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A convenient synthetic route to a useful synthon: 4-bromo-2-pyridinecarboxaldehyde

Nicolas Zaman, Régis Guillot, Katell Sénéchal-David *, Marie-Laure Boillot

Institut de Chimie Moléculaire et des Matériaux d'Orsay, ECI, UMR8182, Université Paris Sud XI, 15 rue G. Clémenceau, 91405 ORSAY Cedex, France

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ABSTRACT

We have developed a novel four-step method to synthesise 4-bromo-2-pyridinecarboxaldehyde, from 2-picoline-*N*-oxide via 4-nitro-2-pyridinecarboxaldehyde, under mild reaction conditions.

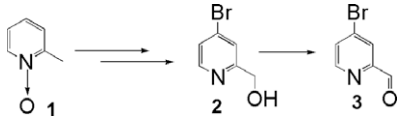
4-Bromo-2-pyridinecarboxaldehyde is a versatile synthon, widely used in various processes such as pharmaceutical multi-step syntheses (as described in recent patents).[1] The bromine group allows a large range of functionalisations via Suzuki[2] or Stille[3] cross-coupling, for example, while the carboxaldehyde group gives access to a panel of dissymmetric condensation reactions.

Despite its interest as a useful versatile synthon, the synthesis of 4-bromo-2-pyridinecarboxaldehyde remains tedious with ill-defined or drastic reaction conditions, and had only been described by two groups in the last two decades.[4,5]

Both procedures start from 2-picoline-*N*-oxide **1** and involve a Swern oxidation of 4-bromo-2-pyridylmethanol **2** as the final step to give 4-bromo-2-pyridinecarboxaldehyde **3** (Scheme 1).[4,5]

The difficulty lies in the introduction of the bromine atom at the 4-position of the pyridine ring, even activated as its *N*-oxide derivative. In fact, direct bromination of 2-picoline-*N*-oxide, described by Profft,[6] requires the use of concentrated HBr heated at 160 °C inside a glass autoclave, followed by an arduous isolation step. The introduction of the bromine atom at the 4-position of the pyridine ring, seems more convenient via a nitro group substitution.[4,5]

Jones et al. choose a five-step procedure with the bromine group introduction in the second one:[4] (i) nitration of 2-picoline-*N*-oxide with fuming nitric acid, (ii) then bromination of 4-nitro-2-picoline-*N*-oxide **4**, with drastic use of 48% HBr and urea, at 160 °C, as described by Suzuki.[7] (iii) A Boekelheide rearrangement,[8] using an excess of acetic anhydride, (iv) followed by the hydrolysis of the intermediate acetate gave the 4-bromo-2-pyridylmethanol **2**, (v) finally oxidised with DMSO and oxalyl chloride.[4] Yields of the first two steps are uncertain.[7]



Scheme 1. Synthetic procedure described previously.[4,5]

Ashimori et al. preferred a six-step procedure via 4-bromo-2-picoline:[5] (i) nitration of 2-picoline-*N*-oxide as well with fuming nitric acid, (ii) followed by the reduction with PCl_3 converted 4-nitro-2-picoline-*N*-oxide **4** to 4-nitro-2-picoline. Subsequent treatments with (iii) acetyl bromide, (iv) oxidation to carboxylic acid with $KMnO_4$, (v) conversion to mixed anhydride with $ClCO_2Et$ and then (vi) a final reduction with $LiAlH_4$ permitted to obtain 4-bromo-2-pyridylmethanol **2** with three more steps. The global yield is then around 5% after the final (vii) Swern oxidation step.[5]

The harsh reaction conditions associated with these protocols, the poor description of some key steps and the relatively low yields prompted us to design a new synthetic pathway to 4-bromo-2-pyridinecarboxaldehyde **3**.

