Chem. Pharm. Bull. 30(8)2820—2824(1982)

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

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

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

(Received February 17, 1982)

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 rearrangment 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.

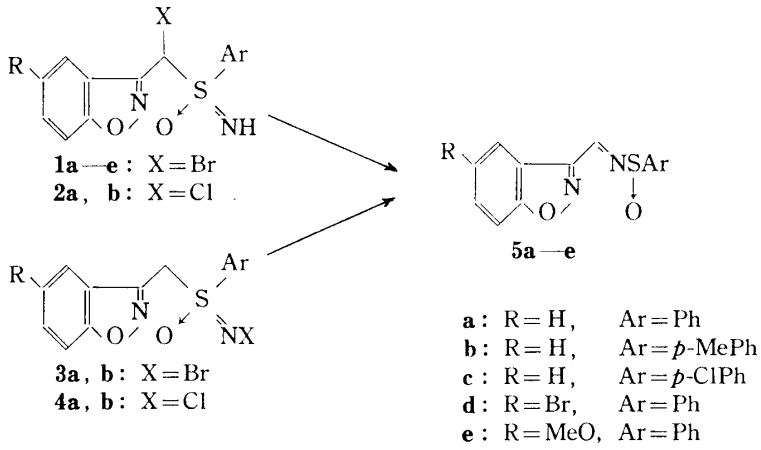

Chart 1

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_2CO_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_2CO_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_2CO_3, 5 h	**5a**	85
3b	K_2CO_3, 5 h	**5b**	85
4a	DBU, 5 min	**5a**	83
4a	K_2CO_3, 3.5 h	**5a**	85
4b	DBU, 5 min	**5b**	85
4b	K_2CO_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 (^{1}H-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 ^{1}H-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, CHNHS), and 4.20 (d, J=8.1 Hz, 1H, NHNHCH); deuteration with D_2O resulted in disappearance of the peaks at δ 6.24, 5.56, and 4.20 and in collaps of the double doublet peak at δ 5.92 into a singlet. Meanwhile, the reaction of **5a** with butylamine afforded benzenesulfinamide[6] and 3-butyliminomethyl-1,2-benzisoxazole (**7**), which gave 1,2-benzisoxazole-3-carbaldehyde (**8**) on acidic hydrolysis. The structure of the aldehyde **8** wase 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]

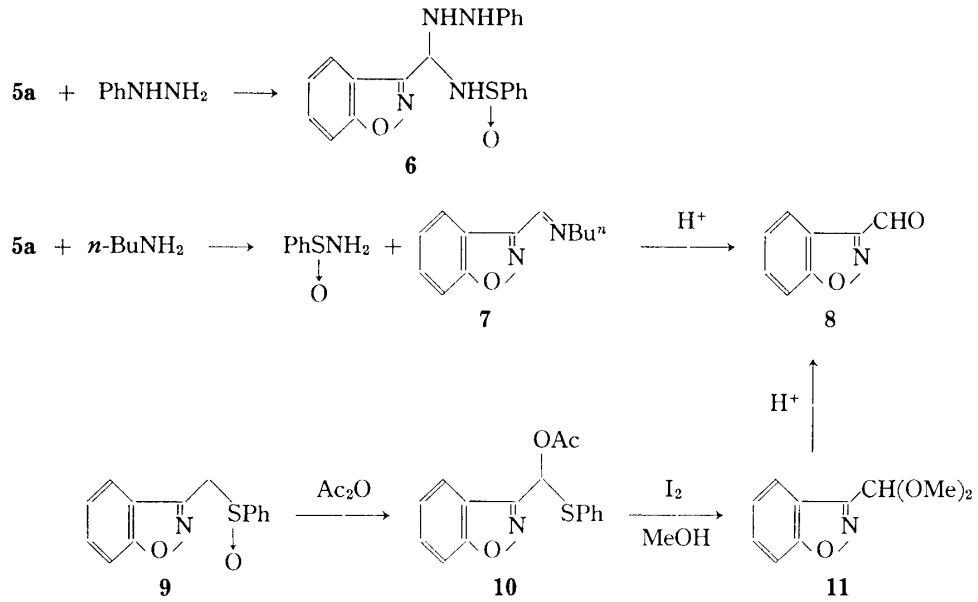

Chart 2

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 ($CDCl_3$) in the presence of DBU. Thus, when the reactions of **1**—**4** with DBU were carried out in $CDCl_3$ 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 $CDCl_3$ 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

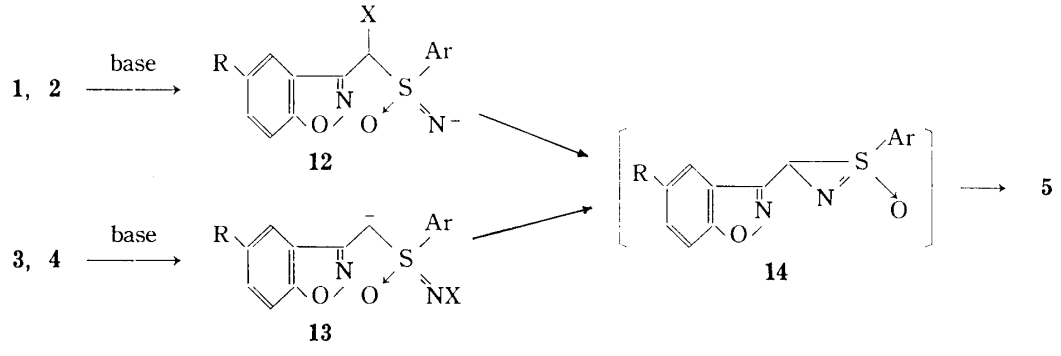

Chart 3

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-butanesulfinamide, 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. ^{1}H-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 ^{1}H-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 ($TolSO^+$). **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 5[a]

