Studies of Substituent Effect in the Formation of Benzonitrile Oxides and 1,3-Dipolar Adducts of the Benzonitrile Oxides with 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranose

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Coupling reagents were prepared from corresponding benzaldehyde oximes by successive treatment with chlorine and Et_3N; the products were used without purification because of their instability. The reactions of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (1) with the coupling reagents obtained from benzaldehyde oxime (2a) and phenylacetaldehyde oxime (2b) gave normal 1,3-dipolar addition products (3a and 3b, respectively) in good yields. The reactions of 1 with the coupling reagents obtained from *p*- (2c), *m*- (2d), and *o*-methoxybenzaldehyde oxime (2e) gave the 1,3-addition products chlorinated on the benzene ring; 3c and 3d from 2c, 3e and 3f from 2d, and 3g from 2e. On the other hand, the reactions of 1 with the coupling reagents obtained from *p*-chloro- (2f) and *p*-nitrobenzaldehyde oxime (2g) gave no 1,3-addition product.

Keywords benzonitrile oxide; benzaldehyde oxime; coupling reagent; substituent effect; 1,3-dipolar addition reaction; 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose

Nitrile oxides, 1,3-dipolar compounds, are highly reactive to various unsaturated bonds such as C=C, C≡C, C≡N, and so on, and afford the corresponding isoxazolines[1] and other unsaturated heterocyclic compounds.[2] Furthermore, it has been reported that benzonitrile oxides reacted with aniline, phenol, and benzoic acid to give the corresponding 1,3-addition products.[3] Benn and Yelland[4] and Jensen and Kjaer[5] synthesized naturally occurring *S*-glycosides, glucosinolates, by the reaction of nitrile oxides with a mercaptosugar derivative, 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**1**). In this paper, we report the substituent effect on the formation of benzonitrile oxides from benzaldehyde oximes having various substituents and 1,3-dipolar addition reactions of the benzonitrile oxides with **1**.

The coupling reagents used in this study were obtained by the reactions of corresponding benzaldehyde oximes with chlorine according to the method of Benn and Yelland.[4] The reaction of **1** with the coupling reagents obtained from benzaldehyde oxime (**2a**) and phenylacetaldehyde oxime (**2b**), which have no other substituent on the benzene ring, gave corresponding 1,3-addition products (**3a** and **3b**, respectively) in high yields. When benzaldehyde oximes substituted with an electron-donating group (OCH_3) on the benzene ring were used as starting materials for the coupling reagents, all 1,3-addition products were substituted with one or two chlorine(s) at the *para*- or/and *ortho*-position with respect to the OCH_3 group on the benzene ring. The reaction of **1** with the coupling reagent obtained from *p*-methoxybenzaldehyde oxime (**2c**) gave **3c** and **3d**. Product **3c** showed aromatic proton signals at δ 7.62 (1H, d, J=2.2 Hz), 7.44 (1H, dd, J=8.6, 2.2 Hz), and 6.99 (1H, d, J=8.6 Hz) as well as the signals of the protons on the sugar moiety. The electron impact mass spectrum (EI-MS) of **3c** showed a parent ion peak at m/z 547 and a fragment ion peak at m/z 530 ($M^+ - OH$). Product **3d** showed a singlet peak of aromatic protons at δ 7.59 (2H) in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum and showed a fragment ion peak at m/z 564 ($M^+ - OH$) in the EI-MS. The reaction of **1** with the coupling reagent obtained from *m*-methoxybenzaldehyde oxime (**2d**) gave 1,3-addition products (**3e** and **3f**) together with another sugar product (**4**). Product **3e** showed the same fragment ion peak at m/z 530 ($M^+ - OH$) as **3c** in the EI-MS. The ^{1}H-NMR spectrum of **3e** showed, in addition to the signals of the OCH_3 group and sugar moiety, aromatic proton signals at δ 7.38 (1H, d, J=9.3 Hz), 6.97 (1H, dd, J=9.3, 3.1 Hz), and 6.96 (1H, d, J=3.1 Hz). These results allow two possible structures for **3e** with respect to the position of chlorine on the benzene ring; structure A (chlorine at C-6) and structure B (chlorine at C-4) (Fig. 1). The exact structure of **3e** was elucidated by means of a nuclear Overhauser method. Irradiation of the singlet due to the methoxy group at δ 3.82 resulted in enhancement of the signals of two aromatic protons (H-2 and H-4) by *ca.* 11%. This result suggests that chlorine is substituted at the *para*-position with respect to the OCH_3 group on the benzene ring in **3e**. Product **3f** showed two singlets due to aromatic protons at δ 7.50 (1H) and 6.80 (1H). The EI-MS of **3f** showed the same fragment ion peak at m/z 564 ($M^+ - OH$) as that of **3d**. The EI-MS of **4** showed a parent peak at m/z 436 and fragment ion peaks at m/z 376 ($M^+ - HOAc$) and 331 ($M^+ - SCH(CH_3)OCH_2CH_3$). The ^{1}H-NMR spectrum of **4** showed only the signals of the 2-ethoxyethyl group in addition to the signals of the sugar moiety. Hall and Ubertini[6] reported that diethyl ether reacted with chlorine to produce explosive 2-chloroethyl ethyl ether ($CH_3CH(Cl)OCH_2CH_3$). Saito and Tsuchiya[7] reported that **1** readily reacted with alkyl bromide to give alkyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside. These reports support the view that 2-chloroethyl ethyl ether was generated by the reaction of diethyl ether with

