Nucleophilic aromatic substitution of methyl 3-nitropyridine-4-carboxylate

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The nitro group of methyl 3-nitropyridine-4-carboxylate (**1**) has successfully been replaced by nitrogen, oxygen and sulphur nucleophiles by nucleophilic aromatic substitution to give the 3-azido, 3-methoxy, 3-phenoxy and 3-thiophenoxypyridine-4-carboxylates (**2a** – **d**).

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Introduction .

In general, aromatic substrates are very unreactive towards nucleophilic substitution. However, substitution is accelerated by electron-withdrawing groups *o* or *p* to the leaving group. A hetero-N atom in the ring is also activating. Surprisingly, the nitro group, which is not generally displaced in aliphatic systems, is a particularly good leaving group in nucleophilic aromatic substitutions [1,2].

These effects and the synthetic potential for the replacement of a nitropyridine group have been demonstrated by our results for the nucleophilic aromatic substitution of the nitro group in 3-nitro-4-carboxylate (**1**). Results are given for different nucleophiles that have been tested to yield new substitution products. This is part of an investigation of the chemistry of nitropyridines which is now in progress in our laboratories, based on the fact that a number of substituted 3-nitropyridines have now become readily available through an improved nitration method [3,4].

Results and Discussion.

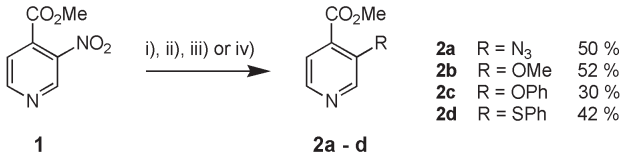
The azide ion easily replaced the nitro group to afford the 3-azide substitution product **2a**. Infrared spectroscopy confirmed the absence of the ir nitro frequencies (1344 and 1528 cm^{-1}) of the precursor and the presence of the characteristic strong azide ir frequency of 2110 cm^{-1}. Similar nucleophilic aromatic substitution of the nitro group by azide has been observed in our laboratory for the sodium azide reaction of 4-cyano-3-nitropyridine affording 3-azido-4-cyanopyridine in high yield [5].

Correspondingly, the methoxy, phenoxy and the thiophenoxy substitution products **2b-d** have been prepared. The methoxy compound **2b** has previously been prepared by nucleophilic aromatic substitution of the 3-bromo analogue with sodium methoxide [6] and later by photochemical methoxylation at the 3-position of methyl pyridine-4-carboxylate in methanol under oxygen in the presence of sulphuric acid [7,8].

^{1}H nmr showed complete conversion of the 3-nitro substrate (**1**) into the 3-methoxy substitution product (**2b**) after 5 hours reflux with sodium methoxide in methanol. The ester substrate **1** was very sensitive to moisture by the methanol/methoxide reaction conditions. An immediate hydrolysis of the methyl ester **1** into 3-nitro-4-carboxylic acid was observed when traces of water were present.

The phenoxy substitution product **2c** was prepared from **1** by phenol/sodium hydride in DMSO. ^{1}H nmr showed complete conversion of the starting material into the diaryl ether product **2c** after 20 minutes heating. The thiophenoxy product **2d** was prepared in a same manner. To our knowledge, the 3-pyridyl-phenyl ether **2c** and the thio ether **2d** have not previously been described. However, the non-pyridine analogue, the corresponding biphenyl ether, methyl *o*-phenoxybenzoate, is an herbicide agent [9] and has shown fungicidal activity [10].

Scheme 1



1 **2a - d**

i) NaN_3, DMSO, ii) NaOMe, MeOH, iii) PhOH, NaH, DMSO, iv) PhSH, NaH, THF

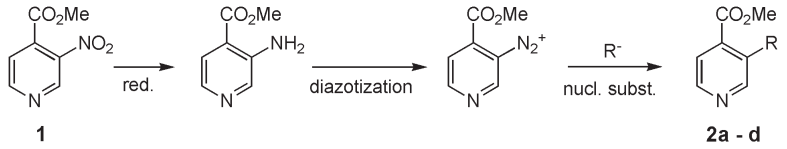
The substitution of the electronegative nitro substituent with oxygen and sulphur nucleophiles can be followed by the characteristic ^{1}H nmr low frequency values and the increased shielding effect of the appearing substitution products **2a-d**, especially for H-2 and H-6.

