

SYNTHESIS OF HALOXYDROXYPYRAZINES AND THEIR SYNTHETIC UTILITY

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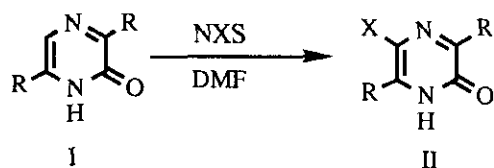
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Abstract---Treatment of hydroxypyrazines with *N*-halosuccinimide (NXS; X = Cl, Br, I) in *N,N*-dimethylformamide (DMF) at room temperature afforded haloxyhydroxypyrazines in good yields. Their synthetic utility was examined.

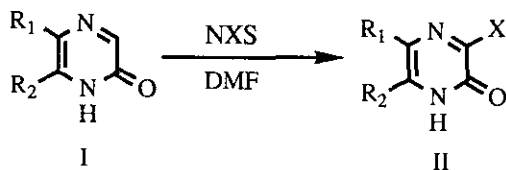
Halopyrazines can become useful intermediates for the synthesis of pyrazine derivatives, which have many biological activities.¹ Because monocyclic diazines such as pyrazine are π -deficient aromatic heterocycles, it is well known that direct and low temperature halogenation of their heterocycles occurs with difficulty, if at all. However, once electron-donating groups are introduced into a pyrazine ring, electrophilic substitution reactions easily take place. For example, aminopyrazines² and methoxypyrazine *N*-oxides³ were able to be halogenated to give the corresponding haloaminopyrazines and halomethoxypyrazine *N*-oxides, respectively.

Hydroxypyrazines were treated with bromine in the presence of pyridine to give bromohydroxypyrazines in moderate yields.⁴ Sato reported a modified method using aqueous sodium hydroxide instead of pyridine.⁵ Recently, our group described the synthesis of chlorohydroxypyrazines *via* dichloropyrazines.⁶ However, little is known about the simplicity and efficiency during synthesis of haloxyhydroxypyrazines. In this paper, we wish to report a facile synthesis of haloxyhydroxypyrazines and their synthetic utility.

We conducted the reaction of some hydroxypyrazines (**Ia-g**) with *N*-halosuccinimide (NXS; X = Cl, Br, I) in *N,N*-dimethylformamide (DMF) at room temperature (Tables I and II). To our surprise, in the ¹H-nmr spectra of the haloxyhydroxypyrazines, a hydroxyl proton could not be detected. Perhaps, this is due to the rapid tautomerization between the amide form and the iminol form.

Table I. Reaction of 3,5-Dialkyl-2-hydroxypyrazines (**Ia-d**) with NXS

R	I	X	II	Yield (%)
Et	Ia	Cl	IIa	88
		Br	IIb	78
		I	IIc	83
iPr	Ib	Cl	IId	85
		Br	IIe	81
		I	IIf	96
iBu	Ic	Cl	IIg ⁷	79
		Br	IIh	93
		I	IIi	100
secBu	Id	Cl	IIj ⁸	65
		Br	IIk	70
		I	III	59

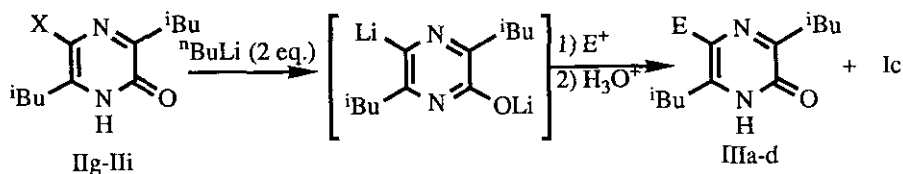
Table II. Reaction of 5,6-Disubstituted 2-Hydroxypyrazines (**Ie-g**) with NXS

R ₁	R ₂	I	X	II	Yield (%)
Ph	Ph	Ie	Cl	IIm ⁹	57
			Br	II _n ⁴	68
			I	IIo	53
Me	Ph	If	Cl	IIp	50
			Br	IIq	38
			I	IIr	43
Me	Me	Ig	Cl	IIs	37
			Br	II _t ⁴	70
			I	IIu	56

Next, we carried out the reaction of halohydroxypyrazines with some electrophiles, that is, compounds (**IIg-i**) were derived to the dianions in the presence of 2 eq. ⁿBuLi, which were then treated with some electrophiles such as benzaldehyde, methyl 4-methylbenzoate, methyl isobutyrate, and methyl formate (Table III).

