Convenient Synthesis of 3-(1-carboxyalkyl)pyrido[2,3-*d*]pyrimidine-2,4-diones.

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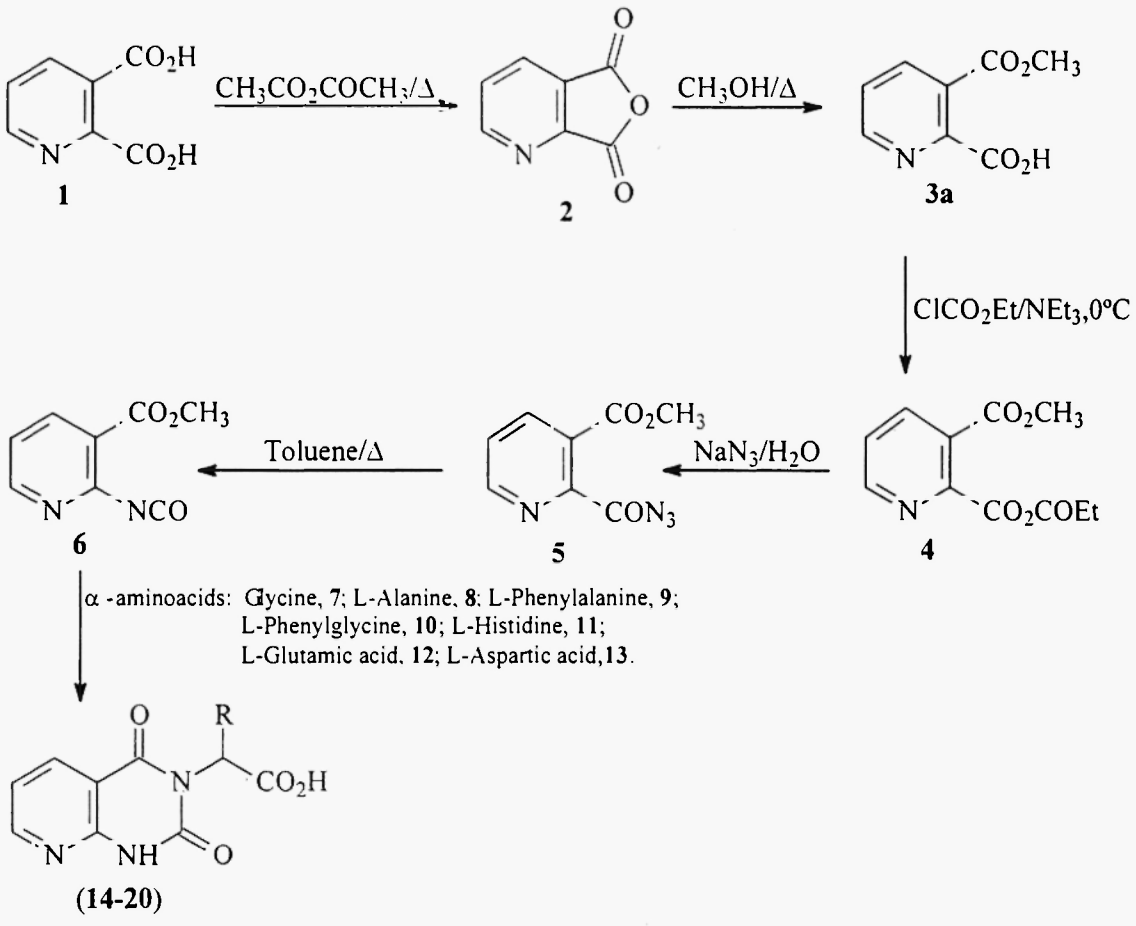
Abstract: Cheap and safety synthetic route to obtain 3-(1-carboxyalkyl)pyrido[2,3-*d*]pyrimidinediones (carboxyalkyl = -$CHRCO_2H$; R = H, **7**; CH_2, **8**; CH_2Ph, **9**; Ph, **10**; $CH_2(C_3H_3N_2$, **11**; $(CH_2)_2CO_2H$, **12**; CH_2CO_2H, **13**) starting from 2,3-pyridinedicarboxylic acid, **1**, is described. A process scheme consistent with empirical observations is proposed.

