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Novel Base-Induced Rearrangements of α - and *N*-Halo Derivatives of
S-Aryl-*S*-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides
to the Corresponding *N*-Sulfinylimines¹⁾

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The title α - and *N*-halosulfoximides **1**–**4** undergo base-induced rearrangement reactions to give the same *N*-sulfinylimines **5**, suggesting that these rearrangements all involve the intermediacy of a cyclic sulfoximide, a thiazirine *S*-oxide **14**, which has a novel three-membered ring system with an endocyclic S=N group.

Keywords—1,2-benzisoxazole; rearrangement; *N*-halosulfoximide; α -halosulfoximide; *N*-sulfinylimine; thiazirine *S*-oxide; three-membered S=N heterocycle; three-membered cyclic sulfoximide

Among numerous publications on the synthesis and properties of sulfoximide derivatives which possess a wide variety of chemical and biological interest,²⁾ only a few deal with the reactivities of the halo derivatives, especially the α -halo derivatives.³⁾ In the previous papers,⁴⁾ we have reported the rearrangement reaction of *N*-halo-*S*-aryl-*S*-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides **3** and **4** to the corresponding α -halosulfoximides, *S*-aryl-*S*-[(1,2-benzisoxazol-3-yl)halomethyl]sulfoximides **1** and **2**. We now wish to report that the halosulfoximides **1**–**4** undergo base-induced rearrangement reactions of new types to give the corresponding *N*-sulfinylimines, 3-arylsulfinyliminomethyl-1,2-benzisoxazoles **5** (Chart 1). The results of these interesting rearrangements are summarized in Tables I and II.

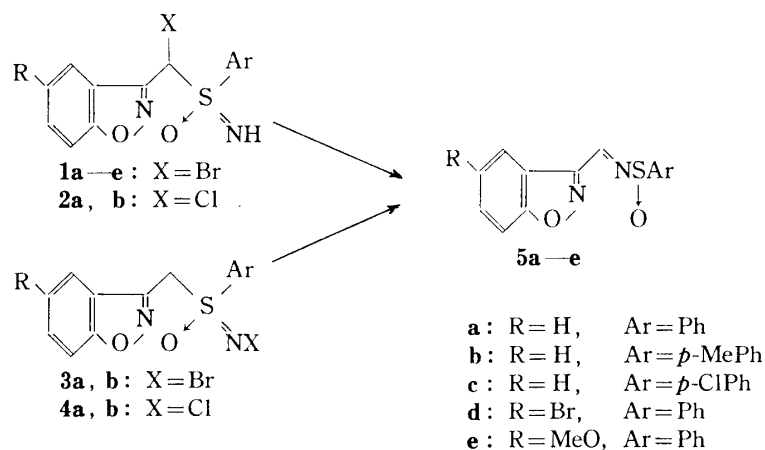


Chart 1

As shown in Table I, the α -bromosulfoximides **1a**–**e** were readily rearranged into **5a**–**e** in good yields on treatment with 1,5-diazabicyclo[5.4.0]-5-undecene (DBU) at room temperature. The α -chlorosulfoximides **2a, b** underwent no rearrangement under the same mild conditions; however, under reflux in chloroform for 5 h, **2a, b** gave **5a, b** in 15% and 16% yields, respectively. Treatment of the α -halosulfoximides **1** and **2** with potassium carbonate at room temperature caused no reaction, but under reflux in chloroform for 6–7 h, **1a** and **2a** gave **5a** in 22% and 8% yields, respectively. In contrast, the *N*-halosulfoximides **3** and **4** readily

TABLE I. Rearrangement of α -Halosulfoximides **1** and **2** with Base^{a)}

Compd.	Reaction conditions	Product	Yield(%) ^{b)}
1a	DBU, 2 h	5a	86
1a	K ₂ CO ₃ , 6 h	5a	22 ^{c)}
1b	DBU, 2 h	5b	83
1c	DBU, 2 h	5c	80
1d	DBU, 2 h	5d	70
1e	DBU, 4 h	5e	74
2a	DBU, 5 h	5a	15 ^{d)}
2a	K ₂ CO ₃ , 7 h	5a	8 ^{c)}
2b	DBU, 5 h	5b	16 ^{d)}

a) The reaction was carried out in chloroform with a slight excess of DBU at room temperature or with 2 molar equiv. of potassium carbonate under reflux unless otherwise noted.

b) Isolated yield after column chromatography.

c) Recoveries of **1a** and **2a** were 65% and 85%, respectively.

d) Under reflux. Recoveries of **2a** and **2b** were 65% and 63%, respectively.

