Selective vicarious nucleophilic amination of 3-nitropyridines

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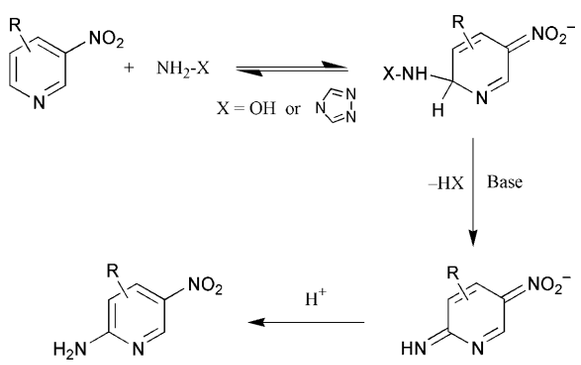
Nine 3-nitropyridine compounds and 4-nitroisoquinoline have been aminated in the 6-position (for 4-nitroisoquinoline in the 1-position) by vicarious nucleophilic substitution reactions. Two amination reagents were used, hydroxylamine and 4-amino-1,2,4-triazole. The yields were from moderate to good. Use of hydroxylamine gave an easy work-up procedure by which almost pure product was obtained directly, but 4-amino-1,2,4-triazole gave better yields of the aminated product for some of the substrates. By this, a general method for the preparation of 3- or 4-substituted-2-amino-5-nitropyridines was obtained.

Introduction

We have reported a new method for the nitration of pyridine compounds. This has made a number of β-nitropyridines readily available, and we are now exploring the chemistry of these compounds.[1] The electron deficient nature of the pyridine ring is enhanced by the introduction of the nitro group in the 3-position. These compounds would therefore be expected to be susceptible to attack by nucleophiles, with attack at the positions *ortho*- and *para*- to the nitro group being favoured. We have reported one such reaction, the addition of sodium sulfite to 3-nitropyridine to give 5-hydroxyaminopyridine-2-sulfonic acid as the final product.[2] In extension of this, we now report the vicarious amination[3] of 4- and 5-substituted 3-nitropyridines. The goal was to obtain 2-amino-5-nitropyridines selectively which would be useful starting compounds for the synthesis of biological active compounds. The 2,5 substitution pattern of pyridine is the base for many pharmaceuticals and crop protecting agents. However, in general it has been difficult to obtain this pattern with high regioselectivity.[4] With a number of 2-amino-5-nitropyridine compounds available, it would be possible to synthesise a large number of 2,5-substituted pyridines as both these groups may be substituted with a number of substituents, for example by the Sandmeyer reaction (the nitro group first requiring reduction to an amino group).

Some examples of syntheses of aminonitropyridines have been reported. Thus, Wozniak *et al.* aminated some 3-nitropyridines by liquid ammonia–potassium permanganate. This procedure gave mixtures of *ortho* and *para* isomers (relative to the nitro group).[5] Seko and Miyake reported the amination of a few substituted nitropyridines by the use of *O*-methylhydroxylamine as aminating agent.[6] However, they did not report results for any 4- or 5-substituted 3-nitropyridines. Makosza and Bialecki used sulfenamides as aminating agents. With 4-ethoxy-3-nitropyridine this gave 2-amino-4-ethoxy-5-nitropyridine (75% yield) and with 6-methoxy-3-nitropyridine gave 2-amino-3-nitro-6-methoxypyridine (42%).[7] 2-Amino-5-nitropyridines have also been obtained by nitration of 2-aminopyridines, the resulting nitramines were rearranged to the 2-amino-5-nitropyridines. This procedure is not suitable for large scale synthesis and also gave considerable amounts of the 2-amino-3-nitropyridine isomers.[8]

Thus, there is only a limited number of methods available for the amination of nitropyridines and none of these have been employed for an extensive number of substrates. A general process for the preparation of these compounds might therefore be of some use. The vicarious nucleophilic amination appeared to be of special interest as both reagents and reaction conditions for this type of reaction are comparatively simple. Two different amination reagents were used, hydroxylamine and 4-amino-1,2,4-triazole. Several of the products have not been reported previously. The reaction is outlined in Scheme 1.



