A Facile One-pot Synthesis of Pyrido[2,3-*d*]-pyrimidines and Pyrido[2,3-*d*:6,5-*d*′]dipyrimidines†

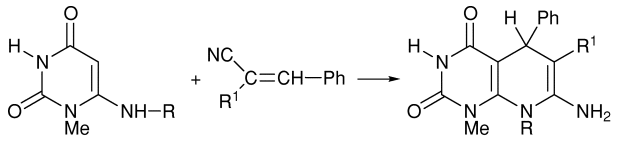
J. Chem. Research (S), 1999, 112–113†

Shaker Youssif,* Said El-Bahaie and Esam Nabih

Department of Chemistry, Faculty of Science, University of Zagazig, Egypt

The reactions of enaminones (6-aminouracils) **1a–c** and **4** with cyano olefins **2a–b** and **5a–f** led to the formation of pyrido[2,3-*d*]pyrimidines **3a–f** and **6a–f** in good yield, while the treatment of 4-amino-2-thiouracil **4** with aromatic aldehydes afforded pyridodipyrimidines **7a–c**.

The preparation of pyrido[2,3-*d*]pyrimidines has been reported by a number of investigators and may involve suitably substituted 6-aminouracils[1–4] followed by annelation of the pyridine ring or cyclocondensation of 2-amino-3-cyanopyridines[5–8] with suitable reagents. The importance of pyrido[2,3-*d*]pyrimidines as biologically active compounds includes their use as antitumor,[9] antibacterial[10–13] and anticonvulsive[14] agents. This prompted us to continue our research program on the cyclization of 6-anilinouracil derivatives.[15] We allowed 1-methyl-6-anilinouracils[15] **1** to react with reactive cyano compounds like benzylidenemalononitrile[16] **2a** and benzylidenecyanoacetate **2b** producing 6-cyano-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **3a–c** and the corresponding ethoxycarbonyl compounds **3a–f** respectively, as shown in Scheme 1. The products were fully characterized through spectral and elemental analysis. The structure of **3a** was indicated by broad IR bands at 3460–3360 cm^{-1} corresponding to the chelated amino group and at 2210 cm^{-1} corresponding to CN group; the ^{13}C NMR spectrum shows 17 lines.

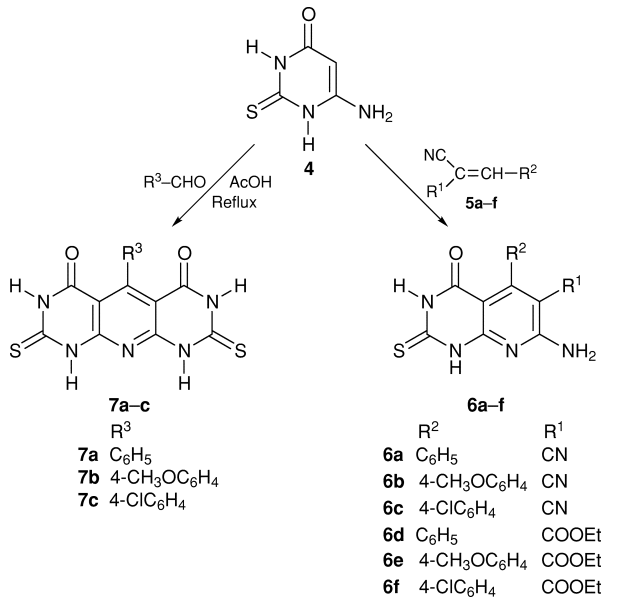


1a–c **2a–b** **3a–f**

	R	R^1
3a	C_6H_5	CN
3b	4-$CH_3OC_6H_4$	CN
3c	4-BrC_6H_4	CN
3d	C_6H_5	COOEt
3e	4-$CH_3OC_6H_4$	COOEt
3f	4-BrC_6H_4	COOEt