TABLE II. Rearrangement of *N*-Halosulfoximides **3** and **4** with Base^{a)}

Compd.	Reaction conditions	Product	Yield(%) ^{b)}
3a	DBU, 5 min	5a	56 ^{c)}
3a	K ₂ CO ₃ , 5 h	5a	85
3b	K ₂ CO ₃ , 5 h	5b	85
4a	DBU, 5 min	5a	83
4a	K ₂ CO ₃ , 3.5 h	5a	85
4b	DBU, 5 min	5b	85
4b	K ₂ CO ₃ , 3.5 h	5b	85

a) The reaction was carried out in dichloromethane at room temperature with a slight excess of DBU or 2 molar equiv. of potassium carbonate.

b) Isolated yield after column chromatography.

c) *S*-[(1,2-Benzisoxazol-3-yl)methyl]-*S*-phenylsulfoximide was also obtained in 22% yield.

underwent the rearrangement reaction on treatment either with DBU or with potassium carbonate at room temperature, affording **5** in good yields, shown in Table II.

The structure of the *N*-sulfinylimines **5** was confirmed by elemental and spectral analyses and also by chemical transformations of the representative **5a** (Chart 2). The infrared (IR) spectra of **5** showed strong bands at around 1610 and 1110 cm⁻¹ considered to be due to the C=N and SO groups, respectively, but no characteristic bands of the sulfoximide structure at around 1220, 1110, and 1000 cm⁻¹ due to the NSO group.⁵⁾ Their proton nuclear magnetic resonance (¹H-NMR) spectra showed a singlet peak of the CH=N group at δ 9.25–9.28. Their mass spectra showed a base peak due to the ArSO⁺ ion. The reaction of **5a** with phenylhydrazine in ethanol gave the adduct, *N*-[(1,2-benzisoxazol-3-yl)(2-phenylhydrazino)methyl]benzenesulfinamide (**6**). The structure of **6** was confirmed by elemental and spectral analyses. Its IR spectrum showed strong bands at 3050 (NH), 1601 (C=N), 1025 and/or 1040 (SO) cm⁻¹. Furthermore, its ¹H-NMR spectrum (100 MHz) showed the presence of the partial structure PhNHNHCHNH–: δ 6.7–8.1 (m, 14H, arom), 6.24 (s, 1H, PhNH), 5.92 (dd, *J*=8.1 and 9.7 Hz, 1H, NHCHNH), 5.56 (d, *J*=9.7 Hz, 1H, CHNH), and 4.20 (d, *J*=8.1 Hz, 1H, NHNHCH); deuteration with D₂O resulted in disappearance of the peaks at δ 6.24, 5.56, and 4.20 and in collapse of the double doublet peak at δ 5.92 into a singlet. Meanwhile, the reaction of **5a** with butylamine afforded benzenesulfinamide⁶⁾ and 3-butyliminomethyl-1,2-benzisoxazole (**7**), which gave 1,2-benzisoxazole-3-carbaldehyde (**8**) on acidic hydrolysis. The structure of the aldehyde **8** was confirmed by elemental and spectral analyses and also by comparison with a sample which was alternatively prepared from (1,2-benzisoxazol-3-yl)methyl phenyl sulfoxide (**9**)^{4b)}

