SIMPLE SYNTHESES OF PYRROLO- AND FUROPYRIMIDINE DERIVATIVES[1]

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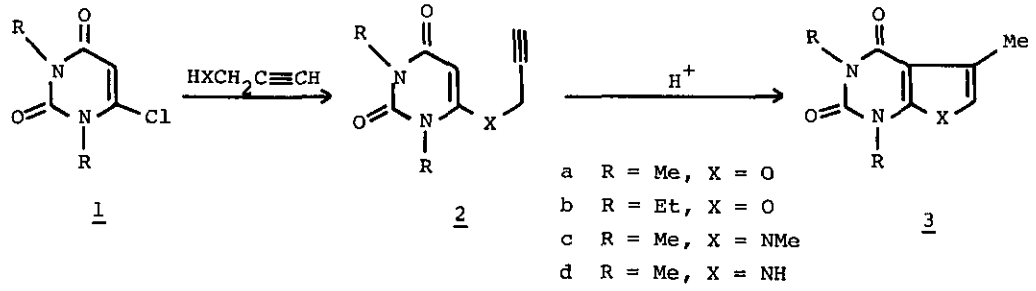
Abstract —— Simple and efficient syntheses of furo[2,3-d]-pyrimidine-2,4-diones, 7-deazacaffeines and dihydrofuro-pyrimidine-2,4-diones from 5- or 6-substituted pyrimidines by acid catalyzed cyclization reactions are described.

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 $PdCl_2$-CuCl-O_2 system in aqueous DMF of various 6-allylaminouracils.[2] 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_2Cl_2 followed by evaporation under a reduced pressure gave 1,3-dimethyl-6(2-propynyl-oxy)uracil (2a, mp 150-151°C)[3] 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)[3] in 56.7% yield.

A solution of 2a in conc. H_2SO_4 was allowed to stand at room temperature for 2 days. After neutralization with aqueous ammonia, the reaction mixture was extracted with CH_2Cl_2 and evaporation of the solvent provided a crystalline compound (3a, mp 143-144°C)[4] in 87% yield. This product has an empirical formula $C_9H_{10}N_2O_3$ which was derived from elemental and mass spectral analyses. ^1H NMR

spectrum of 3a has a signal at δ 7.00 (s, 1H) which can be attributable to an aromatic proton and a signal at δ 2.26 (s, 3H) which can be assigned to methyl protons on a furan ring. In ^{13}C NMR spectrum, signals at δ 8.82 (s, aromatic methyl carbon) and at δ 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.[5] When 2b was treated in a similar manner, a compound (3b, mp 83-84°C) was obtained in 88.7% yield.[6]



1 2 3

a R = Me, X = O
b R = Et, X = O
c R = Me, X = NMe
d R = Me, X = NH

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-tetramethyl-pyrrolo[2,3-d]pyrimidine-2,4[1H,3H]-dione (3c, mp 224-225°C; 9-methyl-7-deaza-caffeine) in 96.9% yield.[7] 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.[7] 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 H_2O, 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,[8] 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: $C_9H_{12}N_2O_3$; MS m/e = 196 (M^+); ^1H NMR ($CDCl_3$) δ 1.53 (3H, d, J = 6.10Hz, C-CH_3), 2.58-2.79 (1H, m, -$\overset{5}{C}H_2$-), 3.12-3.33 (1H, m, -$\overset{5}{C}H_2$-), 3.31 (6H, s, N-CH_3), 5.00-5.20 (1H, m, O-CH-Me); ^{13}C NMR ($CDCl_3$) δ 21.39 (q, C-CH_3), 27.37 (q,

