Studies on Pyrazines, 8 (1). An Improved Syntheses of 2-Amino-3,5-dibromo- and 2-Amino-5-bromopyrazines

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The titled dibromopyrazine (**2**) was prepared in 54% yield by the modified procedure for bromination of 2-aminopyrazine (**1**) using bromine and pyridine in chloroform solution. Similarly, 2-amino-5-bromopyrazine (**3**) was directly prepared in 36% yield by bromination using 1.2 equivalents of the above reagents.

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2-Amino-3,5-dibromopyrazine (**2**) is important as an intermediate for the synthesis of antibacterial 3- and 5-methoxy-2-sulfanilamidopyrazines (2-4). The established method for the synthesis of this dibromopyrazine involves treatment of 2-aminopyrazine (**1**) in acetic acid with bromine in the presence of sodium acetate as an acceptor for hydrogen bromide, and gives only 13.6% yield of **2** (2). Therefore, a convenient method of effecting the bromination is desirable. In this connection, we previously reported (5) that 2-amino-6-methylpyrazine was converted into the corresponding 3,5-dibromopyrazine in 91% yield by bromination using pyridine and chloroform instead of sodium acetate and acetic acid, respectively. We have now found that this method for the bromination is also effective on the conversion of **1** into **2** improving the yield to 54%.

Scheme I

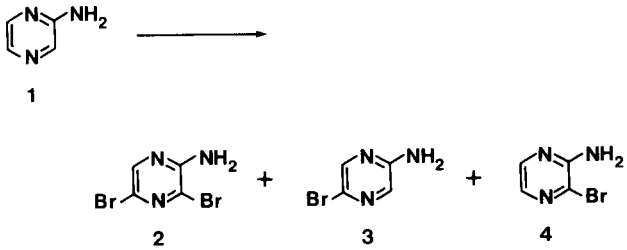

Table I

Bromination of 2-Aminopyrazine (**1**)

Equivalents of Bromine and Pyridine	Products (yield, %) 2	3	4
1.1	7	35	0.5
1.2	10	36	≈0
1.3	13	31	≈0
2.1	54	0	0

The bromination of **1** into **2** was carried out in the dark using 2.1 equivalents of bromine and pyridine in chloroform solution. The reaction proceeded easily at ambient temperatures between 35-38° (6), whereas at temperatures below 5° a prolonged reaction time was required to complete the transformation into **2**.

The earlier work in our laboratory (5) had also shown that the bromination at the para position to the amino substituent preferred to that at ortho position, *i.e.*, at the initial stage of bromination 2-amino-6-methylpyrazine was converted only into the corresponding 5-bromopyrazine. In the present work, this finding was successfully applied to synthesis of 2-amino-5-bromopyrazine (**3**). The optimum yield of **3** (36%) was obtained on using 1.2 equivalents of the reagents (see Table I). Under the above conditions, the 3-bromo- (**4**) and 3,5-dibromopyrazine (**2**) were also formed as the minor products, but the desired product **3** was easily isolated by silica gel chromatography. The monobromopyrazine **3** has been prepared by a four-step sequence of reactions starting from 3-aminopyrazinecarboxylic acid in 45% overall yield (7). Therefore, the controlled bromination of **1** is a more practical method for the preparation of **3**. Similarly, the direct one-step transformation into 2-amino-5-chloropyrazine (**5**) was achieved by treatment of **1** with chlorine (26% yield). Our procedure was limited, however, to the above two halogenations since an attempt for iodination of **1** in the same manner proved unsuccessful.

EXPERIMENTAL

All melting points were determined in capillary tubes and are uncorrected. Nmr spectra were recorded on a JEOL JNM-MH-100 instrument with tetramethylsilane as an internal standard, and mass spectra on a Hitachi M-70 instrument at 20 eV.

2-Amino-3,5-dibromopyrazine (**2**).

