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Simple Syntheses of 1,3-Dialkylpyrrolo- and Furopyrimidines¹⁾

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Simple and efficient syntheses of 7-deazacaffeines, 9-deazatheophyllines, furo[2,3-*d*]pyrimidines and furo[3,2-*d*]pyrimidines from 5- or 6-substituted pyrimidines by means of intramolecular cyclization reactions are described.

Keywords—1,3-dialkylallylaminouracil; 1,3-dialkylpropargylaminouracil; furo[2,3-*d*]pyrimidine; furo[3,2-*d*]pyrimidine; pyrrolo[2,3-*d*]pyrimidine; pyrrolo[3,2-*d*]pyrimidine; palladium complex; thermal reaction; acid-catalyzed cyclization

As a part of our synthetic studies on heterocyclic compounds, we recently reported a new and convenient synthesis of 1,3-dialkylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones from 6-allylamino- and 6-(substituted allyl)aminouracils by using a palladium complex or by thermal cyclization.²⁾ Furthermore, we found that 5- or 6-substituted uracils undergo an acid-catalyzed cyclization reaction to give the substituted pyrrolo- and furopyrimidines in fairly good yields.¹⁾ In this report, we present additional information and complete experimental details of our work.

1,3-Dimethyl-5-(substituted allyl)aminouracils (**2a,c,d**) were prepared from the reaction of 5-bromo-1,3-dimethyluracil (**1**) and substituted allyl amines and were heated under reflux in tetralin to give the Claisen rearrangement products, 5-amino-1,3-dimethyl-6-(substituted allyl)uracils (**3a** and **3c**), and cyclization products (**4** and **5³⁾**), but **3d** was not obtained by this thermal reaction.

5-Amino-6-crotyl-1,3-dimethyluracil (**3b**) was directly prepared by reflux of **1** and α -methyl allylamine but **2b** was not isolated in this reaction. Cyclization products (**4**, **5** and **6**) were also prepared by the pyrolysis of **3a** or **3b** in tetralin in low yield. It is reasonable to suppose that the cyclization compounds were formed *via* intermediate (**3**) as shown in Chart 1.

1,3-Dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione derivatives were not obtained from 5-allylaminouracils (**2**) by using a palladium complex similar to that used for the preparation of 1,3-dimethylpyrido[2,3-*d*]pyrimidines from 6-(substituted allyl)aminouracils.²⁾

6-Chloro-1,3-dimethyluracil (**7**)⁴⁾ was warmed with sodium in allyl alcohol to give 6-allyloxy-1,3-dimethyluracil (**8**) which afforded the Claisen rearrangement product, 5-allyl-6-hydroxy-1,3-dimethyluracil (**9**), in 82.2% yield under reflux in dioxane and 1,3,6-trimethyl-5,6-dihydrofuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**10**) in 6.9% yield under reflux in dimethylformamide (DMF). The mass and nuclear magnetic resonance (NMR, ¹H and ¹³C) spectral data and elemental analysis were consistent with the indicated structure (**10**).

Heating of **9** in DMF under reflux gave **10** in low yield, while treatment of **9** in conc. H₂SO₄ at room temperature (method A) afforded the same dihydrofuro compound (**10**) in 74.4% yield (73.3% yield by reflux of **9** in 48% HBr solution; method B). On the other hand, an expected methyl ketone, 1,3-dimethyl-6-(2-oxo-propoxy)uracil (**11**), was obtained as the

Chart 1

only isolable product in low yield by the $\text{PdCl}_2\text{--CuCl--O}_2$ oxidation⁵⁾ of **8**.

5-Allyloxy-1,3-dimethyluracil (**12**)⁶⁾ was prepared from the reaction of 5-hydroxy-1,3-dimethyluracil⁷⁾ and allyl bromide and gave the Claisen rearrangement compound (**13**) on pyrolysis.⁶⁾ Acid treatment of **13** in the same manner as for **9** afforded the expected 1,3,6-trimethyl-6,7-dihydrofuro[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**15**) in 59.2% yield (78.4% yield by reflux of **13** in 48% HBr solution). This compound (**15**) was also obtained by similar acid treatment of **12** in low yield (3.7%) together with **13**.

Moreover, treatment of **13** with palladium (II) acetate or the $\text{PdCl}_2\text{--CuCl--O}_2$ combination gave the furopyrimidine (**16**)⁸⁾ in 11.1% and 6.1% yields, respectively. On the other hand, 1,3-dimethyl-5-(2-oxo-propoxy)uracil (**14**) was obtained from **12** in 9.6% yield by using the $\text{PdCl}_2\text{--CuCl--O}_2$ system.

The results of these reactions (Chart 2) show that the dihydrofuropyrimidines are easily prepared from 5- or 6-allyl-substituted hydroxyuracils (**9** and **13**) by means of the acid-catalyzed cyclization reactions. Next, we attempted to synthesize furopyrimidines, 7-deazacaffeines and 9-deazatheophyllines by the method described above and obtained satisfactory results.

