The Reaction of Benzonitrile Oxides with *S,S*-Dimethyl-*N*-(2,4,6-trihalophenyl)sulfimides. The Formation of Benzoxazole Derivatives

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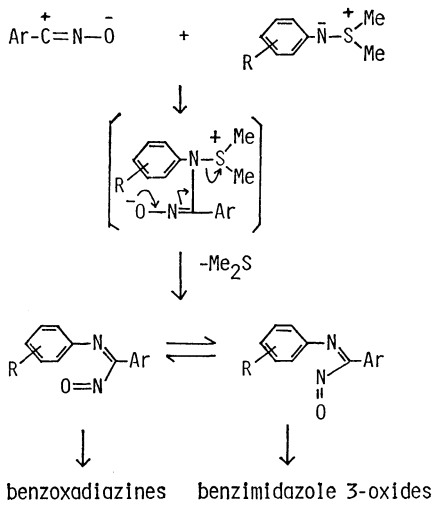
The reactions of nitrile oxides with *S,S*-dimethyl-*N*-(2,4,6-trihalophenyl)sulfimides gave unusual products, which structure was determined to be 2-aryl-4,6-dihalobenzoxazoles from their elementary analyses and spectral data. While the reactions with *S,S*-dimethyl-*N*-(2-bromophenyl)- or *S,S*-dimethyl-*N*-(2,4-dibromophenyl)-sulfimide gave 1,2,4-benzoxadiazine derivatives. A plausible reaction mechanism for the unusual formation of benzoxazoles was proposed.

Nitrile oxides are typical 1,3-dipoles and are known to react with various unsaturated bonds, not only with carbon-carbon unsaturated bonds but also with hetero unsaturated ones. Many studies have also been reported on the reaction with ylides.[1,2] We reported before that benzimidazole 3-oxides and/or benzoxadiazines were obtained in the reactions of aromatic nitrile oxides with *N*-aryl-*S,S*-dialkylsulfimides, and suggested that the reaction proceed *via* nitroso intermediacy as shown in Scheme 1.[3] Gilchrist *et al.* reported the formation of 1,2,4-benzoxadiazines in the reaction of nitrile oxides with *N*-aryl-*S,S*-dimethylsulfimides.[4] As a support of nitroso intermadiacy, though it is in an indirect manner, dibenzyl sulfide was isolated in the reaction with *N*-aryl-*S,S*-dibenzylsulfimides.[5]

During the course of the study, we attempted the reactions of nitrile oxides with *S,S*-dimethyl-*N*-(2,4,6-trihalophenyl)sulfimides, in expectation to isolate or detect the nitroso intermediate. In the reactions, however, unusual reaction products were isolated against the expectation, as reported in the previous communication.[6] We describe here the result of the further investigation of the reactions with *S,S*-dimethyl-*N*-(2,4,6-trihalophenyl)sulfimides together with the reactions with *S,S*-dimethyl-*N*-(2-halophenyl)sulfimides.

Results and Discussion

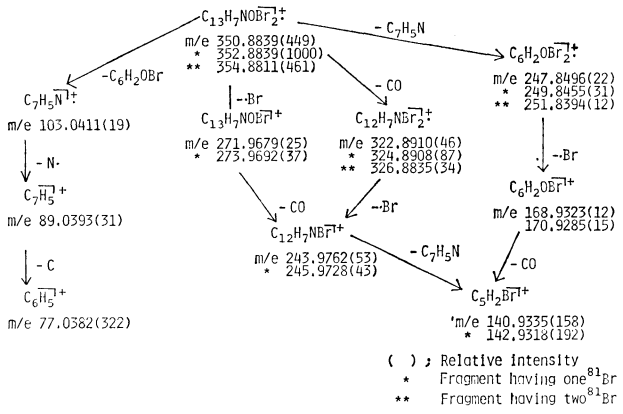
We tried the reactions of benzonitrile oxide (**1a**) and *p*-chloro- (**1b**) and *p*-bromobenzonitrile oxide (**1c**) with *S,S*-dimethyl-*N*-(2,4,6-tribromophenyl) sulfimide (**2a**) and *S,S*-dimethyl-*N*-(2,4,6-trichlorophenyl)sulfimide (**2b**). The results of the reactions and the analytical data of the reaction products are shown in Table 1. High resolution mass spectra of the products gave the molecular formulae of $C_{13}H_6NOXY_2$ (X=H,Cl,Br; Y=Br,Cl), which were consistent with the analytical data. The molecular formulae shows the loss of dimethyl sulfide, one halogen and one nitrogen atoms from the sum of the two starting components.



