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# Two Step Synthesis of Pyrido[2,3-d]pyrimidines from Acyclic Precursors. Cyclization of 2-Cyanamino-4,6-diphenylpyridine-3carbonitrile by Hydrogen Halides

Pedro Victory,\*,† Joan Cirujeda and Anton Vidal-Ferran

Departament de Química Orgànica, CETS Institut Químic de Sarrià (Universitat Ramon Llull), Via Augusta 390, E-08017 Barcelona, Spain

*Abstract:* The cyclization of 2-cyanamino-4,6-diphenylpyridine-3-carbonitrile promoted by hydrogen halides takes place regiospecifically leading in all the cases to the 4-amino-2-halogen substituted pyrido[2,3-d]pyrimidine. This procedure completes a flexible and straightforward approach to aromatic pyrido[2,3-d]pyrimidines from acyclic precursors.

#### INTRODUCTION

Orthofused nitrogen containing heterocycles have been widely used as inhibitors of dihydrofolate reductase (DHFR)<sup>1</sup> and amongst these, methotrexate and aminopterin are classical antimetabolites that inhibit DHFR. Both purine and pyrimidine nucleotide biosyntheses require folate coenzymes. The inhibition of DHFR interrupts the cycling of dihydrofolate back to tetrahydrofolate and has a dramatic negative effect upon cell growth. The 8-deaza analogs of methotrexate and aminopterin (containing a 2,4-diaminopyrido-[2,3-d] pyrimidine moiety, **3** with X=NH<sub>2</sub> in Scheme 1) have been prepared<sup>2</sup> and have also shown to be effective inhibitors of DHFR. Other derivatives of the pyrido[2,3-d]pyrimidine system have shown antibacterial, antitumor, anti epileptic, diuretic and potassium-sparing activities.<sup>3</sup> Interest in these properties has led to the development of various synthetic strategies towards these substances. Pyrido[2,3-d]pyrimidines have normally been obtained via two general routes: a) formation of the pyridine ring by cyclization of suitable substituents of a pyrimidine<sup>4</sup> and b) formation of the pyrimidine ring by cyclization of suitable substituents of a pyridine.<sup>5</sup> The cyclization reactions of  $\alpha$ . $\omega$ -dinitriles promoted by anhydrous hydrogen halides have been widely used for the synthesis of heterocycles.<sup>6,7</sup> Following the synthesis of pyrido[2,3d]pyrimidines according to a 'b' type methodology developed by our group,<sup>6</sup> we wish to report here a concise and efficient two-step synthesis of aromatic pyrido [2,3-d]pyrimidines from acyclic precursors (Scheme 1). The first step in this strategy consists of the preparation of 2 whose synthesis from enones and malononitrile in only one step has been previously reported by our group.8

<sup>†</sup> Deceased on the 15th October 1994. Any further correspondence should be addressed to A. Vidal-Ferran (Departament de Química Orgànica, Universitat de Barcelona, Martí i Franquès 1-11, E-08028 Barcelona, Spain).

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In this efficient procedure, the use of sodium cyanamide as the base firstly catalyses the addition of malononitrile to the enone and secondly drives the cyclization to yield 2 as the sole compound.<sup>9</sup> In this paper we wish to report the conversion of dinitriles 2 into aromatic pyrido[2,3-d]pyrimidines promoted by hydrogen halides, which completes a flexible and straightforward approach to this interesting kind of compounds.

## **RESULTS AND DISCUSSION**

The cyclization of 2-cyanamino-4,6-diphenylpyridine-3-carbonitrile, **4**, was carried out in benzene using two different reaction temperatures (ambient temperature and reflux) and two different hydrogen halides (dry hydrogen bromide and dry hydrogen chloride). The reaction was regiospecific and led to a 4-amino substituted pyrido[2,3-d]pyrimidine irrespective of the reaction temperature or the hydrogen halide (Scheme 2). The other possible pyrido[2,3-d]pyrimidine (the 2-amino substituted derivative) was not detected. The most efficient cyclization conditions involved the use of hydrogen bromide at reflux (75%)



