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# Substitution reactions of 5-nitropyridine-2-sulfonic acid. A new pathway to 2,5-disubstituted pyridines

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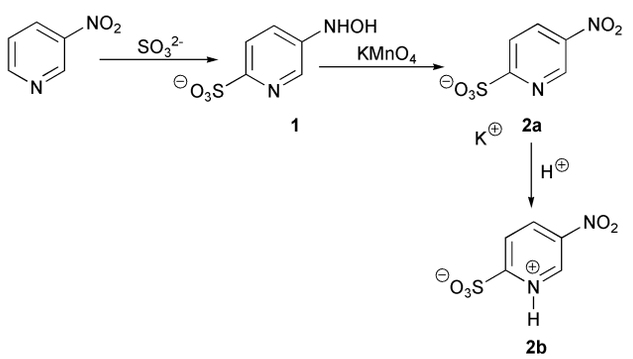
We have investigated reactions of 5-nitropyridine-2-sulfonic acid and its potassium salt in which substitution of the sulfonate group by oxygen, nitrogen and halogen nucleophiles has been attempted. By this approach, 2-methoxy- (95% yield), 2-ethoxy- (97%), 2-isopropoxy- (65%), 2-amino- (92%), 2-butylamino- (76%), 2-diethylamino- (62%), 2-ethylamino- (32%), 2-benzylamino- (77%), 2-(*R*-1-phenylethylamino)- (71%) and 2-chloro-5-nitropyridine (87%) have been obtained. No reactions were observed with phenols or anilines. With *t*-BuOH, 2-hydroxy-5-nitropyridine was formed together with 2-methylpropene.

We have previously reported a simple preparation of 5-nitropyridine-2-sulfonic acid (**2**) from the readily available 3-nitropyridine (Scheme 1)[1] and proposed this as a novel starting material for 2,5-disubstituted pyridines. This substitution pattern is important in many biologically active compounds.[2] One commonly-used starting compound in previous approaches to this system has been 2-chloro-5-nitropyridine (**3**). However, it is prepared by a multistep synthesis[3,4] and new starting materials are therefore of interest.




**Scheme 1**

The sulfonate group is used as a leaving group in nucleophilic aromatic substitutions, for example, in the reaction with hydroxy ions to give the corresponding phenol. The conditions for this reaction are drastic, typically 200–300 °C in molten alkali hydroxide.[5] However, for activated substrates, less extreme conditions suffice.[6] In 5-nitropyridine-2-sulfonic acid (**2**), the sulfonate group should be activated by both the ring nitrogen atom and the *para* nitro group. Substitution reactions under milder conditions might therefore be possible. Indeed, some time ago it was reported that **2** had been reacted with a number of nucleophiles under less drastic reaction conditions.[7] Thus, a new starting material for 2,5-disubstituted pyridines might be available. Encouraged by the earlier report,[7] we initiated an investigation of the substitution reactions of **2**.

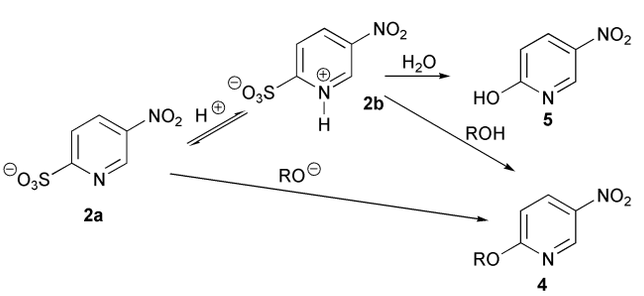
## Results and discussion

We have treated **2** with several different types of nucleophiles, oxygen nucleophiles (alcohols, alcoholates and phenols); nitrogen nucleophiles (amines and anilines); halides and cyanides. In the preparation of **2** for use as the starting material for further reactions, either as the salt **2a** or the acid **2b**, the product contains inorganic salts. These did not have any influence on the substitution reactions reported here. As the removal of the inorganic material requires considerable effort, the salt-containing preparations were used in the reactions. The actual concentrations of **2a** or **2b** were determined from $^1$H NMR spectroscopy with an internal standard, sodium acetate, present. The yields reported correspond to the starting quantities of **2a** or **2b** determined by this method. In the earlier report on the reactions of **2**, a water solution of its potassium salt was treated with a methanol solution of sodium methoxylate.[7] In our hands this procedure did not give the reported 70% yield of 2-methoxy-5-nitropyridine (**4a**), but only a 15% yield. The major product was 2-hydroxy-5-nitropyridine (**5**, 80%). The reported experimental details were not comprehensive, and the products were characterised by melting points only.[7] From this it appeared that a thorough investigation of the reactions of **2** was warranted.

### Reactions with alcohols

The reported substitution reactions of arylsulfonic acids are usually carried out under alkaline conditions, presumably to increase the reactivity of the nucleophiles. However, with **2b** as substrate, both the *para* nitro group and the positively charged ring nitrogen should activate the sulfonate group. Under these conditions the alcohols in their neutral states might be active enough to permit substitution of the sulfonate group. We have therefore investigated the reaction under both acidic and basic conditions. It was also clear from our experience with aqueous solutions that water would compete with other nucleophiles for the substitution of the sulfonate group. The reactions with alcohols were therefore run under water free conditions.

