CONVENIENT SYNTHESIS OF 3-(1-CARBOXYALKYL)PYRIDO-[2,3-*d*]PYRIMIDINE-2,4-DIONES

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A cheap and safe synthetic route to obtain 3-(1-carboxyalkyl)pyrido[2,3-d]pyrimidinediones (carboxyalkyl = –CHRCO$_2$H; R = H; CH$_2$; CH$_2$Ph; Ph; CH$_2$ (C$_3$H$_3$N$_2$); (CH$_2$)$_2$CO$_2$H; CH$_2$CO$_2$H) starting from 2,3-pyridinedicarboxylic acid is described. A process scheme consistent with empirical observations is proposed.

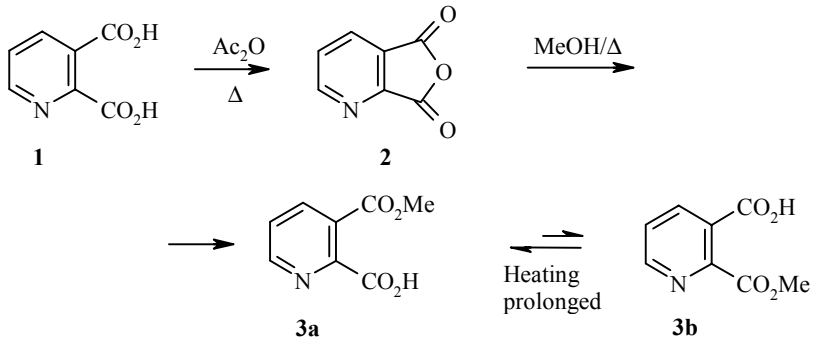
Keywords: amino acids, pyrido[2,3-*d*]pyrimidine, pyridinecarboxylic acids.

Pyrimidine derivatives are common sources for new potential therapeutic agents. In particular, pyrido[2,3-*d*]pyrimidines have been found to have important biological properties such as antibacterial or antitumor activities [1-5]. Despite this fact and the ubiquitous character of that kind of compounds, few general processes to obtain 3-(1-carboxyalkyl)pyrido[2,3-*d*]pyrimidine-2,4-diones have been reported, which is quite surprising considering the intense research activity centered on such compounds [6, 7]. On the other hand, the utility of compounds with notable biological properties could be limited by its synthetic cost. This premise demands an accurate selection of reagents, solvents, and procedures. We now wish to report a general method, cheap and safe, for the successful synthesis of 3-(1-carboxyalkyl)pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives.

A convenient starting compound to obtain the desired pyridopyrimidinediones was found to be the 2,3-pyridinedicarboxylic acid (**1**), which is a cheap, stable, and nontoxic compound.

This reagent was easily dehydrated in refluxed acetic anhydride to give anhydride **2**. Previous report [8] showed that **2** reacts with refluxed methanol to afford two isomeric methyl carboxypyridinecarboxylates **3a** and **3b** (Scheme 1), **3a** increasing as the heating is prolonged.

Scheme 1



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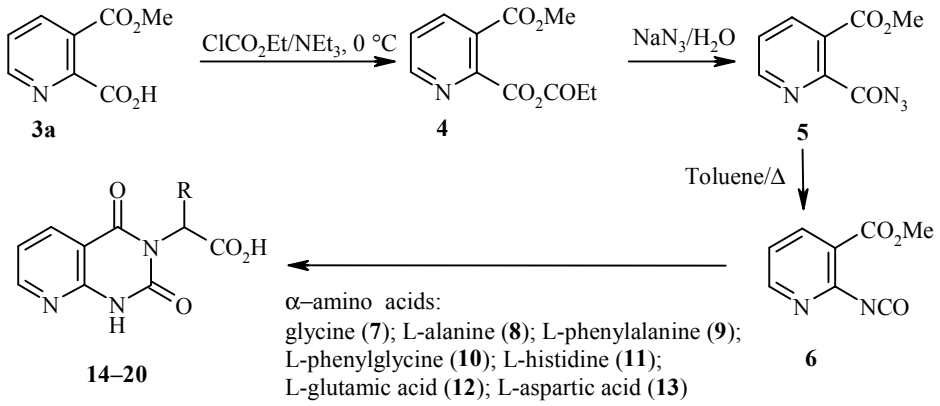
Reaction of monoester **3a** with $ClCO_2Et$ in dry basic media (NEt_3/KOH) led to the formation of the unstable anhydride **4**. This compound is moisture sensitive, decomposing on air within 1 h. If dried solvent and N_2 atmosphere was used, the compound remained stable for a time longer than 1 day. It was determined by using thin layer chromatography standard methods that a fresh solution of **4** had to be used in 30 min. Compound **4** prepared in such a manner reacted with an aqueous solution of NaN_3 to afford the acyl azide **5** with the CON_3 group in position 2, which was characterized by the $\nu(N_3)$ IR absorption (2160 cm^{-1}). Refluxing azide **5** in toluene gaves rise to isocyanate **6** by the Curtius rearrangement [9, 10], which was supported by IR and elemental analysis.

