Synthesis and Reactions of 5,6-Dichloro-3-nitropyrazinamine

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Received October 20, 1982

The synthesis of 5,6-dichloro-3-nitropyrazinamine has been carried out by decarboxylative nitration of 5,6-dichloro-3-nitropyrazine-2-carboxylic acid. The nitro heterocycle was found to undergo a variety of reactions, which include nucleophilic displacement of the 6-chloro group by amines, acetylation of the free amino group with acetyl chloride, bromo-deamination with isoamylnitrite in bromoform, as well as the formation of imidazolo and triazolo condensed ring systems.

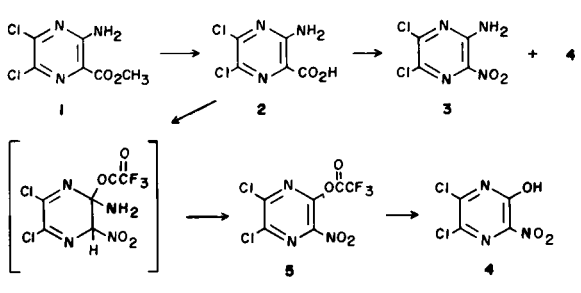
J. Heterocyclic Chem., **20**, 1089 (1983).

As part of a program to prepare novel nitroheterocycles, we have investigated the synthesis and reactions of 5,6-dichloro-3-nitropyrazinamine (**3**). There are, in the literature, only a few references to nitropyrazines (1,2,3) and outside of the patent literature, no thorough study of the chemistry of any nitropyrazine has been reported.

We have found that treatment (1,2) of 5,6-dichloro-3-aminopyrazine-2-carboxylic acid (**2**) (4), obtained by base hydrolysis of methyl ester **1**, with sulfuric acid/sodium nitrate of sulfuric acid/nitric acid resulted in a smooth decarboxylation reaction affording the desired 5,6-dichloro-3-nitropyrazinamine (**3**), along with the hydroxypyrazine **4** as a side-product. Although **3** is readily separated from **4** by column chromatography, attempts were made to minimize the yield of **4** primarily by diminishing the concentration of water in the reaction mixture. The best yield of **3** was thus achieved by decarboxylative nitration of **2** in fuming nitric acid/fuming sulfuric acid mixture. In a separate experiment, it was found that treatment of **2** with anhydrous nitric acid/trifluoroacetic acid followed by an ice quench gave **4** as the exclusive product of reaction. We anticipate that under these conditions an intermediate derived from **2** is trifluoroacetoxylated to give **5**, which is hydrolyzed to **4** during the ice quench.

As expected (1,2), nucleophilic substitution by amines on **3** was facile. For example, treatment of **3** with ethanolamine at room temperature gave 2-[(6-amino-3-chloro-5-nitropyrazinyl)amino]ethanol (**6**) in high yield. Conversion of **3** to its mono-*N*-acetyl derivative **7** was effected in an acetyl chloride/sodium bicarbonate slurry to give **7**, contaminated with a small amount of the *N,N*-diacetyl analogue. Treatment of **7** at room temperature with ethanolamine resulted in an exothermic reaction with formation of *N*-[5-chloro-6-[(2-hydroxyethyl)-amino]-3-nitropyrazinyl]acetamide (**8**). Although **3** was successfully converted to its *N*-acetyl derivative **7**, the low nucleophilicity of the amino nitrogen is manifest by the lack of reaction of **3** with *t*-butylisocyanate and methanesulfonyl chloride under standard conditions.

