A Facile Entry to Fused Pyrimidines: Preparation of Pyrimido[4,5-*b*]quinoline and Pyrido[2,3-*d*: 6,5-*d'*]dipyrimidine Derivatives

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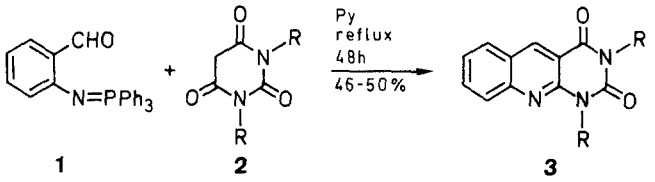
A number of pyrimido[4,5-*b*]quinolines **3** and pyrido[2,3-d: 6,5-*d'*]-dipyrimidines have been prepared by reaction of *N,N'*-disubstituted barbituric acids with the iminophosphorane derived from *o*-azidobenzaldehyde or 6-amino-5-formyl-1,3-dimethyluracil.

Fused pyrimidines are common sources to develop new potential therapeutic agents. Among these, 5-deazaflavins (5-deazaisoalloxazines) have been studied in both enzymatic and model systems to provide mechanistic insight into flavin-catalysed reactions. Several routes for the preparation of 5-deazaflavins have been previously described: a) cyclization of 6-(*N*-alkylanilino)uracils with one-carbon reagents such as the Vilsmeier reagent,[1,2] dimethylformamide–dimethylacetal,[3] triethyl orthoformate,[4] and carbon disulfide;[5] b) oxidative cyclization of bis(6-substituted-aminouracyl)methanes with diethyl azodicarboxylate;[6] and c) condensation of 6-(*N*-alkylanilino)uracils with *o*-halogenobenzaldehydes.[7]

We have been interested recently in exploiting the unique reactivities afforded by the iminophosphorane funtion in developing efficient strategies for the preparation of fused uracils.[8,9] We now report a new, facile one-pot synthesis of pyrimido[4,5-*b*]quinoline derivatives (5-deazaflavins) involving an aza-Wittig reaction of iminophosphorane **1** derived from *o*-azidobenzaldehyde[10] with *N,N'*-dialkylbarbituric acids **2**.

The starting *N,N'*-dialkylbarbituric acids **2** are prepared easily from malonic acid and the corresponding *N,N'*-dialkylurea[11] (for **2a**) or *N,N'*-dialkylcarbodiimide[12] (for **2b–d**); the *N,N'*-diarylbarbituric acid **2e** is prepared from malonyl chloride and the corresponding diarylurea. The reaction of iminophosphorane **1** with several *N,N'*-dialkylbarbituric acids **2** in pyridine at reflux temperature (48 h) leads directly to the 1,3-dialkylpyrimido[4,5-*b*]quinoline-2,4-(1*H*,3*H*)-diones **3** (Scheme 1). The structure of compounds **3** was determined by microanalyses and spectral data. (Tables 1 and 2). The mass spectra show the expected molecular ion peaks, and the IR spectra show two absorption bands in the region ν = 1709–1715 and 1660–1667 cm^{-1} due to the two carbonyl groups. In the ^1H NMR spectra, the characteristic chemical shifts of the H-5 is found at δ = 8.97–9.08 as a singlet, while the ^{13}C NMR spectra show two signals at δ = 150.4–150.8 and 160.1–160.7 due to the carbon atoms of the two carbonyl groups.

On the other hand, the 6-amino-5-formyl-1,3-dimethyluracil[13] (**4**) reacts with *N,N'*-dialkylbarbituric acids **2** in pyridine solution at reflux (48 h) to give directly the corresponding pyrido[2,3-*d*: 6,5-*d'*]dipyrimidines **5** in 47–67% yield (Scheme 2). It is worth noting that no general synthetic route for the preparation of compounds type **5** has been described, except the preparation of **5a** by coupling of two molecules of 6-amino-1,3-dimethyluracil