Scheme 1.

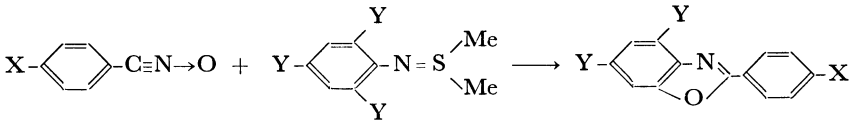
Mass fragmentation pattern of the product **3a** is shown in Scheme 2. Elimination of CO and benzonitrile from the molecular ion is observed to occur independently. The fragmentation pattern is common to the other reaction products and is very similar to those of benzoxazole and 1,2-benzisoxazole derivatives.[7] The unusual reaction products are suggested to have benzoxazole or 1,2-benzisoxazole structure.

In order to determine the structure of the product, we compared the UV and ^{13}C NMR spectra of them with those of 2-phenylbenzoxazole (**4**) and 3-phenyl-1,2-benzisoxazole (**5**), which were synthesized by methods of Somayajulu[8] and of Minisci,[9] respectively. UV spectra of the products **3a**—**f** and the reference compounds **4** and **5** are listed in Table 2. Absorption maxima of **3a**—**f** are at 305—316 nm with ε_{max} of $(2.6—3.8)\times10^4$. The spectral pattern of the products resembles to that of **4** more closely than that of **5**. ^{13}C NMR spectral data are listed in Table 3. The signals due to C-2, C-3a and C-7a of 2-phenylbenzoxazole (**4**) are at 162.1, 141.5, and 150.1 ppm.[10] On the other hand, the signals due to C-3, C-3a, and C-7a of 3-phenyl-1,2-benzisoxazole (**5**) are at 157.2, 120.4, and 163.8 ppm. The signals at 162—164 ppm of the reaction products **3a**—**f** can be assigned to be C-2



Scheme 2. Mass fragmentation of **3a**.

Table 1. Yields and analytical data of 2-aryl-4,6-dihalobenzoxazoles (**3a—f**)



1a—c **2a—b** **3a—f**

Compd	X	Y	Yield/%	Mp θ_m/°C		Anal. (%) Found	Anal. (%) Calcd	MS (M^+) Found	MS (M^+) Calcd
3a	H	Br	37	148—149	C	44.02	44.23	350.8839	350.8894
					H	1.83	2.00		
					N	3.74	3.97		
3b	Cl	Br	50	182—183	C	40.96	40.30	384.8505	384.8505
					H	1.36	1.56		
					N	3.71	3.62		
3c	Br	Br	51	181—183	C	36.08	36.15	428.8038	428.7999
					H	1.35	1.40		
					N	3.19	3.24		
3d	H	Cl	46	143—144.5	C	58.87	59.09	262.9870	262.9906
					H	2.76	2.65		
					N	5.11	5.30		
3e	Cl	Cl	43	190—191	C	52.22	52.26	296.9391	296.9517
					H	2.25	2.01		
					N	4.77	4.69		
3f	Br	Cl	57	196—197	C	45.45	45.48	340.8936	340.9011
					H	1.89	1.75		
					N	4.16	4.18		

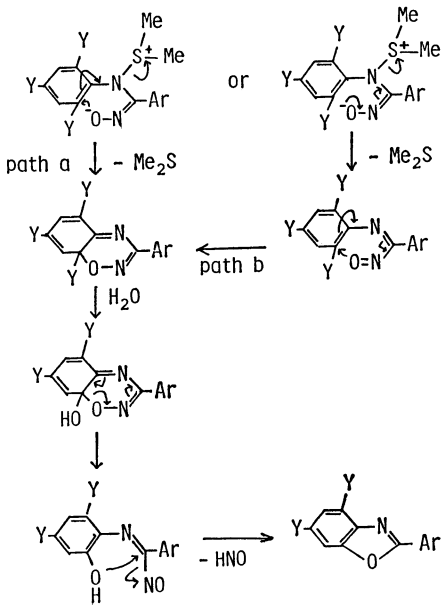
Table 2. UV and visible spectra of 2-aryl-4,6-dihalobenzoxazoles

Compd	λ_{max}/nm	$\varepsilon_{max} \times 10^{-4}$
3a	310	2.90
3b	316	3.21
3c	315	3.76
3d	305	2.57
3e	310	3.17
3f	311	3.34
4	299	2.14
5	287	0.71

carbon atom of benzoxazole structure. Assignment of the other signals is shown in the Table.