Scheme 2

yield). The cyclization of **4** was much slower when hydrogen chloride was used. The difference in reactivity of the two hydrogen halides could be easily anticipated on the basis of the difference in acidity (hydrogen chloride is less acidic than hydrogen bromide) and nucleophilicity of their conjugated bases (bromide is more nucleophilic than chloride anion). As the cyclization reaction starts with the protonation of one cyano group followed by the formation of the imidoyl halide,<sup>6,10</sup> hydrogen chloride appeared not to be acidic enough and the chloride not nucleophilic enough to make the reaction proceed at an acceptable rate. A detailed mechanistic study of this process will be reported in due course. The UV absorption spectra of **5** and **6** in MeOH were very similar both in shape and in absorption frequencies ( $\lambda_{max}$  for **5** (nm): 217, 271, 338 and 395; log  $\varepsilon$  for **5** (dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 4.38, 4.38, 4.15 and 2.16 and  $\lambda_{max}$  for **6**: 216, 269, 338 and 395; log  $\varepsilon$  for **6**: 4.40, 4.39, 4.16 and 2.63). This suggested that both **5** and **6** had the same distribution of functional groups in the chromophore and hence that both had the amino group in the same position (either in the 4 or 2 position). The <sup>13</sup>C-NMR spectra of both compounds were extremely similar. The observed chemical shifts of the seven signals of the pyrido[2.3–*d*]pyrimidine moiety differed by less than 0.8 ppm except for the carbon atom bearing the

When dioxane was used as the solvent a different product was obtained irrespective of the reaction temperature and hydrogen halide (Scheme 2). The non-halogenated compound, **7**, was obtained under all the different experimental conditions tested. Mass spectrometry (molecular ion at m/z 314 for C<sub>19</sub>H<sub>13</sub>N<sub>4</sub>O) and ir spectroscopy (lactam CO stretching at 1640 cm<sup>-1</sup>) suggested that **7** was the formal hydrolysis product of **5** and **6**. This assumption was confirmed by converting **7** into a chloro substituted pyrido[2,3-*d*]pyrimidine with phosphorus oxytrichloride. The spectroscopic data of the converted compound agreed with the data for compound **5** obtained by cyclization of **4** with hydrogen chloride in benzene. Significantly, the formation of **7** required that a molecule of water was formed. Since dioxane was the only oxygen containing compound in the mixture, it was assumed that the water was formed from the decomposition of dioxane by hydrogen chloride or hydrogen bromide. The *N*-cyano group in **4** would be hydrolysed to a substituted urea that would then cyclize intramolecularly affording **7**. The nucleophilic displacement of the bromide or chloride in **5** or **6** by water seemed to be a less likely reaction pathway for the formation of **7** since the reaction proceeded at the same rate irrespective of the hydrogen halide. The cyclization reaction in dioxane was further found to be regiospecific. The 2-amino substituted pyrido[2,3-*d*]pyrimidin-2(1*H*)-one was not detected.

halogen. This contirmed the assumption than both 5 and 6 possessed the amino group in the same position.

We confirmed the structure of **5** and **6** by comparison with an unambiguously 4-amino substituted pyrido[2,3-*d*]pyrimidine (4-Amino-5,7-diphenylpyrido[2,3-*d*]pyrimidine, **10**) which was synthesised by an alternative method. Thus, the treatment of **8**<sup>8</sup> with formamidine in DMSO at room temperature resulted in the substitution of the methylsulphonyl group by formamidine to give **9**. This compound was converted after heating into the expected pyrido[2,3-*d*]pyrimidine system **10**, together with a decomposition product of the substituted formamidine, **11** (Scheme 3). The comparison of the <sup>13</sup>C-NMR data and the electronic absorption spectra of **5** and **6** with **10** allowed the unequivocal structure determination of the former as 4-amino substituted pyrido[2,3-*d*]pyrimidines. All the chemical shifts of the carbon in the pyrido[2,3-*d*]pyrimidine ring in compounds **5**, **6** and **10** were similar with the exception of the carbon that bears different substituents. The absorption maxima in the uv spectra of all three compounds were located at almost coincident frequencies indicating the same distribution of the functional groups in the aromatic skeleton.

