NOVEL SYNTHESIS OF PYRIDO[3,4-*d*]PYRIMIDINES, PYRIDO[2,3-*d*]-PYRIMIDINES, AND QUINAZOLINES *VIA* PALLADIUM-CATALYZED OXIDATIVE COUPLING

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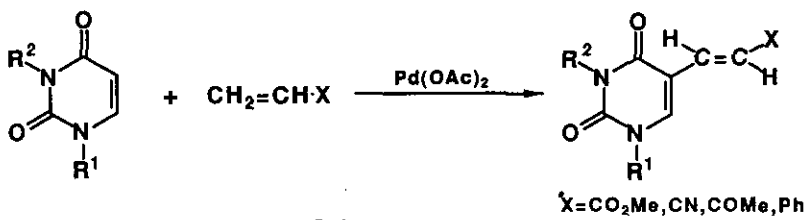
Abstract — Oxidative-coupling of 6-azavinyl(or vinyl)-1,3-dimethyluracil derivatives (**1**, **5**, and **7**) with electron-deficient olefins in the presence of palladium acetate led to the formation of the corresponding 6-substituted pyrido[3,4-*d*]pyrimidines (**4**), pyrido[2,3-*d*]pyrimidines (**6**), and quinazolines (**8** and **9**), respectively, *via* an intermediacy of azatriene.

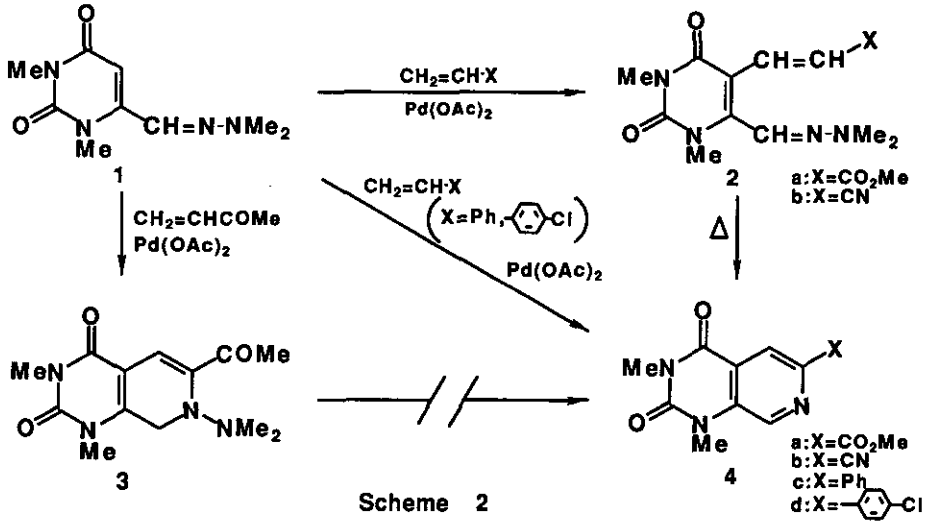
The pyrido[2,3-*d*]pyrimidines and quinazolines, deaza analogs of pteridines, have been of interest for their potential biological activities.[1,2] Thus, there have been ample precedents on the synthesis of these fused pyrimidines.[1,3] Our recent work has provided a convenient method for the preparation of (*E*)-5-(2-substituted vinyl)uracil derivatives by a palladium-catalyzed oxidative coupling with electron-deficient olefins as shown in Scheme 1.[4] Upon employment of the methodology, we studied on vinylation of 6-azavinyl(or vinyl)uracil derivatives, because the resulting triene derivatives could cause a facile cyclization to give the desired bicyclic fused pyrimidines. This paper describes in detail a novel and efficient method for the synthesis of pyrido[3,4-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines, and quinazolines.



Scheme 1

1,3-Dimethyluracil-6-carboxaldehyde dimethylhydrazone (**1**), which was easily prepared by condensation of 6-formyluracil with *N*,*N*-dimethylhydazine and subsequent methylation with dimethylformamide dimethyl-