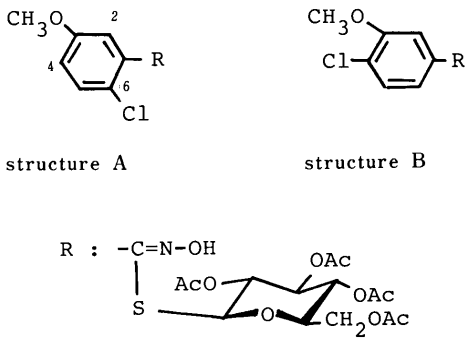


Fig. 1

chlorine during the preparation of the coupling reagents and reacted with **1** to afford **4**. The reaction of **1** with the coupling reagent obtained from *o*-methoxybenzaldehyde oxime (**2e**) gave a 1,3-addition product (**3g**) together with **4**. Product **3g** showed three aromatic proton signals at δ 7.41 (1H, dd, J=9.0, 2.8 Hz), 7.33 (1H, d, J=2.8 Hz), and 6.94 (1H, d, J=9.0 Hz). The EI-MS of **3g** showed the same fragment ion peak at m/z 530 ($M^+ - OH$) as those of **3c** and **3e**. On the other hand, the reaction of **1** with the coupling reagent obtained from *p*-chloro- (**2f**) and *p*-nitrobenzaldehyde oxime (**2g**) gave only **4** as a sugar product but no 1,3-addition product. The coupling reagents obtained from **2f** and **2g** gave products **5** and **6**, respectively. Products **5** and **6** showed a parent ion peak at m/z 261 and 272, respectively, and fragment ion peaks due to $M^+ - OCH_2CH_3$ and $M^+ - CH(CH_3)OCH_2CH_3$ at m/z 216 and 227, and m/z 188 and 199, respectively. In the ^{1}H-NMR spectra of **5** and **6**, the signals of a 2-ethoxyethyl group were observed. Thus, when the coupling reagents obtained from **2f** and **2g** were used, although benzohydroximoyl chloride intermediates (*p*-Cl-C_6H_4C(Cl)=N-OH and *p*-NO_2-C_6H_4-C(Cl)=N-OH, respectively) were easily obtained, the rate of the reactions of the intermediates with 2-chloroethyl ethyl ether was faster than that of formation of nitrile oxides from the intermediates, and consequently **5** and **6** were obtained, whereas **1** reacted exclusively with 2-chloroethyl ethyl ether to give **4**. These re-

