Amination of 4-Nitropyridazine 1-Oxides by Liquid Ammonia/Potassium Permanganate

Hanna Tondys and Henk C. van der Plas*

Laboratory of Organic Chemistry, Agricultural University,
De Dreijen 5, 6703 BC Wageningen,
The Netherlands

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Treatment of 4-nitropyridazine 1-oxide (**1a**) 3-methoxy-6-chloro-4-nitropyridazine 1-oxide (**1b**) or 3,6-dimethoxy-4-nitropyridazine 1-oxide (**1c**) with a solution of potassium permanganate in liquid ammonia gives in reasonable-to-good yields the corresponding 5-amino-4-nitropyridazine 1-oxides (75%, 54% and 62%, respectively). 3,6-Dimethoxypyridazine (**4a**) and 3-methoxypyridazine (**4b**) are converted into the corresponding 4-aminopyridazines **6a**,**6b** on treatment with potassium amide/liquid ammonia/potassium permanganate (yield 50 and 22% respectively). In the last-mentioned reaction besides **6b** 3,3'-dimethoxy 4,4'-bipyridazine (**7**, 23%) was obtained. It is suggested that the neutral 1:1 σ-adducts formed between (**1a-1c**) and liquid ammonia and the anionic σ-adducts, formed between (**5a-5b**) and potassium amide are intermediates in this amino-oxidation reaction.

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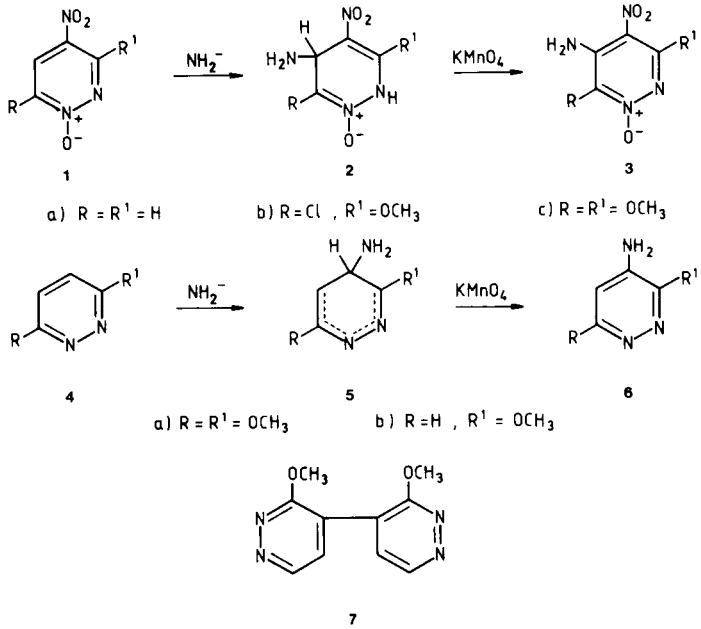
In a series of papers from this laboratory it has been shown that the 1:1 σ-adduct formed between an azaaromatic and liquid ammonia or between an azaaromatic and potassium amide can easily be converted into the corresponding amino compound on treatment with potassium permanganate [1]. This amination-oxidation procedure has been found to be very useful especially for the preparation of aminoazaaromatics, which by the classical Chichibabin procedure (using sodamide or potassium amide in an aprotic solvent) [2] cannot be obtained or only with difficulty. The synthetic utility of our method is demonstrated by the broad variety of azaaromatics which can be converted into the corresponding amino compounds: 2-aminoquinoline from quinoline (at -60°) [3], 4-aminoquinoline from quinoline (at +20°) [3], 4-aminopyrimidine from pyrimidine [4], 4-aminopyridazine from pyridazine [4], aminopyrazine from pyrazine [4], 5-amino-1,2,4-triazine from 1,2,4-triazine [5], 6-amino-3R-1,2,4,5-tetrazines from 3R-1,2,4,5-tetrazines [6], amino-1,X-naphthyridines (X = 5, 6, 7, 8) [7] and 4-aminopteridine from pteridine [8].

From the substituted azaaromatics we investigated mainly the amination of the nitro compounds. 4-Amino-3-nitroquinoline is obtained from 3-nitroquinoline [3], 4-amino-5-nitropyrimidine is formed from 5-nitropyrimidine [9] and a series of 4-amino-3-nitro-1,X-naphthyridine (X = 5, 6, 7, 8) is easily obtained from 3-nitro-1,X-naphthyridines [7]. Convincing nmr evidence has been presented that in the liquid ammonia all these azaaromatics are converted into the corresponding aminodihydroazaaromatics; it is very probable that these σ-adducts undergo the dehydrogenation reaction.

