NEW SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINES. I.
REACTION OF 6-ALKOXY-5-CYANO-3,4-DIHYDRO-2-PYRIDONES
WITH GUANIDINE AND CYANAMIDE

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Abstract - The first step of a new synthesis of pyrido[2,3-d]pyrimidines,
the substitution of the enolic alkoxyl group of 6-alkoxy-5-cyano-3,4-
dihydro-2-pyridones (2) by guanidine and cyanamide is described. By this
procedure a series of 2,4-diamino-5,6-dihydropyrido[2,3-d]pyrimidin-
7(8H)-ones (5) and 6-cyanamino-5-cyano-3,4-dihydro-2-pyridones (3) have
been synthesized. Products 3 have been isolated in this work for the
first time, and tautomeric equilibrium with the cyanimino form has been
detected in every case.

Pyrido[2,3-d]pyrimidines have been normally obtained by two general ways: a) formation
of the pyridine ring by cyclization of suitable substituents of a pyrimidine1, and b) formation of the pyrimidine ring by cyclization of suitable substituents of a pyridine2.

In the last years our group has been studying a new synthesis of pyrido[2,3-d]pyrimidines
following a 'b' type methodology as depicted in scheme 1. In this way, any α,β-unsatu-
rated ester can be converted, in a maximum of four synthetic steps, into heterocycles
having a large variety of substituents in carbons C-2, C-4, C-5 and C-6.

Our synthesis begins with the preparation of 6-alkoxy-5-cyano-3,4-dihydro-2-pyridones
(2) by a Michael reaction between propanedinitrile and an α,β-unsaturated ester
in an alcoholic solvent. Table 1 shows the products 2 which have been obtained in this
work, inclusive of some others previously reported by our group3,4 for comparison
purposes. Yields are generally better with methanol than with ethanol, due to the
lower thermic level of the reaction that is carried out at reflux.

The reaction of 2 with some amines has been described in a previous paper6. In particular
the reaction with hydrazine and phenylhydrazine at low temperature leads to the hydrazino
substituted pyridone.

Now we wish to report the results obtained in the reaction of 2 with guanidine and
cyramide as nucleophiles.
Scheme 1

Table 1

<table>
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<th>R₁</th>
<th>R₂</th>
<th>R=Me</th>
<th>R=Et*</th>
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<th>3</th>
<th>4</th>
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</tr>
<tr>
<td>b</td>
<td>H</td>
<td>CH₃</td>
<td>49</td>
<td>--</td>
<td>74</td>
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<td></td>
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<tr>
<td>c</td>
<td></td>
<td></td>
<td>57</td>
<td>--</td>
<td>74</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>CH(OCH₃)₂</td>
<td>H</td>
<td>72*</td>
<td>60</td>
<td>80</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>C₆H₅</td>
<td>H</td>
<td>85</td>
<td>80</td>
<td>95</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>2-furyl</td>
<td>H</td>
<td>87</td>
<td>75</td>
<td>63</td>
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</tr>
<tr>
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<td>2-thienyl</td>
<td>H</td>
<td>90</td>
<td>70</td>
<td>91</td>
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</tr>
<tr>
<td>h</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>88</td>
<td>--</td>
<td>94</td>
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</table>

*Previously reported by our group³,⁴
Reaction of 2a-h (R=CH₃) with guanidine in methanol at reflux provides 2,4-diamino-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones (6a-h) in good yields (Table 1).

Substitution of the methoxyl group of 2a-h (R=CH₃) by cyanamide carried out in dioxane at reflux, in the presence of a stoichiometric amount of sodium, affords 8a-h in quantitative yield for all the studied members of the family. Systems like 8 have usually been the starting material for the synthesis of pyrimidines⁶,⁷ and we ourselves actually synthesized ⁵ the corresponding 2-amino-5,6-dihydro-4-methoxypyrido[2,3-d]pyrimidin-7(8H)-one by addition of methanol to 8a.

Treatment of sodium salts 8a-h with the stoichiometric quantity of hydrogen chloride in either methanol or ethanol has allowed the isolation of 3a-h (Table 1).

Scheme 2

![Scheme 2](image)

The ir spectra of the whole family in the solid state exhibit two C=O bands (1760-1700 cm⁻¹), two stretching N-H bands (3220-3100 cm⁻¹) due to the cis associated amide and four CN bands more or less resolved (2260-2150 cm⁻¹). As elemental analyses are correct for every product, the multiplicity of bands confirms the tautomeric equilibrium expected, which is clearly detected in some cases (for example 3a) by ¹H-nmr thanks to the lucky chemical shift of the malonic proton of 111 which appears as a 0.5 protons doublet (δ =4.7, J=11Hz) which collapses to a singlet upon irradiation at 2.64 ppm, and the amine proton of 1 as a 0.5 protons broad signal (δ =4.91).