Compd.	mp(°C)	Formula	Analysis(%) Calcd/(Found) C	H	N	S	Hal.	^{1}H-NMR, δ
5a	135—137	$C_{14}H_{10}N_2O_2S$	62.21	3.73	10.36	11.86	—	9.28 (s, 1H, CH=N);
			(62.28	3.51	10.45	12.13	—)	7.2—8.4 (m, 9H, arom)
5b	114—115	$C_{15}H_{12}N_2O_2S$	63.36	4.26	9.85	11.28	—	9.28 (s, 1H, CH=N);
			(63.61	4.19	10.00	10.98	—)	7.2—8.4 (m, 8H, arom); 2.41 (s, 3H, CH_3)
5c	151—153	$C_{14}H_9ClN_2O_2S$	55.18	2.98	9.19	10.52	11.63	9.25 (s, 1H, CH=N);
			(55.18	2.68	9.26	10.50	11.61)	7.3—8.4 (m, 8H, arom)
5d	128—130	$C_{14}H_9BrN_2O_2S$	48.15	2.60	8.02	9.18	22.88	9.26 (s, 1H, CH=N);
			(48.21	2.51	8.15	8.98	23.11)	7.3—8.5 (m, 8H, arom)
5e	143—145	$C_{15}H_{12}N_2O_3S$	59.99	4.03	9.33	10.67	—	9.27 (s, 1H, CH=N);
			(60.02	3.98	9.33	10.38	—)	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 $C_{20}H_{18}N_4O_2S$: 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 benzenesulfinamide,[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. ^{1}H-NMR (100 MHz): δ 0.99 (t, J=6.8 Hz, 3H, $CH_2C\underline{H}_3$), 1.3—2.0 (m, 4H, $CH_2C\underline{H}_2$-$C\underline{H}_2CH_3$), 3.76 (dt, J=1.4 and 6.4 Hz, 2H, $CH{=}NC\underline{H}_2CH_2$), 7.2—8.4 (m, 4H, arom), 8.64 (t, J=1.4 Hz, 1H, $C\underline{H}{=}NCH_2$).

A solution of **7** (320 mg) in 1 N HCl (10 ml) was stirred for 1 h at room temperature and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 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 $C_8H_5NO_2$: C, 65.30; H, 3.43; N, 9.52. Found: C, 64.89; H, 3.36; N, 9.53. ^{1}H-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 $CHCl_3$ and washed with aq. K_2CO_3. The organic layer was dried over Na_2SO_4 and the $CHCl_3$ 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. ^{1}H-NMR: δ 2.18 (s, 3H, CH_3CO), 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 $CHCl_3$ and washed with aq. hypo. The organic layer was dried over Na_2SO_4 and the $CHCl_3$ 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. ^{1}H-NMR: δ 3.51 (s, 6H, $2\times CH_3O$), 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 $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated *in vacuo* to give 2.1 g of the aldehyde **8**, whose IR and ^{1}H-NMR spectra were in agreement with those of the product described above.

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) Preliminary report of this study: T. Yoshida, S. Naruto, H. Uno, and H. Nishimura, *J. Chlm. Soc., Chem. Commun.*, **1982**, 106.
2) For reviews: N. Furukawa, *Yuki Gosei Kagaku Kyokai Shi*, **29**, 922 (1971); C.R. Johnson, *Accounts Chem. Res.*, **6**, 341 (1973); *Idem*, "Comprehensive Organic Chemistry," Vol. 3, ed. by D.N. Jones, Pergamon Press, London, 1979, pp. 223—232; 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*) H. Morita, H. Itoh, N. Furukawa, and S. Oae, *Chem. Lett.*, **1978**, 817; *b*) T. Akasaka, N. Furukawa, and S. Oae, *ibid.*, **1979**, 529; *c*) *Idem*, *Tetrahedron Lett.*, **1979**, 2035; *d*) C.R. Johnson and H.G. Corkins, *J. Org. Chem.*, **43**, 4136, 4140 (1978).
4) *a*) T. Yoshida, S. Naruto, and H. Nishimura, *Tetrahedron Lett.*, **21**, 2315 (1980); *b*) T. Yoshida, S. Naruto, H. Uno, and H. Nishimura, *Chem. Pharm. Bull.*, **30**, 1175 (1982).
5) S. Oae, K. Harada, K. Tsujihara, and N. Furukawa, *Int. J. Sulfur Chem.* Part A, **2**, 49 (1972).
6) K. Mori and Y. Ueda, *Yakugaku Zasshi*, **91**, 940 (1971); *Idem*, *Chem. Pharm. Bull.*, **20**, 829 (1972).
7) M. von Strandtmann, D. Connor, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **9**, 175 (1972).
8) P. Stoss and G. Satzinger, *Chem. Ber.*, **111**, 1453 (1978) and references cited therein; P.K. Claus, P. Hofbauer, and W. Rieder, *Tetrahedron Lett.*, **1974**, 3319; E. Cohnen and J. Mahnke, *Chem. Ber.*, **105**, 757 (1972); *Idem*, *ibid.*, **106**, 3368 (1973); A.C. Barnes, P.D. Kennewell, and J.B. Taylor, *Chem. Commun.*, **1973**, 776; T.R. Williams and D.J. Cram, *J. Org. Chem.*, **38**, 20 (1973); Y. Tamura, M. Tsunekawa, T. Miyamoto, and M. Ikeda, *ibid.*, **42**, 602 (1977); K. Schaffner-Sabba, H. Tomaselli, B. Henrici, and H.B. Renfroe, *ibid.*, **42**, 952 (1977); R.H. Rynbrandt and D.P. Balgoyen, *ibid.*, **43**, 1824 (1978).