

Oxidative Methylation of Some Nitropyridines

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Abstract. 2-, 3-, 4-Nitropyridine (**1a**, **i**, **j**) and some simple derivatives of 3-nitropyridine (**1b–h**) undergo dehydro-methylation in a solution of potassium permanganate in

liquid methylamine. In the case of 2- and 6-chloro and 6-methoxy derivatives of 3-nitropyridine (**1b–d**) dechloro- or demethoxy-methylation occurs as well.

It has been reported that 3-nitropyridine and some of its derivatives were dehydroaminated in a solution of potassium permanganate in liquid ammonia [1, 2]. As intermediates in these amination reactions amino- σ -adducts are formed which are subsequently oxidized by KMnO_4 to the aminonitro products. The mentioned reactions are not too selective and often mixtures of amino nitropyridines are formed. These results induced us to study whether or not the methodology described above could also be applied to introduce methyl-amino groups to some nitropyridines, using a similar system of reagents i.e. liquid methylamine/potassium permanganate (LMA/PP). Moreover, in view of the broad range of applications in technique and medical treatment of methylamino derivatives of nitroaza-aromatics and of nitrobenzenes [3], methylamino nitro-pyridines synthesized in this manner could show useful properties.

The methylation of some nitropyridines was carried out at the *b.p.* (ca. -7°C) of liquid methylamine. The products were identified by spectroscopic data or by comparison of their properties with those of reference samples.

Amination of 3-nitropyridine (**1a**) with LMA/PP affords 6-(methylamino)-3-nitropyridine (**3a**) in moderate yield and a small amount of 2,6-bis(methylamino)-3-nitropyridine (**3b**). Contrary to the analogous amination of **1a** with $\text{NH}_3/\text{KMnO}_4$ 2- and 4-amino products are not formed. It is interesting to mention that the ^1H NMR spectrum of a solution of 3-nitropyridine in liquid methylamine not containing potassium permanganate does not show the presence of intermediary methylamino- σ -adducts, like **2**. If this adduct is present, its concentration is apparently too low to be detectable by NMR technique.

The reaction of 2-chloro-3-nitropyridine (**1b**) with LMA/PP gives, as the main product, 2,6-bis(methylamino)-3-nitropyridine (**3b**) and some 2-(methylamino)-3-nitropyridine (**3c**). Besides dehydromethylation in the 6 position, dechloro-methylation in position 2 takes place as well. On the other hand, the reaction of the isomer of **1b**, 6-chloro-3-nitropyridine (2-chloro-5-nitropyridine) (**1c**) with LMA/PP yields exclusively the dechloro-methylamino product i.e. 6-(methylamino)-3-nitropyridine (**3a**). In both reactions of **1b** and **1c**

with LMA/PP we could not detect any chloro-(methyl-amino)-nitropyridine.

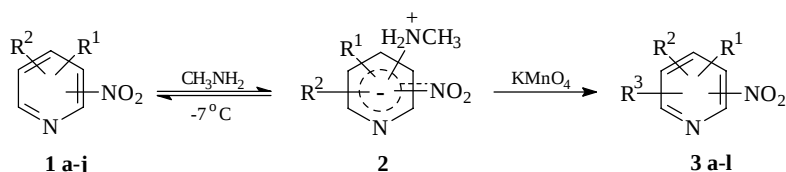
Amination of 6-methoxy-3-nitropyridine (2-methoxy-5-nitropyridine) (**1d**) with LMA/PP affords 2,6-bis(methylamino)-3-nitropyridine (**3b**) and a small amount of 6-methylamino-3-nitropyridine (**3a**). Besides dehydromethylation, the 6-methoxy group in **1d** is replaced by the methyl-amino group.

The reaction of 2-amino-3-nitropyridine (**1e**) with LMA/PP gives exclusively 2-amino-6-(methylamino)-3-nitropyridine (**3e**) in fair good yield. However, analogous reaction of the isomeric 6-amino-3-nitropyridine (2-amino-5-nitropyridine) (**1f**) affords only 3% of the 2-(methylamino) derivative **3f**.