^{1}H NMR spectral data are shown in Table 4. The signals due to H-5 and H-7 of **3a—c** happened to appear at the same chemical shift in $CDCl_3$, but became separated in D_2SO_4. For example, the signals of **3a** at 7.64 ppm in $CDCl_3$ comes to appear at 8.58 and 8.50 separetedly in D_2SO_4. The recovered samples from the D_2SO_4 solutions were confirmed to be unchanged from the orginal ones. In the case of **3d—f**, the signals due to H-5 and H-7 were observed at different positions even in $CDCl_3$. The data are well consistent with the proposed 2-arylbenzoxazole structure.

The data mentioned above, however, cannot definitely rule out the isomeric structure of 2-aryl-5,7-dihalobenzoxazoles. But the melting point of **3a** is 148—149 °C (See Table 1) and much different from that of 5,7-dibromo-2-phenylbenzoxazole which was reported to melt at 175—176 °C.[11]

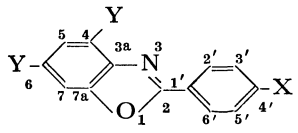


Scheme 3. Reaction route to the 2-arylbenzoxazole.

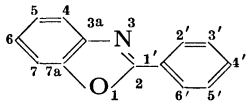
Thus the structure of the reaction products was determined to be 2-aryl-4,6-dihalobenzoxazole.

This structure determination was further confirmed by an independent synthesis of the authentic sample of 2-phenyl-4,6-dichlorobenzoxazole by the condensation of benzaldehyde with 3,5-dichloro-2-aminophenol. Infrared, ^{1}H NMR, and mass spectra of the authentic sample were the same as those of the compound **3d**. Also the melting point and R_f-value of thin layer chromatography were the same.

Table 3. ^{13}C NMR Spectra of 2-aryl-4,6-dihalobenzoxazoles (**3a—f**), 2-phenylbenzoxazole(**4**), and 3-phenyl-1,2-benzisoxazole (**5**)



3a—f



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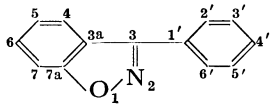
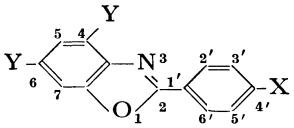


5

Compd	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	C-1′	C-2′,6′	C-3′,5′	C-4′
3a	163.8	141.0	117.8	130.5	126.0	113.2	150.8	—	127.9	128.8	132.1
3b	163.0	141.1	118.2	130.8	124.6	113.2	—	—	129.3	129.3	138.6
3c	162·3	141.5	118.2	130.8	124.4	113.3	150.1	—	129.3	129.3	138.6
3d	163.6	138.6	125.7	124.9	130.2	109.6	150.6	129.5	127.5	128.5	131.7
3e	162.2	138.2	124.3	125.1	130.5	109.7	150.7	—	128.8	129.0	131.9
3f	162.6	138.5	126.7	125.1	131.2	109.7	150.6	130.5	128.9	131.9	133.3
4	162.1	141.5	119.6	125.1	124.4	110.5	150.1	130.6	127.0	128.8	131.4
5	157.2*	120.4	123.8	122.1	130.2	110.1	163.8	134.3	128.0	129.1	129.7

* C-3.

