Amination of 4-Nitro- and 4-Cyanopyridazines by Liquid Ammonia/Potassium Permanganate

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4-Nitro-3-R¹-6-R²-pyridazines (**1**) (**a**, R¹ = R² = 2-pyridyl; **b**, R¹ = H, R² = phenyl; **c**, R¹ = H, R² = *p*-methoxyphenyl; **d**, R¹ = R² = H) are aminated by liquid ammonia/potassium permanganate to the corresponding 5-amino-4-nitropyridazines **3a-d**. The 4-cyano-3-R¹-6-R²-pyridazines **4a,b** are only aminated in the presence of *potassium amide* in liquid ammonia/potassium permanganate to give the 5-amino-4-cyanopyridazines **6a,b**. The 5-amino-4-nitropyridazines **3a,b,d** are converted to the 4,5-diaminopyridazines **7a,b,d** by reduction over a Pd/C catalyst. Reaction of **7b** with glyoxal leads to 5-phenylpyrazino[2,3-*d*]pyridazine (**8b**).

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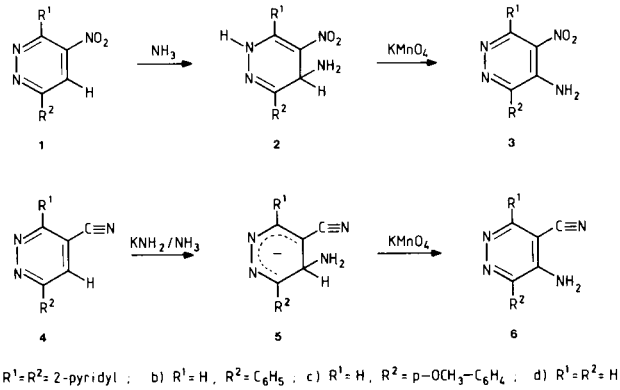
In a series of papers from this laboratory it has been shown that the 1:1 σ-adduct formed between an azaaromatic and ammonia or the amide ion can easily be converted into the corresponding amino compound on treatment with potassium permanganate [1]. The synthetic utility of this method is demonstrated by the broad variety of azaaromatics that can be transformed into the corresponding amino compounds by this methodology. With increasing π-electron-deficiency of the azaaromatic ring the amination becomes easier, and tetrazines [2], triazines [3,4] and nitrodiazines [5,6] usually undergo amination in liquid ammonia/potassium permanganate, thus these heterocycles do not require potassium amide as the aminating agent. Pyridazine compounds are aminated at C-4 (or C-5) and require potassium amide/potassium permanganate [4], while for 4-nitropyridazine 1-oxides only liquid ammonia/potasium permanganate is used for amination at C-5 [6].

In a previous paper we published the synthesis of 4-nitro-, **1a-d**, and 4-cyanopyridazines **4a,b** using a cycloaddition reaction between tetrazines and nitro- or cyanoenamines [7]. We now report on the amination of these compounds using liquid ammonia (with or without potassium amide)/potassium permanganate. Upon dissolving 3,6-bis(2-pyridyl)-4-nitropyridazine (**1a**) in liquid ammonia the corresponding 5-amino-2,5-dihydropyridazine (**2a**) (see Scheme 1) is formed nearly instantaneously. The nmr spectrum of the solution shows a singlet at 5.75 ppm, corresponding to an upfield shift of 3.1 ppm for H-5 and reflects the $sp^2 \rightarrow sp^3$ change of hybridization of C-5 upon addition of ammonia. This upfield shift is in agreement with shifts observed previously for the formation of similar σ-adducts of azaaromatics with ammonia [6,8]. Upon reaction of adduct **2a** with potassium permanganate the compound undergoes dehydrogenation into 5-amino-3,6-bis(2-pyridyl)-4-nitropyridazine (**3a**). The 6-aryl-4-nitropyridazines **1b** and **1c** are also converted into the dihydro derivatives, *i.e.* **2b** and **2c**, upon dissolution in liquid ammonia. The nmr spectra of both **2b** and **2c** show besides a characteristic low field doublet at 8.2 ppm only one doublet at 5.15 ppm with J = 1.2 Hz, due to coupling of H-5 with H-3. Only one set of resonances is observed, leading to the conclusion that addition takes place at only one of the two possible C-H sites. Upon addition of potassium permanganate the 5-amino-4-nitropyridazines **3b** and **3c** are formed in high yield. Additional evidence for the presence of the amino group at C-5 comes from the ^{13}C-nmr spectra of these compounds, showing that the remaining hydrogen-bearing pyridazine carbon atom has a chemical shift of 143 ppm. As this shift is not expected to be very much influenced by the *meta*-amino group and is about the same as found for C-3 in the compounds **1b** and **1c** (141 ppm) [17], it can safely be attributed to C-3. The ^{13}C-^{1}H coupling constant of 189 Hz for C-3 in **3b** and **3c** is also in agreement with the presence of the hydrogen at C-3, rather than at C-5 [7].

