Studies on Pyrazines. 35 [1]. An Improved Synthesis of Bromopyrazines from Hydroxypyrazines

Nobuhiro Sato* and Nobuhiko Narita

Department of Chemistry, Yokohama City University, Yokohama 236-0027, Japan

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The synthesis of bromopyrazines from hydroxypyrazines was successfully effected by the procedure *via* trimethylsilyloxypyrazines, the sequence of which proceeds under mild conditions and does not require the isolation of intermediate.

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Halogenopyrazines are versatile intermediates for synthesis of numerous pyrazine compounds, most of which are derived from chloropyrazines [2]. Thus the chlorine on a pyrazine ring is readily displaced by various nucleophiles due to the adjacent electron-withdrawing ring nitrogen, while it survives exposure to organolithium reagents leading instead to *ortho*-lithiation [3]. In contrast, 2-bromopyridine undergoes lithium-halogen exchange with butyllithium to form 2-lithiopyridine in excellent yield [4]. Accordingly, bromopyrazines would be similarly lithiated to afford lithiopyrazines, which are expected to provide a useful building block for the construction of naturally occurring pyrazine-included materials. Many bromopyrazines has been prepared by heating hydroxypyrazines, or rather tautomeric 2(1*H*)-pyrazinone, in phosphorus tribromide or phosphorus oxybromide [5], in which the reaction conditions were carefully modified depending on the substrate. In this paper we report a more convenient method for that conversion which is promoted through the intermediate of trimethylsilyloxypyrazines.

Treatment of hydroxypyrazine **1a** with refluxing hexamethyldisilazane in the presence of chlorotrimethylsilane for 30 minutes gave trimethylsilyloxypyrazine **2a**. Two doublets in the ^{1}H nmr spectrum of the crude product **2a** appear at δ 8.21 and 8.49 with the coupling constant of 1.3 Hz, whose values, particularly the latter, are characteristic of 2,5-disubstituted pyrazines [6]. Without purification, the key intermediate **2a** was heated in phosphorus tribromide for 1 hour to produce bromopyrazine **3a** in 77% overall yield. In the same fashion, bromopyrazines **3** were synthesized from the corresponding hydroxypyrazines, and the results are summarized in Table 1. An exception is 2-bromo-5-methyl-3-phenylpyrazine (**3f**), which somehow cannot be formed under identical conditions and 62% of the starting material was recovered. It is noteworthy that the reaction time of bromination to **3g** was drastically shortened by the current procedure, together with substantial increase in the yield, compared to that of the direct transformation [5].

Table 1

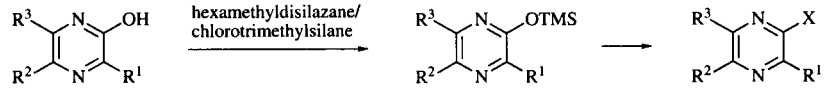
Bromination of Hydroxypyrazines

Starting material	Temperature (°) [1]	Time (hour)	Product	Yield (%)
1a	150	1	**3a**	77
1b	170	3	**3b**	81
1c	170	1	**3c**	68
1d	150	2	**3d**	74
1e	150	1	**3e**	62
1f	150	2	**3f**	0 [2]
1g	150	2	**3g**	77

[1] Internal temperature. [2] A 62% of the starting material was recovered.

We next engaged in the application of the existing methodology to the other halogenation. Attempted chlorination of trimethylsilyloxypyrazines **2a** and **2c** with refluxing phosphorus oxychloride did not provide any of the desired chloropyrazines **4**. When intermediates **2** were treated in phosphorus pentachloride at 200° for 1 hour, chloropyrazines **4a-d** and **4g** were successfully obtained in good yields as shown in Table 2. However, the present procedure suffers from overchlorination, *e.g.*, dichloropyrazines **5** and **6** were obtained from **1a**, together with main product of **4a**.

