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Iminophosphorane-Mediated Synthesis of Fused Uracils. A Facile One-pot Preparation of Pyrimido[4,5-*d*]pyrimidine Derivatives.

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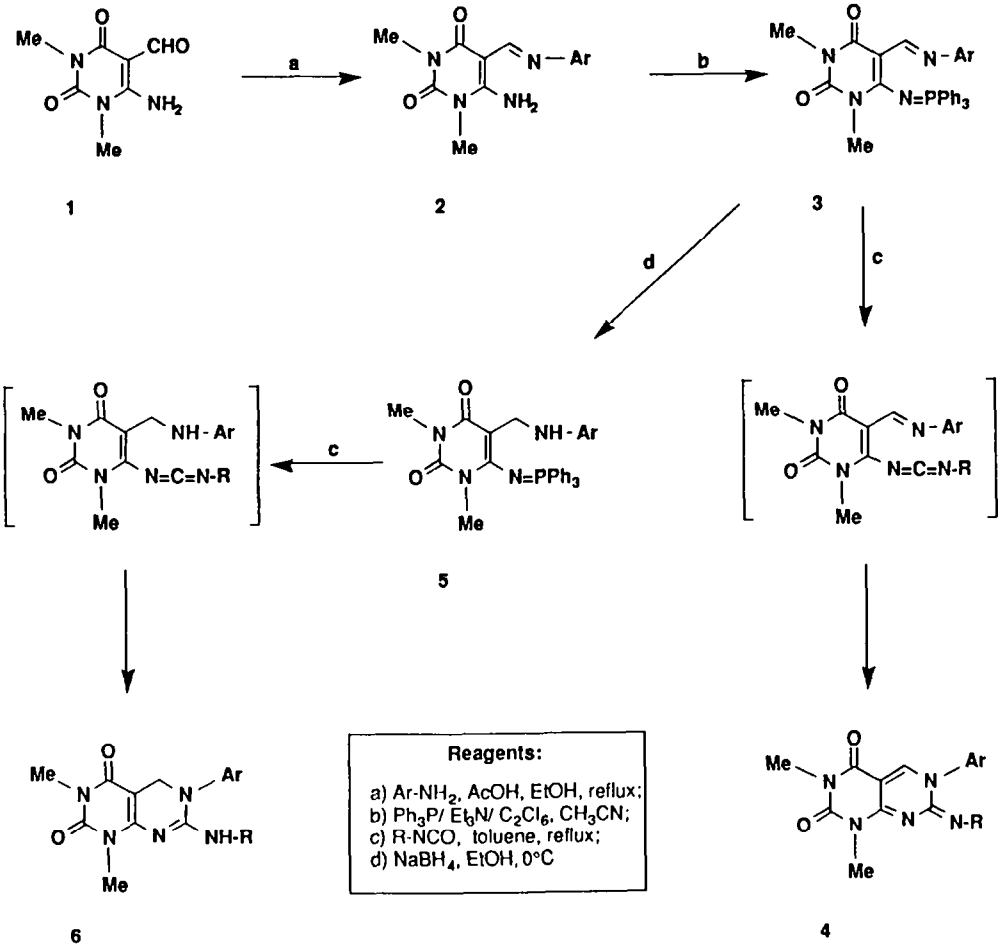
Abstract.- The aza Wittig-type reaction of iminophosphoranes **3**, 5-[(*N*-Arylimino)methyl]-6-[(triphenylphosphoranylidene)amino]-1,3-dimethyl uracils, with aromatic isocyanates leads to the functionalized pyrimido[4,5-*d*]pyrimidines **4**. Iminophosphoranes **5**, prepared from **3** by selective reduction with sodium borohydride, undergo dihydropyrimido annelation by reaction with isocyanates to give 7-amino-6-aryl-1,3-dimethyl-1,2,3,4,5,6-hexahydropyrimido[4,5-*d*]pyrimidines **6**.

Compounds containing a fused pyrimidine ring represent a broad class of compounds which have received considerable attention over the past years due to their wide range of biological activity[1] With the development of clinically useful anticancer (5-fluorouracil[2]) and antivirical drugs (AZT[3],BVDU[4]), there has recently been remarkable interest in the preparation of annelated uracils. However, the pyrimido[4,5-*d*]pyrimidine-2,4-dione ring system is rare and its synthesis has been achieved in only a limited number of ways, mostly involving the use of 6-amino uracils as starting materials. These 6-amino uracils are either converted directly to pyrimido[4,5-*d*]pyrimidines by the reaction of N-acylisothiocyanates[5], isocyanatoformate[6], and dimethyl cyanoimidodithiocarbonate[7] or indirectly by processes involving formylation followed by reaction with amides[8] or sequential treatment with methylamine/isocyanates[9]. We have been interested recently in exploiting the unique reactivities afforded by the iminophosphorane function in developing efficient strategies for the preparation of polyheterocycles. In this context, we have found that the tandem aza-Wittig/electrocyclization strategy has shown to be an useful protocol for the preparation of fused indoles[10], and pyridines[11]. We report herein two fundamentally new and apparently general methods for the preparation of some derivatives of the pyrimido[4,5-*d*]pyrimidine ring system. Our approaches are centered on the aza Wittig-type reaction of iminophosphoranes derived from 6-amino-5-formyl uracil derivatives with isocyanates to give uracil-carbodiimides which cleanly undergo heterocyclization either by electrocyclic ring-closure or by intramolecular amination on the carbodiimide moiety.

Results.- The 6-amino-5-formyl-1,3-dimethyluracil **1** was prepared by a previously reported procedure[12]. Treatment of compound **1** with aromatic amines in the presence of acetic acid in ethanol at reflux temperature leads to the corresponding aldimines **2** in high yields. The key intermediate iminophosphoranes **3** are readily available from **2** by treatment with the triphenylphosphine/triethylamine/

hexachloroethane system in dry acetonitrile. Aza Wittig-type reaction of iminophosphoranes **3** with several aromatic isocyanates in dry toluene at reflux temperature leads directly to the 7-arylimino-6-aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydropyrimido[4,5-*d*]pyrimidines **4** in good yields. However, attempts to apply this transformation to aliphatic isocyanates, carbon disulfide and carbon dioxide resulted only in the recovery of unaltered starting materials.