For some purposes this direct nitro substitution may be a more convenient and rapid pathway than the traditional three-step procedure *via* diazotization as shown in Scheme 2:

Conclusion.

The nitro group of 3-nitropyridine-4-carboxylate (**1**) has been demonstrated to be easily replaced by nucleophilic aromatic substitution by azide, methoxy, phenoxy and thiophenoxy anions. The results demonstrate the good leaving group ability of the nitro group in methyl 3-nitropyridine-4-carboxylate (**1**) in nucleophilic aromatic substitution reactions.

Scheme 2



This one-step nitro substitution reaction represents a superior alternative to the traditional three-step procedure going *via* the amine and the standard substitution of a diazonium salt.

EXPERIMENTAL

Chemicals: NaN_3, phenol (Merck), thiophenol, NaOMe (Fluka), NaH (Sigma-Aldrich); Solvents: *pro analysi* quality. ^1H / ^{13}C nmr: Bruker Avance DPX 300 and 400 MHz spectrometers, chemical shifts are reported in ppm downfield from TMS. J values are given in Hz. ms: Finnigan MAT 95 XL (EI / 70 eV). ir: Nicolet 20SXC FT-IR spectrophotometer. All melting points are uncorrected, measured by Griffin apparatus. Flash chromatography: Silica (sds, 60 A, 40-63 μm). Methyl 3-nitropyridine-4-carboxylate (**1**) was prepared from methyl pyridine-4-carboxylate by nitration according to the literature [11,12].

Methyl 3-Azidopyridine-4-carboxylate (**2a**).

A solution of methyl 3-nitropyridine-4-carboxylate (**1**, 100 mg, 0.55 mmol) and NaN_3 (117 mg, 3.27 mmol, 3.3 equivalents) in dry DMSO (2 ml) was heated to 85 °C for 20 min. Alternatively, the solution was left stirring for 16 hrs. at 45 °C. Addition of acetone (2 ml) followed by flash chromatography (diethyl ether) afforded a crystalline product, pure by ^1H and ^{13}C nmr (44 mg, 50 %). The reaction was also carried out in DMSO-d_6 and monitored by ^1H nmr; mp 46.5-47 °C (diethyl ether); ir (film) 3004s, 2110s, 1716m, 1643s, 1420m, 1362m, 1221s, 1092m cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.67 (d, J 4.96, 1H, H-5), 8.48 (d, J 4.96, 1H, H-6), 8.64 (s, 1H, H-2); ^{13}C nmr (75 MHz, DMSO-d_6): δ 53.2, 123.7, 129.2, 134.7, 144.0, 146.3, 164.5; ms: m/z 178 (M^+, 7 %), 150 (52), 147 (25), 123 (57), 119 (17), 118 (11), 108 (67), 107 (37), 64 (100).); HRMS: calcd for $C_7H_6N_4O_2$; 178.0491; observed 178.0489.

Methyl 3-methoxypyridine-4-carboxylate (**2b**).

