A SIMPLE SYNTHESIS OF 1,3-DIALKYLPYRIDO[2,3-d]PYRIMIDINES

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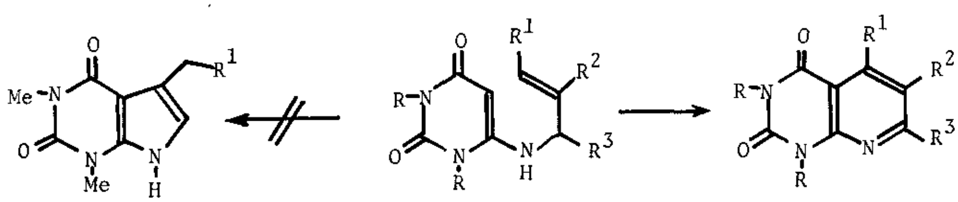
Abstract ---- A novel and simplified synthesis of 1,3-dialkyl-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-diones from 6-allylamino- and 6-(substituted allyl)aminouracils by $PdCl_2$-CuCl catalyzed oxidative cyclization is described.

The pyrido[2,3-d]pyrimidine ring system is found in a number of biologically active compounds.[1] Numerous derivatives containing this ring system have been synthesized as potential antitumor[2] and antibacterial[3] agents. Some pyrido[2,3-d]-pyrimidines also exhibit antimalarial,[4] antihypertensive,[5] antiallergic,[6] analgesic,[7] antiphlogistic,[7] antipyretic[7] and anticonvulsive[7] activities. We found a facile method for the preparation of pyrido[2,3-d]pyrimidines in the course of our attempts to synthesize 7-deazacaffeine (I) from 6-allylaminouracil (IIa). Tsuji et al.[8] reported a method to prepare methyl ketones from terminal olefins using the $PdCl_2$-CuCl-O_2 combination. It was hoped that application of this reagent combination to IIa might afford I via a π-allylpalladium complex intermediate. Oxidation of I proceeded very smoothly by treatment with the $PdCl_2$-CuCl-O_2 system in aqueous DMF. The product isolated, however, was not I but 1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (IIIa).

In order to determine the scope and limitation of this reaction, several 1,3-dialkyl-6-(substituted allyl)aminouracils (IIb-h) (Table 1) were prepared from 1,3-dialkyl-6-chlorouracils and substituted allylamines, and subjected to the oxidation reaction. In every case, the corresponding pyridopyrimidine (III) was obtained as the only isolable product in fair to low yield (Table 2). The mass and ^1H NMR spectral data are consistent with the structure of the respective products (Table 3). The ^1H NMR spectra of IIIc and IIIg were identical respectively to those reported[9] for 1,3,5-trimethyl- and 1,3,7-trimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione. Compounds IIIc and IIIg had been prepared[9] in low yields by reaction of 6-amino-1,3-dimethyluracil with crotonaldehyde and methyl vinyl ketone, respectively. Compound IIIa had been synthesized[10] but the yield was not reported. The method for preparation of alkylated pyridopyrimidines described herein is quite simple and versatile. Though the yields of the products are only fair to low, they might be improved upon. In conclusion, on the basis of chemical shift and aromatic ortho and meta coupling, the structures of products (III) were clarified and it is very interesting that in practice, these reactions of 6-allylamino- and 6-(substituted allyl)amino uracils by $PdCl_2$-$CuCl$-O_2 complex system proceed via intramolecular dehydrogenative cyclization to give III.



I II III

General procedure

A mixture of CuCl (10 mmol) and $PdCl_2$ (2 mmol) in DMF (10 ml) and water (1 ml) was stirred in an oxygen atmosphere until absorption of oxygen ceased. Compound II (10 mmol) was added and the mixture was stirred under oxygen overnight, then diluted with 3N HCl (5 ml), extracted with ether, dried (Na_2SO_4), and evaporated. The residue was purified by recrystallization or by column chromatography.

Table 1. Compounds II prepared by condensation of 1,3-dialkyl-6-chlorouracils with 6-substituted allylamines

Compounds	R	R^1	R^2	R^3	mp °C	MS(75eV) m/e (M^+)	yield(%)
IIa	Me	H	H	H	164-165	195	57
b	Et	H	H	H	205-206	223	60
c	Me	Me	H	H	163-164	209	57
d	Et	Me	H	H	145-146	237	53
e	Me	H	Me	H	135-136	209	45
f	Et	H	Me	H	151-152	237	50
g	Me	H	H	Me	112-113	209	56
h	Et	H	H	Me	76-78	237	53

Table 2. 1,3-Dialkylpyrido[2,3-d]pyrimidine-2,4(1H, 3H)-diones

Compounds	R	R^1	R^2	R^3	mp °C	MS(75 eV) m/e (M^+)	yield(%)
IIIa	Me	H	H	H	164-164.5	191	50
b	Et	H	H	H	210-211	219	37
c	Me	Me	H	H	158-159	205	14
d	Et	Me	H	H	96-97	233	22
e	Me	H	Me	H	159	205	25
f	Et	H	Mt	H	210-210.5	233	36
g	Me	H	H	Me	157-158	205	12
h	Et	H	H	Me	96-97	233	12

Table 3. ^{1}H NMR parameters of pyrimido[2,3-d]pyrimidines III*

Compounds	Me	CH_2	H-5	H-6	H-7
IIIa	3.63(s), 3.70(s)		8.66(dd)	7.17(dd)	8.43(dd)[a]
b	1.23(t), 1.33(t)	4.13(q), 4.40(q)	8.65(dd)	7.17(dd)	8.45(dd)[b]
c	2.80(s), 3.43(s), 3.66(s)			6.96(d)	8.42(d)[c]
d	1.30(t), 1.33(t), 2.80(s)	4.12(q), 4.42(q)		6.97(d)	8.43(d)[d]
e	2.40(s), 3.46(s), 3.67(s)		8.48(d)		8.25(d)[e]
f	1.30(t), 1.33(t), 2.40(s)	4.16(q), 4.43(q)	8.27(d)		8.47(d)[f]
g	2.60(s), 3.46(s), 3.69(s)		8.31(d)	7.05(d)[g]	
h	1.21(t), 1.33(t), 2.60(s)	4.13(q), 4.32(q)	8.37(d)	7.02(d)[h]	

*(s) singlet, (d) doublet, (dd) double doublet, (t) triplet, (q) quartet

a) $J_{5,6}$ = 7.69 Hz, $J_{5,7}$ = 1.83 Hz, $J_{6,7}$ = 4.76 Hz.

b) $J_{5,6}$ = 7.69 Hz, $J_{5,6}$ = 1.83 Hz, $J_{6,7}$ = 4.76 Hz.

c) $J_{6,7}$ = 5.40 Hz.

d) $J_{6,7}$ = 5.20 Hz.

e) $J_{5,7}$ = 1.80 Hz.

f) $J_{5,7}$ = 1.83 Hz.

g) $J_{5,6}$ = 7.50 Hz.

h) $J_{5,6}$ = 7.50 Hz.

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