# Novel Reaction of Carbon Suboxide. Synthesis of 6-Amino-4-hydroxy-2(1*H*)-pyridone Derivatives



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The reaction of 2-cyanoacetamidines **1** with carbon suboxide **2** afforded 6-amino-4-hydroxy-2(1*H*)-pyridones **4**. Compounds **4** were also obtained by reaction of amidines **1** and 2,4,6-trichlorophenylmalonates **3**.

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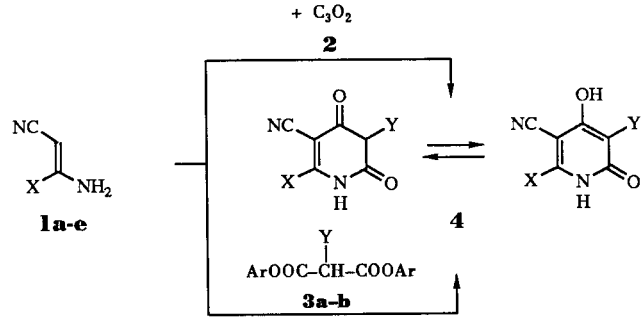
Several research groups have long shown an interest in malonylheterocycles such as 4-hydroxy-2-pyrones and -2-pyridones, and 6-hydroxypyrimid-4-ones for their biological properties.

Among the different synthetic methods available, one of the most versatile in the preparation of these compounds provides for the use of an appropriate 1,3-binucleophile with a malonic acid derivative [1]. The preparation of 4-hydroxy-2(1*H*)-pyridones is also known by the reaction of enamines and azomethines with malonic acid derivatives [2]. Pursuing studies on the reactivities of carbon suboxide and other malonic acid derivatives [3], in the present work we describe the reactions of 2-cyanoacetamidines, extremely versatile synthons in the formation of heterocyclic

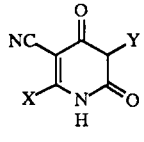



**1a**, x = pyrrolidino
**1b**, x = morpholino
**1c**, x = 4-methylpiperazino
**1d**, x = 4-phenylpiperazino
**1e**, x = 4-ethoxycarbonylpiperazino

**3a**, Ar = $C_6H_2Cl_3$, Y = H
**3a**, Ar = $C_6H_2Cl_3$, Y = $C_2H_5$

Table 1

Physical and Analytical Data of Compounds **4**



| Compound No. | X | Y | Method | Yield (%) | Mp (°C) | Formula | Analysis % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **4a** | pyrrolidino | H | A | 40 | 310 [a] | $C_{10}H_{11}N_3O_2$ | 58.53 | 5.40 | 20.48 |
| | | | B | 83 | | | 58.50 | 5.38 | 20.45 |
| **4b** | morpholino | H | A | 40 | 266 [b] | $C_{10}H_{11}N_3O_3$ | 54.23 | 5.01 | 19.00 |
| | | | B | 47 | | | 54.25 | 5.03 | 19.03 |
| **4c** | 4-methylpiperazino | H | A | 53 | 210 [b] | $C_{11}H_{14}N_4O_2$ | 56.40 | 6.02 | 23.92 |
| | | | B | 85 | | | 56.45 | 6.00 | 23.89 |
| **4d** | 4-phenylpiperazino | H | A | 40 | 255 [a] | $C_{16}H_{16}N_4O_2$ | 64.85 | 5.44 | 18.91 |
| | | | B | 84 | | | 64.80 | 5.42 | 18.93 |
| **4e** | 4-ethoxycarbonyl-piperazino | H | A | 30 | 258 [c] | $C_{13}H_{16}N_4O_4$ | 53.42 | 5.52 | 19.17 |
| | | | B | 65 | | | 53.39 | 5.50 | 19.14 |
| **4f** | pyrrolidino | $C_2H_5$ | B | 75 | 259 [a] | $C_{12}H_{15}N_3O_2$ | 61.78 | 6.48 | 18.02 |
| | | | | | | | 61.75 | 6.46 | 18.04 |
| **4g** | morpholino | $C_2H_5$ | B | 46 | 265 [b] | $C_{12}H_{15}N_3O_3$ | 57.82 | 6.07 | 16.86 |
| | | | | | | | 57.79 | 6.05 | 16.84 |
| **4h** | 4-methylpiperazino | $C_2H_5$ | B | 60 | 265 [b] | $C_{13}H_{18}N_4O_2$ | 59.52 | 6.92 | 21.36 |
| | | | | | | | 59.50 | 6.90 | 21.34 |
| **4i** | 4-phenylpiperazino | $C_2H_5$ | B | 60 | 267 [a] | $C_{18}N_{20}N_4O_2$ | 66.65 | 6.22 | 17.27 |
| | | | | | | | 66.60 | 6.20 | 17.25 |
| **4j** | 4-ethoxycarbonyl-piperazino | $C_2H_5$ | B | 42 | 255 [c] | $C_{15}H_{20}N_4O_4$ | 56.24 | 6.29 | 17.49 |
| | | | | | | | 56.30 | 6.27 | 17.52 |