The conversion **3**→**4** involves initial aza Wittig reaction between the iminophosphorane and isocyanate to give a carbodiimide as intermediate (evidenced by I.R.) which easily undergoes electrocyclic ring-closure to give the cyclic valence tautomer pyrimido[4,5-*d*]pyrimidine **4** in good yields. Relatively few examples of thermal induced 6π-electrocyclization of conjugated heterocumulenes have been documented; it has only been mentioned for the thermal cyclization of 1-oxo-2-azahexatrienes[13] (β-carbamoylvinyl isocyanates), and 2-azahexatrienes[14] (1Z-1,3-diene isocyanates, 1Z-1,3-diene carbodiimides,

styryl isocyanates, β-heteroarylvinyl carbodiimides). However, there have been no reports dealing with synthetic applications of 6π-electrocyclizations of 1,5-diazahexatrienes, to the best of our knowledge.

Mass spectra of compounds **4** show molecular ion peaks. In the ^{1}H-NMR spectra the N-methyl groups at position 1 and 3 appear as singlets at δ =3.34-3.42 and δ =3.37-3.47 ppm respectively, whereas the H-5 proton appears as a singlet at δ =8.30-8.81 ppm, and in the ^{13}C-NMR spectra the quaternary carbons appear at C_2=151.5-153.7; C_4=154.8-157.7; C_{4a}=94.7-102.3; C_7=157.5-159.5 and C_{8a}=147.3-150.1 ppm (values assigned by decoupling methods and 2D H-C correlation techniques).

We also report a simple general procedure for the preparation of the previously unreported 5-unsubstituted-1,2,3,4,5,6-hexahydropyrimido[4,5-*d*]pyrimidine ring system bearing an amino group in the 7-position, under neutral conditions, based on the ready synthesis and subsequent aza Wittig-type reaction of iminophosphoranes **5**. Dihydropyrimido annelation occurs via a carbodiimide moiety, available from the reaction of the iminophosphorane and an isocyanate, which then undergoes ring-closure by nucleophilic attack of the adjacent amino group to give a six-membered heterocyclic ring.

Iminophosphoranes **3** undergo selective reduction by the action of sodium borohydride in methanol at 0°C to give the corresponding 5-arylaminomethyl-1,3-dimethyl-6-(triphenylphosphoranylidene)amino uracils **5** as crystalline solids in 95-97% yield. The IR spectra of compounds **5** show absorption due to the N-H bond at 3375 cm^{-1}. In the ^{1}H-NMR spectra the methylene group at 5-position appears as a singlet at δ=3.55-3.58 ppm, and in the ^{13}C-NMR spectra the quaternary carbon atoms of the heterocyclic ring appear at C_2=152.21-152.50; C_4=164.16-164.23; C_5=96.77-97.60 (J=4Hz); C_8=154.35 (J=7.4Hz) ppm.

The reaction of iminophosphoranes **5** with several isocyanates in dry toluene leads to the corresponding 7-amino-6-aryl-1,3-dimethyl-1,2,3,4,5,6-hexahydropyrimido[4,5-*d*]pyrimidines **6** in good yields. The IR spectra show absorption bands due to the N-H bond at 3324-3250 cm^{-1}. The ^{1}H-NMR spectra suggest an exocyclic N-H for **6**; e.g.(**6a** Ar^1=Ph, R=PhCH$_2$), the exocyclic methylene protons appear as a doublet and the amino proton as a triplet. Three characteristic signals appear as singlets at δ =3.13-3.32,.δ=3.28-3.43 and δ=4.48-4.62 ppm due to the N-methyl groups at positions 1 and 3, and the methylene group of the dihydropyrimidine ring respectively. In the ^{13}C-NMR spectra the N-methyl groups at positions 1 and 3 appear at δ=29.02-29.87 and δ=27.22-28.06 ppm respectively, while the methylene group of the dihydropyrimidine ring appears at δ=47.71-48.68 ppm and the quaternary carbon C_{4a} occurs at δ=77.64-84.00 ppm. The EI-mass spectra show the expected molecular ion peaks and the fragmentation pattern is in accord with the proposed structure.

In spite of much work on annelation of a pyrimidine ring to an existing one[15], no general methods for preparation of fused dihydropyrimidines bearing a basic group at position 2 have been described. It has only been briefly mentioned[16] that 2-amino-3-aminomethyl pyrazine reacts with S-methylthiouronium chloride to give 2-amino-3-guanidinomethyl pyrazine which undergoes cyclization to 3,4-dihydropteridine.

The present study demonstrates that tandem aza-Wittig/electrocyclic ring-closure and heterocumulene-mediated annelation strategies afford new entries to a variety of substituted fused uracils. Because of

their simplicity, the experimental one-pot procedure and good yields the investigated reactions provide a method for the preparation of different pyrimido[4,5-*d*]pyrimidines which compares favourably with other approaches to this ring system.

EXPERIMENTAL

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions on a Nicolet FT-5DX spectrophotometer. NMR spectra were recorded on a Bruker AC-200 (200 MHz). Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer. Microanalyses were performed on a Perkin-Elmer 240C instrument.