**a) Reactions under basic conditions.** These reactions were carried out on the potassium salt of the 5-nitropyridine-2-sulfonic acid (**2a**, Scheme 2). The yields in Table 1 were




**Scheme 2**

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**Table 1** Formation of 2-alkoxy-5-nitropyridine (**4**) from potassium 5-nitropyridine-2-sulfonate (**2a**)[a]

$$RONa + 2\text{-}K^{+\,-}O_3S\text{-}C_5NH_3\text{-}5\text{-}NO_2\ (\mathbf{2a}) \rightarrow 2\text{-}RO\text{-}C_5NH_3\text{-}5\text{-}NO_2\ (\mathbf{4}) + 2\text{-}OH\text{-}C_5NH_3\text{-}5\text{-}NO_2\ (\mathbf{5})$$

| R | Yield **5** (%)[b] | Yield **4** (%)[c] | Product |
|---|---|---|---|
| Me | 0 | 95 | 2-Methoxy-5-nitropyridine (**4a**) |
| Et | 0 | 97 | 2-Ethoxy-5-nitropyridine (**4b**) |
| *i*Pr | 17 | 41 | 2-Isopropoxy-5-nitropyridine (**4c**) |
| Bn | 0 | 69 | 2-Benzyloxy-5-nitropyridine (**4d**) |
| *t*Bu[d] | 0 | 0 | 2-*t*-Butoxy-5-nitropyridine (**4e**) |

[a] The alcoholates were made by adding NaH to the alcohol also used as solvent. [**2a**] = 28 mM; reaction time 16–40 h; reaction temperature 23 °C. [b] From $^1$H NMR; [c] Isolated yields; [d] Reaction temperature 83 °C.

**Table 2** Reaction of 5-nitropyridine-2-sulfonic acid (**2b**) with alcohols under acidic conditions (**2b** as acid)[a]

$$ROH + 2\text{-}HO_3S\text{-}C_5NH_3\text{-}5\text{-}NO_2\ (\mathbf{2b}) \rightarrow 2\text{-}RO\text{-}C_5NH_3\text{-}5\text{-}NO_2\ (\mathbf{4}) + 2\text{-}OH\text{-}C_5NH_3\text{-}5\text{-}NO_2\ (\mathbf{5})$$

| R | Reaction temp./°C | Yield **5** (%)[b] | Yield **4** (%)[c] | Product |
|---|---|---|---|---|
| Me | 65 | 0 | 94 | 2-Methoxy-5-nitropyridine (**4a**) |
| Et | 78 | 17 | 72 | 2-Ethoxy-5-nitropyridine (**4b**) |
| *i*Pr | 82 | 26 | 65 | 2-Isopropoxy-5-nitropyridine (**4c**) |
| Bn | 110 | 0 | 0 | 2-Benzyloxy-5-nitropyridine (**4d**) |
| *t*Bu | 83 | 100 | 0 | 2-*t*-Butoxy-5-nitropyridine (**4e**) |

[a] The alcohols acted as solvents. [**2b**] = 32 mM; Reaction time 20 h. [b] From $^1$H NMR; [c] Isolated yields.

calculated on the basis of the starting concentration of **2a** as determined by $^1$H NMR spectroscopy with an internal standard.

In addition to the alcohols in Table 1, phenol and 4-methoxyphenol were reacted with **2a** in DMF at room temperature with $Et_3N$ or Na. In neither case was a reaction observed.

The formation of 2-hydroxy-5-nitropyridine (**5**) in the reaction with *i*PrOH is surprising as compound **2a** did not react with water to give **5** under basic conditions. One possibility would be that **5** was formed from 2-isopropoxy-5-nitropyridine (**4c**) by a substitution reaction at the isopropyl group with the anion of 2-hydroxy-5-nitropyridine (**5**) acting as a leaving group. This would be analogous to the reaction shown in Scheme 3.

**b) Reactions under acidic conditions.** 5-Nitropyridine-2-sulfonic acid (**2b**) was prepared from its potassium salt by the use of an acidic ion exchange resin. As for the reaction under basic conditions, the sulfonic acid (**2b**) was not isolated, and the yields in Table 2 are those calculated from the starting concentration of **2b** as determined by $^1$H NMR spectroscopy with internal standard.

In addition to the alcohols in Table 2, phenol and 4-methoxyphenol were reacted with **2a** in DMF at 100 °C. In neither case was a reaction observed. Benzyl alcohol did not give the expected product even if its reaction under basic conditions gave 2-benzyloxy-5-nitropyridine (**4d**) in 69% yield at room temperature.

From these results it is evident that both under acidic and basic conditions, the present method gave good to excellent yields for the methoxy, ethoxy and isopropoxy compound (**4**, R = Me, Et and *i*Pr). For *t*-butyl alcohol, no 2-*t*-butoxy-5-nitropyridine (**4e**) was obtained, only 2-hydroxy-5-nitropyridine (**5**). Table 2 shows that under acidic conditions, 2-hydroxy-5-nitropyridine (**5**) was an important by-product, even when the alcohols were carefully dried. This was probably caused by an acid catalysed elimination reaction with the alcohol, producing water and the corresponding olefin. In the reaction with *t*-butyl alcohol which gave **5** as the only pyridine product, 2-methylpropene could indeed be isolated. Under basic conditions (Table 1) no 2-hydroxy-5-nitropyridine (**5**) was formed in the reaction with sodium methoxylate or ethoxylate.

