Iminophosphorane-Mediated Synthesis of Pyrido[2,3-*d*]pyrimidine Derivatives

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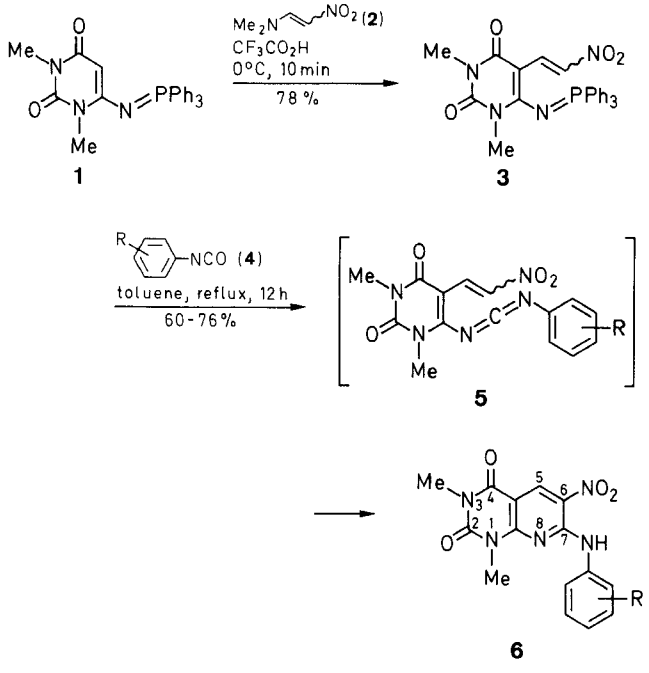
The 5-(2-nitroethenyl)-6-[(triphenylphosphoranylidene)amino]-pyrimidine derivative **3**, prepared from 1,3-dimethyl-2,4-dioxo-6-[(triphenylphosphoranylidene)amino]-1,2,3,4-tetrahydropyrimidine (**1**) and 1-dimethylamino-2-nitroethylene (**2**), reacts with aryl isocyanates **4** to give 7-arylamino-1,3-dimethyl-2,4-dioxo-6-nitro-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines **6** in good yield.

The tandem aza-Wittig/electrocyclization strategy has been shown to be a useful method for the construction of various heterocyclic systems, e.g., those of thieno[3,2-*c*]pyridine, thieno[2,3-*c*]pyridine, furo[3,2-*c*]pyridine,[1] pyrazolo[3,4-*d*]pyrimidine, 1,2,3-triazolo[4,5-*d*]pyrimidine, thiazolo[4,5-*d*]pyrimidine,[2] pyrido[3,4-*b*]indoles, pyrido[4,3-*b*]indoles, pyrimido[4,5-*b*]indoles,[3] and pyrazolo[3,4-*b*]pyridines.[4]

We now report a new, facile synthesis of pyrido[2,3-*d*]pyrimidine derivatives **6** involving an aza-Wittig type reaction of iminophosphorane **3** with arylisocyanates **4** to give intermediates **5** containing a 1,3-diaza-1,2,4,6-heptatetraene moiety, and electrocyclic ring closure of **5** to yield the cyclization products **6**. The pyrido[2,3-*d*]pyrimidine derivatives **6** may be of medicinal interest since they can be regarded not only as 5-deazapteridines but also as 8-azaquinazolines.[5] In spite of considerable work on the synthesis of the pyrido[2,3-*d*]pyrimidine system, no methods based on the formation of the 6,7 bond have been reported.[6]



4, 6	R	4, 6	R
a	H	**e**	4-Me
b	4-Cl	**f**	4-OMe
c	3-Cl	**g**	3-OMe
d	4-F		

The key intermediate **3** is easily prepared in 78% yield from the iminophosphorane 1,3-dimethyl-2,4-dioxo-6-[(triphenylphosphoranylidene)amino]-1,2,3,4-tetrahydropyrimidine[7] (**1**) and 1-dimethylamino-2-nitroethylene (**2**).[8] The reaction of iminophosphorane **3** with several aryl isocyanates **4** in dry toluene at reflux temperature (12 h) leads directly to the 7-arylamino-1,3-dimethyl-6-nitro-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines **6** in good yields. Attempts to apply this transformation to aliphatic isocyanates resulted only in the recovery of unalterated starting material. Presumably, the conversion **3** → **6** involves an initial aza-Wittig reaction between the iminophosphorane **3** and the isocyanate **4** to give a carbodiimide **5** as highly reactive intermediate which undergoes electrocyclic ring closure followed by 1,3-proton shift to afford the final product **6**.

