Studies on Pyrazines. 16 [1]. Palladium-Catalyzed Cyanation of 2-Amino-5-bromopyrazines

Nobuhiro Sato* and Masakazu Suzuki

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

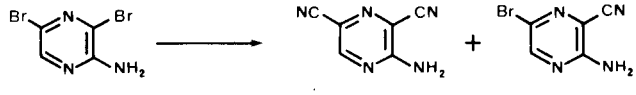
Received April 13, 1987

We report here a synthesis of 2-amino-5-cyano- **3** and 2-amino-3,5-dicyanopyrazines **4** by palladium(0)-catalyzed cyanation of the corresponding pyrazine amino bromides **1** and **2**.

J. Heterocyclic Chem., **24**, 1371 (1987).

Our continuing interest in the synthesis of 2,5-difunctional pyrazines [2,3] led us to seek a more convenient route to 2-amino-5-cyanopyrazine (**3**) as a versatile intermediate for synthesis of the otherwise inaccessible pyrazines. The amino nitrile **3** was first prepared by cyanation of 2-amino-5-bromopyrazine (**1**) with copper(I) cyanide in aqueous ethanol at 170°, which was, without isolation, hydrolyzed to afford 5-aminopyrazinecarboxylic acid in 17% yield along with a 22% yield of 5-aminopyrazinecarboxamide [4]. Since the starting material **1** was recently found to be directly prepared from commercially available 2-aminopyrazine by controlled bromination [3], we describe in this paper a more efficient cyanation procedure for **1** into the pyrazine amino nitrile **3** as well as a synthesis of 2-amino-3,5-dicyanopyrazine (**4**) in similar fashion.

1 3



2 4 6

Displacement of bromo or iodo substituent of dialkyl- or diarylpyrazines by cyano group was readily achieved by heating with copper(I) cyanide in pyridine or picoline [5,6]. However, this procedure was not effective for conversion of **1** into **3**, also the starting material **1** could not be recovered. Several improved attempts, *e.g.*, using DMF or HMPA instead of the basic solvents [7] or heating with sodium dicyanocuprate in DMF [8], also frustrated in the preparation of cyanopyrazine **3**. The inertness of **1** in the above instances was elucidated due to a strong electron-donating effect of the amino group toward the pyrazine ring resulting in suppression of nucleophilic attack of cyanide ion on the brominated carbon atom at C-5. On the other hand, displacement of the poorly reactive chloro substituent from pyrazines by the cyanide could not be satisfactorily accomplished by treating with copper(I) cyanide [5]. But these chloropyrazines were recently shown to be convertible into the cyanopyrazines in excellent yields by palladium-catalyzed cyanation [9]. Application of this procedure to synthesis of **3**, *i.e.*, treatment of **1** with potassium cyanide and tetrakis(triphenylphosphine)palladium(0) (**5**) in refluxing DMF for 2.5 hours, failed and resulted in only recovery of a 90% yield of unchanged starting material **1**. The addition of 18-crown-6 and particularly copper(I) iodide to the above reaction mixture, however, brought about successfully the replacement of the bromo substituent affording the desired cyanopyrazine **3**, yield which was optimized to 88%.

A fairly different situation from the above cyanation reactions of **1** was observed in those of 2-amino-3,5-dibromopyrazine (**2**). Thus, reaction of **2** with copper(I) cyanide in refluxing pyridine for 2 hours gave a mixture of 2-amino-3,5-dicyanopyrazine (**4**) and 2-amino-5-bromo-3-cyanopyrazine (**6**) in 9 and 28% yields, respectively. Contrary to our expectation, prolonged heating decreased both yields of **4** and **6**. The facile formation of **6** from **2** was rationalized to a much greater susceptibility of the bromo substituent *ortho* to amino group than the *para* one to nucleophiles [10]. Introduction of electron-withdrawing cyano group led the pyrazine ring to be electron-deficient resulting in the attack of second cyanide ion to form **4**. Treatment of **2** with potassium cyanide in the presence of 18-crown-6 and the palladium catalyst **5** in DMF at 110-120° afforded a 56% yield of the monocyanopyrazine **6** together with a 6% yield of 2-amino-3-cyanopyrazine (**7**) [11] and the amino bromide **1** (2%). These compounds **1** and **7** formed by debromination of the starting dibromopyrazine **2** and the pyrazine bromo nitrile **6**, respectively, with triphenylphosphine which produced with the oxidative addition of the palladium catalyst **5** to dibromopyrazine **2**, followed by hydrolysis. The preferential reductive displacement of bromine *ortho* to the amino group in **2** is closely similar to debromination of 3,5-dibromophenol with triphenylphosphine [12]. Eventually, the dicyanopyrazine **4** was also prepared by the procedure employed in synthesis of **3** from **1**. The best yield (50%) was obtained

by heating **2** with 3 equivalents of potassium cyanide and of copper(I) iodide in the presence of 3 mole % of **5** and the crown ether in DMF for 1 hour. Attempts for constructing 2,4-diaminopteridines or pterins having a C-6 substituent from **4** are under investigation and will be described in future publications.