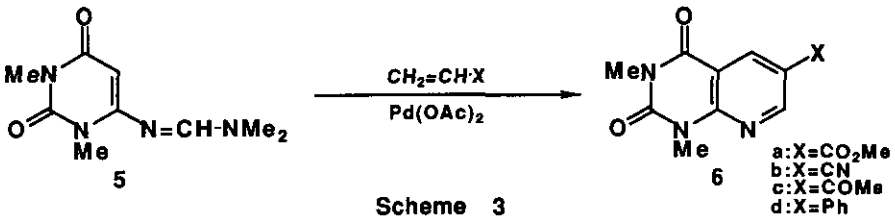
acetal (DMF-DMA), was treated with methyl acrylate and acrylonitrile in the presence of stoichiometric amount of palladium acetate in refluxing acetonitrile to give the corresponding (*E*)-5-(2-substituted vinyl)-uracils (**2a** and **2b**) in 67% and 66% yields, respectively. Although the 5-vinyluracils (**2**) were recovered unchanged upon heating in chlorobenzene, addition of acetic acid to the reaction medium facilitated the cyclization of **2** leading to the quantitative formation of pyrido[3,4-*d*]pyrimidine derivatives (**4a** and **4b**). When methyl vinyl ketone was employed as an olefin in the above coupling reaction, the product was proved to be not a 5-vinyluracil derivative but 7, 8-dihydropyrido[3,4-*d*]pyrimidine derivative (**3**), whose structure was determined on the basis of nmr spectrum. Several attempts for aromatization of **3**, however, were failure under thermal conditions employed. On the other hand, analogous treatment of **1** with styrene and 4-chlorostyrene resulted in the direct formation of 6-phenylpyrido[3,4-*d*]pyrimidines (**4c** and **4d**) in 40% and 50% yields, respectively, without allowing isolation of azatriene intermediates (Scheme 2).



Scheme 2

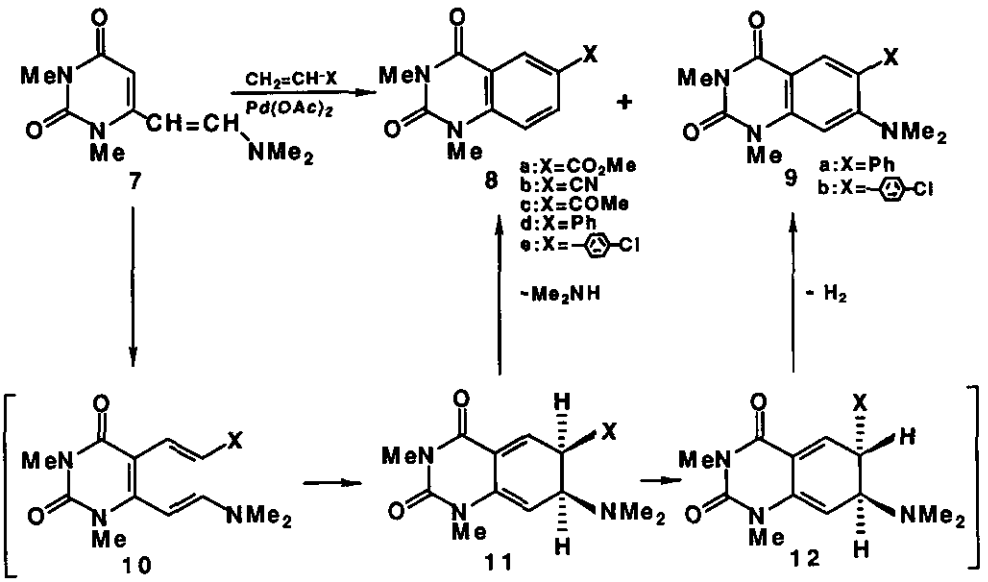
Employment of 6-dimethylaminomethylenamino-1,3-dimethyluracil (**5**) in place of **1** in the oxidation coupling makes it possible in principle to prepare pyrido[2,3-*d*]pyrimidine derivatives. Although treatment of **5** with methyl acrylate in refluxing acetonitrile gave a complex mixture of products, the oxidative coupling and cyclization smoothly occurred by use of acetic acid as a solvent to give directly 6-methoxycarbonylpyrido[2,3-*d*]pyrimidine derivative (**6a**) in 89% yield. Analogous treatment of **5** with olefins such as acrylonitrile, methyl vinyl ketone, and styrene also produced the corresponding 6-substituted pyrido[2,3-*d*]pyrimidines (**6b-d**) in good yields (Scheme 3). Wamhoff *et al.* have reported[5] a preparative

method of the pyrido[2,3-*d*]pyrimidines (**6a-c**) using the same starting compound (**5**) and electron-deficient olefins *via* two-step reaction involving [4+2]cycloaddition with olefins and subsequent oxidation of the resulting cyclo-adducts.



