Studies on Pyrazines. 9 (1). The Facile Synthesis of Pyrazine 1-Oxides Substituted at C-2 with Cyano, Methoxycarbonyl and Carboxy Groups

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The peroxysulfuric acid oxidation of 2-cyanopyrazine (**1**) gave its 1-oxide **3** (18% yield) and pyrazinecarboxamide (8% yield), while that of methyl pyrazinecarboxylate (**2**) provided the 1- and 4-oxides in 15 and 7% yields, respectively. On the other hand, pyrazinecarboxylic acid 1-oxide (**7**) was prepared by condensation of 2-methylpyrazine 1-oxide (**8**) with benzaldehyde followed by oxidative cleavage (47% overall yield).

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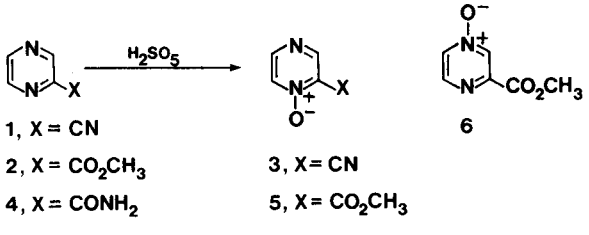
In continuation of our research on pyrazine *N*-oxides (2), we now report convenient synthetic methods for the titled *N*-oxides (3). Recently, peroxysulfuric acid oxidation was demonstrated to be an effective means for the direct conversion of 2-chloropyrazines into the corresponding 1-oxides (2,4). We found that the oxidation method could be also successfully applied to *N*-oxidation of 2-cyanopyrazine (**1**) and methyl pyrazinecarboxylate (**2**) to their 1-oxides.

The oxidation of **1** with peroxysulfuric acid generated *in situ* from potassium persulfate and concentrated sulfuric acid gave 2-cyanopyrazine 1-oxide (**3**) and pyrazinecarboxamide (**4**) in 18 and 8% yields, respectively, the latter of which was easily removed by chromatography on silica gel. On the other hand, the persulfate oxidation of **2** gave a mixture of the 1- (**5**) and 4-oxides (**6**) in 15 and 7% yields, respectively, which were separated by silica gel chromatography.

Determination of the position of the N-O group in the new *N*-oxide **5** was easily accomplished by comparison with ir and nmr spectra of the isomer **6**, *i.e.*, the 1-oxide **5** exhibits the N-O stretching frequency lower than the 4-oxide **6** (2,3a,4) and these *N*-oxides show respectively the coupling constants characteristic of the ring protons of 2-substituted pyrazine 1- and 4-oxides (2) (see Table I).

Scheme I



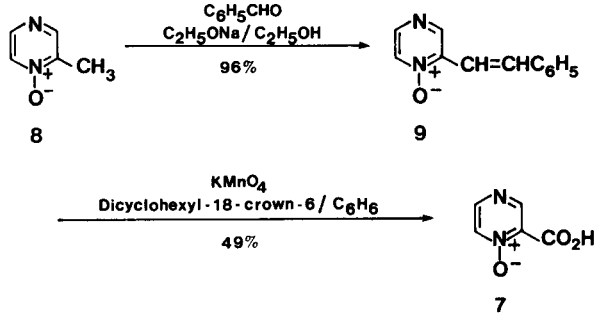
1, X = CN
2, X = CO_2CH_3
4, X = $CONH_2$
3, X = CN
5, X = CO_2CH_3
6

The difference in the selectivities of *N*-oxidation between **1** and **2** is elucidated as follows. Because the *N*-oxidation of pyrazines involves nucleophilic attack of the lone pair of electrons of nitrogen on the outermost oxygen of peracid, the orientation in substituted pyrazines is governed by the relative basicities of the ring nitrogen (5-7). The regiospecificities in the persulfate oxidations of 2-chloropyrazine (2,4) and **1**, therefore, are caused by strongly electron-withdrawing chloro and cyano substituents, respectively, which severely reduced the basicities of the ring nitrogen particular at N-1. In other words, the most basic nitrogen N-4 favors protonation in sulfuric acid resulting in exclusive oxidation on the remaining nitrogen to form the 1-oxides (8). However, the carbomethoxy group makes less difference in the basicities of nitrogens compared to the above substituents (9). This behavior lowers the selectivity of *N*-oxidation in sulfuric acid at low *p*H resulting in the competitive formations of 1- and 4-oxides.

The persulfate oxidation method was not adaptable to pyrazinecarboxylic acid or pyrazinecarboxamide (**4**), *i.e.*, the attempted oxidation of these pyrazines failed to give any *N*-oxides.

One other effort in the present work is the synthesis of pyrazinecarboxylic acid 1-oxide (**7**) by a two-step sequence of reactions starting from 2-methylpyrazine 1-oxides (**8**) (see Scheme II).