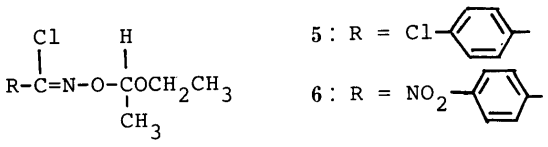


Fig. 2

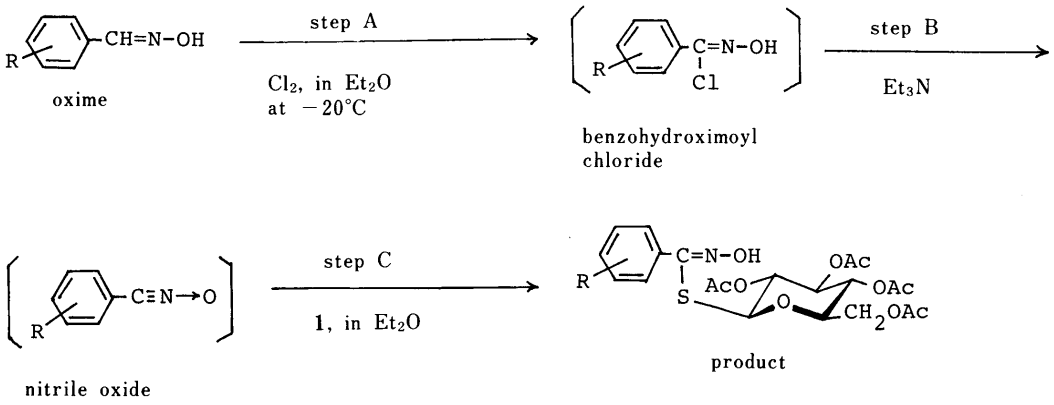
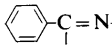
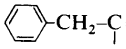
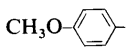
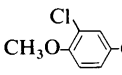
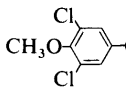
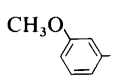
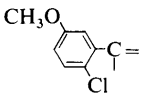
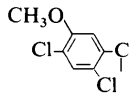
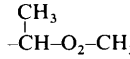
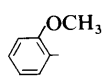
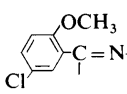


Chart 1

TABLE I. Products (Yields) in the Reactions of 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**1**) with the Coupling Reagents Obtained from Corresponding Oximes

Oxime R-CH=N-OH		Product (%)			
	R		R		R
2a		**3a**	 (89)		
2b		**3b**	 (92)		
2c		**3c**	 (75)	**3d**	 (12)
2d		**3e**	 (36)	**3f**	 (10)
		4[a]	 (23)		
2e		**3g**	 (16)	**4**[a]	(32)
2f		**4**[a]	(42)		
2g		**4**[a]	(38)		

a) Compound **4** was obtained by the reaction of **1** with 2-chloroethyl ethyl ether generated during the preparation of the coupling reagent.

Table II. ^{1}H-NMR Data (270 MHz)[a]

	Aromatic protons	OCH_3	H-1	H-2,3,4	H-5	H-6	H-6′	Acetyl	Others
3a	7.40—7.55 (5H)	—	4.45 (d, 9.9)[b]	4.96—5.11	3.03 (m)	3.95 (dd, 12.5, 2.6)	4.10 (dd, 12.5, 4.8)	1.96, 1.97 2.05, 2.11	9.04 (OH)
3b	7.25—7.39 (5H)	—	4.97 (d, 9.5)	4.96—5.04	3.48 (m)	4.00 (dd, 12.5, 2.0)	4.14 (dd, 12.5, 5.7)	1.96, 1.97 2.01, 2.08	9.21 (OH) 3.96 (s, $-CH_2$)
3c	6.99 (1H, d, 8.6) 7.44 (1H, dd, 8.6, 2.2) 7.62 (1H, d, 2.2)	3.92	4.53 (d, 9.5)	5.04—5.09	3.23 (m)	4.07 (dd, 12.5, 2.4)	4.20 (dd, 12.5, 4.4)	1.98, 1.99 2.06, 2.11	9.28 (OH)
3d	7.59 (2H, s)	3.96	4.61 (d, 9.7)	5.06—5.09	3.35 (m)	4.11 (dd, 12.6, 2.2)	4.22 (dd, 12.6, 4.2)	1.99, 1.99 2.07, 2.10	8.83 (OH)
3e	6.96 (1H, d, 3.1) 6.97 (1H, dd, 9.3, 3.1) 7.38 (1H, d, 9.3)	3.82	4.22 (d, 9.7)	4.99—5.08	2.88 (m)	3.91 (dd, 12.5, 2.2	4.07 (dd, 12.5, 3.9)	1.95, 1.97 2.05, 2.09	9.03 (OH)
3f	6.98 (1H, s) 7.50 (1H, s)	3.91	4.31 (d, 9.7)	4.98—5.16	2.95 (m)	(3.97—4.12)		1.97, 1.99 2.06, 2.09	9.76 (OH)
3g	6.94 (1H, d, 9.0) 7.33 (1H, d, 2.8) 7.41 (1H, dd, 9.0, 2.8)	3.86	4.24 (d, 9.9)	4.98—5.07	3.17 (m)	3.91 (dd, 12.6, 2.0)	4.10 (dd, 12.6, 4.0)	1.96, 1.98 2.06, 2.10	8.55 (OH)

a) All spectra were obtained in $CDCl_3$. b) Coupling constants are given in hertz (Hz).

sults are consistent with the report of Rajagopalan and Talaty[8] that *p*-chlorobenzohydroximoyl chloride reacted with methanesulfonyl chloride in the presence of Et_3N to produce *O*-(methylsulfonyl) *p*-chlorobenzohydroximoyl chloride, but no 1,3-addition product.