[a] From 2-ethoxyethanol. [b] From 1-Propanol. [c] From Ethanol/water.

Table 2
Spectroscopic Data of Compounds **4**

| Compound No. | IR (nujol) ν $cm^{-1}$ | $^1H$ NMR δ (ppm) |
|---|---|---|
| **4a** | 3250, 2190, 1635, 1610, 1585 | (DMSO-$d_6$): 1.80 (m, 4H, $2CH_2$), 3.31 (s, 2H, $CH_2$), 3.54 (m 4H, $CH_2NCH_2$), 5.20 (s, 1H, OH), 7.48 (s, 1H, H-3), 11.20 (br s, 1H, NH) |
| **4b** | 3140, 2220, 1640, 1610, 1580 | (DMSO-$d_6$): 3.34 (m 4H, $CH_2NCH_2$), 3.61 (s, 2H, $CH_2$), 3.63 (m 4H, $CH_2OCH_2$), 11.50 (br s, 1H, NH) |
| **4c** | 3400, 2220, 1640, 1580 | (DMSO-$d_6$): 2.35 (s, 3H, $CH_3$), 2.70, 3.53 (m, 8H piperazinyl), 3.41 (s, 2H, $CH_2$), 10.55 (br s, 1H, NH) |
| **4d** | 3400, 2200, 1640, 1600, 1580 | (Pyridine-$d_5$): 3.21, 3.87 (m, 8H piperazinyl), 3.77 (s, 2H, $CH_2$), 5.33 (br s, 2H, OH and NH), 6.85 (m, 3H, Ar), 7.20 (m, 2H, Ar) |
| **4e** | 3490, 2220, 1700, 1650, 1590 | (DMSO-$d_6$): 1.18 (t, 3H, $CH_3$), 3.40, 3.58 (m, 8H piperazinyl), 3.60 (s, 2H, $CH_2$), 4.00 (q, 2H, $CH_2$), 11.20 (br s, 1H, NH) |
| **4f** | 3240, 3140, 2210, 1640, 1590 | (DMSO-$d_6$): 0.85 (t, 3H, $CH_3$), 1.82 (m, 4H, $2CH_2$), 2.29 (q, 2H, $CH_2$), 3.52 (m 4H, $CH_2NCH_2$), 7.40 (br s, 2H, OH and NH) |
| **4g** | 3240, 2220, 1650, 1620 | (DMSO-$d_6$): 0.88 (t, 3H, $CH_3$), 2.34 (q, 2H, $CH_2$), 3.38 (m 4H, $CH_2NCH_2$), 3.61 (m 4H, $CH_2OCH_2$), 10.40 (br s, 2H, OH and NH) |
| **4h** | 3350, 2220, 1630, 1580 | (Pyridine-$d_5$): 1.20 (t, 3H, $CH_3$), 2.02 (s, 3H, $CH_3$), 2.86 (q, 2H, $CH_2$), 2.32, 3.56 (m, 8H piperazinyl), 5.36 (br s, 2H, OH and NH) |
| **4i** | 3260, 2200, 1620, 1580 | (Pyridine-$d_5$): 1.22 (t, 3H, $CH_3$), 2.87 (q, 2H, $CH_2$), 3.13 and 3.65 (m, 8H piperazinyl), 5.25 (br s, 2H, OH and NH), 6.85 (m, 3H, Ar), 7.20 (m, 2H, Ar) |
| **4j** | 3200, 2200, 1665, 1630, 1600, 1580 | (Pyridine-$d_5$): 1.03 (t, 3H, $CH_3$), 1.20 (t, 3H, $CH_3$), 2.86 (q, 2H, $CH_2$), 3.47 (m, 8H piperazinyl), 4.05 (q, 2H, $CH_2$), 5.60 (br s, 2H, OH and NH) |