Preparation of 6-Amino-5-[(*N*-arylimino)methy]-1,3-dimethyl uracils. 2

To a solution of 6-amino-5-formyl-1,3-dimethyl uracil **1** (1g, 5.4 mmol) in ethanol (30 ml) was added the appropriate aromatic amine (6.5 mmol). The reaction mixture was stirred at reflux temperature for 8h. After cooling, the crystalline precipitated was collected by filtration and recrystallized from ethanol to give **2** as colorless crystals. The following derivatives **2** were obtained:

2a: 5-[(*N*-Phenylimino)methyl] (75%), m.p.247-249°C (Found: C, 60.31; H, 5.67; N, 21.42. $C_{13}H_{14}N_4O_2$ requires: C, 60.45; H, 5.46; N, 21.69); i.r. (Nujol) 3307, 1704, and 1614 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.17 (s, 3H, N_3-CH_3), 3.34 (s, 3H, N_1-CH_3), 7.09-7.39 (m, 5H, aryl), 8,69 (s, 1H, CH=N), 8.31 (s, 1H, NH), 11.11 (s, 1H, NH); ^{13}C n.m.r. δ (DMSO-d_6): 27.37 (N_3-CH_3), 29.12 (N_1-CH_3), 85.90 (C_5), 120.68 (C_o), 124.58 (C_p), 129.12 (C_m), 150.14 (C_6), 151.25 (C_i), 155.06 (C_2), 156.68 (CH=N), 161.40 (C_4); m/z (%): 258 ($M^{\cdot}$, 47), 257 (35), 181 (36), 154 (49), 144 (17), 104 (15), 77 (100).

2b: 5-[*N*-(p-Tolylimino)methyl] (80%), m.p.242-244°C.(Found: C, 50.35; H, 4.97; N, 16.76. $C_{14}H_{16}N_4O_2$ requires: C, 50.60; H, 4.85; N, 16.86); i.r. (Nujol) 3319, 1710, and 1619 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 2.29 (s, 3H, Ar-CH_3), 3.16 (s, 3H, N_3-CH_3), 3.33 (s, 3H, N_1-CH_3), 7.01 (d, 2H, J=8Hz), 7.16 (d, 2H, J=8Hz), 8.27 (s, 1H, NH), 8.89 (s, 1H, CH=N), 11.14 (s, 1H, NH); ^{13}C n.m.r. δ (DMSO-d_6): 20.43 (Ar-CH_3), 27.37 (N_3-CH_3), 29.11 (N_1-CH_3), 85.82 (C_5), 120.45 (C_o), 129.64 (C_m), 133.76 (C_p), 148.68 (C_i), 150.18 (C_6), 155.04 (C_2), 156.19 (CH=N), 161.43 (C_4); m/z (%): 272 ($M^{\cdot}$, 25), 271 (16), 181 (25), 154 (73), 130 (23), 118 (17), 105 (25), 91 (72), 57 (100).

2c: 5-[*N*-(p-Methoxyphenylimino)methyl] (72%), m.p.192-194°C.(Found: C, 58.17; H, 5.69; N, 19.54. $C_{14}H_{16}N_4O_3$ requires: C, 58.32; H, 5.59; N, 19.43); i.r. (Nujol) 3358, 1710, and 1653 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 3.16 (s, 3H, N_3-CH3), 3.32 (s, 3H, N_1-CH_3), 3.75 (s, 3H, Ar-OCH3), 6.94 (d, 2H, J=8Hz), 7.08 (d, 2H, J=8Hz), 8.21(s, 1H, NH), 8.67 (s, 1H, CH=N), 11.15 (s, 1H, NH); ^{13}C n.m.r. δ ($CDCl_3$): 27.94 (N_3-CH_3), 28.15 (N_1-CH_3), 55.46 (Ar-OCH3), 87.49 (C_5), 114.43 (C_m), 121.53 (C_o), 142.98 (C_i), 150.69 (C_6), 154.91 (C_2+CH=N), 157.52 (C_p), 162.29 (C_4); m/z (%): 288 ($M^{\cdot}$, 25), 287 (6), 273 (15), 188 (14), 181 (15), 154 (57), 121 (100), 109 (44), 92 (27), 82 (40), 77 (41), 57 (84).

Preparation of 5-[(*N*-Arylimino)methyl]-1,3-dimethyl-6-[(triphenylphosphoranylidene)amino] uracils 3.

To a solution of the appropriate uracil **2** (4mmol) in dry acetonitrile (25 ml), were added triphenylphosphine (0.976g, 4 mmol), triethylamine (0.708g, 7 mmol) and hexachloroethane (0.838g, 4 mmol). The reaction mixture was stirred at reflux temperature under nitrogen for 22h. After cooling, the separated solid was collected by filtration, washed with cold water, dried and recrystallized from acetonitrile to give **3** as light yellow crystals. The following derivatives **3** were obtained:

3a: 5-[(*N*-Phenylimino)methyl] (66%), m.p.219°C.(Found: C, 71.62; H, 5.41; N, 10.62. $C_{31}H_{27}N_4O_2P$ requires: C, 71.80; H, 5.25; N, 10.80); i.r. (Nujol) 1699, 1619, and 1449 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 3.40 (s, 3H, N_3-CH_3), 3.49 (s, 3H, N_1-CH_3), 6.81-6.84 (m, 5H, aryl), 7.30-7.51 (m, 15H, aryl), 8.18 (s, 1H, CH=N); ^{13}C n.m.r. δ ($CDCl_3$): 27.83 (N_3-CH_3), 31.10 (N_1-CH_3), 95.09 (C_5), 120.57, 123.37, 127.45 (J=100.3Hz), 128.50, 129.32 (J=13Hz), 132.25 (J=10Hz), 132.86 (J=3.6Hz), 133.57, 152.34 (C_2), 152.54 (C_6), 156.45 (CH=N), 164.27 (C_4); m/z (%): 518 (M^+, 8), 44 (13), 427 (22), 426 (67), 262 (20), 183 (100), 144 (19), 108 (49), 77 (87).