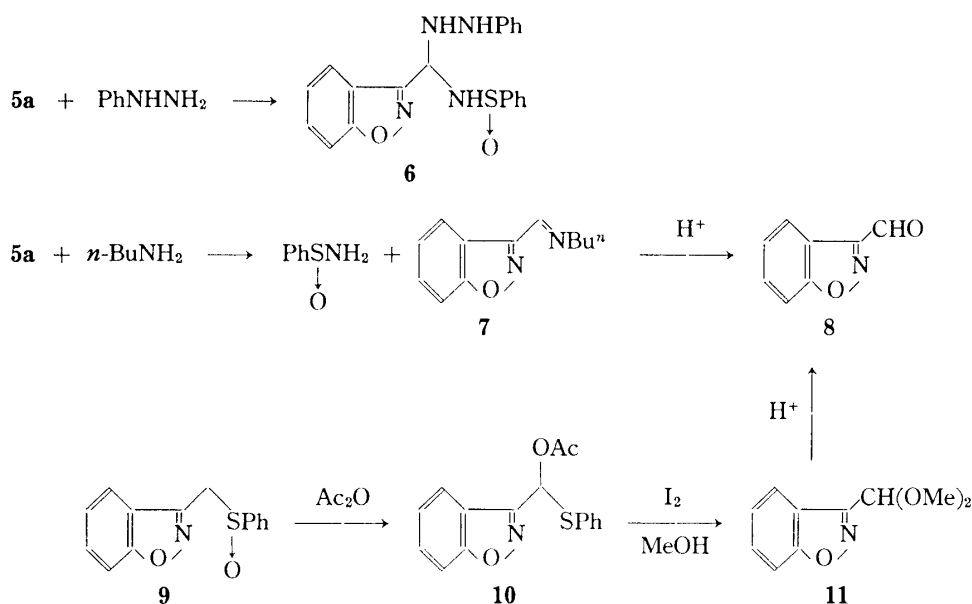


Chart 2

according to the method of Strandtmann *et al.*,⁷⁾ as shown in Chart 2. The data described above support the *N*-sulfinylimine structure of compounds 5.

Interestingly, the α -methylene and methine protons of the halosulfoximides 1–4 were found to be exchangeable with the deuterium of chloroform-*d*₁ (CDCl₃) in the presence of DBU. Thus, when the reactions of 1–4 with DBU were carried out in CDCl₃ at room temperature, 1, 3, and 4 underwent partial H–D exchange together with the rearrangement reaction, whereas the α -chlorosulfoximides 2 underwent only almost complete H–D exchange in 6–7 h. These results clearly suggest the formation of the α -carbanions of 1–4 under the rearrangement conditions. Similarly, the α -methylene protons of *S*-[(1,2-benzisoxazol-3-yl)methyl]-*S*-phenylsulfoximide underwent almost complete H–D exchange with CDCl₃ in 20 h in the presence of DBU at room temperature. The ability to form the α -carbanion may be explained in terms of tautomerism of the 1,2-benzisoxazole ring, whose C=N bond shows the nature of a masked carbonyl group, as described previously.⁴⁾

On the basis of the results described above, a plausible mechanism for the present interesting rearrangements may involve the formation of the sulfoximidoyl anion 12 or the α -carbanion 13, followed by loss of halide ion with ring closure to afford the same cyclic sulfoximide intermediate, a thiazirine *S*-oxide 14, which has a novel three-membered ring system with an endocyclic S=N group (Chart 3).

Cyclic sulfoximide derivatives with four- to seven-membered rings and an exo- or endocyclic S=N group have been synthesized.⁸⁾ Johnson and Corkins^{3d)} reported the intermediacy of a