4-Nitropyridazine 1-oxide (**1a**) and 6-chlor-3-methoxy-4-nitropyridazine 1-oxide (**1b**) have been reported to undergo covalent amination at C-5, when dissolved in liquid ammonia [10,11]. We became interested whether by treatment of these covalent adducts with potassium permanganate the amino group could be introduced at C-5 in those 4-nitropyridazine 1 oxides [12].

When **1a** is added to a solution of potassium permanganate in liquid ammonia at −70°, in 75% yield 5-amino-4-nitropyridazine 1-oxide (**3a**) is obtained. The ^{1}H nmr spectrum of **3a** exhibits two singlets (δ = 9.01 ppm (H-3) and 7.90 ppm (H-6), proving that the amino group is indeed present at C-5. By a similar procedure, **1b** gives the corresponding 5-amino compound **3b** (62%). In the last-mentioned reaction no indication for an amino-demethoxylation or amino-dechlorination is found.



When compound **1c** is dissolved in liquid ammonia the ^{1}H nmr spectrum exhibits, besides the peaks of both methoxy groups (4.10 and 3.77 ppm), a singlet at 5.13 ppm. This peak is attributed to the resonance signal of the hydrogen, attached to the sp^3-carbon in the σ-adduct **2c**. The upfield shift $\Delta\delta$ observed for the hydrogen at C-5 amounts to 2.87 ppm. This $\Delta\delta$ value reflects the sp^2 → sp^3 change of hybridisation of C-5 and is in agreement with upfield shifts observed previously [10] for the compounds **1a** ($\Delta\delta$ = 4.05 ppm) and **1b** (Δ = 3.71 ppm). Addition of potassium permanganate to this mixture results in the formation of 5-amino-3,6-dimethoxy-4-nitropyridazine 1-oxide (**3c**, 54%). Also in this reaction no amino-demethoxylation is observed.

When we compared the reactivity of the N-oxides **1a-1c** with the "deoxygenated" pyridazines **4a-4b** we observed by ^{1}H nmr spectroscopy that **4a** when dissolved in liquid ammonia, does not give an covalent σ-adduct. However, when in the liquid ammonia potassium amide is present, the anionic covalent σ-adduct 4-amino-dihydro-3,6-dimethoxypyridazinide (**5a**) is formed, as unequivocally proved by the upfield shift of H-5 ($\Delta\delta$ = 3.53 ppm). Addition of potassium permanganate to this solution gives in about 50% yield 4-amino-3,6-dimethoxypyridazine (**6a**).

Very similarly, treatment of a solution of 3-methoxypyridazine (**4b**) in liquid ammonia, containing potassium amide, with potassium permanganate gives 4-amino-3-methoxypyridazine (**6b**). No indication for the formation of 5-amino-3-methoxypyridazine was obtained. As side-product in this reaction we could also isolate a product, which structure was proved by nmr spectroscopy, mass spectroscopy and microanalysis to be 3,3'-dimethoxy-4,4'-bipyridazine (**7**).

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded with a Hitachi model EPI-G3. The ^{1}H nmr spectra were taken on a Hitachi Perkin-Elmer R-24B spectrometer using tetramethylsilane (TMS, δ = 0) as an internal standard. In liquid ammonia and liquid ammonia containing potassium amide, ammonia was used as an internal standard (δ = 0.95 ppm). The spectra were recorded on a Varian EM-390 spectrometer. The mass spectra were recorded with an AEI MS 902 instrument.

General Procedure of Amination of the *N*-Oxides **1a-c**.

To a solution of potassium permanganate (2-3, equivalents in 20-30 ml of liquid ammonia at −70°, 1 mmole of the appropriate 4-nitropyridazine 1-oxide **1a-c** was added. After 15 minutes a brown colour was observed. After the mixture was stirred for additional 10 minutes cold chloroform (20 ml) was added to the liquid ammonia solution. The ammonia was evaporated and the whole residue was extracted with warm ethyl acetate. The residue obtained after evaporation of the ethyl acetate was extracted with ether and the remaining solid material crystallized form an appropriate solvent. The crude residue left after evaporation of the solvent was crystallized from an appropriate solvent.

5-Amino-4-nitropyridazine 1-Oxide (**3a**).

4-Nitropyridazine 1-oxide (**1a**, 0.42 g, 3 mmoles) [13] was aminated according to the procedure given above. The residue obtained after working up as indicated above was crystallized from methanol to give 0.35 g (75%) of **3a**, yellow needles, mp 287-288°; ms:m/e 156 (M$^+$), m/e 140 (M$^+$-16); ir (potassium bromide): 3420, 3290 cm^{-1} (NH stretching); ^{1}H nmr (DMSO-d$_6$): δ 9.00 (s, H-3), 8.33 (br s, NH$_2$), 7.90 (s, H-6).

