Chem. Pharm. Bull. 30(4)1175—1182(1982)

Halogenation Reaction of *S*-Aryl-*S*-[(1,2-benzisoxazol-3-yl)methyl]sulfoximide

Toyokichi Yoshida,* Shunsuke Naruto, Hitoshi Uno, and Haruki Nishimura

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., 33-94, Enoki-cho, Suita, Osaka 564, Japan

(Received August 31, 1981)

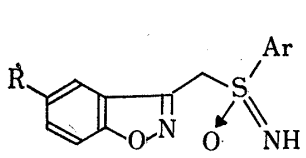
The reactions of the title free sulfoximide with *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) afforded the corresponding α-halogenated "free" sulfoximides in good yields. The α-bromination proceeded *via* a facile *N*-bromination followed by a bromine transfer reaction of the resulting *N*-bromosulfoximide. The NCS chlorination, in contrast, proceeded *via* direct α-chlorination, not *via* *N*-chlorination. However, in the presence of potassium carbonate or silica gel *N*-chlorination occurred predominantly in the NCS chlorination.

Keywords——1,2-benzisoxazole; halogenation; *N*-halosulfoximide; α-halo sulfoximide; rearrangement; induction period

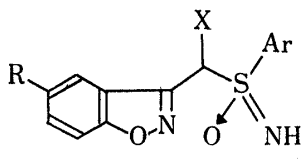
Since sulfoximide chemistry was first studied in 1950 by Bentley *et al.*,[1] much attention has been focused on the syntheses and properties of sulfoximides, and many derivatives have been found to possess a wide variety of interesting chemical and biological properties.[2] *N*-Unsubstituted (free) sulfoximides are known to undergo *N*-halogenation with a number of halogenating agents[3] and the resulting *N*-halosulfoximides have been used as halogenating agents.[3b,e,4] It was expected, therefore, that *N*-halosulfoximide containing an active methylene group could undergo rearrangement of the halogen atom. However, no research has been reported of this possibility.

Meanwhile, Uno *et al.*[5] have been studying 1,2-benzisoxazole derivatives which have interesting biological activities, and found that the α-methylene group of 1,2-benzisoxazole-3-acetic acid is unusually activated to electrophiles, especially to halogen electrophiles, suggesting that the C=N bond of the 1,2-benzisoxazole ring has the nature of a "masked" carbonyl group. Therefore, it appeared to be of interest to examine the chemical and biological properties of sulfoximide derivatives bearing a 1,2-benzisoxazole ring.

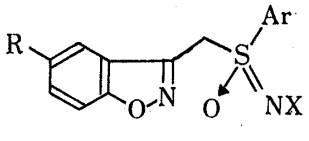
This paper deals with the synthesis and halogenation reaction of *S*-aryl-*S*-[(1,2-benzisoxazol-3-yl)methyl]sulfoximide **1**, including the rearrangement of its *N*-halo derivatives **4** and **5** to the corresponding α-halo derivatives **2** and **3**,[6] and the direct α-chlorination of **1**. Concerning the α-halogenation of sulfoximide derivatives, only chlorination of *N*-methyl- and *N*-chlorosulfoximides,[3d] and bromination of cyclic derivatives[7] have been reported. Hence, this paper is the first report on the rearrangement of *N*-halosulfoximide and on the α-halogenation of free sulfoximide.



1



2 : X=Br
3 : X=Cl



4 : X=Br
5 : X=Cl

	a	b	c	d	e	f
R	H	H	H	Br	MeO	H
Ar	Ph	*p*-MePh	*p*-ClPh	Ph	Ph	*p*-BrCH$_2$Ph

Chart 1

Results and Discussion

Preparation of Free Sulfoximide 1

Free sulfoximide **1** was prepared as shown in Chart 2. α-Bromo-1,2-benzisoxazole-3-acetic acid[8] was treated with arylmercaptide to give the arylthioacetic acid **6**, which was pyrolyzed to the sulfide **7**. The sulfide **7** was oxidized to the sulfoxide **8** by using NBS[9] in aqueous tetrahydrofuran. Successive treatment of **8** with *O*-mesitylenesulfonylhydroxylamine (MSH)[10] and base gave **1**.