Scheme 1



1a-g **2a-g** **3** X = Br, **4** X = Cl, **12** X = I

	R^1	R^2	R^3		R^1	R^2	R^3
a	H	Ph	H	**e**	Me	Ph	H
b	Ph	H	H	**f**	Ph	Me	H
c	H	Ph	Ph	**g**	Ph	Ph	Ph
d	Ph	Ph	H				

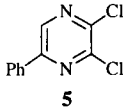
Table 2

Chlorination of Hydroxypyrazines [1]

Starting material	Product	Yield (%)
1a	**4a**	46
	5	10
	6	4
1b	**4b**	65
1c	**4c**	69
1d	**4d**	66
1e	**7**	32
	8	8
1f	**9**	31
	10	26
1g	**4g**	94

[1] Under reaction conditions at 200 ° (bath temperature) for 1 hour.

In the case of methyl substituted hydroxypyrazines **1e** and **1f**, chlorination occurs not merely on the pyrazine ring but on the methyl side chain to furnish chloromethyl chloropyrazines **7-10**. In terms of the multisubstitution, this chlorination method seems to be restricted however it may still be useful for the synthesis of chloropyrazines.



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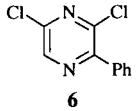

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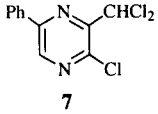

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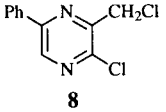

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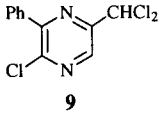

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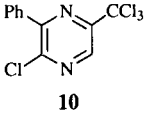

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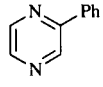
Iodopyrazines are an attractive class of compounds because of their high reactivity, though only several halides have been synthesized by halogen exchange of chloropyrazines with sodium iodide and hydriodic acid [7]. Incidentally, an attempt to convert hydroxypyrazines into iodopyrazines by treating with phosphorus triiodide failed [7]. By analogy with the above halogenation, intermediate **2a** was heated with phosphorus triiodide at 170° for 1 hour. This reaction did not lead to iodopyrazine but to a 36% yield of 2-phenylpyrazine (**11**). This outcome is not surprising because the halogenating reagent is often used for deoxygenation [8]. Under controlled conditions using 5 equivalents of phosphorus triiodide in refluxing 1,1,2-trichloroethane, iodopyrazines **12a** and **12c** were obtained in 15 and 22% yields, respectively. Apparently, this iodination method is of little practical value because of low yields, prolonged reaction time and the somewhat unstable phosphorus triiodide, but it appears to play a potential role in the preparation of iodopyrazines. A number of attempts, *e.g.*, iodine-triphenylphosphine-imidazole, iodotrimethylsilane or potassium iodide-crown ether, were unsuccessful in effecting the iodination of trimethylsilyloxypyrazines **2**.



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In conclusion, it is suggested that the proposed method is peculiarly efficient for bromination of hydroxypyrazines, furthermore, this procedure is more facile compared with our previous preparation of bromopyrazines, in which chloropyrazines are heated with phosphorus tribromide in a sealed vessel at temperatures above 200 ° [9]. Finally, an attempted conversion of 2,3-dihydroxy-5,6-dimethylpyrazine into the dibromopyrazine failed because the disilyloxypyrazine intermediate was not formed.

EXPERIMENTAL

All melting points were determined using a Büchi 535 apparatus and are uncorrected. The nmr spectra were obtained with JEOL JNM EX270 instrument with solutions in deuteriochloroform containing tetramethylsilane as the internal standard.

General Procedure for the Bromination of Hydroxypyrazines **1**.

Trimethylsilyloxypyrazine **2** was prepared by the procedure of Vorbrüggen and Streklke for the trimethylsilylation of 2-thiouracil [10]. Hydroxypyrazine **1** (10 mmoles) was placed under argon, and hexamethyldisilazane (25 ml, 0.12 mole) and chlorotrimethylsilane (0.38 ml, 3 mmoles) were added *via* a syringe. The mixture was stirred and refluxed for 30 minutes and then concentrated *in vacuo*. Phosphorus tribromide (20 ml) was added to the residual oil, and the mixture was stirred under the conditions given in Table 1. After being cooled, the mixture was poured onto crushed ice. The solution was made basic with sodium hydrogencarbonate, extracted with ethyl acetate (3 x 30 ml). The extract was then washed with water, dried over magnesium sulfate and concentrated. Extraction of the residue with hot hexane followed by sublimation *in vacuo* gave bromopyrazine **3**.