Methyl 3-nitropyridine-4-carboxylate (**1**, 210 mg, 1.153 mmol) in freshly distilled methanol (10 ml) was added to freshly made sodium methoxide in methanol (1.5 *M*, 0.945 ml, 1.417 mmol, 1.25 equivalents) under N_2 at –5 °C. The reaction mixture was refluxed for 5 hrs. ^1H nmr showed complete conversion of the substrate (**1**) into the methoxy substitution product (**2b**). Ether (50 ml) and a NH_4Cl solution were added to the reaction mixture. After extraction, drying and concentration *in vacuo*, the crystalline product was obtained (100 mg, 52 %) by flash chromatography (diethyl ether/dichloromethane 1:1) pure by ^1H and ^{13}C nmr; mp 59.5 - 60 °C (hexane) (lit. [6] 58 °C); ir (KBr) 3028w, 2958w, 1720s, 1593m, 1558m, 1498m, 1323s, 1109s, 1070s, 1018s, 958m, 838m, 786s, 713m, 665m cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.94 (s, 3H), 7.50 (d, J 4.9, 1H, H-5), 8.27 (d, J 4.9, 1H, H-6), 8.39 (s, 1H, H-2); ^{13}C nmr (100 MHz, D_2O): δ 55.7, 59.8, 126.9, 129.7, 138.9, 145.5, 156.5, 168.3; ms: m/z 167 (M^+, 100 %), 152 (17), 136 (21), 134 (29), 106 (2); HRMS: calcd for $C_8H_9NO_3$; 167.05824, observed 167.05849.

Methyl 3-Phenoxypyridine-4-carboxylate (**2c**).

Methyl 3-nitropyridine-4-carboxylate (**1**, 100 mg, 0.55 mmol) and phenol (66.43 mg, 0.062 ml, 0.7 mmol, 1.2 equivalent) were dissolved in dry DMSO (2 ml) and NaH (19.76 mg, 0.82 mmol, 1.5 equivalent) was added. The reaction mixture was heated to 85 °C for 20 minutes. ^1H nmr showed complete conversion of the starting material. The reaction mixture was added HCl (10 %), extracted with EtOAc and concentrated *in vacuo*. The crude product was purified by flash chromatography (diethyl ether/dichloromethane 1:1) yielding 37 mg (30 %) oily product, pure by ^1H nmr; ir (film) 3015w, 1716s, 1362m, 1222m cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.99 (d, J 6.0, 2H, *o*-PhH), 7.15 (m, 1H, *p*-PhH), 7.36, (d, J 6.0, 2H, *m*-PhH), 7.73 (d, J 5.2, H-5), 8.03 (s, 1H, H-2), 8.48 (d, J 5.2, 1H, H-6); ^{13}C nmr (75 MHz, $CDCl_3$): δ 52.8, 115.3, 118.1, 124.0, 124.2, 130.0, 143.5, 144.7, 151.2, 156.9, 164.7; ms: m/z 230 (M+1, 12 %), 229 (M^+, 100 %), 197 (55), 170 (11), 115 (11), 108 (12); HRMS: calcd for $C_{13}H_{11}NO_3$; 229.0739, observed 229.0741.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.57; H, 4.90; N, 6.18.

Methyl 3-Thiophenoxypyridine-4-carboxylate (**2d**).

The reaction was carried out as above for the preparation of the phenoxy product **2c**, replacing phenol with thiophenol (56.77 mg, 0.5 mmol, 1.1 equivalent) and DMSO (2 ml) with THF (5 ml). The crystalline product (**2d**, 56 mg, 42 %), pure by ^1H and ^{13}C nmr, was obtained after flash chromatography (hexane/acetone 3:1); mp 75 °C (hexane); ir (film) 3064w, 2948w, 1723s, 1456m, 1436s, 1396m, 1279s, 1220m, 1197m, 1178m, 1098s, 1038m, 971m, 780s, 750s, 700s cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6): δ 3.90 (s, 3H) 7.4-7.6 (m, 5H), 7.76 (d, J 5.0, 1H, H-5), 8.03 (s, 1H, H-2), 8.49 (d, J 5.0, 1H, H-6); ^{13}C nmr (75 MHz, DMSO-d_6): δ 53.2, 123.4, 127.5, 127.9, 129.8, 129.9, 130.6, 131.1, 134.7, 135.7, 165.3; ms: m/z 245 (M^+, 51 %), 232 (16), 214 (12), 186 (19), 158 (5), 123 (100), 115 (20), 109 (14); HRMS: calcd for $C_{13}H_{11}NO_2S$; 245.0511, observed 245.0515.

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.68; H, 4.42; N, 5.54.

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