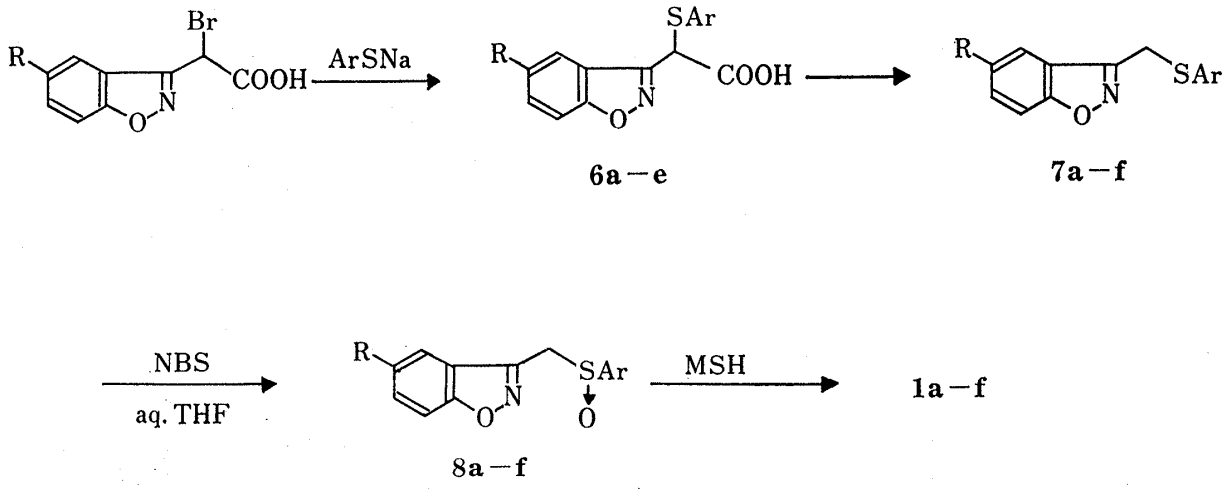


Chart 2

Bromination of Free Sulfoximide 1

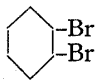
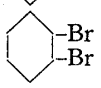
The reactions of **1** with bromine/pyridine and with NBS in commercial chloroform for 2—4 h at room temperature gave α-bromo "free" sulfoximide, *S*-aryl-*S*-[(1,2-benzisoxazol-3-yl)bromomethyl]sulfoximide **2**, in 80—90% and *ca.* 60% yields, respectively, as a mixture of diastereomers (see "Experimental"). This result is surprising in view of the fact that free sulfoximide derivatives readily undergo *N*-halogenation with various halogenating agents,[3] but would not be unexpected if the α-bromo sulfoximide **2** were produced *via* the corresponding *N*-bromosulfoximide **4**. As expected, *N*-bromo-*S*-aryl-*S*-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides **4a**, **b** were obtained in 90% yields by treatment of **1a**, **b** with NBS in dichloromethane for 5 min at room temperature.

These findings suggest that the foregoing α-bromination of **1** with NBS proceeded *via* a facile *N*-bromination followed by a bromine transfer reaction of the resulting *N*-bromosulfoximide **4**. In order to confirm this, the decomposition reaction of **4** was carried out and indeed the bromine transfer reaction of **4** easily proceeded to give the α-bromo sulfoximide **2** as shown in Table I.

Inspection of the data in Table I reveals an interesting feature of this rearrangement reaction. In the dark no decomposition occurred. In the presence of a light source, even a room light (a fluorescent lamp), however, the bromine transfer reaction easily proceeded at room temperature and showed a clear induction period (Fig. 1).

The effect of solvent was remarkable; an increase in the concentration of ethanol in the solvent enhanced the rate of this reaction and decreased the yields of radical products. Thus, in dichloromethane and in refluxing carbon tetrachloride **4b** gave *S*-(*p*-bromomethylphenyl)-sulfoximides **1f** and **2f** in 10—25% yields either in the presence or in the absence of a radical initiator, while in chloroform containing 5% ethanol (5% EtOH–$CHCl_3$) the yields of these radical products decreased to only trace amounts. Meanwhile, in the presence of cyclohexene

Table I. Decomposition Reaction of *N*-Bromosulfoximide **4**[a]

Compd.	Reaction conditions	Products and yields (%)[b]			
		1a	**2a**		
4a	5% EtOH–$CHCl_3$,[c] 1.5 h	38.5	56.6		
	1% EtOH–$CHCl_3$,[c] 2.5 h	35.2	58.1		
	CH_2Cl_2, 10 h	31.5	58.5		
	1% EtOH–$CHCl_3$, in the dark, 1 week	No decomposition			
	5% EtOH–$CHCl_3$,  (10 equiv.), 7 h[d]	65.7	7.7		22.2[e]
	CH_2Cl_2,  (10 equiv.), 24 h	—[f]	—[f]		36.8[e]
		1b	**1f**	**2b**	**2f**
4b	5% EtOH–$CHCl_3$, 1.5 h	43.4	Trace	47.1	Trace
	1% EtOH–$CHCl_3$, 2.5 h	34.1	2.5	47.8	5.1
	CH_2Cl_2, 10 h	24.5	25.4	22.5	16.8
	CCl_4, reflux, 10 h	31.2	18.5	18.6	9.9
	CCl_4, BPO(5%), reflux, 3 h	26.0	15.1	20.6	11.2

a) The reaction was carried out at room temperature in the presence of a room light unless otherwise stated.
b) Determined by HPLC.
c) Chloroform containing 5% or 1% ethanol.
d) The other product is 1-bromo-2-ethoxycyclohexane[3c] (23.3%).[e]
e) Determined by GLC.
f) Yields of **1a** and **2a** were not determined.