Scheme 3

The method described above was applicable to (*E*)-6-(2-dimethylaminovinyl)uracil derivative (**7**) for the synthesis of quinazolines. Reactions of **7** with olefins such as methyl acrylate, acrylonitrile, and methyl vinyl ketone in the presence of palladium acetate in acetonitrile gave exclusively 6-substituted quinazolines (**8a-c**) in good yields. On the other hand, the reaction of **7** with styrene and 4-chlorostyrene resulted in the concurrent formation of 6-aryl-7-dimethylaminoquinazolines (**9a** and **9b**) (30% and 50% yields) together with 6-aryl-quinazolines (**8d** and **8e**) (22% and 60% yields), respectively.



Scheme 4

The formation of **8** and **9** may be rationalized as shown in Scheme 4. Electrocyclic reactions of triene intermediates (**10**) give *cis*-dihydroquinazoline (**11**) as a sole product according to a disrotatory mode. Subsequent *trans*-elimination of dimethylamine in **11** produces the quinazolines (**8**). When the 6-substituent of **11** is an aryl group, **11** possibly isomerizes to some extent into more stable *trans*-isomer (**12**) owing to the steric hindrance between a dimethylamino group and a bulky phenyl group. The *trans*-isomer (**12**) preferentially undergoes oxidation rather than *cis*-elimination of dimethylamine to give the 7-dimethylaminoquinazoline (**9**).

EXPERIMENTAL

Mps were determined on a Yanagimoto melting-point apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded on a JEOL TNM-GX270 (270 MHz) spectrometer with tetramethylsilane in $CDCl_3$ or sodium 2,2-dimethyl-2-silapentane-5-sulphonate in $(CD_3)_2SO$ as internal standards. Mass (ms) spectra were taken with a JEOL JMS-D300 machine operating at 70 eV. Ultraviolet (uv) spectra were obtained from ethanol on a Shimadzu UV-260 spectrometer.

1,3-Dimethyluracil-6-carboxaldehyde Dimethylhydrazone (1) A mixture of 6-formyluracil[6] (560 mg, 4 mmol), *N,N*-dimethylhydrazine (240 mg, 4 mmol) and dimethylformamide (DMF) (20 ml) was stirred at ambient temperature. The reaction solution was evaporated to dryness under reduced pressure. The residue was triturated with water to give uracil-6-carboxaldehyde dimethylhydrazone in 89% yield. mp >300 °C. ^{1}H-Nmr (DMSO-d_6) δ: 3.08 (s, 6H, NMe_2), 5.45 (s, 1H, 5-H), 6.75 (s, 1H, CH=N), 10.05 and 10.73 (each br s, each 1H, 2 x NH). Ms *m/z*: 182 (M^+). The crude hydrazone (273 mg, 1.5 mmol) was refluxed in a mixture of dimethylformamide dimethylacetal (490 mg, 4.1 mmol) and DMF (10 ml) for 10 min. The reaction solution was evaporated to dryness under reduced pressure and the residue was triturated with ether to give a crude product. Recrystallization from ethanol gave **1** (280 mg, 89%), mp 176-178 °C (lit.,[5] mp 165-166 °C). The nmr spectra of **1** were identical with those in the literature.[5] Ms *m/z*: 210 (M^+).

5-[(*E*)-2-Methoxycarbonylvinyl]-1,3-dimethyluracil-6-carboxaldehyde Dimethylhydrazone (2a) A mixture of **1** (210 mg, 1 mmol), methyl acrylate (103 mg, 1.2 mmol), and palladium acetate (270 mg, 1.2 mmol) in acetonitrile (5 ml) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in chloroform (50 ml). The insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure and then purified by column chromatography (silica gel; benzene/ethyl acetate) to give **2a** (67%), mp 175-176 °C (ligroin). ^{1}H-Nmr ($CDCl_3$) δ: 3.19 (s, 6H, NMe_2),

3.40 and 3.55 (each s, each 3H, 2 x NMe), 3.75 (s, 3H, OMe), 6.77 (s, 1H, CH=N), 7.13 and 7.66 (each d, each J = 16 Hz, each 1H, vinyl H). Ms *m/z*: 294 (M^+). Uv λmax (EtOH) nm (ε); 367 (15500), 286 (30500). *Anal.* Calcd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04. Found: C, 53.00; H, 6.23; N, 19.02.

