CONVENIENT SYNTHESIS OF PYRIDO[4,3-*d*]PYRIMIDINE-2,4-(1*H*,3*H*)-DIONES

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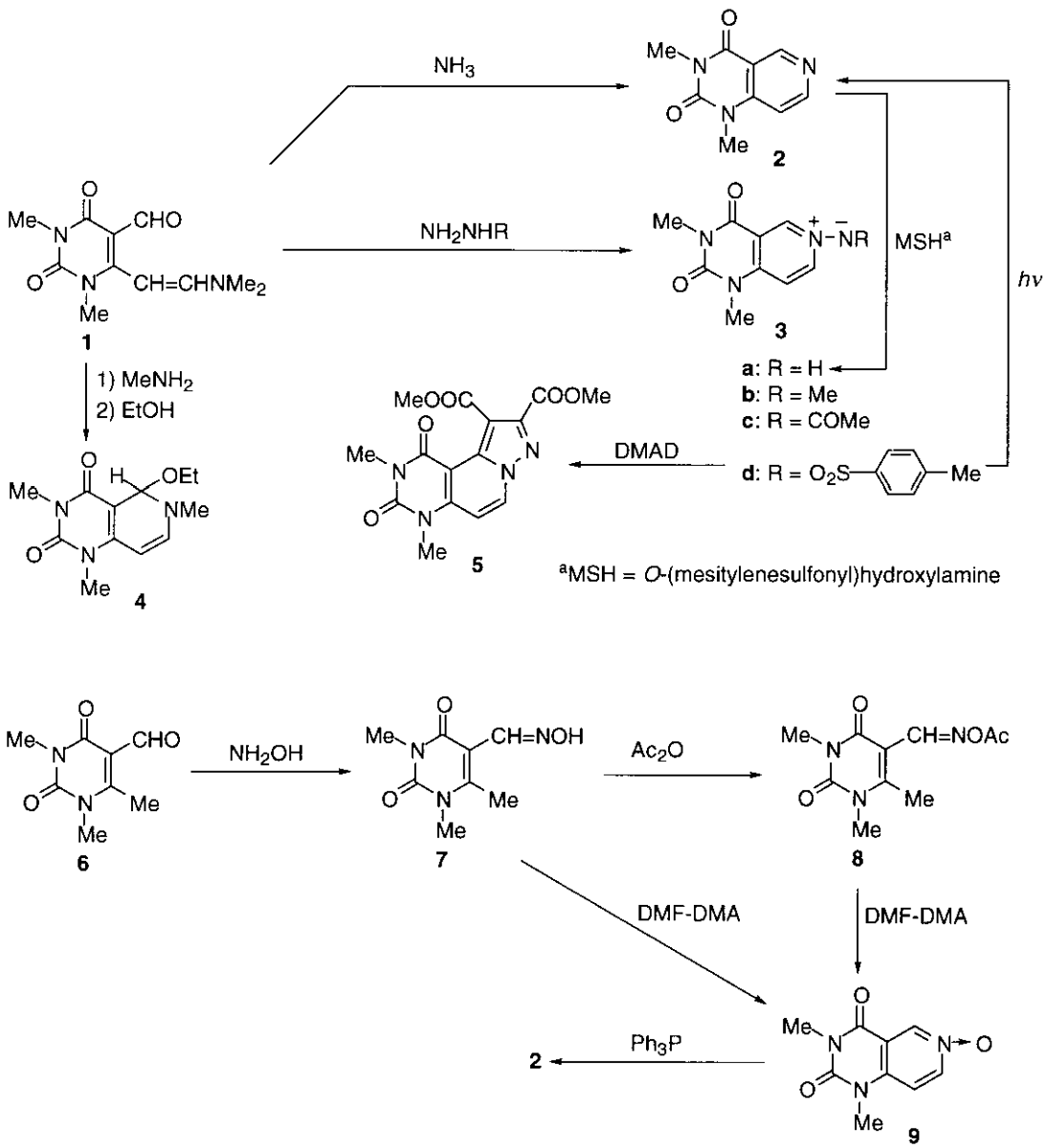
Abstract — A convenient synthesis of pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones is described. Treatment of 5-formyl-1,3-dimethyl-6-(2-dimethylamino)-vinyluracil (**1**) with ammonia and hydrazines affords the corresponding pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**2** and **3**), respectively. Similar reaction of 5-cyano- and 5-ethoxycarbonyluracils (**10** and **15**) with ammonia led to formation of 5-amino- and 5-hydroxylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**11** and **16**), respectively.

