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# The Reaction of Some Brominated Aminopicolines with Acetic Anhydride and with Copper(I) Cyanide

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Some time ago we reported the synthesis of a number of brominated aminopicolines [1] and since this time we have investigated their use in the preparation of other heterocycles e.g. pyrido[1,4]thiazines [2]. We were now interested in the conversion of some of these compounds to the corresponding cyano aminopicolines and attempted to prepare these by the reaction of the former with cuprous cyanide.

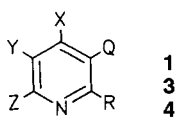
The desired starting materials **1** and **2** were synthesised according to [1] and some were further characterised either as their monoacetyl **3** and **5** and/or their diacetyl derivatives **4** and **6**. From the reaction of **2b** with excess acetic anhydride both the monoacetyl and diacetyl derivatives were obtained, whilst although two products were also produced from the treatment of **2a** with excess acetic anhydride, only the major product was isolated.

The $^1$H-NMR spectra of two of the diacetyl derivatives i.e. **4c** and **4d** were much more complex than expected, although analytical, chromatographic, infrared and mass spectral data were consistent with the proposed structures. Additionally, both diacetyl derivatives showed only eight resonances in the $^{13}$C-NMR spectra again in accord with expectations. Diacyl derivatives of pyridine amines have been previously reported by several groups [3] and acylation unlike sulphonylation (which leads to the formation of two isomeric disulphonyl derivatives corresponding to attack both exclusively at the exocyclic nitrogen and at each of the nitrogen atoms in the system [4]) is known to occur only at the amino function [5]. Since it is well documented that methyl groups attached to pyridine rings are involved in long range coupling [6], the $^1$H-NMR spectra of **4c,d** were examined in detail. At 90 MHz the spectra of **4c** contained signals at 7.812, 7.831, 7.821 and 7.841 ppm (H-4) and, 8.486 and 8.505 ppm (H-6). These data suggest coupling constants of 1.75 Hz ($J_{4,6}$) and 0.87 Hz ($^4J_{Me,H\text{-}4}$). The relative line intensities were 9 : 12 : 7 : 12 (H-4) and 11 :12 (H-6). For **4d** the 90 MHz spectrum contained the following features : 7.861, 7.875 and 7.885 ppm (H-4) and, 8.354, 8.363 and 8.378 ppm (H-6). Coupling constants could not be determined from this spectrum. The relative line intensities for **4d** were 17 : 17 : 20 (H-4) and 15 : 16 : 16 (H-6). Clearly these spectra are not first order. In neither spectrum was any splitting of the methyl group evident.

At 360 MHz the $^1$H-NMR spectrum of **4c** consisted of seven lines which are clearly due to two quartets with relative line intensities approximating to 1 : 3 : 3 : 1 (H-4) whilst H-6 appeared as two doublets (relative line intensities very close to 1 : 1 and 1 : 1) and the ring methyl group was split into four lines. From the data $J_{4,6}$ was deduced to be 2.39 Hz and the long range $^4J$ and $^6J$ coupling constants were calculated as 0.77 Hz (Me,H-4) and 0.56 Hz (Me,H-6) respectively.

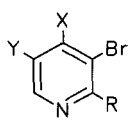
The 360 MHz spectrum of **4d** contained the following features: a seven line complex (H-4), a six line complex (H-6) and a triplet (ring methyl group). The relative line intensities were (in order of increasing frequency) 1.5 : 11 : 10 : 10 : 12 : 2 (H-4), 1 : 3 : 3 : 1 : 3 : 3 (H-6) and 4 : 10 : 5 (ring methyl group). From the data the most likely coupling constants were deduced to be $J_{4,6}$ 2.07 Hz, $^4J_{Me,H\text{-}4}$ 0.80 Hz and $^4J_{Me,H\text{-}6}$ 0.75 Hz. The coupling constant derived from the methyl splitting was 0.75 Hz. From both these spectra the coupling constants are in relatively good agreement with those reported [6]. Both amines **1c** and **1d** (in addition to some other amines reported in [1]) also showed long range coupling between the ring protons and the methyl group of about 0.87 Hz at 90 MHz.