Introduction and discussion: Pyrimidine derivatives are common sources to develop 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 process to obtain 3-(1-carboxyalkyl)pyrido[2,3-*d*]pyrimidine-2,4-diones have been reported, which is quite surprising given the intense research activity centered on such compounds (6, 7). On the other hand, the utility of the compounds with notable biological properties could be limited by its synthetic cost. For this, we are interested in developing cheap and safety process that could be achieved in any world laboratory with minimum equipment. Therefore, this premise demands an accurate selection of reagents, solvents and procedures. We now wish to report a general method, cheap and safety, to the successful synthesis of 3-(1-carboxyalkyl)pyrido[2,3-*d*]pyrimidine-dione derivatives.

A convenient started compound to obtain the expected pyrimidinediones was found to be the 2,3-pyridinedicarboxylic acid, **1**, which is a cheap, stable and no toxic compound.



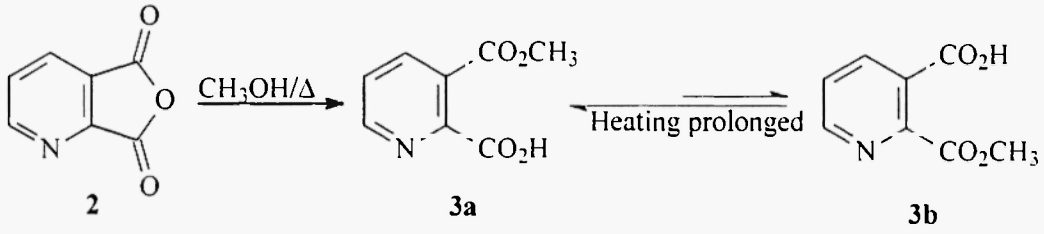
R = H, **14**; CH_3, **15**; CH_2Ph, **16**; Ph, **17**; $CH_2(C_3H_3N_2)$, **18**; $(CH_2)_2CO_2H$, **19**; CH_2CO_2H, **20**.

Schema 1

That reagent was easily deshydrated in refluxed acetic anhydride to give rise the compound **2**. Previously report (8) shown that **2** reacts with refluxed methanol to afford the 3-methyl, **3a**, and 2-methyl, **3b**, carboxypyridinecarboxylates (Scheme 2), **3a** increasing as the heating is prolonged.

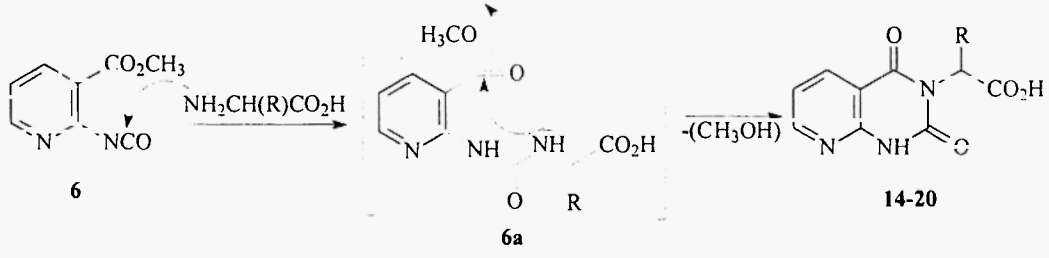
Reaction of **3a** with ethyl chloroformiate in dry basic media (NEt_3/KOH) leds to the formation of the unstable **4**. This compound is moisture sensitive, discomposing in air atmosphere within 1h. If dried solvent and N_2 atmosphere was used them the compound remained stable for time larger than 1 day. Due to the fact that as dry solvent as the use of inert condition are expensive, which renders larger the cost of the synthetic procedure, we studied the adequate time to obtain **4** with the best yield under air conditions. It was determined by using layer chromatography standard methods that freshly solution of **4** had to be used before 30 min. Compound **4** prepared as such as mode, reacted with an aqueous solution of NaN_3 to afford **5** that bring an acyl azide group on position 2, which was authenticated by the $\nu(N_3)$ IR absorption (2160 cm^{-1}). Refluxing **5** in toluene, **6** was obtained by Curtius'

rearrangement (9, 10) which yields NCO from CON_3 group, which was supported by IR and elemental analysis.