3b: 5-[*N*-(p-Tolylimino)methyl] (60%), m.p.222°C.(Found: C, 71.93; H, 5.42; N, 10.29. $C_{32}H_{29}N_4O_2P$ requires: C, 72.17; H, 5.49; N, 10.52); i.r. (Nujol) 1699, 1625, and 1438 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.21 (s, 3H, Ar-CH_3), 3.33 (s, 3H, N_3-CH_3), 3.52 (s, 3H, N_1-CH_3), 6.57 (d, 2H, J=8Hz), 6.93 (d, 2H, J=8Hz), 7.44-7.60 (m, 15H, aryl), 9.37 (s, 1H, CH=N); ^{13}C n.m.r. δ ($CDCl_3$): 20.29 (Ar-CH_3), 27.41 (N_3-CH_3), 30.53 (N1-CH_3), 97.19 (C_5), 120.10, 128.30 (J=11Hz), 129.42 (J=98Hz), 129.54, 131.55 (J=4Hz), 131.38, 131.73 (J=10Hz), 132.41, 152.29 (C_2), 155.75 (C_6), 157.18 (CH=N), 164.63 (C_4); m/z (%): 532 (M^+, 5), 426 (36), 262 (22), 183 (100), 152 (14), 118 (12), 108 (79), 91 (58), 77 (21).

3c: 5-[*N*-(p-Methoxyphenylimino)methyl] (90%), m.p.250-252°C. (Found: C, 69.77; H, 5.58; N, 9.95. $C_{32}H_{29}N_4O_3P$ requires: C, 70.06; H, 5.33; N, 10.21); i.r. (Nujol) 1704, 1630, and 1460 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 3.40 (s, 3H, N_3-CH_3), 350,(s, 3H, N_1-CH_3), 3.66 (s, 3H, CH_3O), 5.60 (d, 2H, J=8.8Hz), 6.40 (d, 2H J=8.8Hz), 7.31-7.51 (m, 15H, aryl), 8.15 (s, 1H, CH=N); ^{13}C n.m.r. δ ($CDCl_3$): 27.83 (N_3-CH_3), 31.10 (N_1-CH_3), 55.21 (CH_3O), 95.10 (C_5), 113.16, 121.36, 128.11 (J=12Hz), 131.08 (J=2.5Hz), 131.45 (J=10Hz), 132.46 (J=107Hz), 145.98 (q), 152.36 (C_2, J=3Hz), 154.50 (C_6, J=11.5Hz), 155.67 (CH=N), 156.27 (q), 164.28 (C_4); m/z (%): 548 (M^+, 1), 426 (39), 262 (28), 201 (7), 185 (21), 183 (100), 152 (11), 129 (12), 108 (85), 77 (28).

Preparation of 7-Arylimino-6-aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydropyrimido[4,5-*d*]pyrimidines 4.

To a solution of the iminophosphorane **3** (5 mmol) in dry toluene (30 ml) was added the appropriate isocyanate (7.5 mmol). The reaction mixture was stirred at reflux temperature under nitrogen for 24h. After cooling, the separated solid was collected by filtration and recrystallized from acetonitrile to give **4** as crystalline solids. The following derivatives **4** were obtained:

4a: 7-(p-Chlorophenyl)imino-6-phenyl (79%), m.p.260-262°C (yellow crystals). (Found: C, 61.18; H, 4.19; N, 17.52. $C_{20}H_{16}ClN_5O_2$ requires: C, 60.99; H, 4.09; N, 17.78); i.r. (Nujol) 1721, 1670, and 1625 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$+TFA): 3.34 (s, 3H, N_3-CH_3), 3.42 (s, 3H, N_1-CH_3), 7.30 (s, 4H, aryl), 7.56 (s, 5H, aryl), 8.59 (s, 1H, H5); ^{13}C n.m.r. δ ($CDCl_3$+TFA): 28.57 (N_3-CH_3), 30.00 (N_1-CH_3), 101.82 (C_{4a}), 126.03, 126.34, 129.00, 131.21, 132.21 (q), 133.05, 133.95 (q), 136.06 (q), 149.85 (C_{8a}), 152.13 (C_5), 153.30 (C_2), 157.15 (C_7), 157.87 (C_4); m/z (%): 395 (M^++2, 2), 393 (M^+, 6), 392 (8), 282 (3), 280 (6), 129 (30), 127 (100), 99 (20), 77 (14).

4b: 7-(p-Fluorophenyl)imino-6-phenyl (72%), m.p.283-285°C (yellow crystals). (Found: C, 63.41; H, 4.63; N, 18.46. $C_{20}H_{16}FN_5O_2$ requires: C, 63.65; H, 4.27; N, 18.56); i.r. (Nujol): 1716, 1655, and 1608 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$+TFA): 3.42 (s, 3H, N_3-CH_3), 3.47 (s, 3H, N_1-CH_3), 7.08 (t, 2H, J=8Hz), 7.27 (m, 2H, aryl), 7.67 (m, 5H, aryl), 8.81 (s, 1H, H5); ^{13}C n.m.r. δ ($CDCl_3$+TFA): 28.66 (N_3-CH_3), 30.19 (N_1-CH_3), 102.28 (C4a), 116.36 (J=23Hz), 126.29, 126.77 (J=9Hz), 129.53 (J=3.4Hz), 131.91, 133.66, 134.97(q), 149.87(C8a), 152.47(C5), 153.70(C2), 157.75 (C7), 158.38 (C4), 162.00 (J=252Hz); m/z(%): 377 (M^+, 6), 376 (12), 176 (10), 160 (11), 135 (10), 104 (18), 82 (37), 77 (100).

