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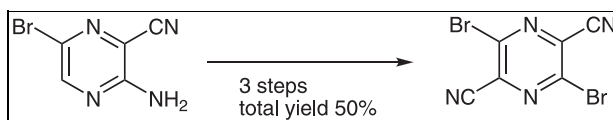
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Symmetrically functionalized pyrazine of 3,6-dibromopyrazine-2,5-dicarbonitrile was synthesized in three or four steps from 3-aminopyrazinecarbonitrile or its 6-bromo derivatives.

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## INTRODUCTION

A number of fully substituted pyrazines have received significant attention due to their optical properties. As an intermediate in synthesis of such molecules, symmetrically functionalized pyrazines, for example, 3,6-diaminopyrazine-2,5-dicarbonitrile [2], *N,N'*-di(*t*-butoxycarbonyl)-2,5-bis(tri-*n*-butylstannyl)-3,6-diaminopyrazine, 2,5-diiodo-3,6-dicarbonylpyrazine [3], 2,5-dibromo-3,6-dichloropyrazine, and 3,6-dichloropyrazine-2,5-dicarbonitrile [4], have been used. These highly functionalized compounds, with the exception of the first one, have been conducted by multistep sequence starting from less substituted pyrazines, and the synthetic approaches are of great interest. In other words, synthesis of pyrazines having two same functionalities at the 2 and 5 carbons, including their 3,6-disubstituted derivatives, has been known to be considerably daunting project compared with that of the other 2,3- and 2,6-isomers [5]. We now report synthetic pathway toward 3,6-dibromopyrazine-2,5-dicarbonitrile (**1**) which would be expected as a versatile precursor for synthesis of other highly functionalized pyrazines.

## RESULTS AND DISCUSSION

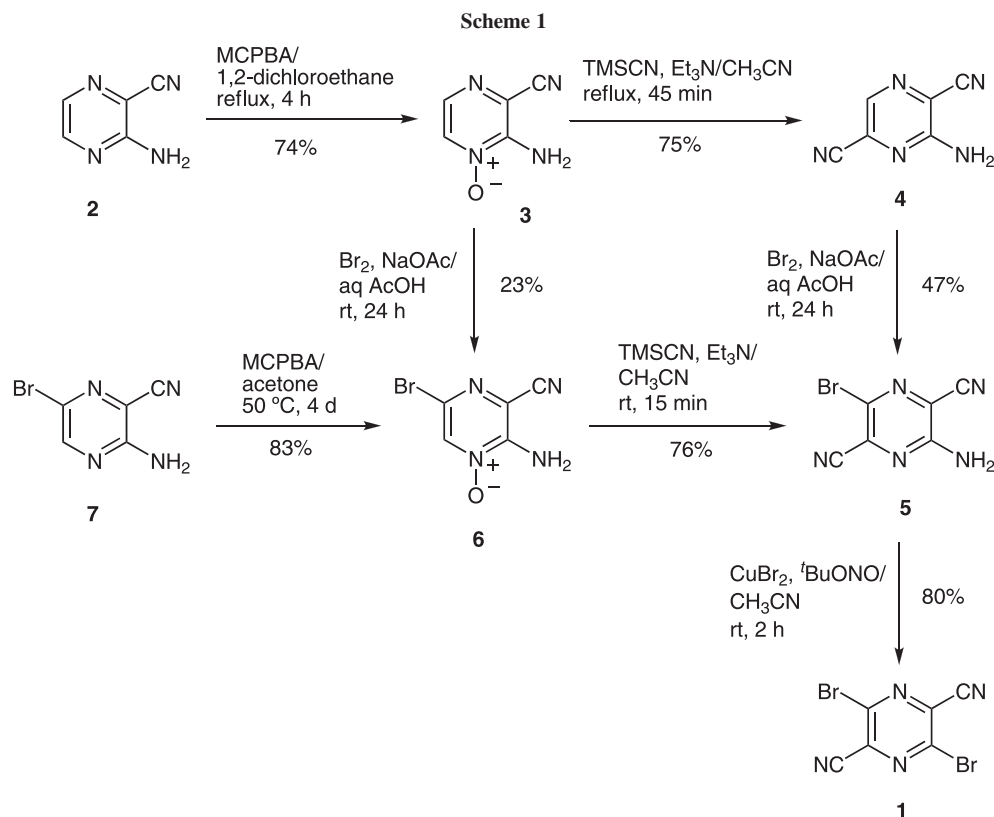
The synthesis of **1** began with *N*-oxidation of 3-aminopyrazinecarbonitrile (**2**), which has been readily prepared by deoxidative cyanation of 3-aminopyrazine 1-oxide with trimethylsilyl cyanide [6]. Thus, the *N*-oxide **3** was obtained by treatment of **2** with 3-chloroperbenzoic acid (Scheme 1) and has been also prepared by condensation of aminomalononitrile with glyoxal and acetone oxime [7], albeit in low yield. Deoxidative cyanation