4a gave 1,2-dibromocyclohexane in 36% and 22% yields in dichloromethane and in 5% EtOH–$CHCl_3$, respectively; in the absence of cyclohexene the liberation of bromine was observed in the early stage of the reaction.

These results cited above clearly indicate that the bromine transfer reaction of **4** proceeds through an initial photo-induced radical process (an induction period) followed by a bromination process in which the bromine molecule formed in the initial step should act as the active brominating species by two mechanisms. One is a radical mechanism proceeding *via* a chain process like the "Goldfinger mechanism"[11] as in the bromination of olefins[3e] and toluene[4] with *N*-bromo-*S*,*S*-diphenylsulfoximide. The other is an ionic process which involves the electrophilic attack of bromine molecule on the active methylene group and seems to be mainly operative in solvents containing ethanol. The activation of the methylene group of **1** to an electrophile may be explained in terms of the strong electron-withdrawing inductive effect and/or (more likely) the tautomerization of the 1,2-benzisoxazole ring, whose C=N bond shows the nature of a "masked" carbonyl group,[5c,d] as illustrated in Chart 3.

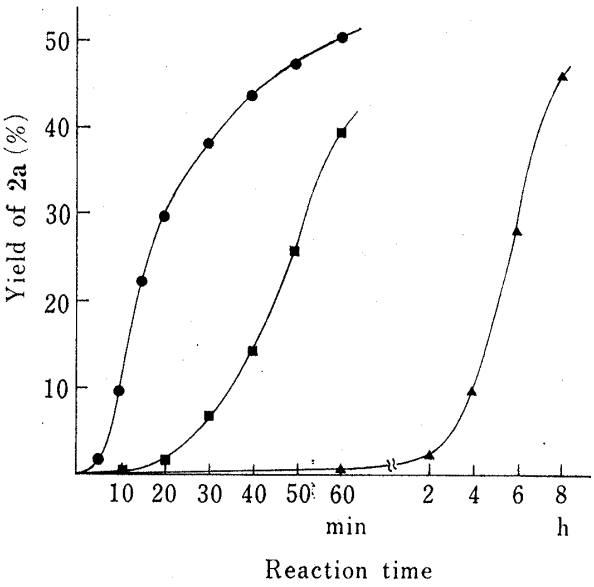


Fig. 1. Change of Yield of **2a** with Time in the Decomposition Reaction of **4a**

●: in 5%EtOH–$CHCl_3$, ■: in 1%EtOH–$CHCl_3$, ▲: in CH_2Cl_2.

Chart 3

Chlorination of Free Sulfoximide 1

The reaction of **1a**—**c** with NCS in chloroform for 24 h at room temperature gave α-chloro sulfoximides **3a**—**c** in *ca.* 70% yields as a mixture of diastereomers (see "Experimental"). By analogy, this α-chlorination was thought to proceed in the same manner as the NBS bromination, although the corresponding *N*-chlorosulfoximide **5** could not be isolated in this reaction, in contrast with the NBS bromination. The *N*-chlorosulfoximides **5a**, **b**, however, were easily obtained in 90% yields by treatment of **1a**, **b** with *tert*-butyl hypochlorite (BHC) in dichloromethane for 5 min at room temperature.

In order to investigate whether the *N*-chlorosulfoximide **5** is an intermediate in the α-chlorination of **1** with NCS, the decomposition reaction of **5** was examined. The results summarized in Table II, however, show an unexpected feature of this reaction.

Table II. Decomposition Reaction of *N*-Chlorosulfoximide **5**[a]

Compd.	Reaction conditions	Products and yields(%)[b]	
		1a	**3a**
5a	5% EtOH–$CHCl_3$, 24 h	81.3	6.1
	1% EtOH–$CHCl_3$, 48 h	66.6	12.7
	CH_2Cl_2, 1 week	32.8	22.5
	CH_2Cl_2, in the dark, 2 weeks	No decomposition	
		1b	**3b**
5b	5% EtOH–$CHCl_3$, 48 h	78.5	3.9
	CH_2Cl_2, 1 week	34.1	9.1

a) The reaction was carried out at room temperature in the presence of a room light unless otherwise stated.
b) Determined by HPLC.

The *N*-chlorosulfoximide **5** decomposed at room temperature to give **1** and **3** in the presence of a light source, suggesting that the reaction was photochemically initiated, as in the case of the *N*-bromo derivative **4**, though the rate was strongly dependent on the solvent used. In every case examined, however, the yields of **3** were very low in comparison with those in the NCS chlorination of **1**. This result seems to be contrary to our expectation stated above.