Schema 2

Finally, the expected 3-substituted-pyrido[2,3-*d*]pyrimidine-2,4-diones were synthesized in good yield by reaction of α-amino acids **7-13** with **6** in a alkaline (NaOH, pH 8-9) dioxane/water mixture at refluxed temperature. A pathway for this step likely includes (Scheme 3) the attack of α-amino acid nitrogen atom on the isocyanate group carbon that leads to the formation of the ortho-carbomethoxyureide intermediate **6a**. Subsequent ring closure with elimination of methanol gives rise to compounds **14-20**.



Scheme 3

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). NMR ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ spectra were recorded on Bruker AVANCE DRX 300. Peak positions are relative to tetramethylsilane (^{1}H, $^{13}C\{1H\}$). IR spectra were recorded (from KBr discs) on a IR-ATI Mattson Infinity Series. 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-carboxypyridinecarboxylate, **3**.

A suspension of 2,3-pyridinedicarboxylic acid, **1**, 1.50 g (8.98 mmole) in 15 ml of acetic anhydride was refluxed for 4 h under dry air and the resulting solution kept at 8 °C for 12 h. The white precipitate was solved in 20 ml of methanol and

stirred at 45 °C for 24 h. The solvent was removed and the solid washed with hexane and recrystallized in hot toluene. 1.23 g (Yield, 76 %), mp 111-113°C; IR (KBr): 1730 (C=O), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.90 (s,3H), 7.40-7.80 (m, 3H).

3-carbomethoxy-2-pyridylisocyanate, **6**.

Into a strong stirred solution of 1 g (5.25 mmole) of 3-methyl-carboxypyridinecarboxylate, **3**, in 15 ml of tetrahydrofuran at 0°C, was slowly added 1.54 ml (11.05 mmole) of dry triethylamine and 0.80 ml (8.28 mmole) of Ethyl Chloroformiate. After 30 min a solution of 0.90 g (13.74 mmole) of sodium azide in 5.40 ml of water was slowly added and then stirred for 1 h at room temperature. The tetrahydrofuran was eliminated by reduced pressure and the resulting mixture extracted with ethyl acetate (3x10ml). The different fractions were collected, dried by sodium sulfate, the solvent removed by reduced pressure, and the resulting yellow solid refluxed in toluene for 2 h. The organic phase was decanted, concentrated to haft volume and kept at room temperature for all night. The white powder precipitated, was filtered out washed with ether (3 x 5 ml) and air dried, 0.90 g (Yield, 91 %); IR (KBr): 2253 (N=C=O), 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.90 (s, 3H), 7.30-7.70 (m, 3H).

3-(1-carboxyalkyl)pyrido[2,3-*d*]pyrimidine-2,4-diones, **14-20**.

Into 10 ml of water was introduced 11 mmoles of the respective α-amino acids **7-13** and 10 ml of NaOH (1 N) (or 20 ml if **12** or **13** is used). The mixture was stirred for 10 minutes at room temperature and them a solution of 10 mmoles of the isocyanate **3** in 10 ml of dioxane added. The resulting yellow solution was kept at 60°C for 4.5 h and the solvent removed. The resulting molasses obtained was solved in 5 ml of water and acidified at pH = 2 by adding 2 *M* hydrochloric acid. The resulting precipitate was filtered out, washed with water (2x2 ml) and air dried. Analytical pure compound were obtained by recrystallization in hot methanol.

3-Carboxymethyl-2,4(1H,3H)pyrido-pyrimidinedione, **14**.

(Yield, 85 %); mp 328-330°C; IR (KBr): 3125 (NH), 1662 (C=O), 1725 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.56 (s, 2H, CH_2), 7.60-7.80 (m, 3H, Py), 11.79 (s, 1H, NH); ms: m/z. Calcd for $C_9H_7N_3O_4$: 221.1720. Found: 222 [M+1].

Anal. Calcd. For $C_9H_7N_3O_4$: C, 48.87 ; H, 3.19 ; N, 19.00. Found: C, 48.90; H, 3.29; N, 18.86.

3-(1-Carboxyethyl)-2,4(1H,3H)pyrido-pyrimidinedione, **15**.