The pharmacological activity of fused pyrimidine derivatives has been of great interest to medicinal chemists in connection with an antimetabolite of folates and purine bases of nucleic acid.[1,2] Although the synthesis of various types of fused pyrimidines has been documented,[2] there have been few reports[2b] on the synthetic method of pyrido[4,3-*d*]pyrimidines. We have investigated the synthetic procedures of fused pyrimidines by utilizing 5-functionalized 6-methyluracils.[3] The present paper describes a convenient synthesis of pyrido[4,3-*d*]pyrimidine-2,4-diones from 5-formyl (or cyano, ethoxycarbonyl)-6-dimethylaminovinyl-1,3-dimethyluracils easily prepared by the condensation of the 6-methyluracils with *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA).[4]

The reaction of 5-formyl-1,3-dimethyl-6-(2-dimethylamino)vinyluracil (**1**) with methanolic ammonia at room temperature afforded 1,3-dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**2**) in 84% yield.

Analogous reactions of **1** with hydrazine hydrate, methylhydrazine, acetylhydrazine and *p*-toluenesulfonylhydrazine gave the corresponding *N*(6)-imide products in 57-78% yields. The structures of **3a-d** were determined on the basis of the microanalytical results and spectral data. The ultimate proof of the structures was provided by an alternate synthesis of **3a** from **2** using *O*-(mesitylenesulfonyl)-hydroxylamine (MSH) according to Tamura *et al.*'s method.[5]

Scheme 1



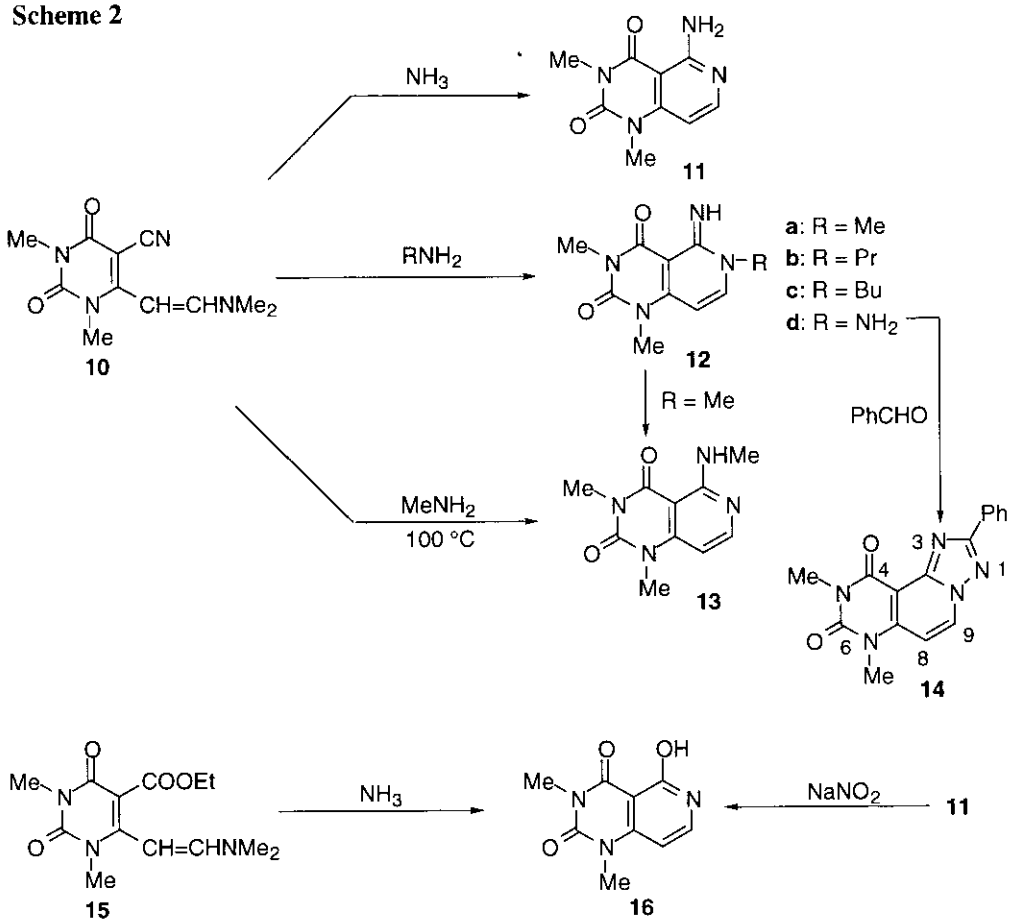
Furthermore, the *N*-*p*-toluenesulfonylimide (**3d**) led to the formation of **2** in 73% by irradiation with a 400 W high-pressure mercury lamp for 2 h. On the basis of the azomethine structure of **3**, the 1,3-dipolar cycloaddition was carried out with dimethyl acetylenedicarboxylate as a dipolarophile. Upon heating of **3d** with the acetylenedicarboxylate in DMF at 60 ℃, the tricyclic product (**5**) was obtained in 98% yield. This result supported the *N*(6)-imide structure of **3**.