In conclusion, the results shown above demonstrate that it is possible to synthesise in two steps from acyclic precursors analogues of biologically important heterocyclic compounds. Furthermore, the halogen in 4-amino-2-halogen substituted pyrido[2.3-d]pyrimidines can be easily replaced by a wide variety of oxygen

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and nitrogen nucleophiles which gives more versatility to this synthesis.<sup>6e</sup> Cyclization and formally nucleophilic substitution by water took place in only one step using dioxane as the solvent in the cyclization process.

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### **EXPERIMENTAL SECTION**

Melting points were determined on a Büchi-Tottoli apparatus, and are uncorrected. NMR spectra were recorded either on a Bruker AC-80 spectrometer or a Varian XL-200/F-19 spectrometer with  $d_6$ -DMSO as the solvent and sodium  $d_4$ -3-trimethylsilylpropionate as internal standard. Ultraviolet-visible spectra were run on a Perkin-Elmer Lambda-2 instrument. Infrared spectra were recorded as KBr disks with a Bomem Michelson-100 FT-IR spectrometer. Mass spectra were recorded either on a Hewlett-Packard 5998 A spectrometer, both operating at 70 eV. Combustion analyses were performed on a Carlo-Erba CHNS-O/EA 1108 analyser.

General procedure for the cyclization of 2-cyanamino-4,6-diphenylpyridine-3-carbonitrile with hydrogen halides. To a stirred solution of 1.0 g (3.4 mmol) of 2-cyanamino-4,6-diphenylpyridine-3-carbonitrile 4 in the appropriate solvent, a stream of either dry HCl or dry HBr was bubbled at the chosen temperature. The flask was then scaled and the solution allowed to stir. The solid was filtered, washed with the solvent and suspended in 50 ml of a saturated solution of ammonia in methanol. The solvent was removed under reduced pressure. Water (30 ml) was then added to the residual solid, the mixture was stirred for 5 min and finally filtered and recrystallized.

*HBr/ Benzene/80* °*C*: HBr was bubbled through the solution over 2h and allowed to stir for a further 18 h. 0.96 g of 4-amino-2-bromo-5,7-diphenylpyrido[2,3-*d*]pyrimidine **5** (75% yield) were obtained after recrystallization from ethanol: mp 266-267°C (Found: C, 60.72; H, 3.36; N, 14.76. C<sub>19</sub>H<sub>13</sub>N<sub>4</sub>Br requires C, 60.49; H, 3.47; N, 14.85);  $v_{max}$ (KBr)/cm<sup>-1</sup> 3467, 3284 and 3066 (NH), 1640 (NH), 1577, 1538, and 1498 (C=C and C=N), 744 and 697 (Ph);  $\delta_{H}$  (80 MHz) 3.37 (2H, br s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 7.54-8.39 (11H, m, Ph + H on C-6);  $\delta_{C}$  (50MHz) 104.8 (C-4a), 120.6 (C-6), 127.7-137.5 (Ph), 150.5 (C-5), 152.1 (C2), 160.0 (C7)\*, 160.7 (C8a)\*, 162.9 (C4)\* (\* exchangeable assignation); *m/z* 376 (M\*, 30.5%), 378 (32.7), 298 (9.0), 297 (40.5), 270 (5.0), 255 (23.7);  $\lambda_{max}$  (MeOH)/nm 217, 271, 338 and 395 (log  $\varepsilon$  dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup> 4.38, 4.38, 4.15 and 2.16).

*HBr/Benzene/25* °C: HBr was bubbled through the solution over 2h and allowed to stir for a further 24 h. 0.60 g of 4-amino-2-bromo-5.7-diphenylpyrido[2,3–d]pyrimidine 5 (47% yield) were obtained after recrystallization from ethanol. Spectroscopic data coincided with those described at 80° C.

