
[c]The ratio of **5a** to **5b**.
[d]The ratio of *exo* to *endo* isomer.

in the presence of 10 or even 1.5 equiv. of 2,3-dimethyl-1,3-butadiene afforded 6-benzoyl-5,6-dihydro-3,4-dimethyl-2*H*-thiapyran (**3**) and 2-hydroxybenzothiazole (**2**) in good yields (entries 1–2) [11]. The reaction of **1** in the presence of other substituted butadienes, such as *trans, trans*-1,4-diphenyl-1,3-butadiene and 2-methyl-1,3-butadiene, also afforded the cycloadducts; **4** and **5** (**5a:5b** = 2:1) in 45 and 68% yields, respectively (entries 3–4). The same reaction of **1** with 2-methyl-1,3-butadiene in the presence of 1.5 equiv. of triethylamine at a lower temperature (70°C) afforded a mixture of **5** (**5a:5b** = 3.5:1) and **2** in 83 and 83% yields, respectively (entry 5). The preferential formation of the 3-methyl substituted dihydrothiapyran derivative **5a** over **5b** (entries 4 and 5) showed the same regio-selectivity as reported previously by Vedejs' group [2b]. They correlated the selectivity with the results of an *ab initio* quantum mechanical calculation [2c]. As seen in entries 6–9, the addition of triethylamine again improved the yields of **6** and **7** substantially, a result of the milder conditions (shorter reaction time and lower reaction temperature, namely, 70°C). Diels-Alder cycloadducts of anthracene with various thioaldehydes are well known to be useful thioaldehyde precursors because they undergo the *retro*-Diels-Alder reaction thermally. Here, as shown in entry 10, a cycloadduct of anthracene **8** was obtained quantitatively, and it shows high thermal stability. As shown in entry 10, we were able to obtain **8** as a crystalline solid that could be stored at room temperature (RT) without decomposition for a prolonged time. This adduct **8** was found to undergo the *retro*-Diels-Alder reaction above 100°C.

From the NMR study of **6**, only *exo*-**6** was observed (entry 6), while no selectivity was observed as shown in entry 7 when 1.5 equiv. of triethylamine was added. The *exo–endo* ratio of **7** was 1:10 in the cases reported in both entries 8 and 9. The assignment and ratio determination of the *exo–endo* iso-

mer for **7** and **8** was readily performed by NMR spectrometry, without separation of the isomers as described later.

The NMR spectrum of *endo*-**6** displayed the 3-H methyne hydrogen as a doublet with a coupling constant, $J_{3H,4H}$ = ca. 4 Hz, while the 3-H of *exo*-**6** appeared as a singlet. The coupling constant value for the *endo*-**6** indicates the relation between the 3-H and the 4-H, the vicinal hydrogens, with a rather small dihedral angle, and the singlet peak for *exo*-**6** indicates the possible placement of the 3- and the 4-H with an ca. 90°C dihedral angle; this clearly suggests that *cis*-relation between the 3- and the 4-H hydrogens, as depicted in Figure 1. In the NOESY experiment, the 3-H showed a weak NOESY correlation to the 7-H in *endo*-**6**; and, in *exo*-**6**, the 3-H also showed a weak correlation to the 5-H. In the COSY spectrum of the product mixture, the set of correlation peaks facilitated the selection of the set of signal of both *exo*- and *endo*-**6**.

Finally, the *exo–endo* ratio was determined by the integration of both methyne 3-H protons of the *exo–endo* mixture. The identification of *endo*-**7** was established by NMR spectrometry similarly to the procedure described earlier. However, the full assignment of the NMR spectrum of *exo*-**7** was not performed because of the relatively small content (less than 10%) of the *exo*-isomer as against the *endo*-one in this reaction mixture.

Contrary to our results, Vedejs and coworkers reported that the reaction of 2-oxo-2-phenylethanethial, formed by the photolysis of phenacyl sulfide with cyclopentadiene, afforded the *endo*-cycloadduct as the predominant product (*exo*:*endo* = 1:3) [5]. The difference in the *exo–endo* ratio between Vedejs' and our results is probably due to the thermodynamical equilibration between *exo*- and *endo*-**6**, depending on the *retro*-Diels-Alder reaction of **6** under our conditions, affording thermodynamically more stable *exo*-**6** in better than, or the same yield as, *endo*-**6** [5]. It is interesting that, contrary to the result in the case of cyclopentadiene (*exo*-**6** only), the high *endo*-ratio (*exo*:*endo* = 1:10) was observed in product **7** in the case of trapping by cyclohexadiene under similar conditions, even after having been equilibrated thermodynamically (reaction time = 24 h). This result suggests that the steric hindrance between the methylene linkages of cyclohexadiene and the benzoyl group is important under both kinetic and thermodynamic conditions in the course of the cycloaddition reaction. Vedejs and coworkers also reported similar results [2b].