Table 4. ^{1}H NMR spectra of 2-aryl-4,6-dihalobenzoxazoles



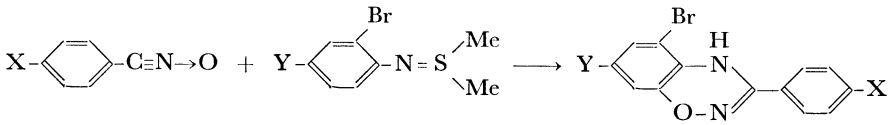
Compd	X	Y	In $CDCl_3$ δ	In D_2SO_4 δ*	Assignment
3a	H	Br	7.64(s, 2H)	8.59 and 8.50	H-5 and 7
			7.46(m, 1H)	8.43	H-4′
			7.52(m, 2H)	8.33	H-3′ and 5′
			8.20(m, 2H)	8.91	H-2′ and 6′
3b	Cl	Br	7.58(s, 2H)	8.56 and 8.50	H-5 and 7
			7.46(d, 2H)	8.23	H-3′ and 5′
			8.08(d, 2H)	8.78	H-2′ and 6′
3c	Br	Br	7.61(s, 2H)	8.52 and 8.46	H-5 and 7
			7.60(d, 2H)	8.36	H-3′ and 5′
			8.06(d, 2H)	8.67	H-2′ and 6′
3d	H	Cl	7.31(d, 1H)		H-7
			7.42(d, 1H)		H-5
			7.45(m, 1H)		H-4′
			7.49(m, 2H)		H-3′ and 5′
			8.18(m, 2H)		H-2′ and 6′
3e	Cl	Cl	7.37(d, 1H)		H-7
			7.49(d, 1H)		H-5
			7.50(d, 2H)		H-3′ and 5′
			8.18(d, 2H)		H-2′ and 6′
3f	Br	Cl	7.37(d, 1H)		H-7
			7.47(d, 1H)		H-5
			7.63(d, 2H)		H-3′ and 5′
			8.07(d, 2H)		H-2′ and 6′

* ppm from external TMS.

In order to see the scope and limitation of this unusual formation of 2-arylbenzoxazole derivatives, we tried the reaction of nitrile oxide (**1a—c**) with only one ortho-substituted *N*-arylsulfmides, such as *S,S*-dimethyl-*N*-(2-bromophenyl)sulfmide (**2c**) and *S,S*-dimethyl-*N*-(2,4-dibromophenyl)sulfimide (**2d**). The reaction products in the reactions were benzoxadiazine derivatives and no benzoxazole derivatives nor benzimidazole 3-oxide were formed. The yields of the 1,2,4-benzoxadiazines were very high as seen in Table 5. The result that no benzimidazole 3-oxide was formed is consistent with the mechanistic consideration previously reported.[3]

The reaction mechanism leading to benzoxazole formation is not obvious yet, but may be considered to be the same as that for the 1,2,4-benzoxadiazine formation at the initial stage of the reaction. The subsequent stages may be such as illustrated in Scheme 3. In this reaction, the intervention of a nitroso intermediate can neither be regarded nor disregarded at present, but by taking its intervention into consideration, the reactions of nitrile oxides with *N*-phenyl-

TABLE 5. YIELDS AND ANALYTICAL DATA OF 3-ARYL-4*H*-1,2,4-BENZOXADIAZINES (**6a—f**)



1a—c **2c—d** **6a—f**

Compd	X	Y	Yield/%	Mp θ_m/°C		Anal. (%) Found	Calcd
6a	H	H	86	111—112	C	54.12	54.00
					H	2.84	3.14
					N	9.81	9.69
6b	Cl	H	92	95— 96	C	48.79	48.26
					H	2.29	2.49
					N	8.68	8.66
6c	Br	H	85	106—107	C	42.18	42.43
					H	1.92	2.19
					N	7.26	7.61
6d	H	Br	80	113—115	C	42.86	42.43
					H	2.22	2.19
					N	7.08	7.61
6e	Cl	Br	91	147—149	C	38.80	38.80
					H	2.01	1.75
					N	7.03	6.96
6f	Br	Br	80	142—143	C	34.96	34.94
					H	1.28	1.58
					N	5.97	6.27

sulfimide, *N*-(2,6-dihalophenyl)sulfmides, and *N*-(2-azaaryl)sulfimides can be interpreted in terms of the same type of the intermediacy. The reaction of *N*-(2-pyridyl)sulfimide with a nitrile oxide, for example, have been reported to give a 1,2,4-triazolo[1,5-*a*]pyridine derivative *via* nitroso intermediate.[12] In the reaction forming benzoxazole derivatives presented here, the cyclized intermediate from the nitroso intermediate has a halogen substituent at the angular carbon atom which is linked with oxygen atom. This type of C–Cl bond is considered to be highly susceptible to hydrolysis. Therefore, the intermediate hydrolyzed with moisture in the reaction mixture, then once ring opened and recyclized to the benzoxazole with loss of the nitroso group. This mechanistic speculation is based on an assumption of the participation of water in the reaction. A further investigation as to the effect of some nucleophiles as well as water is now under progress and will be presented elsewhere.