The reaction of the chloro compound (**IIg**) with methyl 4-methylbenzoate did not proceed. While the reactions of others proceeded to produce the corresponding compounds (**IIIa-d**) in 23-81 % yields, accompanied with the dehalogenated compound (**Ic**).

Table III. Reaction of 5-Halo-2-hydroxy-3,6-diisobutylpyrazines (**IIg-i**) with Some Electrophiles in the Presence of 2 eq. *n*-BuLi



Entry	Electrophile	X	Product (Yield %)
1		I	IIIa (60), Ic (38)
2		Br	IIIa (66), Ic (3)
3		Cl	-----
4		I	IIIb (81), Ic (-)
5		Br	IIIb (55), Ic (25)
6		I	IIIc (41), Ic (47)
7		Br	IIIc (55), Ic (41)
8		I	IIId (23), Ic (75)
9	HCOOMe	Br	IIId (57), Ic (23)

In these reactions, the alkylations occurred only at 5-position of the pyrazine ring. Addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) did not have any effect on the reaction. When 3 eq. *n*-BuLi was employed as a base, better results were not obtained. In addition, we tried to apply 5,6-disubstituted 3-halo-2-hydroxypyrazines to the reactions. However, all attempts ended in failure to give the dehalogenated compounds and the starting materials.

Further, we examined the reactions of halohydroxypyrazines (**IIm-o**, **IIu**) with cuprous phenylacetylide. 3-Iodo- and 3-bromo-2-hydroxypyrazines containing alkyl and aryl groups (**IIn**, **o** and **u**) were treated with cuprous phenylacetylide to give 5,6-disubstituted 2-phenylpyrazino[2,3-*b*]furans (**IVa**, **IVb**) in 57-92 % yields (Table IV). The reactions of 5-iodo- and 5-bromo-2-hydroxy-3,6-diisobutylpyrazines (**IIh**, **i**) with cuprous phenylacetylide gave the corresponding 5-substituted compounds (**V**) (Tables V).

Table VI. Physical Properties and Analytical Data of Compounds II, III, IV, and V

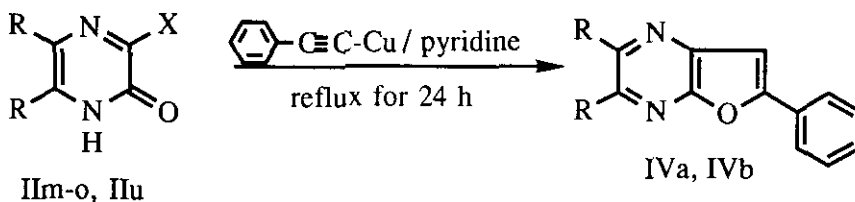
Compd.	mp (°C) (Recryst. Solvent)	Molecular Formula	Anal. (Calcd); C, H, N (Found); C, H, N			Ir (ν C=O) (KBr, cm^{-1})	$^1\text{H-Nmr}$ (CDCl_3 , δ)	Ms (m/z) (M^+)
IIa	109-110 ($\text{H}_2\text{O-MeOH}$)	$\text{C}_8\text{H}_{11}\text{N}_2\text{OCl}$	51.48 51.40	5.94 5.96	15.01 14.96	1650	1.26 (3H, t, $J = 7.5$ Hz), 1.31 (3H, $J = 7.5$ Hz), 2.72 (2H, q, $J = 7.5$ Hz), 2.80 (2H, q, $J = 7.5$ Hz)	186
IIb	134-135 (Isopropyl ether)	$\text{C}_8\text{H}_{11}\text{N}_2\text{OBr}$	41.58 41.47	4.80 4.77	12.12 12.06	1660	1.25 (3H, t, $J = 7.4$ Hz), 1.30 (3H, t, $J = 7.6$ Hz), 2.72 (2H, q, $J = 7.6$ Hz), 2.79 (2H, q, $J = 7.4$ Hz)	232
IIc	154 (Isopropyl ether)	$\text{C}_8\text{H}_{11}\text{N}_2\text{OI}$	34.55 34.72	3.99 3.93	10.07 10.19	1635	1.23 (3H, t, $J = 7.5$ Hz), 1.28 (3H, t, $J = 7.5$ Hz), 2.71 (2H, q, $J = 7.5$ Hz), 2.77 (2H, q, $J = 7.4$ Hz)	278
II d	175 ($i\text{PrOH}$)	$\text{C}_{10}\text{H}_{15}\text{N}_2\text{OCl}$	55.94 55.79	7.04 7.02	13.05 12.93	1630	1.26 (6H, d, $J = 6.8$ Hz), 1.33 (6H, d, $J = 7.0$ Hz), 3.31 (1H, m), 3.36 (1H, m)	214
II e	184-185 ($i\text{PrOH}$)	$\text{C}_{10}\text{H}_{15}\text{N}_2\text{OBr}$	46.34 46.42	5.83 5.86	10.81 10.82	1625	1.25 (6H, d, $J = 6.9$ Hz), 1.34 (6H, d, $J = 7.0$ Hz), 3.30 (1H, m), 3.34 (1H, m)	258
II f	195-197 (Isopropyl ether)	$\text{C}_{10}\text{H}_{15}\text{N}_2\text{OI}$	39.23 39.32	4.94 4.96	9.15 9.18	1640	1.23 (3H, d, $J = 6.9$ Hz), 1.24 (3H, d, $J = 6.8$ Hz), 1.32 (6H, d, $J = 7.0$ Hz), 3.18 (1H, m), 3.30 (1H, m)	306
II h	138-139 (Isopropyl ether)	$\text{C}_{12}\text{H}_{19}\text{N}_2\text{OBr}$	50.18 50.48	6.67 6.71	9.75 9.82	1645	0.97 (6H, d, $J = 6.7$ Hz), 1.01 (6H, d, $J = 6.7$ Hz), 2.19 (2H, m), 2.57 (2H, d, $J = 7.4$ Hz), 2.64 (2H, d, $J = 7.1$ Hz)	286
II i	134-135 (Isopropyl ether)	$\text{C}_{12}\text{H}_{19}\text{N}_2\text{OI}$	43.12 43.40	5.73 5.73	8.38 8.36	1655	0.96 (6H, d, $J = 6.8$ Hz), 1.02 (6H, d, $J = 6.9$ Hz), 2.18 (2H, m), 2.55 (2H, d, $J = 6.4$ Hz), 2.63 (2H, d, $J = 7.2$ Hz)	334