Scheme 2



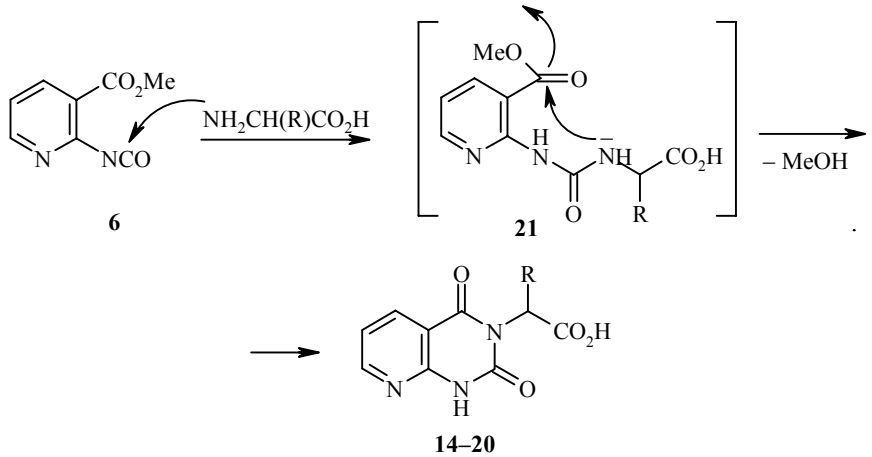
3a **4** **5** **6** **14–20**

R = H (**14**); Me (**15**); CH_2Ph (**16**); Ph (**17**); $CH_2(C_3H_3N_2)$ (**18**); $(CH_2)_2CO_2H$ (**19**); CH_2CO_2H (**20**)

Finally, reaction of α-amino acids **7-13** with isocyanate **6** in an alkaline (NaOH, pH 8-9) refluxed dioxane/water mixture gave the desired 3-sub-stituted pyrido[2,3-*d*]pyrimidine-2,4-diones **14-20** in good yield (Scheme 3).

A pathway for this step likely includes (Scheme 3) attack of the α-amino acid nitrogen atom on the isocyanate group carbon, which leads to the formation of the *ortho*-carbomethoxyureide intermediate **21**. Subsequent ring closure with elimination of methanol gives rise to compounds **14-20**.

Scheme 3



6 **21** **14–20**

EXPERIMENTAL

All reagents were of analytical grade and were used without further purification. All reactions were monitored by thin layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (MERCK), and compounds were visualized under UV light (254 nm). Deuterated solvents for NMR measurements were dried over molecular sieves (0.4 nm). ^{1}H, ^{13}C NMR $\{^{1}H\}$ spectra were recorded on Bruker AVANCE DRX 300 relative to tetramethylsilane. IR spectra were recorded (for KBr discs) on an IR-ATI Mattson Infinity Series instrument. Mass spectra were obtained using JEOL JMS DX 100 and DX 300 spectrometers. Elemental analysis (C, H, N, S) was performed on an EAGER 200 elemental analyser.