2-Amino-5-chloro-3-nitro- (**1g**) and 2-amino-5-bromo-3-nitropyridine (**1h**) undergo with LMA/PP dehydro-methylation in position 6 to give the corresponding 6-(methylamino) compounds **3g** and **3i** with good yield. In both these reactions some 2,6-diamino-5-chloro(or 5-bromo)-3-nitropyridines **3h** and **3j**, respectively, were isolated. This is probably due to the dehydrogenation of the *N*-methyl group to the imino group in **3g** and **3i** and subsequent elimination of carbon dioxide in alkaline medium.

Finally, we tried to aminate 2-nitropyridine (**1i**) and 4-nitropyridine (**1j**) with LMA/PP. Both these nitro compounds proved to be completely resistant for the amination with liquid $\text{NH}_3/\text{KMnO}_4$ [1]. By contrast, **1i** and **1j** undergo dehydro-methylation with LMA/PP to afford 4-(methylamino)-2-nitropyridine (**3k**) and 3-(methylamino)-4-nitropyridine (**3l**) respectively, with low yields.

Summing up the results we can conclude that in some cases oxidative methylation of nitropyridines occurs differently from oxidative aminations. The reactions are more selective, and the chloro and the methoxy group in the active 2 or 6 positions are replaced by the NHCH_3 group. Methylation of 3-nitropyridines occurs mainly in position 6. Perhaps the strong nucleophile – methylamine is repulsed by negative charge on the oxygen of the nitro group and this causes a more difficult attack in the adjacent positions 2 and 4. Also may be that an intact (push-pull) conjugation between



1	R ¹	R ²	3	R ¹	R ²	R ³	Yield (%)
a	3-NO ₂	H	a	3-NO ₂	6-NHCH ₃	H	65
b	3-NO ₂	2-Cl	b	3-NO ₂	2-NHCH ₃	6-NHCH ₃	3
c	3-NO ₂	6-Cl	c	3-NO ₂	2-NHCH ₃	H	55
d	3-NO ₂	6-OCH ₃	a	3-NO ₂	6-NHCH ₃	H	4
e	3-NO ₂	2-NH ₂	b	3-NO ₂	2-NHCH ₃	H	75
f	3-NO ₂	6-NH ₂	a	3-NO ₂	6-NHCH ₃	H	51
g	3-NO ₂	2-NH ₂	e	3-NO ₂	2-NH ₂	6-NHCH ₃	4
h	3-NO ₂	5-Cl	f	3-NO ₂	2-NHCH ₃	6-NH ₂	61
i	3-NO ₂	5-Br	g	3-NO ₂	2-NH ₂	5-Cl	3
j	2-NO ₂	H	h	3-NO ₂	2-NH ₂	5-Cl	77
k	2-NO ₂	H	i	3-NO ₂	2-NH ₂	5-Br	4
l	4-NO ₂	H	j	3-NO ₂	2-NH ₂	5-Br	64
			k	2-NO ₂	4-NHCH ₃	H	3
			l	4-NO ₂	3-NHCH ₃	H	3(10) ^a
							16

^a) After prolonged (4 h) reaction time.

the pyridin nitrogen atom and the nitro group is essential or that the higher regioselectivity of methylamine compared to ammonia is more due to steric than electronic effects. The described reactions can be used for the preparation of some (methylamino)nitropyridines difficultly accessible by alternative routes, particularly since recently a convenient method for the synthesis of 3-nitropyridine from pyridine was found [4, 5].

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Experimental

m.p. (uncorrected): Kofler plate. IR(KBr pellets): UR-20 spectrometer. ¹H NMR: Tesla BS-587A(80 MHz); TMS as internal standard. MS: LKB GC/MS 9000 apparatus. Silica gel (Merck 230–400 mesh) or neutral aluminium oxide was used for the column chromatography. Preparative thin layer chromatography (PTLC) was carried out on standard plates (20 × 40 cm); Merck Silica gel 60 PF- 254.