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and are uncorrected. The infrared spectra (potassium bromide) were recorded on a Hitachi 260-10 spectrometer, and the ^{1}H-nmr spectra on a JEOL JNM-MH-100 instrument with tetramethylsilane as an internal standard and dimethylsulfoxide-d_6 was used as the solvent.

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

A mixture of **1** (0.348 g, 2.0 mmoles), freshly powdered potassium cyanide (0.326 g, 5.0 mmoles), copper(I) iodide (0.953 g, 5.0 mmoles), 18-crown-6 (0.040 g, 0.15 mmole), and **5** (0.035 g, 0.03 mmole) in dry DMF (10 ml) was stirred at room temperature for 20 minutes under argon and then quickly refluxed in an oil bath preheated to about 200°. The resulting clear solution was stirred under reflux for 2 hours and then cooled to room temperature. The deep amber-colored solution was poured into chloroform (200 ml), and an insoluble matter which formed was removed by filtration and washed well with chloroform. The combined filtrate and washings were evaporated *in vacuo*, and the residual solid was dissolved in benzene-ethyl acetate (2:1). The solution was passed through a column of Florisil (25 g), eluted with the same solvent to give 0.212 g (88%) of **3**, which was recrystallized from ethanol to provide pale yellow needles, mp 206-207°; ir: 2230 cm^{-1} C≡N); ^{1}H-nmr: δ 7.60 (br s, NH_2, 2H), 7.93, 8.42 (d, pyrazine, each 1H, J = 1.3 Hz).

Anal. Calcd. for $C_5H_4N_4$: C, 50.00; H, 3.36; N, 46.65. Found: C, 49.55; H, 3.36; N, 46.63.

2-Amino-3,5-dicyanopyrazine (**4**).

A mixture of **3** (1.265 g, 5.0 mmoles), freshly powdered potassium cyanide (0.978 g, 15.0 mmoles), copper(I) iodide (2.860 g, 15.0 mmoles), 18-crown-6 (0.106 g, 0.40 mmoles), and **5** (0.173 g, 0.15 mmoles) in dry DMF (50 ml) was stirred at room temperature for 20 minutes under argon, and the resulting clear solution was refluxed in the same manner described above. After refluxing for 1 hour, the dark solution was worked up as predescribed to give 0.52 g of crude products after the Florisil treatment. The mixture was chromatographed over silica gel (50 g), which was eluted with hexane-ethyl acetate (2:1) to afford **6** (0.103 g, 10%), mp 180-182° (from ethanol), lit [13] mp 181-183°; ir: 2240 cm^{-1} (C≡N); ^{1}H-nmr: δ 7.56 (br s, NH_2, 2H), 8.42 (s, H-6, 1H). Successive elution provided **4** (0.362 g, 50%), which was recrystallized from ethanol to give colorless needles, mp 223-225°; ir: 2245 cm^{-1} (C≡N); ^{1}H-nmr: δ 8.35 (bs s, NH_2, 2H), 8.73 (s, H-6, 1H).

Anal. Calcd. for $C_6H_3N_5$: C, 49.66; H, 2.08; N, 48.26. Found: C, 49.42; H, 2.16; N, 47.92.

REFERENCES AND NOTES

[1] Part **15**: N. Sato and Y. Kato, *J. Heterocyclic Chem.*, **23**, 1677 (1986).

[2] N. Sato and S. Arai, *J. Heterocyclic Chem.*, **19**, 407 (1982).

[3] N. Sato, *J. Heterocyclic Chem.*, **19**, 673 (1982).

[4] R. C. Ellingson and R. L. Henry, *J. Am. Chem. Soc.*, **71**, 2798 (1949).

[5] G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **78**, 2141 (1956).

[6] A. Hirschberg, A. Peterkofsky, and P. E. Spoerri, *J. Heterocyclic Chem.*, **2**, 209 (1965).

[7] L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).

[8] H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **34**, 3626 (1969).

[9] Y. Akita, M. Shimazaki, and A. Ohta, *Synthesis*, 974 (1981).

[10] B. Camerino and G. Palamidessi, *Gazz. Chim. Ital.*, **90**, 1807 (1960).

[11] Mp 189-191° (from water), lit [11a] mp 189°; ^{1}H-nmr: δ 7.30 (br s, NH_2, 2H), 7.91, 8.29 (d, pyrazine, each 1H, J = 2.4 Hz); [a] A. Albert and K. Ohta, *J. Chem. Soc. (C)*, 1540 (1970).

[12] H. Hoffmann, L. Horner, H. G. Wippel, and D. Michael, *Chem. Ber.*, **95**, 523 (1962).

[13] E. J. Cragoe and J. H. Jones, U. S. Patent 3,341,540; *Chem. Abstr.*, **68**, 105237 (1968).