1 2 3

2, 3	R
a	Me
b	Et
c	*i*-Pr
d	*c*-C_6H_{11}
e	4-MeC_6H_4

Scheme 1

Table 1. Pyrimido[4,5-*b*]quinolines **3** and Pyrido[2,3-*d*: 6,5-*d'*]dipyrimidines **5** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b]	MS (70 eV) *m/z* (%)
3a	50	195	$C_{13}H_{11}N_3O_2$ (241.2)	241 (M^+, 74), 213 (54), 212 (33), 184 (6), 156 (10), 129 (100), 128 (19), 115 (11)
3b	53	155	$C_{15}H_{15}N_3O_2$ (269.3)	269 (M^+, 18), 241 (21), 213 (28), 183 (22), 169 (61), 156 (20), 141 (27), 128 (100), 115 (33), 101 (40)
3c	48	153	$C_{17}H_{19}N_3O_2$ (297.4)	297 (M^+, 5), 255 (11), 214 (47), 213 (89), 211 (34), 197 (77), 183 (100), 170 (51), 143 (68), 129 (13), 128 (66), 115 (36)
3d	46	235	$C_{23}H_{27}N_3O_2$ (377.5)	377 (M^+, 1), 211 (7), 149 (10), 129 (12), 120 (15), 118 (25), 83 (100)
3e	35	304	$C_{25}H_{19}N_3O_2$ (393.4)	393 (M^+, 2), 232 (23), 190 (10), 143 (32), 132 (48), 115 (60), 104 (52), 91 (96), 65 (100)
5a	46	320	$C_{13}H_{13}N_5O_4$ (303.3)	303 (M^+, 25), 275 (10), 246 (5), 218 (15), 191 (100), 161 (12), 133 (16), 106 (13)
5b	48	191	$C_{15}H_{17}N_5O_4$ (331.3)	331 (M^+, 100), 303 (45), 289 (11), 276 (11), 275 (78), 259 (11), 245 (24), 191 (13), 161 (11)
5c	46	126	$C_{17}H_{21}N_5O_4$ (359.4)	359 (M^+, 76), 317 (50), 276 (24), 275 (100), 259 (32), 202 (10), 190 (5)
5d	67	200	$C_{23}H_{29}N_5O_4$ (439.5)	439 (M^+, 3), 359 (18), 358 (96), 277 (14), 276 (100), 275 (7), 259 (6), 202 (5)
5e	47	279	$C_{25}H_{21}N_5O_4$ (455.5)	455 (M^+, 40), 323 (19), 322 (95), 294 (20), 293 (14), 210 (100), 209 (39), 182 (13), 133 (15), 91 (35)

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses obtained: C ±0.28, H ±0.25, N ±0.26.

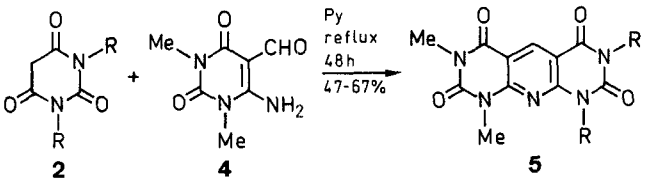
Table 2. Spectral Data of Pyrimido[4,5-*b*]quinolines **3** and Pyrido[2,3-*d*: 6,5-*d'*]dipyrimidines **5**