Synthesis of Starting and Reference Compounds

2-Nitro- [6], 3-nitro- [7], 4-nitro- [8], 2-amino-3-nitro- [9, 10], 6-amino-3-nitro-(2-amino-5-nitro-) [9, 10], 2-chloro-3-nitro- [11], 6-chloro-3-nitro-(2-chloro-5-nitro-) [11], 6-methoxy-3-nitro-(2-methoxy-5-nitro-) [12], 2-amino-5-chloro-3-nitro- [13], 2-amino-5-bromo-3-nitro- [14], 2,6-diamino-5-chloro-3-nitro- [1] and 2,6-diamino-5-bromo-3-nitropyridine [1] were prepared according to literature procedures.

6-Amino-2-(methylamino)-3-nitropyridine(3f)

6-Amino-2-chloro-3-nitropyridine (30mg; 0.17 mmol) [1] was dissolved in 5 ml of methanol (saturated at 0 °C with gaseous

methylamine). The solution was kept at room temp. for 24 h. Then 10 ml of water was added. The solid was filtered off and recrystallized from toluene to yield 20 mg(70%) of **3f**; yellow needles with *m.p.* 216–218 °C. – MS(70 eV); *m/z*(%): 168(100)[M⁺]. – ¹H NMR(DMSO): δ/ppm = 8.85 (br. s, NH₂), 8.00 (d, 4H), 7.40 (br. s, NH), 5.91 (d, 5H), 2.98 (d, CH₃), *J*_{4,5} = 9.2 Hz, *J*_{CH₃,NH} = 4.2 Hz.

C₆H₈N₄O₂ Calcd.: C 42.86 H 4.80 N 33.32 (168.16) Found: C 42.80 H 4.55 N 33.61.

Methylation of Nitropyridines (General Procedure)

0.2–1.0 g of potassium permanganate was added to 25–30 ml of liquid methylamine and 0.1–0.5 g of nitropyridine, and the resulting mixture was stirred at –7 °C for 0.5 h (KMnO₄ dissolved). After evaporation of methylamine ca. 50 ml of water was added to the residue, and the mixture was extracted continuously with chloroform for 20 h. The residue obtained after evaporation of the solvent from the extract was worked up in the manner described below.

Methylation of 3-Nitropyridine (1a)

0.1 g (0.8 mmol) of **1a** was treated according to the general procedure. The residue obtained was separated, by PTLC, dissolved in chloroform, and developing the chromatograms with dichloromethane. The bands obtained were extracted with chloroform. From the first band (the highest *R_f*), after crystallization from hexane 5 mg (3%) of 2,6-bis(methylamino)-3-nitropyridine (**3b**) was obtained; yellow needles with *m.p.* 166–168 °C. – MS (70 eV); *m/z*(%): 182(100)[M⁺]. – ¹H NMR(CDCl₃): δ/ppm = 8.80 (br. s, NH), 8.14 (d, 4H), 5.77 (d, 5H), 3.08 (t, CH₃), *J*_{4,5} = 9.3 Hz, *J*_{CH₃,NH} = 5.1 Hz. C₇H₁₀N₄O₂ Calcd.: C 46.15 H 5.53 N 30.75 (182.2) Found: C 46.21 H 5.53 N 30.48.

The residue from the extracts of the second band was crystallized from heptane to afford 80 mg (65%) of 6-(methylamino)-3-nitropyridine (**3a**); yellow needles with *m.p.* 177–

178 °C (Lit. [15] 180–181°C). – MS (70 eV); m/z (%): 153(100)[M^+]. – ^1H NMR(CDCl_3): δ /ppm = 9.03 (d, 2H), 8.21 (dd, 4H), 6.37 (d, 5H), 5.41 (br. s, NH), 3.04 (d, CH_3), $J_{2,4} = 2.7$ Hz, $J_{4,5} = 9.3$ Hz, $J_{\text{CH}_3,\text{NH}} = 5.4$ Hz.

Methylation of 2-Chloro-3-nitropyridine (**1b**)

0.2 g (1.26 mmol) of **1b** was treated according to the general procedure. The residue was separated by column chromatography (silicagel, 2.5×50 cm) using chloroform as eluent. The first fraction (300 ml) was washed with hexane to yield 8 mg (4%) of 2-(methylamino)-3-nitropyridine (**3c**); orange crystals with $m.p.$ 61–62 °C (Lit.[16] 63–64 °C). – MS (70 eV); m/z (%): 153(61)[M^+]. The second fraction, washed with hexane, gave 0.11 g (55%) of 2,6-bis(methylamino)-3-nitropyridine (**3b**); yellow crystals with $m.p.$ 166–168 °C. The compound showed properties identical ($m.p.$, IR and ^1H NMR) to those of **3b** obtained from **1a**.