of **3** to dicarbonitrile **4** should be prompted by electron-withdrawing effect of the existing cyano group because it involves nucleophilic attack of cyanide ion on the para carbon. In contrast, electrophilic bromination of **4** was impeded by those cyano substituents, and purification of the desired product **5** from unreacted precursor **4** is somewhat formidable. The inverse reaction sequence *via* bromopyrazine *N*-oxide **6** was still suffered by far lower yield of **6**. However, synthesis of *N*-oxide **6** was efficiently achieved by oxidation of **7** with 3-chloroperbenzoic acid in 83% yield. Reaction of **6** with trimethylsilyl cyanide proceeded smoothly at room temperature to give a 76% yield of the product **5**, when the starting material **6** was completely consumed within 10 min. Nitrosation of **5** followed by bromination was realized by treating with *t*-butyl nitrite and copper(II) bromide in acetonitrile at room temperature to give an 80% yield of **1**. The IR spectrum for **1** has several prominent bands because of symmetrical molecule, and the <sup>13</sup>C-NMR obviously shows three carbons.

## EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum One. NMR spectra were obtained with a Bruker Avance 600 (600 MHz <sup>1</sup>H, 150.9 MHz <sup>13</sup>C) instrument using tetramethylsilane as internal standard.

**2-Amino-3-cyanopyrazine 1-oxide (3).** To a stirred mixture of **2** (0.500 g, 4.16 mmol) in 1,2-dichloroethane (35 mL), 3-chloroperbenzoic acid (70%, 1.99 g, 8.08 mmol) was added portionwise, and the resulting mixture was refluxed for 4 h. The hot mixture was filtered, and the insoluble matter was



washed with 1,2-dichloroethane. The filtrate and washings were concentrated to dryness *in vacuo*, and the residue was recrystallized from ethanol (20 mL) containing several drops of dimethylformamide to give **3** (0.420 g, 74%) as pale yellow tiny prisms, mp 251–252°C (lit. [7] mp 251–253°C).

IR (potassium bromide): 3355, 2245 (C≡N), 1629, 1313, 1200, 869  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  7.86 (d,  $J = 3.8$  Hz, 1H, H-5), 7.98 (s, 2H, NH<sub>2</sub>), 8.48 (d,  $J = 3.8$  Hz, 1H, H-6).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  112.0 (C-3), 114.9 (C≡N), 134.0 (C-6), 134.3 (C-5), 150.8 (C-2).

**3-Aminopyrazine-2,5-dicarbonitrile (4).** A mixture of **3** (0.600 g, 4.4 mmol) in anhydrous acetonitrile (30 mL) containing freshly distilled triethylamine (3.0 mL) was placed under argon, and trimethylsilyl cyanide (2.6 mL, 21 mmol) was added dropwise *via* a syringe. The mixture was refluxed with stirring for 45 min and then cooled to room temperature. The solvents were removed *in vacuo*, and the residue was purified by chromatography on silica gel (30 g) using hexane-ethyl acetate (3:1) as eluent to afford dicyanitrile **4** (0.481 g, 75%). The analytical sample was obtained by recrystallization from benzene as yellow tiny needles, mp 216–216.5°C.

IR (potassium bromide): 3383, 3180, 2237 (C≡N), 1647, 1530, 1439, 1212  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  7.93 (s, 2H, NH<sub>2</sub>), 8.38 (s, 1H, H-6);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  114.7 (C-2), 115.4 (C≡N), 115.9 (C≡N), 130.2 (C-5), 135.5 (C-6), 155.8 (C-3). Anal. Calcd. for C<sub>6</sub>H<sub>3</sub>N<sub>5</sub>: C, 49.66; H, 2.08; N, 48.26. Found: C, 49.94; H, 2.08; N, 48.08.

**3-Amino-6-bromopyrazine-2,5-dicarbonitrile (5).** From pyrazinedicarbonitrile **4**. A solution of Br<sub>2</sub> (0.54 mL, 11 mmol) in acetic acid (1.0 mL) was added to a stirred mixture of **4**

(0.800 g, 5.5 mmol) in wet acetic acid (acetic acid 10 mL and water 1.0 mL) containing sodium acetate (1.3 g) in the dark, and the mixture was stirred at room temperature for 24 h. Ice water (50 mL) was added to quench the reaction, and the mixture was extracted with ether (4 × 30 mL). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate followed by water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give powder (0.712 g), which was recrystallized from hexane (100 mL) containing several drops of 2-propanol to yield yellow prisms (0.580 g, 47%); mp > 280°C.