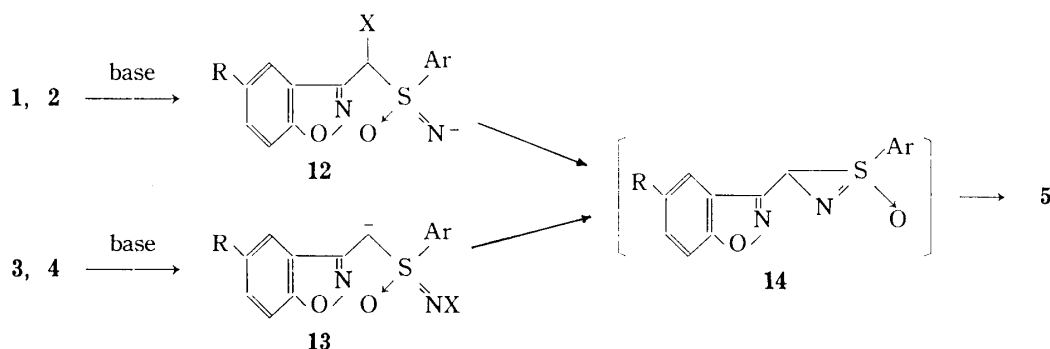


Chart 3

three-membered cyclic sulfoximide with an exocyclic S=N group in the Ramberg-Backlund type reaction of α -halo-*N*-(*p*-tolylsulfonyl)sulfoximides to give alkenes, and also that the reaction of *S*-butyl-*S*-(1-chlorobutyl)sulfoximide with potassium hydroxide in refluxing methanol gave 1-butanefulfinamide, the production of which could be rationalized in a number of ways, including a three-membered S-N heterocyclic intermediate, though the available data did not permit a definite conclusion. The present results do seem to provide support for the three-membered S-N heterocyclic intermediate.

Further extensions of these interesting reactions to *S*-benzyl derivatives are under investigation.

Experimental

All melting points were measured on an Ishii micro melting point apparatus and are uncorrected. ^1H -NMR spectra were recorded on a Varian EM 360 (60 MHz) spectrometer unless otherwise noted or a Varian HA 100D (100 MHz) spectrometer with tetramethylsilane as an internal standard in CDCl_3 . The following abbreviations are used: s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; m, multiplet. IR spectra were taken in KBr disks with a Hitachi EPI-G3 spectrophotometer. Mass spectra were recorded on a Hitachi RM 61 spectrometer.

3-Arylsulfinyliminomethyl-1,2-benzisoxazoles 5. Rearrangement Reactions of the Halosulfoximides 1—4 with Base (Tables I and II)—The reaction was carried out with a 0.15–0.2 M solution of the halosulfoximide under the conditions stated in Tables I and II. After an appropriate reaction time, the reaction mixture was subjected to silica gel column chromatography and eluted with CHCl_3 to afford **5**. Recrystallization from acetonitrile gave a pure product. The elemental analyses and ^1H -NMR spectral data are summarized in Table III. The IR and mass spectral data are as follows. **5a**: IR ν cm^{-1} : 1608, 1593 (C=N), 1106 (SO); mass m/z : 270 (M^+), 125 (PhSO^+). **5b**: IR ν cm^{-1} : 1613, 1593 (C=N), 1105 (SO); mass m/z : 284 (M^+), 139 (ToISO^+). **5c**: IR ν cm^{-1} : 1615, 1595 (C=N), 1115, 1105, and/or 1089 (SO); mass m/z : 304 (M^+), 159 (ClPhSO^+). **5d**: IR ν cm^{-1} : 1606 (C=N), 1119 (SO). **5e**: IR ν cm^{-1} : 1618, 1598 (C=N), 1107 (SO).

TABLE III. 3-Arylsulfinyliminomethyl-1,2-benzisoxazoles **5a**

Compd.	mp(°C)	Formula	Analysis(%) Calcd/(Found)					^1H -NMR, δ
			C	H	N	S	Hal.	
5a	135–137	$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$	62.21 (62.28)	3.73 3.51	10.36 10.45	11.86 12.13	—	9.28 (s, 1H, CH=N); 7.2–8.4 (m, 9H, arom)
5b	114–115	$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$	63.36 (63.61)	4.26 4.19	9.85 10.00	11.28 10.98	—	9.28 (s, 1H, CH=N); 7.2–8.4 (m, 8H, arom); 2.41 (s, 3H, CH_3)
5c	151–153	$\text{C}_{14}\text{H}_9\text{ClN}_2\text{O}_2\text{S}$	55.18 (55.18)	2.98 2.68	9.19 9.26	10.52 10.50	11.63 11.61	9.25 (s, 1H, CH=N); 7.3–8.4 (m, 8H, arom)
5d	128–130	$\text{C}_{14}\text{H}_9\text{BrN}_2\text{O}_2\text{S}$	48.15 (48.21)	2.60 2.51	8.02 8.15	9.18 8.98	22.88 23.11	9.26 (s, 1H, CH=N); 7.3–8.5 (m, 8H, arom)
5e	143–145	$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$	59.99 (60.02)	4.03 3.98	9.33 9.33	10.67 10.38	—	9.27 (s, 1H, CH=N); 7.1–8.1 (m, 8H, arom); 3.89 (s, 3H, CH_3O)

a) Data for compounds **5** prepared from **1** with DBU are listed.

