# A Practical Synthesis of 4-Chloro-3-(hydroxymethyl)pyridine by Regioselective One-Pot Lithiation/Formylation/Reduction of 4-Chloropyridine

Domenico Albanese,[a] Michele Penso,*[a] Maurizio Zenoni[b]

[a] CNR-CSSSSO and Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy
Fax +39(2)2364369; E-mail: michele.penso@unimi.it
[b] ACS-Dobfar, Via Addetta 8, I-20067 Tribiano, Italy
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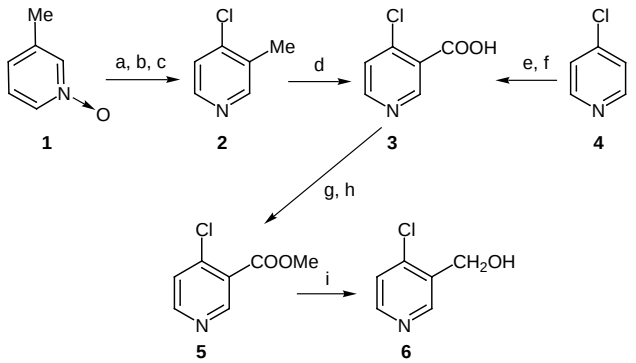
**Abstract:** 4-Chloro-3-(hydroxymethyl)pyridine was prepared and isolated as its hydrochloride in 85% yield from 4-chloropyridine by formylation with dimethylformamide of the corresponding 3-lithium salt, followed by in situ reduction of the resulting 4-chloro-3-formylpyridine through a crossed-Cannizzaro reaction with aqueous formaldehyde.

**Key words:** 4-Chloro-3-hydroxymethylpyridine, crossed Cannizzaro reaction, regioselective lithiation, aromatic formylation, 4-chloro-3-formylpyridine

4-Chloro-3-(hydroxymethyl)pyridine **(6)** can be used as a starting material for the preparation of several polyfunctionalized molecules which can be linked to cephalosporins, generating a new class of antibiotics that show interesting antimicrobial activities.[1,2]

To our surprise, a literature search revealed only few reports on the synthesis of the target compound **6** or its direct precursor, e.g. methyl 4-chloronicotinate **(5)**. One procedure[3] involves the use of 3-picoline *N*-oxide **(1)** as a cheap starting material, which is transformed into methyl 4-chloronicotinate **(5)** through the steps described in Scheme 1. Even if this synthesis is easy to conduct on a laboratory scale, it does not result in a viable process as a consequence of the low overall yield obtained. An alternative route to **5** is the selective C-3 lithiation of 4-chloropyridine **(4)** with lithium diisopropylamide (LDA) in THF at –78 °C and carboxylation with anhydrous carbon dioxide to give 4-chloronicotinic acid **(3)**,[4] followed by esterification. The last and crucial step of both procedures is the reduction of **5** with lithium aluminum hydride.[5] After several attempts to optimize this reaction we concluded that methyl 4-chloronicotinate **(5)**, due to its low stability, is not a good starting material for the preparation of **6**. Actually, **5** polymerizes very rapidly and the reduction, reported to proceed in 74% yield,[5] gave in our hands only lower yields of an impure product.

Gribble and Saulnier[6] had reported the regioselective silylation of 4-chloropyridine at C-3 position to give 4-chloro-3-trimethylsilylpyridine in 92% yield by lithiation with LDA and reaction with trimethylsilyl chloride. We could therefore devise a more efficient route to **6** via the regioselective lithiation of **4** with LDA[4] followed by formylation affording directly **6**. In an initial experiment the formylation of **7** (Scheme 2), prepared as previously described[4,6]