By similar acid treatment (method A), 1,3-dialkyl-6-propargyloxyuracils (**17**, $\text{R}=\text{CH}_3$ or C_2H_5), prepared by the reaction of 1,3-dialkyl-6-chlorouracils (**7**) and propargyl alcohol, afforded the expected 1,3-dialkyl-5-methyl-furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones (**18**, $\text{R}=\text{CH}_3$ or C_2H_5) in 62.2% ($\text{R}=\text{CH}_3$) and 88.7% ($\text{R}=\text{C}_2\text{H}_5$) yields, respectively. The $^1\text{H-NMR}$ spectrum of this compound (**18**, $\text{R}=\text{CH}_3$) clearly indicated the presence of an aromatic proton (δ 7.00, 1H, s) and a methyl group on a furan ring (δ 2.26, 3H, s). The $^{13}\text{C-NMR}$ spectrum of **18** ($\text{R}=\text{CH}_3$) shows a signal due to aromatic carbon at δ 134.83 (doublet) and an aromatic methyl carbon at δ 8.82 (singlet). In the same way, 1,3-dimethyl-6(*N*-methyl-*N*-propargyl)aminouracil (**19**, $\text{R}^4=\text{CH}_3$), obtained by the reaction of **7** ($\text{R}=\text{CH}_3$) and *N*-methylpropargylamine, was treated with acid to give the desired 1,3,5,7-tetramethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**20**, $\text{R}=\text{CH}_3$; 9-methyl-7-deazacaffeine) in 77.5% yield. Furthermore, 7-deazacaffeine (**20**, $\text{R}=\text{H}$)⁹⁾ was also prepared by similar acid treatment of 1,3-dimethyl-6-propargylaminouracil (**19**, $\text{R}=\text{H}$) in 71.0% yield. The structural features of **20** are supported by the spectral data. This method for the preparation of alkylated furo[2,3-*d*]pyrimidines and pyrrolo[2,3-*d*]pyrimidines, described

Chart 2

Chart 3

herein, is quite simple and efficient.

Heating of **19** ($R^4 = H$) in DMF under reflux gave 1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**21**)²⁾ in 11.0% yield. However, treatment of **19** ($R^4 = CH_3$) in tetralin under reflux gave 1,3,6-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**22**)²⁾ in 38.0% yield and 7,8-dihydro-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**23**) in 12.2% yield. The structure of **23**, which is the expected cyclization product, was assigned on the basis of the spectral data. The formation of **22** shows that the methyl group migrates from the N_8 position to C_6 during the thermal reaction.

Treatment of 1,3-dimethyl-5-propargyloxyuracil (**24**), which was prepared from 5-hydroxy-1,3-dimethyluracil and propargyl bromide, in DMF under reflux gave the same results as reported by Fox *et al.*⁸⁾ The methyl ketone (**14**) was obtained by acid treatment (method A) of **24** in 57.5% yield.

1,3-Dimethyl-5-propargylaminouracil (**26**), prepared by the reaction of 5-amino-1,3-dimethyluracil (**25**) and propargyl bromide, afforded the desired 1,3,6-trimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**4**; 8-methyl-9-deazatheophylline) in 64.6% yield on reflux in DMF, but the starting material (**26**) was completely recovered after acid treatment in the same manner as described above. This compound (**4**) was also obtained by pyrolysis of **2a** in low yield.

The structure of **4** was elucidated on the basis of the spectral data. Moreover, treatment of **26** with palladium (II) acetate afforded 1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**27**) in 40.3% yield as shown in Chart 4.

Chart 4

Thus, several fused pyrimidines were easily prepared from 1,3-dialkyl-5-(or -6-) substituted uracils by the cyclization reactions described herein.

Experimental

All melting points were determined on a micro hot-stage apparatus (Mitamura, Tokyo) and are uncorrected. Infrared (IR) spectra ($\nu_{\max}$) in KBr disks were recorded on a Hitachi 215 infrared spectrophotometer and are

expressed in cm^{-1} . NMR spectra (^1H and ^{13}C) were measured on a JNM-FX 100 spectrometer (JEOL, Tokyo) at 100 MHz and chemical shifts are expressed relative to 1% tetramethylsilane (TMS) as an internal standard; s=singlet, d=doublet, t=triplet, br=broad and m=multiplet. Mass spectra (MS) were obtained on a GCMS-9000 spectrometer (Shimadzu, Tokyo) and a JMS-DX 300 instrument. Elemental analyses were done by the staff of the Analytical Center of the School of Pharmaceutical Sciences, Kitasato University (Tokyo), to whom our thanks are due. Thin-layer chromatography (TLC) was performed on Merck precoated Silica gel 60 F₂₅₄ plates.

Preparative TLC was done with the same commercial product, 20 × 20 cm, with a thickness of 0.25, 0.5 or 2.0 mm. All the chemicals used were of reagent grade, and were used without further purification.

General Procedure for the Synthesis of 1,3-Dimethyl-5-(substituted allyl)aminouracils (2c,d)—A gently stirred solution of 5-bromo-1,3-dimethyluracil and a substituted allylamine was refluxed for 5 h. The reaction mixture was concentrated *in vacuo*, then the residue was extracted with EtOAc or CH_2Cl_2 and the organic layer was washed with two portions (small amounts) of water and saturated aqueous NaCl, and dried over MgSO_4 . After removal of the solvent, the residue was purified by crystallization from an appropriate solvent.

1,3-Dimethyl-5-(β -methylallyl)aminouracil (2c)—According to the general procedure, the crude product was obtained from 1,3-dimethyl-5-bromouracil (**1**, 4.07 g) and β -methylallylamine (40 ml), and recrystallized from EtOAc-ether to give a pale yellow powder, mp 59–60 °C. Yield 2.15 g (55.2%). ^1H -NMR (CDCl_3) δ : 1.75 (3H, s, $-\text{CH}_3$), 3.36, 3.39 (each 3H, s, NCH_3), 3.51 (2H, s, br, NHCH_2-), 4.24 (1H, br, NH), 4.92 (2H, s, br, $\text{C}=\text{CH}_2$), 6.15 (1H, s, H-6). MS m/z : 209 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.39; H, 7.32; N, 20.38.