The reactions under basic conditions, presumably with the alcoholates as reacting species, took place at room temperature in contrast to those with the sulfonic acid itself which needed elevated temperatures for completion (Tables 1 and 2). Nevertheless, the sulfonic acid **2b** was more reactive than 2-chloro-5-nitropyridine (**3**) which did not react with either alcohols or water under acidic conditions. This difference in reactivity was clearly shown in a competition experiment in which equimolecular amounts of **2b** and **3** were reacted with isopropanol at 82 °C. Under these conditions only **2b** reacted.

The results in Table 1 and 2 may be compared to those obtained by other methods. The common starting compound is 2-chloro-5-nitropyridine (**3**). In reaction with sodium methoxide excellent yields of 2-methoxy-5-nitropyridine (**4a**) (90–99%) were obtained,[8,9] with sodium ethoxide an equally high yield, 98%, was reported.[8] On the other hand, for the 2-isopropoxy-5-nitropyridine (**4c**) a low yield, 19%, was reported from the reaction of 2-iodopropane and sodium 5-nitro-2-pyridineoxide.[8]

Our yields for 2-methoxy- (**4a**) and 2-ethoxy-5-nitropyridine (**4b**) were of the same order as those reported and for 2-isopropoxy-5-nitropyridine (**4c**) our results are better than those reported and our route appears to be the only practical one.

## Reactions with amines

The substitution reactions with amines were all carried out on the potassium salt of the sulfonic acid (**2a**). We have reported the syntheses of 2-amino- and 2-alkylamino-5-nitropyridine (**6**) from 3-nitropyridine by vicarious nucleophilic substitution[10] and by oxidative amination.[11] The yields from these reactions were dependent on the reaction conditions. We have therefore investigated the effect of the reaction conditions on the yields. The results given in Table 3 are the results from the optimised conditions.

From Table 3 it is clear that the substitution of the sulfonate group with amines proceeds in good yields. The reaction conditions are also straightforward: mixing of the appropriate amine

**Table 3** Reaction of potassium 5-nitropyridine-2-sulfonate (**2a**) with ammonia and amines, $R^1R^2NH$[a]

$$R^1R^2NH + 2\text{-}K^{+\,-}O_3S\text{-}C_5NH_3\text{-}5\text{-}NO_2\ (\mathbf{2a}) \rightarrow 2\text{-}R^1R^2N\text{-}C_5NH_3\text{-}5\text{-}NO_2\ (\mathbf{6})$$

| $R^1R^2$ | Solvent | Product | Yield (%) |
|---|---|---|---|
| H, H | Water | 2-Amino-5-nitropyridine (**6a**) | 92 |
| Bu, H | Water | 2-Butylamino-5-nitropyridine (**6b**) | 76 |
| Et, Et | Water | 2-Diethylamino-5-nitropyridine (**6c**) | 62 |
| Et, Et | DMF | 2-Diethylamino-5-nitropyridine (**6c**) | 45[b] |
| Bn, H | Water | 2-Benzylamino-5-nitropyridine (**6e**) | 77 |
| *R*-1-Phenylethyl, H | Water | 2-(*R*-1-Phenylethylamino)-5-nitropyidine (**6f**) | 71 |
| Ph, H | Water | No reaction | |

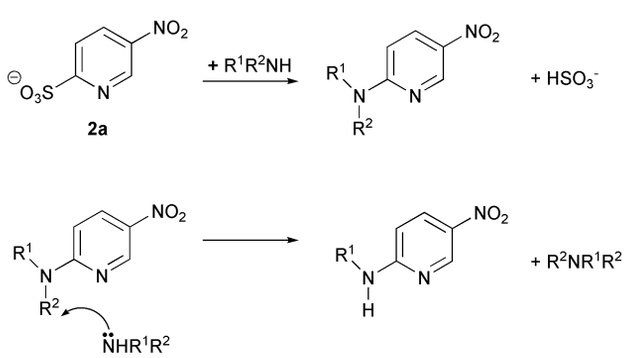
[a] Reaction time 18 h; Reaction temperature 23 °C. [b] 2-Ethylamino-5-nitropyridine (**6d**) was obtained in 32% yield.

and **2a** with water as solvent gives the product after stirring overnight at room temperature.

The result from the reaction with ammonia is particularly interesting. 2-Amino-3-nitropyridine (**6a**) is a common starting material for 2-chloro-5-nitropyridine (**3**), an important compound for the synthesis of other 2,5-substituted pyridines. It has traditionally been made by nitration of 2-aminopyridine.[12] This procedure includes both the exothermal rearrangement of the initially formed nitramine and the separation of the 3- and 5-nitropyridines thus formed. The present process is simpler than this.

The experiment with diethylamine in DMF gave the disubstituted amine, 2-ethylamino-5-nitropyridine (**6d**) as a significant by-product, conceivably formed by a nucleophilic attack on one of the ethylamino groups (Scheme 3).

This might indicate that 2-amino-5-nitropyridine (**6a**) could act as a leaving group in nucleophilic substitution reactions. To test this, and also to investigate the stereochemistry of such a reaction we made 2-(*R*-1-phenylethylamino)-5-nitropyridine (**6f**) and reacted this with alkoxy ions. However, no 2-amino-5-nitropyridine (**6a**) was formed. This is therefore not a general leaving group.