Scheme 1

Results and discussion

Hydroxylamine as aminating agent (Procedure A)

Reaction of a number of 3-nitropyridines with hydroxylamine and base afforded 2-amino-5-nitropyridines as the only observed isomer. The yields are given in Table 1. Seko and Miyake used zinc dichloride as a catalyst in their reaction with *O*-methylhydroxylamine and claimed it to be essential for the reaction.[6] We found that our reaction took place without zinc dichloride, but use of one equivalent increased the yield from 45 to 54% (Table 1, entries 1 and 2). Ethanol was found to be the best solvent for the reaction, but methanol and even water could be used (Table 1, entries 3 and 4). Potassium hydroxide was used as base, potassium methoxide (from potassium *tert*-butoxide) in dry methanol gave a lower yield (Table 1, entry 3). With electron donating groups on the pyridine ring, the reaction was slower and it was necessary to add more hydroxylamine and base after 5 hours of stirring (Table 1, entries 5, 6, 9, 10, 11, 12). Pure products were obtained by evaporation of the organic phase after extraction, any by-products remained in the water phase. The advantage of this procedure is its selectivity, use of inexpensive hydroxylamine and the easy work-up.

4-Amino-1,2,4-triazole as aminating agent (Procedure B)

Katritzky and Laurenzo have reported amination of substituted nitrobenzenes by the use of 4-amino-1,2,4-triazole in a

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Table 1 Yields (isolated) for the amination of R-3-nitropyridines by hydroxylamine to give R-2-amino-5-nitropyridines

Entry	R	Base	Solvent	Yield (%)	Product
1	H	KOH	EtOH	45[a]	2-Amino-5-nitropyridine
2	H	KOH	EtOH	54	2-Amino-5-nitropyridine
3	H	Bu^{t}OK	MeOH	42	2-Amino-5-nitropyridine
4	H	KOH	H_2O	26	2-Amino-5-nitropyridine
5	4-CH_3	KOH	EtOH	42	2-Amino-4-methyl-5-nitropyridine
6	5-CH_3	KOH	EtOH	56	2-Amino-3-methyl-5-nitropyridine
7	4-CO_2CH_3	CH_3ONa	MeOH	30	Methyl 2-amino-5-nitroisonicotinate
8	4-CN	KOH	EtOH		Complex mixture
9	4-CHO (protected as the dioxolane)	KOH	EtOH	47	2-Amino-4-(1,3-dioxolan-2-yl)-5-nitropyridine
10	4-$COCH_3$ (protected as the dioxolane)	KOH	EtOH	63	2-Amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine
11	4-Ph	KOH	EtOH	64	2-Amino-4-phenyl-5-nitropyridine
12	5-Ph	KOH	EtOH	35	2-Amino-3-phenyl-5-nitropyridine
13	4-Nitroisoquinoline	KOH	EtOH	23	1-Amino-4-nitroisoquinoline

[a] No $ZnCl_2$ added.

Table 2 Yields (isolated) for the amination of R-3-nitropyridines by 4-amino-1,2,4-triazole to give R-2-amino-5-nitropyridines

