CONVENIENT AND PRACTICAL SYNTHESIS OF 5-CHLORO-4-HYDROXY-2(1*H*)-PYRIDINONE

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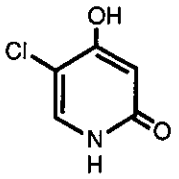
Abstract - 5-Chloro-4-hydroxy-2(1*H*)-pyridinone (**1**) was prepared by 4-step reactions via the key intermediate 5-chloro-3-cyano-4-methoxy-2(1*H*)-pyridinone (**5**). This synthetic route has several advantages over the reported methods in procedure, yield and applicability.

The biochemical rationale for the use of leucovorin and methotrexate to modulate and thereby enhance the cytotoxiciy of 5-fluorouracil has been well described.[1] Recently, antitumor agents[2] derived by biochemical modulation of 5-fluorouracil were investigated on the clinical practice in the world scale. We have been searching 5-chloro-4-hydroxy-2(1*H*)-pyridinone (CHP) (**1**) for a possible antitumor activity[3] as a biochemical modulator of 5-fluorouracil.



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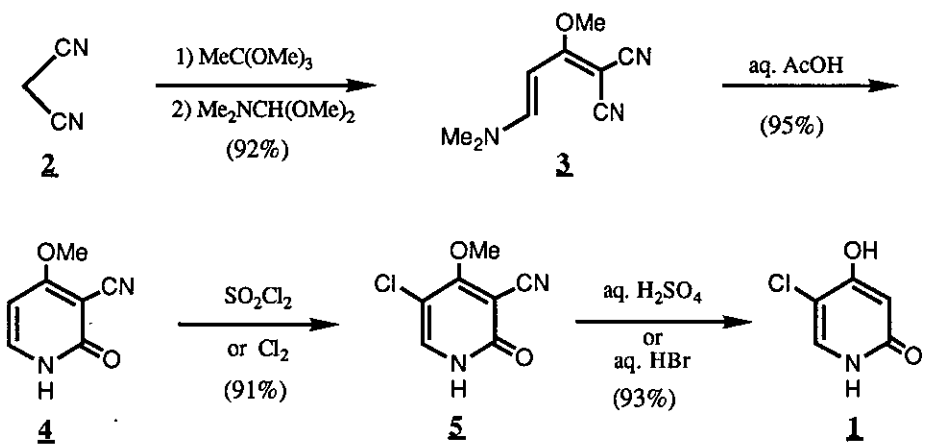
The 2(1*H*)-pyridinone (**1**) has been known as a potent dihydropyrimidine dehydrogenase inhibitor,[4] but the synthetic routes reported by several workers[5] via 4-hydroxy-2(1*H*)-pyridinone[6] or 3,4-dichloro-2-ethoxypyridine[5a] required multi-step procedures and their overall yields were low as shown Table 1 (No. 1, 2, 3 and 4). In addition, these methods have several weak points such as low applicability to large scale synthesis, necessity of the use of a special equipment (e.g. a sealed tube) and time-consuming procedures. These observations prompted us to develop a simple and convenient method for the synthesis of CHP (**1**). This paper deals with the improved synthetic route to **1** with applicability to a large scale preparation in good overall yield (74%) starting from malononitrile.

Table 1. Comparison of our method (No. 5) with reported methods (No. 1 - 4) in the preparation of **1** from commercially available starting materials.

No	Starting material	Steps of reaction	Overall yield (%)	Remark	Ref.
1	4-nitropyridine *N*-oxide	5	12	using a sealed tube	5b, 5c, 6a
2	diethyl acetone - 1,1'-dicarboxylate	6	26	using a sealed tube	5b, 5c, 6c
3	1-methoxy-1-buten-3-yne	6	25	using a sealed tube	5b, 5c, 6b
4	4-nitropyridine *N*-oxide	7	13	-	5a
5	malononitrile	4	74	-	7

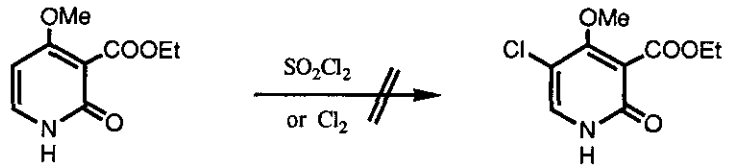
Malononitrile (**2**) was converted to a 2(1*H*)-pyridinone derivative (**4**) in 87% yield by Mittelbach's procedure[7] (Scheme 1). The selective and high yield chlorination at the C-5 position of **4** was performed by sulfuryl chloride or chlorine gas.

