

SIMPLE SYNTHESSES OF PYRROLO- AND FUROPYRIMIDINE DERIVATIVES<sup>1</sup>

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**Abstract** — Simple and efficient syntheses of furo[2,3-d]-pyrimidine-2,4-diones, 7-deazacaffeines and dihydrofuro-pyrimidine-2,4-diones from 5- or 6-substituted pyrimidines by acid catalyzed cyclization reactions are described.

As part of our work directed toward the synthesis of fused pyrimidine derivatives having biological activity, we have recently described a new synthesis of pyrido[2,3-d]pyrimidines by the oxidative cyclization with the PdCl<sub>2</sub>-CuCl-O<sub>2</sub> system in aqueous DMF of various 6-allylaminouracils.<sup>2</sup> As an extension of these studies, we wish to report here facile synthetic routes to the substituted pyrrolo- and furo-pyrimidines by acid catalyzed intramolecular cyclization reactions of 5- or 6-substituted pyrimidines.

1,3-Dimethyl-6-chlorouracil (1, R = Me) was stirred with sodium in propargyl alcohol for 2 h by warming and the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> followed by evaporation under a reduced pressure gave 1,3-dimethyl-6(2-propynyloxy)uracil (2a, mp 150-151°C)<sup>3</sup> in 80% yield. Similarly, treatment of 1 (R = Et) under the same conditions described above led to the formation of the 1,3-diethyl-6(2-propynyloxy)uracil (2b, mp 102-103°C)<sup>3</sup> in 56.7% yield.

A solution of 2a in conc. H<sub>2</sub>SO<sub>4</sub> was allowed to stand at room temperature for 2 days. After neutralization with aqueous ammonia, the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and evaporation of the solvent provided a crystalline compound (3a, mp 143-144°C)<sup>4</sup> in 87% yield. This product has an empirical formula C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub> which was derived from elemental and mass spectral analyses. <sup>1</sup>H NMR

spectrum of 3a has a signal at  $\delta$  7.00 (s, 1H) which can be attributable to an aromatic proton and a signal at  $\delta$  2.26 (s, 3H) which can be assigned to methyl protons on a furan ring. In  $^{13}\text{C}$  NMR spectrum, signals at  $\delta$  8.82 (s, aromatic methyl carbon) and at  $\delta$  134.83 (d, aromatic carbon) are appeared. From these data, the compound (3a) was assigned to be 1,3,5-trimethylfuro[2,3-d]pyrimidine-2,4[1H,3H]-dione.<sup>5</sup> When 2b was treated in a similar manner, a compound (3b, mp 83-84°C) was obtained in 88.7% yield.<sup>6</sup>

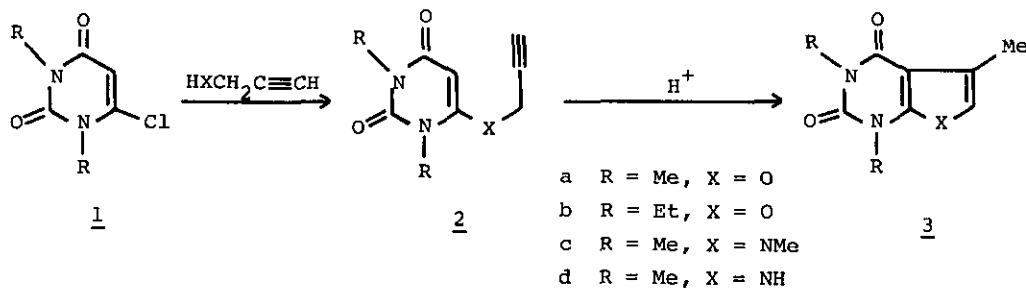


Chart 1

Furthermore, 1,3-dimethyl-6-(N-methyl-N-propargyl)aminouracil (2c, mp 112-113°C), obtained from the reaction of 1 (R = Me) with N-methylpropargylamine in 95% yield, was treated by acid in a manner described above to give desired 1,3,5,7-tetramethylpyrrolo[2,3-d]pyrimidine-2,4[1H,3H]-dione (3c, mp 224-225°C; 9-methyl-7-deazacaffeine) in 96.9% yield.<sup>7</sup> 7-Deazacaffeine (3d, mp >300°C) was also prepared by acid treatment of 1,3-dimethyl-6-propargylaminouracil (2d, mp 225-227°C) in 85.8% yield.<sup>7</sup> This method for preparation of alkylated furo[2,3-d]pyrimidines and pyrrolo[2,3-d]pyrimidines described herein is quite simple and efficient.