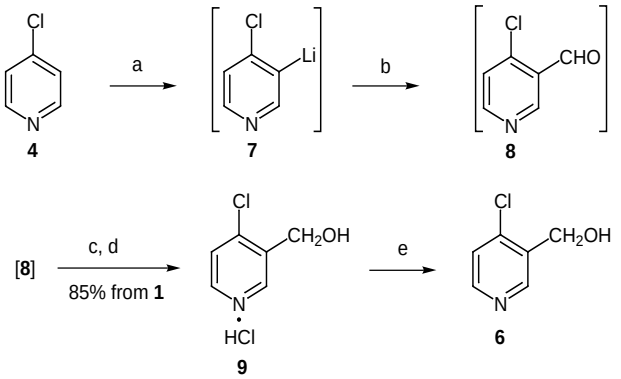



a) $H_2SO_4$-$HNO_3$, Δ; 83%. b) $PCl_3$, $CHCl_3$, Δ; 81%. c) $KHCO_3$, $H_2O$, 0 °C; 100%. d) $KMnO_4$, $H_2O$, 90 °C; 41%. e) LDA, THF, $CO_{2\ gas}$, -78 °C. f) $HCl_{aq}$, 89% from **4**. g) $SOCl_2$, Δ. h) MeOH, 0-20 °C; 90%. i) LAH, $Et_2O$, 0 °C.

**Scheme 1**

by treating **4** with LDA (1.1 mol equiv) in THF at –78 °C, was carried out by addition of 1.23 mol equivalents of DMF at –78 °C followed by quenching with water. Under these reaction conditions the only product recovered from the organic layer after extraction with dichloromethane and standard aqueous workup, although in low yield (< 50%), is the desired alcohol **6**. This alcohol, together with the lithium salt of 4-chloronicotinic acid (recovered from the aqueous layer), are derived from the intermediate aldehyde **8** through a Cannizzaro disproportionation which is promoted by the aqueous LiOH formed by the hydrolysis of LDA.[7] Although the synthetic utility of this process is limited because only 50% of the aldehyde can form the corresponding alcohol, the yield can be greatly improved by quenching the reaction mixture with an aldehyde more reactive than **8**. The formylation step was therefore followed by the addition of an aqueous 40% (w/v) formaldehyde solution (1.5 mol equiv). Formaldehyde participates in the reduction of the generated aldehyde **8** through a crossed Cannizzaro reaction,[8,9] producing lithium formate as byproduct.

After extraction with dichloromethane and standard aqueous workup, the pyridine hydrochloride **9** was prepared by treatment with anhydrous hydrogen chloride at 0 °C in an overall yield of 85%. Finally, the free base **6** was obtained




a) LDA, THF, -78 °C, 1 h. b) DMF, -78 °C, 1 h. c) $CH_2O$, $H_2O$, 25 °C, 1.5 h. d) $HCl_{gas}$, $CH_2Cl_2$, 0 °C, 15 min. e) $KHCO_3$, $H_2O$, 0 °C; 100%

**Scheme 2**

in quantitative yield by treatment of an aqueous solution of **9** with potassium hydrogen carbonate.

4-Chloro-3-formylpyridine **(8)** can be obtained from the crude product of the formylation reaction by acidification with aqueous 10% acetic acid, extraction with dichloromethane and usual aqueous workup. The crude aldehyde **8** was characterised by $^1$H NMR analysis, but it was unstable and hence was not subjected to further purification.

In conclusion we have developed a large scale, high yield, one-pot procedure for the preparation of 4-chloro-3-hydroxymethylpyridine **(6)**, using a combination of direct regioselective lithiation/formylation and crossed Cannizzaro reduction of 4-chloropyridine **(4)**.

Commercial 4-chloropyridine hydrochloride was used as purchased. A commercial 2 M solution of lithium diisopropylamide (LDA) in THF was used. Commercial solvents were of anal grade: THF ($H_2O \leq 0.05\%$) and DMF ($H_2O \leq 0.01\%$). Melting points were determined on a Büchi 535 apparatus and are corrected. $^1$H NMR spectra were recorded on a Bruker WP 80 SY or 300 AC spectrometer using TMS as external reference; δ are in ppm and *J* values are in Hz. GC/MS analyses were performed on a HP5 (30 m x 0.25 mm, 0.25 μm) column, using a Varian Saturn 3 detector.

**4-Chloro-3-(hydroxymethyl)pyridine (6)**
**4-Chloropyridine (4)**

To a solution of $KHCO_3$ (20 g, 0.2 mol) in distilled $H_2O$ (40 mL) cooled at 0 °C was added portionwise 4-chloropyridine hydrochloride (30 g, 0.2 mol) over 10 min. The heterogeneous mixture was extracted with $CH_2Cl_2$ (5 x 30 mL). The combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). After evaporation of the solvent under vacuum (40 mbar) at 20 °C, the free base **4** (21.86 g, 96%) was obtained as an oil.