We report here this synthesis, using mild reaction conditions, also starting from 2-picoline-*N*-oxide **1**, the substitution of the nitro group for the bromine atom being performed during the final step (Scheme 2).[9]

(i) Nitration of 2-picoline-*N*-oxide **1** is realised by in situ nitric acid generation to afford 4-nitro-2-picoline-*N*-oxide **4**. At this stage, the substitution of the nitro group for bromine atom is not

* Corresponding author. Tel.: +33 01 69 15 74 36; fax: +33 01 69 15 47 54.
E-mail address: ksenechal@icmo.u-psud.fr (K. Sénéchal-David).

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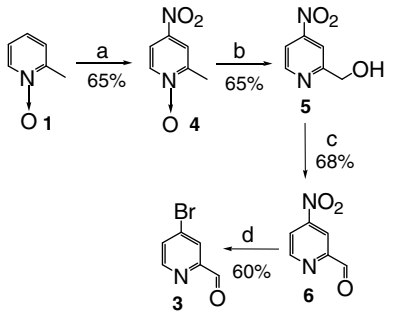

Scheme 2. Reagents and conditions: (a) $NaNO_3$, H_2SO_4, 95–100 °C; (b) (i) $(CF_3CO)_2O$, CH_2Cl_2, 25 °C, 3 days; (ii) K_2CO_3, CH_3OH, rt, 4 h; (c) MnO_2, CH_2Cl_2, 25 °C, 3 days; (d) AcBr, 60 °C, 8 h.[9]

possible using acetyl bromide. In fact, an undesired product is mainly obtained.[10] (ii) The Boekelheide rearrangement is performed using trifluoroacetic anhydride, at 25 °C. After solvent and excess reagent evaporation, the crude ester intermediate is directly saponified by stirring it with K_2CO_3 in a methanol solution to give 4-nitro-2-pyridylmethanol **5**, in good yield. (iii) Instead of using a Swern oxidation to get aldehyde **6**, we preferred a simpler method, using MnO_2 as the oxidising reagent[11] at 25 °C. (iv) Finally, acetyl bromide allows the substitution of the nitro group for the bromine atom in good yield. This synthesis is carried out under an argon atmosphere due to the extreme air sensitivity of the 4-bromo-2-pyridinecarboxaldehyde **3** towards oxidation to the corresponding carboxylic acid. Compound **3** is obtained as crystals without any purification (the X-ray diffraction study is reported in the Supplementary data). Moreover, it is necessary to store this compound under an inert atmosphere and to use it rapidly.

In conclusion, we have elaborated a novel, convenient four-step synthetic route to the versatile synthon 4-bromo-2-pyridinecarboxaldehyde, in a 17% global yield. This method makes this interesting synthon easily accessible in a few synthetic steps performed under mild reaction conditions.

Supplementary data

Supplementary data (X-ray diffraction study of 4-bromo-2-pyridine-carboxaldehyde) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.027.