4c: 7-(p-Tolyl)imino-6-phenyl. (71%), m.p.303-305°C (yellow prisms). (Found: C, 67.41; H, 5.29; N, 18.52. $C_{21}H_{19}N_5O_2$ requires: C, 67.59; H, 5.13; N, 18.77); i.r.(Nujol): 1721,1655, and 1636 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$+TFA): 2.32 (s, 3H, Ar-CH_3), 3.34 (s, 3H, N_3-CH_3), 3.42 (s, 3H, N_1-CH_3), 7.18 (d, 2H, J=7.5Hz), 7.33 (d, 2H, J=7.5Hz), 7.53 (s, 4H, aryl), 7.56 (s, 1H, aryl), 8.55 (s, 1H, H5); ^{13}C n.m.r. δ ($CDCl_3$+TFA): 20.93 (Ar-CH_3), 28.42 (N_3-CH_3), 29.84 (N_1-CH_3), 101.26 (C_{4a}) 124.39, 126.44, 129.30, 130.99, 131.63 (q), 131.84, 136.50 (q), 137.12 (q), 150.12 (C_{8a}), 152.20 (C_5), 153.12 (C_2), 157.46 (C_7), 157.67 (C_4); m/z (%): 373 (M^+, 53), 372 (100), 282 (5), 234 (5), 225 (7), 182 (9), 158 (20) ,156 (15), 104 (21), 91 (30), 77 (67).

4d: 7-(p-Methoxyphenyl)imino-6-phenyl. (70%), m.p.243-245°C (orange prisms). (Found: C, 64.52; H, 5.19 ;N, 18.18. $C_{21}H_{19}N_5O_3$ requires: C, 64.77; H, 4.92; N, 17.98); i.r. (Nujol): 1716,1665, and 1631 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 3.34 (s, 3H, N_3-CH_3), 3.41 (s, 3H, N_1-CH_3), 3.75 (s, 3H, Ar-OCH_3), 6.77 (d, 2H, J=8.8Hz), 7.10 (d, 2H, J=8.8Hz), 7.46 (s, 4H, aryl), 7.49 (s, 1H, aryl), 8.34 (s, 1H, H5). ^{13}C n.m.r. δ ($CDCl_3$): 27.84 (N_3-CH_3), 28.93 (N_1-CH_3), 55.28 (Ar-OCH_3), 94.86 (C_{4a}), 113.31, 124.10, 126.41, 128.97, 129.36, 140.47 (q), 140.88 (q), 147.33 (C_{8a}), 151.56 (C_2), 152.32 (C_5), 154.79 (C_4), 155.39 (q), 159.33 (C_7); m/z(%): 389 (M^+, 81), 388 (87),374 (36), 225 (5), 194 (6), 166 (8), 147 (15), 133 (20), 108 (20), 104 (52), 82 (51), 77 (100).

4e: 7-(p-Chlorophenyl)imino-6-(p-tolyl) (70%), m.p.247-249°C (yellow crystals). (Found: C, 61.59; H, 4.60; N, 17.10. $C_{21}H_{18}ClN_5O_2$ requires: C, 61.84; H, 4.45; N, 17.17); i.r. (Nujol) 1721, 1665, and 1625 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.40 (s, 3H, Ar-CH_3), 3.34 (s, 3H, N_3-CH_3), 3.36 (s, 3H, N_1-CH_3), 6.99 (d, 2H, J=8.5Hz), 7.17 (d, 2H, J=8.5Hz), 7.30 (s, 4H, aryl), 8.36 (s, 1H, H5); ^{13}C n.m.r. δ ($CDCl_3$): 21.18 (Ar-CH_3), 27.92 (N_3-CH_3), 28.94 (N_1-CH_3), 95.28 (C_{4a}), 124.33, 126.07, 128.10, 128.28(q), 130.08, 138.12 (q), 139.38 (q), 146.54 (q), 148.55 (C_{8a}), 151.46 (C_2), 152.40 (C_5), 155.05 (C_4), 159.27 (C_7); m/z (%): 409 (M^++2, 4), 408 (21), 407 (M^+, 46), 406 (58), 405 (100), 387 (3), 385 (6), 296 (5), 91 (10).

4f: 7-(p-Fluorophenyl)imino-6-(p-tolyl) (62%), m.p.245-247°C (yellow prisms). (Found: C, 64.28; H,

4.83; N, 18.17. $C_{21}H_{16}FN_5O_2$ requires: C, 64.44; H, 4.63; N, 17.89); i.r. (Nujol) 1704, 1665, and 1631 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.40 (s, 3H, Ar-CH_3), 3.34 (s, 3H, N_3-CH_3), 3.37 (s, 3H, N_1-CH_3), 6.91 (t, 2H, J=8.6Hz), 7.03 (dd, 2H, ^{3}J=8.9, ^{4}J=5.2Hz), 7.31 (s, 4H, aryl), 8.36 (s, 1H, H5); ^{13}C n.m.r. δ ($CDCl_3$): 21.15 (Ar-CH_3), 27.88 (N_3-CH_3), 28.87 (N_1-CH_3), 95.10 (C_{4a}), 114.63 (J=22Hz), 124.09 (J=7.7Hz), 126.09, 130.15, 138.17 (q), 139.31 (q), 143.78 (J=3.5Hz), 148.35 (C_{8a}), 151.51 (C_2), 152.41 (C_5), 155.00 (C_4), 158.98 (J=240.4Hz), 159.30 (C_7); m/z (%): 391 (M^+, 60), 390 (100), 333 (5), 298 (4), 176 (5), 167 (6), 135 (4), 91 (10).

4g: 7-(p-Tolyl)imino-6-(p-tolyl) (71%), m.p.280-282°C (yellow crystals). (Found: C, 68.39; H, 5.32; N, 17.84. $C_{22}H_{21}N_5O_2$ requires: C, 68.20; H, 5.46; N, 18.07); i.r. (Nujol) 1716, 1665, and 1631 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.29 (s, 3H, Ar-CH_3), 2.41 (s, 3H, Ar-CH_3), 3.35 (s, 3H, N_3-CH_3), 3.39 (s, 3H, N_1-CH_3), 7.00 (d, 2H, J=7.5Hz), 7.05 (d, 2H, J=7.5Hz), 7.29 (d, 2H, J=8Hz), 7.35 (d, 2H, J=8Hz), 8.36 (s, 1H, H5); ^{13}C n.m.r. δ ($CDCl_3$): 20.89 (Ar-CH_3), 21.17 (Ar-CH_3), 27.87 (N_3-CH_3), 28.92 (N_1-CH_3), 94.92 (C_{4a}), 122.81, 126.14, 128.72, 129.99, 132.01 (q), 138.37 (q), 139.14 (q), 144.95 (q), 147.95 (C_{8a}), 151.63 (C_2), 152.43 (C_5), 154.80 (C_4), 159.42 (C_7); m/z (%): 387 (M^+, 54), 386 (100), 329 (5), 296 (6), 239 (5), 224 (5), 196 (8), 172 (10), 165 (12), 91 (23).

