Facile and Efficient Synthesis of 4-Alkyl Derivatives of 3-Carbamoyl- and 3,5-Dicarbamoylpyridines as Nicotinamide Mimetics

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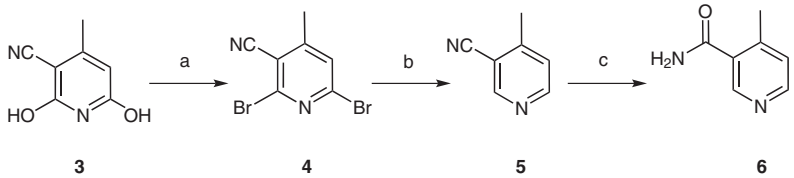
Abstract: Nicotinamide plays a key role in many biological processes and, as a consequence, its derivatives could be attractive for the synthesis of biologically active compounds. Here a rapid and efficient way of preparing alkyl derivatives of nicotinamide, precisely, 4-alkyl-3-carbamoylpyridine and 4-alkyl-3,5-dicarbamoylpyridine is reported. The synthetic route developed adopts mild reaction conditions and produces target compounds in higher yields compared with methods described in literature.

Key words: amides, drugs, hydrogenation, nicotinamide derivatives, nitrile hydrolysis, pyridines

Nicotinamide is an essential nutrient, a precursor of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), and participates with different roles in many biological processes. Recently a number of other new biological activities of nicotinamide have been described; for example, it is a direct reaction product and a potent physiological inhibitor of Sir2 enzymes, a unique class of NAD^+-dependent protein deacetylases (class III Histone/Protein deacetylases).[1] Furthermore, pyridine derivatives are substrates or inhibitors of transglycosidation reactions catalyzed by Sir2.[2] In this context, it could be of interest to evaluate the title compounds as NAD and nicotinamide mimetic models and also as intermediates for the preparation of further derivatives, such as carboxylic acids and esters, to be studied, for example, as modulator of sirtuine enzyme. The synthesis of 4-alkyl derivatives of 3-carbamoylpyridine (Scheme 1) and 3,5-dicarbamoylpyridine (Scheme 2) is reported here.

For the synthesis of 3-carbamoyl-4-methylpyridine (**6**), the corresponding 3-cyano-4-methylpyridine (**5**) was chosen as the starting material (Scheme 1). This nitrile was prepared in two steps, from 3-cyano-2,6-dihydroxy-4-methylpyridine (**3**), modifying the procedure described by Bobbit and Scola.[3] The conversion of **3** to the corresponding pure 3-cyano-2,6-dibromo-4-methylpyridine (**4**) in 75% yield was carried out by treatment with phosphorous oxybromide; heating to melting point and refluxing for two hours at 190–200 °C. Bobbit and Scola obtained the 2,6-dichloro derivative by reaction with phosphorus oxychloride at high temperature in an autoclave. In our hands, any attempt to obtain the 2,6-dichloro derivative failed; instead complex mixtures of polychlorinated compounds were obtained in which the hydrogens of the 4-methyl group are substituted by one or more chlorine atoms. The bromination reaction is more selective than chlorination and, moreover, bromine is a better leaving group for the subsequent step. In fact, the hydrogenolysis of **4** was carried out in THF–NH_4OH solution simply by adding a reducing metal, such as Zn powder, and boiling the reaction mixture for two hours. The cyano derivative **5** was then converted to the corresponding nicotinamide derivative **6** with a selective alkaline hydrolysis accomplished by treatment with alkaline ion-exchange resin, for example, Amberlite IRA 410.

The salts **7** and **8** were obtained by condensing cyanoacetamide with acetaldehyde in the presence of piperidine[4] and propionaldehyde in the presence of ammonia, respectively (Scheme 2). Also in this case, the conversion of **7** and **8** to the corresponding dibromo derivatives **9a**,**b** was conducted successfully in good yields, avoiding polychlorination products, by treatment with phosphorous oxybromide, by heating to melting point and refluxing for one hour at 170 °C. Hydrogenolysis of **9a**,**b** proceeded in good yields in the presence of $Pd/CaCO_3$ by simply bubbling H_2 through the reaction mixture at room temperature and atmospheric pressure to afford 4-methylpyridine-3,5-dicarbonitrile (**10a**) and 4-ethyl-1,2-dihydropiridine-3,5-dicarbonitrile (**10b**).



Scheme 1 *Reagents and conditions:* (a) $POBr_3$, 190 °C; (b) Zn, NH_4OH–THF; (c) 10% aq NaOH, IRA 410.