3-Methyl-2-carboxypyridine-3-carboxylate (**3a**). A suspension of 2,3-pyridinedicarboxylic acid (**1**) (1.50 g, 8.98 mmol) in acetic anhydride (15 ml) was refluxed for 4 h under dry air and the resulting solution was kept at 8°C for 12 h. The white precipitate was dissolved in MeOH (20 ml) and stirred at 45°C for 24 h. The solvent was removed and the solid washed with hexane and recrystallized from hot toluene. Yield 76%; mp 111-113°C. IR spectrum (KBr), ν, cm^{-1}: 1730 (C=O), 1680 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.99 (3H, s, OCH_3); 7.40-7.80 (3H, m, Py).

3-Carbomethoxy-2-pyridylisocyanate (**6**). Into an efficiently stirred solution of **3a** (1 g, 5.25 mmol) in THF (15 ml) at 0°C, were slowly added NEt_3/KOH (1.54 ml, 11.05 mmol) and $ClCO_2Et$ (0.80 ml, 8.28 mmol). After 30 min a solution of NaN_3 (0.90 g, 13.74 mmol) in H_2O (5.40 ml) was slowly added and the mixture stirred for 1 h at room temperature. The THF was eliminated by reduced pressure and the resulting mixture extracted with AcOEt (3 × 10 ml). The different fractions were collected, dried with Na_2SO_4, the solvent removed by reduced pressure, and the resulting yellow solid refluxed in toluene for 2 h. The organic phase was decanted, concentrated to half volume, and kept at room temperature overnight. The compound precipitated as a white powder was filtered off, washed with Et_2O (3 × 5 ml), and air dried. 0.90 g (Yield 91%). IR spectrum (KBr), ν, cm^{-1}: 2253 (N=C=O), 1725 (C=O). Mass spectrum, found, *m/z*: 178 [M]. $C_8H_6N_2O_3$. Calculated, *m/z*: 178.147. ^{1}H NMR ($CDCl_3$), δ, ppm: 3.90 (3H, s, OCH_3); 7.30-7.70 (3H, m, Py).

3-(1-Carboxyalkyl)pyrido[2,3-*d*]pyrimidine-2,4-diones (**14-20**). Into H_2O (10 ml) was introduced the respective α-amino acids **7-13** (11 mmol) and 1 N NaOH (10 ml or 20 ml if **12** or **13** is used). The mixture was stirred for 10 min at room temperature and a solution of the isocyanate **6** (10 mmol) in dioxane (10 ml) added. The resulting yellow solution was kept at 60°C for 4.5 h and the solvent removed. The resulting molasses obtained was dissolved in water (5 ml) and the solution was acidified to pH 2 by adding 2 N HCl. The precipitate was filtered off, washed with H_2O (2 × 2 ml), and air dried. Analytically pure compounds were obtained by recrystallization from hot MeOH.

3-Carboxymethylpyrido[2,3-*d*]pyrimidine-2,4-(1H,3H)-dione (**14**). Yield 85%; mp 328-330°C. IR spectrum (KBr), ν, cm^{-1}: 3125 (NH), 1662 (C=O), 1725 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.56 (2H, s, CH_2); 7.60-7.80 (m, 3, Py); 11.79 (s, 1, NH). Mass spectrum, found, *m/z*: 222 [M+1]. $C_9H_7N_3O_4$. Calculated, *m/z*: 221.1720. Found, %: C 48.90; H 3.29; N 18.86. $C_9H_7N_3O_4$. Calculated, %: C 48.87; H 3.19; N 19.00.

3-(1-Carboxyethyl)pyrido[2,3-*d*]pyrimidine-2,4-(1H,3H)-dione (**15**). Yield 80%; mp 228-230°C. IR spectrum (KBr), ν, cm^{-1}: 3120 (NH), 1682 (C=O), 1720 (C=O). ^{1}H NMR spectrum (methanol-d_4), δ, ppm: 1.63 (3H, d, CH_3); 5.88 (1H, q, CH); 8.00-8.60 (3H, m, Py); 8.65 (1H, s, NH). Mass spectrum, found, *m/z*: 236 [M+1]. $C_{10}H_9N_3O_4$. Calculated, *m/z*: 235.2067. Found, %: C 51.11; H 3.90; N 17.70. $C_{10}H_9N_3O_4$. Calculated, %: C 51.06; H 3.85; N 17.86.