In order to clarify this point, the reaction of **1** with NCS was examined under several conditions and the results are summarized in Table III. Either in the presence or in the absence of a light source the reaction of **1** with NCS proceeded smoothly at room temperature to give the α-chloro sulfoximide **3** in good yield and was finished within 24 h, independently of the solvent used. For example, even in the dark **1a** reacted with NCS in dichloromethane for 24 h to give **3a** in 71% yield, whereas in the dark the *N*-chlorosulfoximide **5a** was stable for 2 weeks in dichloromethane (see Table II). Furthermore, the proton nuclear magnetic resonance (^{1}H-NMR) inspection during the course of the α-chlorination of **1a** with NCS in chloroform-d_1 indicated that no detectable amount of **5a** was produced. These observations appear to exclude the possibility of the intermediacy of *N*-chlorosulfoximide **5** in the α-chlorination of **1** with NCS.

The rate of this α-chlorination was strongly affected by the reaction temperature; at 0°C the reaction of **1a** with NCS required over 1 week for completion. The addition of acids such as trichloroacetic or *p*-toluenesulfonic acid apparently enhanced the rate of this reaction. The presence of *p*-quinone, however, had little effect. These findings seem to indicate that this α-chlorination is not of a radical type, but involves an ionic process.

Meanwhile, the addition of pyridine or *trans*-stilbene also had little effect, suggesting that in this α-chlorination NCS itself acts as the active chlorinating species, not merely as a controlled source of chlorine molecule.[13]

Table III. Reaction of Free Sulfoximide **1** with NCS[a)]

Compd.	Reaction conditions	Products and yields (%)[b)]	
		3a	**5a**
1a	5% EtOH–$CHCl_3$, 24 h	68.1	
	1% EtOH–$CHCl_3$, 24 h	64.6	
	CH_2Cl_2, 24 h	68.2	
	5% EtOH–$CHCl_3$, in the dark, 24 h	68.0	
	CH_2Cl_2, in the dark, 24 h	71.2	
	$CDCl_3$, in the dark, 24 h	(77)	(0)
	$CDCl_3$, 0°C, in the dark, 1 week[c)]	(60)	(20)
	$CDCl_3$, *p*-quinone (1 equiv.), 24 h	(75)	(0)
	$CDCl_3$, CCl_3COOH (10%), 12 h	(76)	(0)
	$CDCl_3$, pyridine-d_5 (10%), 24 h	(74)	(0)
	$CDCl_3$, *trans*-stilbene (1.5 equiv.), 24 h	(73)	(0)
	$CDCl_3$, K_2CO_3 (1 equiv.), 10 min[d)]	(0)	(50)
	$CDCl_3$, SiO_2,[e)] 2 h	(10)	(72)
		3b	
1b	5% EtOH–$CHCl_3$, 24 h	72.5	
	CH_2Cl_2, 24 h	72.0	
	5% EtOH–$CHCl_3$, in the dark, 24 h	69.2	
	CH_2Cl_2, in the dark, 24 h	65.9	

a) The reaction was carried out at room temperature in the presence of a room light unless otherwise stated.
b) Determined by HPLC and values in parentheses by ^{1}H-NMR.
c) The reaction was approximately 90% completed.
d) The reaction was approximately 55% completed: prolonged reaction caused the further rearrangement of **5a** to the corresponding *N*-sulfinylimine[12)].
e) Kieselgel 60 (Merck) 1.0 g/**1a** 300 mg.

On the basis of the results cited above, the α-chlorination of **1** with NCS is considered to proceed through the direct electrophilic α-attack of NCS, in contrast to the α-bromination of **1** with NBS.

Although it is difficult to explain why the imino group of **1** is less reactive to NCS than to BHC and NBS, there are two possible explanations. One is that the nucleophilicity of the imino group of **1** is decreased because of the electron-withdrawing inductive effect of the 1,2-benzisoxazole ring. The other is that NCS is too much less electrophilic than BHC and NBS to react with the deactivated imino group. It seems likely, therefore, that at room temperature the NCS chlorination of **1** can occur at the α-position activated by the 1,2-benzisoxazole ring as mentioned above. At lower temperature, *N*-chlorination may be able to compete with α-chlorination because the rate of α-chlorination is retarded.

On the other hand, in the presence of potassium carbonate or, interestingly, silica gel, *N*-chlorination occurred predominantly in the reaction of **1a** with NCS as shown in Table III. The function of potassium carbonate or silica gel is likely to be to increase the nucleophilicity of the imino nitrogen by deprotonation or adsorption of the imino proton, respectively.

Since the present interesting results are based on the reaction of "special" free slfoximide **1**, we are investigating some extensions of these reactions in order to examine the generality of these results.

Experimental

All melting points were measured on a Ishii micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM-360 spectrophotometer with tetramethylsilane as an internal standard in $CDCl_3$ unless otherwise stated. The following abbreviations are used: s, singlet; bs, broad singlet; d, doublet; q, quartet; m, multiplet. High performance liquid chromatography (HPLC) was carried out on a Waters 204 machine using a nucleosil $_{10}C_{18}$ column and 2% aq. AcOH–EtOH (55: 45) as an eluent. Gas-liquid chromatography (GLC) was carried out on a Yanaco G180 using a column packed with 10% SP-100 on Chromosorb WAW.