5-Crotylamino-1,3-dimethyluracil (2d)—According to the general procedure, the crude product was obtained from **1** (7.3 g) and crotylamine (48 ml), and recrystallized from EtOAc to give a colorless powder, mp 76–77 °C. Yield 4.41 g (61.9%). ^1H -NMR (CDCl_3) δ : 1.73 (3H, d, $J=6$ Hz, $=\text{CHCH}_3$), 3.38, 3.41 (each 3H, s, NCH_3), 3.48 (2H, br, $-\text{NHCH}_2$), 4.00 (1H, br, NH), 5.52–5.74 (2H, m, $-\text{CH}=\text{CH}-$), 6.08 (1H, s, H-6). MS m/z : 209 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.42; H, 7.29; N, 20.14.

5-Amino-6-crotyl-1,3-dimethyluracil (3b)—A solution of **1** (6.0 g) in α -methylallylamine (24 ml) was refluxed overnight. The reaction mixture was concentrated *in vacuo*, then the residue was extracted with EtOAc and the organic layer was washed with saturated aqueous NaCl, and dried over MgSO_4 . After removal of the solvent, the residue was crystallized from ether and purified by recrystallization from EtOAc to give a white powder mp 101 °C. Yield 1.82 g (31.7%). ^1H -NMR (CDCl_3) δ : 1.70 (3H, s, $-\text{CH}_3$), 3.30 (2H, br, $\text{C}-\text{CH}_3$), 2.46–3.20 (2H, br, NH_2), 3.42 (6H, s, $2 \times \text{NCH}_3$), 5.48 (2H, dd, $J=4$ Hz, $-\text{CH}=\text{CH}-$). ^{13}C -NMR (CDCl_3) δ : 17.79 (q), 28.51 (q), 30.51 (t), 31.67 (q), 118.95 (s), 122.90 (d), 128.16 (d), 131.81 (s), 150.72 (s), 160.37 (s). MS m/z : 209 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.12; H, 7.25; N, 19.80.

Thermal Reaction of 2a⁶—A solution of **2a** (1.00 g) in tetralin (10.0 ml) was refluxed for 48 h under a nitrogen atmosphere. Then CH_2Cl_2 (10 ml) was added, and the mixture was extracted with 0.01 N aqueous HCl. The extract was neutralized with 20% aqueous NaOH, and extracted with CHCl_3 . The CHCl_3 layer was washed with water, dried over anhydrous MgSO_4 , and evaporated *in vacuo*. The residue was purified by silica gel column chromatography with benzene-ether as an eluent to give **3a** (0.0368 g, 3.6%, colorless solid)⁶ and **4** (0.07 g, 7.1%, mp 279–280 °C). The spectral and analytical data for **4** are described later.

Thermal Reaction of 2c—A solution of **2c** (0.50 g) in tetralin (5.0 ml) was refluxed for 12 h under a nitrogen atmosphere. The procedure described in the case of the thermal reaction of **2a** yielded a crude product, which was purified by preparative TLC (EtOAc) to give pale yellow needles (**3c**), mp 80–81 °C (from ether). Yield 0.10 g (20%). ^1H -NMR (CDCl_3) δ : 1.86 (3H, s, $-\text{CH}_3$), 3.30 (4H, m, $-\text{CH}_2-$ and NH_2), 3.37, 3.42 (each 3H, s, NCH_3), 4.64 and 4.90 (2H, $=\text{CH}_2$). MS m/z : 209 (M^+). The high-resolution MS showed m/z : 209.11806 (Calcd 209.11646). Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.72; H, 7.25; N, 19.93.

Thermal Reaction of 2d—A solution of **2d** (2.0 g) in tetralin (20 ml) was refluxed for 8 d under a nitrogen atmosphere. The procedure described in the case of the thermal reaction of **2a** yielded a crude product, which was purified by recrystallization from EtOAc to give colorless plates (**5**), mp 249–251 °C (lit.³) mp 248 °C. Yield 0.4025 g (20.5%). ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.54 (3H, s, $\text{C}-\text{CH}_3$), 3.31, 3.48 (each 3H, s, $2 \times \text{NCH}_3$), 7.62 (1H, d, $J=8.6$ Hz, $=\text{CH}$), 7.87 (1H, d, $J=8.6$ Hz). This compound (**5**) was shown to be identical with an authentic sample prepared from 5-amino-1,3-dimethyluracil and crotonaldehyde.³

Thermal Reaction of 3b—A solution of **3b** (0.50 g) in tetralin (5.0 ml) was refluxed for 50 h under a nitrogen atmosphere. The procedure described in the case of the thermal reaction of **2a** yielded a crude solid, which was filtered off and recrystallized from MeOH to give **5** (1.7 mg). On the other hand, the mother liquor was purified by preparative TLC (benzene: EtOAc = 1 : 1) to give a white powder **6**, mp 247 °C (from EtOAc). Yield 0.051 g (10.5%). ^1H -NMR (CDCl_3) δ : 1.34 (3H, t, $J=7.7$ Hz, $\text{C}-\text{CH}_3$), 2.74 (2H, q, $J=7.7$ Hz, $-\text{CH}_2-$), 3.46, 3.49 (each 3H, s, $2 \times \text{NCH}_3$), 5.77 (1H, s, $=\text{CH}$), 11.42 (1H, br, $-\text{NH}$). ^{13}C -NMR (CDCl_3) δ : 13.45 (q), 21.49 (t), 27.92 (q), 32.06 (q), 92.25 (d), 109.30 (s), 136.54 (s), 145.46 (s), 151.74 (s), 155.69 (s). MS m/z : 207 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.84; H, 6.13; N, 20.26.