4h: 7-(p-Methoxyphenyl)imino-6-(p-tolyl) (60%), m.p.245-247°C (orange prisms). (Found: C, 65.25; H, 5.33; N 17.61. $C_{22}H_{21}N_5O_3$ requires: C, 65.50; H, 5.25; N, 17.36); i.r. (Nujol) 1721, 1665, and 1619 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.40 (s, 3H, Ar-CH_3), 3.35 (s, 3H, N_3-CH_3), 3.41 (s, 3H, N_1-CH_3), 3.76 (s, 3H, Ar-OCH_3), 6.78 (d, 2H J=9Hz), 7.09 (d, 2H, J=9Hz), 7.28 (d, 2H, J=7,5Hz), 7.33 (d, 2H, J=7.5Hz), 8.34 (s,1H, H5); ^{13}C n.m.r. δ ($CDCl_3$): 21.22 (Ar-CH_3), 27.92 (N_3-CH_3), 29.00 (N_1-CH_3), 55.39 (Ar-OCH_3), 94.67 (C_{4a}), 113.44, 124.16, 126.21, 130.04, 138.44 (q), 139.19 (q), 140.78 (q), 147.65 (C_{8a}), 151.69 (C_2), 152.50 (C_5), 154.86 (C_4), 155.47 (q), 159.49 (C_7); m/z (%): 403 (M^+, 85), 402 (100), 388 (26), 201 (5), 173 (5), 155 (6), 147 (8), 118 (10), 91 (10).

4i: 7-(p-Tolyl)imino-6-(p-methoxyphenyl) (62%), m.p.233-235°C (orange prisms). (Found: C, 65.23; H, 5.17; N, 17.21. $C_{22}H_{21}N_5O_3$ requires: C, 65.50; H, 5.25; N, 17.36); i.r. (Nujol) 1721, 1665, and 1642 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.28 (s, 3H, Ar-CH_3), 3.34 (s, 3H, N_3-CH_3), 3.38 (s, 3H, N_1-CH_3), 3.84 (s, 3H, Ar-OCH_3), 6.97 (d, 2H, J=8.8Hz), 7.01 (d, 4H, J=1.7Hz), 7.36 (d, 2H, J=8.8Hz), 8.34 (s, 1H, H5); ^{13}C n.m.r. δ ($CDCl_3$): 20.88 (Ar-CH_3), 27.87 (N_3-CH_3), 28.92 (N_1-CH_3), 55.51 (Ar-OCH_3), 94.89 (C_{4a}), 114.51, 122.80, 127.57, 128.74, 132.04 (q), 133.62 (q), 144.95 (q), 147.92 (q), 151.63 (C_2), 152.51 (C_5), 154.79 (C_4), 159.44 (C_7), 159.75 (q); m/z (%): 403 (M^+, 58), 402 (82), 388 (12), 255 (5), 224 (6), 201 (7), 173 (25), 172 (34), 171 (23), 157 (16), 134 (38), 131 (44), 118 (17), 107 (44), 91 (88), 82 (72), 77 (100).

Preparation of 5-Arylaminomethyl-1,3-dimethyl-6-(triphenylphosphoranylidene)amino uracils. 5
A solution of sodium borohydride (0.28g, 7.5 mmol) in dry methanol (20 ml) was added dropwise to a solution of the appropriate iminophosphorane **3** (5 mmol) in the same solvent (20 ml), and the reaction mixture was stirred for 30 min. Then the volatile materials were removed under reduced pressure at 25°C and the residual material was slurried with cold water (15 ml). The separated solid was collected by

filtration, air dried and recrystallized from acetonitrile to give **5** as colorless crystals. The following derivatives **5** were obtained:

5a: 5-Phenylaminomethyl (97%), m.p.210-212°C. (Found: C, 71.31; H, 5.89; N, 10.53. $C_{31}H_{29}N_4O_2P$ requires: C, 71.52; H, 5.61; N, 10.76); i.r. (Nujol) 3375, 1687, 1608, and 1455 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 3.28 (s, 3H, N_3-CH_3), 3.33 (s, 3H, N_1-CH_3), 3.59 (s, 2H, CH_2), 4.05 (s, 1H, NH), 6.26 (d, 2H, J=8Hz), 6.59 (t, 1H, J=8Hz), 6.99 (t, 2H, J=7.8Hz), 7.37-7.63 (m, 15H, aryl); ^{13}C n.m.r. δ ($CDCl_3$): 27.75 (N_3-CH_3), 31.88 (N_1-CH_3), 40.61 (CH_2), 96.76 (C_5, J=4.5Hz), 113.27, 116.65, 128.49, 128.62 (J=11.1Hz), 130.45 (J=101Hz), 131.60 (J=3Hz), 132.03 (J=10Hz), 148.47 (q), 152.49 (C_2), 154.35 (C_6, J=7.4Hz), 164.16 (C_4); m/z (%): 520 (M^+, 2), 428 (3), 262 (10), 183 (100), 152 (14), 108 (45), 104 (58), 93 (75), 77 (80), 66 (43).