Compound	IR (nujol) ν (cm^{-1})	^1H NMR (200 MHz) (solvent/TMS)[a] δ, J (Hz)	^{13}C NMR (50 MHz) (solvent/TMS)[a] δ
3a	1709, 1660	3.42 (s, 3H, N_1-CH_3), 3.79 (s, 3H, N_3-CH_3), 7.63 (t, 1H, J = 7, H-7), 7.93 (t, 1H, J = 7, H-8), 8.01 (d, 1H, J = 8, H-6), 8.09 (d, 1H, J = 8, H-9), 9.08 (s, 1H, H-5)	29.17 (N_3-CH_3), 30.64 (N_1-CH_3), 110.84 (C-4a), 124.0 (C-5a), 124.11 (C-7), 127.81 (C-9), 130.11 (C-6), 136.28 (C-8), 144.58 (C-5), 144.57 (C-10a), 147.58 (C-9a), 150.37 (C-2), 160.1 (C-4)
3b	1705, 1660	1.25 (t, 3H, J = 7), 1.32 (t, 2H, J = 7), 4.10 (q, 2H, J = 7), 4.45 (q, 2H, J = 7), 7.42 (ddd, 1H, J = 8, 8, 1, H-7), 7.72 (ddd, 1H, J = 8, 8, 1, H-8), 7.83 (dd, 1H, J = 8, 1, H-6), 7.89 (dd, 1H, J = 8, 1, H-9), 8.88 (s, 1H, H-5)	13.00 (CH_3), 13.15 (CH_3), 37.00 (CH_2), 37.72 (CH_2), 111.10 (C-4a), 124.60 (C-5a), 125.50 (C-7), 128.10 (C-9), 129.10 (C-6), 132.80 (C-8), 139.85 (C-5), 147.82 (C-10a), 149.91 (C-9a), 150.61 (C-2), 161.05 (C-4)
3c	1715, 1667	1.57 (d, 6H, J = 7.1, 2 × CH_3), 1.66 (d, 6H, J = 7.1, 2 × CH_3), 5.33 [m, 1H, J = 7.1, $CH(CH_3)_2$], 5.97 [m, 1H, J = 7.1, $CH(CH_3)_2$], 7.49 (t, 1H, J = 7, H-7), 7.78 (t, 1H, J = 7, H-8), 7.90 (d, 1H, J = 8.8, H-6), 7.96 (d, 1H, J = 8.8, H-9), 8.97 (s, 1H, H-5)	19.56 (2 × CH_3), 19.68 (2 × CH_3), 46.52 (CH), 46.89 (CH), 111.17 (C-4a), 124.50 (C-5a), 125.44 (C-7), 128.01 (C-9), 128.97 (C-6), 132.67 (C-8), 139.92 (C-5), 148.42 (C-10a), 149.41 (C-9a), 150.44 (C-2), 161.53 (C-4)
3d	1709, 1670	1.22–1.89 (m, 16H), 2.52 (m, 4H), 4.91 (m, 1H), 5.56 (m, 1H), 7.49 (t, 1H, J = 7, H-7), 7.80 (t, 1H, J = 6.9, H-8), 7.92 (d, 1H, J = 8.1, H-6), 7.98 (d, 1H, J = 8.5, H-9), 8.97 (s, 1H, H-5)	25.32 (CH_2), 25.52 (CH_2), 26.44 (CH_2), 26.62 (CH_2), 28.92 (CH_2), 28.98 (CH_2), 55.08 (CH), 55.37 (CH), 111.85 (C-4a), 124.58 (C-5a), 125.47 (C-7), 128.09 (C-9), 128.97 (C-6), 132.65 (C-8), 139.97 (C-5), 148.53 (C-10a), 149.39 (C-9a), 150.82 (C-2), 161.69 (C-4)
3e	1722, 1672	2.38 (s, 3H, Ar-CH_3), 2.43 (s, 3H, Ar-CH_3), 7.46 (ddd, 1H, J = 7, 8, 1, H-7), 8.15 (m, 10H_{arom}), 7.90 (d, 1H, J = 8, H-9), 9.08 (s, 1H, H-5)	21.27 (CH_3), 21.34 (CH_3), 111.13 (C-4a), 124.62 (C-5a), 125.53 (C-7), 128.12 (C-9), 129.13 (C-6), 132.83 (C-8), 139.84 (C-5), 147.80 (C-10a), 149.90 (C-9a), 150.61 (C-2), 161.07 (C-4)
5a	1722, 1670	3.50 (s, 6H, N_1-CH_3 + N_9-CH_3), 3.77 (s, 6H, N_3-CH_3 + N_7-CH_3), 9.09 (s, 1H, H-5)	28.73 (2 × CH_3), 30.18 (2 × CH_3), 106.43 (C-4a + C-5a), 141.04 (C-5), 151.31 (C-9a + C-10a), 153.62 (C-2 + C-8), 160.41 (C-4 + C-6)
5b	1712, 1672	1.31 (t, 3H, J = 7), 1.40 (t, 3H, J = 7), 3.55 (s, 3H, N_3-CH_3), 3.81 (s, 3H, N_7-CH_3), 4.18 (q, 2H, J = 7), 4.48 (q, 2H, J = 7), 9.23 (s, 1H, H-5)	12.48 (2 × CH_3CH_2), 29.19 (N_7-CH_3), 30.47 (N_3-CH_3), 38.42 (N_3-CH_2), 39.64 (N_1-CH_2), 106.72 (C-4a), 107.08 (C-5a), 141.95 (C-5), 150.94 (C-10a), 151.96 (C-9a), 153.44 (C-2), 153.86 (C-8), 161.27 (C-4), 161.59 (C-6)
5c	1720, 1680	1.53 [d, 6H, J = 6.9, $CH(CH_3)_2$], 1.64 (d, 6H, J = 6.9, $CH(CH_3)_2$], 3.48 (s, 3H, N_9-CH_3), 3.75 (s, 3H, N_7-CH_3), 5.28 [m, 1H, (N_1-$CH(CH_3)_2$], 5.66 [m, 1H, N_3-$CH(CH_3)_2$], 9.11 (s, 1H, H-5)	19.26 (2 × CH_3), 19.54 (2 × CH_3), 28.36 (N_7-CH_3), 30.21 (N_9-CH_3), 46.69 (CH), 47.97 (CH), 105.95 (C-4a), 107.26 (C-5a), 140.90 (C-5), 150.02 (C-10a), 151.15 (C-9a), 152.95 (C-2), 153.50 (C-8), 159.81 (C-4), 159.93 (C-6)
5d	1715, 1676	1.17–1.47 (m, 6H), 1.66–1.97 (m, 10H), 2.39–2.62 (m, 4H), 3.48 (s, 3H, N_9-CH_3), 3.75 (s, 3H, N_7-CH_3), 4.87 (m, 1H), 5.22 (m, 1H), 9.10 (s, 1H, H-5)	25.17 (CH_2), 25.41 (CH_2), 26.27 (CH_2), 26.54 (CH_2), 28.44 (N_7-CH_3), 28.67 (CH_2), 28.98 (CH_2), 30.28 (N_9-CH_3), 55.19 (CH), 56.74 (CH), 106.00 (C-4a), 107.37 (C-5a), 140.98 (C-5), 150.43 (C-10a), 151.21 (C-9a), 152.91 (C-2), 153.65 (C-8), 159.87 (C-4), 160.08 (C-6)
5e	1739, 1718	2.40 (s, 3H, Ar-CH_3), 2.44 (s, 3H, Ar-CH_3), 3.26 (s, 3H, N_9-CH_3), 3.44 (s, 3H, N_7-CH_3), 7.18–7.34 (m, 8H_{arom}), 9.18 (s, 1H, H-5)	21.25 (2 × Ar-CH_3), 28.47 (N_7-CH_3), 29.57 (N_9-CH_3), 106.69 (C-4a), 106.85 (C-5a), 127.95 (C_o), 128.28 (C_o), 129.94 (C_m), 130.04 (C_m), 131.71 (C_p), 132.56 (C_p), 138.92 (C_i), 138.98 (C_i), 141.25 (C-5), 150.77 (C-10a), 151.04 (C-9a), 153.44 (C-2), 154.55 (C-8), 159.79 (C-4), 160.02 (C-6)