Scheme 1

On the other hand, the reaction of 4-amino-2-thiouracil[17] **4** with arylidenemalononitriles **5a–c** and arylidenecyanoacetates **5d–f** afforded the thiones **6a–c** and **6d–f** respectively, as shown in Scheme 2, fully confirmed by spectral and elemental analysis. The IR spectra of **6a** exhibited sharp bands at 3439 and 3321 cm^{-1} (NH_3), and 2215 cm^{-1} (CN); Its NMR ^1H spectrum showed a singlet at δ 7.72 (NH_2) and a doublet at δ 7.50–7.29 (aromatic protons). The yields of compounds **6a–f** were lower than of **3a–f**; this may be due to the higher nucleophilicity at C-5 of *N*-alkyluracils than that of uracil itself. It has been found that the intramolecular cyclization of 6-(*N*-alkylanilino)uracils with dimethylformamide (DMF)–$POCl_3$[18] or with *o*-haloarylaldehydes[19] in DMF or with arylaldehydes[20] in acetic acid afforded 5-deazaflavins. In the present work, we found that



7a–c

	R^3
7a	C_6H_5
7b	4-$CH_3OC_6H_4$
7c	4-ClC_6H_4

6a–f

	R^2	R^1
6a	C_6H_5	CN
6b	4-$CH_3OC_6H_4$	CN
6c	4-ClC_6H_4	CN
6d	C_6H_5	COOEt
6e	4-$CH_3OC_6H_4$	COOEt
6f	4-ClC_6H_4	COOEt

Scheme 2

the treatment of 4-amino-2-thiouracil **4** by heating with aryl aldehydes in acetic acid under reflux afforded pyridodipyrimidines **7a–c** as shown in Scheme 2; 5-deazaflavins were not obtained.

The structures of compounds **7a–c** were established on the basis of satisfactory analytical and spectral data and particularly the ^{13}C NMR spectra which showed only 9 lines for **7a** and 10 lines for **7b**; the mass spectrum of **7b** gave a molecular ion peak at *m*/*z* 385.

Experimental

Melting points were determined with an electrothermal Gallenkamp apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer in with $(CD_3)_2SO$ as solvent and with Me_4Si as internal standard. Electron impact mass spectra were recorded on a Mat 1125 70 eV spectrometer. IR spectra were recorded on a Perkin-Elmer 1430 spectrometer. The microanalyses were performed in the microanalytical laboratory, University of Cairo, Giza, Egypt.

General Procedure for the Synthesis of 6-*Substituted* 2-*Amino*-5-*phenyl*-8-*aryl*-5,8-*dihydropyrido*[2,3-d]*pyrimidine*-2,4(1H,3H)-*dione* **3a–f**.—A mixture of equimolar amounts of uracils **1** and the appropriate 3-phenyl-2-substituted cyano olefins **2** (2 mmol) in absolute ethanol (10 ml) in the presence of trimethylamine (5 drops) was heated at reflux for 3–6 h. The reaction mixture was concentrated and then cooled. The solid obtained was filtered off, washed with ethanol and recrystallized from DMF–EtOH (2:1). The products **3a–f** were obtained in 70–90% yield and their physical constants are as follows:

3a: Yield (83%); mp 302–303 °C; ^1H NMR δ 11.10 (s, 1H), 7.35–7.15 (m, J_o 7, J_m 3 Hz, 10H), 6.04 (brs, 2H), 4.66 (s, 1H), 2.78 (s, 3H); ^{13}C NMR δ 31.94 (N–C-1), 36.68 (C-5), 66.94, 102.94, 119.97, 126.68, 127.03, 127.16, 127.87, 128.24, 129.47, 141.38, 143.76, 148.81, 151.20, 155.20, 161.47; *m*/*z* (%) 371 (9), 307 (14), 305 (23), 304 (44), 295 (18), 294 (100), 261 (10), 251 (19), 228 (21),

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

102 (13), 91 (18), 77 (30), 66 (48) (Calc. for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.85. Found: C, 67.88; H, 4.60; N, 18.79%).

3b: Yield (89%); mp 319–320 °C; ^{1}H NMR δ 10.95 (s, 1H), 7.38–7.16 (m, J_m 3, J_o 8 Hz, 7H), 6.92–6.87 (d, J_m 2, J_o 6.8 Hz, 2H), 5.92 (s, 2H), 4.64 (s, 1H), 3.76 (s, 3H), 2.92 (s, 3H); ^{13}C NMR δ 32.17 (N–C-1), 36.59 (C-5), 55.67, 66.39, 102.17, 114.94, 120.09, 126.69, 127.04, 128.28, 128.89, 133.85, 144.02, 148.95, 151.29, 155.42, 158.97, 161.49; *m*/*z* (%) 401 (11), 337 (20), 335 (63), 334 (61), 325 (16), 324 (84), 258 (71), 121 (14), 102 (12), 77 (10), 66 (100) (Calc. for $C_{22}H_{19}N_5O_3$: C, 65.82; H, 4.77; N, 17.44. Found: C, 65.76; H, 4.74 N, 17.38%).