We also wanted to aminate 4-nitropyridazine (**1d**) itself. The preparation of 4-nitropyridazine (**1d**) from tetrazine [9] and 1-dimethylamino-2-nitroethene was successful, but **1d** decomposes to 4-hydroxypyridazine and other compounds with evolution of nitrous fumes when we tried to isolate this compound. However, in an ethereal solution, **1d** is stable. The gc/ms analyses showed that in this solu-

Scheme 1

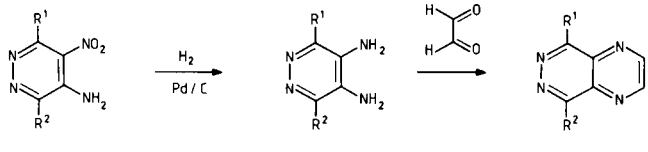


a) R¹=R²= 2-pyridyl ; b) R¹= H , R²= C₆H₅ ; c) R¹= H , R²= p-OCH₃-C₆H₄ ; d) R¹= R²= H

tion only one compound is present and that its mass spectrum agrees with 4-nitropyridazine (m/e: 125 (M^+), 79 (M^+-NO_2)). The nmr spectrum shows resonances in the aromatic region at 9.93 ppm (dd, J = 0.8 Hz and 2.7 Hz, H-3), 9.72 ppm (dd, J = 0.8 Hz and 5.6 Hz, H-6) and 8.30 ppm (dd, J = 2.7 Hz and 5.6 Hz, H-5). When a solution of 4-nitropyridazine (**1d**) in ether was added to liquid ammonia containing potassium permanganate 4-amino-5-nitropyridazine (**3a**) was isolated after the usual work-up. The ^{1}H-nmr spectrum of **3d** featured only two signals at 9.24 and 8.95 ppm, with a coupling constant of 0.7 Hz, indicating that the hydrogen atoms are present at C-3 and C-6. Therefore, amination has occurred at C-5. The infrared spectra of compounds **3a-d** all show the expected nitro- and amine vibration frequencies.

The 4-cyanopyridazines **4a** and **4b** do not undergo σ-adductformation upon dissolution of these compounds in liquid ammonia. However, when liquid ammonia containing potassium amide was used, and the nmr spectrum of this solution was measured a signal was observed at 4.85 ppm for the solution of **4a**, and at 4.45 ppm (doublet, J = 1.5 Hz) for the solution of **4b**. These data indicate the formation of the dihydropyridazines **5a** and **5b**, respectively. Oxidation with potassium permanganate gives the 5-amino-4-cyanopyridazines **6a** and **6b**, respectively, in moderate yield (see Scheme 1). The ^{13}C-nmr spectrum of **6b** shows that the hydrogen-bearing pyridazine carbon atom resonates at 149.7 ppm, which does not deviate much from the ^{13}C-shift of C-3 in compound **4b**, which resonates at 148.3 ppm [7]. The ^{13}C-^{1}H coupling constant of 185 Hz also indicates the presence of a hydrogen at C-3, rather than at C-5 [7]. The infrared spectra of **6a,b** show the expected cyano- and amine vibration frequencies.