5-[(*E*)-2-Cyanovinyl]-1,3-dimethyluracil-6-carboxaldehyde Dimethylhydrazone (2b) A mixture of **1** (210 mg, 1 mmol), acrylonitrile (64 mg, 1.2 mmol), and palladium acetate (270 mg, 1.2 mmol) in acetonitrile (5 ml) was refluxed for 6 h. The reaction solution was treated as described above to give **2b** (66%), mp 152-153 °C (ligroin). ^{1}H-Nmr ($CDCl_3$) δ: 3.22 (s, 6H, NMe_2), 3.39 and 3.54 (each s, each 3H, 2 x NMe), 6.65 (s, 1H, CH=N), 6.80 and 7.31 (each d, each J = 16 Hz, each 1H, vinyl H). Ms *m/z*: 261 (M^+). Uv λmax (EtOH) nm (ε); 365 (16000), 283 (31000). *Anal.* Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.81. Found: C, 55.23; H, 5.75; N, 26.70.

6-Acetyl-7-dimethylamino-1,3-dimethyl-7,8-dihydropyrido[3,4-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (3) A mixture of **1** (210 mg, 1 mmol), methyl vinyl ketone (84 mg, 1.2 mmol), and palladium acetate (270 mg, 1.2 mmol) in acetonitrile (5 ml) was refluxed for 6 h. The reaction solution was treated as described above to give **3** (68%), mp 150-151 °C (EtOH). ^{1}H-Nmr ($CDCl_3$) δ: 2.30 (s, 1H, COMe), 2.78 (s, 6H, NMe_2), 3.35 and 3.36 (each s, each 3H, 2 x NMe), 4.23 (s, 2H, CH_2), 6.53 (s, 1H, 5-H). Ms *m/z*: 278 (M^+). Uv λmax (EtOH) nm (ε); 289 (2700), 257 (6650), 219 (18000). *Anal.* Calcd for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13. Found: C, 55.90; H, 6.53; N, 19.92.

6-Methoxycarbonyl-1,3-dimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (4a) A mixture of **2a** (294 mg, 1 mmol) and acetic acid (1 ml) in chlorobenzene (5 ml) was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethyl acetate to give **4a** (99%), mp 204-205 °C. ^{1}H-Nmr ($CDCl_3$) δ: 3.52 and 3.74 (each s, each 3H, 2 x NMe), 4.05 (s, 3H, OMe), 8.81 and 8.82 (each s, each 1H, 5-H and 7-H). Ms *m/z*: 249 (M^+). Uv λmax (EtOH) nm (ε); 325 (4900), 273 (15600), 228 (21000). *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.17; H, 4.55; N, 16.97.

6-Cyano-1,3-dimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (4b) A mixture of **2b** (261 mg, 1 mmol) and acetic acid (1 ml) in chlorobenzene (5 ml) was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give **4b** (95%), mp 203-204 °C. ^{1}H-Nmr ($CDCl_3$) δ: 3.52 and 3.73 (each s, each 3H, 2 x NMe), 8.45 and 8.80 (each s, each 1H, 5-H and 7-H). Ms *m/z*: 216 (M^+). Uv λmax (EtOH) nm (ε); 323 (5200), 272 (16200), 227 (21500). *Anal.* Calcd for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.40; H, 3.70; N, 26.15.

1,3-Dimethyl-6-phenylpyrido[3,4-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (4c) A mixture of **1** (210 mg, 1 mmol), styrene (125 mg, 1.2 mmol), and palladium acetate (270 mg, 1.2 mmol) in acetonitrile (5 ml) was refluxed for 4 h. The reaction solution was treated as described for the preparation of **2a** to give **4c** (40%), mp 240-241 °C (AcOEt). ^{1}H-Nmr ($CDCl_3$) δ: 3.53 and 3.73 (each s, each 3H, 2 x NMe), 7.45 (m, 3H, aromatic H), 8.06 (m, 2H, aromatic H), 8.45 and 8.81 (each s, each 1H, 5-H and 7-H). Ms *m/z*: 267 (M^+). Uv λmax (EtOH) nm (ε); 347 (5000), 276 (27000), 231 (16500). *Anal.* Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.11; H, 4.92; N, 15.54.