Thermal Reaction of 3a⁶—A solution of **3a** (35.9 mg) in tetralin (2.0 ml) was refluxed for 22 h under a nitrogen atmosphere. The procedure described in the case of the thermal reaction of **2a** yielded a crude product, which was

purified by recrystallization from MeOH to give **4** (6.1 mg).

6-Allyloxy-1,3-dimethyluracil (8)—6-Chloro-1,3-dimethyluracil (5.22 g) was added to allyl alcohol (30 ml) containing 1.5 g of sodium. The solution was heated at 30–40 °C under a nitrogen atmosphere with stirring for 30 min, then cooled and evaporated *in vacuo*. The residue was partitioned between water and EtOAc, and the organic layer was dried over MgSO₄. After removal of the solvent, the crystals that resulted were washed with ether and recrystallized from CH₂Cl₂–ether to give white needles, mp 124–125 °C. Yield 3.35 g (57.2%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1710, 1650, 1620. MS m/z : 196 (M⁺). ¹H-NMR (CDCl₃) δ : 3.32 (3H, s, NCH₃), 3.38 (3H, s, NCH₃), 4.56 (2H, d, J = 5.4 Hz), 5.12 (1H, s, =CH–), 5.36–5.52 (2H, m, =CH₂), 5.80–6.22 (1H, m, =CH–). ¹³C-NMR (CDCl₃) δ : 27.78 (q), 28.80 (q), 70.56 (t), 78.50 (d), 119.88 (t), 130.11 (d), 151.26 (s), 160.12 (s), 163.05 (s). Anal. Calcd for C₉H₁₂N₂O₃: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.43; H, 6.16; N, 14.34.

Thermal Reaction of 8—1) A solution of **8** (1.0 g) in dioxane (80 ml) was stirred at 100 °C for 4 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and purified by preparative TLC (EtOAc: MeOH = 4:1). The solid was filtered off and recrystallized from CH₂Cl₂–ether to give white needles (**9**), mp 55–60 °C. Yield 0.822 g (82.2%). Further purification of this compound could not be achieved because of its lability. IR $\nu_{\text{max}}^{\text{KBr}}$: 3375, 1680, 1440. ¹H-NMR (CDCl₃) δ : 2.67 (2H, d, J = 7.32 Hz, –CH₂–), 3.29 (6H, s, 2 × NCH₃), 4.01 (1H, br, OH), 5.04–5.25 (2H, m, =CH₂), 5.43–5.50 (1H, m, =CH–). ¹³C-NMR (CDCl₃) δ : 28.80 (q), 46.68 (t), 75.97 (s), 121.92 (t), 128.35 (d), 150.68 (s), 169.97 (s). MS m/z : 196 (M⁺). The high-resolution MS showed m/z 196.08550 (Calcd 196.08480).

2) A solution of **8** (0.5 g) in DMF (20 ml) was heated at 150 °C with stirring overnight under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and purified by preparative TLC (EtOAc: MeOH = 4:1) to give **10** (0.035 g, 6.9%).

Thermal Reaction of 9—A solution of **9** (0.82 g) in DMF (20 ml) was stirred at 130–140 °C for 5 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and purified by preparative TLC (EtOAc) to give **10** (0.040 g, 4.8%).

1,3,6-Trimethyl-5,6-dihydrofuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (10)—Method A: A solution of **9** (0.8 g) in conc. H₂SO₄ (20 ml) was stirred at room temperature for 4 d. After neutralization with aqueous NH₃, the reaction mixture was extracted with CH₂Cl₂. The extract was washed with H₂O and dried over MgSO₄. After removal of the solvent, the residue was recrystallized from CH₂Cl₂–ether to give white prisms, mp 85–87 °C. Yield 0.595 g (74.4%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1700, 1620. ¹H-NMR (CDCl₃) δ : 1.53 (3H, d, J = 6.1 Hz, C–CH₃), 2.17 (1H, dd, J = 13.43 Hz, –CH₂–), 2.68 (1H, dd, J = 13.43 Hz, –CH₂–), 3.31, 3.33 (each 3H, s, 2 × NCH₃), 5.00–5.20 (1H, m, –CH–). ¹³C-NMR (CDCl₃) δ : 21.39 (q), 27.34 (q), 28.99 (q), 32.80 (t), 84.01 (d), 85.23 (s), 151.11 (s), 159.78 (s), 161.01 (s). MS m/z : 196 (M⁺). Anal. Calcd for C₉H₁₂N₂O₃: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.29; H, 6.13; N, 14.44.

Method B: A solution of **9** (0.386 g) in 48% HBr (20 ml) was heated at 80 °C for 20 min. The reaction mixture was poured into ice-H₂O, neutralized with aqueous NH₃, and extracted with CH₂Cl₂. The organic solution was dried over MgSO₄ and evaporated to dryness. The solid that resulted was recrystallized from CH₂Cl₂–ether to give **10** (0.285 g, 73.3%).