A solution of bromine (16.80 g, 0.105 mole) in 100 ml of chloroform was added at room temperature in the dark to a stirred solution of 2-aminopyrazine (**1**) (4.757 g, 0.050 mole) and pyridine (8.340 g, 0.105 mole) in 400 ml of the same solvent over a period of 1 hour. The mixture was further stirred for 30 minutes, and water (50 ml) was added to the mixture. After vigorous stirring for 10 minutes, the organic layer was separated, washed with water (50 ml), and dried over magnesium sulfate. After evaporation *in vacuo*, the residue was dissolved in benzene, and the solution was passed through a column of Florisil (25 g). Evaporation of the elute gave 6.865 g (54%) of **2**, mp 113-114° [lit (2) mp 114°]. An analytical sample was obtained by sublimation at 80° (0.1 mm) and recrystallization from cyclohexane as colorless needles without any change in the melting point; nmr (DMSO-d_6): δ 6.94 (s, NH_2, 2H), 8.16 (s, aromatic, 1H); ms: 255 (48), 253 (100), 251 (M^+, 46), 174 (29), 172 (28), 147 (14), 145 (13).

Anal. Calcd. for $C_4H_3Br_2N_3$: C, 18.99; H, 1.20; N, 16.61. Found: C, 18.98; H, 1.19; N, 16.63.

2-Amino-5-bromopyrazine (**3**).

A solution of bromine (19.20 g, 0.12 mole) in 200 ml of chloroform was added over a period of 2.5 hours to a stirred solution of **1** (9.511 g, 0.10 mole) in pyridine (9.52 g, 0.12 mole) in 800 ml of chloroform. Procedure for the addition and successive work-up were followed in the predescribed manner. Isolation of **3** from the reaction mixture was carried out by chromatography on silica gel (100 g). The chromatogram was developed first with benzene to afford 2.581 g (10%) of **2** and subsequently a trace of a mixture of 2-amino-3-bromopyrazine (**4**) and **3**. Further elution with ethyl acetate gave 7.26 g (42%) of **3**, which was sublimed at 80° (0.1 mm); the yield was 6.248 g (36%), mp 113-114° [lit (7) mp 113.6°]. An analytical sample was obtained by recrystallization from cyclohexane as colorless needles without any change in the melting point; nmr (DMSO-d_6): δ 6.63 (s, NH_2, 2H), 7.74 and 8.06 (2 doublets, aromatic, 2H, J = 1.3 Hz); ms: 175 (100), 173 (M^+, 98), 148 (52), 146 (52).

Anal. Calcd. for $C_4H_4BrN_3$: C, 27.61; H, 2.32; N, 24.15. Found: C, 27.86; H, 2.32; N, 23.94.

By the same method except with the use of chlorine, 2-amino-5-chloropyrazine (**5**) was obtained in 26% yield, mp 132-134° [lit. (8) mp 130°]; nmr (DMSO-d_6): δ 6.60 (s, NH_2, 2H), 7.71 and 8.00 (2 doublets, aromatic, 2H, J = 1.3 Hz); ms: 131 (33), 129 (M^+, 100), 104 (28), 102 (90).

Anal. Calcd. for $C_4H_4ClN_3$: C, 37.08; H, 3.11; N, 32.44. Found: C, 37.34; H, 3.10; N, 32.28.

2-Amino-5-halopyrazines which were obtained above were identified by comparison with ir and nmr spectra of the corresponding authentic samples which were prepared by the established procedures (7,9). The coupling constant of 1.3 Hz which is observed in nmr spectra of both **3** and **5** is characteristic for the 3,6 ring protons in pyrazine series (8,10).

REFERENCES AND NOTES

(1) For the previous paper in this series, see: N. Sato, submitted to *J. Heterocyclic Chem.*, **19**, 407 (1982).

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(3) British Patent 958,626 (1964); *Chem. Abstr.*, **61**, 5668 (1964).

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(5) N. Sato, *J. Heterocyclic Chem.*, **17**, 143 (1980).

(6) The bromination was initially carried out at room temperature but the temperature of reaction mixture became 7-10° higher than room temperature because of the exothermal reaction.

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