[a] Solvent: $CDCl_3$ for **3c–e**, **5c–e** and $CDCl_3$ + TFA for **3a,b** and **5a,b**.

(2a) with several one-carbon inserting reagents such as formamide,[14] dimethylsulfoxide,[15] ethoxymethylenemalononitrile,[16] *N*-nitrosodimethylamine/phosphorus oxychloride,[17] and Vilsmeier reagent.[18,19] However, these methods require strong reaction conditions and the yields are low. Recently, the reaction of 1,4-dihydropyridine bisenamino esters with phenyl isocyanate to give the corresponding bisurea, which is cyclized by the action of bases to give the 5,10-dihydropyrido[2,3-*d*: 6,5-*d'*]dipyrimidine-2,4,6,8-tetraone has been described.[20]

Structural elucidation of compounds **5** was accomplished by their analytical and spectral data. (Tables 1 and 2). The mass spectra show the expected molecular ion peaks, and the IR spectra show two strong absorption bands in the region ν = 1739–1712 and 1680–1657 cm^{-1} due to the



5	R
a	Me
b	Et
c	*i*-Pr
d	*c*-C_6H_{11}
e	4-MeC_6H_4

Scheme 2

carbonyl groups, except for compound **5e** which shows four absorption bands in the region ν = 1739–1657 cm^{-1}. In the ^1H NMR spectra, the H-5 proton appears in the region δ = 9 as a singlet, in addition to the sets of signals due to the *N*-substituents. The ^{13}C NMR spectra show four signals in the region δ = 152.9–161.6 due to the four carbon atoms of the four carbonyl groups, except for compound **5a** which clearly show two signals.