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*HCl/ Benzene/* 25 °C: HCl was bubbled through the solution over 2h and allowed to stir for a further 43 days. 0.38 g of 4-amino-2-chloro-5,7-diphenylpyrido[2,3–*d*]pyrimidine **6** (34% yield) were obtained after recrystallization from ethanol: mp 284-285°C (Found: C, 68.32; H, 3.93; N, 16.85. C<sub>19</sub>H<sub>13</sub>N<sub>4</sub>Cl requires C, 68.57; H, 3.94; N, 16.83);  $v_{max}$ (KBr)/cm<sup>-1</sup> 3480, 3290 and 3030 (NH), 1575, 1560, 1540, 1530 and 1490 (C=C and C=N), 785, 775 and 705 (Ph);  $\delta_{\rm H}$  (80 MHz) 3.30 (2H, br s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 7.53-8.26 (11H, m, Ph + H on C-6);  $\delta_{\rm C}$  (50MHz) 104.5 (C-4a), 120.5 (C-6), 127.7-137.6 (Ph), 150.3 (C-5), 159.8 (C2), 160.4 (C7)\*, 160.9 (C8a)\*, 163.7 (C4)\* (\* exchangeable assignation); *m/z* 332 (M<sup>+</sup>, 68.9%), 334 (23.7), 333 (47.1), 331 (100), 297 (3.2), 296 (3.4), 295 (13.8);  $\lambda_{max}$  (MeOH)/nm 216, 269, 338 and 395 (log ε dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup> 4.40, 4.39, 4.16 and 2.63).

*HCl/Benzene/80 °C:* HCl was bubbled intermittently over 20 h and stirred for a further 21 days. After this time  ${}^{13}$ C-NMR of the mixture indicated a mixture of **4** and **6**.

*HBr/ Dioxane/100 °C*: HBr was bubbled through the solution over 75 minutes and allowed to stir for a further 6 days. 0.7 g of 4-amino-5,7-diphenylpyrido[2,3–*d*]pyrimidin-2(1*H*)-one hemihydrate (66% yield) were obtained after recrystallization from ethanol: mp 266.5-267.5 °C (Found: C, 70.54; H, 4.72; N, 17.17.  $C_{19}H_{15}N_4O_{1.5}$  requires C, 70.58; H, 4.68; N, 17.33. Amount of water found 3.14 %.  $C_{19}H_{14}N_4O_{.1/2}H_2O$  requires 2.79 %);  $v_{max}$ (KBr)/cm<sup>-1</sup> 3450 and 3140 (NH), 1660, 1640 and 1630 (C=O and NH), 1590, 1570, 1520 and 1510 (C=C and C=N), 750 and 690 (Ph);  $\delta_{\rm H}$  (80 MHz) 3.46 (2H, br s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 7.52-8.31 (11H, m, Ph + H on C-6);  $\delta_{\rm C}$  (50MHz) 100.4 (C-4a), 116.6 (C-6), 127.3-137.7 (Ph), 149.8 (C-5), 154.2 (C2)\*, 155.7 (C7)\*, 158.5 (C8a)\*, 162.5 (C4)\* (\* exchangeable assignation); *m/z* 314 (M\*, 46.3%), 313 (100), 295 (3.6), 270 (5);  $\lambda_{max}$  (MeOH)/nm 219, 251 and 344 (log  $\epsilon$  dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup> 4.22, 4.34 and 4.22).

*HBr/ Dioxane/25 °C:* HBr was bubbled through the solution over 2h and allowed to stir for a further 6 days. 0.54 g of 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidin-2(1*H*)-one hemihydrate (51% yield) were obtained after recrystallization from ethanol. Spectroscopic data coincided with those described at 100° C.

*HCl/ Dioxane/100 °C:* HCl was bubbled through the solution over 2h and allowed to stir for 7 days. 0.54 g of 4-amino-5,7-diphenylpyrido[2,3–d]pyrimidin-2(1*H*)-one hemihydrate were obtained (51% yield) after recrystallization from ethanol. Spectroscopic data coincided with those described when HBr was used.