**Scheme 3**

In conclusion on this point, the salt of 5-nitropyridine-2-sulfonic acid (**2a**) gave high yields of both 2-alkylamino- and 2-dialkylamino-5-nitropyridines (**6**) (Table 3). The simple reaction conditions, water as solvent and reaction at room temperature, make **2a** an attractive starting material for this type of compound.

### Reactions with halides and cyanide

We treated **2b** with potassium chloride, bromide and iodide in DMF, DMSO and water, without observing any reaction. The experiments were performed at both room temperature and at 100 °C, and under both neutral and acidic conditions. However, when potassium 5-nitropyridine-2-sulfonate (**2a**) was reacted with phosphorous pentachloride at 164 °C, an 87% yield of 2-chloro-5-nitropyridine (**3**) was obtained. This compares favourably with the traditional method for its synthesis.[3,4] Encouraged by this we also treated **2a** with phosphorous tribromide and phosphorous pentabromide, but with no success. Attempts to substitute the sulfonate group of **2a** with a cyanide group, using sodium or potassium cyanide in DMSO at room temperature, were also unsuccessful.

### Summary

We have presented substitution reactions of 5-nitropyridine-2-sulfonic acid (**2**) whereby a variety of 2-substituted 5-nitropyridine compounds have been readily prepared. These include 2-alkoxy-5-nitropyridines (**4**), 2-amino- and 2-alkylamino-5-nitropyridines (**6**) and 2-chloro-5-nitropyridine (**3**) in high yield.

## Experimental

NMR spectra were recorded on Bruker DPX 300 or 400 MHz instruments. Sodium acetate was used as an internal standard when $^1$H NMR spectroscopy was used to determine purity. IR spectra were recorded on a Thermo Nicolet FT-IR Nexus spectrometer, with the exception of the IR spectrum of **4c** which was recorded on a Perkin-Elmer 1420 infrared spectrophotometer and the IR spectrum of **6b** which was recorded on a Nicolet 20-SXC FT-IR spectrometer. EI-MS spectra were obtained on a Finnigan MAT 95 XL spectrometer, with the exception of the EI-MS spectrum of **6d** which was a GC-MS spectrum and was recorded on a Fisons Trio 1000 with a BP-1 column. UV-Vis spectra were recorded on a Varian Cary 50 UV-Vis spectrophotometer. Melting points are uncorrected and were measured using a Büchi melting point apparatus. 5-Hydroxyaminopyridine-2-sulfonic acid (**1**) was prepared as previously described.[13]

### Substrates

**Potassium 5-nitropyridine-2-sulfonate (2a).** A solution of **1** (3.45 g, 18.14 mmol) in water (100 ml) was added at a rate of 0.25 ml min$^{-1}$ to a vigorously stirred solution of potassium permanganate (8.18 g, 51.76 mmol) in water (100 ml), at room temperature. After the addition was complete (6 h 40 min), the reaction was stirred at room temperature for another 10 h. To the mixture was then added methanol (5 ml), it was stirred for 3 h and filtered. The water of the filtrate was evaporated. Drying under reduced pressure gave a light yellow powder (4.35 g), (1. batch). The brown solid ($MnO_2$) from the filtration was added to water (500 ml), and stirred for 20 h. Another filtration, evaporation and drying under reduced pressure gave more of the light yellow powder (0.75 g), (2. batch). $^1$H NMR spectroscopy with internal standard showed the purities to be 48 wt% and 41 wt%, respectively. This gave an overall yield of 55%. $^1$H NMR (300 MHz; $D_2O$; $(CH_3)_3SiCD_2CD_2CO_2Na$) $\delta$ 8.19 (1H, d, $J$ = 8.6), 8.83 (1H, dd, $J$ = 2.5, 8.6), 9.44 (1H, d, $J$ = 2.3); $^{13}$C NMR (100 MHz; $D_2O$; $(CH_3)_3SiCD_2CD_2CO_2Na$) $\delta$ 124.7,

137.4, 147.8, 148.1, 165.9; IR (KBr): $\nu$/cm$^{-1}$ 3469 (m), 3138 (m), 3101 (m), 2170 (w), 1693 (w), 1647 (m), 1600 (s), 1568 (m), 1535 (s), 1449 (w), 1367 (s), 1322 (m), 1225 (s), 1157 (s), 1113 (s), 1040 (s), 1013 (m), 983 (w), 935 (w), 872 (w), 861 (m), 825 (w), 758 (s), 719 (m), 678 (w), 648 (s), 618 (s), 561 (s), 467 (m), 408 (w). The low purities were due to inorganic salts not detectable by $^1$H NMR.

**5-Nitropyridine-2-sulfonic acid (2b). 2a** (2.80 g, 48 wt% purity, 5.55 mmol) was dissolved in water (50 ml), and passed through a column of Ion Exchanger Amberlite® IR-120 (28 cm long, 2.5 cm id). The eluate was stripped of water and dried under reduced pressure to a light yellow powder (1.68 g) with the same spectroscopic properties as 5-nitropyridine-2-sulfonic acid (**2b**).[1] $^1$H NMR spectroscopy with internal standard showed the purity to be 64 wt%. The low purity was due to inorganic salts with no signals in $^1$H NMR. This gave a yield in the acidification step of 95%.