Experimental

Melting points were measured using a micro-melting-point measuring apparatus (Yazawa Co., Ltd.) and are uncorrected. IR spectra were recorded with a JASCO IRA-1 spectrophotometer. Mass spectra were recorded with a Hitachi RMU-7L high-resolution mass spectrometer. UV spectra were recorded with a JASCO UVIDEC-505 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with JEOL JMN-MH 100 and FX-60 spectrometers respectively, and chemical shifts were reported in ppm from internal tetramethylsilane, unless otherwise cited. Column chromatography was conducted on silica gel (Wakogel C-200) with chloroform as an eluent.

Materials. Benzonitrile oxide and *p*-substituted benzonitrile oxides were generated at low temperature from the corresponding benzhydroxamoyl chlorides, which were synthesized by the usual methods.[13] *N*-aryl-*S*,*S*-dimethylsulfimides were prepared from dimethyl sulfoxide, substituted anilines, and trifluoroacetic anhydride.[14]

Reaction of Sulfimides with Nitrile Oxides. A General Procedure: A solution of hydroxamoyl chloride (1 mmol) in 10 ml of tetrahydrofuran (THF) was cooled below −10 °C. An equimolar amount of triethylamine was added to the solution through microsyringe. The solution became turbid due to the precipitation of triethylammonium chloride. Then an equimolar amount of sulfmide in 10 ml of THF was added dropwise to the mixture, during which the reaction mixture was kept below −10 °C. After the mixture was allowed to stand at ambient temperature overnight, triethylammonium chloride was separeted by filtration and the solvent was removed by evaporation under reduced pressure. The residue was worked up with column chromatography on silica gel (Wakogel C-200) with chloroform as an eluent to give a 2-arylbenzoxazole, which was recrystallized from methanol. Some typical examples follow.

*Reaction of Benzonitrile Oxide (**1a**) wiih* S,S-*Dimethyl*-N-*(2,4,6-tribromophenyl)sulfimide (**2a**)*: Into a cooled solution of 0.65 g (1 mmol) of benzhydroxamoyl chloride in 10 ml of THF was added 140 μl (1 mmol) of triethylamine at a temperature below −10 °C. A white precipitate of triethylammonium chloride deposited. Then 0.391 g (1 mmol) of **2a** in 5 ml of THF was added dropwise to the mixture kept below −10 °C, through a dropping funnel, which was washed with 5 ml of THF. The mixture was allowed to stand at ambient temperature overnight. Triethylammonium chloride was separeted by filtration and the filtrate was evaporated. The residue was worked up with column chromatography. 2-Phenyl-4,6-dibromobenzoxazole (**3a**) was isolated and weighed 0.13 g (37%). It was purified

by recrystallization from methanol.

Reaction of p-*Bromobenzonitrile Oxide (**1c**) with* S,S-*Dimethyl*-N-*(2-bromophenyl)sulfimide (**2c**)*: A solution of 0.236 g (1 mmol) of *p*-bromobenzhydroxamoyl chloride in 10 ml of THF was cooled below −10 °C by an ice-salt bath. Triethylamine 140 μl (1 mmol) was added into the solution through microsyringe, depositing a white precipitate of triethylammonium chloride. Then 0.235 g (1 mmol) of **2c** in 5 ml of THF solution was added dropwise through a dropping funnel to the mixture, during which the reaction mixture was kept below −10 °C. The dropping funnel was washed with 5 ml of THF. The solution was allowed to stand at ambient temperature overnight. Triethylammonium chloride was removed by filtration and the solvent was evaporated. The residue was worked up with column chromatography. 3-(*p*-Bromophenyl)-5-bromo-4*H*-1,2,4-benzoxadiazine (**6c**) 0.310 g (85%) was isolated and recrystallized from ether-petroleum ether.

Independent Synthesis of 2-Phenyl-4,6-dichlorobenzoxazole: 3,6-Dichloro-2-aminophenol was synthesized by method of Hodgson and Wignall.[15] The condensation reaction was carried out according to the method of Osman and Bassiouni[16] with a slight modification. A mixture of the 2-aminophenol 1.6 g (9 mmol) and benzaldehyde 3.8 g (36 mmol) was heated to reflux for 10 h. The reaction mixture was then cooled to room temperature and poured into methanol to give a precipitate, which was collected by filtration and dried. 2-Phenyl-4,6-dichlorobenzoxazole 1.4 g (60%) was isolated and recrystallized from methanol.

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