Scheme 1



The key intermediate (**5**) was easily purified by washing with a mixture of methyl alcohol and diisopropyl ether. The satisfied analitical data of **5** were obtained. Demethylation, hydrolysis and subsequent decarboxylation of **5** were easily achieved by refluxing in 40% sulfuric acid or 47% hydrobromic acid without by-products. Whereas, when conc. hydrochloric acid was used in stead of 47% hydrobromic acid, the hydrolysis was not achieved. In contrast to **4**, ethyl 1,2-dihydro-4-methoxy-2-oxo-3-pyridinecarboxylate (**6**)[8] could not be converted to the chloride (**7**) (Scheme 2), but **6** was decomposed under the same reaction conditions.

Scheme 2



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EXPERIMENTAL

Melting points were recorded on a Yanagimoto micromelting apparatus and are not corrected. ^{1}H Nmr spectra were taken on a JEOL EX-270 (270 MHz) spectrometer in DMSO-d_6. Chemical shifts are expressed in ppm downfield from internal Me_4Si. Mass spectra were obtained with a JEOL JMS-SX102A spectrometer. Ir spectra were recorded on a Hitachi I-3000 spectrophotometer. Elemental analyses were carried out with a Yanagimoto C H N Corder MT-5.

1,1-Dicyano-2-methoxy-4-(*N*,*N*-dimethylamino)-1,3-butadiene (3)

Title compound was prepared from malononitrile (2) (134.8 g, 2.0 mol), 1,1,1-trimethoxyethane (331 ml, 2.6 mol) and 1,1-dimethoxytrimethylamine (320 ml, 2.4 mol) according to Mittelbach's procedure[7] to give 324.6 g (92%). mp 128 - 129°C. (lit.,[7] mp 130°C).

3-Cyano-4-methoxy-2(1*H*)-pyridinone (4)

A solution of 1,1-dicyano-2-methoxy-4-(*N*,*N*-dimethylamino)-1,3-butadiene (3) (303 g, 1.71 mol) in 80% aq. acetic acid (2 l) was heated at 130°C for 2 h, and concentrated *in vacuo*. The residual solid was collected by filtration and washed with water to give 244 g (95%) of 4 as pale yellow needles. Analytical sample was recrystallized from MeOH, mp 293 - 294°C. (lit.,[7] mp 278°C). ^{1}H Nmr : δ 3.98 (3H, s), 6.36 (1H, d, J = 7.4 Hz), 7.77 (1H, d, J = 7.5 Hz), 12.14 (1H, br s).

5-Chloro-3-cyano-4-methoxy-2(1*H*)-pyridinone (5)

a) To a stirred suspension of 4 (20.0 g, 0.133 mol) in acetic acid (200 ml) was added dropwise sulfuryl chloride (12.8 ml, 0.160 mol) at room temperature. After the addition, the mixture was stirred at 50°C for 4 h, and then concentrated *in vacuo*. To the residual solid was added a mixture of methyl alcohol (15 ml) and diisopropyl ether (15 ml), and the insoluble material was collected by filtration to give 22.3 g (91%) of 5 as a white solid. Analytical sample was recrystallized from MeOH, mp 209 - 211°C. Anal. Calcd for $C_7H_5N_2O_2Cl$: C, 45.55 ; H, 2.73 ; N, 15.18. Found : C, 45.70 ; H, 2.69 ; N, 15.15 . ^{1}H Nmr : δ 4.32 (3H, s), 7.93 (1H, s), 12.41 (1H, br s). Ms (Neg, Fab) m/z : 183 (M^+-1). Ir (KBr) : 3200, 3070, 2230, 1675, 1610 cm^{-1}.

b) To a stirred suspension of **4** (9.6g, 0.052 mol) in acetic acid (100 ml) was added dropwise Cl_2 in CCl_4 (1.69 M, 80 ml) at room temperature. After the addition, the mixture was stirredat 50°C for 4 h, and then worked up in the same manner as described in a) to give 9.0 g (82%) of **5**. Analytical sample was recrystallized from MeOH, mp 209 - 211°C.

5-Chloro-4-hydroxy-2(1*H*)-pyridinone (1)

a) A solution of **3** (5.0 g, 27.1 mmol) in 40% H_2SO_4 (25 ml) was heated at 130°C for 4 h. After neutralization with 20% aqueous NaOH, the mixture was acidified carefully to pH 4.0 - 4.5 by addition of 5% HCl. The precipitated solid was collected by filtration and washed with water to give 3.69 g (91%) of Cl-DHP (**1**) as a white solid. Analytical sample was recrystallized from aq. EtOH, mp 277 - 279°C (decomp.) (lit.,[5a] mp 273 - 274°C (decomp.)).

b) A solution of **3** (5.0 g, 27.1 mmol) in 47% HBr (25 ml) was heated at reflux for 24 h, and concentrated *in vacuo*. The residual solid was dissolved in water and neutralized by addition of 10% aqueous NaOH. The mixture was worked up in the same manner as described in a) to give 3.65 g (93%) of **5**. Analitical sample was recrystallized from aq. EtOH, mp 277-279°C (decomp.).

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