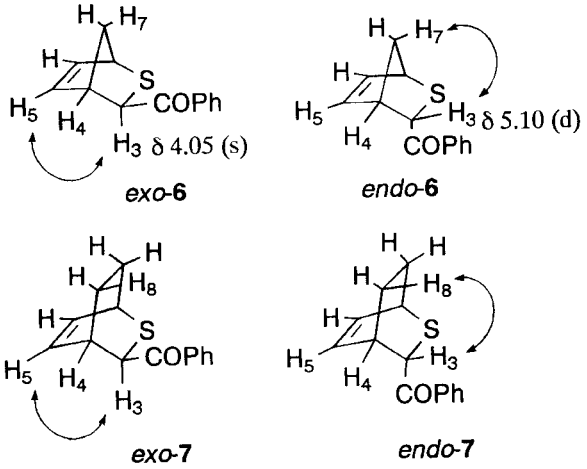


FIGURE 1 Important NOESY correlations for **6** and **7.**

CONCLUSION

As a result, the thermal reaction of phenacyl sulfoxide **1** led to the Diels-Alder cycloadducts of 2-oxo-2-phenylethanethial in the presence of several dienes in good to moderate yield, and thus, sulfoxide **1** was revealed to be useful as a precursor of 2-oxo-2-phenylethanethial. The advantages of using this precursor **1** are the ease of the preparation (only two steps from 2-mercaptobenzothiazole), the stable nature at Rt, and the simple procedure of this thermal reaction.

EXPERIMENTAL

General

All melting points were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ using TMS as internal standard. The elemental analyses were performed by the Microanalytical Laboratory of the Department of Chemical and Biochemical Engineering of Toyama University. All the reactions were monitored by TLC using Silica Gel 60 F_{254} TLC plates, and products were separated by column chromatography using Silica Gel 60, also by preparative layer chromatography using 60 PF_{254} with UV detection. All reagents were of highest quality and were further purified by distillation or recrystallization. Solvents were further purified by general methods.

General Procedure of Thermolysis of **1** *with Dienes*

A solution of **1** and 5–10 equiv. of the diene in dioxane in a Pyrex tube was degassed thoroughly *in vacuo* at dry ice–acetone temperature, and the glass

tube was then sealed and was heated at 100°C for 12–24 hours. After cooling of the tube and its contents, the solvent and the volatile starting materials were removed in *vacuo,* and the residue was chromatographed on a silica-gel preparative plate using ethyl acetate/hexane (1:5) as eluent to afford products **4–8** with **2.**

6-Benzoyl-5,6-dihydro-2,5-diphenyl-2H-thiapyran (**4**). This procedure was employed by using 106 mg of **1** (0.35 mmol) and 5 equiv. of 1,4-diphenyl-1,3-butadiene (1.75 mmol) in 3 mL of dioxane to afford 54 mg of **4** and 38 mg of **2** in 45 and 72% yields, respectively. Spectral data of **4:** colorless oil; ^{1}H-NMR δ 4.00–4.04 (m, 1H), 4.39–4.44 (m, 2H), 6.08–6.13 (m, 1H), 6.17–6.21 (m, 1H), 7.25–7.31 (m, 2H), 7.33–7.42 (m, 8H), 7.47–7.51 (m, 3H), 7.83–7.86 (m, 2H). ^{13}C-NMR δ 39.8, 41.0, 48.4, 127.1, 127.7, 127.9, 128.5, 128.57, 128.56, 128.8, 131.0, 133.0, 135.0, 140.0, 142.5, 192.4. IR (neat) 1680 cm^{-1}. HRMS calcd for $C_{24}H_{20}OS$ 356.1234; found, 356.1238.

6-Benzoyl-5,6-dihydro-3-methyl-2H-thiapyran (**5a**) *and 6-Benzoyl-5,6-dihydro-4-methyl-2H-thiapyran* (**5b**). This procedure was employed by using 102 mg of **1** (0.34 mmol) and 10 equiv. of isoprene (3.4 mmol) in 3 mL of dioxane to afford 50 mg of the oily mixture of **5a** and **5b** and 44 mg of **2** in 68 and 85% yields, respectively. Each ^{1}H-NMR spectrum for **5a** and **5b** was assigned by a NOESY experiment using the mixture without separation because the separation was difficult.

Spectral data of **5a:** ^{1}H-NMR δ 1.78 (s, 3H), 2.39–2.65 (m, 2H), 2.96 (bs, 2H), 4.46 (t, J = 6 Hz, 1H), 5.62–5.65 (m, 1H), 7.43–7.48 (m, 2H), 7.53–7.58 (m, 1H), 7.99–8.02 (m, 2H). **5b:** ^{1}H-NMR δ 1.80 (s, 3H), 2.39–2.65 (m, 2H), 3.02–3.14 (m, 2H), 4.54 (t, J = 5 Hz, 1H), 5.62–5.65 (m, 1H), 7.43–7.48 (m, 2H), 7.53–7.58 (m, 1H), 7.99–8.02 (m, 2H), ^{13}C-NMR of the mixture of **5a** and **5b** δ 24.3, 24.68, 24.73, 26.9, 28.1, 30.7, 40.3, 41.2, 116.9, 121.1, 128.5, 128.6, 130.0, 133.0, 134.3, 135.07, 135.11, 195.4, 195.5. IR (neat) 1690 cm^{-1}. HRMS calcd for $C_{13}H_{14}OS$ 218.0764; found, 218.0760.