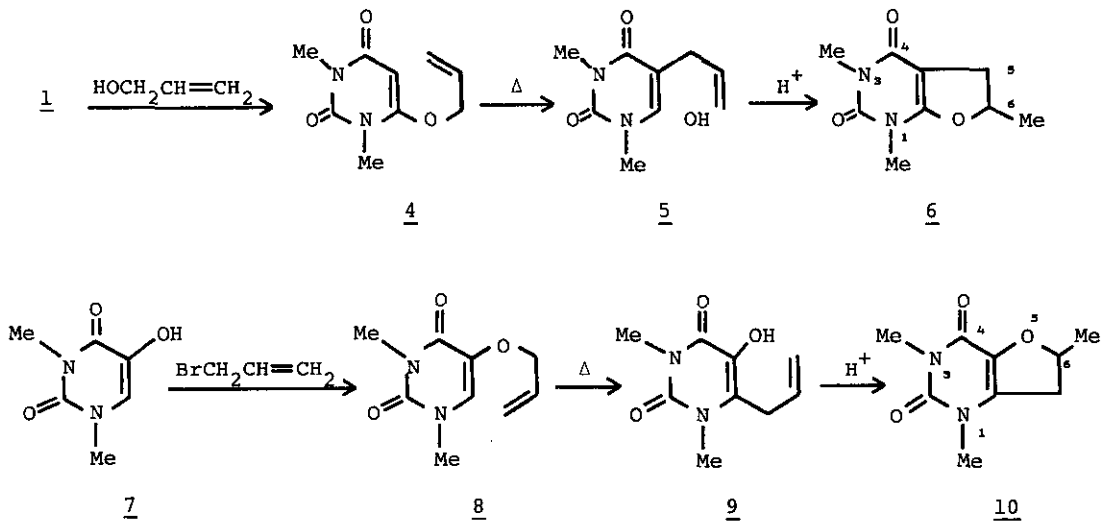


Chart 2

N-CH_3), 28.99 (q, N-CH_3), 32.80 (t, -CH_2-), 84.01 (d, -CHMe), 151.11 (s), 159.78 (s), and 161.01 (s); ν_{KBr}^{max} (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).[9,10] 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}H NMR($CDCl_3$) δ 2.69(1H,t,≡CH), 3.36(1H,s,NCH_3), 3.39(1H,s,NCH_3), 4.76(2H, -CH_2-), 5.26(1H,s,=CH-).

2b: ^{1}H NMR($CDCl_3$) δ 1.22(3H,t,C-CH_3), 1.24(3H,t,C-CH_3), 2.72(1H,t,≡CH), 3.97

(4H,q,C-CH_2x2), 4.75(2H,d,-CH_2-), 5.22(1H,s,=CH-).

4) All compounds reported herein gave satisfactory elemental analyses.

5) 3a: ^{1}H NMR($CDCl_3$) δ 2.26(3H,s,C-CH_3), 3.39(3H,s,N-CH_3), 3.53(3H,s,N-CH_3), 7.00 (1H,s,=CH-); ^{13}C NMR($CDCl_3$) 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: ^{1}H NMR($CDCl_3$) δ 1.24(3H,t,C-CH_3), 1.35(3H,t,C-CH_3), 2.26(3H,s,C-CH_3), 4.05 (2H,q,-CH_2-), 4.07(2H,q,-CH_2-), 6.97(1H,b,=CH-); ^{13}C NMR($CDCl_3$) 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: ^{1}H NMR($CDCl_3$) δ 2.52(1H,s,≡CH), 2.82(3H,s,N-CH_3), 3.29(3H,s,N-CH_3), 3.41 (3H,s,N-CH_3), 3.79(2H,s,-CH_2-), 5.38(1H,s,=CH-).

3c: ^{1}H NMR($CDCl_3$) δ 2.27(3H,s,C-CH_3), 3.36(3H,s,N-CH_3), 3.74(3H,s,N-CH_3), 3.81 (3H,s,N-CH_3), 6.10(1H,s,=CH-); ^{13}C NMR($CDCl_3$) 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: ^{1}H NMR(DMSO-d_6) δ 2.50(1H,s,≡CH), 3.13(3H,s,N-CH_3), 3.26(3H,s,N-CH_3), 3.89 2H,q,-CH_2-), 4.77(1H,s,=CH-), 7.24(1H,b,-NH).

3d: ^{1}H NMR(DMSO-d_6) δ 2.18(3H,s,C-CH_3), 3.19(3H,s,N-CH_3), 3.39(3H,s,N-CH_3), 6.50(1H,s,=CH-), 11.36(1H,b,-NH); ^{13}C NMR(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).

S. Senda and K. Hirota, Chem. Pharm. Bull., 1974, 22, 1459.

M. T. Garcia-Lopez, F.G. de las Heras, and M. Stud, J. Chem. Soc. Perkin 1, 1978, 483.

8) 5: ^{1}H NMR($CDCl_3$) δ 2.67(2H,d,-CH_2-), 3.29(6H,s,N-CH_3x2), 4.01(1H,b,-OH), 5.04-5.25(2H,m,=CH_2), 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: ^{1}H NMR($CDCl_3$) δ 1.52(3H,d,J=5.86Hz,CH-CH_3), 2.74-2.98(1H,dd,-CH_2-), 3.24-3.52(1H,dd, -CH_2-), 3.35(3H,s,N-CH_3), 3.37(3H,s,N-CH_3), 4.80-5.20(1H,m,-CHMe); ^{13}C NMR($CDCl_3$) 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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