***N*-(1,2-Benzisoxazol-3-yl)(2-phenylhydrazino)methyl]benzenesulfinamide (6). Reaction of 5a with Phenylhydrazine**—A solution of **5a** (1.1 g) and phenylhydrazine (1.0 g) in EtOH (25 ml) was stirred for 10 min at 50°C. After the reaction mixture had been cooled, the precipitates were collected by filtration and washed with cold EtOH to afford 0.92 g of **6**. Recrystallization from acetonitrile gave a pure product, mp 127–131°C. Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$: C, 63.47; H, 4.79; N, 14.81; S, 8.47. Found: C, 63.45; H, 4.74; N, 14.97; S, 8.53.

1,2-Benzisoxazole-3-carbaldehyde (8). Reaction of 5a with Butylamine—After a solution of **5a** (540 mg) and butylamine (300 mg) in EtOH (15 ml) had been stirred for 1.5 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in isopropyl ether and cooled in an ice-bath.

The precipitates were collected by filtration and washed with cold isopropyl ether to afford 250 mg (89% yield) of benzenesulfonamide,⁶⁾ mp 122—124°C. The filtrate was concentrated *in vacuo* and the residual oil was subjected to silica gel column chromatography, giving 320 mg of 3-butyliminomethyl-1,2-benzisoxazole (7) as a light yellow oil. ¹H-NMR (100 MHz): δ 0.99 (t, J = 6.8 Hz, 3H, CH₂CH₃), 1.3—2.0 (m, 4H, CH₂CH₂CH₂CH₃), 3.76 (dt, J = 1.4 and 6.4 Hz, 2H, CH=NCH₂CH₂), 7.2—8.4 (m, 4H, arom), 8.64 (t, J = 1.4 Hz, 1H, CH=NCH₂).

A solution of 7 (320 mg) in 1 N HCl (10 ml) was stirred for 1 h at room temperature and extracted with CHCl₃. The extract was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography, giving 200 mg (68% yield) of the aldehyde 8. Recrystallization from pet. ether gave a pure product, mp 64—65°C. *Anal.* Calcd for C₈H₅NO₂: C, 65.30; H, 3.43; N, 9.52. Found: C, 64.89; H, 3.36; N, 9.53. ¹H-NMR: δ 7.2—8.4 (m, 4H, arom), 10.47 (s, 1H, CHO). IR ν cm⁻¹: 1703 (CHO), 1609 (C=N). Mass m/z : 147 (M⁺).

Alternative Preparation of the Aldehyde 8—After a mixture of (1,2-benzisoxazol-3-yl)methyl phenyl sulfoxide (9)^{4b)} (9.5 g) and acetic anhydride (90 ml) had been refluxed for 3.5 h, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CHCl₃ and washed with aq. K₂CO₃. The organic layer was dried over Na₂SO₄ and the CHCl₃ was evaporated off. The residual oil was subjected to silica gel column chromatography, giving 9 g of (1,2-benzisoxazol-3-yl)(phenylthio)methyl acetate (10) as a colorless oil. ¹H-NMR: δ 2.18 (s, 3H, CH₃CO), 7.2—8.0 (m, 10H, CH and arom).

After a solution of the acetate 10 (9 g) and iodine (2 g) in MeOH (100 ml) had been refluxed for 14 h, 2 g of iodine was added and the refluxing was continued for another 10 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in CHCl₃ and washed with aq. hypo. The organic layer was dried over Na₂SO₄ and the CHCl₃ was evaporated off *in vacuo*. The residual oil was subjected to silica gel column chromatography, giving 3.9 g of 1,2-benzisoxazole-3-carbaldehyde dimethyl acetal (11) as a colorless oil. ¹H-NMR: δ 3.51 (s, 6H, 2 $\times$ CH₃O), 5.78 (s, 1H, CH), 7.1—8.1 (m, 4H, arom).

After a suspended solution of the acetal 11 (3.9 g) and 20% aq. HCl (20 ml) had been stirred for 1 h at room temperature, the reaction mixture was extracted with CHCl₃. The extract was dried over Na₂SO₄ and concentrated *in vacuo* to give 2.1 g of the aldehyde 8, whose IR and ¹H-NMR spectra were in agreement with those of the product described above.

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