(Yield, 80 %); mp 228-230°C; IR (KBr): 3120 (NH), 1682 (C=O), 1720 (C=O) cm^{-1}; ^1H NMR (CD_3OD): 1.63 (d, 3H, CH_3), 5.88 (q, 1H, CH), 8.00-8.60 (m, 3H, Py), 8.65 (s, 1H, NH); ms: m/z Calcd. for $C_{10}H_9N_3O_4$: 235.2067. Found: 236 [M+1].

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.06; H, 3.85; N, 17.86. Found: C, 51.11; H, 3.90; N, 17.70.

3-(1-Carboxyphenyl)-2,4(1H,3H)pyrido-pyrimidinedione, **16**.
(Yield, 90 %); mp 203-205°C; IR (KBr): 3120 (NH), 1662(C=O), 1725 (C=O) cm^{-1}: ^1H NMR (DMSO-d_6): δ 6.49 (s, 1H, CHPh), 7.60-8.50 (m, 3H, Py), 10.29 (s, 1H, NH); ms: m/z Calcd. for $C_{15}H_{11}N_3O_4$: 297.2775. Found: 298 [M+1].

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.60; H, 3.73; N, 14.13. Found: C, 60.78; H, 3.85; N, 13.98.

3-(1-Carboxybenzyl)-2,4(1H,3H)pyrido-pyrimidinedione, **17**.
(Yield, 88 %); mp 269-271°C; IR (KBr): 3125 (NH), 1665 (C=O), 1725 (C=O) cm^{-1}; ^1H NMR (CD_3OD): δ 5.86 (m, 1H, CH), 3.54 (m, 2H, CH_2), 8.30-9.00 (m, 3H, Py), 7.20-7.60 (m, 5H, Ph), 8.50 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.80; H, 4.36; N, 13.49.

3-(1-(5-Methyl(1,3-diazol)yl)-2,4(1H,3H)pyrido-pyrimidinedione, **18**.
(Yield, 78 %); m.p. 212-214°C; IR (KBr): 3000 (NH), 1670 (C=O), 1720 (C=O)cm^{-1}; ^1H NMR (CD_3OD): δ 5.83 (m, 1H, CH), 3.65 (m, 2H, CH_2), 7.38 (m, 2H, diazol), 8.50 (broad s, 1H, NHdiazol), 7.70-7.60 (m, 3H, Py), 8.81 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{11}N_5O_4$: C, 51.83; H, 3.68; N, 23.24. Found: C, 51.88; H, 3.80; N, 23.20.

3-(1,2-Dicarboxypropylyl)-2,4(1H,3H)pyrido-pyrimidinedione, **19**.
(Yield, 79 %); mp 251-253°C; IR (KBr): 3375 (NH), 1650 (C=O), 1725 (C=O) cm^{-1}; ^1H NMR (D_2O): δ 2.99 (dd, 2H, $(CH_2)CH_2CO_2H$), J = 6.38 Hz), 3.31 (dt, 2H, $CH_2(CH_2)CO_2H$, J = 7.67 Hz), 5.82 (dd, 1H, N-CH, J = 6.96 Hz,), 8.53 (s, 1H, NH), 7.70-7.94 (m, 3H, Py).

Anal. Calcd. for $C_{12}H_{11}N_3O_6$: C, 49.15; H, 3.78; N, 14.33. Found: C, 49.16; H, 3.88; N, 14.29.

3-(1,2-Dicarboxyethylyl)-2,4(1H,3H)pyrido-pyrimidinedione, **20**.
(Yield, 81 %); m.p. 240-241°C; IR (KBr): 3330 (NH), 1660 (C=O), 1725 (C=O)cm^{-1}; ^1H NMR (D_2O): δ 3.17 (dd, 2H, $CH(CH_2)CO_2H$, J = 6.28Hz), 5.95 (t, 1H, NCH, J = 6.77 Hz), 7.80 (s, 1H, $CH_2CH_2CO_2$-H), 8.55 (s, 1H, NH); 7.60-7.85 (m, 3H, Py).

Anal. Calcd. for $C_{11}H_9N_3O_6$: C, 47.32; H, 3.25; N, 15.05. Found, %: C, 47.34; H, 3.32; N, 14.97.

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