In conclusion, oximes **2a** and **2b** which have no other substituent on the benzene ring give corresponding benzonitrile oxides in the reaction with chlorine (step A in Chart 1) followed by treatment with Et_3N (step B). In the same reactions, the oximes **2c**, **2d**, and **2e** having an electron-donating group (OCH_3) on the benzene ring give benzonitrile oxides which are substituted with one or two chlorine(s) at the *para*- or/and *ortho*-position with respect to the OCH_3 group. All these benzonitrile oxides reacted with **1** (step C) to give corresponding 1,3-addition products. On the other hand, when the oximes **2f** and **2g** having an electron-attracting group (Cl and NO_2, respectively) on the benzene ring were used as the starting material for the coupling reagents, the rate of formation of the benzonitrile oxides was slower, and the benzohydroximoyl chlorides, intermediates of the benzonitrile oxides produced in step A, exclusively reacted with 2-chloroethyl ethyl ether which was produced by the reaction of diethyl ether with chlorine, affording no benzonitrile oxide.

Experimental

Materials Benzaldehyde oximes used in this study were obtained by the reactions of the corresponding benzaldehydes with NH_2OH according to the reported procedures.[9] The coupling reagents were prepared by the reactions of the benzaldehyde oximes with chlorine followed by treatment with Et_3N according to the method of Benn and Yelland.[4] All chemicals and solvents were of reagent grade, and were obtained from commercial sources.

Measurements The thin-layer chromatograms utilized Kieselgel HF_{254} (Merck), and spots were detected by irradiating the plates with ultraviolet (UV) light (254 nm, Manasul-Light) and by spraying with dilute H_2SO_4 followed by heating at 80 °C for 10 min. Column chromatography was done on Wakogel C-200. All melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. ^{1}H-NMR spectra at 270 MHz were recorded with a JEOL JNM-GX 270 FT nuclear magnetic resonance (NMR) spectrometer in $CDCl_3$ containing Me_4Si as an internal standard. EI-MS were obtained with a JEOL JMS-DX 300 mass spectrometer.

Reaction of 1 with the Coupling Reagents The coupling reagent (20 ml) obtained from **2a** (1.5 g) was added to a solution of **1** (2.0 g) in Et_2O (100 ml). The mixture was allowed to stand for 1 h at room temperature, then evaporated to give a residue, which was subjected to column chromatography (benzene–acetone, gradient up to 10% acetone) to afford **3a**. The coupling reagents obtained from **2b**, **2c**, **2d**, and **2e** were reacted similarly with **1**. Yields of products, ^{1}H-NMR, MS spectra, and elemental analyses are listed in Table I, II, III, and IV, respectively.

Reactions of 1 with the Coupling Reagent Obtained from 2f and 2g Compound **1** (1.0 g) was reacted with the coupling reagent obtained from **2f** (0.6 g) by the same method as described for **2a** to give **4** (0.5 g, 42% from **1**, mp 76—78 °C, recrystallized from ether) and **5** (0.7 g, 67% from **2f**, oil). EI-MS of **4** *m/z* (relative intensity, %) 436 (trace, M^+), 376 (2, $M^+ - AcOH$), 331 (20, $M^+ - SCH(CH_3)OCH_2CH_3$), 244 (7), 184 (6), 169

Table III. MS Data for the 1,3-Dipolar Adducts

3a	446 (t, M^+), 386 (t, $M^+ - HOAc$), 331 (20, $M^+ - C_6H_5C(S)=N\text{-}OH$, 229 (5), 184 (11), 171 (11), 170 (9), 169 (100)
3b	480 (t, M^+), 331 (8), 244 (6), 202 (11), 184 (17), 171 (10), 169 (64)
3c	547 (t, M^+), 530 (t, $M^+ - OH$), 331 (15), 199 (5), 185 (22), 184 (19), 183 (44), 169 (100)
3d	564 (t, $M^+ - OH$), 331 (20), 207 (10), 201 (13), 186 (12), 169 (100)
3e	530 (t, $M^+ - OH$), 331 (4), 244 (6), 202 (9), 185 (35), 183 (100), 169 (48)
3f	564 (t, $M^+ - OH$), 331 (13), 251 (5), 244 (9), 235 (8), 219 (54), 217 (84), 203 (49), 201 (68), 188 (32), 186 (49), 184 (22), 176 (25), 174 (37), 169 (100)
3g	530 (t, $M^+ - OH$), 331 (5), 229 (5), 202 (12), 185 (36), 184 (26), 183 (100), 169 (94)

t = trace.