5b: 5-(p-Tolyl) aminomethyl (95%), m.p. 224-225°C. (Found: C, 72.13; H, 5.62; N, 10.33. $C_{32}H_{31}N_4O_2P$ requires: C, 71.89; H, 5.84; N, 10.48); i.r. (Nujol) 3375, 1676, 1619, and 1460 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.19 (s, 3H, Ar-CH_3), 3.27 (s, 3H, N_3-CH_3), 3.32 (s, 3H, N_1-CH_3), 3.54 (s, 2H, CH_2), 4.04 (s, 1H, NH), 6.81 (d, 2H, J=8.3Hz), 7.21 (d, 2H, J=8.3Hz), 7.42-7.64 (m, 15H, aryl); ^{13}C n.m.r. δ ($CDCl_3$): 20.32 (Ar-CH_3), 27.77 (N_3-CH_3), 31.92 (N_1-CH_3), 41.14 (CH_2), 97.06 (C_5, J=4.5Hz), 113.64, 125.89 (q), 128.69 (J=12.3Hz), 129.06, 130.95 (J=102Hz), 131.82 (J=2.9Hz), 132.14 (J=10Hz), 146.33 (q), 152.21 (C_2), 154.35 (C_6, J=7.4Hz), 164.23 (C_4); m/z (%): 534 (M^+, 2), 429 (2), 414 (6), 262 (5) 183 (34), 152 (10),119 (71), 118 (50), 107 (79), 106 (100), 91 (92), 77 (32), 65 (28).

Preparation of 7-Alkyl(aryl)amino-6-aryl-1,3-dimethyl-1,2,3,4,5,6-hexahydropyrimido[4,5-*d*]pyrimidines 6

The appropriate isocyanate (1 mmol) was added dropwise to a stirred solution of the iminophosphorane **5** (1 mmol) in dry toluene (25 ml). The resultant solution was heated at reflux for 48 h. After cooling, the solvent was removed under reduced pressure at 25°C and the residual material was recrystallized from acetonitrile to give **6** as colorless crystals. The following derivatives **6** were obtained:

6a: 7-Benzylamino-6-(p-tolyl) (89%), m.p. 211-213°C. (Found: C, 68.07; H, 5.77; N, 18.23. $C_{22}H_{23}N_5O_2$ requires: C, 67.85; H, 5.95; N, 17.98); i.r. (Nujol) 3250, 1693, and 1632 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.34 (s, 3H, Ar-CH_3), 3.26 (s, 3H, N_3-CH_3), 3.41 (s, 3H, N_1-CH_3), 4.48 (s, 2H, CH_2), 4.55 (d, 2H, J=5.7Hz, CH_2-NH), 5.00 (t, 1H, J=5.7Hz, NH), 7.14-7.34 (m, 9H, aryl); ^{13}C n.m.r. δ ($CDCl_3$): 20.95 (Ar-CH_3), 27.34 (N_3-CH_3), 29.02 (N_1-CH_3), 45.42 (CH_2), 48.68 (CH_2), 82.35 (C_{4a}), 126.31, 127.10, 127.31, 128.50, 131.14, 137.62 (q), 138.35 (q), 138.77 (q), 152.45 (C_{8a}), 152.88 (C_2), 155.53 (C_4), 160.47 (C_7); m/z (%): 389 (M^+, 4), 388 (6), 181 (5), 136 (6), 131 (8), 104 (10), 91 (100), 82 (12), 77(6), 65 (13).

6b: 7-(p-Chlorophenyl)amino-6-phenyl (68%), m.p. 199-200°C. Found: C, 60.42; H, 4.39; N, 17.74. $C_{20}H_{16}ClN_5O_2$ requires: C, 60.68; H, 4.58; N, 17.69); i.r. (Nujol): 3250, 1693, and 1648 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.13 (s, 3H, N_3-CH_3), 3.28 (s, 3H, N_1-CH_3), 4.47 (CH_2), 7.29-7.47 (m, 10H, aryl+NH); ^{13}C n.m.r. δ (DMSO-d_6): 27.22 (N_3-CH_3), 29.12 (N_1-CH_3), 47.71 (C_5), 82.73 (C_{4a}), 119.84, 124.49, 126.85 (q), 128.62,

129.73, 137.89 (q), 138.60, 142.16 (q), 151.71 (C_{8a}), 151.99 (C_2), 153.60 (C_4), 159.48 (C_7); m/z (%): 397 (M^++2, 5), 395 (15), 394 (21), 277 (4), 212 (5), 192 (9), 169 (12), 158 (13), 145 (19), 129 (31), 127 (100), 111 (14), 104 (20), 82 (31), 77 (57).

6c: 7-(p-Fluorophenyl)amino-6-phenyl (71%), m.p.197-198°C. (Found: C, 63.10; H, 4.93; N, 18.33. $C_{20}H_{18}FN_5O_2$ requires: C, 63.32; H, 4.78; N, 18.46); i.r. (Nujol) 3220, 1687, and 1631 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 3.27 (s, 3H, N3-CH_3), 3.38 (s, 3H, N_1-CH_3), 4.57 (s, 2H, CH_2), 6.39 (s, 1H, NH), 6.98 (t, 2H, J=8.5Hz), 7.25-7.52 (m, 7H, aryl); ^{13}C n.m.r. δ ($CDCl_3$): 27.54 (N_3-CH_3), 29.37 (N_1-CH_3), 48.39 (CH_2), 83.32 (C_{4a}), 115.32 (J=22Hz), 124.39 (J=8.1Hz), 126.24, 128.70, 130.66, 133.30 (J=3Hz), 140.36 (q), 152.36 (C_2+C_{8a}), 153.57 (C_4), 159.72 (J=244.8Hz), 160.51 (C_7); m/z (%): 379 (M^+, 66), 378 (95), 364 (15), 302 (8), 269 (7), 212 (20), 276 (28), 161 (35), 158 (28), 145 (41), 135 (13), 110 (14), 104 (35), 92 (54), 91 (87), 77 (100).