Scheme I

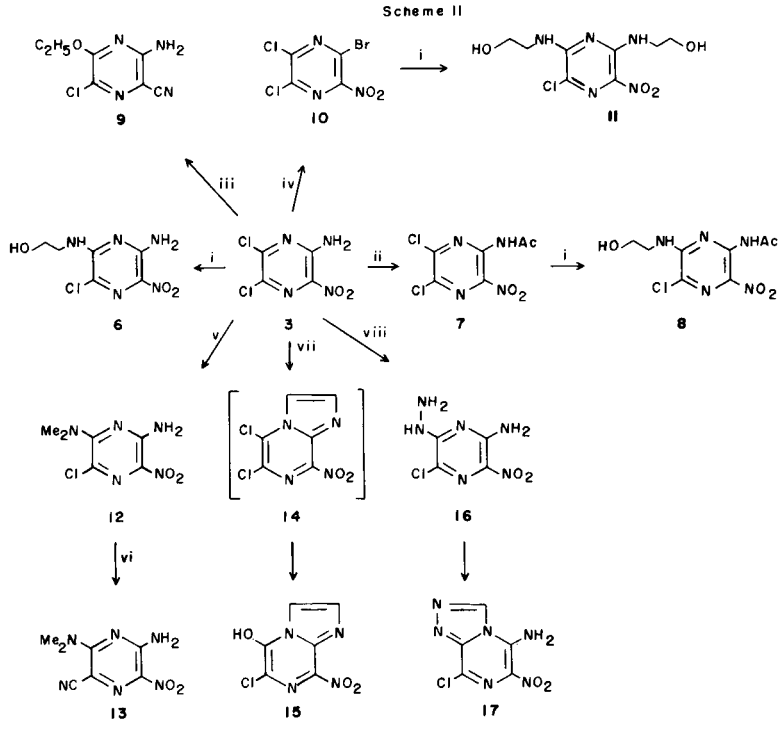


Unexpectedly, the reaction between **3** and cyanide ion proved to take a different course from that observed for amines. Treatment of **3** with sodium cyanide in ethanol resulted in a slow reaction taking several days to complete, which afforded 5-chloro-3-cyano-6-ethoxypyrazinamine **9** in 68% yield. The compound was independently prepared by treatment of 3-amino-5,6-dichloropyrazinecarbonitrile (5) with sodium ethoxide. Treatment of **3** with other sources of cyanide such as tetra-*n*-butylammonium cyanide and cuprous cyanide gave complex product mixtures. However, successful conversion of **3** to a nitrile was achieved by treatment of **3** with dimethylamine to give **12**, followed by reaction with cuprous cyanide in dimethylformamide to afford 5-cyano-6-dimethylamino-3-nitropyrazinamine (**13**).

Diazotization of **3** was carried out according to Cadogan, *et al.*, (6) employing isoamyl nitrite in refluxing bromoform to give a multi-component mixture from which 3-bromo-5,6-dichloronitropyrazine (**10**) was isolated by column chromatography. In this manner, **10**, contaminated by a small amount of alkyl nitrites, was found to be a clear, viscous oil which was stable for months at 0-10° and which, upon treatment with two equivalents of ethanolamine afforded 2-{[3-chloro-6-(2-hydroxyethyl)amino-5-nitropyrazinyl]amino}ethanol (**11**).

In an effort to prepare examples of condensed ring nitropyrazines, **3**, was treated with α-bromoacetaldehyde in ethanolic solution. The product of this reaction was not the expected pyrazine **14**, but was the hydroxy derivative **15**, arising apparently from hydrolysis of **14** by the water formed in the condensation reaction. Despite several attempt to minimize the amount of water present during reaction by addition of drying agents, **15** continued to be the major product. Attempts at converting **15** to **14** by the use of agents such as phosphorus oxychloride, thionyl

Scheme II



Reagents: i = $H_2NCH_2CH_2OH/i$-PrOH/Et_3N; ii = $CH_3COCl/NaHCO_3$; iii = NaCN/EtOH; iv = isoamyl nitrite/$CHBr_3$; v = Me_2NH/i-PrOH/Et_3N; vi = CuCN/DMF; vii = $BrCH_2CHO$/EtOH; viii = H_2NNH_2/EtOH; ix = $HC(OEt)_3$.

chloride and phosphorus pentachloride gave only decomposition. In a second synthetic sequence, hydrazine derivative **16**, readily formed from **3** and hydrazine, underwent facile cyclization with triethyl orthoformate to afford 2-amino-5-chloro-3-nitrotriazolo[3,4-*f*]pyrazine (**17**).