Compounds **2a** and **2b** were used as substrates for the substitution reactions without further purification.

### Substitution reactions with alcohols under acidic conditions

**General procedure.** A mixture of **2b** (0.80 mmol) in the appropriate alcohol (25 ml) was heated at reflux under $N_2$ for 20 h. The solvent was evaporated under reduced pressure, and to the residue was added $CH_2Cl_2$ (15 ml), water (15 ml) and aqueous $NaHCO_3$ (satd.) until pH = 9. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 ml). The combined organic layers were washed with brine (2 × 10 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the solid obtained purified by flash chromatography.

*2-Methoxy-5-nitropyridine (**4a**).* **4a** was obtained with methanol as a white solid (115 mg, 94% yield) with mp 110.0–110.5 °C (lit.[14] 109–110 °C). The flash chromatography system used was 20 ml silica, 1.5 cm column diameter, eluant: $CH_2Cl_2$–pentane = 50 : 50. The spectroscopic data were in accordance with those reported.[1]

*2-Ethoxy-5-nitropyridine (**4b**).* **4b** was obtained with abs. ethanol as a white solid (97 mg, 72% yield) with mp 94.0–95.0 °C (lit.[15] 91–92 °C). The flash chromatography system used was 20 ml silica, 1.5 cm column diameter, eluant: $CH_2Cl_2$–pentane = 60 : 40. The spectroscopic data were in accordance with those reported.[16] $^{13}$C NMR (100 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 14.4, 63.6, 111.3, 133.8, 139.3, 144.9, 167.2.

*2-Isopropoxy-5-nitropyridine (**4c**).* **4c** was obtained with isopropanol as pale yellow crystals (95 mg, 65% yield) with mp 52.5–53.5 °C (lit.[8] 51.5–52.5 °C). Instead of the general work-up procedure, the residue was added to $CH_2Cl_2$ (50 ml) and stirred for 2 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The yellow oil obtained was purified by flash chromatography (20 ml silica, 1.5 cm column diameter, eluant: $CH_2Cl_2$–hexane = 70 : 30). $^1$H NMR (400 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 1.38 (6H, d, $J$ = 6.2, 2 × $CH_3$), 5.43 (1H, heptet, $J$ = 6.2, CH), 6.74 (1H, d, $J$ = 9.1), 8.33 (1H, dd, $J$ = 2.8, 9.1), 9.07 (1H, d, $J$ = 2.8); $^{13}$C NMR (75 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 21.8, 70.6, 111.7, 133.8, 139.0, 144.9, 166.9; IR (KBr): $\nu$/cm$^{-1}$ 3170 (w), 3090 (w), 3070 (w), 2970 (s), 2930 (m), 2870 (w), 1695 (s), 1510 (s), 1470 (s), 1395 (m), 1380 (m), 1345 (s), 1310 (s), 1265 (s), 1175 (m), 1135 (m), 1095 (s), 1000 (m), 935 (s), 875 (m), 835 (s), 795 (m), 760 (s), 715 (m), 675 (s); EIMS (250 °C, 70 eV) $m/z$ (% rel. int.) 183 (M + 1, 6), 182 (M$^+$, 9), 167 (12), 142 (5), 141 (35), 140 (100), 125 (18), 124 (24), 110 (12), 95 (14), 94 (12), 93 (11), 86 (28), 84 (44), 80 (8), 66 (17), 57 (8), 51 (17), 49 (60), 43 (32), 42 (16), 41 (24), 39 (28), 38 (10), 28 (17), 27 (12).

**Reaction with benzyl alcohol.** The reaction mixture was stirred at 110 °C for 20 h, and then concentrated under reduced pressure. $^1$H NMR spectroscopy showed that no formation of 2-benzyloxy-5-nitropyridine (**4d**) had taken place.

**Reaction with *t*-butanol.** After 14 h with reflux nearly all of the solvent had disappeared. $^1$H NMR spectroscopy showed 2-hydroxy-5-nitropyridine (**5**) as the only product. No 2-*t*-butoxy-5-nitropyridine (**4e**) was formed. Connection of a cold-trap with deuterated chloroform at −55 °C to the cooler, made it possible to trap 2-methylpropene.

**Reactions with phenol and 4-methoxyphenol. 2a** was reacted with phenol and 4-methoxyphenol at 100 °C with DMF as solvent. $^1$H NMR spectroscopy showed that no reaction took place.

**Competition experiment between 5-nitropyridine-2-sulfonic acid (2b) and 2-chloro-5-nitropyridine (3).** A mixture of **2b** (0.30 mmol) and **3** (0.30 mmol) in isopropanol (10 ml) was heated at reflux under $N_2$ for 20 h. $^1$H NMR spectroscopy showed that the reaction mixture at this point contained only 2-isopropoxy-5-nitropyridine (**4c**) and **3**. No **2b** was left.

### Substitution reactions with alcohol under basic conditions

**General procedure.** To a mixture of **2a** (0.70 mmol) in the appropriate alcohol (25 ml) was added NaH (67 mg, 2.80 mmol). The mixture was stirred under $N_2$ at room temperature for 16–40 h. Concentrated HCl was added until pH = 4 and the solvent evaporated under reduced pressure. To the residue was added $CH_2Cl_2$ (50 ml) and it was stirred for 1.5 h. The mixture was filtered, and the filtrate concentrated under reduced pressure. The solid obtained was purified by flash chromatography. The flash chromatography systems used and the melting points and spectroscopic properties observed were as described for the reactions run under acidic conditions if nothing else is mentioned.