(continued)

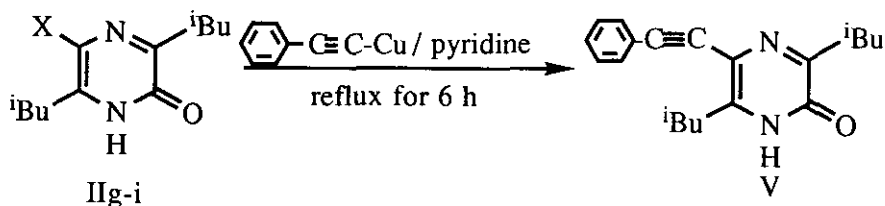
IIk	114-115 (MeOH)	$C_{12}H_{19}N_2OBr$	50.18 50.47	6.67 6.66	9.75 9.86	1640	0.91 (3H, t, J = 7.3 Hz), 0.92 (3H, t, J = 7.2 Hz), 1.22 (1.5H, d, J = 6.8 Hz), 1.23 (1.5H, d, J = 6.8 Hz), 1.30 (3H, d, J = 7.1 Hz), 1.51-1.86 (4H, m), 3.05-3.18 (2H, m)	285
III	91-92 (H ₂ O-MeOH)	$C_{12}H_{19}N_2OI$	43.12 42.88	5.73 5.69	8.38 8.36	1630	0.90 (3H, t, J = 7.4 Hz), 0.93 (3H, t, J = 7.4 Hz), 1.20 (1.5H, d, J = 6.9 Hz), 1.21 (1.5H, d, J = 6.9 Hz), 1.30 (3H, d, J = 7.0 Hz), 1.47-1.86 (4H, m), 2.98 (1H, m), 3.10 (1H, m)	334
IIo	218-220 (decomp.) (H ₂ O-MeOH)	$C_{16}H_{11}N_2OI$	51.35 51.49	2.96 3.01	7.49 7.52	1660	7.23-7.45 (10H, m)	374
IIp	185-192 (H ₂ O- ⁱ PrOH)	$C_{11}H_9N_2OCl$	59.87 59.88	4.11 4.21	12.70 12.58	1650	2.33 (3H, s), 7.44-7.54 (2H, m), 7.52-7.56 (3H, m)	220
IIq	194-195 (Isopropyl ether)	$C_{11}H_9N_2OBr$	49.83 49.90	3.42 3.45	10.57 10.54	1660	2.35 (3H, s), 7.44-7.48 (2H, m), 7.51-7.56 (3H, m)	264
IIr	165-170 (ⁱ PrOH)	$C_{11}H_9N_2OI$	42.33 42.61	2.91 2.94	8.98 8.99	1630	2.36 (3H, s), 7.42-7.46 (2H, m), 7.51-7.55 (3H, m)	312
IIs	209-212 (AcOEt)	$C_6H_7N_2OCl$	45.44 45.55	4.45 4.45	17.67 17.88	1640	2.29 (3H, s), 2.36 (3H, s)	158
IIu	148-150 (decomp.) (AcOEt)	$C_6H_7N_2OI$	28.82 28.90	2.82 2.77	11.20 11.25	1690	2.29 (6H, s)	250
IIIa	117-119 (Isopropyl ether)	$C_{19}H_{26}N_2O_2$	72.58 72.38	8.34 8.33	8.91 8.97	1660	0.87 (3H, d, J = 6.6 Hz), 0.97-0.99 (9H, m), 1.95 (1H, m), 2.39 (1H, m), 2.37-2.40 (2H, m), 2.60-2.69 (2H, m), 4.55 (1H, m), 5.66 (1H, d, J = 7.4 Hz), 7.26-7.36 (5H, m)	314
IIIb	182-187 (Isopropyl ether)	$C_{20}H_{26}N_2O_2$	73.59 73.48	8.03 7.97	8.58 8.53	1640	0.96 (6H, d, J = 6.7 Hz), 1.00 (6H, d, J = 6.6 Hz), 2.22 (2H, m), 2.43 (3H, s), 2.66 (2H, d, J = 7.1 Hz), 2.83 (2H, d, J = 7.3 Hz), 7.24 (2H, d, J = 8.3 Hz), 7.77 (2H, d, J = 8.2 Hz)	326