Treatment of **1** with methanolic $MeNH_2$ at ambient temperature followed by recrystallization from EtOH gave the 5-ethoxy-1,3,6-trimethyl-5,6-dihydropyrido[4,3-*d*]pyrimidine (**4**, 89% yield), which presumably could be formed by displacement of EtOH with the 5-hydroxy group of an intermediary cyclic hemiaminal. Whereas analogous treatment of **1** with hydroxylamine failed to produce the desired *N*(6)-oxide (**9**), this compound was obtained in 56% yield by heating a mixture of 1,3,6-trimethyluracil-5-carbaldehyde oxime (**7**) and DMF-DMA. An alternative two-step synthesis of *N*(6)-oxide (**9**) *via* *O*-acetylated oxime (**8**) improved the yield of **9**. Thus, acetylation of **7** with acetic anhydride and subsequent cyclization with DMF-DMA afforded **9** in 70% yield. The structure of **9** was confirmed by deoxygenation of **9** into **2**. Upon heating of **9** with triphenylphosphine at 150 ℃, the pyrido[4,3-*d*]pyrimidine (**2**) was produced in 58% yield.

5-Cyano-1,3-dimethyl-6-(2-dimethylamino)vinyluracil (**10**) also underwent the cyclization to a pyrido[4,3-*d*]pyrimidine ring system upon treatment with NH_3 in a sealed tube at 100 ℃ to give 5-amino-1,3-dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**11**) in 70% yield. The reaction of **10** with methylamine in MeOH at ambient temperature easily afforded the corresponding 5-imino-1,3,6-trimethylpyrido[4,3-*d*]pyrimidine (**12a**) in 81% yield. On the other hand, when the reaction was carried out in DMF instead of MeOH at 100 ℃ for 1 h in a sealed tube, the 5-methylaminopyrido[4,3-*d*]pyrimidine (**13**) was obtained in 40% yield. This 5-methylamino derivative (**13**) would be formed through the Dimroth rearrangement of the normal cyclization product (**12a**), as shown in Scheme 2, because the 5-imino-1,3,6-trimethylpyrido[4,3-*d*]pyrimidine **12a** easily converted into the 5-methylamino derivatives (**13**) in 60% yield upon treatment of **12a** with methanolic methylamine at 100 ℃. Treatment of **10** with a primary amine, propylamine and butylamine, in refluxing DMF and hydrazine hydrate in refluxing MeOH gave the corresponding 5-iminopyrido[4,3-*d*]pyrimidine (**12b-d**) in good yields. In these cases, the Dimroth rearrangement product could not be detected in the reaction mixture. Since **12d** possesses

bifunctional substituents, the 5-imino and *N*(6)-amino groups, heating of **12d** with benzaldehyde for 30 min, as expected, furnished tricyclic benzylidene product (**14**) in 25% yield.