EXPERIMENTAL

Melting points were determined in air employing a Thomas Hoover apparatus using a capillary tube and are uncorrected. Proton nmr spectra were obtained using a Varian T-60A spectrometer. The elemental analyses were carried out by Dr. W. C. Randall and his staff. The mass spectral analyses were carried out by Dr. H. Ramjit and his staff using an LKB-9000 S at 70 eV.

5,6-Dichloro-3-nitropyrazinamine (**3**).

To 176 ml of concentrated sulfuric acid was added 20.8 g (0.1 mole) of 5,6-dichloro-3-aminopyrazine-2-carboxylic acid (**2**) and after stirring for 5-10 minutes most of the acid had dissolved. This was then cooled to $<5°$ and a solution of 6.3 ml of concentrated nitric acid in 6.3 ml of concentrated sulfuric acid was added dropwise over 30 minutes with the temperature maintained at $<5°$. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for four hours. Evolution of carbon dioxide was apparent during the addition and continued for much of the stirring period. The reaction mixture was then quenched with good agitation into 1 ℓ of ice and the resulting yellow solid was collected by fitration. This yellow solid was dissolved in ethyl acetate, washed with 3 × 250 ml of saturated sodium carbonate and dried over anhydrous sodium sulfate. The ethyl acetate solution was then passed through a silica gel column (500 g of 70-230 mesh) which was eluted with ethyl acetate. Fractions were collected until the impurity, *i.e.*, origin material on analytical tlc (2% methanol/chloroform elution) appeared. Removal of solvents *in vacuo* afforded 9.6 g (46%) of **3** as a yellow solid, mp 169-170°; ms: m/e, 209.

Anal. Calcd. for $C_4H_2Cl_2N_4O_2$: C, 22.99; H, 0.96; N, 26.81; Cl, 33.77. Found: C, 23.13, H, 0.82; N, 27.09; Cl, 34.02.

N-(5,6-Dichloro-3-nitropyrazinyl)acetamide (**7**).

To 1.0 g (0.0048 mole) of 5,6-dichloro-3-nitropyrazinamine (**3**) in 15 ml of acetyl chloride under nitrogen at room temperature was added 0.84 g (0.01 mole) of anhydrous sodium bicarbonate. This mixture was stirred and heated at reflux for 4 days. Excess acetyl chloride was removed on the rotary evaporator and the residue was chromatographed on silica gel (230-400 mesh) with chloroform elution to give 0.7 g (58%) of **7** as a white solid, mp 129-130° (R_f = 0.6 on silica gel with 2% methanol/chloroform); ^{1}H nmr (deuteriochloroform): δ 2.42 (3H, singlet), 9.80 (1H, broad): ms: m/e, 251.

Anal. Calcd. for $C_6H_4Cl_2N_4O_3$: C, 28.70; H, 1.60; N, 22.32. Found: C, 28.90; H, 1.59; N, 21.86.

N-[5-Chloro-6-[(2-hydroxyethyl)amino]-3-nitropyrazinyl]acetamide (**8**).

To 0.8 g (0.013 mole) of ethanolamine in 30 ml of 2-propanol a 0-10° was added 1.3 g (0.013 mole) of triethylamine and 3.3 g (0.013 mole) of **7**. The reaction mixture was cooled for 0.5 hour and allowed to warm to room temperature over 1 hour. The reaction mixture was filtered to give a brown solid which was recrystallized from acetonitrile to afford 3.0 g (83%) of **8** as a pale yellow solid, mp 172-173°; ^{1}H nmr (DMSO-d_6): δ 2.20

(3H, singlet), 3.55 (4H, singlet); ms: m/e 275.

