# SYNTHESIS OF HALOHYDROXYPYRAZINES AND THEIR SYNTHETIC UTILITY

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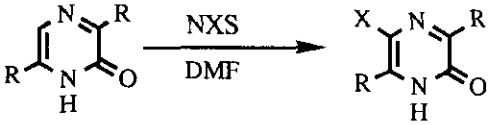
**Abstract**---Treatment of hydroxypyrazines with *N*-halosuccinimide (NXS; X = Cl, Br, I) in *N,N*-dimethylformamide (DMF) at room temperature afforded halohydroxypyrazines in good yields. Their synthetic utility was examined.

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, aminopyrazines [2] and methoxypyrazine *N*-oxides [3] 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 halohydroxypyrazines. In this paper, we wish to report a facile synthesis of halohydroxypyrazins 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 $^1$H-nmr spectra of the halohydroxypyrazines, a hydroxyl proton could not be detected. Perhaps, this is due to the rapid tautomerization between the amide form and the iminol form.

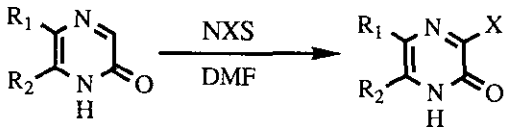
**Table I.** Reaction of 3,5-Dialkyl-2-hydroxypyrazines (**Ia-d**) with NXS




I II

| R | I | X | II | Yield (%) |
|---|---|---|---|---|
| Et | Ia | Cl | IIa | 88 |
| | | Br | IIb | 78 |
| | | I | IIc | 83 |
| $^{i}Pr$ | Ib | Cl | IId | 85 |
| | | Br | IIe | 81 |
| | | I | IIf | 96 |
| $^{i}Bu$ | Ic | Cl | IIg[7] | 79 |
| | | Br | IIh | 93 |
| | | I | IIi | 100 |
| $^{sec}Bu$ | Id | Cl | IIj[8] | 65 |
| | | Br | IIk | 70 |
| | | I | III | 59 |

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



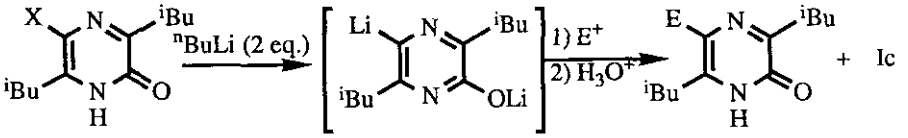

I II

| $R_1$ | $R_2$ | I | X | II | Yield (%) |
|---|---|---|---|---|---|
| Ph | Ph | Ie | Cl | IIm[9] | 57 |
| | | | Br | IIn[4] | 68 |
| | | | I | IIo | 53 |
| Me | Ph | If | Cl | IIp | 50 |
| | | | Br | IIq | 38 |
| | | | I | IIr | 43 |
| Me | Me | Ig | Cl | IIs | 37 |
| | | | Br | IIt[4] | 70 |
| | | | I | IIu | 56 |

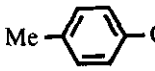
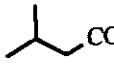
Next, we carried out the reaction of halohydroxypyrazines with some electrophiles, that is, compounds (**IIg-i**) were derived to the dianions in the presence of 2 eq. $^{n}BuLi$, which were then treated with some electrophiles such as benzaldehyde, methyl 4-methylbenzoate, methyl isobutyrate, and methyl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




IIg-IIi IIIa-d

| 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 | HCOOMe | I | IIId (23), Ic (75) |
| 9 | | 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, $cm^{-1}$) | $^1$H-Nmr ($CDCl_3$, δ) | Ms (m/z) ($M^+$) |
|---|---|---|---|---|---|---|---|---|
| IIa | 109-110 ($H_2O$-MeOH) | $C_8H_{11}N_2OCl$ | 51.48<br>51.40 | 5.94<br>5.96 | 15.01<br>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) | $C_8H_{11}N_2OBr$ | 41.58<br>41.47 | 4.80<br>4.77 | 12.12<br>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) | $C_8H_{11}N_2OI$ | 34.55<br>34.72 | 3.99<br>3.93 | 10.07<br>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 |
| IId | 175 ($^i$PrOH) | $C_{10}H_{15}N_2OCl$ | 55.94<br>55.79 | 7.04<br>7.02 | 13.05<br>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 |
| IIe | 184-185 ($^i$PrOH) | $C_{10}H_{15}N_2OBr$ | 46.34<br>46.42 | 5.83<br>5.86 | 10.81<br>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 |
| IIf | 195-197 (Isopropyl ether) | $C_{10}H_{15}N_2OI$ | 39.23<br>39.32 | 4.94<br>4.96 | 9.15<br>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 |
| IIh | 138-139 (Isopropyl ether) | $C_{12}H_{19}N_2OBr$ | 50.18<br>50.48 | 6.67<br>6.71 | 9.75<br>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 |
| IIi | 134-135 (Isopropyl ether) | $C_{12}H_{19}N_2OI$ | 43.12<br>43.40 | 5.73<br>5.73 | 8.38<br>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 |