3c: Yield (78%); mp 308–309 °C; ^{1}H NMR δ 11.40 (s, 1H), 7.59–7.56 (d, J_o 8.8 Hz, 2H), 7.34–7.19 (m, J_m 2.3, J_o 8.1 Hz, 7H), 6.46 (s, 2H), 4.62 (s, 1H), 2.75 (s, 3H); ^{13}C NMR δ 31.81 (N–C-1), 36.40 (C-5), 66.48, 103.22, 120.09, 120.61, 126.76, 126.88, 128.31, 128.94, 132.25, 140.58, 143.35, 148.29, 151.05, 155.10, 161.44; *m*/*z* (%) 451 (8), 449 (8), 384 (9), 383 (7), 382 (8), 375 (14), 374 (97), 372 (100), 331 (19), 329 (20), 294 (27), 155 (11), 140 (7), 127 (7), 102 (17), 77 (16); (Calc. for $C_{21}H_{16}BrN_5O_2$: C, 56.00; H, 3.58; N, 15.54. Found: C, 55.89; H, 3.56; N, 15.37%).

3d: Yield (85%); mp 290–293 °C; ^{1}H NMR δ 10.93 (s, 1H), 7.42–7.15 (m, 10H), 7.12–7.09 (d, 2H), 5.14 (s, 1H), 4.10–4.01 (q, 2H), 2.80 (s, 3H), 1.11–1.06 (t, 3H); ^{13}C NMR δ 14.19 (C–CH_3), 31.58 (N–C-1), 34.16 (O–C), 58.97, 86.00, 105.14, 124.78, 126.57, 127.22, 127.42, 127.78, 129.26, 141.55, 145.60, 148.52, 151.26, 156.21, 161.61, 168.25; *m*/*z* (%) 418 (18), 346 (12), 345 (41), 342 (14), 341 (100), 295 (18), 77 (48) (Calc. for $C_{23}H_{22}N_4O_4$: C, 66.01; H, 5.29; N, 13.38. Found: C, 65.92; H, 5.27; N, 13.21%).

3e: Yield (80%); mp 268–260 °C; ^{1}H NMR δ 10.64 (brs, 1H), 7.28–7.25 (d, *J* 7.3 Hz, 2H), 7.20–7.12 (m, J_m 3, J_o 6.5 Hz, 5H), 7.10–7.07 (d, J_o 7, J_m 2.7 Hz, 2H), 6.88–6.84 (d, J_m 2, J_o 6.9 Hz, 2H), 5.13 (s, 1H), 4.10–4.01 (q, 2H), 3.75 (s, 3H), 2.82 (s, 3H), 1.26–1.06 (t, 3H); ^{13}C NMR δ 14.19 (C–CH_3), 31.86 (N–C-1), 34.00, 55.64, 58.89, 85.24, 104.14, 114.82, 125.96, 127.21, 127.81, 128.64, 133.98, 145.93, 148.56, 151.33, 156.37, 158.75, 161.90, 168.27; *m*/*z* (%) 448 (10), 376 (10), 375 (38), 372 (20), 371 (100), 325 (13), 77 (61), 43 (12) (Calc. for $C_{24}H_{24}N_4O_5$: C, 64.27; H, 5.39; N, 12.49. Found: C, 64.23; H, 5.36; N, 12.35%).

3f: Yield (74%); mp 257–259 °C; ^{1}H NMR δ 10.95 (s, 1H), 7.48–7.44 (d, *J* 8.8 Hz, 2H), 7.24–7.08 (m, J_m 3, J_o 6.6 Hz, 9H), 5.11 (s, 1H), 4.10–4.02 (q, 2H), 2.83 (s, 3H), 1.12–1.06 (t, 3H); ^{13} C NMR δ 14.19 (C–CH_3), 31.40 (N–C-1), 34.23 (O–C), 59.06, 87.00, 105.96, 119.95, 126.02, 127.15, 127.85, 127.88, 132.20, 140.99, 145.24, 148.25, 151.16, 156.06, 161.88, 168.13; *m*/*z* (%) 498 (6), 497 (10), 425 (19), 424 (51), 421 (16), 420 (100), 77 (58), 43 (11) (Calc. for $C_{23}H_{21}BrN_4O_4$: C, 55.53; H, 4.25; N, 11.26. Found: C, 55.49; H, 4.23; N, 11.18%).