*HCl/ Dioxane/* 20  $^{o}C$ : HCl was bubbled through the solution over 2h and allowed to stir for 7 days. 0.44 g of 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidin-2(1*H*)-one hemihydrate were obtained (41% yield) after recrystallization from ethanol. Spectroscopic data coincided with those described when HBr was used.

Synthesis of N<sup>2</sup>-(3-cyano-4,6-diphenyl-2-pyridinyl)formamidine 9. A mixture of 1.0 g (3.0 mmol) of 4,6-diphenyl-2-methylsulfonylpyridine-3-carbonitrile 8, 3.12 g (3.0 mmol) of formamidine acetate, 3.04 g (3.0 mmol) of triethylamine and 20 ml DMSO was stirred at room temperature for 6 days. Water was added, and the solid filtered, washed with water and recrystallized from ethanol.  $N^2$ -(3-cyano-4,6-diphenyl-2-pyridinyl)formamidine 9 (0.52 g, 58%) was obtained:  $v_{max}$ (KBr)/cm<sup>-1</sup> 3460 3340 and 3120 (NH), 2220 (C=N), 1685, 1580, 1570, 1530, and 1490 (C=C and C=N), 780, 760 and 700 (Ph);  $\delta_{\rm H}$  (80 MHz) 7.4-8.2 (11H, m, Ph + H on C-5); *m/z* 298 (M<sup>+</sup>, 64.7%), 297 (100), 271 (37.1), 255 (12.6), 228 (3.5), 227 (6.9).

*Cyclization of* N<sup>2</sup>-(3-cyano-4,6-diphenyl-2-pyridinyl)formamidine, **9**. 0.5 g (1.68 mmol) of **9** were dissolved in 50 ml of absolute methanol and refluxed for 96 hours. The solvent was removed under reduced pressure. The solid was chromatographed through SiO<sub>2</sub> using methylene chloride as the eluent yielding 0.2 g of 2-amino-4,6-diphenylpyridine-3-carbonitrile, **11** (44%). <sup>1</sup>H-NMR and ir data were in agreement with those described for **11**.<sup>11</sup> Further elution with methylene chloride afforded 0.25 g of 4-amino-5,7-diphenylpyrido-[2,3-d]pyrimidine **10** (50%): mp 219-221 °C (reported mp 232-233 °C in ethanol/DMF<sup>12</sup>);  $v_{max}$ (KBr)/cm<sup>-1</sup> 3460, 3385 and 3200 (NH), 1655, 1605, 1580, 1550 and 1495 (NH, C=C and C=N), 770, 700 and 690 (Ph)<sup>+</sup>;

<sup>&</sup>lt;sup>+</sup> The synthesis of **10** has already been reported by another method<sup>12</sup> but no spectroscopic data were supplied by the authors.

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 $δ_{\rm H}$  (80 MHz) 3.51 (2H, br s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 7.54-8.40 (11H, m, Ph + H on C-6), 8.62 (1H, s, H on C-2);  $δ_{\rm C}$  (50MHz) 105.7 (C-4a), 120.2 (C-6), 127.6-138.2 (Ph), 149.8 (C-5), 158.2 (C2), 160.3 (C7), 159.4 (C8a)\*, 162.3 (C4)\* (\* exchangeable assignation); *m*/z 298 (M\*, 60.0%), 297 (100), 270 (4.6), 255 (1.4);  $λ_{\rm max}$  (MeOH)/nm 210, 269, 336 and 397 (log ε dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup> 4.36, 4.35, 4.06 and 3.10).

Conversion of 4-amino-5,7-diphenylpyrido[2,3-d]pyrimidin-2(1H)-one, 7, into 4-amino-2-chloro-5,7diphenylpyrido[2,3-d]pyrimidine, 6. A mixture of 0.5 g (1.59 mmol) of 7 and 24.4 g (14.5 ml, 159 mmol) phosphorous oxytrichloride was refluxed over 21 hours. The POCl<sub>3</sub> was removed under reduced pressure, water added carefully and the solution basified pH 8-9 with a saturated sodium carbonate solution. The solid was filtered, washed with water and recrystallized from ethanol. 40 mg (10%) of 6 were obtained.

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