The conversion of halogenated pyridines to cyanopyridines by the action of cuprous cyanide (Rosenmund–von Braun



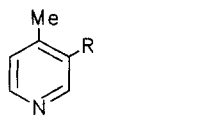
**1** R = $NH_2$
**3** R = NHAc
**4** R = $NAc_2$

| | Q | X | Y | Z |
|---|---|---|---|---|
| **a** | H | Me | Br | H |
| **b** | H | H | Br | Me |
| **c** | Me | H | Br | H |
| **d** | Br | H | Me | H |
| **e** | Br | Me | H | H |

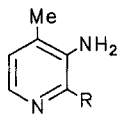


**2** X = $NH_2$
**5** X = NHAc
**6** X = $NAc_2$

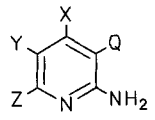
| | R | Y |
|---|---|---|
| **a** | H | Me |
| **b** | Me | H |



**7**
**a** R = Br
**b** R = CN

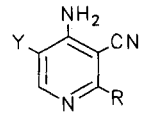


**8**
**a** R = Br
**b** R = CN



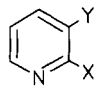
**9**

| | Q | X | Y | Z |
|---|---|---|---|---|
| **a** | H | Me | CN | H |
| **b** | H | H | CN | Me |
| **c** | Me | H | CN | H |
| **d** | CN | H | Me | H |
| **e** | CN | Me | H | H |



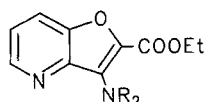
**10**

| | R | Y |
|---|---|---|
| **a** | H | Me |
| **b** | Me | H |

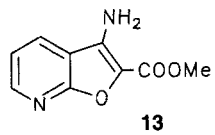


**11**

| | X | Y |
|---|---|---|
| a | I | $OCH_2CO_2Et$ |
| b | CN | $OCH_2CO_2Et$ |
| c | CN | OH |
| d | Cl | CN |



**12**
**a** R = H
**b** R = COPh



**13**

reaction) has been known for more than sixty years. Most of the early examples of this transformation involve heating the neat halopyridine with cuprous cyanide [7] and, despite modifications (see below), the method can still be encountered in the modern chemical literature [8]. Two major modifications have been introduced i.e. (a) the use of potassium cyanide in the presence of Pd(II) salts [9] and (b) the use of aprotic solvents as the reaction medium. This latter development is of more importance in the field of pyridine chemistry where pyridine [10] and (especially) dimethylformamide (DMF) have been used with great success. With respect to the halogenated pyridine, only four examples of the reaction of a halogenated amino pyridine with cuprous cyanide have appeared in the literature [7c–d, 10b, 11c].

From previous experience, we have found that the reaction of halogenated pyridines with cuprous cyanide is best conducted in DMF. For example, **7a** can be converted to **7b** in 75–80% yield by this method. Reaction of **1a–e**, **2a–b** and **8a** [1] with cuprous cyanide in DMF solution gave the corresponding nitriles **9a–e**, **10a–b** and **8b** albeit in low yield. The structures of these new cyano compounds were readily established by analytical and spectroscopic techniques. Only **9c** showed any signs of long range spin–spin coupling at 90 MHz. Analysis of the complex centred on 7.57 ppm (H-4) yielded coupling constants of $J_{4,6}$ of 2.19 Hz and $^4J_{Me,H\text{-}4}$ of 0.87 Hz.

The success of these reactions led us to attempt the reaction with the iodo derivative **11a** [12]. The low yields experienced above, prompted us to carry out the reaction in the absence of solvent. On a small scale **11a** when fused with cuprous cyanide gave **11b** in 65% yield. However, when the reaction scale was quadrupled the yield fell to 34%. The cyano derivative **11b** could also be obtained in 68% yield from **11c** [13] by alkylation with ethyl bromoacetate [12]. Treatment of **11b** with sodium ethoxide in ethanol [14] gave the furo[3,2-b]pyridine **12a**, which was further characterised as the dibenzoyl derivative **12b**. For comparison the corresponding [2,3-b] methyl ester **13** was prepared by the reaction of **11d** [15] with methyl glycolate in the presence of sodium hydride (cf. [16]).

## Experimental

All general experimental details are given in reference [12]. Infrared spectra were recorded for KBr discs in all cases. NMR spectra were measured in deuteriochloroform solution unless otherwise stated. The 360 MHz $^1$H-NMR and 90.6 MHz $^{13}$C-NMR spectra were recorded using a Bruker AM-360. All new compounds gave satisfactory analytical data for C, H and N, and where appropriate for Br. All IR bands are reported in $cm^{-1}$ and NMR data as $\delta$ values from TMS.