Scheme II



8
9
7

Although the *N*-oxides **8** was initially expected to be a useful precursor for the desired *N*-oxides in view of the ready accessibility (10), the methyl group of **8** is entirely resistant to oxidation with selenium dioxide, chromyl chloride, or potassium permanganate, and to the Ortoleva-

Table I

IR (a) and ^1H NMR (b) Spectra of Pyrazine *N*-Oxides

Compound	IR, cm^{-1}		NMR					
			Chemical shift, δ			Coupling constant, Hz		
	N-O	Other	H-3	H-5	H-6	$J_{3,5}$	$J_{3,6}$	$J_{5,6}$
3	1322	2245 (C≡N)	9.16	8.78	8.59	0	0.8	4.4
						(0)	(0.5-0.8)	(4.0-4.3) (2)
5	1334	1740 (C=O)	8.90	8.50	8.17 (c)	0	0.7	4.2
7	1316	1721 (C=O)	9.19	8.88	8.69	0	0.7	4.1
9	1274	1632 (C=C)	8.80	8.24	8.10 (d)	0	0.8	4.2
6	1338	1727 (C=O)	8.79	8.26	8.61 (e)	1.5	0.5	4.0
						(1.2-1.6)	(0-0.8)	(4.0-4.2) (2)

(a) Potassium bromide disc. (b) Compounds **5**, **6**, and **9** were measured in deuteriochloroform and the others in dimethyl sulfoxide-d_6. (c) Other peaks: 4.00 (s, 3H), (d) 7.32 (d, J = 17 Hz, 1H), 7.75 (d, 1H), 7.3-7.65 (m, 5H), (e) 4.04 (s, 3H).

King reaction for subsequent Kröhnke aldehyde synthesis (5,6). The *N*-oxide **8**, however, was easily condensed with benzaldehyde in the presence of a base to form **9** almost quantitatively. This facile condensation is likely to be caused by the *N*-oxide function (11), as 2-methylpyrazine gives no styrylpyrazine under the same conditions. The oxidative cleavage of **9** proceeded effecttively in the presence of crown ether. An interesting finding is that the carboxylic acid **7** can not be converted into the ester **5** by the Fischer method unlike the facile esterification of 2-pyridinecarboxylic acid *N*-oxide under the same conditions (12).

EXPERIMENTAL

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Ir spectra were recorded on a Hitachi 260-10 and EPI-G3 spectrometers, nmr spectra on a JOEL JNM-MH-100 instrument with tetramethylsilane as an internal standard.

2-Cyanopyrazine 1-Oxide (**2**).

To a stirred solution of **1** (5.274 g, 0.050 mole) in 50 ml of concentrated sulfuric acid, prepared at temperature below 10°, potassium persulfate (14.98 g, 0.055 mole) was gradually added at the same temperature. The solution was stirred at room temperature for 16 hours (13), and then poured into 200 ml of ice-water. The aqueous solution was extracted with chloroform (3 × 100 ml) (14), and the extract was washed with water and dried over magnesium sulfate. The aqueous layer and the washings were basified with sodium carbonate (*ca.* 100 g) and extracted with chloroform (5 × 100 ml). The second extract was worked up as in the predescribed manner. Evaporation of the combined extracts gave 1.653 g of colorless solid, which was chromatographed on silica gel (33 g). The first elution with benzene and successively benzene-ethyl acetate (9:1 to 1:1) gave 1.116 g (18%) of **3**. Further development with benzene-ethyl acetate (1:1) afforded 0.490 g (8%) of pyrazinecarboxamide (**4**). An analytical sample of **3** was obtained by recrystallization from methanol as colorless prisms (15), mp 157-159° [lit (3a) mp 156-157°].

Anal. Calcd. for $C_5H_3N_3O$: C, 49.59; H, 2.50; N, 34.70. Found: C, 49.35; H, 2.31; N, 34.56.

2-Methoxycarbonylpyrazine 1- (**5**) and 4-Oxides (**6**).

Pyrazinecarboxylic ester **2** (6.907 g, 0.050 mole) was added with stirring in small portions to concentrated sulfuric acid (50 ml) at temperature below 10°. The mixture was warmed (*ca.* 20°) to dissolve the ester, to the resulting clear solution potassium persulfate (14.87 g, 0.055 mole) was slowly added at temperature below 10°. The solution was stirred at room temperature for 24 hours, and the successive workups were followed using the predescribed manner. Separation of the reaction mixture (6.95 g) was carried out by chromatography on silica gel (100 g). The chromatogram was developed first with benzene-ethyl acetate (9:1) to recover the starting material **2** (2.57 g, 37%). Further elution with the same solvent gave 1.164 g (15%) of 1-oxide **5**, which was recrystallized from methanol to give colorless needles, mp 81-82°.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 46.50; H, 3.89; N, 18.07.

