An Easy and Convenient Synthesis of 6-Methyl-4(1*H*)-pyridone-3-carboxylic Acid

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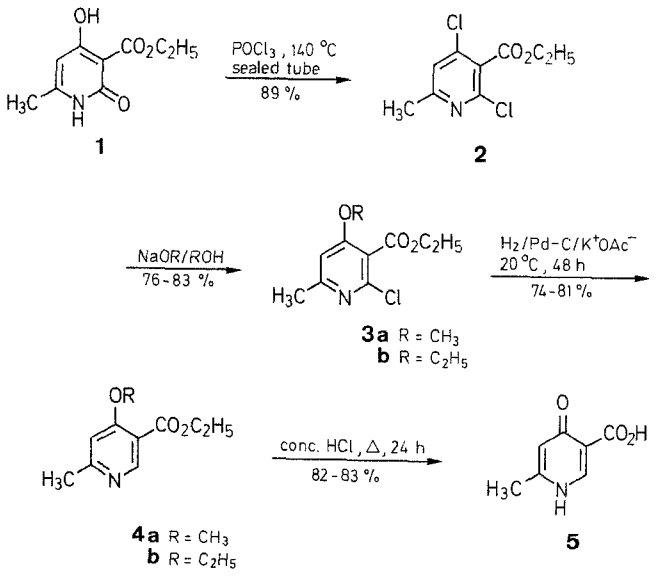
A new and easy synthesis of 6-methyl-4-(1*H*)-pyridone-3-carboxylic acid (**5**), an important component of broad spectrum cephalosporins, is described. It starts from the readily available ethyl 4-hydroxy-6-methyl-2(1*H*)-pyridone-3-carboxylate (**1**), which is treated with phosphoryl chloride to give ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (**2**). Selective substitution of the chlorine in 4-position with alkoxide ion leads to the 4-alkoxypyridine derivatives **3**. Hydrogenolysis of **3** affords ethyl 4-alkoxy-6-methyl-pyridine-3-carboxylates **4**; which are hydrolysed to **5** in one step.

Nicotinic acid derivatives are important intermediates for the synthesis of various pharmaceutical compounds.[1] 4(1*H*)-Pyridone-3-carboxylic acids, especially 6-methyl-4(1*H*)-pyridone-3-carboxylic acid (**5**), are essential components of broad spectrum cephalosporins with antipseudomonal activity.[2-4] 1-Phenyl derivatives of **5** are known as antibacterial agents.[5]

The two known syntheses[6-8] for **5** start from 4-hydroxy-6-methyl-2-pyrone, which is treated either with dimethylformamide dimethylacetal giving dimethylaminomethylene derivatives or with orthoesters and amines giving aminomethylene derivatives. By further reaction with ammonia **5** is obtained in less than 50% yield. The high cost of the starting material and of the reagents used in the first step, i.e. triethylorthoformate and dimethylformamide dimethylacetal, limits the industrial application of these two routes.

We present here a new simple synthesis[9] for **5** starting from ethyl 4-hydroxy-6-methyl-2(1*H*)-pyridone-3-carboxylate (**1**), which is easily available by condensation of diethyl malonate and ethyl 3-amino-2-butenoate.[10] By heating **1** with an excess of phosphoryl chloride in a sealed tube ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (**2**) is obtained in 89% yield; in the literature a yield of only 30% is described.[11,12] Reaction of **2** with one equivalent of sodium methoxide or sodium ethoxide in the corresponding alcohol gives selectively the 4-alkoxy-2-chloro-6-methylpyridine-3-carboxylates (**3**). Hydrogenolysis of **3** in the presence of palladium on charcoal leads to ethyl 4-alkoxy-6-methylpyridine-3-carboxylates **4**, which can be hydrolysed to **5** in 82% yield in one step simply by heating **4** in concentrated hydrochloric acid. The overall yield for the synthesis of **5** starting from **1** is about 50%.



The new route presented here offers a cheap and easy way for 6-methyl-4(1*H*)-pyridone-3-carboxylic acid (**5**). All steps proceed with good yields and require only cheap reagents. Furthermore, the new pyridine derivatives **3** and **4** represent interesting intermediates for further reactions.

Table. Compounds **3** and **4** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
3a	83	56	$C_{10}H_{12}ClNO_3$ (229.7)	1.40 (t, 3H, J = 7); 2.50 (s, 3H); 3.86 (s, 3H); 4.42 (q, 2H, J = 7); 6.68 (s, 1H)
3b	76	63	$C_{11}H_{14}ClNO_3$ (243.7)	1.40 (t, 3H, J = 7); 1.42 (t, 3H, J = 7); 2.50 (s, 3H); 4.14 (q, 2H, J = 7); 4.42 (q, 2H, J = 7); 6.71 (s, 1H)
4a	81	54	$C_{10}H_{13}NO_3$ (195.2)	1.39 (t, 3H, J = 7); 2.52 (s, 3H); 3.90 (s, 3H); 4.33 (q, 2H, J = 7); 6.71 (s, 1H); 8.71 (s, 1H)
4b	74	44	$C_{11}H_{15}NO_3$ (209.3)	1.40 (t, 3H, J = 7); 1.50 (t, 3H, J = 7); 2.51 (s, 3H); 4.12 (q, 2H, J = 7); 4.38 (q, 2H, J = 7); 6.63 (s, 1H); 8.67 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.23, H ±0.10, N ±0.11.

Ethyl 2,3-Dichloro-6-methylpyridine-3-carboxylate (2):
A mixture of ethyl 4-hydroxy-6-methyl-2(1*H*)-pyridone-3-carboxylate (**1**; 59.2 g, 0.3 mol) and $POCl_3$ (201 g, 1.3 mol) is heated in a sealed tube for 4 h at 140°C. After cooling, the mixture is poured onto crushed ice, the precipitate is filtered and recrystallized from a mixture of EtOH and H_2O (1:1); yield: 62.0 g (89%); mp 56°C (Lit.[10] mp 53°C).

Ethyl 2-Chloro-4-ethoxy-6-methylpyridine-3-carboxylate (3b); Typical Procedure:
Compound **2** (23.4 g, 0.1 mol) is added to a solution of sodium (2.29 g, 0.1 mol) in abs. EtOH (50 mL), and the mixture is heated under stirring for 3 h at 60°C. After cooling the solvent is distilled off, the residue is treated with water (50 mL) and neutralized with 2N HCl. The aqueous solution is extracted with CH_2Cl_2 (2 × 50 mL), dried (Na_2SO_4), and evaporated; colorless needles; yield: 18.5 g (76%); mp 63°C (Table)

Ethyl 4-Ethoxy-6-methylpyridine-3-carboxylate (4b); Typical Procedure:
A solution of **3b** (12.2 g, 50.0 mmol) in *i*-C_3H_7OH (100 mL) is treated with KOAc (3.0 g, 30.6 mmol) and hydrogenated in the presence of 10% Pd/C (0.8 g) at 4 bar at 20°C for 48 h. After filtration, the solvent is distilled off to afford **4b** as colorless needles; yield: 7.8 g (74%); mp 54°C (Table).

6-Methyl-4(1*H*)-pyridone-3-carboxylic acid (5); Typical procedure:
A mixture of **4b** (10.5 g, 50.0 mmol) and conc. HCl (50 mL) is heated under reflux for 24 h. The precipitate formed on cooling is filtered off and recrystallized from water; yield: 6.4 g (83%); mp 267°C (Lit.[6] mp 267–268°C).

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