Scheme 2



3 7 8

a) $R^1=R^2=$ 2-pyridyl ; b) $R^1=H$, $R^2=C_6H_5$; d) $R^1=R^2=H$

Reduction of the 4-amino-5-nitropyridazines **3a,b,d** in ethanol with hydrogen over a Pd/C catalyst gives the corresponding 4,5-diaminopyridazines **7a,b,d** in moderate yield (see Scheme 2) as evidenced by the infrared spectra which show the absence of nitro group vibration frequencies. Compound **7d** has been prepared earlier [10,11] and was used for the synthesis of pyrazino[2,3-*d*]pyridazine **8d** [12]. Similarly, we obtained 5-phenylpyrazino[2,3-*d*]pyridazine **8b** upon reaction of 4,5-diamino-6-phenylpyridazine **7b** with glyoxal (see Scheme 2).

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded on a Varian EM-390 spectrometer. Tetramethylsilane (TMS) was used as an internal standard. In liquid ammonia, the solvent peak was used as the standard (δ = 0.95 ppm from TMS). The ^{13}C-nmr spectra were recorded with a Brüker CXP-300 spectrometer. Mass spectra were obtained with an AEI-902 spectrometer and gc-ms analysis was performed on a VG-micromass 7070 F apparatus. Infrared spectra were recorded on a Hitachi EPI-G3 spectrophotometer.

General Procedure for the Amination of the Nitropyridazines **1a-d**.

One mmole of the appropriate 4-nitropyridazine, **1a-d**, [7] was added to a solution of potassium permanganate (2 equivalents) in 20-30 ml of liquid ammonia at −45°. After 0.5 hour, 20 ml of cold chloroform was added to the brown mixture. The ammonia was evaporated and the residue was extracted with warm chloroform and ethyl acetate. The extracts were filtered, concentrated and purified by column chromatography on silica gel with chloroform/methanol 6:1 as eluent.

5-Amino-3,6-bis(2-pyridyl)-4-nitropyridazine (**3a**).

This compound was prepared in a yield of 97%, yellow crystals, mp 215-218° (ethanol); ^{1}H-nmr (deuteriochloroform): δ 8.9-7.3 (pyridine H); ms: m/e 294 (M^+).

Anal. Calcd. for $C_{14}H_{10}N_6O_2$: C, 57.14; H, 3.43. Found: C, 56.67; H, 3.52.

5-Amino-4-nitro-6-phenylpyridazine (**3b**).

The compound was prepared in a yield of 93%, yellow crystals, mp 233-234° (ethyl acetate); ^{1}H-nmr (perdeuteriomethanol): δ 9.33 (s, H-3), 7.62 (phenyl); ^{13}C-nmr: δ 154.8 (C-6), 143.2 (J = 189 Hz, C-3), 138.0 (C-5), 127.7 (C-4); ms: m/e 216 (M^+).

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.78. Found: C, 55.76; H, 3.58.

5-Amino-6-(4-methoxy)phenyl-4-nitropyridazine (**3c**).

The compound was prepared in a yield of 98%, yellow crystals, mp 217-218° (chloroform); ^{1}H-nmr (perdeuteriomethanol): δ 9.32 (s, H-3), 7.6-7.0 (phenyl), 3.9 (OCH_3); ^{13}C-nmr: δ 154.8 (C-6), 143.0 (J = 189 Hz, C-3), 138.1 (C-5), 127.6 (C-4); ms: m/e 246 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.65; H, 4.09. Found: C, 53.54; H, 4.02.

5-Amino-4-nitropyridazine (**3d**).

Tetrazine [9] (250 mg) and 1-dimethylamino-2-nitroethene (450 mg) were refluxed in 25 ml of chloroform for four days in a nitrogen atmosphere. Column chromatography on silica gel with ether as eluent gave a light yellow fraction (Rf ~ 0.5) containing 4-nitropyridazine (**1d**) according to gc-ms analysis and ^{1}H-nmr spectroscopy. This fraction was concentrated and used in the amination procedure. The yield of yellow crystals was 18% (calculated on tetrazine), mp 227° dec (ethanol); ^{1}H-nmr (perdeuteriomethanol): δ 9.25 (d, J = 0.7 Hz, H-3), 8.95 (d, H-6); ^{13}C-nmr: δ 146.2 (J = 187 Hz, C-6), 143.8 (J = 187 Hz, C-3), 140.4 (C-5), 126.4 (C-4); ms: m/e 140 (M^+).

Anal. Calcd. for $C_4H_4N_4O_2$: C, 34.29; H, 2.88. Found: C, 34.31; H, 2.96.