Table IV. Elemental Analyses and Melting Points of 1,3-Dipolar Adducts

	Formula	Calcd			Found			mp (°C)
		C	H	N	C	H	N	
3a	$C_{21}H_{25}NO_{10}S$	52.17	5.21	2.97	52.31	5.15	2.86	133—135[a]
3b	$C_{22}H_{27}NO_{10}S$	53.11	5.47	2.82	52.98	5.36	2.66	164—166[b]
3c	$C_{22}H_{26}ClNO_{11}S$	48.22	4.78	2.56	48.09	4.77	2.51	77—79[a]
3d	$C_{22}H_{25}Cl_2NO_{11}S$	45.37	4.33	2.40	45.13	4.42	2.36	Oil
3e	$C_{22}H_{26}ClNO_{11}S$	48.22	4.78	2.56	48.11	4.76	2.41	204—205[a]
3f	$C_{22}H_{25}Cl_2NO_{11}S$	45.37	4.33	2.40	45.11	4.37	2.33	Oil
3g	$C_{22}H_{26}ClNO_{11}S$	48.22	4.78	2.56	47.99	4.81	2.63	Oil

a) Recrystallized from ether–petroleum ether. b) Recrystalized from EtOH.

(47). ^{1}H-NMR ($CDCl_3$) δ: 1.21 and 1.22 (each t, J=7.0 Hz, $-OCH_2C\underline{H}_3$), 1.54 and 1.63 (each d, J=6.4 Hz, $-SCHC\underline{H}_3$), 2.01—2.08 (Ac), 3.40—3.63 ($-OC\underline{H}_2-CH_3$), 3.66—3.82 ($-OC\underline{H}_2CH_3$ and H-5), 4.09—4.28 (m, H-6 and -6′) 4.70 (q, $SC\underline{H}CH_3$) 4.74 and 4.76 (each d, J=10.3 Hz, 10.5 Hz, H-1), 5.00 (q, J=6.4 Hz, $-SC\underline{H}CH_3$), 5.03 (H-2), 5.24 (H-3), 5.84 (H-4). All protons were assigned by the decoupling method and it was confirmed that **4** was a mixture of diastereoisomers with respect to the 2-ethoxyethyl group. *Anal.* Calcd for $C_{18}H_{28}O_{10}S$: 49.53; H, 6.47. Found: C, 49.46; H, 6.41. EI-MS of **5** *m/z* (relative intensity, %) 263 (15, M^++2), 261 (26, M^+), 216 (9, $M^+-OCH_2CH_3$), 190 (8), 188 (15, $M^+-CH(CH_3)OCH_2CH_3$), 176 (12), 174 (52), 172 (83), 160 (21). ^{1}H-NMR of **5** ($CDCl_3$) δ: 1.21 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.52 (3H, d, J=5 Hz, $-CHC\underline{H}_3$), 3.72 (2H, m, $OC\underline{H}_2CH_3$), 5.37 (1H, q, J=5 Hz, $C\underline{H}CH_3$), 7.26 (2H, d, J=9 Hz, H-2 and -6), 7.72 (2H, d, J=9 Hz, H-3 and -5). *Anal.* Calcd for $C_{11}H_{13}Cl_2NO_2$: C, 50.40; H, 5.00; N, 5.34. Found: C, 50.60; H, 5.01; N, 5.32. Reaction of **1** with the coupling reagent obtained from **2g** gave **4** (38% from **1**) and **6** (62% from **2g**, oil). EI-MS of **6** *m/z* (relative intensity, %) 272 (t, M^+), 227 (2.0, $M^+-OCH_2CH_3$), 199 (2.0, $M^+-CH(CH_3)OCH_2CH_3$), 183 (17.2), 137 (5.8), 123 (9.0), 102 (16.9), 76 (13.1), 75 (15.5), 74 (8.6), 73 (100). ^{1}H-NMR ($CDCl_3$) δ=1.24 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.57 (3H, d, J=5.3 Hz, $CHC\underline{H}_3$), 3.68 and 3.89 (each 1H, m, $OC\underline{H}_2CH_3$), 5.49 (1H, q, J=5.4 Hz, $C\underline{H}CH_3$), 8.06 (2H, d, J=9.3 Hz, H-2 and -6), 8.26 (2H, d, J=9.3 Hz, H-3 and -5). *Anal.* Calcd for $C_{11}H_{13}ClN_2O_4$: C, 48.45; H, 4.81; N, 10.27. Found: C, 48.58; H, 4.87; N, 10.15.

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