Methylation of 6-Chloro-3-nitropyridine (**1c**)

0.2 g (1.26 mmol) of **1c** was treated according to the general procedure. The residue was crystallized from methanol to give 0.14 g (75%) of 6-(methylamino)-3-nitropyridine (**3a**). The compound was identical ($m.p.$, IR, ^1H NMR) to **3a** obtained from **1a**.

Methylation of 6-Methoxy-3-nitropyridine (**1d**)

0.1 g of **1d** was treated according to the general procedure. The residue was separated by column chromatography (silicagel, 3×35 cm) using chloroform/methanol (97.5 : 2.5) as the eluent. From the first fraction (50 ml) 5 mg (5%) of starting material was recovered. The second fraction (100 ml) was washed with hexane to yield 40 mg of 2,6-bis(methylamino)-3-nitropyridine (**3b**). The compound showed the same properties as those of **3b** prepared from **1b**. The third fraction (200 ml) was separated again, on a PTLT plate, developing the chromatogram with dichloromethane. From the first band (the highest R_f) 20 mg of **3b** was obtained. Total yield of **3b** was 60 mg (51%). The product obtained from the second band was washed with hexane to yield 5 mg (4%) of 6-(methylamino)-3-nitropyridine (**3a**). The compound was identical ($m.p.$, IR) to **3a** obtained from **1a**.

Methylation of 2-Amino-3-nitropyridine (**1e**)

0.15 g (1.08 mmol) of **1e** was treated according to the general procedure. The residue was crystallized from chloroform to afford 0.11 g (61%) of 2-amino-6-(methylamino)-3-nitropyridine (**3e**); orange crystals with $m.p.$ 238.5–240 °C. – MS (70 eV); m/z (%): 168(100)[M^+]. – ^1H NMR(DMSO): δ /ppm = 7.93 (d, 4H), 7.82 (br.s, NH_2), 7.73 (br. s, NH), 5.94 (d, 5H), 2.85 (d, CH_3), $J_{4,5} = 9.4$ Hz, $J_{\text{CH}_3,\text{NH}} = 4.1$ Hz.
 $\text{C}_6\text{H}_8\text{N}_4\text{O}_2$ Calcd.: C 42.86 H 4.80 N 33.32 (168.16) Found: C 42.54 H 4.64 N 33.07.

Methylation of 6-Amino-3-nitropyridine (**1f**)

0.3 g (2.16 mmole) of **1f** was treated according to the general procedure. The residue was dissolved in 50 ml of dichloromethane and filtered off from a solid (A). The solution was separated by column chromatography (aluminum oxide, 4×40 cm) using dichloromethane as the eluent. The first fraction (250 ml) was crystallized from benzene to yield 11 mg (3%) of 6-amino-2-(methylamino)-3-nitropyridine (**3f**); yellow needles with $m.p.$ 216–218 °C. The compound showed

properties identical ($m.p.$, IR, ^1H NMR) to those of **3f** obtained from 6-amino-2-chloro-3-nitropyridine. The second fraction (300 ml) was combined with the solid A to afford 0.21 g (70%) of recovered starting material **1f**.

Methylation of 2-Amino-5-chloro-3-nitropyridine (**1g**)

0.5 g (2.3 mmole) of **1g** was treated according to the general procedure. The residue was crystallized from chloroform to afford the product B. The mother liquor was concentrated and separated by column chromatography (aluminum oxide, 4×40 cm) using chloroform as eluent. The first fraction (200 ml) was crystallized from chloroform and combined with the product A from **1f** to yield 0.45 g (77%) of 2-amino-5-chloro-6-(methylamino)-3-nitropyridine (**3g**); orange needles with $m.p.$ 202–203 °C (in sealed capillary). – MS (70 eV); m/z (%): 204(33), 202(100)[M^+]. – ^1H NMR(CDCl_3): δ /ppm = 8.22 (s, 4H), 5.69 (br.s, NH_2 , NH), 3.07 (d, CH_3), $J_{\text{CH}_3,\text{NH}} = 4.9$ Hz.
 $\text{C}_6\text{H}_7\text{ClN}_4\text{O}_2$ Calcd.: C 35.57 H 3.48 N 27.65 (202.60) Found: C 35.42 H 3.18 N 27.82.