Synthesis of 6-*Substituted* 7-*Amino*-5-*aryl*-2-*thioxo*-2,3-*dihydropyrido*[2,3-*d*]*pyrimidin*-4(1*H*)-*one* **6a**–**f**.—The compounds **6a**–**f** were prepared in 70–90% yield by the method described for the synthesis of **3a**–**f**.

6a: Yield (79%); mp > 380 °C; ^{1}H NMR δ 12.65 (s, 1H), 12.07 (s, 1H), 7.61 (s, 2H), 7.42–7.40 (m, J_m 3, J_o 6.2 Hz, 3H), 7.28–7.25 (d, J_m 2.3, J_o 9 Hz, 2 h); ^{13}C NMR δ 90.13, 100.35, 115.05, 126.83, 127.54, 128.80, 136.29, 154.30, 157.22, 158.80, 160.85, 175.96; *m*/*z* (%) 295 (100), 294 (49), 262 (12), 237 (9), 146 (28), 77 (51) (Calc. for $C_{14}H_9N_5OS$: C, 56.95; H, 3.07; N, 23.71. Found: C, 56.88; H, 2.98; N, 23.54%).

6b: Yield (72%); mp > 380 °C; ^{1}H NMR δ 12.70 (brs, 1H), 12.07 (s, 1H), 7.68 (s, 2H), 7.24–7.21 (d, J_o 8.7 Hz, 2H), 6.98–6.95 (d, J_o 8.6 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR δ 55.02 (O–C), 78.11, 90.18, 100.31, 112.94, 115.13, 128.06, 129.32, 133.28, 154.22, 157.33, 159.44, 175.73; *m*/*z* (%) 325 (100), 324 (32), 292 (15), 267 (13), 77 (18), 66 (72) (Calc. for $C_{15}H_{11}N_5O_2S$: C, 55.38; H, 3.40; N, 21.53. Found: C, 55.29; H, 3.34; N, 21.37%).

6c: Yield (78%); mp > 360 °C; ^{1}H NMR δ 12.70 (brs, 1H), 12.08 (s, 1H), 7.72 (s, 2H), 7.50–7.46 (d, J_m 2, J_o 8.4 Hz, 2H), 7.33–7.29 (d, 2H); ^{13}C NMR δ 89.93, 100.28, 114.96, 127.69, 129.52, 133.22, 135.13, 154.15, 157.31, 157.47, 160.75, 175.88; *m*/*z* (%) 331 (36), 330 (32), 329 (100), 328 (45), 296 (14), 271 (11), 180 (23), 164 (9) (Calc. for $C_{14}H_8ClN_5OS$: C, 51.00; H, 2.44; N, 21.24. Found: C, 50.89; H, 2.41; N, 21.00%).

6d: Yield (86%); mp 288–289 °C; ^{1}H NMR δ 11.59 (s, 1H), 11.51 (s, 1H), 8.06 (dd, 2H), 7.5 (m, 3H), 6.37 (s, 2H), 4.37–4.29 (q, 2H), 1.34–1.29 (t, 3H); ^{13}C NMR δ 13.89 (C–CH_3), 62.31 (O–CH_2), 78.11, 102.28, 125.38, 129.22, 130.68, 131.28, 133.29, 138.01, 154.28, 155.01, 161.61, 174.79; *m*/*z* (%) 342 (10), 270 (11), 269 (38), 266 (20), 220 (12), 77 (15), 43 (10) (Calc. for $C_{16}H_{14}N_4O_3S$: C, 56.13; H, 4.12; N, 16.36. Found: C, 56.05; H, 4.09; N, 16.11%).