Scheme 2



Having learned from the above results, 5-ethoxycarbonyl-1,3-dimethyl-6-(2-dimethylamino)vinyluracil (**15**) was prepared in 33% yield from 5-ethoxycarbonyl-1,3,6-trimethyluracil according to the procedure[2] reported for the synthesis of **1** and **10**. Treatment of **15** with methanolic ammonia at ambient temperature for 48 h afforded the corresponding 5-hydroxypyrido[4,3-*d*]pyrimidine (**16**) in 27% yield. The same compound (**16**) was obtained in 86% yield by treatment of the 5-aminopyrido[4,3-*d*]pyrimidine (**11**) with eight molar equivalents of $NaNO_2$ in the presence of acetic acid.

In conclusion, we have described the synthesis of pyrido[4,3-*d*]pyrimidine derivatives (**2**, **3**, **4**, **9**, **11**, **12**,

13, and **16**) starting from the readily available 6-(2-dimethylamino)vinyluracil derivatives (**1**, **10** and **15**) substituted by functional groups such as cyano, formyl, and ethoxycarbonyl groups. Interestingly, the 5-aminopyrido[4,3-*d*]pyrimidine (**11**) was found to have greater inhibitory activity against cyclic AMP phosphodiesterase than theophylline. Biological activities of the pyrido[4,3-*d*]pyrimidines prepared here will be reported elsewhere.

EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All column chromatography was carried out with silica gel (Wakogel, C-300). All reactions were monitored by thin layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (MERCK), and compounds were visualized under UV light (254 nm). Melting points were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were determined with a JEOL GX-270 or Hitachi Perkin-Elmer R-20B spectrometer using tetramethylsilane (TMS) in $CDCl_3$ or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) in DMSO-d_6 and trifluoroacetic acid (CF_3COOH) as an internal standard. Coupling constants (J) are reported in hertz (Hz). MS were obtained in a JEOL JMS-D 300 machine operating at 70 eV. Microanalyses were carried out at the Microanalytical Laboratory of our university.

1,3-Dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2) (a) A mixture of 5-formyl-1,3-dimethyl-6-(2-dimethylamino)vinyluracil (**1**)[4] (0.47 g, 2.0 mmol) and methanolic ammonia (40 %, 5 mL) was stirred at ambient temperature for 20 min. The resulting precipitates were filtered and recrystallized from EtOH to give 0.32 g of **2** (84 %): mp 174-175 ℃; MS (EI$^+$) m/z 191 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 3.18 and 3.37 (each s, each 3H), 7.34 (d, 1H, J = 6.0 Hz), 8.63 (d, 1H, J = 6.0 Hz), 8.91 (s, 1H). *Anal.* Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.53; H, 4.78; N, 22.00.

(b) A mixture of **3d** (0.36 g, 1.0 mmol) and AcOH (2 mL) in CH_2Cl_2 (200 mL) was irradiated with a 400 W high pressure marcury lamp at ambient temperature for 2 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution. The CH_2Cl_2 layer was washed with water, and dried over anhydrous magnesium sulfate. The solvents were evaporated off, and the residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 30 : 1) to give 0.14 g of **2** in 73 % yield, which was identical with the

sample prepared above.

(c) A mixture of **9** (150 mg, 0.72 mmol) and triphenylphosphine (500 mg, 1.90 mmol)) was heated at 150 ℃ for 24 h. The reaction mixture was purified by silica gel column chromatography ($CHCl_3$: MeOH = 30 : 1) to give 80 mg of **2** in 58 % yield, which was identical with the sample prepared above.

1,3-Dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione 6-Imide (3a) (a) A mixture of **1**[4] (0.50 g, 2.1 mmol) and 98% hydrazine hydrate (0.13 g, 2.6 mmol) in isopropanol (40 mL) was stirred at ambient temperature for 4 h. The resulting precipitates were filtered, washed with ether and recrystallized from EtOH to give 0.34 g of **2** (78 %): mp 219-220 ℃ (decomp); MS (EI^+) m/z 206 (M^+); ^1H NMR (CF_3COOH) δ 3.60 and 3.80 (each s, each 3H), 7.80 (d, 1H, J = 8.0 Hz), 8.83 (dd, 1H, J = 8.0 and 1.0 Hz), 9.51 (d, 1H, J = 1.0 Hz). *Anal.* Calcd for $C_9H_{10}N_4O_2 \cdot 1/7H_2O$: C, 51.78; H, 4.97; N, 26.84. Found: C, 51.95; H, 4.90; N, 26.57.