Potentiometric titration of 3a presents a unique inflexion point allowing the calculation of the pKₐ as 8.5 that would correspond to the more acidic tautomer, assuming a fast enough interconversion rate.

Products 3 are of great interest because of their special 1,3-dicarbonitrile substructure which is completely unknown in the literature. On the other hand, 3 is one of the most complex N,N-dicyano substituted systems ever employed in the synthesis of fused pyrimidines and we will study the addition of acids and bases onto it in order to compare the results with those that have been predicted⁶,⁹.
EXPERIMENTAL

The ir spectra were obtained on a Perkin Elmer 683 spectrophotometer. The 1H-nmr spectra were recorded on a Varian XL 200/F-19 and a Perkin Elmer R-24 spectrophotometers with TMS as an internal standard in the solvents as indicated. Mass spectra were obtained on a Hitachi-Perkin Elmer RM 50 and Hewlett-Packard 5930A mass spectrometers. Melting points were determined on a Büchi-Tottoli apparatus, and are uncorrected.

5-Cyano-3,4-dihydro-6-methoxy-2-pyridones 2a–h. (General procedure). To a solution of sodium in anhydrous methanol, the specified quantity of propanedinitrile was added and the mixture left to cool down. The corresponding \( \text{C} = \text{C} \)-unsaturated ester was added slowly and the mixture refluxed for the specified time. The solvent was distilled in vacuo and the residue dissolved in the minimum quantity of water. Careful neutralization to pH 7 allowed the precipitation of a solid which was filtered and washed with cold water. The precipitate was dissolved in chloroform and the solution was dried with anhydrous magnesium sulphate. Distillation of the solvent in vacuo yielded the corresponding pyridones. Proportion of reagents is shown in each case (ester:propanedinitrile:sodium, methanol (1/0.0.0.0 mol of ester), reaction time (h)).

5-Cyano-3,4-dihydro-6-methoxy-3-methyl-2-pyridone (2i); yield: 49%, (1:1.19:1.43, 1.8, 1.5); mp 146-147°C (from benzene); ir (KBr): 3180, 3095 (NH), 2195 (CN), 1685 (100), 1635 cm\(^{-1}\); 1H-nmr (CDCl\(_3\)): \( \delta \) 8.65 (br s, 1H, NH), 4.05 (s, 3H, CH\(_3\)O), 2.90-2.15 (m, 3H, CH and CH\(_2\)), 1.17 ppm (d, J 6 Hz, 3H, CH\(_3\)). ms: 166 (M\(^+\), 32), 151 (100). Anal. Calcd. for \( \text{C}_{11}\text{H}_{14}\text{N}_{2}\text{O}_2 \): C, 57.82; H, 6.07; N, 16.86. Found: C, 58.01; H, 6.09; N, 16.56.

5-Cyano-3,4-dihydro-6-methoxy-3,4-dihydro-6-methoxy-2-pyridone (2j); yield: 72%, (1:1:1.7, 1.0, 2.5); mp 98-99°C (lit.\(^{12}\), mp 98-99°C).

5-Cyano-3,4-dihydro-6-methoxy-3,4-dihydro-6-methoxy-2-pyridone (2k); mp 143-144°C (from a 1:5 mixture of hexane:benzene); ir (KBr): 3200, 3120 (NH), 2200 (CN), 1695 (CO), 1640 cm\(^{-1}\); 1H-nmr (CDCl\(_3\)): \( \delta \) 8.82 (br s, 1H, NH), 7.13 (s, 5H, H arom), 4.0 (s, 3H, CH\(_3\)O), 3.8 (t, J 6 Hz, 1H, CH), 2.80 and 2.73 ppm (ABX system, J\(_{xx}\) 5 Hz, 2H, CH\(_2\)); ms: 228 (M\(^+\), 80), 115 (100). Anal. Calcd. for \( \text{C}_{13}\text{H}_{12}\text{N}_{2}\text{O}_2 \): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.24; H, 5.28; N, 12.06.