General Procedure for the Amination of the 4-Cyanopyridazines **4a,b**.

One mmole of the appropriate cyanopyridazine **4a,b** [7] was added to a solution of potassium amide, prepared by dissolving 100 mg of potassium in 25 ml of liquid ammonia. After 0.25 hour 800 mg of potassium permanganate was added at −45°. The mixture was refluxed for 1.5 hours, then 30 ml of ethyl acetate was added and ammonia was evaporated. The residue was extracted with warm chlorform and ethyl acetate. The extracts were filtered, concentrated and subjected to column chromatography on silica gel with ether/dichloromethane 1:4 as eluent.

5-Amino-3,6-bis(2-pyridyl)-4-cyanopyridazine (**6a**).

This compound was prepared in a yield of 45%, light yellow crystals, mp 194-195° (ethanol); ^{1}H-nmr (perdeuteriomethanol): δ 8.9-7.3 (pyridine

H); ir: (cm^{-1}) 2215 (CN-stretching); ms: m/e 274 (M^+).

Anal. Calcd. for $C_{15}H_{10}N_6$: C, 65.68; H, 3.68. Found: C, 65.73; H, 3.70.

5-Amino-4-cyano-6-phenylpyridazine (**6b**).

This compound was prepared in a yield of 24%, colourless crystals, mp 220-221° (ethanol); ^{1}H-nmr (perdeuteriomethanol): δ 8.80 (s, H-3), 7.8-7.4 (phenyl); ^{13}C-nmr: δ 150.7 (C-6), 149.7 (J = 185 Hz, C-3), 144.8 (C-5), 91.5 (C-4); ir: (cm^{-1}) 2225 (CN-stretching); ms: m/e 196 (M^+).

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.33; H, 4.11. Found: C, 67.65; H, 4.14.

Reduction of the 5-Amino-4-nitropyridazines **3a**,**b**,**d**.

A solution of 100 mg of the 5-amino-4-nitropyridazine, **3a**,**b**,**d**, in 50 ml of absolute ethanol containing 20 mg 5% Pd/C was shaken for 0.5 hour in a Parr apparatus. After filtration and concentration the 4,5-diaminopyridazine was isolated.

3,6-Bis(2-pyridyl)-4,5-diaminopyridazine (**7a**).

This compound was prepared in a yield of 49%, light yellow crystals, mp >340° (ethanol); ms: m/e 264 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_6$: C, 63.62; H, 4.58; N, 31.80. Found: C, 63.39; H, 4.39; N, 31.58.

4,5-Diamino-6-phenylpyridazine (**7b**).

Purification by column chromatography on silica gel with dichloromethane/methanol 3:1 as eluent. This compound was prepared in a yield of 49%, off-white crystals, mp 212-214° (chloroform: the compound was obtained as the hemihydrate); ^{1}H-nmr (perdeuteriomethanol): δ 8.30 (s, H-3), 7.52 (phenyl); ms: m/e 186 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_4 \cdot \frac{1}{2}H_2O$: C, 61.52; H, 5.68; N, 28.70. Found: C, 61.62; H, 5.66; N, 28.79.

4,5-Diaminopyridazine (**7d**).

This compound was prepared in a yield of 57%; ^{1}H-nmr (perdeuteriomethanol): δ 8.27 (H-3 and H-6). The infrared spectrum of the hydrochloride is identical to the reported spectrum [10].

5-Phenylpyrazino[2,3-*d*]pyridazine (**8b**).

A solution of 4,5-diamino-6-phenylpyridazine (**7b**) (50 mg) in 5 ml of absolute ethanol containing 1.5 equivalents of glyoxal was refluxed for 3 hours. The solution was concentrated and the product was recrystallized from diisopropyl ether. The yield was 29 mg of yellow **8b** (52%); mp 177-178°; ^{1}H-nmr (perdeuteriomethanol): δ 9.81 (H-8), 9.31 (H-2 and H-3), 8.2-7.5 (phenyl); ms: m/e Found: 208.0773, Calcd. for $C_{12}H_8N_4$: 208.0749.

Anal. Calcd. for $C_{12}H_8N_4$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.08; H, 3.81; N, 26.83.

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