(continued)

IIIc	131-135 (H ₂ O-MeOH)	C ₁₇ H ₂₈ N ₂ O ₂	69.82 69.55	9.65 9.55	9.58 9.59	1640	0.96-1.02 (18H, m), 2.08 (1H, m), 2.19-2.32 (2H, m), 2.68 (2H, d, J = 7.0 Hz), 2.91 (2H, d, J = 6.9 Hz), 2.93 (2H, d, J = 7.2 Hz)	292
IIIId	200-203 (Isopropyl ether)	C ₁₃ H ₂₀ N ₂ O ₂	66.07 65.92	8.53 8.56	11.86 11.73	1650	0.96-1.01 (12H, m), 2.06 (1H, m), 2.21 (1H, m), 2.70 (2H, d, J = 7.1 Hz), 2.97 (2H, d, J = 7.3 Hz), 9.94 (1H, s)	236
IVa	167-168 (H ₂ O-MeOH)	C ₂₄ H ₁₆ N ₂ O	82.74 82.58	4.63 4.67	8.04 7.93	-----	7.28-7.34 (7H, m), 7.44-7.54 (7H, m), 7.99 (2H, m)	348
IVb	155-156 (iPrOH)	C ₁₄ H ₁₂ N ₂ O	74.98 75.00	5.39 5.39	12.49 12.59	-----	2.63 (3H, s), 2.65 (3H, s), 7.14 (1H, s), 7.43-7.53 (3H, m), 7.90 (2H, m)	224
V	223-224 (AcOEt)	C ₂₀ H ₂₄ N ₂ O	77.88 77.76	7.84 7.87	9.08 9.07	1645	0.99 (6H, d, J = 6.7 Hz), 1.06 (6H, d, J = 6.6 Hz), 2.24 (2H, m), 2.70 (2H, d, J = 7.2 Hz), 2.71 (2H, d, J = 7.2 Hz), 7.33-7.37 (3H, m), 7.51-7.55 (2H, m)	308

Table IV. Reaction of 5,6-Disubstituted 3-Halo-2-hydroxypyrazines (**IIm-o**, **IIu**) with Cuprous Phenylacetylide

Entry	II	R	X	IV	Yield (%) of IV
1	IIm	Ph	Cl	IVa	trace
2	IIn	Ph	Br	IVa	57
3	IIo	Ph	I	IVa	92
4	IIu	Me	I	IVb	89

Table V. Reaction of 5-Halo-2-hydroxy-3,6-diisobutylpyrazines (**IIg-i**) with Cuprous Phenylacetylide