5-Cyano-3,4-dihydro-6-methoxy-2-pyridone (2l); yield: 87%, (1:1.3:1.9, 2.2. 5); mp 116-117°C (from diethyl ether); ir (KBr): 3200, 3110 (NH), 2200 (CN), 1695 (CO), 1640 cm\(^{-1}\); 1H-nmr (CDCl\(_3\)): \( \delta \) 8.7 (br s, 1H, NH), 7.2 (m, 1H, furan ring), 6.2-6.0 (m, 2H, furan ring), 4.0 (s, 3H, CH\(_3\)O), 3.8 (t, J 5 Hz, 1H, CH), 2.8 ppm (d, 2H, CH\(_2\)); ms: 216 (M\(^+\), 51), 122 (100). Anal. Calcd. for \( \text{C}_{11}\text{H}_{10}\text{N}_{2}\text{O}_3 \): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.54; H, 4.58; N, 12.98.
5-Cyano-3,4-dihydro-6-methoxy-4-(2-thienyl)-2-pyridone (2g); yield: 90%; (1:1.25:1.25, 2.3, 5); mp 135-136°C (from 1:5 mixture of hexane:benzene); ir (KBr): 3200, 3100 (NH), 2200 (CN), 1700 (CO), 1635 cm⁻¹; ¹H-nmr (CDCl₃): δ 9.0 (s, 1H, NH), 7.75 (m, 1H, thiophene ring), 6.9 (m, 2H, thiophene ring), 4.25 (s, 3H, CH₃O), 2.9 ppm (m, 2H, CH₂); ms: 234 (M⁺, 85), 191 (100). Anal. Calcd. for C₁₁H₁₀N₂O₂S: C, 56.41; H, 4.30; N, 11.96; S, 13.66. Found: C, 56.48; H, 4.29; N, 11.75; S, 13.90.

5-Cyano-3,4-dihydro-6-methoxy-4-(2-pheyl)-2-pyridone (2h); yield: 88%; (1:1.3:1.9, 4.5, 5); mp 174-175°C (from a 1:5 mixture of hexane:benzene); ir (KBr): 3220, 3170 (NH), 2200 (CN), 1710 (CO), 1630 cm⁻¹; ¹H-nmr (CDCl₃): δ 8.4 (s, 1H, NH), 7.2 (s, 10H, H arom), 4.05 (s, 3H, CH₃O), 3.9 ppm (s, 2H, CH); ms: 304 (M⁺, 121), 193 (100). Anal. Calcd. for C₁₉H₁₆N₂O₂: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.98; H, 5.30; N, 9.58.

2,4-Diamino-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-one (6a); (General procedure). To a solution of sodium (0.011 g-atoms) in anhydrous methanol (30 ml, 5.5 mmol of guanidine carbonate were added and the mixture was refluxed for 15 min. The mixture was filtered and 5 mmol of the desired 5-cyano-3,4-dihydro-6-methoxy-2-pyridone (2) were added to the filtrate. The solution was refluxed for 20 h. The desired product was obtained as a precipitate from the mixture by filtration and washed with methanol and diethyl ether. Recrystallization from ethanol gave the following pyrido[2,3-d]pyrimidines 6:

2,4-Diamino-5,6-dihydro-5-methylpyrido[2,3-d]pyrimidin-7(8H)-one (6b); yield: 97%; mp 287-288°C; ir (KBr): 3460, 3340, 3230, 3120 (NH), 1670 cm⁻¹ (CO); ms: 193 (M⁺, 100). Anal. Calcd. for C₈H₁₁N₅O: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.38; H, 5.61; N, 36.05.

2,4-Diamino-5,6-dihydro-6-methylpyrido[2,3-d]pyrimidin-7(8H)-one (6b); yield: 87%; mp >300°C; ir (KBr): 3460, 3340, 3340, 3230, 3220, 3090 (NH), 1695 cm⁻¹ (CO); ms: 193 (M⁺, 100). Anal. Calcd. for C₈H₁₁N₅O: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.60; H, 5.92; N, 36.10.

2,4-Diamino-5,6-dihydro-6-methylpyrido[2,3-d]pyrimidin-7(8H)-one (6b); yield: 97%; mp >300°C; ir (KBr): 3495, 3470, 3390, 3220, 3090 (NH), 1670 cm⁻¹ (CO); ms: 233 (M⁺, 80), 191 (100). Anal. Calcd. for C₁₂H₁₅N₅O: C, 56.64; H, 6.48; N, 30.02. Found: C, 56.66; H, 6.70; N, 29.69.

2,4-Diamino-5,6-dihydro-5-phenylpyrido[2,3-d]pyrimidin-7(8H)-one (6b); yield: 89%; mp 303-304°C (dec.); ir (KBr): 3500, 3490, 3320, 3180 (NH), 1690 cm⁻¹ (CO); ms: 255 (M⁺, 100). Anal. Calcd. for C₁₃H₁₃N₅O: C, 61.12; H, 5.13; N, 27.43. Found: C, 61.03; H, 5.14; N, 27.43.

2,4-Diamino-5,6-dihydro-5-(2-furyl)-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-one (6f); yield: 82%; mp 290°C (dec.) (lit.5 mp 290°C (dec.)).

2,4-Diamino-5,6-dihydro-5-phenylpyrido[2,3-d]pyrimidin-7(8H)-one (6f); yield: 89%; mp 303-304°C (dec.); ir (KBr): 3500, 3490, 3320, 3180 (NH), 1690 cm⁻¹ (CO); ms: 255 (M⁺, 100). Anal. Calcd. for C₁₂H₁₃N₅O: C, 53.87; H, 4.52; N, 28.56. Found: C, 54.16; H, 4.64; N, 28.93.

