Studies on Pyrazines. 18 [1].
A New and Convenient Synthesis of 2-Amino-3-cyanopyrazine

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The titled compound, 2-amino-3-cyanopyrazine (**1**), was prepared by reaction of 3-aminopyrazine 1-oxide (**7**) with trimethylsilyl cyanide. Furthermore, conditions of individual steps in synthetic route to **7** starting from 2-pyrazinecarboxamide were optimized.

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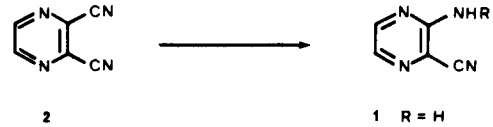
Recently, 2-amino-3-cyanopyrazine (**1**) has gained importance as a key building block for a new and versatile synthetic approach to 6-substituted 2,4-diaminopteridines involving palladium-catalyzed coupling reaction of the 5-bromo derivative of **1** with terminal acetylenes followed by annulation of pyrimidine ring and functionalization of the 6-alkynyl substituent [2,3]. This useful intermediate **1** for pteridine synthesis was first prepared by esterification of 3-aminopyrazinecarboxylic acid followed by ammonolysis and then dehydration of the resulting carboxamide with phosphorus pentachloride [4]. A direct construction of the aminopyrazinecarboxamide by condensation of 2-amidino-2-aminoacetamide with glyoxal [5], and an improved procedure for dehydration of the carbamoyl to the cyano group with phosphoryl chloride were subsequently demonstrated [6]. The condensation of aminomalononitrile tosylate with monooxime of glyoxal followed by phosphorus trichloride deoxygenation of the resulting 1-oxide also gave the desired product **1** [7]. These synthetic routes to **1** suffered certain disadvantages, including relative inaccessibility of the starting materials, or poor overall yields. We are currently engaged in a program aimed at the development of a more convenient synthetic route to the titled compound **1**.

As a potential precursor to **1**, we first chose 2,3-dicyanopyrazine (**2**) because of its ease of accessibility by condensation of diaminomaleonitrile with glyoxal [8,9], as well as its susceptibility of a cyano group to substitution with alcohols or amines [10,11]. Particularly, an attractive instance to our synthesis was the one-step conversion of **2** into 2-methylamino-3-cyanopyrazine (**3**). Thus, **2** was treated with aqueous methylamine and triethylamine as the catalyst in tetrahydrofuran to give the aminopyrazine **3** in 74% yield [12]. This method of application to the synthesis of **1** using ammonium hydroxide instead of aqueous methylamine provided, after 24 hours of being stirred at room temperature, an only a 5% yield of the target product **1**, which was separated with difficulty from the unchanged starting material **2**. Prolonging the reaction time and varying the amount of the reagents had no effect on improving the yield of **1** and the contamination with **2**. Under the above amination conditions without the reaction to run for 48 hours, 2-chloro-3-cyanopyrazine (**4**), carrying a more effective leaving chloro substituent than the cyano group, was converted to the amino compound **1** in 28% yield although the unchanged starting material **2** was recovered in 56% yield. Changing the reagent to methanolic ammonia gave a 16% yield of **1** along with a 67% yield of 2-cyano-3-methoxypyrazine (**5**). Compound **5** has been earlier prepared by treating **4** with methanolic sodium methoxide at room temperature [13] or by refluxing **2** in methanol containing dimethylformamide and triethylamine [10]. In general, amination or methoxylation of halopyrazines requires elevated temperatures and occasional pressure. Therefore, the much greater reactivities of **2** and **4** demonstrated above are apparently rationalized in terms of strongly electron-withdrawing cyano group, which facilitates nucleophilic displacement with the adjacent cyano or chloro substituent. At this point, more interesting is the observation that the preferential conversion of **5** to **1** in the reaction of **4** with methanolic ammonia is opposite to the usual trend on nucleophilicities of methanol and ammonia.