1,3-Dimethyl-6-(2-oxo-propoxy)uracil (11)—A mixture of CuCl (0.5 g) and PdCl₂ (0.18 g) in DMF (5.0 ml) and H₂O (0.6 ml) was stirred under a stream of oxygen at room temperature for 3 h. Compound **8** (0.99 g) was added and the mixture was stirred under oxygen for 1 h at 80–90 °C. The reaction mixture was evaporated to dryness and the residue was extracted with CHCl₃. Evaporation of the organic layer gave a crude mixture, which was isolated by column chromatography. The major product (0.029 g) eluted with ether–benzene (2:8) was recrystallized from EtOAc to give white needles, mp 124–125 °C. Yield 0.0196 g (1.84%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1680, 1610, 1460. ¹H-NMR (CDCl₃) δ : 2.32 (3H, s, COCH₃), 3.37, 3.48 (each 3H, s, 2 × NCH₃), 4.71 (2H, s, –CH₂–), 5.01 (1H, s, =CH–). ¹³C-NMR (CDCl₃) δ : 26.30 (q), 27.95 (q), 29.12 (q), 72.80 (t), 78.73 (d), 151.18 (s), 159.69 (s), 162.86 (s), 199.26 (s). MS m/z : 212 (M⁺). Anal. Calcd for C₉H₁₂N₂O₄: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.80; H, 5.85; N, 13.16.

Pd (II) Oxidation of 12⁶⁾—A mixture of CuCl (0.5 g) and PdCl₂ (0.18 g) in DMF (5.0 ml) and H₂O (0.6 ml) was stirred in a stream of oxygen at room temperature for 3 h. A solution of **12** (0.495 g) in DMF (6 ml) was added and the mixture was stirred under oxygen for 10 min at 80–90 °C, then evaporated *in vacuo*. The residue was extracted with CH₂Cl₂ and evaporation of the CH₂Cl₂ gave a crude product, which was separated by preparative TLC (EtOAc: benzene = 1:1). The major product was recrystallized from CH₂Cl₂–ether to give white needles (**14**), mp 100–101 °C. Yield 0.051 g (9.6%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1735, 1640, 1460. ¹H-NMR (CDCl₃) δ : 2.19 (3H, s, COCH₃), 3.35, 3.38 (each 3H, s, NCH₃), 4.62 (2H, s, –CH₂–), 7.23 (1H, s, =CH–). ¹³C-NMR (CDCl₃) δ : 26.18 (q), 28.24 (q), 37.05 (q), 75.85 (t), 132.04 (d), 132.98 (s), 150.53 (s), 160.16 (s), 204.55 (s). MS m/z : 212 (M⁺). Anal. Calcd for C₉H₁₂N₂O₄: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.00; H, 5.70; N, 13.16. The Pd (II) acetate oxidation of **13** in AcOH at room temperature afforded **15** in 9.1% yield.

Pd (II) Oxidation of 13⁶⁾—Palladium (II) acetate (0.112 g) was added to a solution of **14** (0.098 g) in AcOH (10 ml). The reaction mixture was heated at 80 °C for 10 min with stirring under a nitrogen atmosphere. The reaction mixture was poured into ice-H₂O and neutralized with 20% aqueous NaOH, then extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried over MgSO₄ and evaporated *in vacuo*. The resulting products were separated by preparative TLC (EtOAc: benzene = 1:1) and the major product was recrystallized from EtOH to give

16 [10.8 mg, 11.1%, mp 212–213 °C (lit.⁸) mp 210–211 °C]. This compound (**16**) was also obtained by PdCl₂–CuCl–O₂-catalyzed oxidative cyclization in 6.1% yield.

1,3,6-Trimethyl-6,7-dihydrofuro[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (15): Acid Treatment of 12 or 13—1) According to the general procedure (method A, stirring at room temperature (r.t.) for 2 d), the crude product was obtained from a solution of **13** (98 mg) in conc. H₂SO₄ (10 ml), and recrystallized from CH₂Cl₂–ether to give white needles, mp 139–141 °C. Yield 58 mg (59.2%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1705, 1680. ¹H-NMR (CDCl₃) δ : 1.52 (3H, d, *J* = 5.86 Hz, C–CH₃), 2.83 (1H, dd, *J* = 16.60 Hz, –CH₂–), 3.36 (1H, dd, *J* = 16.60 Hz, –CH₂–), 3.35, 3.37 (each 3H, s, 2 × NCH₃), 4.80–5.20 (1H, m, –CH₂–). ¹³C-NMR (CDCl₃) δ : 21.68 (q), 28.36 (q), 33.19 (q), 37.18 (t), 78.31 (d), 132.35 (s), 134.11 (s), 151.35 (s), 155.40 (s). MS *m/z*: 196 (M⁺). Anal. Calcd for C₉H₁₂N₂O₃: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.04; H, 5.99; N, 14.03.

2) According to the general procedure (method B, stirring at 100 °C for 5 h), the crude product was obtained from a solution of **13** (0.3 g) in 47% HBr (20 ml), and separated by preparative TLC (EtOAc: benzene = 1 : 1). The major product was recrystallized from CH₂Cl₂–ether to give **15** (0.151 g, 78.4%).