*2-Methoxy-5-nitropyridine (**4a**).* **4a** was obtained with methanol as a white solid (102 mg, 95% yield). The reaction mixture was stirred for 16 h.

*2-Ethoxy-5-nitropyridine (**4b**).* **4b** was obtained with abs. ethanol as a white solid (114 mg, 97% yield). The reaction mixture was stirred for 20 h.

*2-Isopropoxy-5-nitropyridine (**4c**).* **4c** was obtained with isopropanol as pale yellow crystals (56 mg, 41% yield). The reaction mixture was stirred for 40 h.

*2-Benzyloxy-5-nitropyridine (**4d**).* **4d** was obtained with benzyl alcohol. The reaction mixture was stirred for 20 h. The work-up did not follow the general procedure. After acidification of the reaction mixture, $CH_2Cl_2$ (20 ml) and water (30 ml) were added. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 ml). The combined organic layers were washed with brine (2 × 20 ml) and dried ($MgSO_4$). The $CH_2Cl_2$ was evaporated, and benzyl alcohol distilled off under reduced pressure. The white solid left was purified by flash chromatography (50 ml silica, 2.25 cm column diameter, eluant: $CH_2Cl_2$–pentane = 50 : 50). This gave **4d** as a white solid (111 mg, 69% yield) with mp 100–104 °C (lit.[8] 107–108 °C). $^1$H NMR (400 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 5.49 (2H, s), 6.88 (1H, d, $J$ = 9.2), 7.4 (5H, m), 8.37 (1H, dd, $J$ = 2.8, 9.1), 9.10 (1H, d, $J$ = 2.8); $^{13}$C NMR (100 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 69.2, 111.5, 127.8, 128.3, 128.5, 128.6, 134.0, 135.9, 144.8, 166.8; IR (KBr): $\nu$/cm$^{-1}$ 3066 (w), 3033 (w), 2938 (w), 2360 (m), 2342 (m), 1601 (s), 1578 (s), 1506 (s), 1481 (s), 1451 (s), 1400 (s), 1342 (s), 1314 (s), 1274 (s), 1144 (w), 1112 (m), 1036 (m), 1017 (w), 982 (m), 916 (m), 879 (m), 836 (m), 827 (w), 811 (m), 767 (m), 749 (s), 738 (w), 720 (m), 702 (m), 541 (m), 507 (m), 461 (w), 420 (m); EIMS (200 °C, 70 eV) $m/z$ (% rel. int.) 230 (M$^+$, 25), 229 (8), 213 (5), 197 (8), 183 (4), 154 (4), 124 (5), 107 (8), 92 (12), 91 (100), 77 (5), 65 (12), 51 (4).

**Reaction with potassium *t*-butoxide.** The general procedure was not followed. **2a** (0.70 mmol) was refluxed in 1 M potassium *t*-butoxide in *t*-butanol (10 ml) for 23 h. The reaction mixture was acidified and concentrated under reduced pressure.

$^1$H NMR spectroscopy showed that no reaction had taken place.

**Reactions with phenol and 4-methoxyphenol. 2b** was reacted with phenol and 4-methoxyphenol at room temperature with DMF as solvent. Both sodium metal and triethylamine were tried to generate phenoxide ions. $^1$H NMR spectroscopy showed that no reaction took place.

### Substitution reactions with amines

**General procedure.** A 25 volume% solution of the appropriate amine in water (20 ml) was added to **2a** (0.60 mmol) and stirred at room temperature for 18 h. The reaction mixture was then concentrated under reduced pressure, and to the residue was added $CH_2Cl_2$ (50 ml) and water (50 ml). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 25 ml). The combined organic layers were washed with brine (2 × 50 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the obtained solid purified by flash chromatography.

*2-Amino-5-nitropyridine (**6a**).* **6a** was obtained with ammonia as a yellow solid (77 mg, 92% yield) with mp 190.0–191.5 °C (lit.[11] 188–189 °C). The flash chromatography system used was 20 ml silica, 1.5 cm column diameter, eluant: 2% EtOH in $CH_2Cl_2$. The spectroscopic data were in accordance with those reported.[11] UV-Vis(EtOH): $\lambda_{max}$ = 220 nm, $\varepsilon$ = 9761, $\lambda_{max}$ = 345 nm, $\varepsilon$ = 14283.