### Acetyl and diacetyl derivatives from amines (1a–1d) and (2a–2b). General Procedure

A solution of the appropriate amine (2.0 g, 10.7 mmol) in dry pyridine (25 ml) was treated with acetic anhydride (1.1 mol equiv. in the case of **1a,b** and 2.5 mol. equiv. for **1c,d** and **2a,b**) and the mixtures heated at 100 °C for 2–6 hours (monoacetyl derivatives) or for 18–20 hours (diacetyl derivatives). The excess reagent was destroyed by the addition of a few drops of water and the solvents were removed at reduced pressure. The reaction mixtures from **1a,b** gave solids which were treated with water, filtered, the crude solids dried and then recrystallised. The reaction mixtures from **1c,d** and **2a,b** were purified by column chromatography on silica gel using light petroleum/ether mixtures as the eluant. Both **5b** and **6b** were distilled (Kugelrohr) prior to recrystallisation. The following compounds were obtained:

From **1a**, *2-acetylamino-5-bromo-4-methylpyridine* (**3a**) (80%) *m.p.* 156–157 °C (from AcOEt/ether). – $^1$H-NMR: 2.20 (3H, s), 2.41 (3H, s), 8.20 (3H, complex, becoming 8.14 (1H, s) and 8.27 (1H, s) on exchange). – IR: 3270, 3200, 3160, 3030 (all N-H), 1695, 1670 (both C=O). – MS *m/z* (%) : 230 (20) and 228 (20).

From **1b**, *2-acetylamino-5-bromo-6-methylpyridine* (**3b**) (88%) *m.p.* 158–159 °C (from AcOEt/PE). – $^1$H-NMR: 2.12 (3H, s), 2.48 (3H, s), 7.60 (1, d), 7.84 (1H, d), 8.08 (1H, broad s, exchangeable). – IR: 3255, 3110, 3060 (all N-H), 1670 (C=O). – MS *m/z* (%) 230 (17) and 228 (17).

From **1c**, *5-bromo-2-diacetylamino-3-methylpyridine* (**4c**) (70%) *m.p.* 88–89 °C (from PE). – $^1$H-NMR: 2.20 (3H, s), 2.27 (6H, s), 7.82 (1H, dd), 8.49 (1H, d). – $^{13}$C-NMR: 17.079, 26.380, 121.132, 139.828, 142.427, 148.566, 150.390, 171.949. – IR: 1720 (C=O) 1700. – MS *m/z* (%) : 272 (1) and 270 (1).

From **1d**, *3-bromo-2-diacetylamino-5-methylpyridine* (**4d**) (59%) *m.p.* 65–66 °C (from cyclohexane). – $^1$H-NMR: 2.28 (6H, s), 2.41 (3H, s), 7.88 (1H, t), 8.36 (1H, t). – $^{13}$C-NMR: 17.731, 26.225, 120.340, 136.340, 142.707, 148.819, 148.980, 171.774. – IR: 1730, 1710 (both C=O). – MS *m/z* (%) : 272 (5) and 270 (4.5).

From **2a**, *3-bromo-4-diacetylamino-5-methylpyridine* (**6a**) (53%) *m.p.* 85–86 °C (from PE) – $^1$H-NMR: 2.24 (3H, s),

2.29 (6H, s), 8.52 (1H, s), 8.73 (1H, s). – IR: 1735, 1730, 1700 (all C=O). – MS *m/z* (%) : 272 (2) and 270 (2).
From **2b** (in order of elution), *3-bromo-4-diacetylamino-2-methylpyridine* (**6b**) (53%) *m.p.* 85–86 °C (from PE). – $^1$H-NMR: 2.30 (3H, s), 2.78 (3H, s), 7.05 (1H, d), 8.54 (1H, d). – IR: 1730, 1710 (both C=O). – MS *m/z* (%) : 230 (25) and 228 (27) (both M-42) and
*4-acetylamino-3-bromo-2-methylpyridine* (monohydrate) (**5b**) (26%) *m.p.* 84–85 °C (from PE). – $^1$H-NMR: 2.29 (3H, s), 2.69 (3H, s), 8.00 (1H, s, exchangeable), 8.27 (2H, $A_2B_2$ q). – IR: 3630, 3400, 3335, 3190 (all N-H), 1700 (C=O). – MS *m/z* (%): 230 (6) and 228 (6).

*4-Methyl-3-cyanopyridine* (**7b**)

A mixture of **7a** (50.0g, 0.2907 mol) [17], cuprous cyanide (32.56g) and dry DMF (400 ml) was heated under reflux for 8 hours. The mixture was cooled, poured into cold water (2500 ml) and the resulting green solid removed by filtration. The solid was washed several times with water, suspended in water (500 ml) and treated with ethylene diamine (75 ml) [18] to afford a purple solution. The solution was extracted several times with ethyl acetate until no more product could be detected in the extracts, the combined extracts dried and carefully concentrated *in vacuo*. The residue was dissolved in hot petroleum ether, and concentrated to afford the title compound as long colourless needles (27.4g, 80%) *m.p.* 45–46 °C [lit. *m.p.* 45–46 °C [19]]. – $^1$H-NMR: 2.55 (3H, s), 7.22 (1H, d), 8.33 (1H, d), 8.65 (1H, s). – IR: 2240 (CN).