2-Bromo-5-phenylpyrazine (**3a**).

This compound was obtained as colorless needles, mp 107.5-108° (from ethanol); ^{1}H nmr: 7.52 (3H, m), 7.98 (2H, m), 8.73 (1H, d, J = 1.3 Hz), 8.78 (1H, d, J = 1.7 Hz); ^{13}C nmr: 126.8, 129.2, 130.3, 135.1, 139.0, 141.7, 146.8, 151.3.

Anal. Calcd. for $C_{10}H_7N_2Br$: C, 51.09; H, 3.00; N, 11.92. Found: C, 51.51; H, 2.93; N, 11.82.

2-Bromo-3-phenylpyrazine (**3b**).

This compound was obtained as colorless needles, mp 89-91° (from ethanol) (lit [5] mp 90-91°); ^{1}H nmr: 7.49 (3H, m), 7.76 (2H, m), 8.32 (1H, d, J = 2.3 Hz), 8.60 (1H, d, J = 2.3 Hz); ^{13}C nmr: 128.1, 129.3, 129.5, 137.2, 140.0, 142.3, 142.4, 155.5.

2-Bromo-5,6-diphenylpyrazine (**3c**).

This compound was obtained as colorless tiny needles, mp 149-150° (from ethanol) (lit [5] mp 149-150°); ^{1}H nmr: 7.32 (6H, m), 7.43 (4H, m), 8.68 (1H, s); ^{13}C nmr: 128.28, 128.34, 128.9, 129.2, 129.5, 129.7, 137.0, 137.4, 137.7, 144.3, 150.9, 153.0.

2-Bromo-3,5-diphenylpyrazine (**3d**).

This compound was obtained as colorless needles, mp 130.5-131.5° (from ethanol); ^{1}H nmr: 7.51 (6H, m), 7.86 (2H, m), 8.07 (2H, m), 8.73 (1H, s); ^{13}C nmr: 126.4, 127.6, 128.6, 129.0, 129.1, 129.7, 134.6, 136.9, 137.1, 138.7, 150.0, 153.5.

Anal. Calcd. for $C_{16}H_{11}N_2Br$: C, 61.76; H, 3.56; N, 9.00. Found: C, 61.34; H, 3.42; N, 8.90.

2-Bromo-3-methyl-5-phenylpyrazine (**3e**).

This compound was obtained as colorless needles, mp 86.5-87° (from ethanol); ^{1}H nmr: 2.75 (3H, s), 7.50 (3H, s), 7.98 (2H, m), 8.58 (1H, m); ^{13}C nmr: 23.6, 126.3, 128.5, 129.5, 134.8, 138.2, 139.4, 150.0, 153.6.

Anal. Calcd. for $C_{11}H_9N_2Br$: C, 53.04; H, 3.64; N, 11.25. Found: C, 52.64; H, 3.54; N, 11.10.

2-Bromo-3,5,6-triphenylpyrazine (**3g**).

This compound was obtained as pale yellow needles, mp 179.5-180° (from ethanol) (lit [5] mp 178-180°); ^{1}H nmr: 7.30 (6H, m), 7.52 (7H, m), 7.91 (2H, m); ^{13}C nmr: 128.1, 128.30, 128.34, 128.9, 129.1, 129.5, 129.68, 129.72, 135.7, 136.9, 137.1, 137.4, 149.9, 150.3, 151.4.

General Procedure for the Chlorination of Hydroxypyrazines **1**.

A mixture of silylether **2**, which was prepared from hydroxypyrazine (1.0 mmole) by the above procedure, and phosphorus pentachlolide (4.5 g, 21 mmoles) was stirred and heated at 200° (bath temperature), and then worked up as described above. Separation and purification of compounds **5-10** were carried out by preparative hplc using 10 μm silica gel (2.2 x 30 cm) eluted with hexane-ethyl acetate.