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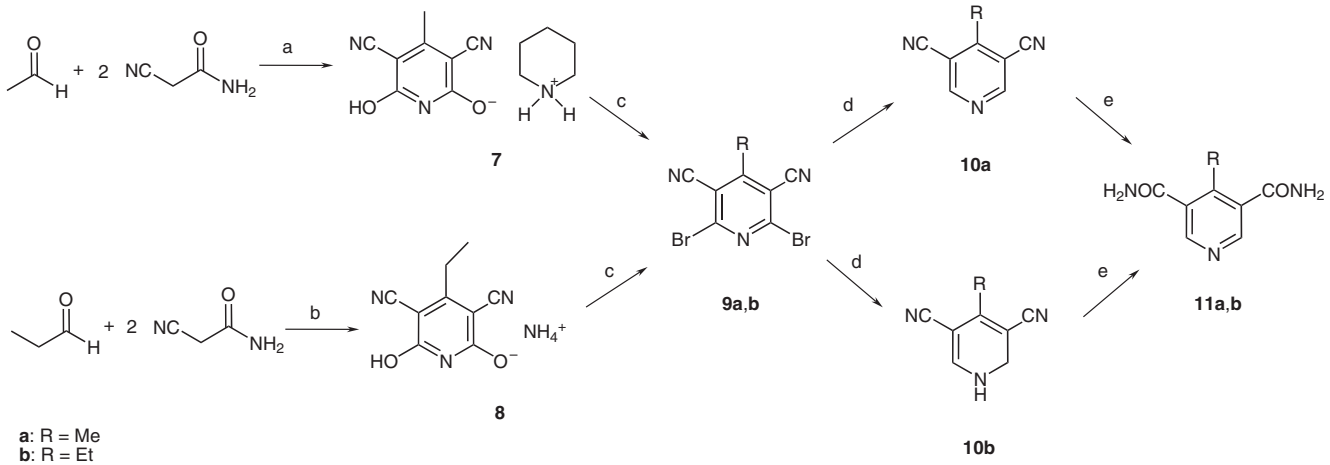

Scheme 2 *Reagents and conditions:* (a) piperidine–MeOH; (b) aq 25% NH_3; (c) $POBr_3$, 190 °C; (d) H_2, $Pd/CaCO_3$, EtOH–benzene (1:1); (e) 10% aq NaOH, IRA 410.

Selective hydrolysis of the cyano group in **10a**,**b** with Amberlite IRA 410 resin caused also the oxidation of 1,2-dihydropyridine, generating amide derivatives **11a**,**b**. It is noteworthy that ^{1}H NMR spectra of solutions of **10b** in DMSO-d_6 shelved at room temperature in air, showed the progressive oxidation to the corresponding 4-ethylpyridine-3,5-dicarbonitrile.

Chemical reagents and solvents used in this study were purchased from Sigma-Aldrich Chemical Co. and were of analytical grade. Melting points were determined on a Tottoli apparatus and are uncorrected. IR spectra were registered on neat compounds on a Perkin-Elmer Spectrum-One spectrophotometer equipped with an ATR detector; band frequencies are reported in wavenumber (cm^{-1}). ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shift values, unless otherwise stated, are reported as δ (ppm) relatively to TMS as internal reference; coupling constants are given in Hz. Yields of all reactions refer to the purified products.

2,6-Dihydroxy-4-methylpyridine-3-carbonitrile (3)
This compound was prepared according to Bobbit and Scola;[3] mp 295–300 °C.

IR (neat): 2223, 1597 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 5.57 (s, 1 H, H-5), 2.21 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 162.3, 161.5, 160.8, 117.6, 93.2, 89.5, 21.1.

Anal. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.87; H, 4.39; N, 18.27.

2,6-Dibromo-4-methylpyridine-3-carbonitrile (4)
A mixture of **3** (2.00 g, 13.3 mmol) and $POBr_3$ (7.64 g, 26.6 mmol) was heated in a sand bath and maintained at 190 °C for 2 h. The reaction mixture was then cooled to r.t. and quenched by the addition of ice. The obtained suspension was extracted with $CHCl_3$ (4 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The solid residue was purified by silica gel column chromatography (eluent: $CHCl_3$) to give pure **4** (2.77 g, 10.0 mmol, 75%); mp 137–140 °C.

IR (neat): 2230, 1560 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.48 (s, 1 H, H-2), 1.26 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 155.7, 144.3, 143.1, 128.2, 114.6, 114.0, 20.7.

Anal. Calcd for $C_7H_4Br_2N_2$: C, 30.47; H, 1.46; N, 10.15. Found: C, 30.07; H, 1.73; N, 9.78.