The isomeric 4-oxide **6** was obtained by successive elution with ethyl acetate (0.509 g, 7%) (15), mp 169-171° from methanol [lit (16) mp 166.5-167.5°].

(*E*)-2-(α-Styryl)pyrazine 1-Oxide (**9**).

A solution of 2-methylpyrazine 1-oxide **8** (1.100 g, 0.010 mole) and benzaldehyde (2.13 g, 0.02 mole) in 10 ml of absolute methanol containing sodium (0.23 g, 0.01 mole) was refluxed and stirred for 2 hours. Excess benzaldehyde and methanol was removed by steam distillation, and the resulting aqueous solution was allowed to stand in a refrigerator overnight. The precipitates which formed was collected by filtration, washed with chilled water, and dried in air to afford 1.906 g (96%) of **9**, mp 168-170°. An analytical sample was obtained by recrystallization from ethanol as colorless needles, mp 170-171°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.14. Found: C, 72.71; H, 5.13; N, 14.21.

2-Pyrazinecarboxylic Acid 1-Oxide (**7**).

A mixture of **9** (0.396 g, 2.0 mmoles), dicyclohexyl-18-crown-6 (0.082 g, 0.22 mmole), and potassium permanganate (0.843 g, 5.33 mmoles) in 60 ml of benzene was rolled in a ball mill for 3 hours. Manganese dioxide which formed was collected by filtration, and washed with benzene, 0.1 *N* aqueous sodium hydroxide (50 ml), and finally with water. The filtrate and washings were washed with ether, and the aqueous layer was stirred with 20 ml of Amberlite IR-120B (hydrogen form). The solution was evaporated to dryness *in vacuo* affording a colorless solid, which was washed with ether (4 × 10 ml) to remove benzoic acid. The resulting solid sublimed at 120-130° (0.1 mm) to give 0.136 g (49%) of **7**, mp 138-139° [lit (3a) mp 138-139.5°]. Recrystallization from water gave an analytical sample as colorless prisms without any change in the melting point.

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.86; H, 2.88; N, 20.00. Found: C, 42.68; H, 2.85; N, 20.11.

Acknowledgment.

The authors thank Mr. R. Araki for his assistance and Drs. J. Adachi and T. Nakagawa for their helpful discussions.

REFERENCES AND NOTES

(1) For the previous paper in this series, see: N. Sato, *J. Heterocyclic Chem.*, **19**, 673 (1982).

(2) N. Sato, *J. Org. Chem.*, **43**, 3367 (1978).

(3) These *N*-oxides except 2-methoxycarbonylpyrazine 1-oxide were previously prepared by a several step sequence of reactions commencing with a 2-chloropyrazine 1-oxide, however, this synthetic route was less readily adaptable for large-scale preparation because of the involvment of pyrolysis of 2-pyrazinesulfonic sodium salt 1-oxide with potassium cyanide. (a) S. Okada, A. Kosasayama, T. Konno, and F. Uchimaru, *Chem. Pharm. Bull.*, **19**, 1344 (1971).

(4) C. E. Mixan and R. G. Pews, *J. Org. Chem.*, **42**, 1869 (1977).

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(7) G. W. H. Cheeseman and E. S. G. Werstiuk, *Adv. Heterocyclic Chem.*, **14**, 99 (1972).

(8) Although the nucleophilicity of the nitrogen N-1 is reduced by both electron-withdrawing substituent such as chlorine or cyano group and protonated nitrogen, the electrophilicity of peroxysulfuric acid is sufficient to effect oxidation, reference 4.

(9) The difference in the basicities of nitrogens in substituted pyrazine is estimated from p*k*a of the corresponding 2- and 3-isomers of pyridine. Reference: A. Albert, "Physical Methods in Heterocyclic Chemistry", A. R. Katritzky, eds, Academic Press, New York, NY, Vol. 1, p 1.

(10a) M. Asai, *Yakugaku Zasshi*, **79**, 1273 (1959); (b) W. H. Gumprecht, T. E. Beukelman, and R. Paju, *J. Org. Chem.*, **29**, 2477 (1964).

(11) Similarly 2-methylpyrazine 4-oxide gave 2-(α-styryl)pyrazine 4-oxide (mp 186-188°) in 71% yield.

(12) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, s133 (1949).

(13) The prolonged reaction time decreased the yield of **3**, *e.g.*, the reaction for 24 hours gave only 7% yield of **3**.

(14) If the extraction from acidic medium was neglected, the yield of the desired *N*-oxide was reduced to less than 10%.

(15) These compounds were identified by comparison with ir and nmr spectra of the corresponding authentic samples which were prepared by the published procedures, reference 3a and 16.

(16) F. Uchimaru, S. Okada, A. Kosasayama, and T. Konno, *Chem. Pharm. Bull.*, **19**, 1337 (1971).