IR (potassium bromide): 3466, 3353, 2234 (C≡N), 1627, 1544, 1386, 1214  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  8.09 (s, 2H, NH<sub>2</sub>);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  113.9 (C-2), 114.6 (C≡N), 114.7 (C≡N), 124.1 (C-6), 132.5 (C-5), 154.9 (C-3); Anal. Calcd. for C<sub>6</sub>H<sub>2</sub>N<sub>5</sub>Br: C, 32.17; H, 0.90; N, 31.26. Found: C, 32.41; H, 0.87; N, 31.14.

From *N*-oxide **6**: A solution of **6** (0.432 g, 2.0 mmol) in anhydrous acetonitrile (24 mL) containing distilled triethylamine (1.4 mL, 10 mmol) was placed in argon, and trimethylsilyl cyanide (0.96 mL, 7.7 mmol) was added dropwise. The mixture was stirred at room temperature for 15 min, and then ethanol (1 mL) was added. After stirring for 15 min, the mixture was concentrated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel (20 g) using hexane-ethyl acetate (3:1) to afford **5** (0.343 g, 76%).

**2-Amino-5-bromo-3-cyanopyrazine 1-oxide (6).** From *N*-oxide **3**: A solution of Br<sub>2</sub> (0.04 mL, 0.78 mol) in acetic acid (0.2 mL) was added to a stirred mixture of **3** (0.068 g, 0.50 mmol) in wet acetic acid (acetic acid 0.9 mL and water 0.08 mL) containing

sodium acetate (0.123 g) in the dark, and the mixture was stirred at room temperature for 24 h. Ice water (30 mL) was added, and the mixture was extracted with dichloromethane ( $8 \times 10$  mL). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate followed by water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (16 g) using with hexane-ethyl acetate (2:1) to give **6** (0.025 g, 23%). Further elution gave the starting material **3** (14 mg, 21%). The analytical sample of **6** was prepared by recrystallization from 2-propanol to give yellow tiny needles, mp 216°C.

IR (potassium bromide): 3291, 2235 (C $\equiv$ N), 1643, 1463, 1312, 1192, 1117, 890  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  8.15 (s, 2H, NH $_2$ ), 8.87 (s, 1H, H-6);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  109.7 (C-3), 114.2 (C $\equiv$ N), 122.2 (C-5), 135.7 (C-6), 150.9 (C-2). Anal. Calcd. for C $_5$ H $_3$ N $_4$ OBr: C, 27.93; H, 1.41; N, 26.15. Found: C, 28.20; H, 1.30; N, 26.13.

From 6-bromo-3-aminopyrazinecarbonitrile (**7**): A solution of **7** [8,9] (1.993 g, 10.0 mmol) and 3-chloroperbenzoic acid (70%, 3.88 g, 15.8 mmol) in acetone (100 mL) was stirred at 50°C (inner temperature), and after 24 h another portion of 3-chloroperbenzoic acid (1.94 g, 7.9 mmol) was added. The mixture was further stirred at that temperature for 3 days, and then concentrated to dryness *in vacuo*. The residue was purified by flash-chromatography on silica gel (50 g) using with hexane-ethyl acetate (3:1) to give **6** (1.783 g, 83%).

**3,6-Dibromopyrazine-2,5-dicarbonitrile (1).** Conversion of **5** to **1** was carried out according to the procedure of Doyle et al. [10]. A solution of **5** (0.448 g, 2.0 mmol) in anhydrous acetonitrile (4 mL) was added to a stirred mixture of CuBr $_2$  (0.670 g, 3.0 mmol) and *t*-BuONO (0.57 mL, 4.8 mmol) in anhydrous acetonitrile (10 mL) under argon. The mixture was stirred at room temperature for 2 h and then poured into 3M hydrochloric acid (80 mL) containing sulfamic acid (0.30 g). The resulting solution was extracted with dichloromethane ( $3 \times 20$  mL), and the combined extracts were washed with brine, dried over magnesium sulfate, filtered, and

concentrated to dryness *in vacuo*. The residue was purified by short column chromatography on silica gel (20 g) using with hexane-ethyl acetate (4:1) to give **1** (0.461 g, 80%). The analytical sample was obtained by recrystallization from benzene as colorless tiny needles, mp is not determined because of sublimation on heating.

IR (potassium bromide): 2236 (C $\equiv$ N), 1366, 1295, 1165, 1101  $\text{cm}^{-1}$ ;  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  112.6 (C $\equiv$ N), 134.3 (C-2,5), 140.8 (C-3,6). Anal. Calcd. for C $_6$ N $_4$ Br $_2$ : C, 25.03; N, 19.46. Found: C, 24.57; N, 19.01.

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