4-Methylpyridine-3-carbonitrile (5)
To the nitrile **4** (1.00 g, 3.6 mmol) dissolved in anhyd THF (25 mL) were added Zn powder (5 g) and 15% aq NH_3 (100 mL) and the suspension was refluxed for 4 h. The reaction mixture was cooled to r.t., the Zn residue was filtered off, and the solution was extracted with $CHCl_3$ (7 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a crude residue that was purified by silica gel column chromatography ($CHCl_3$–EtOAc, 6:4 v/v) to give (0.34 g, 2.9 mmol, 80%) **5**; mp 44–46 °C.

IR (neat): 2227, 1593 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.90 (s, 1 H, H-2), 8.69 (d, J = 5.1 Hz, 1 H, H-6), 7.52 (d, J = 5.1 Hz, 1 H, H-5), 2.50 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 152.6, 152.4, 150.7, 124.8, 115.8, 110.8, 20.0.

Anal. Calcd for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.93; H, 5.26; N, 23.78.

4-Methylpyridine-3-carboxamide (6)
To 4-methylpyridine-3-carbonitrile (**5**; 0.50 g, 4.2 mmol) dispersed in freshly degassed H_2O (25 mL) was added anionic exchange resin IRA 410 (1.0 g) previously conditioned as follows: IRA 410 (1 g) was suspended in 10% aq NaOH (15 mL) and stirred at r.t. for 90 min, after this time the resin was filtered and washed with degassed H_2O until the pH of washings was nearly 7. The suspension containing **6** and IRA 410 was refluxed for 1 h and then the resin was filtered off and washed with boiling water (2 × 10 mL). The combined aqueous portions were lyophilized to give pure **6** (0.49 g, 3.6 mmol, 86%); mp 159–161 °C (Lit.[3] mp 167–167.5 °C).

IR (neat): 3304, 1667, 1598 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 10.3 (s, 1 H, NH), 8.45 (d, J = 4.9 Hz, 1 H, H-6), 7.92 (br s, 1 H, NH_a), 7.56 (br s, 1 H, NH_b), 7.27 (d, J = 4.9 Hz, 1 H, H-5), 2.37 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 163.7, 159.9, 119.3, 82.4, 44.29, 22.71, 22.09, 19.9.

Anal. Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 62.04; H, 6.02; N, 19.97.

Piperidinium 3,5-Dicyano-4-methyl-6-hydroxypyridin-2-olate (7)

A mixture of cyanoacetamide (5.98 g, 71.0 mmol), piperidine (12.17 g, 143.0 mmol) and MeOH (45 mL) was heated until complete dissolution. The obtained solution was cooled to r.t. and acetaldehyde (1.56 g, 35.50 mmol) was then added, maintaining the mixture for 24 h under vigorous stirring. The volume of the obtained suspension was halved under reduced pressure and the white precipitate was collected, washed with EtOAc (3 × 10 mL), and dried under reduced pressure to give pure **7** (6.49 g, 24.9 mmol, 70%); mp 245–247 °C.

IR (neat): 3143, 2197, 1655 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.00 (m, 4 H, 2 CH_2), 2.17 (s, 3 H, CH_3), 1.63 (m, 4 H, 2 CH_2), 1.55 (m, 2 H, CH_2).

^{13}C NMR (DMSO-d_6): δ = 163.7, 159.9, 119.3, 82.4, 44.29, 22.71, 22.09, 19.9.

Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.53; H, 6.07; N, 20.37.

Ammonium 3,5-Dicyano-4-ethyl-6-hydroxypyridin-2-olate (8)

This compound was prepared according to the procedure described by Lukes and Kuthan.[4] Cyanocetamide (6.02 g, 71.4 mmol) was suspended in H_2O (40 mL), then 25% aq NH_3 (2 mL) and propionaldehyde (2.14 g, 37.0 mmol) were added. The mixture was stirred for 20 h at r.t. The obtained white precipitate was collected by filtration, washed with small portions of cold MeOH, and dried under reduced pressure to give pure **8** (5.34 g, 25.9 mmol, 70%); mp >300 °C.

IR (neat): 3165, 2210, 1666 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.45 (q, J = 7.6 Hz, 2 H, CH_2), 1.13 (t, J = 7.6 Hz, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 165.9, 164.2, 118.9, 81.3, 27.4, 14.0.

Anal. Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 51.97; H, 5.06; N, 26.85.

2,6-Dibromo-4-methylpyridine-3,5-dicarbonitrile (9a)

A mixture of **7** (2.00 g, 7.7 mmol) and $POBr_3$ (4.41 g, 15.4 mmol) was carefully heated in a sand bath at 170 °C and maintained under stirring at this temperature for 1 h. After cooling to r.t., the reaction was quenched by the addition of ice and the obtained suspension was extracted with $CHCl_3$ (5 × 50 mL). The combined organic extracts were collected, dried (Na_2SO_4), and evaporated under vacuum to give a crude residue from which pure **9a** (1.96 g, 6.50 mmol, 84%) was obtained by silica gel column chromatography (eluent: $CHCl_3$); mp 152–155 °C.