**Cyanopyridines from the brominated aminopicolines (1a–e), (2a,b) and (8a). General Procedure**

A mixture of the appropriate brominated aminopicoline (2.0 g, 10.7 mmol), cuprous cyanide (1.1g, 22.3 mmol) and dry DMF (100 ml) was heated under reflux for 20 hours. The cooled mixture was poured into water (800 ml) and, since no significant precipitation as noted in the previous example, ethylene diamine (5 ml) was added. The mixture was extracted several times with ethyl acetate, the dried extracts concentrated *in vacuo* and the solid residues treated with a little ether. The solids were filtered and recrystallised from an appropriate solvent or solvent mixture. The following cyano derivatives were thus obtained.
From **1a**, *2-amino-5-cyano-4-methylpyridine* (**9a**) (39%) *m.p.* 160.5–162.5 °C (from toluene). – $^1$H-NMR: 2.40 (3H, s), 4.90 (2H, broad s, exchangeable), 6.36 (1H, s), 8.29 (1H, s). – IR: 3440, 3330, 3140 (all $NH_2$), 2220 (CN). – MS *m/z* (%): 133 (100).
From **1b**, *2-amino-5-cyano-6-methylpyridine* (**9b**) (37%) *m.p.* 167–167 °C (from toluene). – 1H-NMR: 2.40 (3H, s), 6.28 (1H, d), 6.83 (2H, broad s, exchangeable), 7.52 (1H,). – IR: 3435, 3420, 3340, 3180 (all $NH_2$), 2230 (CN). – MS *m/z* (%): 133 (100).
From **1c**, *2-amino-5-cyano-3-methylpyridine* (**9c**) (21%) *m.p.* 203–205 °C (from MeOH/AcOEt). – $^1$H-NMR: 2.04 (3H, s), 6.81 (2H, broad s, exchangeable), 7.57 (1H, complex), 8.21 (1H, s). – IR: 3440, 3345, 3180 (all $NH_2$), 2230 (CN). – MS *m/z* (%) : 133 (100).
From **1d**, *2-amino-3-cyano-5-methylpyridine* (**9d**) (29%) *m.p.* 166–167 °C (from toluene) [lit. *m.p.* 169–170 °C [20a] and 166–168 °C [20b]]. – $^1$H-NMR: 2.21 (3H, s), 5.20 (2H, broad s, exchangeable), 7.50 (1H, d), 8.09 (1H, d). – IR: 3405, 3330, 3180 (all $NH_2$), 2230 (CN). – MS *m/z* (%): 133 (100).
From **1e**, *2-amino-3-cyano-4-methylpyridine* (**9e**) (37%) *m.p.* 151–152.5 °C (from AcOEt) [lit. *m.p.* 148 °C [21a] and 150–151°C [21b]]. – $^1$H-NMR: 2.44 (3H, s), 4.20 (2H, broad s, exchangeable), 6.57 (1H, d), 8.08 (1H, d). – IR: 3425, 3340, 3230, 3140 (all $NH_2$), 2220 (CN). – MS *m/z* (%): 133 (100).
From **8a**, *3-amino-2-cyano-4-methylpyridine* (**8b**) (4%) *m.p.* 122 –124 °C (from acetone/ether). – $^1$H-NMR: 2.23 (3H, s), 4.43 (2H, broad s, exchangeable), 7.14 (1H, d), 7.96 (1H, d). – IR: 3460, 3430, 3370, 3260, 3240 (all $NH_2$), 2235 (CN). – MS *m/z* (%): 133 (100). This compound also showed 0.125 mole water in the elemental analysis.
From **2a**, *4-amino-3-cyano-5-methylpyridine* (**10a**) (13%) *m.p.* 220–221°C (with decomp., from AcOEt). – $^1$H-NMR: 2.06 (3H, s), 6.78 (2H, broad s, exchangeable), 8.05 (1H, s), 8.29 (1H, s). – IR: 3405, 3370, 3130 (all $NH_2$), 2225 (CN). – MS *m/z* (%): 133 (100). This compound showed 0.1 mole water in the elemental analysis.
From **2b**, *4-amino-3-cyano-2-methylpyridine* (**10b**) (13%) *m.p.* 226–228 °C (with decomp., from AcOEt). – $^1$H-NMR: 2.44 (3H, s), 6.51 (1H, d), 6.90 (2H, broad s, exchangeable), 7.99 (1H, d). – IR: 3425, 3345, 3080 (all $NH_2$), 2220 (CN). – MS *m/z* (%): 133 (100).

