Studies on Pyrazines. 29 [1]. High Regioselective Synthesis of Chloropyrazines from 3-Substituted Pyrazine 1-Oxides

Nobuhiro Sato* and Megumi Fujii

Department of Chemistry, Yokohama City University, Yokohama 236, Japan
Received April 8, 1994

Reaction of 3-methoxy- or 3-chloropyrazine 1-oxides with refluxing phosphoryl chloride in the presence of amine led to a high regioselective formation of 3-substituted 2-chloropyrazines. In contrast, the use of chloroacetyl chloride instead of phosphoryl chloride enabled different regioselectivity to yield 6-substituted 2-chloropyrazines, particularly 3-methoxycarbonylpyrazine 1-oxide was almost exclusively converted into methyl 6-chloropyrazinecarboxylate under the conditions without the amine.

J. Heterocyclic Chem., **31**, 1177 (1994).

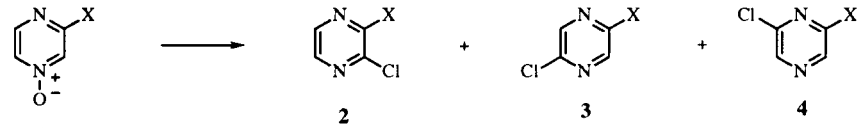
Halogenopyrazines are an important class of compounds in pyrazine chemistry since they can undergo facile displacement of the halogen atoms with nucleophiles producing numerous otherwise-inaccessible pyrazines [2,3]. A common method for preparation of the chloropyrazines involves deoxydative chlorination of pyrazine *N*-oxides with phosphoryl chloride or other acid chlorides [4]. However, chlorination of pyrazine *N*-oxides bearing a substituent on the C-3 carbon with phosphoryl chloride proceed non-regioselectively in most cases to furnish all possible isomers of the substitution products [5]. Therefore a new procedure to overcome this disadvantage is highly desired. We now describe a regioselective synthesis of monosubstituted chloropyrazines by amine added to the reaction of 3-methoxycarbonyl-, 3-methoxy- and 3-chloropyrazine 1-oxides **1a-c** with phosphoryl or chloroacetyl chlorides.

The current project was first prompted by our previous finding that the deoxydative thiation of pyrazine *N*-oxides with 4-methoxytoluene-α-thiol in the presence of diethylcarbamoyl chloride is promoted by added zinc bromide to increase markedly in both yield and ratio of substitution on the carbon β to the *N*-oxide functionality [6]. However, an attempt to react pyrazine *N*-oxide **1b** and **1c** with phosphoryl chloride in the presence of Lewis acid, *i.e.*, iron(III) chloride, tin(II) chloride, tin(IV) chloride, titanium(IV) chloride, zinc chloride or zirconium(IV) chloride, frustrated the yield improvement and the non-selective product distribution in their reactions with phosphoryl chloride alone.

Unlike the above *N*-oxides **1b** and **1c**, reaction of 3-methoxycarbonylpyrazine 1-oxide **1a** with refluxing phosphoryl chloride provided a more than 85% yield of 2-chloro-6-methoxycarbonylpyrazines **4a**, and the 2-chloro-3- and -5-substituted isomers **2a** and **3a** formed in only 7% combined yield. When the *N*-oxide **1a** was treated in refluxing acetyl chloride [4], the ratio of **4a**:**3a** was raised to 96:4 and the formation of **2a** was fully suppressed. This reaction, however, suffers from a yield reduced to 68% and a longer period (to 35 hours) for the completion of reaction. The use of chloroacetyl chloride, whose boiling point of 106° is equal to that of phosphoryl chloride, instead of acetyl chloride led to an increase in the overall yield to 89% with almost the same ratio by the reaction being refluxed for 2 hours. Under identical conditions, the *N*-oxides **1b** and **1c** gave their chloro products in only 47 and 7% yields, respectively. An addition of amine to the reaction expedited the chlorination to produce mainly the β-chloro compound **4** in moderate yields. Higher boiling amines than chloroacetyl chloride, such as DBU, pyridine and diethylaniline were employed for the above purpose and the results are summarized in Table 1. Interestingly, these amines were also proved to favor α-chlorination in the reaction of **1** with phosphoryl chloride as can be seen from Table 1, in which diethylaniline is shown to be best effected for the substitution reaction of **1b** and **1c**. Each of the isomeric chlorinated pyrazines could easily be separated by high performance liquid chromatography and the isolated products were identified by comparison with authentic samples by ^{1}H-nmr spectroscopy, which are summarized in Table 2.