(b) A mixture of **2** (0.36 g, 2.0 mmol) and *O*-(mesitylenesulfonyl)hydroxylamine (MSH) (0.73 g, 4.0 mmol) in CH_2Cl_2 (50 mL) was stirred at ambient temperature for 30 min. The resulting precipitates were filtered to give 0.69 g of the mesitylenesulfonate of **3a** (85 %), which was added to a suspension of potassium carbonate (0.26 g, 1.9 mmol) in DMF (10 mL). The mixture was stirred at ambient temperature for 6 h. The resulting precipitates were collected by filtration to give **3a** (82 %), which was identical with the sample prepared above.

1,3-Dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione 6-Methylimide (3b) A mixture of **1**[4] (0.40 g, 1.7 mmol) and methylhydrazine (0.5 mL, 9.4 mmol) in isopropanol (30 mL) was stirred at ambient temperature for 4 h. The resulting precipitates were filtered, washed with ether and recrystallized from EtOH to give 0.21 g of **3b** (57 %): mp180-181 ℃; MS (EI^+) m/z 220 (M^+); ^1H NMR (CF_3COOH) δ 3.20, 3.58 and 3.85 (each s, each 3H), 7.88 (d, 1H, J = 7.0 Hz), 8.84 (dd, 1H, J = 7.0 and 1.5 Hz), 9.54 (d, 1H, J = 1.5 Hz). *Anal.* Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.52; H, 5.68; N, 25.24.

1,3-Dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione 6-Acetylimide (3c) A mixture of **1**[4] (0.24 g, 1.0 mmol) and acetylhydrazine (0.11 g, 1.5 mmol) in EtOH (10 mL) was refluxed for 1.25 h. After cooling, the resulting precipitates were filtered and recrystallized from EtOH to give 0.17 g of **3c** (68 %): mp 250-252 ℃; MS (EI^+) m/z 248 (M^+); ^1H NMR (DMSO-d_6) δ 1.85, 3.33 and 3.60 (each s, each

3H), 7.81 (d, 1H, J = 7.0 Hz), 8.72 (dd, 1H, J = 7.0 and 2.0 Hz), 9.15 (d, 1H, J = 2.0 Hz). *Anal.* Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.33; H, 4.98; N, 22.50.

1,3-Dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione 6-*p*-Toluenesulfonylimide (3d) A mixture of **1**[4] (0.24 g, 1.0 mmol) and *p*-toluenesulfonylhydrazine (0.22 g, 1.2 mmol) in EtOH (10 mL) was refluxed for 4 h. After cooling, the resulting precipitates were filtered and recrystallized from EtOH to give 0.24 g of **3c** (59 %): mp 272-274 ℃; MS (EI$^+$) m/z 360 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.38, 3.43 and 3.65 (each s, each 3H), 7.13 (d, 2H, J = 7.0 Hz) 7.48 (d, 1H, J = 7.0 Hz), 7.53 (d, 2H, J = 7.0 Hz), 8.46 (dd, 1H, J = 7.0 and 2.0 Hz), 8.78 (d, 1H, J = 2.0 Hz). *Anal.* Calcd for $C_{16}H_{16}N_4O_4$: C, 53.32; H, 4.47; N, 15.55. Found: C, 53.27; H, 4.43; N, 15.61.

5-Ethoxy-1,3,6-trimethyl-5,6-dihydropyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4) A mixture of **1**[4] (0.48 g, 2.0 mmol) and methanolic ammonia (40 %, 1 mL) was stirred at ambient temperature for 1 h. The reaction solution was evaporated under reduced pressure and the residue was recrystallized from EtOH to give 0.45 g of **4** (89 %): mp 104-105 ℃; MS (EI$^+$) m/z 251 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.0 Hz), 3.30, 3.38 and 3.40 (each s, each 3H), 3.60 (q, 2H, J = 7.0 Hz), 5.20 (d, 1H, J = 8.0 Hz), 5.98 (d, 1H, J = 1.5 Hz), 6.81 (d, 1H, J = 8.0 Hz). *Anal.* Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.28; H, 6.80; N, 16.82.