6-(4-Chlorophenyl)-1,3-dimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (4d) A mixture of **1** (210 mg, 1 mmol), 4-chlorostyrene (165 mg, 1.2 mmol), and palladium acetate (270 mg, 1.2 mmol) in acetonitrile (5 ml) was refluxed for 10 h. The reaction solution was treated as described for the preparation of **2a** to give **4d** (50%), mp 209-210 °C (AcOEt). ^{1}H-Nmr ($CDCl_3$) δ: 3.52 and 3.72 (each s, each 3H, 2 x NMe), 7,42 and 8.02 (each d, each J = 8 Hz, each 2H, aromatic H), 8.42 and 8.79 (each s, each 1H, 5-H and 7-H). Ms *m/z*: 302 (M^+). Uv λmax (EtOH) nm (ε); 348 (4500), 280 (26600), 235 (165200). *Anal.* Calcd for $C_{15}H_{12}N_3O_2$ C, 59.71; H, 4.01; N, 13.93. Found: C, 59.57; H, 4.03; N, 13.91.

General Procedure for the Preparation of 6-Substituted 1,3-Dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (6a-d) A mixture of 6-dimethylaminomethylenamino-1,3-dimethyluracil (**5**)[5] (210 mg, 1 mmol), olefins (1.2 mmol), and palladium acetate (270 mg, 1.2 mmol) in acetic acid (7 ml) was refluxed for 4-6 h. The solvent was removed under reduced pressure and water (10 ml) was added to the residue. The aqueous solution was extracted with chloroform (3 x 20 ml). The extract was evaporated under reduced pressure and then the residue was triturated with ether to give a crude product (**6a-d**).

6-Methoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (6a) Yield: 89%, mp 128-129 °C (EtOH) (lit.,[5] mp 126-127 °C). The nmr spectra of **6a** were identical with those in the literature.[5] Ms *m/z*: 249 (M^+). Uv λmax (EtOH) nm (ε); 310 (10500), 272 (19900), 215 (26000).

6-Cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (6b) Yield: 70%, mp 181-182 °C (AcOEt) (lit.,[5] mp 182-183 °C). The nmr spectra of **6b** were identical with those in the literature.[5] Ms *m/z*: 216 (M^+). Uv λmax (EtOH) nm (ε); 307 (9700), 272 (18800), 214 (25200).

6-Acetyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (6c) Yield: 73%, mp 167-168 °C (AcOEt) (lit.,[5] mp 162-163 °C). The nmr spectra of **6c** were identical with those in the literature.[5] Ms *m/z*: 267 (M^+). Uv λmax (EtOH) nm (ε); 331 (5400), 272 (24500), 228 (22900).

1,3-Dimethyl-6-phenylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*, 3*H*)-dione (6d) Yield: 60%, mp 138-139 °C (EtOH). ^{1}H-Nmr ($CDCl_3$) δ: 3.53 and 3.78 (each s, each 3H, 2 x NMe), 7.45 (m, 3H, aromatic H), 7.64 (m, 2H, aromatic H), 8.67 and 8.91 (each s, each 1H, 5-H and 7-H). Ms *m/z*: 267 (M^+). Uv λmax (EtOH) nm (ε); 331 (5400), 272 (24500), 228 (22900). *Anal.* Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.21; H, 4.91; N, 15.58.

General Procedure for the Preparation of 6-Substituted 1,3-Dimethylquinazoline-2,4(1*H*, 3*H*)-dione (8a-e) and 6-Substituted 7-Dimethylamino-1,3-dimethylquinazoline-2,4(1*H*, 3*H*)-dione (9a,b) A mixture of 6-(2-dimethylaminovinyl)-1,3-dimethyluracil (**7**)[5,7] (209 mg, 1 mmol), olefins (1.2 mmol), and palladium acetate (270 mg, 1.2 mmol) in acetonitrile (5 ml) was refluxed for 2-5 h. The solvent was removed under reduced pressure and the residue was dissolved in chloroform (50 ml). The insoluble material was removed by filtration. The filtrate is concentrated under reduced pressure and then purified by column chromatography (silica gel; benzene/ethyl acetate) to give **8a-e** and **9a,b**.

6-Methoxycarbonyl-1,3-dimethylquinazoline-2,4(1*H*, 3*H*)-dione (8a) Yield: 64%, mp 222-223 °C (AcOEt). ^{1}H-Nmr ($CDCl_3$) δ: 3.51 and 3.65 (each s, each 3H, 2 x NMe), 3.99 (s, 3H, OMe), 7.26 (d, 1H, J = 9 Hz, 8-H), 8.33 (dd, J = 9 and 2 Hz, 1H, 7-H), 8.89 (d, J = 2 Hz, 1H, 5-H). Ms *m/z*: 248 (M^+). Uv λmax (EtOH) nm (ε); 310 (2900), 275 (16400), 229 (352000). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.81; H, 4.90; N, 11.17.