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9. *General procedure*: *(a) Preparation of 4-nitro-2-picoline-N-oxide* **4**: To a solution of 2-picoline-*N*-oxide **1** (9.06 g, 83 mmol) and H_2SO_4 32% (50 mL), kept in an ice bath, $NaNO_3$ (7.77 g, 91 mmol) was added slowly. After complete dissolution, the colourless solution was heated at 95–100 °C, for 2 h. After cooling to room temperature, the yellow solution was poured onto crushed ice, and basified with K_2CO_3. The yellow precipitate was filtered off, dissolved in dichloromethane. The organic layer was dried over $MgSO_4$, and the solvent was removed under pressure to yield a pale yellow solid (8.32 g, 54 mmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 8.00 (dd, J = 7.6 Hz J = 3.2 Hz, 1H), 8.15 (d, J = 3.2 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 17.8, 117.7, 120.3, 139.5, 141.4, 150.3. IR (KBr): 3114, 3080, 3049, 1611, 1514, 1457, 1345, 1337, 1286, 1269, 1200, 1092, 933, 844, 786, 750, 661 cm^{-1}. Anal. Calcd for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.40; H, 3.76; N, 18.20. (b) *Preparation of 4-nitro-2-pyridylmethanol* **5**: To a yellow solution of 4-nitro-2-picoline-*N*-oxide **4** (0.92 g, 6 mmol) in dichloromethane (25 mL), a solution of trifluoroacetic anhyd (2.5 mL, 18 mmol) in dichloromethane (5 mL) was added dropwise. The red solution was stirred at room temperature for 3 days. Solvent was evaporated. Methanol (20 mL) and an aqueous saturated K_2CO_3 solution (10 mL) were added, and the mixture was stirred at room temperature for 4 h. Methanol was evaporated, and the compound was extracted with dichloromethane (3 × 25 mL). Combined organic layers were washed with brine solution (25 mL), dried over $MgSO_4$, and the solvent removed was under vacuum. A yellow solid (0.58 g, 4 mmol, 65%) was isolated. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (s large, 1H), 4.88 (s, 2H), 7.90 (dd, J = 5.2 Hz, J = 1.7 Hz, 1H), 8.05 (d, J = 1.7 Hz, 1H), 8.81 (d, J = 5.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 64.6, 113.4, 115.2, 151.2, 154.6, 163.6. IR (KBr): 3260, 3114, 3056, 3027, 2960, 1581, 1539, 1416, 1366, 1352, 1305, 1233, 1045, 1003, 935, 855, 741, 689 cm^{-1}. Anal. Calcd for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.80; H, 3.90; N, 18.17. (c) *Preparation of 4-nitro-2-pyridinecarboxaldehyde* **6**: A mixture of 4-nitro-2-pyridylmethanol **5** (1.77 g, 11.5 mmol), dichloromethane (300 mL), MnO_2 (6 g, 69 mmol) was stirred at 25 °C, for 3 days. The heterogeneous solution was filtrated through Celite and dichloromethane was evaporated. The crude was purified by column chromatography (silica gel, dichloromethane) to give compound **6** as a yellow oil (1.15 g, 7.6 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (dd, J = 5.4 Hz, J = 2.3 Hz, 1H), 8.59 (d, J = 2.3 Hz, 1H), 9.09 (d, J = 5.4 Hz, 1H), 10.15 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 114.4, 120.0, 152.7, 154.9, 155.9, 191.2. IR (KBr plates): 3096, 2852, 2708, 1714, 1602, 1575, 1537, 1355, 1216, 1079, 994, 923, 863, 738, 682, 659 cm^{-1}. Anal. Calcd for $C_6H_4N_2O_3$: C, 47.38; H, 2.65; N, 18.42. Found: C, 47.00; H, 2.62; N, 18.07. (d) *Preparation of 4-bromo-2-pyridinecarboxaldehyde* **3**: Under argon atmosphere, into a 2-necked round-bottomed flask, acetyl bromide (30 mL, 403 mmol) was added rapidly to 4-nitro-2-pyridinecarboxaldehyde **6** (1.90 g, 12.5 mmol). The red mixture was heated at 60 °C overnight. A red solid was precipitated. After cooling to room temperature, the mixture was poured onto crushed ice, and the resulting solution was basified with Na_2CO_3. The compound was extracted with diethylether (3 × 100 mL). Combined organic layers were washed with brine solution (25 mL), dried over $MgSO_4$, and the solvent was removed under vacuum. A yellow oily crude (1.45 g, 7.5 mmol) crystallised to give compound **3** in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, J = 5.2 Hz J = 2.3 Hz, 1H), 8.06 (d, J = 2.3 Hz, 1H), 8.56 (d, J = 5.2 Hz, 1H), 10.00 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 125.3, 131.1, 134.3, 151.1, 153.8, 192.2. IR (KBr): 3051, 2925, 2847, 1765, 1569, 1371, 1235, 1200, 1017, 837, 682 cm^{-1}. X-ray diffraction study is reported in Supplementary data.
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