5,7-Dimethyl-2,3-bis(methoxycarbonyl)pyrazolo[2',3'-1,2]pyrido[4,3-*d*]pyrimidine-4,6-(5*H*,7*H*)-dione (5) A mixture of **3d** (0.18 g, 0.5 mmol) and acetylenedicarboxylic acid dimethyl ester (0.11 g, 0.75 mmol) in DMF (10 mL) was heated at 60 ℃ for 1.7 h. The reaction solution was evaporated under reduced pressure and the residue was triturated with EtOH, filtered and recrystallized from EtOH-water to give 0.17 g of **5** (98 %): mp >300 ℃; MS (EI$^+$) m/z 346 (M$^+$); ^{1}H NMR (CF_3COOH) δ 3.55, 3.80, 4.09 and 4.15 (each s, each 3H), 6.10 (d, 1H, J = 8.0 Hz), 7.33 (d, 1H, J = 8.0 Hz). *Anal.* Calcd for $C_{15}H_{14}N_4O_6$: C, 52.03; H, 4.07; N, 16.18. Found: C, 52.17; H, 4.16; N, 16.19.

1,3,6-Trimethyluracil-5-carbaldehyde Oxime (7) A mixture of 5-formyl-1,3,6-trimethyl-uracil (**6**)[6] (1.82 g, 10.0 mmol), hydroxylamine hydrochloride (0.84 g, 12.0 mmol) and triethylamine (1.12 g, 12 mmol) in EtOH (30 mL) was stirred at ambient temperature for 3 h. The resulting precipitates were filtered and recrystallized from EtOH to give 1.57 g of **7** (80 %): mp 180-181 ℃; MS (EI$^+$) m/z 197 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 2.55, 3.19 and 3.40 (each s, each 3H), 8.04 (s, 1H), 11.01 (s, 1H, deuterium exchangeable).

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.69; H, 5.53; N, 21.28.

5-Acetoxyiminomethyl-1,3,6-trimethyluracil (8) A mixture of **7** (1.97 g, 10.0 mmol), acetic anhydride (1.53 g, 15.0 mmol) in pyridine (30 mL) was stirred at ambient temperature for 3 h. The reaction solution was evaporated under reduced pressure and the residue was triturated with water, filtered and recrystallized from EtOH-water to give 1.73 g of **5** (72 %): mp 155-156 ℃; MS (EI^+) m/z 239 (M^+); ^1H NMR ($CDCl_3$) δ 2.72, 3.34 and 3.50 (each s, each 3H), 8.60 (s, 1H). *Anal.* Calcd for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 50.01; H, 5.50; N, 17.67.

1,3-Dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione 6-Oxide (9) (a) A mixture of **7** (0.59 g, 3.0 mmol) and *N*,*N*-dimethylformamide dimethylacetal (1.5 mL) in DMF (7.5 mL) was heated at 80 ℃ for 3 h. The reaction solution was evaporated under reduced pressure and the residue was recrystallized from EtOH to give 0.35 g of **9** (56 %): mp 270-271 ℃; MS (EI^+) m/z 207 (M^+); ^1H NMR (DMSO-d_6) δ 3.35 and 3.55 (each s, each 3H), 7.59 and 8.49 (each d, each 1H, J = 8.0 Hz), 8.53 (s, 1H). *Anal.* Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.90; H, 4.45; N, 20.16.

(b) A mixture of **8** (0.48 g, 2.0 mmol) and *N*,*N*-dimethylformamide dimethylacetal (1 mL) in DMF (5 mL) was heated at 80 ℃ for 3 h.. The reaction solution was evaporated under reduced pressure and the residue was triturated with EtOH. The resulting precipitates were filtered to give 0.40 g of **9** (97 %), which was identical with the sample prepared above.