*2-n-Butylamino-5-nitropyridine (**6b**).* **6b** was obtained with *n*-butylamine as a yellow solid (89 mg, 76% yield) with mp 104.5–105.5 °C (lit.[17] 102 °C). The flash chromatography system used was 20 ml silica, 1.5 cm column diameter, eluant: 1.5% EtOH in $CH_2Cl_2$. $^1$H NMR (300 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 0.97 (3H, t, $J$ = 7.3, $CH_3$), 1.44 (2H, m, $CH_2$), 1.64 (2H, m, $CH_2$), 3.39 (2H, m, br.), 5.30 (1H, s, br., NH), 6.34 (1H, d, $J$ = 9.3), 8.19 (1H, dd, $J$ = 2.5, 9.3), 9.01 (1H, d, $J$ = 2.5); $^{13}$C NMR (100 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 13.8, 20.1, 31.3, 42.1, 105 (v. br.), 133.1 (br.), 135.4, 147.1, 161.3; $^{13}$C NMR (75 MHz; $D_2O$–conc. HCl; $(CH_3)_3SiCD_2CD_2CO_2Na$) $\delta$ 15.8, 22.3, 32.2, 45.6, 117 (br.), 138.1 (br.), 138.5, 139.1, 157.0; IR (KBr): $\nu$/cm$^{-1}$ 3233 (s), 3155 (w), 3095 (m), 2995 (w), 2960 (s), 2930 (m), 2867 (s), 1606 (s), 1548 (w), 1497 (m), 1459 (w), 1424 (m), 1330 (s), 1291 (s), 1165 (m), 1114 (s), 1011 (m), 946 (w), 834 (m), 767 (m), 669 (m), 556 (m); EIMS (250 °C, 70 eV) *m*/*z* (% rel. int.) 196 (M + 1, 7), 195 (M$^+$, 24), 179 (9), 166 (26), 153 (23), 152 (100), 139 (28), 136 (5), 122 (21), 120 (11), 106 (52), 93 (7), 81 (5), 78 (16), 66 (12), 57 (5), 41 (11), 29 (4); UV-Vis(EtOH): $\lambda_{max}$ = 227 nm, $\varepsilon$ = 7950, $\lambda_{max}$= 364 nm, $\varepsilon$ = 15500.

*2-Diethylamino-5-nitropyridine (**6c**).* **6c** was obtained with diethylamine as a yellow solid (73 mg, 62% yield) with mp 75.5–77.0 °C (lit.[18] 75.2–76.2 °C). The flash chromatography system used was 20 ml silica, 1.5 cm column diameter, eluant: 0.5% EtOH in $CH_2Cl_2$. The spectroscopic data were in accordance with those reported.[19] IR (KBr): $\nu$/cm$^{-1}$ 3102 (w), 2980 (m), 2926 (m), 2602 (w), 2438 (w), 1596 (s), 1568 (s), 1527 (s), 1476 (s), 1449 (m), 1431 (s), 1380 (m), 1327 (s), 1280 (s), 1187 (m), 1114 (s), 1075 (m), 1016 (w), 993 (w), 939 (w), 829 (m), 796 (w), 782 (m), 764 (m), 739 (m), 605 (w), 560 (m), 534 (w), 499 (w), 420 (m); UV-Vis(EtOH): $\lambda_{max}$ = 231 nm, $\varepsilon$ = 6250, $\lambda_{max}$ = 375 nm, $\varepsilon$ = 20625.

**Substitution reaction with diethylamine in refluxing DMF.** A mixture of **2a** (0.50 mmol), diethylamine (10 ml) and DMF (10 ml) was heated with reflux under $N_2$ for 20 h. The reaction mixture was then concentrated under reduced pressure, and to the residue was added $CH_2Cl_2$ (30 ml) and water (30 ml). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 ml). The combined organic layers were washed with brine (2 × 20 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. This gave a yellow oil which contained **6c** and 2-ethylamino-5-nitropyridine (**6d**) (**6c** : **6d** = 3 : 2 from $^1$H NMR). Separation on a flash column (20 ml silica, 1.5 cm column diameter, eluant: 0.5% EtOH in $CH_2Cl_2$) gave **6c** (44 mg, 45% yield) with melting point and spectroscopic properties as described above and **6d** (27 mg, 32% yield) with mp 119.5–120.5 °C (lit.[17] 122 °C). The $^1$H NMR data were in accordance with those reported.[20] $^{13}$C NMR (100 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 14.5, 37.1, 105 (v. br.), 133.0 (br.), 135.8, 147.1, 161.1; IR (KBr): $\nu$/cm$^{-1}$ 3347 (s), 3227 (m), 2981 (m), 2933 (w), 1604 (s), 1549 (m), 1498 (m), 1474 (m), 1456 (w), 1424 (w), 1368 (w), 1323 (s), 1286 (s), 1165 (w), 1138 (m), 1109 (s), 1060 (w), 994 (w), 938 (w), 827 (m), 808 (w), 765 (m), 731 (w), 671 (m), 660 (w), 544 (m), 501 (m), 425 (m); EIMS (250 °C, 70 eV) *m*/*z* (% rel. int.) 168 (M + 1, 6), 167 (M$^+$, 54), 153 (7), 152 (100), 139 (34), 124 (6), 120 (14), 119 (9), 109 (7), 107 (7), 106 (92), 94 (9), 93 (12), 81 (6), 79 (13), 78 (37), 77 (5), 66 (24), 65 (10), 64 (8), 54 (7), 53 (6), 52 (15), 51 (20); UV-Vis(EtOH): $\lambda_{max}$ = 260 nm, $\varepsilon$ = 13368, $\lambda_{max}$ = 363 nm, $\varepsilon$ = 16368.

For the two following compounds, the general procedure was not used because the amines were not soluble in water.