Entry	II	X	Yield (%) of V
1	IIg	Cl	--
2	IIh	Br	11 (62) ^a
3	IIi	I	67 (23) ^a

a: Yields of starting materials

EXPERIMENTAL

No correction are made for any melting points. ¹H-Nmr spectral data were obtained using a Varian Gemini-300 or a Bruker AM-400 in CDCl₃ using TMS as internal standard. Other spectral data were obtained using the following instruments. Ir spectra: Japan Spectroscopic Co. A-100; Ms: Hitachi M-80 spectrometer. Starting 2-hydroxypyrazines were synthesized according to known methods: 3,6-diethyl- (**Ia**),¹⁰ 3,6-diisopropyl- (**Ib**),¹¹ 3,6-diisobutyl- (**Ic**),¹¹ 3,6-di-sec-butyl- (**Id**),⁸ 5,6-diphenyl- (**Ie**),¹² 5-methyl-6-phenyl- (**If**),¹³ and 5,6-dimethyl-2-hydroxypyrazine (**Ig**).¹²

Synthesis of Halohydroxypyrazines (II) : General Procedure.

To a DMF solution (5 ml) of 2-hydroxypyrazine (5 mmol), NXS (5.5 mmol) was added. The reaction mixture was stirred at room temperature overnight. The resulting mixture was then poured into ice water (50 ml). The precipitates were collected by suction, dried, and then recrystallized from appropriate solvents. When precipitation did not occur, the aqueous layer was extracted with an appropriate solvent (ex. AcOEt). After the usual work-up, the residue was purified by recrystallization or medium-pressure column chromatography.

Reaction of Halohydroxypyrazines with Electrophiles in the Presence of 2 eq. ⁿBuLi: General Procedure.

To a dry THF solution (5 ml) of 1.6 M ⁿBuLi in hexane (2.5 ml, 4 mmol), a halohydroxypyrazine (2 mmol) in dry THF (10 ml) was added at -78 °C under an atmosphere of argon. The reaction mixture was stirred while maintaining the temperature for 20 min. An electrophile (2.4 mmol) in dry THF (5 ml) was then added dropwise. The reaction mixture was further stirred at -78 °C for 20 min and at room temperature overnight. To the yellow solution, sat. aq. NH₄Cl (5 ml) was added, and then the pH was adjusted to 6-7 by adding 5 % HCl. The reaction mixture was diluted with Et₂O (30 ml), and separated. The aqueous layer was extracted with Et₂O (20 ml x 2). The organic layer was combined, washed with sat. aq. NaCl (20 ml x 3) and dried over Na₂SO₄. The solvent was evaporated, and then the residue was purified by medium pressure liquid chromatography (hexane-AcOEt).

Reaction of 5,6-Disubstituted 3-Halo-2-hydroxypyrazines (II_{m-o} and u) and

5-Halo-2-hydroxy-3,6-diisobutylpyrazine (II_{g-i}) with Cuprous Phenylacetylide: General Procedure.

A mixture of a halohydroxypyrazine (1.77 mmol), cuprous phenylacetylide (290 mg, 1.77 mmol), and dry pyridine (10 ml) was refluxed for 6-24 h under an atmosphere of argon. The solvent was evaporated under reduced pressure, and the residue was purified by medium pressure liquid chromatography (hexane-AcOEt).

REFERENCES

1. C. B. Barlin, 'The Pyrazines,' John Wiley & Sons, Inc., New York, 1982, p 1.
2. M. V. Jovanovic, Heterocycles, 1984, **22**, 1195.
3. W. W. Paudler and M. V. Jovanovic, J. Org. Chem., 1983, **48**, 1064.
4. G. Karmas and P. E. Spoerri, J. Am. Chem. Soc., 1956, **78**, 4071.
5. N. Sato, J. Heterocycl. Chem., 1978, **15**, 665.

6. A. Ohta, A. Kojima, and C. Sakuma, Heterocycles, 1990, **31**, 1274.
7. A. Ohta, Chem. Pharm. Bull., 1964, **12**, 125.
8. R. A. Baxter and F. S. Spring, J. Chem. Soc., 1947, 1179.
9. A. Hirschberg and P. E. Spoerri, J. Heterocycl. Chem., 1969, **6**, 975.
10. G. T. Newbold, F. S. Spring, and W. Sweeny, J. Chem. Soc., 1948, 1855.
11. A. Ohta, M. Shimazaki, H. Tamamura, Y. Mamiya, and T. Watanabe, J. Heterocycl. Chem., 1983, **20**, 951.
12. Y. A. Tota and R. C. Elderfield, J. Org. Chem., 1942, **7**, 313.
13. A. Ohta, S. Masano, S. Iwakura, A. Tamura, H. Watahiki, M. Tsutsui, Y. Akita, and T. Watanabe, J. Heterocycl. Chem., 1982, **19**, 465.

Received, 2nd September, 1991