3) According to the general procedure (method B, stirring at 80 °C for 1 h), the crude product was obtained from a solution of **12** (0.2 g) in 47% HBr (20 ml) and separated by preparative TLC (EtOAc: benzene = 1 : 1). After recrystallization, **15** (7.4 mg, 3.7%) and **14** (35.4 mg, 17.7%) were obtained.

1,3-Dimethyl-6-(2-propynyloxy)uracil (17, R = Me)—6-Chloro-1,3-dimethyluracil (**7**, R = Me, 5.22 g) was added to propargyl alcohol (30 ml) containing 1.5 g of sodium under a nitrogen atmosphere. The solution was stirred at room temperature for 30 min, and evaporated *in vacuo*. The residue was partitioned between H₂O and CH₂Cl₂, and the CH₂Cl₂ solution was dried over MgSO₄. After removal of the solvent, the crystals that resulted were washed with ether and recrystallized from CH₂Cl₂–isopropyl ether to give white needles, mp 150–151 °C. Yield 4.18 g (72.0%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1700, 1660, 1620. ¹H-NMR (CDCl₃) δ : 2.69 (1H, t, *J* = 3.6 Hz, $\equiv$ CH), 3.36, 3.39 (each 3H, s, 2 × NCH₃), 4.76 (2H, d, *J* = 3.2 Hz, –CH₂–), 5.26 (1H, s, =CH–). ¹³C-NMR (CDCl₃) δ : 27.92 (q), 28.88 (q), 57.60 (t), 75.19 (d), 78.36 (d), 79.09 (d), 151.21 (s), 159.49 (s), 162.85 (s). MS *m/z*: 194 (M⁺). Anal. Calcd for C₉H₁₀N₂O₃: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.60; H, 5.20; N, 14.55.

1,3-Diethyl-6-(2-propynyloxy)uracil (17, R = Et)—According to the method used in the synthesis of 1,3-dimethyl-6-(2-propynyloxy)uracil (**17**, R = Me), the crude product was obtained from 6-chloro-1,3-diethyluracil (**7**, R = Et, 4.05 g) and propargyl alcohol (40 ml), and recrystallized from CH₂Cl₂–isopropyl ether to give colorless needles, mp 102–103 °C. Yield 1.787 g (68.8%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1640, 1470, 1435. ¹H-NMR (CDCl₃) δ : 1.22 (3H, t, *J* = 7.08 Hz, C–CH₃), 1.24 (3H, t, *J* = 7.08 Hz, C–CH₃), 2.72 (1H, t, *J* = 2.2 Hz, $\equiv$ CH), 3.97 (4H, q, *J* = 7.08 Hz, 2 × –CH₂–), 4.75 (2H, d, *J* = 2.2 Hz, O–CH₂–), 5.22 (1H, s, =CH–). ¹³C-NMR (CDCl₃) δ : 12.96 (q), 13.84 (q), 36.30 (t), 37.72 (t), 57.45 (t), 75.34 (d), 78.31 (d), 79.33 (d), 150.43 (s), 159.35 (s), 162.57 (s). MS *m/z*: 222 (M⁺). Anal. Calcd for C₁₁H₁₄N₂O₃: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.20; H, 6.35; N, 12.67.

1,3,5-Trimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (18, R = Me). Acid Treatment of 17 (R = Me)—According to the general procedure (method A, stirring at r.t. for 2 d), the crude product was obtained from a solution of **17** (R = Me, 0.7 g) in conc. H₂SO₄ (20 ml), and recrystallized from CH₂Cl₂–ether to give white needles (**18**, R = Me), mp 143–144 °C. Yield 0.446 g (62.2%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1660, 1520, 1420. ¹H-NMR (CDCl₃) δ : 2.26 (3H, d, *J* = 1.22 Hz, C–CH₃), 3.39, 3.53 (each 3H, s, 2 × NCH₃), 7.00 (1H, d, *J* = 1.22 Hz, =CH–). ¹³C-NMR (CDCl₃) δ : 8.82 (q), 27.97 (q), 29.19 (q), 97.02 (s), 119.97 (s), 134.83 (d), 150.68 (s), 155.49 (s), 158.86 (s). MS *m/z*: 194 (M⁺). Anal. Calcd for C₉H₁₀N₂O₃: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.92; H, 5.06; N, 14.22.

1,3-Diethyl-5-methylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (18, R = Et). Acid Treatment of 17 (R = Et)—According to the general procedure (method A, stirring at r.t. for 2 weeks), the crude product was obtained from a solution of **17** (R = Et, 0.666 g) in conc. H₂SO₄ (20 ml), and recrystallized from ether–*n*-hexane to give white needles (**18**, R = Et), mp 83–84 °C. Yield 0.59 g (88.7%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1690, 1650, 1520. ¹H-NMR (CDCl₃) δ : 1.24 (3H, t, *J* = 7.08 Hz, C–CH₃), 1.35 (3H, t, *J* = 7.08 Hz, C–CH₃), 2.26 (3H, d, *J* = 1.47 Hz, C–CH₃), 4.05 (2H, q, *J* = 7.08 Hz, –CH₂–), 4.07 (2H, q, *J* = 7.08 Hz, –CH₂–), 6.97 (1H, d, *J* = 1.47 Hz, =CH–). ¹³C-NMR (CDCl₃) δ : 8.87 (q), 13.21 (q), 13.74 (q), 36.50 (t), 38.40 (t), 97.31 (s), 119.97 (s), 134.78 (d), 149.84 (s), 155.40 (s), 158.71 (s). MS *m/z*: 222 (M⁺). Anal. Calcd for C₁₁H₁₄N₂O₃: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.74; H, 6.27; N, 12.55.