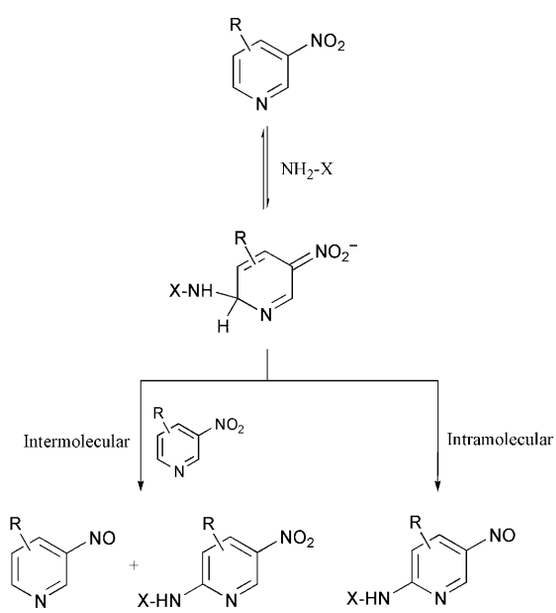
Entry	R	Base	Solvent	Yield (%)	Product
1	H	Bu^{t}OK	DMSO	76	2-Amino-5-nitropyridine
2	H	KOH	DMSO	56	2-Amino-5-nitropyridine
3	H	Bu^{t}OK	MeCN	26	2-Amino-5-nitropyridine
4	H	Bu^{t}OK	DMF	44	2-Amino-5-nitropyridine
5	4-CH_3	Bu^{t}OK	DMSO	61	2-Amino-4-methyl-5-nitropyridine
6	5-CH_3	Bu^{t}OK	DMSO	59	2-Amino-3-methyl-5-nitropyridine
7	4-CO_2CH_3	Bu^{t}OK	DMSO	11	Methyl 2-amino-5-nitroisonicotinate
8	4-CN	Bu^{t}OK	DMSO		Complex mixture
9	4-CHO (protected as the dioxolane)	Bu^{t}OK	DMSO	47	2-Amino-4-(1,3-dioxolan-2-yl)-5-nitropyridine
10	4-$COCH_3$ (protected as the dioxolane)	Bu^{t}OK	DMSO	65	2-Amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine
11	4-Ph	Bu^{t}OK	DMSO	79	2-Amino-4-phenyl-5-nitropyridine
12	5-Ph	Bu^{t}OK	DMSO	66	2-Amino-3-phenyl-5-nitropyridine
13	4-Nitroisoquinoline	Bu^{t}OK	DMSO	65	1-Amino-4-nitroisoquinoline

vicarious nucleophilic substitution reaction.[9] We wished to investigate this for the amination of 3-nitropyridines and compare the results with those from the reactions with hydroxylamine. Reaction of 3-nitropyridines with 4-amino-1,2,4-triazole and base indeed gave 2-amino-5-nitropyridines with the same high regioselectivity as the reaction with hydroxylamine. The yields for the different substrates are given in Table 2. The reaction was performed in dimethyl sulfoxide with potassium *tert*-butoxide as base. Introductory experiments indicated that the reaction had to be carried out in dilute solutions, and also that the rate of addition of the nitropyridine to the DMSO solution had to be sufficiently slow in order to avoid formation of byproducts.

Dimethylformamide and tetrahydrofuran were also tried as solvents but both gave lower yields than DMSO.

The use of the two amination reagents, hydroxylamine and 4-amino-1,3,4-triazole gave similar yields for several of the substrates. For methyl 3-nitroisonicotinoate hydroxylamine gave the better yield (30% *vs*. 11% with 4-amino-1,3,4-triazole) while 4-amino-1,3,4-triazole gave better results for 3-nitropyridine (76% *vs*. 54% with hydroxylamine), 4-methyl-3-nitropyridine (61% *vs*. 42% with hydroxylamine) and 4-phenyl-3-nitropyridine (79% *vs*. 64% with hydroxylamine). For 4-cyanopyridine the yield was very low and a complex reaction mixture was obtained. A substitution of the nitro group may have taken place. It is known that the nitro group may be substituted when situated at an electron deficient carbon.[10] We have observed such a reaction with 4-cyano-3-nitropyridine and sodium azide by which 3-azido-4-cyanopyridine was obtained in high yield.[11]

Another possible side-reaction would be an intra- or intermolecular reduction of the nitro group to a nitroso group (Scheme 2). This type of reaction is known for reaction of nitrobenzene with aniline[3] and we observed an analogous reaction from sodium sulfite and 3-nitropyridine.[2] The nitroso compounds might then react further with amines to give azo compounds or with hydroxylamine to give azoxy compounds, explaining the deep brown colour of the reaction mixture.