systems [4].

First the reactions between amidines **1** and carbon suboxide **2**, were carried out, which gave discrete yields of 6-amino-4-hydroxy-2(1*H*)-pyridone derivatives **4a-e**. The structure of the derivatives **4** was assigned on the basis of the analytical and spectroscopic data reported in Tables 1 and 2. Particularly, $^1H$ nmr (DMSO-$d_6$) showed a singlet between 3.61 and 3.31 ppm related to the protons in C-3 and a broad signal between 11.50 and 10.55 ppm, which collapses after deuteration, due to the NH group. In most **4** derivatives, a further broad exchangeable singlet between 5.20 and 5.50 due to the OH group could be seen, which shows existence of a tautomeric equilibrium in solution, as had been seen in similar molecules synthesized by us [5].

At the same time, we reacted amidines **1** with the diethyl malonic acid without obtaining any result.

Subsequently using the bis-2,4,6-trichlorophenylmalonates **3a-b** as reagents, 4-hydroxy-2(1*H*)-pyridone derivatives were obtained in good yields. As expected, in solution C-3 substituted pyridones are to be found prevalently in the form of 4-hydroxy-2(1*H*)-pyridone, as can be seen from the $^1H$ nmr spectra which clearly show the ethyl resonances at 0.85 ppm (triplet integrating for 3H with J = 7) and 2.30 ppm (quartet, 2H) as well as broad bands for the NH and OH groups.

Carbon suboxide and active malonic esters proved useful in obtaining the 6-amino-4-hydroxy-2(1*H*)-pyridone derivatives in one step.

## EXPERIMENTAL

The melting points were determined on Köfler hot stage and are uncorrected. The ir spectra were obtained in nujol with a Perkin-Elmer 398 spectrophotometer. The $^1H$ nmr spectra were recorded on a Varian Unity 300 spectrometer with shifts given in ppm downfield from internal hexamethyldisiloxane. The elemental analyses (C, H, N) were carried out with a Carlo Erba model 1106 Elemental Analyzer. The amidines **1** were obtained with a previously described procedure [4a].

6-Amino-4-hydroxy-2(1*H*)-pyridone Derivatives **4**. General Procedure.

Method A.

Carbon suboxide (16 mmoles) was added during one hour at -70° to a stirred solution of amidine **1** (16 mmoles) in dry dichloromethane. When the addition was completed, the mixture was stirred at 0° for 5 hours, and then kept at room temperature with stirring for 48 hours. The precipitate was filtered and crystallized from a suitable solvent to give pyridones **4**.

Method B.

A mixture of amidine **1** (10 mmoles) and bis-2,4,6-trichlorophenylmalonate **3** (10 mmoles) was heated to 150-160° for 5 hours. After cooling, the residue was treated with ethyl acetate and the resulting precipitate was filtered, washed with ethyl acetate and recrystallized.

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