A generally accepted mechanism for deoxydative chlorination of 3-substituted pyrazine 1-oxides is illustrated in

Scheme 1



1, **2**, **3**, **4** **a** X = CO_2Me, **b** X = OMe, **c** X = Cl

Table 1

Formation of Chloropyrazines from 3-Substituted Pyrazine 1-Oxides

N-Oxide	Reagent [a]	Yield (%)	Product and ratio (%) α 2	3	β 4	α : β
1a	$POCl_3$	93	4	4	92	8 : 92
	$POCl_3$/DBU	92	11	29	60	40 : 60
	$POCl_3$/Pyr	41	25	23	52	48 : 52
	$POCl_3$/DEA	58	30	48	22	78 : 22
	$ClCH_2COCl$	89	0	5	95	5 : 95
	$ClCH_2COCl$/DBU	80	0	22	78	22 : 78
	$ClCH_2COCl$/Pyr	23	0	17	83	17 : 83
	$ClCH_2COCl$/DEA	66	0	10	90	10 : 90
1b	$POCl_3$	71	46	5	49	51 : 49
	$POCl_3$/DBU	73	44	5	51	49 : 51
	$POCl_3$/Pyr	43	70	15	15	85 : 15
	$POCl_3$/DEA	72	85	7	8	92 : 8
	$ClCH_2COCl$	47	25	0	75	25 : 75
	$ClCH_2COCl$/DBU	46	3	5	92	8 : 92
	$ClCH_2COCl$/Pyr	32	3	3	94	6 : 94
	$ClCH_2COCl$/DEA	16	28	5	67	33 : 67
1c	$POCl_3$	70	56	3	41	59 : 41
	$POCl_3$/DBU	72	53	10	37	63 : 37
	$POCl_3$/Pyr	45	86	6	8	92 : 8
	$POCl_3$/DEA	55	77	13	10	90 : 10
	$ClCH_2COCl$	7	100	0	0	100 : 0
	$ClCH_2COCl$/DBU	48	4	5	91	9 : 91
	$ClCH_2COCl$/Pyr	52	7	6	87	13 : 87
	$ClCH_2COCl$/DEA	38	14	9	77	23 : 77

[a] DBU: 1,8-diazabicyclo[5.4.0]undec-5-ene. Pyr: pyridine. DEA: diethylaniline.

Table 2

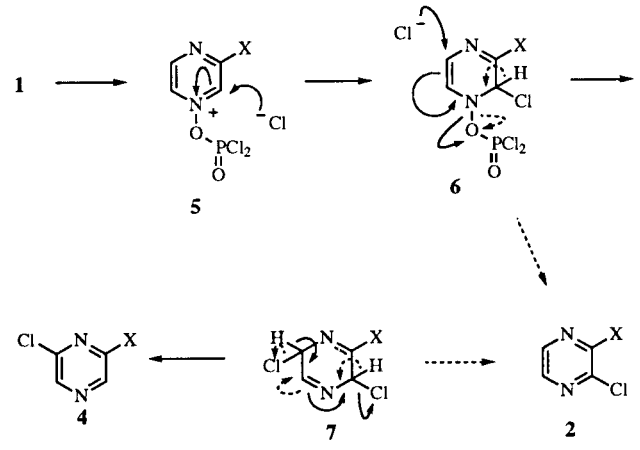
^{1}H-Nmr Spectra of Chloropyrazines [a]

Compound [b]	^{1}H Nmr δ, ppm
2a	4.05 (3H, s), 8.54 (1H, d, J = 2.3 Hz), 8.59 (1H, d)
3a	4.08 (3H, s), 8.71 (1H, d, J = 1.3 Hz), 9.10 (1H, d)
4a	4.05 (3H, s), 8.79 (1H, s), 9.21 (1H, s)
2b	4.06 (3H, s), 7.94 (1H, d, J = 2.6 Hz), 8.03 (1H, d)
4b	3.99 (3H, s), 8.13 (1H, s), 8.15 (1H, s)
2c	8.33 (s)
3c	8.40 (s)
4c	8.53 (s)

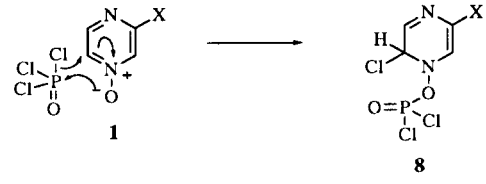
[a] The nmr spectra was obtained with JEOL JNM EX270 instrument with solution in deuteriochloroform containing tetramethylsilane as the internal standard. [b] All compounds were identified with the authentic samples which were prepared in our earlier work [5].