Scheme 2

The acetyl and the formyl group had to be protected by use of ethane-1,2-diol before the amination to avoid nucleophile attack on the carbonyl group.

In conclusion, we have investigated two different procedures to selectively transform 3-nitropyridines into 2-amino-5-nitropyridines in moderate to good yields. The use of hydroxylamine was a simpler and cheaper procedure. In large scale preparations this procedure would be better because of the easy work-up to give pure products even if the yields were only

moderate for several of the substrates. The use of 4-amino-1,2,4-triazole demanded an inert atmosphere and dimethyl sulfoxide as solvent. As the yields were better for some of the substrates this may be the preferred procedure for small-scale preparations.

Experimental

The spectroscopic and analytical equipment used have been reported elsewhere.[1] Elemental analyses were carried out by the Laboratory of Organic Elemental Analysis, Prague Institute of Chemical Technology, Czech Republic. The organic extracts were dried over $MgSO_4$. The starting compounds were prepared as described in earlier papers.[1] Dinitrogen pentoxide was prepared from dinitrogen tetroxide and ozone.[12] Protection of the carbonyl groups prior to amination and nitration was carried out by standard methods.[13,14]

Amination of 3-nitropyridines

Procedure A, with hydroxylamine. The 3-nitropyridine compound (10 mmol) in ethanol (50 ml) was added dropwise to a stirred solution of hydroxylamine hydrochloride (30 mmol), potassium hydroxide (80 mmol) and zinc dichloride (10 mmol) in ethanol (100 ml). In some cases (Table 1, entries 5, 6, 9, 10, 11) more hydroxylamine (15 mmol) and potassium hydroxide (20 mmol) were added after 5 hours of stirring. The reaction mixture was stirred overnight at room temperature, and poured into water (200 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 ml), the combined organic phase washed with water, dried and evaporated to give the 2-amino-5-nitropyridine compound.

Procedure B, with 4-amino-1,2,4-triazole. The 3-nitropyridine compound (10 mmol) in dimethyl sulfoxide (30 ml) was added dropwise to a stirred solution of 4-amino-1,2,4-triazole (35 mmol) and potasium *tert*-butoxide (20 mmol) in dimethyl sulfoxide (60 ml) under nitrogen atmosphere. The reaction mixture was stirred for 5 hours at room temperature, and then poured into water (200 ml) saturated with NH_4Cl.

The aqueous phase was extracted with CH_2Cl_2 (3 × 100 ml), the combined organic phases evaporated, and the residue recrystallized from water–methanol to give the 2-amino-5-nitropyridine compound.

Physical and analytical data for the prepared compounds are given below.

2-Amino-5-nitropyridine. Mp 188–189 °C (lit.[5] 188–189 °C); IR (KBr): 3501, 3363, 1648, 1632, 1583, 1570, 1494, 1473, 1333, 1285, 1129, 842 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.50 (d, 1H, H^3, J = 9.39 Hz), 7.52 (br s, 2H, NH_2), 8.12 (dd, 1H, H^4, J = 2.80, 9.31 Hz) 8.84 (d, 1H, J = 2.78 Hz H^6).

2-Amino-4-methyl-5-nitropyridine. Mp 219–220 °C (lit.[8] 220 °C) IR (KBr): 3406, 3329, 3121, 1654, 1608, 1544, 1492, 1452, 1372, 1332, 1290, 1279, 1109, 954, 841 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 5.03 (br s, 2H, NH_2), 6.33 (s, 1H, H^3), 8.93 (s, 1H, H^6).