2-Chloro-5-phenylpyrazine (**4a**).

This compound was obtained as colorless needles, mp 97-98° (from ethanol) (lit [11] mp 98.5-99°); ^{1}H nmr: 7.50 (3H, m), 7.97 (2H, m), 8.62 (1H, d, J = 1.7 Hz), 8.77 (1H, d, J = 1.7 Hz); ^{13}C nmr: 126.3, 128.6, 129.6, 134.6, 140.3, 143.3, 147.0, 150.4.

2-Chloro-3-phenylpyrazine (**4b**).

This compound was obtained as tiny colorless needles, mp 66° (from ethanol) (lit [12] mp 66-67°); ^{1}H nmr: 7.50 (3H, m), 7.80 (2H, m), 8.35 (1H, d, J = 2.6 Hz), 8.59 (1H, d, J = 2.6 Hz); ^{13}C nmr: 128.2, 129.3, 129.6, 136.1, 141.9, 142.2, 147.5, 153.4.

2-Chloro-5,6-diphenylpyrazine (**4c**).

This compound was obtained as tiny colorless needles, mp 119-120° (from ethanol) (lit [13] mp 126-127°); ^{1}H nmr: 7.32 (6H, m), 7.43 (4H, m), 8.60 (1H, s); ^{13}C nmr: 127.8, 127.9, 128.4, 128.7, 129.1, 129.2, 136.6, 137.0, 141.0, 145.9, 150.2, 151.7.

2-Chloro-3,5-diphenylpyrazine (**4d**).

This compound was obtained as tiny pale needles, mp 108-109° (from ethanol) (lit [11] mp 108-109°); ^{1}H nmr: 7.52 (6H, m), 7.91 (2H, m), 8.08 (2H, m), 8.76 (1H, s); ^{13}C nmr: 126.9, 128.4, 129.3, 129. 6, 130.1, 135.1, 136.4, 138.7, 145.2, 150.3, 151.8.

2,3-Dichloro-5-phenylpyrazine (**5**).

This compound was obtained as tiny colorless needles, mp 105° (from ethanol) (lit [14] mp 106-107°); ^{1}H nmr: 7.51 (3H, m), 7.99 (2H, m), 8.71 (1H, s); ^{13}C nmr: 126.9, 129.1, 130.7, 133.6, 138.3, 145.2, 146.7, 150.7.

2,6-Dichloro-3-phenylpyrazine (**6**).

This compound was obtained as tiny colorless needles, mp 56° (from hexane) (lit [9] mp 57-58°); ^{1}H nmr: 7.50 (3H, m), 7.79 (2H, m), 8.60 (1H, s); ^{13}C nmr: 128.3, 129.3, 129.9, 135.0, 141.9, 145.2, 145.4, 151.2.

2-Chloro-3-dichloromethyl-5-phenylpyrazine (**7**).

This compound was obtained as tiny colorless needles, mp 95-96° (from hexane); ^{1}H nmr: 7.15 (1H, s), 7.50 (3H, m), 8.05 (2H, m), 8.78 (1H, s); ^{13}C nmr: 67.4, 127.0, 129.2, 130.7, 134.1, 141.7, 143.0, 148.4, 150.9.

Anal. Calcd. for $C_{11}H_7N_2Cl_3$: C, 48.30; H, 2.58; N, 10.24. Found: C, 48.20; H, 2.47; N, 10.14.

2-Chloro-3-chloromethyl-5-phenylpyrazine (**8**).

This compound was obtained as tiny colorless needles, mp 131.5-133° (from hexane); ^{1}H nmr: 4.86 (2H, s), 7.52 (3H, m), 8.02 (2H, m), 8.76 (1H, s); ^{13}C nmr: 43.8, 127.0, 129.2, 130.4, 134.6, 140.6, 146.6, 149.4, 150.8.

Anal. Calcd. for $C_{11}H_8N_2Cl_2$: C, 55.26; H, 3.37; N, 11.72. Found: C, 54.83; H, 3.26; N, 11.51.

2-Chloro-5-dichloromethyl-3-phenylpyrazine (**9**).