From the second fraction (400 ml), after crystallization from dichloromethane, 20 mg (4%) of 2,6-diamino-5-chloro-3-nitropyridine (**3h**) was obtained; yellow crystals with $m.p.$ 292–294 °C (in sealed capillary) (Lit. [1] 295–296.5 °C). The compound was identical (IR, ^1H NMR) to a reference sample.

Methylation of 2-Amino-5-bromo-3-nitropyridine (**1h**)

0.5 g (2.3 mmole) of **1h** was treated according to the general procedure. The residue was separated by column chromatography (aluminum oxide, 4×35 cm) using chloroform as eluent. The first fraction (300 ml) was crystallized from octane to yield 0.36 g (64%) of 2-amino-5-bromo-6-(methylamino)-3-nitropyridine (**3i**); yellow crystals with $m.p.$ 198–200 °C. – MS (70 eV); m/z (%): 248 (100), 246 (100)[M^+]. – ^1H NMR(CDCl_3): δ /ppm = 8.37 (s, 4H), 5.70 (br.s, NH_2 , NH), 3.06 (d, CH_3), $J_{\text{CH}_3,\text{NH}} = 5.1$ Hz.
 $\text{C}_6\text{H}_7\text{BrN}_4\text{O}_2$ Calcd.: C 29.16 H 2.86 N 22.67 (247.06) Found: C 29.34 H 2.62 N 22.65.
 The second fraction (500 ml) was crystallized from dichloromethane to give 15 mg (3%) of 2,6-diamino-5-bromo-3-nitropyridine (**3j**); yellow crystals with $m.p.$ 267–268 °C (Lit. [1] 270–272 °C). The compound showed properties (IR, ^1H NMR) identical to those of reference sample.

Methylation of 2-Nitropyridine (**1i**)

0.2 g (1.61 mmol) of **1i** was treated according to the general procedure. The residue was separated by column chromatography (aluminum oxide, 3×25 cm) using chloroform as eluent. From the first fraction (150 ml) 0.11 g (55%) of **1i** was recovered. The second fraction was crystallized from hexane to yield 8 mg (3%) of 4-(methylamino)-2-nitropyridine (**3k**); orange needles with $m.p.$ 108 °C. – MS (70 eV); m/z (%): 153(100) [M^+]. – ^1H NMR(CDCl_3): δ /ppm = 7.91 (dd, 5H), 7.87 (br.s, NH), 7.43 (d, 6H), 7.37 (d, 3H), 3.05 (d, CH_3), $J_{3,5} = 1.7$ Hz, $J_{5,6} = 3.9$ Hz, $J_{\text{CH}_3,\text{NH}} = 5.6$ Hz.
 $\text{C}_6\text{H}_7\text{N}_3\text{O}_2$ Calcd.: C 47.06 H 4.61 N 27.44 (153.14) Found: C 46.90 H 4.55 N 27.32.

Methylation of 4-Nitropyridine (**1j**)

0.3 g (2.41 mmole) of **1j** was treated according to the general procedure. The residue was purified by column chromatography

graphy (aluminium oxide, 2×20 cm) using chloroform as the eluent and then crystallized from hexane to afford 58 mg (16%) of 3-(methylamino)-4-nitropyridine (**31**); orange crystals with *m.p.* 119.5–120.5 °C. – MS(70 eV); *m/z*(%): 153[M⁺]. – ¹H NMR(CDCl₃): δ /ppm = 8.52 (s, 2H), 7.99 (d, 5H), 7.88 (d, 6H), 7.64 (br.s, NH), 3.15 (d, CH₃), $J_{5,6} = 5.6$ Hz, $J_{\text{CH}_3, \text{NH}} = 6.6$ Hz.

C₆H₇N₃O₂ Calcd.: C 47.06 H 4.60 N 27.44
(153.14) Found: C 46.84 H 4.51 N 27.4.

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