**2-Benzylamino-5-nitropyridine (6e).** Benzylamine (0.32 g, 3.0 mmol) and **2a** (0.60 mmol) were mixed in water (10 ml) and stirred vigorously for 20 h. During this time the product precipitated. Filtration and drying under reduced pressure gave **6e** as yellow crystals (106 mg, 77% yield) with mp 133.5–134.5 °C (lit.[18] 130.1–131.1 °C). The spectroscopic data were in accordance with those reported.[21] $^{13}$C NMR (100 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 46.3, 106 (v. br.), 127.5, 127.9, 129.0, 133.1, 136.2, 137 (br.), 146.9, 161.0; IR (KBr): $\nu$/cm$^{-1}$ 3221 (m), 1603 (s), 1546 (m), 1493 (s), 1455 (m), 1424 (s), 1334 (s), 1290 (s), 1165 (m), 1119 (s), 1033 (w), 1009 (m), 956 (w), 907 (m), 841 (m), 823 (m), 767 (s), 740 (s), 693 (m), 670 (w), 550 (s), 511 (m), 495 (m); UV-Vis(EtOH): $\lambda_{max}$ = 361 nm, $\varepsilon$ = 18698.

**2-(*R*-1-Phenylethylamino)-5-nitropyridine (6f).** *R*-1-Phenylethylamine (10 ml) and **2a** (0.60 mmol) were mixed in water (30 ml) and stirred vigorously for 20 h. To the reaction mixture was added $CH_2Cl_2$ (50 ml) and water (50 ml). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 25 ml). The combined organic layers were washed with brine (2 × 50 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a yellow liquid which contained **6f** dissolved in *R*-1-phenylethylamine. These were separated by distillation to give **6f** as a yellow oil which was purified by flash chromatography (50 ml silica, 2.0 cm column diameter, eluant: $CH_2Cl_2$–pentane = 90 : 10). This gave **6f** as yellow crystals (104 mg, 71% yield) with mp. 79.5–81.0 °C (lit.[22] 83 °C). $^1$H NMR (400 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 1.62 (3H, d, $J$ = 6.8, $CH_3$), 4.6 (1H, m, br., CH), 5.3 (1H, s, br., NH), 6.22 (1H, d, $J$ = 9.3), 7.3 (5H, m), 8.11 (1H, dd, $J$ = 2.7, 9.3), 9.00 (1H, d, $J$ = 2.7); $^{13}$C NMR (100 MHz; $CDCl_3$; $Me_4Si$) $\delta$ 23.6, 52.1, 105.4 (br.), 125.5, 127.7, 129.0, 133.1, 136.1, 142.8, 146.9, 160.4; IR (KBr): $\nu$/cm$^{-1}$ 3405 (s), 3062 (w), 3029 (w), 2991 (w), 2968 (m), 2921 (w), 2864 (w), 2610 (w), 2534 (w), 2442 (w), 2360 (w), 1607 (s), 1575 (s), 1524 (s), 1492 (s), 1474 (s), 1448 (m), 1395 (w), 1374 (m), 1326 (s), 1286 (s), 1245 (s), 1204 (m), 1159 (m), 1110 (s), 1092 (m), 1026 (s), 1013 (m), 996 (m), 942 (m), 914 (w), 835 (s), 766 (s), 729 (m), 703 (s), 689 (m), 566 (m), 533 (s), 519 (m), 491 (m), 414 (m); EIMS (200 °C, 70 eV) *m*/*z* (% rel. int.) 244 (M$^+$, 12), 243 (64), 229 (14), 228 (99), 182 (24), 166 (6), 139 (8), 120 (20), 106 (9), 105 (100), 104 (18), 103 (11), 91 (8), 79 (16), 78 (11), 77 (20), 51 (8); UV-Vis(EtOH): $\lambda_{max}$ = 361 nm, $\varepsilon$ = 18698.

**Reaction with aniline. 2b** was reacted with aniline at room temperature and at 100 °C with DMF as solvent. $^1$H NMR spectroscopy showed that no reaction took place.

### Substitution reactions with halides and cyanide

**2-Chloro-5-nitropyridine (3).** A mixture of **2a** (2.00 mmol) and $PCl_5$ (4.17 g, 20.00 mmol) was heated to reflux for 0.5 h.

Xylene (2 × 10 ml) was added and the mixture distilled under reduced pressure to remove excess $PCl_5$. The residue was purified by flash chromatography (50 ml silica, 2.5 cm column diameter, eluant: pentane–$CH_2Cl_2$ = 60 : 40). This gave **3** as a white solid (275 mg, 87% yield) with mp 110.0–111.5 °C (lit.[7] 109 °C). The spectroscopic properties were the same as for commercial 2-chloro-5-nitropyridine (**3**).

**Reactions with phosphorous tribromide and phosphorous pentabromide. 2a** was reacted with $PBr_5$ at 100 °C with chloroform or toluene as solvent, and with $PBr_3$ at 80 °C with no solvent. $^1$H NMR spectroscopy showed that no 2-bromo-5-nitropyridine was formed in any of the reactions.

**Reactions with potassium halides. 2b** was reacted with potassium chloride, bromide and iodide at 100 °C in both DMF and DMSO. Conc. sulfuric acid and *p*-toluenesulfonic acid were tried as acid catalysts. $^1$H NMR spectroscopy showed that no substitution products were formed in any of the reactions.

**Reactions with cyanides. 2a** was reacted with sodium and potassium cyanide in DMSO at room temperature. $^1$H NMR spectroscopy showed that no 2-cyano-5-nitropyridine was formed in any of the reactions.

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