Preparation of Aryl (1,2-Benzisoxazol-3-yl)methyl Sulfoxides 8a—f——8a—e: To a solution of α-bromo-1,2-benzisoxazole-3-acetic acid (0.1 mol) and NaOH (4.0 g, 0.1 mol) in EtOH (100 ml)–H_2O (40 ml) was added all at once a solution of aryl hydrosulfide (0.1 mol) and NaOH (0.1 mol) in EtOH (30 ml)–H_2O (30 ml). After the mixture had been stirred for 1 h at room temperature, the EtOH was evaporated off *in vacuo*. The residual aq. solution was washed with $CHCl_3$, acidified with conc. HCl, and then extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residual crude **6** was heated at 120—130°C until the evolution of CO_2 ceased (about 20 min). After being cooled, the resulting oil was dissolved in $CHCl_3$ and washed with aq. NaOH. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude **7** was dissolved in THF (150 ml)–H_2O (20 ml) and an excess of NBS was added. After the mixture had been stirred for 30 min at room temperature, the THF was evaporated off *in vacuo* and the resulting precipitates were extracted with $CHCl_3$. The extract was washed with aq. NaOH, dried over Na_2SO_4, and concentrated *in vacuo*. The residual crystals were recrystallized from CH_2Cl_2–isopropyl ether to give pure sulfoxides **8a—e** in total yields of 60—70%. Compounds **6** and **7**, except for **6a** and **7a, b**, were not isolated as pure products. **6a**: mp 85—86°C (ether–pet. ether). ^{1}H-NMR, δ: 5.43s (1H, CH), 7.1—8.1 m (9H, arom), 9.7—10.5b (1H, COOH). *Anal.* Calcd for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91; S, 11.24. Found: C, 62.93; H, 3.99; N, 4.83; S, 11.34. **7a**: mp 71—72°C (hexane). ^{1}H-NMR, δ: 4.41s (2H, CH_2), 7.1—7.9m (9H, arom). *Anal.* Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.60; N, 5.81; S, 13.29. Found: C, 69.69; H, 4.55; N, 5.79; S, 13.22. **7b**: mp 59—60°C (hexane). ^{1}H-NMR, δ: 2.30s (3H, CH_3), 4.38 S (2H, CH_2), 6.9—8.0m (8H, arom). *Anal.* Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.55. Found: C, 70.43; H, 5.22; N, 5.56; S, 12.36. **8a**: mp 109—110°C. ^{1}H-NMR, δ: 4.45s (2H, CH_2), 7.0—7.9m (9H, arom). *Anal.* Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.33; H, 4.17; N, 5.57; S, 12.61. **8b**: mp 117—119°C. ^{1}H-NMR, δ: 2.38s (3H, CH_3), 4.45s (2H, CH_2), 7.15—7.9m (8H, arom). *Anal.* Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.56; H, 4.62; N, 5.09; S, 11.62. **8c**: mp 134—136°C. ^{1}H-NMR, δ: 4.88s (2H, CH_2), 7.2—7.9m (8H, arom). *Anal.* Calcd for $C_{14}H_{10}ClNO_2S$: C, 57.64; H, 3.45; Cl, 12.15; N, 4.80; S, 10.99. Found: C, 57.74; H, 3.23; Cl, 12.37; N, 5.11; S, 10.69. **8d**: mp 166—169°C. ^{1}H-NMR, δ: 4.42s (2H, CH_2), 7.3—8.1m (8H, arom). *Anal.* Calcd for $C_{14}H_{10}NO_2SBr$: C, 50.01; H, 3.00; Br, 23.77; N, 4.17; S, 9.54. Found: C, 50.18; H, 3.00; Br, 23.99; N, 4.35; S, 9.26. **8e**: mp 143—146°C. ^{1}H-NMR, δ: 3.84s (3H, CH_3), 4.45s (2H, CH_2), 6.9—7.9m (8H, arom). *Anal.* Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88; S, 11.16. Found: C, 62.57; H, 4.45; N, 4.69; S, 11.01.

8f: A solution of the sulfide **7b** (3.0 g), NBS (2.1 g), and a catalytic amount of benzoyl peroxide (BPO) in CCl_4 (30 ml) was refluxed for 1.5 h. The solution was cooled, the precipitates were filtered off and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in THF (50 ml)–H_2O (10 ml) and NBS (2.0 g) was added. After being stirred for 1 h at room temperature, the reaction mixture was worked up in the same manner as described above to give 1.0 g of product whose ^{1}H-NMR spectrum showed it to be a mixture of **8f** (80%) and **8b** (20%). ^{1}H-NMR, δ: 2.39s (3H × 0.2, CH_3 of **8b**), 4.45s and 4.49s (SCH_2 and $BrC\underline{H}_2Ph$), 7.1—7.9m (8H, arom).