We have subsequently investigated this convenient intramolecular cyclization reaction with alkylated 5- and 6-allylpyrimidines.

1,3-Dimethyl-6-chlorouracil (1, R = Me) was allowed to warm with sodium in allyl alcohol for 2 h and after addition of  $\text{H}_2\text{O}$ , the reaction mixture was extracted with ethyl acetate. Evaporation of the solvent gave 6-allyloxy-1,3-dimethyluracil (4, mp 124-125°C) in 63.3% yield. The Claisen rearrangement product (5, mp 55-60°C), prepared by heating of a solution of 4 in dioxane in 64.4% yield,<sup>8</sup> was subjected to acid treatment in a same manner as above to give 6.

A crystalline compound (6, mp 85-87°C) was obtained as the only isolable product in 74.0% yield:  $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3$ ; MS  $m/e = 196$  ( $\text{M}^+$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.53 (3H, d,  $J = 6.10\text{Hz}$ , C- $\text{CH}_3$ ), 2.58-2.79 (1H, m,  $-\overset{5}{\text{C}}\text{H}_2-$ ), 3.12-3.33 (1H, m,  $-\overset{5}{\text{C}}\text{H}_2-$ ), 3.31 (6H, s, N- $\text{CH}_3$ ), 5.00-5.20 (1H, m, O-CH-Me);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.39 (q, C- $\text{CH}_3$ ), 27.37 (q,

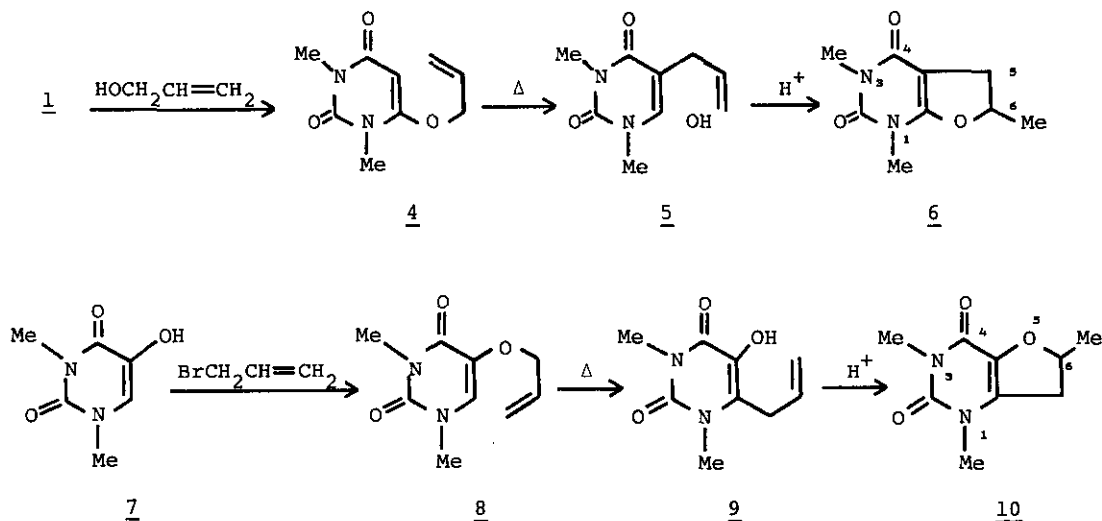


Chart 2

$\text{N-CH}_3$ ), 28.99 (q,  $\text{N-CH}_3$ ), 32.80 (t,  $-\text{CH}_2-$ ), 84.01 (d,  $-\text{CHMe}$ ), 151.11 (s), 159.78 (s), and 161.01 (s);  $\nu_{\text{KBr}}^{\text{max}}$  ( $\text{cm}^{-1}$ ) 2960, 2760, 1700, 1620.

These data show that this material has a dihydrofuran ring accompanying a secondary methyl group in the molecule. Thus, the compound (6) was assigned to be 1,3,6-trimethyl-5,6-dihydrofuro[2,3-d]pyrimidine-2,4[1H,3H]-dione. Similarly, expected 1,3,6-trimethyl-6,7-dihydrofuro[3,2-d]pyrimidine-2,4[1H,3H]-dione (10, mp 139-141°C) was obtained in 90% yield by acid treatment of the Claisen rearrangement product (9).<sup>9,10</sup> Compounds (6) and (10) were also prepared by warming of 5 or 9 in 48% HBr at 70-80°C in 73.6% and 78.4% yield, respectively.

In conclusion, substituted pyrrolo- and furopyrimidines could be synthesized in good yields by new and facile cyclization reaction such as acid treatment at room temperature.