3-exo-Benzoyl-2-thiabicyclo[2.2.1]hept-5-ene (*exo*-**6**). This procedure was employed by using 101 mg of **1** (0.33 mmol) and 10 equiv. of cyclopentadiene in 3 mL of dioxane to afford 33 mg of **6** (*exo* only) and 26 mg of **2** in 42 and 52% yields, respectively. Spectral data of *exo*-**6:** colorless oil; ^{1}H-NMR δ 1.75–1.78 (m, 1H), 1.87–1.90 (m, 1H), 3.67 (bs, 1H), 4.05 (s, 1H), 4.15 (bs, 1H), 6.09 (dd, J = 3, 6 Hz, 1H), 5.45 (dd, J = 2, 5 Hz, 1H), 7.44–7.48 (m, 2H), 7.54–7.58 (m, 1H), 7.93–7.96 (m, 2H). ^{13}C-NMR δ 46.4, 49.3, 52.2, 52.9, 128.2, 128.6, 133.2, 133.3, 137.0, 138.6, 197.7. HRMS calcd for $C_{13}H_{12}OS$ 216.0608; found, 216.0613. IR (neat) 1680 cm^{-1}.

3-endo-Benzoyl-2-thiabicyclo[2.2.2]oct-5-ene (*endo*-**7**). This procedure was employed by using 100 mg of **1** (0.33 mmol) and 10 equiv. of 1,3-cyclohexadiene (3.3 mmol) in 3 mL of dioxane to afford 61 mg of **7** and 42 mg of **2** in 73 and 83% yields, respectively. Spectral data of *endo*-**7** (as a mixture of 10% *exo*-**7**; colorless oil): ^{1}H-NMR δ 1.52–1.59 (m, 3H), 1.70–1.85 (m, 1H), 3.27–3.55 (m, 2H), 4.72 (d, J = 2 Hz, 1H), 6.44–6.52 (m, 2H), 7.40–7.45 (m, 2H), 7.51–7.55 (m, 1H), 7.86–7.90 (m, 2H). ^{13}C-NMR δ 23.4, 29.4, 31.0, 35.4, 53.1, 128.4, 128.6, 133.07, 133.10, 133.2, 135.9, 157.7. IR (neat) 1680 cm^{-1}.

12-Benzoyl-9,10-dihydro-11-thia-9,10-ethanoanthracene (**8**). This procedure was employed by using 103 mg of **1** (0.34 mmol) and 5 equiv. of anthracene (1.70 mmol) in 3 mL of dioxane to afford 111 mg of **8** and 52 mg of **2** in quantitative yield. Spectral data of **8**: mp 153.1–157.5 (dec); ^{1}H-NMR δ 4.69 (d, J = 2 Hz, 1H), 5.11 (d, J = 2 Hz, 1H), 5.21 (s, 1H), 7.12–7.26 (m, 6H), 7.34–7.43 (m, 3H), 7.48–7.52 (m, 1H), 7.62–7.64 (m, 1H), 7.75–7.77 (m, 2H). ^{13}C-NMR δ 46.2, 46.8, 53.9, 121.3, 122.5, 124.3, 126.0, 126.3, 126.5, 126.9, 128.15, 128.22, 128.5, 133.3, 136.7, 139.2, 142.1, 142.5, 143.4, 195.5. IR (neat) 1690 cm^{-1}. HRMS calcd for $C_{22}H_{16}OS$ 328.0921; found, 328.0899.

General Procedure of Thermolysis of **1** *with Dienes and Base*

A solution of **1** and 10 equiv. of dienes, and 1.5 equiv. of triethylamine in dioxane in a Pyrex tube was degassed thoroughly in vacuo at dry ice–acetone temperature, and the glass tube was sealed and then heated at 70°C for 1.2–6 hours. After cooling of the tube and its contents, the solvent and the volatile starting materials were removed in *vacuo,* and the residue was chromatographed on silica-gel preparative plate using ethyl acetate/hexane (1:5) as eluent to afford products **5a–b**, **6**, and **7**, with **2**. The regio- or stereoisomer ratios of **5a–b**, **6**, and **7** were determined by NMR spectrometry.

3-endo-Benzoyl-2-thiabicyclo[2.2.1]hept-5-ene (*endo*-**6**). Yield 78% (*exo:endo* = 1:1); IR (neat) 1680 cm^{-1}. HRMS calcd for $C_{13}H_{12}OS$ 216.0608; found, 216.0613.

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[12] In the previous article (Ref. [11b]), we reported the acceleration and improvement of the yield on the formation of thiapyran cycloadducts by the addition of triethylamine.