Preparation of Free Sulfoximide 1——1a—e: To a cooled solution of the sulfoxide **8** (0.05 mol) in 100 ml of CH_2Cl_2 was added 2—3 molar equiv. of MSH. The mixture was stirred for 10 h at room temperature. Ether (50 ml) was added to the reaction mixture and the resulting white precipitates were collected by filtration. The dried precipitates were suspended in $CHCl_3$ and shaken with aq. NaOH. The organic layer

Table IV. *S*-Aryl-*S*-[(1,2-benzisoxazol-3-yl)methyl]sulfoximide **1**

Compd.	mp (°C)	Yield (%)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	S	Hal.	^{1}H-NMR, δ
1a	133—135	86	$C_{14}H_{12}N_2O_2S$	61.75 (61.92	4.44 4.46	10.27 10.15	11.77 11.64	— —)	3.12 bs (1H, NH); 4.87 s (2H, CH_2); 7.2—8.2 m (9H, arom)
1b	139—142	84	$C_{15}H_{14}N_2O_2S$	62.92 (62.95	4.93 5.14	9.78 9.47	11.20 11.03	— —)	2.42 s (3H, CH_3); 3.10 bs (1H, NH); 4.83 s (2H, CH_2); 7.1—8.0 m (8H, arom)
1c	136—139	78	$C_{14}H_{11}N_2O_2SCl$	54.82 (54.88	3.62 3.27	9.13 8.78	10.45 10.43	11.56 11.75)	3.22 bs (1H, NH); 4.87 s (2H, CH_2); 7.3—8.2 m (8H, arom)
1d	165—168	77	$C_{14}H_{11}N_2O_2SBr$	47.88 (48.00	3.16 3.00	7.97 7.70	9.13 9.21	22.75 22.95)	3.18 bs (1H, NH); 4.83 s (2H, CH_2); 7.3—8.2 m (8H, arom)
1e	154—156	58	$C_{15}H_{14}N_2O_3S$	59.59 (59.88	4.67 4.54	9.26 9.24	10.60 10.47	— —)	3.18 bs (1H, NH); 3.86 s (3H, CH_3); 4.84 s (2H, CH_2); 7.1—8.1 m (8H, arom)

a) Based on the consumed sulfoxide.

was separated, dried over Na_2SO_4, and concentrated to dryness. The residual crystals were recrystallized from EtOH or CH_2Cl_2–isopropyl ether to give pure sulfoximides **1a—e** (Table IV).

1f: MSH (2.0 g) was added to a solution of the above-mentioned mixture of the sulfoxides **8f** and **8b** (0.9 g) in 10 ml of CH_2Cl_2, and the mixture was stirred for 10 h. The reaction mixture was worked up in the manner described above to yield 0.37 g of product. This product was revealed to be a mixture of **1f** (90%) and **1b** (10%) by HPLC and ^{1}H-NMR (100 MHz)[14] analyses. ^{1}H-NMR (100 MHz), δ in $CDCl_3$: 2.42s (3H×0.1, CH_3 of **1b**), 2.8bs (1H, NH), 4.48s (2H×0.9, $BrC\underline{H}_2Ph$), 4.82s (2H, SCH_2), 7.2—7.9m (8H, arom).

Preparation of α-Halo Free Sulfoximides 2 and 3——2a—e and 3a—c: A solution of the free sulfoximide **1** (6 mmol) and a slight excess of Br_2/pyridine, NBS, or NCS in 20 ml of commercial $CHCl_3$ was stirred for 2—3 h, 3—4 h, or 24 h, respectively, at room temperature under a room light. The reaction mixture was washed with dilute aq. K_2CO_3, then the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was chromatographed on a silica gel column using $CHCl_3$ as an eluent to afford α-halo sulfoximides **2** and **3**. Recrystallization from CH_2Cl_2–isopropyl ether gave pure **2a—e** and **3a—c** (Table V). All α-halo sulfoximides **2a—e** and **3a—c** were isolated as mixtures of diastereomers; the ^{1}H-NMR spectra showed two distinct methine singlets, as shown in Table V.