This compound was obtained as tiny colorless needles, mp 92.5-93.5° (from hexane); ^{1}H nmr: 6.79 (1H, s), 7.50 (3H, m), 7.83 (2H, m), 8.78 (1H, s); ^{13}C nmr: 68.5, 128.3, 129.5, 130.1, 135.1, 140.2, 147.5, 151.1, 151.4.

Anal. Calcd. for $C_{11}H_7N_2Cl_3$: C, 48.30; H, 2.58; N, 10.24. Found: C, 48.01; H, 2.45; N, 10.02.

2-Chloro-5-trichloromethyl-3-phenylpyrazine (**10**).

This compound was obtained as tiny colorless needles, mp 63-64.5° (from hexane); ^{1}H nmr: 7.53 (3H, m), 7.93 (2H, m), 8.98 (1H, s); ^{13}C nmr: 94.3, 128.4, 129.8, 130.4, 134.8, 137.8, 147.8, 151.2, 151.9.

Anal. Calcd. for $C_{11}H_6N_2Cl_4$: C, 42.90; H, 1.96; N, 9.10. Found: C, 43.08; H, 1.90; N, 9.00.

2-Chloro-3,5,6-triphenylpyrazine (**4g**).

This compound was obtained as tiny colorless needles, mp 187.5-188° (from ethanol); ^{1}H nmr: 7.31 (6H, m), 7.52 (7H, m), 7.96 (2H, m); ^{13}C nmr: 128.16, 128.24, 128.3, 128.9, 129.1, 129.5, 129.6, 129.7, 129.8, 136.1, 136.9, 137.5, 143.6, 149.3, 149.77, 149.84.

Anal. Calcd. for $C_{22}H_{15}N_2Cl$: C, 77.08; H, 4.41; N, 8.17. Found: C, 77.32; H, 4.46; N, 7.90.

General Procedure for the Iodination of Hydroxypyrazines **1**.

A mixture of silylether **2**, which was prepared from hydroxypyrazine (1.0 mmole) by the above procedure, phosphorus triiodide (2.0 g, 5 mmoles) and 1,1,2-trichloroethane (10 ml) was stirred under reflux for 24 hours, and then worked up as described above.

2-Iodo-5-phenylpyrazine (**12a**).

This compound was obtained in 15% yield and recrystallized from ethanol to give tiny colorless needles, mp 120.5-121°; ^{1}H nmr: 7.51 (3H, m), 7.98 (2H, m), 8.80 (1H, d), 8.87 (1H, d); ^{13}C nmr: 115.6, 126.7, 129.1, 130.3, 135.1, 142.9, 151.3, 152.1.

Anal. Calcd. for $C_{10}H_7N_2I$: C, 42.58; H, 2.50; N, 9.93. Found: C, 42.64; H, 2.40; N, 9.77.

2-Iodo-5,6-diphenylpyrazine (**12c**).

This compound was obtained in 22% yield and recrystallized from ethanol to give tiny colorless needles, mp 151-152° (lit [7] mp 141-142°); ^{1}H nmr: 7.29 (6H, m), 7.43 (4H, m), 8.82 (1H, s); ^{13}C nmr: 114.6, 128.27, 128.34, 128.9, 129.1, 129.4, 129.7, 137.2, 137.4, 149.7, 151.0, 154.1.

Anal. Calcd. for $C_{16}H_{11}N_2$ I: C, 53.65; H, 3.10; N, 7.82. Found: C, 53.62; H, 3.03; N, 7.67.

2-Phenylpyrazine (**11**).

This compound was obtained from hydroxypyrazine **1a** with phosphorus triiodide, which was recrystallized from ethanol to give colorless needles, mp 70-72° (lit [15] mp 72-73°); ^{1}H nmr: 7.53 (3H, m), 8.02 (2H, m), 8.52 (1H, d, J = 1.7 Hz), 8.64 (1H, dd, J = 1.7, 2.6 Hz), 9.04 (1H, d, J = 2.6 Hz); ^{13}C nmr: 126.8, 128.9, 129.8, 136.2, 142.1, 142.8, 144.0, 152.7.

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