Scheme 1



2 **1** R = H; **3** R = CH_3

Scheme 2

4 **5**

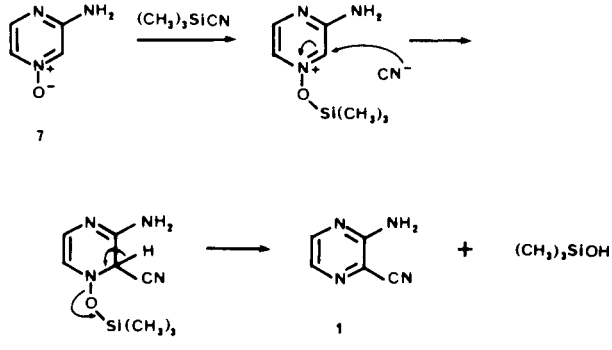
Cyanation of 2-amino-3-halopyrazine would also be expected to be a useful synthetic route to **1**. Certainly, we recently showed a successful palladium-catalyzed cyanation into 2-amino-5-cyano- and 2-amino-3,5-dicyanopyrazines from the corresponding bromopyrazines [14]. We at-

tempted to apply this methodology to the synthesis of **1** by use of 2-amino-3-chloropyrazine (**6**).

Then, **6** was treated with 1.5 equivalents of potassium cyanide in the presence of 5 mole percent each of tetrakis-(triphenylphosphine)palladium(0), copper(I) iodide and 18-crown-6 in refluxing dimethylformamide for 2 hours. However, the reaction did not go to completion, giving an inseparable mixture of **1** and the starting material **6** (4 and 69% yields, respectively, by ^{1}H-nmr). Longer periods under reflux brought about considerable decomposition of both the starting material **6** and the product **1**. These situation were not improved even on using one molar equivalent of copper(I) iodide. Presumably, the poor reactivity of **6** is attributed to a less reactive chloro substituent than the bromo substituent [16]. Because of the fair inaccessibility of 2-amino-3-bromo- or -3-iodopyrazine as the starting material, this methodology depending on palladium-catalyzed cyanation appeared to be far less efficient for the synthesis of **1**.

A more practical synthetic route to **1** was achieved by the reaction of 3-aminopyrazine 1-oxide (**7**) with trimethylsilyl cyanide. This strategy is based upon a procedure recently developed for the preparation of 2-cyanopyridines by treating pyridine *N*-oxides with the above silyl reagent [17]. The formation of cyano heterocycles was explained to involve an initial formation of a Si-O bond and then nucleophilic attack of the cyanide ion at the position α to the *N*-oxide function followed by cleavage of the N-O bond. Treatment of the *N*-oxide **7** with trimethylsilyl cyanide, generated *in situ* from sodium cyanide and trimethylsilyl chloride, in dimethylformamide containing triethylamine at 95-100° for 6 hours gave an 80% yield of **1**. A plausible pathway for formation of **1** is outlined in Scheme 3. The

Scheme 3



trimethylsilanol which was produced as the leaving group undergoes condensation with trimethylsilyl cyanide or chloride to furnish a stable hexamethyldisiloxane and hydrogen cyanide or chloride, which is trapped with triethylamine [17]. Unlike exclusive chlorination of **7** with phosphoryl chloride to 2-amino-3-chloropyrazine (**6**) [18], a small amount of the isomeric 2-amino-5- and -6-cyanopyrazines (by tlc) [14] was formed, which was easily removed by recrystallization from water. The details of reaction are now in progress and will be reported elsewhere together with reactions of other pyrazine *N*-oxides in the near furture.