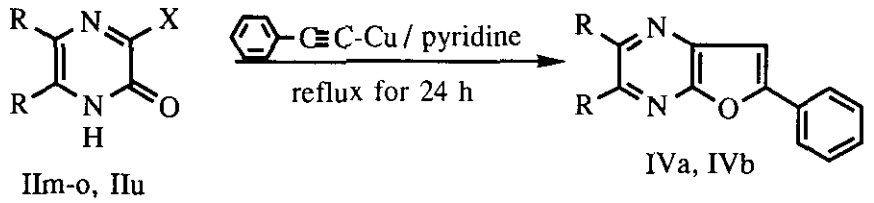
*(continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| IIk | 114-115 (MeOH) | $C_{12}H_{19}N_2OBr$ | 50.18<br>50.47 | 6.67<br>6.66 | 9.75<br>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 |
| IIl | 91-92 ($H_2O$-MeOH) | $C_{12}H_{19}N_2OI$ | 43.12<br>42.88 | 5.73<br>5.69 | 8.38<br>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.) ($H_2O$-MeOH) | $C_{16}H_{11}N_2OI$ | 51.35<br>51.49 | 2.96<br>3.01 | 7.49<br>7.52 | 1660 | 7.23-7.45 (10H, m) | 374 |
| IIp | 185-192 ($H_2O$-$^i$PrOH) | $C_{11}H_9N_2OCl$ | 59.87<br>59.88 | 4.11<br>4.21 | 12.70<br>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<br>49.90 | 3.42<br>3.45 | 10.57<br>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<br>42.61 | 2.91<br>2.94 | 8.98<br>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<br>45.55 | 4.45<br>4.45 | 17.67<br>17.88 | 1640 | 2.29 (3H, s), 2.36 (3H, s) | 158 |
| IIu | 148-150 (decomp.) (AcOEt) | $C_6H_7N_2OI$ | 28.82<br>28.90 | 2.82<br>2.77 | 11.20<br>11.25 | 1690 | 2.29 (6H, s) | 250 |
| IIIa | 117-119 (Isopropyl ether) | $C_{19}H_{26}N_2O_2$ | 72.58<br>72.38 | 8.34<br>8.33 | 8.91<br>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<br>73.48 | 8.03<br>7.97 | 8.58<br>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 | $C_{17}H_{28}N_2O_2$ | 69.82 | 9.65 | 9.58 | 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 |
| | ($H_2O$-MeOH) | | 69.55 | 9.55 | 9.59 | | | |
| IIId | 200-203 | $C_{13}H_{20}N_2O_2$ | 66.07 | 8.53 | 11.86 | 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 |
| | (Isopropyl ether) | | 65.92 | 8.56 | 11.73 | | | |
| IVa | 167-168 | $C_{24}H_{16}N_2O$ | 82.74 | 4.63 | 8.04 | ------- | 7.28-7.34 (7H, m), 7.44-7.54 (7H, m), 7.99 (2H, m) | 348 |
| | ($H_2O$-MeOH) | | 82.58 | 4.67 | 7.93 | | | |
| IVb | 155-156 | $C_{14}H_{12}N_2O$ | 74.98 | 5.39 | 12.49 | ------- | 2.63 (3H, s), 2.65 (3H, s), 7.14 (1H, s), 7.43-7.53 (3H, m), 7.90 (2H, m) | 224 |
| | ($^i$PrOH) | | 75.00 | 5.39 | 12.59 | | | |
| V | 223-224 | $C_{20}H_{24}N_2O$ | 77.88 | 7.84 | 9.08 | 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 |
| | (AcOEt) | | 77.76 | 7.87 | 9.07 | | | |

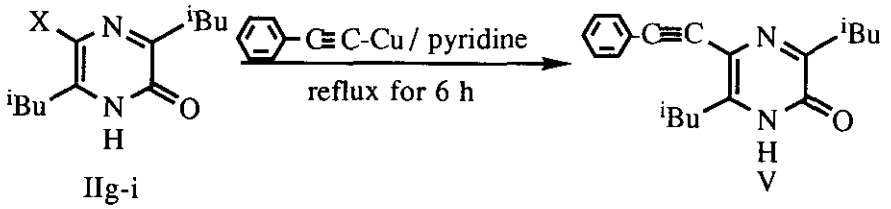
**Table IV.** Reaction of 5,6-Disubstituted 3-Halo-2-hydroxypyrazines (**IIm-o, IIu**) with Cuprous Phenylacetylide




IIm-o, IIu IVa, IVb

| 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




IIg-i V

| 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. $^1$H-Nmr spectral data were obtained using a Varian Gemini-300 or a Brucker AM-400 in $CDCl_3$ 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. $^{n}$BuLi: General Procedure.

To a dry THF solution (5 ml) of 1.6 M $^{n}$BuLi 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. $NH_4Cl$ (5 ml) was added, and then the pH was adjusted to 6-7 by adding 5 % HCl. The reaction mixture was diluted with $Et_2O$ (30 ml), and separated. The aqueous layer was extracted with $Et_2O$ (20 ml x 2). The organic layer was combined, washed with sat. aq. NaCl (20 ml x 3) and dried over $Na_2SO_4$. 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 (**IIm-o and u**) and 5-Halo-2-hydroxy-3,6-diisobutylpyrazine (**IIg-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).

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