The structure of compounds **6** was determined by microanalyses and spectral data. Salient features of the mass, IR, and ^{1}H-NMR spectra are given in the Table. The mass spectra show the expected molecular ion peaks, and the IR spectra show absorption bands in the region ν = 3358–3313 cm^{-1} due to the amino group. In the ^{1}H-NMR spectra, the characteristic chemical shifts of the *N*-methyl groups are found at δ = 3.44–3.64, and those of H-5 at δ = 9.17–9.24 as singlets.

The above method demonstrates that the tandem aza-Wittig/electrocyclization strategy provides a new entry to a variety of pyrido[2,3-*d*]pyrimidine derivatives with various anilino groups at the pyridine ring. Advantages of the present method are: easy availability of starting materials, good yields in the iminophosphorane preparation as well as in the cyclization step, and experimental simplicity of the one-pot procedure.

1,3-Dimethyl-5-(2-nitroethenyl)-2,4-dioxo-6-[(triphenylphsophoranylidene)amino]-1,2,3,4-tetrahydropyrimidine (3):

To a well-stirred solution of 1-dimethylamino-2-nitroethylene[8] (**2**; 0.87 g, 7.5 mmol) in CF_3CO_2H (10 mL) at 0°C is added 1,3-dimethyl-2,4-dioxo-6-[(triphenylphosphoranylidene)amino]-1,2,3,4-tetrahydropyrimidine[7] (**1**; 2.07 g, 5 mmol) and the mixture is stirred under N_2 for 10 min. During this time, the color of the solution changes from light yellow to dark. The mixture is then allowed to warm up to r.t. and is poured into ice water (50 mL). The aqueous solution is extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases are dried (Na_2SO_4) for 12 h. The solvent is removed under reduced pressure and the residual material is recrystallized from EtOH to give **3**; yield: 1.89 g (78%), yellow prisms; mp 286°C.

$C_{26}H_{23}N_4O_4P$	calc.	C 64.19	H 4.76	N 13.15
(486.5)	found	64.38	4.59	13.26

MS (70 eV): *m/z* = 486 (M^+, 3), 441 (16), 440 (55), 262 (15), 184 (19), 183 (100), 108 (48), 107 (21), 77 (15).

IR (Nujol): ν = 1704, 1642, 1529, 1302, 1274, 724, 690 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.32 (s, 3 H), 3.54 (s, 3 H), 7.50–7.72 (m, 16 H), 7.93 (d, 1 H, J = 12 Hz).

Table. 7-Anilino-1,3-dimethyl-6-nitro-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines **6** Prepared

Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	MS (70 eV)[d] *m/z* (%)	IR (Nujol)[e] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[f] δ, *J* (Hz)
6a	67	198–200	$C_{15}H_{13}N_5O_4$ (327.3)	327 (M^+, 97), 282 (21), 225 (17), 224 (55), 209 (10), 196 (18), 195 (20), 194 (24), 181 (42), 168 (73), 167 (100), 140 (35), 137 (20), 119 (21), 103 (12), 91 (28), 77 (94)	3347, 1698, 1642, 1608, 1455, 1421, 1381, 1336, 1257, 1115, 1092, 753	3.44 (s, 3H), 5.56 (s, 3H), 7.61–7.68 (m, 5H), 9.22 (s, 1H), 10.59 (s, 1H)
6b	76	218–220	$C_{15}H_{12}ClN_5O_4$ (361.7)	363 ($M^+ + 2$, 30), 361 (M^+, 82), 318 (13), 316 (39), 260 (9), 258 (27), 217 (18), 215 (43), 204 (50), 203 (40), 202 (49), 201 (70), 194 (21), 180 (20), 168 (40), 153 (35), 139 (17), 137 (42), 127 (30), 113 (41), 111 (100), 106 (21)	3358, 1704, 1664, 1614, 1455, 1421, 1381, 1313, 1274, 1087, 826, 784	3.46 (s, 3H), 3.64 (s, 3H), 7.42 (d, 2H, $J = 8.8$), 7.55 (d, 2H, $J = 8.8$), 9.23 (s, 1H), 10.55 (s, 1H)
6c	73	207–209	$C_{15}H_{12}ClN_5O_4$ (361.7)	363 ($M^+ + 2$, 34), 361 (M^+, 100), 318 (4), 316 (12), 260 (10), 258 (30), 230 (12), 215 (23), 203 (30), 202 (48), 201 (70), 194 (15), 168 (24), 153 (21), 140 (26), 137 (28), 126 (17), 113 (22), 111 (56), 92 (32), 91 (40), 77 (20)	3350, 1720, 1676, 1614, 1427, 1291, 1262, 1160, 1081, 787, 724, 696	3.46 (s, 3H), 3.64 (s, 3H), 7.24–7.65 (m, 4H), 9.24 (s, 1H), 10.57 (s, 1H)
6d	60	224–226	$C_{15}H_{12}FN_5O_4$ (345.3)	345 (M^+, 78), 300 (100), 299 (21), 271 (15), 242 (39), 227 (11), 214 (31), 213 (19), 199 (45), 188 (68), 187 (46), 186 (58), 185 (75), 158 (27), 137 (30), 135 (22), 133 (20), 121 (35), 107 (22), 106 (15), 91 (26)	3330, 1715, 1670, 1614, 1540, 1427, 1274, 1225, 1206, 1160, 1081, 849	3.46 (s, 3H), 3.56 (s, 3H), 7.17–7.48 (m, 4H), 9.23 (s, 1H), 10.49 (s, 1H)
6e	70	210–212	$C_{16}H_{15}N_5O_4$ (341.3)	341 (M^+, 91), 296 (31), 295 (21), 238 (31), 223 (15), 210 (26), 209 (26), 195 (48), 194 (28), 182 (47), 181 (100), 154 (14), 142 (23), 133 (30), 127 (15), 119 (21), 106 (30), 105 (37), 91 (75)	3313, 1704, 1653, 1608, 1529, 1432, 1381, 1308, 1268, 1217, 1092, 820, 787, 724	2.36 (s, 3H), 3.44 (s, 3H), 3.56 (s, 3H), 6.67 (d, 2H, $J = 8.5$), 7.24 (d, 2H, $J = 8.5$), 9.17 (s, 1H), 10.50 (s, 1H)
6f	68	187–189	$C_{16}H_{15}N_5O_5$ (357.3)	357 (M^+, 100), 342 (15), 312 (19), 297 (17), 211 (34), 197 (26), 155 (12), 149 (11), 134 (22), 127 (15), 123 (52), 106 (16), 92 (18), 77 (17)	3341, 1710, 1670, 1614, 1517, 1460, 1280, 1257, 1030, 832, 787, 764	3.47 (s, 3H), 3.56 (s, 3H), 3.67 (s, 3H), 6.97 (d, 2H, $J = 7$), 7.48 (d, 2H, $J = 7$), 9.19 (s, 1H), 10.44 (s, 1H)
6g	71	194–196	$C_{16}H_{15}N_5O_5$ (357.3)	357 (M^+, 45), 312 (100), 283 (11), 254 (15), 226 (21), 211 (15), 200 (24), 197 (31), 169 (17), 168 (12), 156 (12), 127 (31), 122 (13), 106 (18), 92 (33), 77 (32)	3330, 1704, 1665, 1642, 1619, 1597, 1540, 1432, 1263, 1160, 1093, 787, 752, 690	3.47 (s, 3H), 3.59 (s, 3H), 3.82 (s, 3H), 6.75–7.61(m, 4H), 9.18 (s, 1H), 10.51 (s, 1H)

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalyses: C + 0.25, H + 0.21, N + 0.29.
[d] Recorded on a Hewlett-Packard 5993C instrument.
[e] Recorded on a Nicolet FT 5DX Spectrophotometer.
[f] Recorded at 200 MHz on a Bruker AC-200 Spectrometer.

^{13}C-NMR ($CDCl_3$/TMS): 27.92 (3-CH_3), 32,43 (1-CH_3), 92.94 (d, J = 2.4 Hz, C-5), 127.30 (d, J = 106.7 Hz, C_i), 128.80 (d, J = 13 Hz, C_m), 131.53 (=CH−NO_2), 132.31 (d, J = 10.7 Hz, C_o), 133.41 (d, J = 3 Hz, C_p), 135.69 (−CH=C), 151.64 (J = 2 Hz, C-2), 158.07 (d, J = 10 Hz, C-6), 161.70 (d, J = 1 Hz, C-4).

7-Arylamino-1,3-dimethyl-6-nitro-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidines (6); General Procedure:

A solution of the aryl isocyanate **4** (3 mmol) in dry toluene (10 mL) is added dropwise under N_2 to a well-stirred solution of the iminophosphorane **3** (0.49 g, 3 mmol) in dry toluene (40 mL). The mixture is stirred at reflux temperature for 12 h. After cooling, the solvent is removed under reduced pressure, the residual material is slurried with cold EtOH (10 mL), and the solid is separated by filtration and recrystallized from AcOH.

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