IR (neat): 2237, 1543 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.81 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 156.8, 146.6, 115.0, 112.4, 21.1.

Anal. Calcd for $C_9H_5Br_2N_3$: C, 34.32; H, 1.60; N, 13.34. Found: C, 34.98; H, 1.46; N, 13.92.

2,6-Dibromo-4-ethylpyridine-3,5-dicarbonitrile (9b)

Product **9b** (2.24 g, 7.1 mmol, 73%) was obtained from salt **8** (2.00 g, 9.7 mmol) following the same procedure as described for compound **9a**; mp 122–124 °C.

IR (neat): 2236, 1539 cm^{-1}.

^1H NMR (acetone-d_6): δ = 3.13 (q, J = 7.8 Hz, 2 H, CH_2), 1.38 (t, J = 7.8 Hz, 3 H, CH_3).

^{13}C NMR (acetone-d_6): δ = 164.8, 146.8, 114.1, 113.2, 28.7, 13.9.

Anal. Calcd for $C_9H_5Br_2N_3$: C, 34.32; H, 1.60; N, 13.34. Found: C, 34.98; H, 1.46; N, 13.92.

4-Methylpyridine-3,5-dicarbonitrile (10a)

2,6-Dibromo-4-methylpyridine-3, 5-dicarbonitrile (**9a**; 1.47 g, 4.9 mmol) was dissolved in a 1:1 mixture of EtOH and benzene (50 mL) in a two-necked round-bottomed flask. Pd/$CaCO_3$ (1 g) was then added and H_2 was bubbled through the reaction mixture. The mixture was slowly stirred and maintained under H_2 atmosphere, the product formation was monitored by means of silica gel TLC (EtOAc–$CHCl_3$, 6:4 v/v). After 3 days, the catalyst was removed by filtration and the solvent evaporated under reduced pressure. The remaining thick oil was treated with sat. aq $NaHCO_3$ (15 mL) and the obtained suspension was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow solid that was purified on silica gel column chromatography (EtOAc–$CHCl_3$, 6:4 v/v) to afford pure **10a** (0.51 g, 3.6 mmol, 73%); mp 80–82 °C (Lit.[5] mp 84–85 °C).

IR (neat): 3076, 2193, 1632 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 9.05 (s, 2 H, H-2,6), 2.62 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 156.4, 155.6, 115.8, 111.8, 20.1.

Anal. Calcd for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.35. Found: C, 67.41; H, 3.46; N, 29.15.

4-Ethyl-1,2-dihydropyridine-3,5-dicarbonitrile (10b)

Product **10b** (0.41 g, 2.6 mmol, 67%) was prepared from **9b** (1.23 g, 3.9 mmol) following the same procedure as described for **10a**; mp 155–160 °C (Lit.[6] mp 182–187 °C).

IR (neat): 3313, 2250, 1633 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.38 (br s, 1 H, NH), 7.55 (s, 1 H, H-6), 4.10 (s, 2 H, H-2 + H-2′), 2.30 (q, J = 7.5 Hz, 2 H, CH_2), 1.08 (t, J = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 153.2, 152.9, 118.1, 115.1, 83.6, 77.6, 41.7, 27.1, 13.4.

Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 66.46; H, 6.23; N, 26.01.

4-Methylpyridine-3,5-dicarboxamide (11a)

Product **11a** (0.36 g, 2.0 mmol, 77%) was obtained from **10a** (0.37 g, 2.6 mmol) using the same procedure as described for **6**; mp 240 °C.

IR (neat): 3340, 3188, 1660, 1573 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.51 (s, 2 H, H-2), 8.01 (br s, 2 H, NH_a), 7.67 (br s, 2 H, NH_b), 2.39 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 164.9, 153.8, 142.8, 138.0, 17.9.

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.11; H, 5.39; N, 22.85.

4-Ethylpyridine-3,5-dicarboxamide (11b)

Product **11b** (0.37 g, 1.9 mmol, 95%) was obtained from **10b** (0.32 g, 2.0 mmol) using the same procedure as described for **6**; mp >300 °C.

IR (neat): 3346, 3185, 1677, 1623 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 8.48 (s, 2 H, H-2), 8.03 (br s, 2 H, NH_a), 7.64 (br s, 2 H, NH_b), 2.85 (q, J = 7.6 Hz, 2 H, CH_2), 1.13 (t, J = 7.6 Hz, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 169.9, 148.4, 148.3, 133.8, 22.9, 15.8.

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.66; H, 5.96; N, 21.67.

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