Anal. Calcd. for $C_4H_4N_4O_3$: C, 30.77; H, 2.55; N, 35.89. Found C, 30.77; H, 2.82; N, 35.91.

5-Amino-6-chloro-3-methoxy-4-nitropyridazine 1-Oxide (**3b**).

6-Chloro-3-methoxy-4-nitropyridazine 1-oxide (**1b**), (0.41 g, 2 mmoles) [14] was aminated according to the procedure described above. The residue obtained after extraction with ether was crystallized from methanol yielding 0.273 g (62%) of **3b**, yellow-green needles, mp 205-206°; ms:m/e 220 (M$^+$); ir (chloroform): 3480, 3350 cm^{-1} (NH stretching).

Anal. Calcd. for $C_5H_5ClN_4O$: C, 27.22; H, 2.28; N, 25.40. Found C, 27.50; H, 2.29; N, 25.20.

5-Amino-3,6-dimethoxy-4-nitropyridazine 1-Oxide (**3c**).

This compound was obtained by the amination procedure given above, using 0.49 g (2 mmoles) of 3,6-dimethoxy-4-nitropyridazine 1-oxide (**1c**) [15]. After working-up as indicated above the crude product was crystallized from chloroform or methanol yielding 0.23 g (54%) of **3c**, yellow needles, mp 187-188°; ms:m/e 216 (M$^+$); ir (chloroform): cm^{-1} 3480, 3350 (NH stretching); ^{1}H nmr (deuterochloroform): δ 4.19 (s, OCH$_3$) and 4.11 (s, OCH$_3$).

General Procedure for Aminating the Pyridazines **4a-4b**.

To a stirred solution of liquid ammonia (15-20 ml), containing potassium amide (2.5 equivalents) at −33° the appropriate substrate (1-2 mmoles) was added. After 15 minutes potassium permanganate (3.5 equivalents) was added portion by portion. The resulting mixture was stirred for 30 minutes. Then the reaction mixture was quenched with ammonium sulfate (5 equivalents) and after 10 minutes cold chloroform was added. The ammonia was evaporated off and the whole mixture obtained was extracted with warm chloroform/ethyl acetate. After filtering and evaporation of the solvent the residue was subjected to column chromatography on silica gel for purification.

4-Amino-3,6-dimethoxypyridazine (**6a**).

3,6-Dimethoxypyridazine (**4a**) (0.28 g, 2 mmoles) [16] was aminated according to the procedure described above. The residue was subjected to the chromatography (ethyl acetate/methanol 6:1 as eluent). The main band was extracted with methanol, yield of **6a** was 0.153 g (50%), yellow prisms, mp 178-180° (lit [17,18] 177-180°); ^{1}H nmr (deuterochloroform): δ 6.08 (s, H-5), 4.50 (br s, NH$_2$), 4.08 (s, OCH$_3$), 3.99 (s, OCH$_3$).

4-Amino-3-methoxypyridazine (**6b**).

This compound was prepared from **4b** according to the procedure as described above. The reaction was carried out with 440 mg (4 mmoles) of freshly distilled 3-methoxypyridazine (**4b**). After evaporation of the ammonia, about 1 g of silica gel was added and the whole mixture was dried. The residue was subjected to column chromatography on silica gel for purification (eluent dichloromethane/methanol, 8:1). Two fractions were separated. They were further purified by column chromatography using as eluent dichloromethane/ethylacetate/methanol, 4:4:1. The first fraction (100 mg) was recrystallized from petroleum ether (60-80°), and characterized as **7**, light yellow crystals, mp 168-172°; ^{1}H-nmr (deuterochloroform): δ 8.90 (d, J = 4.5 Hz), 7.45 (d, J = 4.5 Hz) and 4.14 (s, OCH$_3$); ^{13}C nmr (deuterochloroform): (Bruker CXP-300) δ 161.9 (C-3, C-3'), 147.1 ($^1J_{C\text{-}H}$ = 185, C-6, C-6'), 128.8, ($^1J_{C\text{-}H}$ = 167, C-5, C-5'), 122.6 (C-4, C-4') and 55.3 (OCH$_3$).

Anal. Calcd. for $C_{10}H_{10}N_4O_2 \cdot H_2O$: C, 50.84; H, 5.12. Found: C, 50.97; H, 5.28.

The second fraction was identified as **6b**, yield 112 mg (22%) of yellow pale crystals, mp 126-127° (lit [19] 127-128°); ^{1}H nmr and mass spectra are identical with those of an authentic specimen.

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