2-Amino-3-methyl-5-nitropyridine. Mp 256–257 °C (lit.[8] 255 °C); IR (KBr): 3450, 3321, 3119, 1851, 1583, 1477, 1422, 1343, 1292, 1109, 1040, 1018, 941, 770 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH_3), 5.03 (br s, 2H, NH_2), 8.02 (d, 1H, J = 1.94 Hz, H^4), 8.74 (d, 1H, J = 1.94 Hz, H^6).

2-Amino-4-methoxycarbonyl-5-nitropyridine (methyl 2-amino-5-nitroisonicotinate). This was a light brown solid, mp 205–206 °C; IR (KBr): 3441, 3309, 1733, 1649, 1457, 1344, 1303, 1279, 1180, 1079, 986, 876 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.85 (s, 3H, CH_3), 6.52 (s, 1H, H^3) 7.84 (br s, 2H, NH_2), 8.82 (s, 1H, H^6); anal. calcd. for $C_7H_7N_3O_4$: C, 42.65; H, 3.58; N, 21.31. Found: C, 42.50; H, 3.87; N, 21.25%.

2-Amino-4-(1,3-dioxolan-2-yl)-5-nitropyridine. This was a yellow solid, mp 175–177 °C; ^1H-NMR ($CDCl_3$): δ 3.9–4.3 (q, 4H, dioxolane protons), 5.18 (s, 1H, dioxolane proton), 6.57 (s, 1H, H^3), 6.80 (s, 2H, NH_2), 8.89 (s, 1H, H^6); IR 3461, 1548, 1329 cm^{-1}; anal. calcd. for $C_8H_9N_3O_4$: C, 45.50; H, 4.27; N, 19.91. Found: C, 45.27; H, 4.33; N, 19.56%.

2-Amino-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine. This was an orange solid, mp 172–173 °C; IR (KBr): 3459, 3314, 3191, 1691, 1521, 1425, 1369, 1203, 1026, 877 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.72 (m, 2H, dioxolane protons), 4.02 (m, 2H, dioxolane protons), 5.01 (br s, 2H, NH_2), 6.69 (s, 1H, H^3), 8.42 (s, 1H, H^6); anal. calcd. for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.08; H, 4.79; N, 18.67%.

2-Amino-4-phenyl-5-nitropyridine. This was a yellow solid, mp 165–166 °C; IR (KBr): 3412, 3319, 3156, 1652, 1598, 1538, 1481, 1327, 1296, 1134, 848 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.20 (br s, 2H, NH_2), 6.37 (s, 1H, H^3), 7.29 (m, 2H, phenyl protons) 7.43 (m, 3H, phenyl protons), 8.85 (s, 1H, H^6); anal. calcd. for $C_8H_9N_3O_4$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.24; H, 4.42; N, 19.27%.

2-Amino-3-phenyl-5-nitropyridine. This was a yellow solid, mp 175–176.5 °C (lit.[15] 176.5–177 °C); IR (KBr): 3473, 3299, 3116, 1645, 1574, 1485, 1444, 1353, 1334, 1307, 1127, 733 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.36 (br s, 2H, NH_2), 8.18 (d, 1H, J = 2.58 Hz, H^4), 7.50–7.60 (m, 5H, phenyl protons), 9.02 (d, 1H, J = 2.58 Hz, H^6).

1-Amino-4-nitroisoquinoline. This was a yellow solid, mp 277–280 (lit.[16] 283–287 °C); IR (KBr): 3417, 3338, 3087, 1671, 1617, 1580, 1510, 1492, 1449, 1401, 1363, 1285, 1256, 1030, 769 cm^{-1}; ^1H-NMR (DMSO-d_6): δ 7.65 (dd, 1H, J = 8.30, 8.58 Hz, H^7), 7.87 (dd, 1H, J = 8.30, 8.58 Hz, H^6), 8.40 (d, 1H, J = 8.30 Hz, H^8), 8.45 (br s, 2H, NH_2), 8.72 (d, 1H, J = 8.58 Hz, H^5), 8.97 (s, 1H, H^3); anal. calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.89; H, 4.13; N, 22.09%.

Acknowledgement

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