Anal. Calcd. for $C_8H_{10}ClN_5O_4$: C, 34.86; H, 3.66; N, 25.41. Found: C, 34.92; H, 3.58; N, 25.66.

2-[(6-Amino-3-chloro-5-nitropyrazinyl)amino]ethanol (**6**).

To 0.29 g (0.0048 mmole) of ethanolamine in 20 ml of propanol at room temperature was added 0.48 g (0.0048 mole) of triethylamine and 1.0 g (0.0048 mole) of **3** and the resulting mixture stirred for 4 hours. The yellow solid was collected by filtration and recrystallized from acetonitrile to give 0.8 g (72%) of **6** as a yellow solid, mp 196-197°; ^{1}H nmr (DMSO-d_6): δ 3.48 (4H, singlet); ms: m/e 233.

Anal. Calcd. for $C_6H_8ClN_5O_3$: C, 30.85; H, 3.45; N, 29.98. Found: C, 30.84; H, 3.46; N, 29.98.

5-Chloro-3-cyano-6-ethoxypyrazinamine (**9**).

To 1.0 g (0.0048 mole) of **3** in 50 ml of ethanol was added 0.98 g (0.02 mole) of sodium cyanide and the solution refluxed for 4 days. At that time, tlc (silica gel, 5% methanol/chloroform) showed a fluorescent spot at R_f along with several minor components. The reaction mixture was stripped on the rotary evaporator and the residue chromatographed on silica gel (230-400 mesh) with 2% methanol/chloroform elution to afford 0.7 g of tan solid. This was recrystallized from chloroform/hexane to give 0.52 g (55%) of 9 as a tan solid, mp 139-140°; ms: m/e 199.

Anal. Calcd. for $C_7H_7ClN_4O$: C, 42.09; H, 3.54; N, 28.28. Found: C, 42.09; H, 3.50; N, 28.32.

3-Bromo-5,6-dichloronitropyrazine (**10**).

To 25 ml of bromoform heated to 95-100° was added 0.48 g (4.8 mmoles) of isoamyl nitrite and 0.5 g (2.4 mmoles) of **3** was added in one portion and the solution refluxed for 8 hours. Then, another 0.48 g (4.8 mmoles) of isoamyl nitrite was added and the mixture refluxed for 10 hours. the bromoform was stripped on the rotary evaporator and the yellow oily residue chromatographed on silica gel (230-400 mesh) with chloroform elution (R_f = 0.8, silica gel, chloroform). This chromatography afforded 0.3 g of an oil which was **10** contaminated with alkyl nitrites. Material of this purity was used successfully in the following reaction. Mass spectral analysis of this oil gave m/e 271, correct for desired compound.

2-{[3-Chloro-6-(2-hydroxyethyl)amino-5-nitropyrazinyl]amino}ethanol (**11**).

To 0.44 g (7.2 mmoles) of ethanolamine in 25 ml of 2-propanol at 0-10° was added 0.72 g (7.2 mmoles) of triethylamine and 1.0 g of **10** (oil). Ice bath cooling was removed after the initial exotherm, and the reaction mixture was stirred at room temperature for 1 hour. The solvent was stripped on the rotary evaporator to give an orange oil which was triturated with ethanol/chloroform (1:3) to give a yellow solid which was collected by filtration. This solid was chromatographed (silica gel/4% methanol:chloroform elution) to give 0.40 g (29%) of **11** as a yellow solid (R_f = 0.3 in 4% methanol/chloroform), mp 148-150°, ^{1}H nmr (deuteriomethanol-d_4): δ 3.72 (8H, multiplet); ms: m/e 277.

Anal. Calcd. for $C_8H_{12}ClN_5O_4$: C, 34.60; H, 4.36; N, 25.22. Found: C, 34.72; H, 4.38; N, 25.47.

6-Dimethylamino-5-chloro-3-nitropyrazinamine (**12**).