Scheme 2, which involves an initial formation of the dichlorophosphate ester followed by an attack of the chloride ion on the resulting electron-deficient carbon adjacent to the *N*-oxide function and finally aromatization [5]. Our earlier study on the cyanation of the pyrazine *N*-oxides with trimethylsilyl cyanide indicates that the electron-donating groups enhance the substitution leading to highly regioselective formation of 2-substituted 3-cyanopyrazines [7]. The order of reactivity is in agreement with that of *ortho-para* directors in aromatic electrophilic substitution, consequently the substitution is governed at the first stage by the nucleophilicity of the *N*-oxide oxygen. Conversely, electron-withdrawing *meta*-directors brought about the cyanation in a different fashion, in which the substitution occurs prior to trimethylsilylation of the *N*-oxide oxygen. On the other hand, thiation with 4-methoxytoluene-α-thiol or acetoxylation proceeds solely depending upon nucleophilicity of the *N*-oxide oxygen in spite of either category of the substituent [6]. The observed order of reactivity is **1b** > **1a** > **1c**, which agrees with the charges of the *N*-oxide oxygen as well as the energy levels of HOMO orbitals by semi-empirical AM1 molecular orbital calculation [8]. In the present case, the order of reactivity for chlorination is **1a** > **1b** ≳ **1c**, strongly suggests that the deoxydative substitution of *N*-oxide **1a** having a methoxycarbonyl group proceeds in a similar manner as that described for the cyanation of **1a**, *i.e.*, an attack of chloride ion on the ring carbon of **1a** takes place and then the phosphine-oxygen bond formation occurs, or both processes ensue simultaneously, leading to the intermediate **8** as outlined in Scheme 3.

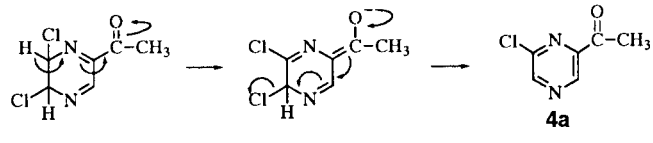
Scheme 2



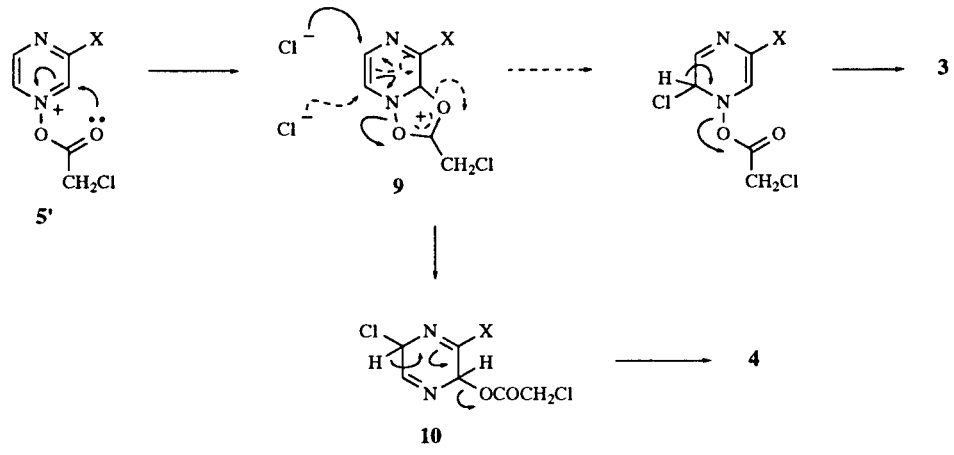
Scheme 3



Scheme 4



Scheme 5



Dehydrogenation from the Meisenheimer complex **6** furnishes the α-chloro products and the process is accelerated by the added amine to result in increasing the proportions of **2** and **3**. A noteworthy aspect is individual α-product distribution which likely corresponds to a ratio of the positions to be first attacked by the chloride ion. Namely the *N*-oxides **1b** and **1c** provided the α-chloro products **2** in more than a 85% proportion whereas 2-chloro-5-methoxycarbonyl pyrazines **3a** formed in preference to the isomer **2a**. In the absence of base the intermediate **6** is susceptible to a second attack of a chloride ion leading to **7**. Particularly, a methoxycarbonyl group facilitates the introduction of the chloride ion into the pyrazine ring by its electron-withdrawing mesomeric effect, as well as dehydrochlorination from the dihydro intermediate **7** to yield the β-chloro product **4a** in good yield as shown in Scheme 4.