$^1$H NMR ($CDCl_3$/TMS): δ = 7.25 (d, 2 H, *J* = 4.8 Hz), 8.46 (d, 2 H, *J* = 4.8 Hz).

$^1$H NMR (DMSO-$d_6$/TMS): δ = 7.45 (dd, 2 H, *J* = 1.5, 4.6 Hz), 8.54 (dd, 2 H, *J* = 1.5, 4.6 Hz).

**4-Chloro-3-formylpyridine (8)**

A 500 mL 4-necked round bottomed flask was dried at 110 °C for 1 h and then allowed to cool to r.t. under argon. The flask was assembled with a mechanical stirrer, an argon inlet, a rubber septum and a dropping funnel with a pressure-equalizing side tube. The apparatus was cooled to –78 °C with a dry ice-acetone bath and a 2 M LDA solution in THF (58 mL, 0.116 mol) was introduced via a cannula and vigorously stirred under argon for 10 min. A solution of 4-chloropyridine **(4**; 11.94 g, 0.105 mol) in anhyd THF (50 mL) was added dropwise over 15 min and the mixture became orange/brick red coloured. After stirring for 1 h at –78 °C, anhyd DMF (10 mL, 0.129 mol) was added by a syringe over 12 min and the mixture was stirred for 1 h. The conversion of the substrate **4** into the aldehyde **8** was monitored by $^1$H NMR analysis as follows. A sample (200 μL) was diluted with $Et_2O$ (200 μL) and hydrolyzed with $H_2O$ (200 μL), the organic phase was separated, dried over molecular sieves (0.4 nm) and evaporated at 30 °C, diluted with $CDCl_3$ (0.7 mL) and its $^1$H NMR spectrum was recorded.

$^1$H NMR ($CDCl_3$/TMS): δ = 7.41 (d, 1 H, *J* = 5.4 Hz), 8.65 (d, 1 H, *J* = 5.4 Hz), 9.02 (s, 1 H), 10.48 (s, 1 H).

**4-Chloro-3-(hydroxymethyl)pyridine Hydrochloride (9)**

After completion of the formylation, an aqueous solution (40% w/v) of formaldehyde (12 mL, 0.158 mol) was added at once, the temperature was allowed to rise to 25 °C and the mixture was vigorously stirred at this temperature for 90 min. The liquid phase was decanted and the remaining solid was washed with $CH_2Cl_2$ (2 x 20 mL) by decanting the $CH_2Cl_2$. The organic-aqueous mixture thus obtained was evaporated at 50 °C under vacuum (20 mbar) then at 20 °C (0.001 mbar). The residue was dissolved in $CH_2Cl_2$ (150 mL) and washed with $H_2O$ (4 x 20 mL) and half saturated NaCl solution (40 mL), dried ($MgSO_4$) and evaporated under vacuum to 70 mL. This solution was cooled in an ice bath to 0 °C and anhyd gaseous HCl was bubbled in for 15 min. After 3–4 min light brown crystals formed and were filtered after 30 min, washed with ice cold $CH_2Cl_2$ (20 mL) and dried under vacuum (20 mbar) at 40 °C; yield:16.0 g (85%); mp 145 °C.

$^1$H NMR (DMSO-$d_6$): δ = 4.67 (s, 2 H), 6.12 (br s, 2 H), 8.18 (d, 1 H, *J* = 6.1 Hz), 8.79 (s, 1 H), 8.83 (d, 1 H, *J* = 6.1 Hz).

**Genertion of 4-Chloro-3-(hydroxymethyl)pyridine (6) from the Hydrochloride 9**

A sample of the hydrochloride **9** was dissolved in cold $H_2O$ and neutralized with 1 equivalent of $KHCO_3$. The free base **6** was recovered in quantitative yield by extraction with $CH_2Cl_2$, drying ($MgSO_4$) and evaporation of the solvent under vacuum; mp 82–83 °C.

$^1$H NMR ($CDCl_3$/TMS): δ = 2.69 (br s, 1 H), 4.81 (s, 2 H), 7.29 (d, 1 H, *J* = 5.3 Hz), 8.40 (d, 1 H, *J* = 5.3 Hz), 8.65 (s, 1 H).

GC/MS (EI): m/z = 144.

Anal. calcd for $C_6H_6ClNO$: C, 50.19; H, 4.21; N, 9.76. Found: C, 50.11; H, 4.26; N, 9.85.

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