6d: 7-(p-Tolyl)amino-6-phenyl (77%), m.p.218-220°C. (Found: C, 67.11; H, 5.72; N, 18.54. $C_{21}H_{21}N_5O_2$ requires: C, 67.23; H, 5.64; N, 18.66); i.r. (Nujol) 3324,1682, and 1650 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.30 (s, 3H, Ar-CH_3), 3.28 (s, 3H, N_3-CH_3), 3.42 (s, 3H, N_1-CH_3), 4.58 (s, 2H, CH_2), 6.31 (s, 1H, NH), 7.09 (d, 2H, J=8.2Hz), 7.21 (d, 2H, J=8.2Hz), 7.34-7.50 (m, 5H, aryl); ^{13}C n.m.r. δ ($CDCl_3$): 20.69 (Ar-CH_3), 27.46 (N_3-CH_3), 29.38 (N_1-CH_3), 48.18 (CH_2), 83.11 (C_{4a}), 122.13, 126.14, 128.48, 129.11, 130.52, 134.30 (q), 134.64 (q), 140.41 (q).152.38 (C_{8a}), 152.56 (C_2), 153.28 (C_4), 161.04 (C_7); m/z (%): 375 (M^+, 15), 374 (20), 360 (4), 269 (4), 212 (7), 172 (14), 159 (20), 158 (24), 145 (34), 131 (25), 117 (10), 104 (31), 91 (28), 82 (54), 77 (100).

6e: 7-(p-Chlorophenyl)amino-6-(p-tolyl) (96%), m.p.222-224°C. (Found: C, 61.33; H, 5.17; N, 16.83. $C_{21}H_{20}ClN_5O_2$ requires: C, 61.54; H, 4.92; N, 17.09); i.r. (Nujol) 3302, 1682, and 1631 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$+TFA): 2.32 (s, 3H, Ar-CH_3), 3.40 (s, 3H, N_3-CH_3), 3.49 (s, 3H, N_1-CH_3), 4.75 (s, 2H, CH_2), 6.99 (d, 2H, J=8.7Hz), 7.10 (d, 2H, J=8.5Hz), 7.20 (d, 2H, J=8.6Hz), 7.24 (d, 2H, J=8.8Hz); ^{13}C n.m.r. δ ($CDCl_3$+TFA): 20.83 (Ar-CH_3), 29.06 (N_3-CH_3), 30.83 (N_1-CH_3), 48.15 (CH_2), 87.93 (C_{4a}), 124.78, 125.79, 129.99, 131.24, 131.31 (q), 134.87 (q), 141.31 (q), 142.53 (q), 150.83 (C_2+C_{8a}), 150.97 (C_4), 160.85 (C_7); m/z (%): 411 (M^++2, 14), 410 (26), 409 (M^+, 45), 408 (73), 396 (4), 394 (12), 192 (25), 176 (25), 159 (47), 131 (23), 118 (48), 91 (100), 82 (62), 65 (36).

6f: 7-(p-Fluorophenyl)amino-6-(p-tolyl). (74%), m.p. 258-260°C. (Found: C, 64.29; H, 4.87; N, 17.62. $C_{21}H_{20}FN_5O_2$ requires: C, 64.11; H, 5.12; N, 17.80); i.r. (Nujol) 3317,1682, and 1631cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.37 (s, 3H, Ar-CH_3), 3.32 (s, 3H, N_3-CH_3), 3.43 (s, 3H, N_1-CH_3), 4.61 (s, 2H, CH_2), 6.94 (t, 2H, J=8.5 Hz), 7.12-7.28 (m, 6H, aryl), NH no observed; ^{13}C n.m.r. δ ($CDCl_3$): 21.00 (Ar-CH_3), 28.00 (N_3-CH_3), 29.87 (N_1-CH_3), 48.31 (CH_2), 83.98 (C_{4a}), 115.49 (J=22.8Hz), 124.97 (J=8.2Hz), 125.81, 131.24, 132.28 (J=3Hz), 136.99 (q), 139.51 (q), 151.83 (C_{8a}). 152.24 (C_2), 153.62 (C_4), 160.16 (J=246Hz), 160.84 (C_7); m/z (%): 393 (M^+, 12), 392 (18), 378 (3), 226 (6), 176 (28), 172 (17), 168 (18), 159 (30), 135 (15), 131 (19), 118 (39), 110 (19), 95 (26), 91 (100), 82 (58), 65 (35).

6g: 7-(p-Tolyl)amino-6-(p-tolyl) (73%), m.p. 224-226 °C. (Found: C, 68.09; H, 5.77; N, 18.18. $C_{22}H_{23}N_5O_2$ requires: C, 67.85; H, 5.95; N, 17.98); i.r. (Nujol): 3313, 1682, and 1631 cm^{-1}; ^1H n.m.r. δ

($CDCl_3$): 2.30 (s, 3H, Ar-CH_3), 2.40 (s, 3H, Ar-CH_3), 3.30 (s, 3H, N_3-CH_3), 3.42 (s, 3H, N_1-CH_3), 4.57 (s, 2H, CH_2), 6.30 (s, 1H, NH), 7.09 (d, 2H, J=7.5Hz), 7.20 (d, 2H, J=7.5Hz), 7.24 (d, 2H, J=7.5Hz), 7.31 (d, 2H, J=7.5Hz); ^{13}C n.m.r. δ. ($CDCl_3$): 20.71 (Ar-CH_3), 27.47 (N_3-CH_3), 29.39 (N_1-CH_3), 48.38 (CH_2), 83.10 (C_{4a}), 122.10, 126.10, 129.10, 131.22, 134.25 (q), 134.70 (q), 137.61 (q), 138.89 (q), 152.39 (C_{8a}), 152.57 (C_2), 153.32 (C_4), 160.57 (C_7), m/z (%): 389 (M^+, 25), 388 (41), 283 (4), 226 (6), 172 (34), 159 (39), 131 (28), 118 (36), 106 (13) 91 (100), 77 (21), 65 (31).

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