5-Amino-1,3-dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11) A mixture of 5-cyano-1,3-dimethyl-6-(2-dimethylamino)vinyluracil (**10**)[4] (1.00g, 4.2 mmol) and NH_4OH (30 %, 5 mL) in DMF (20 mL) was heated in a seald tube at 100 ℃ for 24 h. The reaction solution was evaporated under reduced pressure and the residue was triturated with EtOH. The resulting precipitates were filtered and recrystallized from EtOH to give 0.61 g of **11** (70 %): mp 233-235 ℃; MS (EI^+) m/z 206 (M^+); ^1H NMR (DMSO-d_6) δ 3.26 and 3.39 (each s, each 3H), 6.45 and 8.08 (each d, each 1H, J = 6.0 Hz), 7.76 (br, 2H). *Anal.* Calcd for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.66; H, 4.87; N, 26.89.

5(6*H*)-Imino-1,3,6-trimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (12a) A mixture of **10**[4] (0.50 g, 2.1 mmol) and methanolic methylamine (40 %, 5 mL) in MeOH (10 mL) was stirred at ambient temperature for 4 h. The resulting precipitates were filtered and recrystallized from MeOH to give 0.38 g of **12a** (81 %): mp 237-238 ℃; MS (EI^+) m/z 220 (M^+); ^1H NMR ($CDCl_3$) δ 3.41 (s, 3H) 3.50 (s,

6H), 5.68 and 7.55 (each d, each 1H, J = 8.0 Hz).

5(6*H*)-Imino-1,3-dimethyl-6-propylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (12b) A mixture of **10**[4] (1.00g, 4.3 mmol) and *n*-propylaminine (0.35 g, 6.0 mmol) in DMF (20 mL) was refluxed for 1 h. The reaction solution was evaporated under reduced pressure and the residue was triturated with ether. The resulting precipitates were filtered and recrystallized from EtOH to give 0.85 g of **12b** (80 %): mp 224-225 ℃; MS (EI$^+$) m/z 248 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.75-1.92 (m, 2H), 3.41 and 3.48 (each s, each 3H), 3.92 (t, 2H, J = 7.3 Hz), 5.62 (d, 1H, J = 7.8 Hz), 7.26 (d, 1H, J = 7.8 Hz), 9.50 (br, 1H). *Anal.* Calcd for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.08; H, 6.39; N, 22.35.

6-Butyl-5(6*H*)-imino-1,3-dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (12c) A mixture of **10**[4] (1.00 g, 4.3 mmol) and *n*-butylaminine (0.44 g, 6.0 mmol) in DMF (20 mL) was refluxed for 1 h. The reaction solution was evaporated under reduced pressure and the residue was triturated with ether. The resulting precipitates were filtered and recrystallized from EtOH to give 0.80 g of **12c** (71 %): mp 198-199 ℃; MS (EI$^+$) m/z 262 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3H, J = 7.4 Hz), 1.25-1.60 (m, 2H), 1.65-1.88 (m, 2H), 3.41 and 3.48 (each s, each 3H), 3.96 (t, 2H, J = 7.3 Hz), 5.62 (d, 1H, J = 7.3 Hz), 7.25 (d, 1H, J = 7.3 Hz), 9.52 (br, 1H). *Anal.* Calcd for $C_{13}H_{18}N_4O_2$: C, 59.52; H, 6.92; N, 21.36. Found: C, 59.54; H, 6.92; N, 21.29.

6-Amino-5(6*H*)-imino-1,3-dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (12d) A mixture of **10**[4] (1.00g, 4.3 mmol) and 98% hydrazine hydrate (0.30 g, 6.0 mmol) in MeOH (50 mL) was refluxed for 1 h. After cooling, the resulting precipitates were filtered and recrystallized from DMF to give 0.86 g of **12c** (91 %): mp 258-259 ℃ (decomp); MS (EI$^+$) m/z 221 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 3.28 and 3.44 (each s, each 3H), 5.95 (d, 1H, J = 8.5 Hz), 6.09 (br, 2H), 7.91 (d, 1H, J = 8.5 Hz), 9.10 (br, 1H). *Anal.* Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.69; H, 5.05; N, 31.57.