A mechanism of chlorination using chloroacetyl chloride should be partially different from that by phosphoryl chloride because the yields and product ratios in those reactions do not resemble each other. We recently proposed the formation of a bicyclic intermediate such as **9** for deoxydative acetoxylation of pyrazine *N*-oxides [1,9]. This species is visualized to permit easily the further attack of chloride ion for it should have a longer life-time than the intermediate **6** taking into account the weaker electron-withdrawing ability of the chloroacetoxy moiety. The resulting dihydropyrazine **10** eliminates chloroacetic acid producing β-chloropyrazines **4**. This course of aromatization is evidently controlled by the acidity of the hydrogens in the dihydro intermediate because of the loss of a proton from the ring carbon attached to the more electron-withdrawing chloro substituent surpasses its loss from an α-position. This may be a driving force leading to the presumably exclusive formation of β-chloropyrazines **4b** and **4c**. Since the proton is not sufficiently acidic to eliminate spontaneously, however, the amine is required to aromatize chloropyrazines in contrast to chloropyrazinecarboxylic esters which can form without the base. On the other hand, the α-chloropyrazines **2** and **3** should be generated by an attack of a chloride ion at the alternative α-carbon of the intermediate **9** as shown in Scheme 5.

EXPERIMENTAL

General Procedure of Deoxydative Chlorination of Pyrazine *N*-Oxides **1**.

A mixture of pyrazine *N*-oxide **1** (1.0 mmole) in freshly distilled phosphoryl chloride or chloroacetyl chloride (2.0 ml) was stirred under reflux for 2 hours. In the reactions with the presence of DBU, pyridine or diethylamine, the amine (1.0 mmole) was added *via* a syringe before starting the reaction. The resulting solution was cooled to room temperature and poured into ice-water. After being basified with 30% aqueous sodium hydroxide at *p*H 9, the solution was extracted with chloroform (2 x 10 ml + 2 x 5 ml). The extract was washed with water, dried over magnesium sulfate and filtered. If amine was used, the extract was washed with 3*N* hydrochloric acid prior to washing with water. The chloroform solution from the *N*-oxides **1b** and **1c** was directly subjected to quantitative analysis by gas-chromatography with naphthalene as the internal standard. Evaporation of the chloroform solution provided a mixture of chloropyrazines, whose ratio from **1a** was determined by nmr spectra. The mixture of substitution products was separated by high performance liquid chromatography equipped with the prepacked column (2.2 x 30 cm, 10 μm silica gel) eluted with hexane-ethyl acetate (9:1).

Acknowledgements.

We thank Koei Chemical Co., Ltd., Osaka, Japan, for its gift of 2-chloropyrazine as the starting material for synthesis of 3-methoxy- and 3-chloropyrazine 1-oxides **1a** and **1b**.

REFERENCES AND NOTES

[1] Part **28**: N. Sato, N. Miwa, H. Suzuki and T. Sakakibara, *J. Heterocyclic Chem.*, submitted for publication.

[2] G. B. Barlin, The Pyrazines in The Chemistry of Heterocyclic Compounds, A. Weissberger and E. C. Taylor, eds, Interscience, New York, 1982, p 95.

[3] A. E. A. Porter, Pyrazines and their Benzo Derivatives in Comprehensive Heterocyclic Chemistry, Vol **3**, A. J. Boulton and A. McKillop, eds, Pergamon, Oxford, 1984, p 157.

[4] For example: S. Okada, A. Kosasayama, T. Konno and F. Uchimaru, *Chem. Pharm. Bull.*, **19**, 1344 (1971).

[5] N. Sato, *J. Chem. Res.*, (S) 318; (M) 2860 (1984).

[6] N. Sato, K. Kawahara and N. Morii, *J. Chem. Soc., Perkin Trans. 1*, 15 (1993).

[7] N. Sato, Y. Shimomura, Y. Ohwaki and R. Takeuchi, *J. Chem. Soc., Perkin Trans. 1*, 2877 (1991).

[8] T. Sakakibara, Y. Ohwaki and N. Sato, *Bull. Chem. Soc. Japan*, **66**, 1149 (1993).

[9] N. Sato, N. Miwa and N. Hirokawa, *J. Chem. Soc., Perkin Trans. 1*, 885 (1994).