*(2-Cyanopyrid-3-yloxy)-acetic acid ethyl ester* (**11b**)

(a) From **11a**
An intimate mixture of **11a** (2.7g, 8.8 mmol) and cuprous cyanide (1.4g, 15.6 mmol) was gently warmed to 140 °C and the reaction mixture maintained at 140–160 °C for 3 minutes. The cooled melt was extracted with ethyl acetate, decolourised with carbon, filtered and concentrated *in vacuo* to afford the pure title compound 1.18g (65%) *m.p.* 87–88 °C (from ether/PE).
(b) From **11c**
A mixture of **11c** (440 mg, 3.7 mmol), dry acetone (50 ml), ethyl bromoacetate (600 mg, 3.6 mmol), anhydrous potassium carbonate (500 mg) and potassium iodide (100 mg) was heated under reflux with stirring for 3 hours. The mixture was filtered, the solids washed with acetone and the solvents removed at reduced pressure. The residue was extracted with hot PE, and concentrated to about 10 ml. The solids were removed by filtration, washed with cold PE to yield pure **11b** as small white needles (510 mg, 68%). The *m.p.* and m.*m.p.* were identical to that reported above.
For (**11b**), $^1$H-NMR: 1.30 (3H, t), 4.28 (2H, q), 4.81 (2H, s), 7.24 (1H, dd), 7.47 (1H, dd), 8.34 (1H, dd). – IR: 1750 (C=O). – MS *m/z* (%) : 206 (70).

*3-Amino-furo[3,2-b]pyridine-2-carboxylic acid ethyl ester* (**12a**)

A solution of **11b** (1.1g, 5.3 mmol) in ethanol (50 ml) was treated with a solution of ethanolic sodium ethoxide (from sodium (0.04g, 1.7 mmol) and ethanol (25 ml). The mixture was allowed to stand at room temperature for 20 hours, the solvents removed *in vacuo* and the residue treated with cold water (10 ml). The solids (480 mg) were filtered, washed once with ice cold water and then recrystallised from a mixture of

ethanol and ether to afford the pure amine **12a** as colourless crystals *m.p.* 115–116 °C.
For (**12a**), $^1$H-NMR: 1.45 (3H, t), 4.66 (2H, q), 7.37 (1H, dd), 7.75 (1H, dd), 8.54 (1H, dd). – IR: 3450, 3300, 3160, 3080 (all $NH_2$, 1680 (C=O); MS *m/z* (%): 206 (100).
The dibenzoyl derivative, *3-dibenzoylamino-furo[3,2-b] pyridine-2-carboxylic acid ethyl ester* (**12b**), *m.p.* 192–194 °C (from EtOH), was obtained in 35% yield essentially as described for **6b** using benzoyl chloride in place of acetic anhydride (*vide supra*).
For (**12b**), $^1$H-NMR (hexadeuteriodimethylsulphoxide): 1.22 (3H, t), 4.34 (2H, q), 7.28–7.82 (11H,complex), 8.22 (1H, dd), 8.67 (1H, dd). – IR: 1700 (C=O). – MS *m/z* (%) : 414 (19).

*3-Amino-furo[2,3-b]pyridine-2-carboxylic acid methyl ester* (**13**)

A vigorously stirred solution of **11d** (4.0g, 28.9 mmol) and methyl glycolate (3.24g, 36 mmol) in dry DMF (100 ml) was cooled to about –20 °C and treated portionwise with sodium hydride (1.73g, 73 mmol). After the addition, the mixture was stirred for a further 4 hours at –20 °C and then stirred at ambient temperature overnight. The excess hydride was destroyed by cautious addition of a solution of methanol in DMF, the reaction mixture poured into water (500 ml) and extracted several times with ethyl acetate. After back extraction with water (2×100 ml), the combined dried extracts were concentrated to yield **13** as a yellow solid (3.60g, 65%). Recrystallisation from ethyl acetate gave pure **13** *m.p.* 181–182 °C. – $^1$H-NMR (hexadeuteriodimethylsulphoxide + deuteriochloroform 1:1): 3.84 (3H, s), 6.03 (2H,broad s, exchangeable), 7.23 (1H, dd), 8.35 (2H, complex). – IR: 3450, 3310, 3190 (all $NH_2$), 1685 (C=O); MS *m/z* (%) : 192 (100).

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