The key precursor **7** to **1** in our synthesis has been prepared by two synthetic routes, one of which consists of *N*-oxidation of pyrazinecarboxamide (**8**) and then the Hofmann degradation of the resulting 3-pyrazinecarboxamide 1-oxide (**9**), and other of *N*-oxidation of 2-chloropyrazine followed by amination [19]. In view of the simplicity of the procedures and the cost of the starting material, the former sequence of reactions would seem to be of more convenience for the synthesis of **7**. In the present work, the procedure of the individual steps was modified resulting in a slight increase of their yields. The *N*-oxidation of **8** with peracetic acid at 70° for 8 hours [20] led to the *N*-oxide **9** in 53% yield. When **8** was oxidized with performic acid at 40-50° for 5 hours, the *N*-oxide **9** was formed in 66% yield, which was obtained with analytical purity. The enhanced reactivity on *N*-oxidation of **8** resulted from greater electrophilicity of performic acid compared to peracetic acid [21-24]. Conversion of the amide **9** into the aminopyrazine *N*-oxide **7** has been achieved by the usual Hofmann degradation using bromine [17] in 70% yield. We found that commercially available sodium hypochlorite solution was more effective for the transformation and the best yield (78%) was obtained on using 2.4 equivalents of the reagent.

EXPERIMENTAL

All melting points were determined in capillary tubes on a Büchi 535 or a Laboratory Devices Mel-Temp apparatus and are uncorrected. The infrared spectra were recorded on a Hitachi 260-10 or a JASCO IR-810 spectrometer as potassium bromide pellets, the ^{1}H-nmr spectra on a JEOL JNM-MH-100 instrument with tetramethylsilane as the internal standard, and the exact mass spectra on a JEOL JMS-DX-300 mass spectrometer.

Reaction of 2-Chloro-3-cyanopyrazine (**4**) with Methanolic Ammonia.

Chloropyrazine **4** [25] (0.418 g, 3.0 mmoles) was added in one portion to dry methanol (30 ml) saturated with ammonia gas at 4-5° for 1 hour. The solution was stirred at 0° for 3 hours and then at room temperature for 25 hours, when the starting material was completely consumed (by tlc). The resulting solution was evaporated to dryness *in vacuo*, and the residue was extracted with ethyl acetate. The extract was evaporated to dryness *in vacuo*, and the residue was chromatographed over silica gel (10 g), which was eluted with hexane-ethyl acetate (4:1) to give 0.271 g (67%) of 2-cyano-3-methoxypyrazine (**5**), mp 55°. The analytical sample was prepared by recrystallization from water as colorless prisms, mp 55-56°, lit [13] mp 56°; ir: 2240, 1533, 1393, 1317, 1174, 1149, 998, 869 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.12 (s, 3H), 8.27 (d, 1H, J = 2.6 Hz), 8.34 (d, 1H); ms: m/e Calcd. 135.0432, Found: 135.0470.

Anal. Calcd. for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found:

C, 53.81; H, 3.69; N, 30.89.

Further elution with hexane-ethyl acetate (1:1) provided 0.058 g (16%) of **1**, mp 188-189°. The physical properties of **1** are described below.

3-Pyrazinecarboxamide 1-Oxide (**9**).

A solution of **8** (24.6 g, 0.20 mole) in 90% formic acid (100 ml) and 30% hydrogen peroxide (62.5 ml) was stirred and heated. The temperature was remained between 40-50° by occasional cooling for 4 hours and then at 40° for 1 hour. A colorless solid started to separate from the solution after heating for approximately 10 minutes. The mixture was refrigerated overnight, then filtered, washed well with water and dried in air to give 18.24 g (66%) of the *N*-oxide **9**, mp 305-306° dec, identical in all respects with an authentic sample prepared by oxidation of **8** with peracetic acid [20] in 53% yield. This material was used directly in successive transformation without further purification. An analytical sample was obtained by recrystallization from water (1.0 g/60 ml) to afford colorless microcrystals, mp 305-306° dec, lit [20] mp 300° dec; ir: 3390, 1683, 1595, 1446, 1392, 1311, 1272, 1010, 960 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 7.81 (br s, 1H), 8.41 (br s, 1H), 8.83 (dd, 1H, J = 3.9, 1.6 Hz), 9.03 (dd, 1H, J = 3.9, 0.6 Hz), 9.34 (dd, 1H, J = 1.6, 0.6 Hz).