3-(1-Carboxyphenyl)pyrido[2,3-*d*]pyrimidine-2,4-(1H,3H)-dione (16). Yield 90%; mp 203-205°C. IR spectrum (KBr), ν, cm^{-1}: 3120 (NH), 1662(C=O), 1725 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.49 (1H, s, CHPh); 7.60-8.50 (3H, m, Py); 10.29 (1H, s, NH). Mass spectrum, found, *m/z*: 298 [M+1]. $C_{15}H_{11}N_3O_4$. Calculated, *m/z*: 297.2775. Found, %: C 60.78; H 3.85; N 13.98. $C_{15}H_{11}N_3O_4$. Calculated, %: C 60.60; H 3.73; N 14.13.

3-(1-Carboxybenzyl)pyrido[2,3-*d*]pyrimidine-2,4-(1H,3H)-dione (17). Yield 88%; mp 269-271°C. IR spectrum (KBr), ν, cm^{-1}: 3125 (NH), 1665 (C=O), 1725 (C=O). ^1H NMR spectrum (methanol-d_4), δ, ppm: 5.86 (1H, m, CH); 3.54 (2H, m, CH_2); 8.30-9.00 (3H, m, Py); 7.20-7.60 (5H, m, Ph); 8.50 (1H, s, NH). Found, %: C 61.80; H 4.36; N 13.49. $C_{16}H_{13}N_3O_4$. Calculated, %: C 61.73; H 4.21; N 13.50.

3-(1-(5-Methylimidazolyl)pyrido[2,3-*d*]pyrimidine-2,4-(1H,3H)-dione (**18**). Yield 78%; mp 212-214°C. IR spectrum (KBr), ν, cm^{-1}: 3000 (NH), 1670 (C=O), 1720 (C=O). ^1H NMR spectrum (methanol-d_4), δ, ppm: 5.83 (1H, m, CH); 3.65 (2H, m, CH_2); 7.38 (2H, m, imidazol); 8.50 (1H, br. s, NH imidazol); 7.70-7.60 (3H, m, Py); 8.81 (1H, s, NH). Found, %: C 51.88; H 3.80; N 23.20. $C_{13}H_{11}N_5O_4$. Calculated, %: C 51.83; H 3.68; N 23.24.

3-(1,3-Dicarboxypropyl)pyrido[2,3-*d*]pyrimidine-2,4-(1H,3H)-dione (19). Yield 79%; mp 251-253°C. IR spectrum (KBr), ν, cm^{-1}: 3375 (NH), 1650 (C=O), 1725 (C=O). ^1H NMR spectrum (D_2O), δ, ppm, *J* (Hz): 2.99 (2H, dd, *J* = 6.38, ($\underline{CH_2}$)CH_2CO_2H)); 3.31 (2H, dt, *J* = 7.67, CH_2($\underline{CH_2}$)CO_2H); 5.82 (1H, dd, *J* = 6.96, N–CH); 8.53 (1H, s, NH); 7.70-7.94 (3H, m, Py). Found, %: C 49.16; H 3.88; N 14.29. $C_{12}H_{11}N_3O_6$. Calculated, %: C 49.15; H 3.78; N 14.33.

3-(1,2-Dicarboxyethyl)pyrido[2,3-*d*]pyrimidine-2,4-(1H,3H)-dione (20). Yield 81%; mp 240-241°C. IR spectrum (KBr), ν, cm^{-1}: 3330 (NH), 1660 (C=O), 1725 (C=O). ^1H NMR spectrum (D_2O), δ, ppm, *J* (Hz): 3.17 (2H, dd, *J* = 6.28, CH($\underline{CH_2}$)CO_2H); 5.95 (1H, t, *J* = 6.77, NCH); 7.80 (1H, s, $CH_2CH_2CO_2\underline{H}$); 8.55 (1H, s, NH); 7.60-7.85 (3H, m, Py). Found, %: C 47.34; H 3.32; N 14.97. $C_{11}H_9N_3O_6$. Calculated, %: C 47.32; H 3.25; N 15.05.

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