1,3-Dimethyl-5-methylaminopyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (13) (a) A mixture of **10**[4] (1.00 g, 4.3 mmol) and methanolic methylamine (40 %, 5 mL) in DMF (20 mL) was heated in a seald tube at 100 ℃ for 1 h. The reaction solution was evaporated under reduced pressure and the residue was triturated with ether. The resulting precipitates were filtered and recrystallized from EtOH to give 0.38 g of **13** (40 %): mp 230-232 ℃; MS (EI$^+$) m/z 220 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 3.09 (d, 1H, J =

4.9 Hz), 3.43 and 3.51 (each s, each 3H), 6.23 (d, 1H, J = 5.8 Hz), 8.22 (d, 1H, J = 5.8 Hz), 8.90 (br, 1H). *Anal.* Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.28; H, 5.42; N, 25.54.

(b) A mixture of **12a** (0.20 g, 0.9 mmol) and methanolic methylamine (40 %, 2 mL) in DMF (20 mL) was heated in a seald tube at 100 ℃ for 1 h. After cooling, the resulting precipitates were filtered and recrystallized from EtOH to give 0.12 g of **13** (60 %), which was identical with the sample prepared above.

5,7-Dimethyl-2-phenyl-*s*-triazolo[2', 3'-1,2]pyrido[4,3-*d*]pyrimidine-4,6(5*H*, 7*H*)-dione (14) A mixture of **12d** (200 mg, 0.9 mmol) and benzaldehyde (100 mg, 0.94 mmol) in EtOH (30 mL) was refluxed for 30 min. The reaction solution was evaporated under reduced pressure and the residue was triturated with ether. The resulting precipitates were filtered and recrystallized from EtOH to give 70 mg of **14** (25 %): mp >300 ℃ (decomp); MS (EI$^+$) m/z 307 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 3.45 and 3.72 (each s, each 3H), 7.28 (d, 1H, J = 7.8 Hz), 7.55-7.74 (m, 3H), 8.26-8.38 (m, 2H), 9.32 (d, 1H, J = 7.8 Hz). *Anal.* Calcd for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.40; H, 4.34; N, 22.89.

5-Ethoxycarbonyl-6-(2-dimethylamino)vinyl-1,3-dimethyluracil (15) A mixture of 5-ethoxycarbonyl-1,3,6-trimethyluracil[7] (0.92 g, 4.1 mmol) and *N,N*-dimethylformamide dimethylacetal (0.58 g, 4.9 mmol) in DMF (40 mL) was heated at 90 ℃ for 25 h. The solvent was evaporated off, and the residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 50 : 1) and recrystallyzed from ligroine to give 0.38 g of **15** (33 %): mp 112-114 ℃; MS (EI$^+$) m/z 281 (M$^+$); ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.0 Hz), 2.93 (s, 6H), 3.33 and 3.44 (each s, each 3H), 4.31 (q, 2H, J = 7.0 Hz), 4.61 and 6.83 (each d, each 1H, J = 7.0 Hz). *Anal.* Calcd for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.25; H, 6.84; N, 14.98.

5-Hydroxy-1,3-dimethylpyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (16) (a) A mixture of **15** (150 mg, 0.53 mmol) and methanolic ammonia (40 %, 10 mL) was stirred at ambient temperature for 48 h. The resulting precipitates were filtered and recrystallized from water to give 30 mg of **16** (27 %): mp 233-235 ℃; MS (EI$^+$) m/z 207 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 3.23 and 3.48 (each s, each 3H), 6.41 and 7.78 (each d, each 1H, J = 8.0 Hz), 11.78 (br, 1H). *Anal.* Calcd for $C_9H_9N_3O_3 \cdot 1/2H_2O$: C, 50.00; H, 4.67; N, 19.44. Found: C, 49.89; H, 4.87; N, 19.23.

(b) To a stirring solution of **11** (0.27 g, 1.3 mmol) in AcOH (4.5 mL) and water (2.5 mL) was added $NaNO_2$ (1.00 g, 10.4 mmol) in water (5 mL) over 30 min. The reaction mixture was stirred at ambient

temperature for 4 h. The resulting precipitates were filtered off and the filtrate was evaporated under reduced pressure. The residue was triturated with water and recrystallized from EtOH to give 0.24 g of **16** (86 %), which was identical with the sample prepared above.

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