## REFERENCES AND NOTES

- 1) Presented at 104th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, March 28-30, 1984.
- 2) T. Itoh, T. Imini, H. Ogura, N. Kawahara, T. Nakajima, and K. A. Watanabe, *Heterocycles*, 1983, 20, 2177.
- 3) **2a**:  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  2.69 (1H, t, =CH), 3.36 (1H, s,  $\text{NCH}_3$ ), 3.39 (1H, s,  $\text{NCH}_3$ ), 4.76 (2H,  $-\text{CH}_2-$ ), 5.26 (1H, s, =CH-).
- 2b**:  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.22 (3H, t,  $\text{C-CH}_3$ ), 1.24 (3H, t,  $\text{C-CH}_3$ ), 2.72 (1H, t, =CH), 3.97

(4H,q,C-CH<sub>2</sub>x2), 4.75(2H,d,-CH<sub>2</sub>-), 5.22(1H,s,=CH-).

4) All compounds reported herein gave satisfactory elemental analyses.

5) 3a: <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 2.26(3H,s,C-CH<sub>3</sub>), 3.39(3H,s,N-CH<sub>3</sub>), 3.53(3H,s,N-CH<sub>3</sub>), 7.00(1H,s,=CH-); <sup>13</sup>C NMR(CDCl<sub>3</sub>) 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).

6) 3b: <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.24(3H,t,C-CH<sub>3</sub>), 1.35(3H,t,C-CH<sub>3</sub>), 2.26(3H,s,C-CH<sub>3</sub>), 4.05(2H,q,-CH<sub>2</sub>-), 4.07(2H,q,-CH<sub>2</sub>-), 6.97(1H,b,=CH-); <sup>13</sup>C NMR(CDCl<sub>3</sub>) δ 8.87(q), 13.21(q), 13.73(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).

7) 2c: <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 2.52(1H,s,≡CH), 2.82(3H,s,N-CH<sub>3</sub>), 3.29(3H,s,N-CH<sub>3</sub>), 3.41(3H,s,N-CH<sub>3</sub>), 3.79(2H,s,-CH<sub>2</sub>-), 5.38(1H,s,=CH-).

3c: <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 2.27(3H,s,C-CH<sub>3</sub>), 3.36(3H,s,N-CH<sub>3</sub>), 3.74(3H,s,N-CH<sub>3</sub>), 3.81(3H,s,N-CH<sub>3</sub>), 6.10(1H,s,=CH-); <sup>13</sup>C NMR(CDCl<sub>3</sub>) δ 10.77(q), 27.92(q), 31.97(q), 36.60(q), 100.97(s), 116.42(s), 120.66(d), 137.76(s), 152.04(s), 159.54(s).

2d: <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) δ 2.50(1H,s,≡CH), 3.13(3H,s,N-CH<sub>3</sub>), 3.26(3H,s,N-CH<sub>3</sub>), 3.89(2H,q,-CH<sub>2</sub>-), 4.77(1H,s,=CH-), 7.24(1H,b,-NH).

3d: <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) δ 2.18(3H,s,C-CH<sub>3</sub>), 3.19(3H,s,N-CH<sub>3</sub>), 3.39(3H,s,N-CH<sub>3</sub>), 6.50(1H,s,=CH-), 11.36(1H,b,-NH); <sup>13</sup>C NMR(DMSO-d<sub>6</sub>) 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).

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8) 5: <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 2.67(2H,d,-CH<sub>2</sub>-), 3.29(6H,s,N-CH<sub>3</sub>x2), 4.01(1H,b,-OH), 5.04-5.25(2H,m,=CH<sub>2</sub>), 5.43-5.50(1H,m,=CH-).

9) B. A. Otter, S. S. Saluja, and J. J. Fox, J. Org. Chem., 1972, 37, 2858.

10) 10: <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 1.52(3H,d,J=5.86Hz,CH-CH<sub>3</sub>), 2.74-2.98(1H,dd,-CH<sub>2</sub>-), 3.24-3.52(1H,dd,-CH<sub>2</sub>-), 3.35(3H,s,N-CH<sub>3</sub>), 3.37(3H,s,N-CH<sub>3</sub>), 4.80-5.20(1H,m,-CHMe); <sup>13</sup>C NMR(CDCl<sub>3</sub>) δ 21.64(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).

11) NMR spectra were measured on a JNM-FX100 spectrometer (JEOL, Tokyo) and MS spectra were taken by direct insertion method with 9000B (Shimadzu, Tokyo).

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