TABLE V. *S*-Aryl-*S*-[(1,2-benzisoxazol-3-yl)halomethyl]sulfoximides **2**[a] and **3**

Compd.	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	Br	Cl	N	S	^{1}H-NMR, δ
2a	162—168	86 (61)[b]	$C_{14}H_{11}BrN_2O_2S$	47.88 (47.81	3.16 3.06	22.75 22.98	— —	7.97 7.90	9.13 8.89)	3.57 bs and 4.00 bs (1H, NH); 6.16 s and 6.22 s (1H, CH); 7.2—8.4 m (9H, arom)
2b	144—147	83 (60)	$C_{15}H_{13}BrN_2O_2$	49.33 (49.35	3.59 3.37	21.88 22.15	— —	7.67 7.63	8.78 8.60)	2.42 s and 2.45 s (3H, CH_3); 3.53 bs and 3.97 bs (1H, NH); 6.17 s and 6.24 s (1H, CH); 7.1—8.4 m (8H, arom)
2c	153—156	82 (60)	$C_{14}H_{10}BrClN_2O_2S$	43.60 (43.62	2.61 2.46	20.72 20.57	9.19 9.13	7.26 7.13	8.31 8.05)	3.60 bs and 4.01 bs (1H, NH); 6.17 s and 6.25 s (1H, CH); 7.3—8.4 m (8H, arom)
2d	163—167	80	$C_{14}H_{10}Br_2N_2O_2S$	39.10 (39.16	2.34 2.16	37.16 36.96	— —	6.51 6.40	7.45 7.31)	3.56 bs and 4.01 bs (1H, NH); 6.13 s and 6.19 s (1H, CH); 7.3—8.4 m (8H, arom)
2e	147—149	89	$C_{15}H_{13}BrN_2O_3S$	47.26 (47.06	3.44 3.23	20.96 21.06	— —	7.35 7.17	8.41 8.47)	3.90 bs (1H, NH); 3.91 s (3H, CH_3); 6.16 s and 6.21 s (1H, CH); 7.1—8.2 m (8H, arom)
3a	156—160	71	$C_{14}H_{11}ClN_2O_2S$	54.82 (55.22	3.62 3.45	— —	11.56 12.13	9.13 9.00	10.45 10.21)	3.50 bs and 3.83 bs (1H, NH); 6.12 s and 6.14 s (1H, CH); 7.2—8.4 m (9H, arom)
3b	151—153	64	$C_{15}H_{13}ClN_2O_2S$	56.16 (56.54	4.08 3.86	— —	11.05 11.05	8.73 8.70	9.99 9.89)	2.43 s (3H, CH_3); 3.50 bs (1H, NH); 6.05 s and 6.08 s (1H, CH); 7.1—8.2 m (8H, arom)
3c	142—145	70	$C_{14}H_{10}Cl_2N_2O_2S$	49.28 (49.36	2.95 2.75	— —	20.78 21.23	8.21 7.86	9.40 9.53)	3.50 bs and 3.85 bs (1H, NH); 6.13 s and 6.14 s (1H, CH); 7.2—8.3 m (8H, arom)

a) Data for compound **2** prepared by using bromine/pyridine are listed.
b) Yield in parentheses is based on the reaction with NBS.

2f: The above-mentioned mixture of the sulfoximides **1f** and **1b** (300 mg) was added to a cooled solution of pyridine (65 mg) and Br_2 (130 mg) in $CHCl_3$ (3 ml) and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was worked up in the same manner as described above to yield 160 mg of product. This product was revealed to be a mixture of **2f** (95%) and **2b** (5%) by HPLC analysis. The ^{1}H-NMR (100 MHz)[14] spectrum of this mixture showed **2f** to be a mixture of diastereomers; δ in $CDCl_3$: 2.41s and 2.44s (trace, CH_3 of **2b**), 3.5—4.0bs (1H, NH), 4.46s and 4.49s (2H, $BrC\underline{H}_2Ph$), 6.12s and 6.18s (1H, CH), 7.2—8.2m (8H, arom).

Preparation of *N*-Halosulfoximides 4a, b and 5a, b——An equimolar amount of NBS or BHC was added to a stirred solution of **1** in 20 ml of CH_2Cl_2 at room temperature, and the mixture was stirred for 5 min. The reaction mixture was directly subjected to silica gel column chromatography and eluted with CH_2Cl_2 to afford *N*-halosulfoximide **4** or **5**. Recrystallization from CH_2Cl_2–isopropyl ether gave a pure product (Table VI).

Table VI. *N*-Halo-*S*-aryl-*S*-[(1,2-benzisoxazol-3-yl) methyl]sulfoximides **4** and **5**

Compd.	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	Br	Cl	N	S	^{1}H-NMR, δ
4a	105—109	89	$C_{14}H_{11}BrN_2O_2S$	47.88 (48.32)	3.16 (3.05)	22.75 (22.69)	— (—)	7.97 (8.07)	9.13 (9.16)	5.13 d and 5.15 d (ABq, J=14 Hz, 2H, CH_2); 7.2—8.1 m (9H, arom)
4b	121—124	90	$C_{15}H_{13}BrN_2O_2S$	49.33 (49.74)	3.59 (3.43)	21.88 (22.06)	— (—)	7.67 (7.65)	8.78 (8.77)	2.43 s (3H, CH_3); 5.10 d and 5.13 d (ABq, J=14 Hz, 2H, CH_2); 7.2—8.1 m (8H, arom)
5a	107—112	91	$C_{14}H_{11}ClN_2O_2S$	54.82 (54.46)	3.62 (3.54)	— (—)	11.56 (11.39)	9.13 (9.16)	10.45 (10.17)	5.10 d and 5.12 d (ABq, J=14 Hz, 2H, CH_2); 7.1—8.1 m (9H, arom)
5b	110—114	89	$C_{15}H_{13}ClN_2O_2S$	56.16 (55.99)	4.08 (3.94)	— (—)	11.05 (11.13)	8.73 (8.65)	9.99 (9.89)	2.39 s (3H, CH_3); 5.04 d and 5.06 d (ABq, J=14 Hz, 2H, CH_2); 7.1—8.0 m (8H, arom)