3-Aminopyrazine 1-Oxide (**7**).

Sodium hypochlorite solution (Wako Chem. Inc., the solution was determined to contain 4.0 mmoles/ml of available chlorine by iodometric titration, 30.0 ml, 0.12 mole) was added dropwise to a stirred solution of sodium hydroxide (8.08 g, 0.20 moles) in water (125 ml) at room temperature. The amide **9** (6.956 g, 0.050 mole) was added in one portion to the above solution, and the resulting mixture was heated at 70° with stirring for 1 hour. During this period, the suspension passed into solution. After being cooled below 20°, the solution was acidified at *p*H < 0 with concentrated hydrochloric acid and then again basified at *p*H 9-10 with 2*N* aqueous sodium hydroxide. The mixture was evaporated to dryness *in vacuo*, and the residue was powdered and extracted with chloroform by a Soxlet extractor for 24 hours to give 4.35 g (78%) of **7**, mp 177-178°. This compound was identical in all respects with an authentic material prepared by treatment of **9** with two molar equivalents of bromine in aqueous sodium hydroxide [19] in 70% yield. Sublimation at 180° *in vacuo* and recrystallization from dioxane afforded the analytical sample as yellow prisms, mp 180-181°, lit [19] mp 175°; ir: 3100, 3090, 1661, 1581, 1540, 1190, 980 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.65 (br s, 2H), 7.50 (dd, 1H, J = 4.1, 1.4 Hz), 7.54 (dd, 1H, J = 1.4, 0.8 Hz), 7.90 (dd, 1H, J = 4.1, 0.8 Hz).

2-Amino-3-cyanopyrazine (**1**).

Chlorotrimethylsilane (5.2 ml, 0.041 mole) was added dropwise over a period of 15 minutes to a stirred mixture of the *N*-oxide **7** (1.111 g, 0.010 mole), freshly powdered 97% sodium cyanide (1.56 g, 0.031 mole) and triethylamine (7.0 ml, 0.050 mole) in dry dimethylformamide (50 ml) at room temperature, and the resulting mixture was stirred and heated at 95-100° for 6 hours. After the mixture was somewhat cooled, an insoluble matter was removed by filtration and wahed well with dimethylformamide. The filtrate and washing were evaporated to dryness *in vacuo*. Methanol (30 ml) was added to the residue, and the solution was evaporated to dryness *in vacuo* after stirring for 10 minutes at room temperature. The residual material was carefully sublimed at 150° *in vacuo* and then recrystallized from water (*ca.* 40 ml) to give 0.876 g of **1**, mp 192°, identical in all respects with an authentic compound [14]. A second crop (85 mg, total 80%) was obtained by evaporation of the mother liquor and subsequent recrystallization. The analytical sample was prepared by further recrystallization from water as pale yellow needles, mp 192°, lit [14] mp 189-191°; ir: 3400, 3160, 2209, 1658, 1563, 1527, 1192 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.30 (br s, 2H), 7.92 (d, 1H, J = 2.5 Hz), 8.29 (d, 1H).

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[15] A correction has been made in this paper. On page 1371 (ref [14]) in the right column, from the bottom lines 13 and 12, the compound should read dibromopyrazine **2** not monocyanopyrazine **6** as reported.

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[24] *m*-Chloroperbenzoic acid, the parent acid of which has stronger acidity than acetic acid, is also a better electrophile for *N*-oxidation than peracetic acid. It is well illustrated by *N*-oxidation of 2,6-dichloropyrazine, *i.e.*, the 4-oxide was prepared in 64% yield by treatment with the perbenzoic acid in refluxing chloroform, but in 1.2-4% yield with peracetic acid. Ref: N. Sato and M. Kobayashi, *Bull. Chem. Soc. Japan*, **57**, 3015 (1984).

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