The above methods demonstrate that the reaction of *N,N'*-disubstituted barbituric acids with the iminophosphorane derived from *o*-azidobenzaldehyde or 6-amino-5-formyl-1,3-dimethyluracil afford a general entry to a variety of either pyrimido[4,5-*b*]quinolines or pyrido[2,3-d:6,5-*d'*]dipyrimidines. Due to the easy access of the starting materials, the good yields in the cyclization step, and due to the simplicity of the experimental one-pot procedure these synthetic approaches compare favorably with others methods.

Melting points are uncorrected. IR spectra were recorded on a Nicolet FT 5DX spectrophotometer. ^1H and ^{13}C NMR spectra were obtained using a Bruker AC 200 spectrometer. Mass spectra were recorded on a Hewlett-Packard 5993C instrument.

N,N'-Diethylbarbituric Acid (2b):
To a solution of malonic acid (1.04 g, 10 mmol) in dry THF (30 mL) at 0 °C was added diethylcarbodiimide (2 g, 20 mmol) in the same solvent (20 mL). The mixture was stirred at 0 °C for 1 h, the solvent removed under reduced pressure and the residual material was chromatographed on a silica gel column (40 cm × 3.5 cm, 70–230 mesh) using EtOAc/hexane (1:1) as solvent to give **2b**; yield: 0.56 g (61%), white prisms; mp 62 °C.

$C_8H_{12}N_2O_3$	calc.	C 52.16	H 6.56	N 15.21
(184.2)	found	52.29	6.38	14.98

MS (70 eV): *m/z* = 184 (M+, 23), 143 (24), 114 (13), 113 (21), 98 (43), 85 (56), 70 (99), 56 (100).

IR (Nujol): ν = 1709, 1670, 1292, 1228, 1093, 1022 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.21 (t, 6H, *J* = 7 Hz), 3.65 (s, 2H), 3.93 (q, 4H, *J* = 7 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 13.03 (CH_3), 36.00 (CH_2), 39.55 (C-5), 150.88 (C-2), 164.35 (C-4 + C-6).

1,3-Disubstituted Pyrimido[4,5-*b*]quinolines-2,4-(1*H*,3*H*)-diones (3); General Procedure:
To a solution of the appropriate *N,N'*-dialkylbarbituric acid **2** (3.9 mmol) in pyridine (45 mL) were added the iminophosphorane **1** (1.488 g, 3.9 mmol) and pyridine (0.5 mL) under N_2. The resultant mixture was stirred at reflux temperature for 48 h. After cooling to r.t., H_2O (14 mL) and conc. HCl (36 mL) were added and the mixture was extracted with $CHCl_3$ (2 × 25 mL). The combined organic layers were washed with H_2O (2 × 15 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude product **3** was chromatographed on a silica gel column (40 cm × 3.5 cm, 70–230 mesh) using EtOAc/hexane (1:1) as eluent to give **3** as crystalline solids (Tables 1 and 2).

1,3-Disubstituted 7,9-Dimethylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-(1*H*,3*H*,7*H*,9*H*)-tetraones (5); General Procedure:
To a solution of the appropriate *N,N'*-dialkylbarbituric acid **2** (2 mmol) in pyridine (40 mL) a solution of 6-amino-5-formyl-1,3-dimethyluracil **(4)** (0.366 g, 2 mmol) and piperidine (0.5 mL) were added. The reaction mixture was stirred at reflux temperature for 48 h. After cooling to r.t., H_2O (15 mL) and conc. HCl (40 mL) were added and the resultant solution was extracted with $CHCl_3$ (2 × 25 mL). The combined organic layers were washed with H_2O (2 × 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material was slurried with Et_2O. The formed solid was separated by filtration and recrystallized from MeCN to give **5** as crystalline solids (Tables 1 and 2).

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