6e : Yield (75%); mp 272–274 °C; ^{1}H NMR δ 11.42 (s, 1H), 11.27 (s, 1H), 8.08–8.04 (d, J_o 8.8 Hz, 2H), 7.15–7.11 (d, J_o 8.8 Hz, 2H), 6.30 (s, 2H), 4.35–4.27 (q, 2H), 3.88 (s, 3H), 1.34–1.28 (t, 3H); ^{13}C NMR δ 13.95 (C–CH_3), 55.73 (O–CH_3), 62.01 (O–CH_2), 78.27, 98.84, 114.94, 116.05, 124.00, 131.21, 133.40, 154.30, 161.56, 162.32, 163.56, 174.71; *m*/*z* (%) 372 (20), 300 (12), 299 (31), 296 (19), 219 (100), 173 (52), 77 (71), 43 (12) (Calc. for $C_{17}H_{16}N_4O_4S$: C, 54.83; H, 4.33; N, 15.04. Found: C, 54.68; H, 4.31; N, 14.90%).

6f: Yield (79%); mp 345–346 °C; ^{1}H NMR δ 11.35 (s, 1H), 10.99 (brs, 1H), 7.45–7.41 (d, J_o 8.3 Hz, 2H), 7.27–7.24 (d, J_o 8.3 Hz, 2H), 5.09 (s, 2H), 4.15–4.06 (q, 2H), 1.20–1.14 (t, 3H); ^{13}C NMR δ 13.55 (C–CH_3), 62.12 (O–CH_2), 72.20, 93.66, 116.62, 127.45, 129.48, 132.65, 136.54, 155.16, 159.61, 162.71, 163.51, 174.78; *m*/*z* (%) 378 (30), 377 (22), 376 (100), 304 (39), 294 (15), 261 (10), 288 (18), 77 (59) (Calc. for $C_{16}H_{13}ClN_4O_3S$: C, 51.00; H, 3.47; N, 14.87. Found: C, 50.94; H, 3.44; N, 14.80%).

General Procedure for the Synthesis of 5-*Substituted* 1,3,8,9-*Tetrahydro*-2,8-*dithioxopyrido*[2,3-*d*:6,5-*d*′]*pyrimidine*-4,6(1*H*,7*H*)-*diones* **7a**–**c**.—A solution of 6-amino-2-thiouracil **4** (2.32 mmol) in glacial acetic acid (15 ml) and 0.5 equiv. of the appropriate aromatic aldehyde was heated under reflux for 4 h. The reaction mixture was diluted with water, then allowed to cool to room temperature. The crude product was collected and recrystallized from a suitable solvent. The physical constants are as follows:

7a: Yield (71%); mp 278–280 °C (from ethanol); ^{1}H NMR δ 12.02 (s, 2H), 11.81 (brs, 2H), 7.25–7.06 (m, 5H); ^{13}C NMR δ 72.19, 90.18, 125.22, 126.38, 127.75, 137.85, 153.38, 162.93, 172.72; *m*/*z* (%) 355 (18), 295 (15), 270 (43), 109 (100), 77 (19), 68 (71) (Calc. for $C_{15}H_9N_5O_2S_2$: C, 50.71; H, 2.55; N, 19.71. Found: C, 50.68; H, 2.53; N, 19.55%).

7b: Yield (73%); mp 292–294 °C (from ethanol–DMF 2;1); ^{1}H NMR δ 11.94 (s 2H), 11.75 (brs, 2H), 6.97–6.76 (dd, 4H), 3.70 (s, 3H); ^{13}C NMR δ 54.85 (O–CH_3), 72.19, 90.45, 113.18, 127.43, 129.47, 153.32, 157.03, 162.89, 172.67; *m*/*z* (%) 385 (14), 263 (41), 260 (87), 143 (100), 121 (74), 115 (44), 68 (86), 43 (78) (Calc. for $C_{16}H_{11}N_5O_3S_2$: C, 49.87; H, 2.87; N, 18.17. Found: C, 49.80; H, 2.83; N, 18.01%).

7c: Yield (81%); mp 334–336 °C (from DMF–ethanol 5:1); ^{1}H NMR: δ 11.89 (s, 2H), 11.70 (s, 2H), 7.26–7.08 (dd, 4H); ^{13}C NMR: δ 72.23, 89.99, 127.59, 128.46, 129.86, 137.17, 153.37, 162.91, 172.91; *m*/*z* (%): 391 (26), 389 (48), 329 (16), 304 (45), 264 (66), 205 (23), 143 (100) (Calc. for $C_{15}H_8ClN_5O_2S_2$: C, 46.22; H, 2.06; N, 17.97. Found: C, 46.18; H, 2.00; N, 17.86%).

Received, 18th August 1998; Accepted, 28th October 1998
Paper E/8/06513F

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