1,3-Dimethyl-6-propargylaminouracil (19, R⁴ = H)—A solution of 1,3-dimethyl-6-chlorouracil (**7**, R = Me, 5.0 g) in propargylamine (40 ml) was stirred at room temperature. A solid was gradually deposited from the reaction mixture. The pale yellow crystals that appeared in the reaction flask were collected and washed with a solution of ether and MeOH (4 : 1). The crude product was recrystallized from MeOH to give white needles, mp 225–227 °C. Yield 4.37 g (79.0%). IR $\nu_{\text{max}}^{\text{KBr}}$: 3260, 1690, 1600, 1460. ¹H-NMR (DMSO-*d*₆) δ : 2.50 (1H, br, $\equiv$ CH), 3.13, 3.26 (each 3H, s, 2 × NCH₃), 3.89 (2H, br, –CH₂–), 4.77 (1H, s, =CH–), 7.24 (1H, s, NH). ¹³C-NMR (DMSO-*d*₆) δ : 27.24 (q), 29.34 (q), 31.67 (t), 74.36 (d), 74.90 (d), 79.77 (d), 151.40 (s), 152.91 (s), 161.64 (s). MS *m/z*: 193 (M⁺). Anal. Calcd for C₉H₁₁N₃O₂: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.82; H, 5.71; N, 21.90.

1,3-Dimethyl-6-(*N*-methyl-*N*-propargyl)aminouracil (19, R⁴ = Me)—A solution of 1,3-dimethyl-6-chlorouracil (**7**, R = Me, 4.0 g) in *N*-methylpropargylamine (25 ml) was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* to leave a crystalline solid, which was recrystallized from EtOH–ether to give pale yellow plates, mp 112–113 °C. Yield 4.16 g (87.7%). ¹H-NMR (CDCl₃) δ : 2.52 (2H, t, *J* = 2.2 Hz, $\equiv$ CH), 2.82, 3.29 and 3.41

(each 3H, s, $3 \times \text{NCH}_3$), 3.79 (2H, d, $J=2.2$ Hz, $-\text{CH}_2-$), 5.38 (1H, s, $=\text{CH}-$). ^{13}C -NMR (CDCl_3) δ : 27.68 (q), 33.09 (q), 38.79 (q), 43.37 (t), 74.90 (d), 76.65 (d), 88.64 (d), 152.82 (s), 158.52 (s), 162.81 (s). MS m/z : 207 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.90; H, 6.22; N, 19.99.

1,3,5,7-Tetramethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (20, $\text{R}^4=\text{Me}$). Acid Treatment of 19 ($\text{R}^4=\text{Me}$)—According to the general procedure (method A, stirring at r.t. for 1 d), the crude product was obtained from a solution of 19 ($\text{R}^4=\text{Me}$, 0.4 g) in conc. H_2SO_4 (20 ml), and recrystallized from CHCl_3 -ether to give colorless needles (20, $\text{R}^4=\text{Me}$), mp 224–225 °C. Yield 0.388 g (77.5%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1680, 1640, 1580, 1540. ^1H -NMR (CDCl_3) δ : 2.27 (3H, s, $\text{C}-\text{CH}_3$), 3.36, 3.74 (each 3H, s, $2 \times \text{NCH}_3$), 3.81 (3H, s, NCH_3), 6.10 (1H, s, $=\text{CH}-$). ^{13}C -NMR (CDCl_3) δ : 10.77 (q), 27.92 (q), 31.97 (q), 36.00 (q), 100.97 (s), 116.42 (s), 120.66 (d), 137.76 (s), 152.04 (s), 159.54 (s). MS m/z : 207 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.01; H, 6.27; N, 20.29.

1,3,5-Trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (7-Deazacaffeine, 20, $\text{R}^4=\text{H}$). Acid Treatment of 19 ($\text{R}^4=\text{H}$)—According to the general procedure (method A, stirring at r.t. for 1 d), the crude product was obtained from a solution of 19 ($\text{R}^4=\text{H}$, 0.3 g) in conc. H_2SO_4 (5 ml), and recrystallized from MeOH to give a white powder (20, $\text{R}^4=\text{H}$), mp > 300 °C. Yield 0.251 g (71.0%). IR $\nu_{\text{max}}^{\text{KBr}}$: 3150, 1680, 1620, 1540, 1430. ^1H -NMR ($\text{DMSO}-d_6$) δ : 2.18 (3H, s, $\text{C}-\text{CH}_3$), 3.19, 3.39 (each 3H, s, $2 \times \text{NCH}_3$), 6.50 (1H, s, $-\text{CH}=\text{N}-$), 11.36 (1H, br, NH). ^{13}C -NMR ($\text{DMSO}-d_6$) δ : 10.96 (q), 27.29 (q), 30.16 (q), 97.61 (s), 113.69 (d), 115.30 (s), 138.73 (s), 150.72 (s), 158.91 (s). MS m/z : 193 (M^+). Anal. Calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.11; H, 5.66; N, 21.85.

Thermal Reaction of 19 ($\text{R}^4=\text{H}$)—A solution of 19 ($\text{R}^4=\text{H}$, 0.6 g) in DMF (20 ml) was stirred at 110 °C overnight under a nitrogen atmosphere. The reaction mixture was evaporated to dryness *in vacuo* and the major product was isolated by preparative TLC (EtOAc) and recrystallized from MeOH to give 21 [0.066 g, 11.0%, mp 164–165 °C (lit.²¹) mp 164–164.5 °C].