6-Cyano-1,3-dimethylquinazoline-2,4(1*H*, 3*H*)-dione (8b) Yield: 60%, mp 215-216 °C (MeOH). ^{1}H-Nmr ($CDCl_3$) δ: 3.50 and 3.65 (each s, each 3H, 2 x NMe), 7.30 (d, 1H, J = 9 Hz, 8-H), 7.91 (dd, J = 9 and 2 Hz, 1H, 7-H), 8.53 (d, J = 2 Hz, 1H, 5-H). Ms *m/z*: 215 (M^+). Uv λmax (EtOH) nm (ε); 315 (3200), 272 (20900), 227 (40300). *Anal.* Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.41; H, 4.26; N, 19.40.

6-Acetyl-1,3-dimethylquinazoline-2,4(1*H*, 3*H*)-dione (8c) Yield: 73%, mp 207-208 °C (MeOH) (lit.,[5] mp 197 °C). The nmr spectra of **8c** were identical with those in the literature.[5] Ms *m/z*: 232 (M^+). Uv λmax (EtOH) nm (ε); 325 (shoulder), 284 (18000), 232 (30500).

1,3-Dimethyl-6-phenylquinazoline-2,4(1*H*, 3*H*)-dione (8d) Yield: 60%, mp 190-191 °C (AcOEt). ^{1}H-Nmr ($CDCl_3$) δ: 3.52 and 3.66 (each s, each 3H, 2 x NMe), 7.28 (d, 1H, J = 9 Hz, 8-H), 7.44 (m, 3H, aromatic H), 7.65 (m, 2H, aromatic H), 7.93 (dd, J = 9 and 2 Hz, 1H, 7-H), 8.48 (d, J = 2 Hz, 1H, 5-H). Ms *m/z*: 266 (M^+). Uv λmax (EtOH) nm (ε); 330 (3000), 272 (16500), 233 (37000). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.02; H, 5.25; N, 10.32.

6-(4-Chlorophenyl)-1,3-dimethylquinazoline-2,4(1*H*, 3*H*)-dione (8e) Yield: 22%, mp 158-159 °C (ligroin). ^{1}H-Nmr ($CDCl_3$) δ: 3.52 and 3.65 (each s, each 3H, 2 x NMe), 7.28 (d, 1H, J = 9 Hz, 8-H), 7.43 and 7.57 (each d, each J = 8 Hz, each 2H, aromatic H), 7.88 (dd, J = 9 and 2 Hz, 1H, 7-H), 8.43 (d, J = 2 Hz, 1H, 5-H). Ms *m/z*: 301 (M^+). Uv λmax (EtOH) nm (ε); 332 (3200), 272 (16600), 235 (36600). *Anal.* Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.32. Found: C, 63.77; H, 4.30; N, 9.45.

7-Dimethylamino-1,3-dimethyl-6-phenylquinazoline-2,4(1*H*, 3*H*)-dione (9a) Yield: 30%, mp 263-264 °C (AcOEt). ^{1}H-Nmr ($CDCl_3$) δ: 3.40 (s, 6H, NMe_2), 3.42 and 3.74 (each s, each 3H, 2 x NMe), 6.47 (s, 1H, 8-H), 7.30 (m, 3H, aromatic H), 7.62 (m, 2H, aromatic H), 7.81 (s, 1H, 5-H). Ms *m/z*: 309 (M^+). Uv λmax (EtOH) nm (ε); 336 (29300), 304 (22900), 260 (18500), 221 (12000). *Anal.* Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.67; H, 6.28; N, 13.56.

6-(4-Chlorophenyl)-7-dimethylamino-1,3-dimethylquinazoline-2,4(1*H*, 3*H*)-dione (9b) Yield: 50%, mp 222-223 °C (AcOEt). ^{1}H-Nmr ($CDCl_3$) δ: 3.42 (s, 6H, NMe_2), 3.49 and 3.75 (each s, each 3H, 2 x NMe), 6.45 (s, 1H, 8-H), 7.31 and 7.56 (each d, each J =8 Hz, each 2H, aromatic H), 7.84 (s, 1H, 5-H). Ms *m/z*: 344 (M^+). Uv λmax (EtOH) nm (ε); 338 (28900), 306 (21000), 262 (17600), 223 (10500). *Anal.* Calcd for $C_{18}H_{18}ClN_3O_2$; C, 62.88; H, 5.28; N, 12.22. Found: C, 62.71; H, 5.10; N, 12.00.

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