2,4-Diamino-5,6-dihydro-5-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8H)-one (6f); yield: 88%; mp >300°C; ir (KBr): 3540, 3460, 3330, 3220, 3110 (NH), 1680 cm⁻¹ (CO); ms: 261 (M⁺, 100). Anal. Calcd. for C₁₁H₁₁N₅O₈S: C, 50.57; H, 4.24; N, 26.81; S, 12.25. Found: C, 50.41; H, 4.23; N, 26.82; S, 12.09.
2,4-Diamino-5,6-dihydro-5,6-diphenylpyrido[2,3-d]pyrimidin-7(8H)-one (6b): yield: 75%; mp >300°C (lit.14 mp 313-314°C).

6-Cyanamino-5-cyano-4-(2-furyl)-3,4-dihydro-2-pyridone (3a); yield: 80%; mp 197°C (dec.); ir (KBr): 3180, 3120 (NH), 2240, 2210-2180 (CN), 1740-1710 (CO), 1620 cm⁻¹; ¹H-nmr (DMSO-d₆): 6 8.80 (br s, 5H, NH), 4.6 (br s, 1H, NH and C₆H₅), 3.0-2.5 ppm (m, 2H, CH₂); ms: 238 (M⁺, 3), 131 (100). Anal. Calcd. for C₁₃H₁₂N₄O₂: C, 65.5; H, 4.2; N, 23.72. Found: C, 65.6; H, 4.35; N, 23.2.

6-Cyanamino-5-cyano-4-phenyl-3,4-dihydro-2-pyridone (3e); yield: 96%; mp 197°C (dec.); ir (KBr): 3180, 3120 (NH), 2240, 2210 (CN), 1740-1710 (CO), 1620 cm⁻¹; ¹H-nmr (DMSO-d₆): 6 7.4 (m, 5H, H arom), 5.1-4.8 (br s, 1H, NH and C₆H₅), 3.9-3.8 (m, 1H, CH), 3.1-2.7 ppm (m, 2H, CH₂); ms: 228 (M⁺, 9), 121 (100). Anal. Calcd. for C₁₃H₁₀N₄O₂: C, 65.5; H, 4.2; N, 23.5. Found: C, 65.6; H, 4.35; N, 23.2.

6-Cyanamino-5-cyano-4-(2-furyl)-3,4-dihydro-2-pyridone (3f); yield: 63%; mp 168°C (dec.); ir (KBr): 3180, 3120 (NH), 2240, 2210 (CN), 1750-1710 (CO), 1620 cm⁻¹; ¹H-nmr (DMSO-d₆): 6 7.7 (m, 1H, furan ring), 6.45 (m, 2H, furan ring), 5.1-4.9 (br s, 1H, NH and C₆H₅), 4.2-4.0 (m, 1H, CH), 3.2-2.7 ppm (m, 2H, CH₂); ms: 228 (M⁺, 9), 121 (100). Anal. Calcd. for C₁₃H₁₀N₄O₂: C, 65.5; H, 4.2; N, 23.5. Found: C, 65.6; H, 4.35; N, 23.2.
6-Cyanamino-5-cyano-3,4-dihydro-4-(2-thiophene)-2-pyridone (3g); yield: 91%; mp 165°C (dec.); ir (KBr): 3160, 3120 (NH), 2250, 2220-2180 (CN), 1750-1715 (CO), 1620 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 7.5-7.4 (m, 1H, thiophene ring), 7.2-6.9 (m, 2H, thiophene ring), 5.1-4.7 (br s, 1H, NH and C₅H), 4.3-4.1 (m, 1H, CH), 3.2-2.8 ppm (m, 2H, CH₂); ms: 244 (M⁺, 2), 137 (100). Anal. Calcd. for C₁₁H₆N₄: C, 72.60; H, 4.49; N, 23.05. Found: C, 72.92; H, 4.70; N, 17.49.

6-Cyanamino-5-cyano-3,4-dihydro-3,4-diphenyl-2-pyridone (3h); yield: 94%; mp 203°C (dec.); ir (KBr): 3200, 3100 (NH), 2250, 2220-2180 (CN), 1750-1710 (CO), 1625 cm⁻¹; ¹H-nmr (DMSO-d₆): δ 7.2-7.0 (m, 10H, H arom), 5.1-5.0 (m, 1H, NH and C₅H), 4.3-4.2 ppm (m, 2H, CH); ms: 90 (100). Anal. Calcd. for C₁₉H₁₄N₄O: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.92; H, 4.70; N, 17.49.

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REFERENCES AND FOOTNOTES


10. It is a modification of the previously reported procedure⁴, and presents a lot of advantages in the work-up process.


13. This compound has been previously obtained⁵ in a much lower yield (37%).


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