To 1.3 g (0.029 mole) of dimethylamine in 75 ml of propanol at room temperature was added 2.93 g (0.029 mole) of triethylamine and 6.0 g (0.029 mole) of **3**. The reaction mixture was stirred 10 hours at room temperature. The yellow solid was filtered off and washed with cold chloroform to give 5.8 g (92%) of **12** as a yellow solid, mp 184-186° (1,2).

5-Cyano-6-dimethylamino-3-nitropyrazinamine (**13**).

To 2.0 g (0.0092 mole) of **12** in 30 ml of dimethylformamide was added 1.0 g (0.011 mole) of cuprous cyanide and this mixture heated at 150-160° for 18 hours. The solvent was stripped on the rotary evaporator to give a dark residue which was taken up in 50 ml of ethyl acetate. To this was added 50 ml of saturated sodium cyanide solution and the resulting mixture was stirred at room temperature for 1 hour. The ethyl acetate phase was separated, dried and stripped to give 1.2 g (62%) of **13** as a tan solid, mp 202-206°; ^{1}H nmr (DMSO-d_6): δ 3.28 (6H, singlet); ms: m/e 208.

Anal. Calcd. for $C_7H_8N_6O_2$: C, 40.39; H, 3.87; N, 40.37. Found: C, 40.39; H, 4.00; N, 40.04.

5-Chloro-6-hydrazino-3-nitropyrazinamine (**16**).

To 300 ml of ethanol was added 7.4 g (0.22 mole) of a 95% hydrazine solution. This solution was cooled to 10° and with stirring 20.9 g (0.1 mole) of **3** was added portionwise. A dark precipitate formed immediately and the suspension was stirred for 1 hour at room temperature. The mixture was filtered and the resulting solid washed with ethanol, water, ethyl acetate, ethanol and air dried to afford 18.0 g (88%) of **16** as a brown solid, mp >220°; ms: m/e 205. This solid was treated with acetone to form the isopropylidene derivative, mp 245-246° dec.

Anal. Calcd. for $C_7H_9ClN_6O_2$: C, 34.37; H, 3.71; N, 34.35. Found: C, 34.11; H, 3.66; N, 34.51.

8-Chloro-6-nitro-1,2,4-triazolo[4,3-*a*]pyrazine-5-amine (**17**).

To 5.0 g (0.024 mole) of **16** was added 50 ml of triethyl orthoformate and the resulting suspension was heated at 100° for 1 hour. The reaction mixture was cooled. filtered and the dark brown solid washed with chloroform to give 3.9 g (77%) of **17** as a brown solid, mp >220°, ^{1}H nmr (DMSO-d_6): δ 9.65 (2H, broad singlet), 9.95 (1H, singlet); ms: m/e 214.

Anal. Calcd. for $C_5H_3ClN_6O_2$: C, 27.99; H, 1.41; N, 39.17. Found: C, 28.11; H, 1.40; N, 39.36.

6-Chloro-8-nitroimidazo[1,2-*a*]pyrazin-5-ol (**15**).

To prepare α-bromoacetaldehyde, 12.5 g (63.4 mmoles) of bromoacetaldehyde diethyl acetal was treated with 4.1 ml of 48% hydrobromic acid and 4.1 ml of water and this solution heated at 110° for 1 hour. The reaction mixture was cooled and carefully added to a mixture of 24.4 g of sodium bicarbonate in 200 ml of 2-propanol. This solution was dried over anhydrous sodium sulfate and filtered. To the filtrate was added 8.6 g (41.1 mmoles) of **3** and this solution was heated at reflux under nitrogen for 16 hours. The cooled reaction mixture was filtered to afford 6.8 g (66%) of **15** as a tan solid, mp >220°, ^{1}H nmr (DMSO-d_6): δ 7.45 (1H, doublet), 7.75 (1H, doublet); ms: m/e 214.

Anal. Calcd. for $C_6H_3ClN_4O_3$: C, 33.59; H, 1.41; N, 26.11. Found: C, 33.60; H, 1.33; N, 26.06.

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