Decomposition Reaction of *N*-Halosulfoximides 4 and 5 (Tables I and II)——The reaction was carried out using a 0.1 M solution of *N*-halosulfoximide under the conditions stated in Tables I and II. After an appropriate reaction time, the reaction mixture was washed with 5% aq. K_2CO_3. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual crystals were dissolved in 1 ml of $CHCl_3$ and 19 ml of EtOH and then subjected to HPLC analysis. GLC analysis was carried out using the reaction mixture without the treatment described above.

Reaction of Free Sulfoximide 1 with NCS (Table III)——The reaction was carried out using a 0.1 M solution of **1** with an equimolar amount of NCS under the conditions stated in Table III, except for the case in $CDCl_3$. HPLC analysis was run after the reaction mixture had been worked up as described above. The reaction in $CDCl_3$ was carried out using a 0.2 M solution of **1** with an equimolar amount of NCS, and the reaction mixture was directly subjected to ^{1}H-NMR analysis.

Acknowledgement The authors are grateful to the staff of the analytical section of these laboratories for spectral measurements and elemental analyses.

References and Notes

1) H.R. Bentley, E.E. McDermott, J. Pace, J.K. Whitehead, and T. Moran, *Nature* (London), **165**, 735 (1950); H.R. Bentley and J.K. Whitehead, *J. Chem. Soc.*, **1950**, 2081.
2) For reviews: N. Furukawa, *Yuki Gosei Kagaku Kyokai Shi*, **29**, 922 (1971); C.R. Johnson, *Accounts Chem. Res.*, **6**, 341 (1973); P.D. Kennewell and J.B. Taylor, *Chem. Soc. Rev.*, **4**, 189 (1975); S.L. Huang and D. Swern, *Phosphorus and Sulfur*, **1**, 309 (1976).
3) *a*) R. Appel, H.W. Fehlhaber, D. Hänssgen, and R. Schöllhorn, *Chem. Ber.*, **99**, 3108 (1966); *b*) R. Annunziata, R. Fornasier, and F. Montanari, *Chem. Commun.*, **1972**, 1133; *c*) G. Dauphin, A. Kergomard, and A. Scarset, *Bull. Soc. Chim. Fr.*, **1976**, 862; *d*) C.R. Johnson and H.G. Corkins, *J. Org. Chem.*, **43**, 4136 (1978); *e*) T. Akasaka, N. Furukawa, and S. Oae, *Tetrahedron Lett.*, **1979**, 2035.
4) T. Akasaka, N. Furukawa, and S. Oae, *Chem. Lett.*, **1979**, 529.
5) *a*) H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato, and H. Nishimura, *Chem. Pharm. Bull.*, **24**, 632 (1976); *b*) H. Uno, M. Kurokawa, and H. Nishimura, *ibid.*, **24**, 644 (1976); *c*) H.Uno and M. Kurokawa, *ibid.*, **26**, 312 (1978); *d*) *Idem*, *ibid.*, **26**, 3498 (1978); *e*) H. Uno, M. Kurokawa, Y. Masuda, and H. Nishimura, *J. Med. Chem.*, **22**, 180 (1979).
6) T. Yoshida, S. Naruto, and H. Nishimura, *Tetrahedron Lett.*, **21**, 2315 (1980).
7) Y. Tamura, M. Tsunekawa, T. Miyamoto, and M. Ikeda, *J. Org. Chem.*, **42**, 602 (1977); K. Schaffner-Sabba, H. Tomaselli, B. Henrici, and H.B. Renfroe, *ibid.*, **42**, 952 (1977).
8) M. Ginnella, F. Gualtieri, C. Melchiorre, and A. Orlandoni, *Chimie Therapetique*, **1972**, 127.
9) W. Tagaki, K. Kikukawa, K. Ando, and S. Oae, *Chem. Ind.*, **1964**, 1624.
10) Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis*, **1977**, 1.
11) J. Adam, P.A. Gosselain, and P. Goldfinger, *Nature*, **171**, 704 (1953).
12) This interesting rearrangement reaction will be reported elsewhere.
13) F.G. Bordwell, M.D. Wolfinger, and J.B. O'Dwyer, *J. Org. Chem.*, **39**, 2516 (1974).
14) Measured on a Varian HA-100D spectrometer.