Thermal Reaction of 19 ($\text{R}^4=\text{Me}$)—A solution of 19 ($\text{R}^4=\text{Me}$, 0.6 g) in tetralin (20 ml) was stirred at 200 °C for 5 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness *in vacuo* and the products were purified by preparative TLC (EtOAc) and recrystallized from MeOH to give 22 [0.225 g, 38.0%, mp 161–162 °C (lit.²¹) mp 159 °C], and 23 (0.073 g, 12.2%, mp 107–114 °C. Recrystallized from CH_2Cl_2 -ether), ^1H -NMR (CDCl_3) δ : 2.73, 3.36 and 3.42 (each 3H, s, $3 \times \text{NCH}_3$), 3.79 (2H, dd, $J=4.1$ Hz, $-\text{CH}_2-$), 5.40 (1H, m, $J=9$ and 4.1 Hz, $=\text{CH}-$), 6.63 (1H, d, $J=9$ Hz, $=\text{CH}-$). MS m/z : 207 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2$: C, 57.94; H, 6.32; N, 20.28. Found: C, 58.24; H, 6.35; N, 19.16. The high-resolution MS showed m/z 207.09870 (Calcd 207.10070).

Acid Treatment of 24⁸⁾—According to the general procedure (method A, stirring at r.t. for 3 d), the crude product was obtained from a solution of 24 (0.1 g) in conc. H_2SO_4 (10 ml), and recrystallized from CH_2Cl_2 -ether to give white needles (14, 0.063 g, 57.5%, mp 100–101 °C).

1,3-Dimethyl-5-propargylaminouracil (26)—Propargyl bromide (1.0 ml) was added to a solution of 1,3-dimethyl-5-aminouracil (25, 1.0 g) in MeOH (10 ml) and CH_2Cl_2 (10 ml). The reaction mixture was stirred at room temperature overnight, and evaporated to dryness *in vacuo*. The residue was purified by preparative TLC (EtOAc) and the crystalline product was recrystallized from EtOAc to give white needles, mp 140–142 °C. Yield 0.52 g (41.0%). IR $\nu_{\text{max}}^{\text{KBr}}$: 3350, 1620, 1410. ^1H -NMR (CDCl_3) δ : 2.30 (1H, t, $J=2.44$ Hz, $\equiv\text{CH}$), 3.39, 3.41 (each 3H, s, $2 \times \text{NCH}_3$), 3.84 (2H, d, $J=2.44$ Hz, $-\text{CH}_2-$), 4.25 (1H, br, NH), 6.41 (1H, s, $=\text{CH}-$). ^{13}C -NMR (CDCl_3) δ : 28.26 (q), 33.53 (t), 36.94 (q), 72.17 (d), 79.48 (d), 117.49 (d), 122.95 (s), 149.79 (s), 160.62 (s). MS m/z : 193 (M^+). Anal. Calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.89; H, 5.71; N, 21.53.

1,3,6-Trimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (8-Methyl-9-deazatheophylline, 4)—A solution of 26 (0.61 g) in DMF (20 ml) was refluxed for 40 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness *in vacuo* to leave crystals, which were recrystallized from MeOH to give yellow plates, mp 279–280 °C. Yield 0.498 g (64.6%). IR $\nu_{\text{max}}^{\text{KBr}}$: 3170, 1685, 1630, 1560, 1520. ^1H -NMR (CDCl_3) δ : 2.44 (3H, s, $\text{C}-\text{CH}_3$), 3.46 (6H, s, $2 \times \text{NCH}_3$), 5.75 (1H, s, $=\text{CH}-$), 11.60 (1H, br, NH). ^{13}C -NMR (CDCl_3) δ : 13.50 (q), 27.92 (q), 32.64 (q), 93.61 (d), 109.25 (s), 136.73 (s), 139.42 (s), 151.70 (s), 155.64 (s). MS m/z : 193 (M^+). Anal. Calcd for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.86; H, 5.78; N, 21.93.

1,3-Dimethylpyrido[3,2-*d*]pyrimidine (27)—Palladium (II) acetate (0.112 g) was added to a solution of 26 (0.0965 g) in AcOH (21 ml). The reaction mixture was stirred at room temperature overnight under a nitrogen atmosphere. Distilled water was added to the reaction mixture, and the resulting solution was neutralized with 20% aqueous NaOH, then extracted with CHCl_3 . The CHCl_3 extract was dried over MgSO_4 and evaporated *in vacuo*. The residue was separated by preparative TLC (EtOAc: MeOH = 4:1) and the major product was recrystallized from CHCl_3 -ether to give white needles, mp 240–241 °C. Yield 0.0504 g (40.3%). IR $\nu_{\text{max}}^{\text{KBr}}$: 1700, 1650, 1575. ^1H -NMR (CDCl_3) δ : 3.55, 3.63 (each 3H, s, $2 \times \text{NCH}_3$), 7.62 (1H, s, $=\text{CH}-$), 7.64 (1H, s, $=\text{CH}-$), 8.65 (1H, dd, $J=3.6$ Hz and $J=3.6$ Hz, $-\text{N}=\text{CH}-$). MS m/z : 191 (M^+). Anal. Calcd for $\text{C}_9\text{H}_9\text{N}_3\text{O}_3$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.26; H, 4.73; N, 21.77.

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