SYNTHESIS OF PYRIDO[2,3-*d*]PYRIMIDINES *VIA* PALLADIUM-CATALYZED COUPLING REACTION FOLLOWED BY ELECTROCYCLIC REACTION

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Abstract-Pyrido[2,3-*d*]pyrimidines (**5a-h**) were regioselectively synthesized by the reaction of 5-iodo-6-(dimethylaminomethylene)amino-1,3-dimethyluracil(**3**), which was prepared from the reaction of 6-amino-1,3-dimethyluracil with dimethylformamide dimethyl acetal followed by iodination, with various olefins (**4a-h**) in the presence of a catalytic amount of $Pd(OAc)_2$, CuI, and K_2CO_3 in DMF at 100 °C.

INTRODUCTION

Fused pyridopyrimidines have long received an attention due to their potential biological activities[1] and especially 5,10-dideza-tetrahydrofolic acid (DDATHF) analogs[2] as antifolates over the past years. As such, a large number of works have been published on the synthesis of these fused heterocycles, which usually involve cyclocondensation reactions of appropriate pyridine or pyrimidine intermediates with other reagents.[3-5]

In addition to these two classical condensation methods, two other type methods have been reported: Wamhoff's and Hirota's method. Wamhoff's group reported the synthesis of substituted pyrido[2,3-*d*]pyrimidines from 6-(dimethylaminomethylene)amino-1,3-dimethyluracil

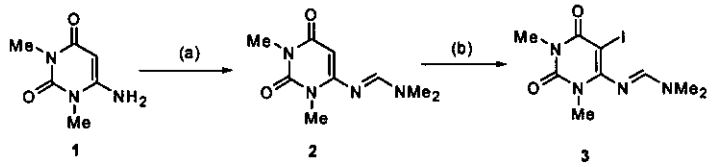
(2) *via* [4+2] cycloaddition reaction with electron-deficient olefins.[6] Uracil (2) was used as electron-sufficient diene in this reaction. One of disadvantages in this method is the limitation to electron-deficient olefins and the other is low yield due to side reaction. Hirota's group synthesized substituted pyrido[2,3-*d*]pyrimidines by the palladium-mediated C-C coupling reaction of electron-deficient olefins with the same uracil (2) in refluxing acetic acid in good yields.[7] However, they used stoichiometic amount of $Pd(OAc)_2$ as a coupling reagent and only electron-deficient olefins.

In this paper, we want to report an efficient synthetic method of pyrido[2,3-*d*]pyrimidines, which is a modified one of Wamhoff's method.

RESULTS AND DISCUSSION

The compound (2) was conveniently prepared by the reaction of 6-amino-1,3-dimethyluracil (1) with dimethylformamide dimethyl acetal (DMF-DMA) at room temperature. This condition is milder and the yield is better than Wamhoff's (66%). 6-(Dimethylaminomethylene)amino-1,3-dimethyluracil (2) was iodinated by the reaction with *N*-iodosuccimide (NIS) in methylene chloride under reflux to give 5-iodo-6-[(dimethylamino)methylene]amino-1,3-dimethyl-uracil (3) in 93% yield (Scheme 1).

Scheme 1.



1 2 3

Reagents and reaction conditions: (a) DMF-DMA, MeOH, rt, 24 h, 81.5%; (b) NIS, CH_2Cl_2, reflux, 30 min, 93%.

Pyrido[2,3-*d*]pyrimidines (**5a-h**) were synthesized by the reaction of 5-iodo-6-(dimethylamino-methylene)amino-1,3-dimethyluracil (3) with electron-rich or electron-deficient olefins in the presence of a catalytic amount of $Pd(OAc)_2$ and CuI in DMF at 100 °C in good to excellent yields. Anhydrous K_2CO_3 was used as a base. When we used triethylamine instead of

anhydrous K_2CO_3 as a base or acetonitrile instead of DMF as a solvent, the reaction did not give any expected product at all and starting material was remained. In a harsh condition (higher temperature), uracil (**3**) was deiodinated. The reaction time and yield under these catalytic conditions are shown in Table 1.

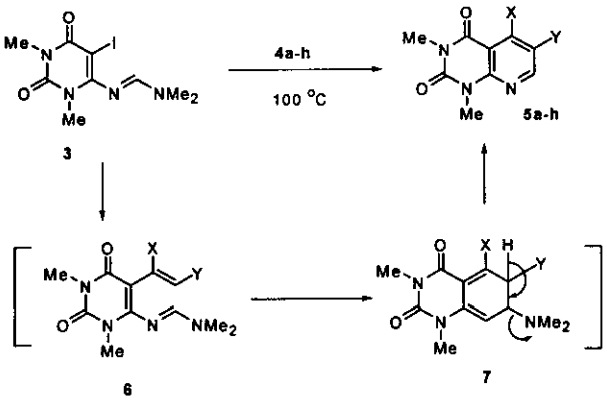
Table **1.** The results of the reactions of **3** with various olefins (**4a–h**)

olefins	product	X	Y	reaction time	yield(%)
4a	**5a**	H	CO_2Et	5 h	76
4b	**5b**	H	CO_2Bu-*t*	4 h	80
4c	**5c**	H	CN	4 h	91
4d	**5d**	H	COMe	3 h	84
4e	**5e**	H	C_6H_5	4 h	94
4f	**5f**	OBu-*t*	H	4 h	99(4:1)[a]
	5f′	H	OBu-*t*		
4g(*trans*)	**5g**	CO_2Me	CO_2Me	6 h	61
	5g′	H	CO_2Me		27
4h(*cis*)	**5h**	CO_2Et	CO_2Et	6 h	70
	5a	H	CO_2Et		25

All yields quoted are of column chromatographed material. [a]Ratio of two isomers was based on ^{1}H NMR.

The reaction seemed to proceed through palladium-catalyzed coupled intermediate (**6**) followed by electrocyclic reaction and elimination of dimethylamine as shown in Scheme 2.

Scheme 2.



Reagents and reaction condition: $Pd(OAc)_2$, CuI, K_2CO_3 in DMF

The reaction did not give any expected product except for the formation of unidentifiable

decomposed compound for 10 h heating at 100 °C without $Pd(OAc)_2$ as a catalyst (even higher temperature). Another evidence for the palladium-catalyzed coupling reaction followed by electrocyclic reaction is the regioselectivity of the reaction with styrene (**4e**) and especially *tert*-butyl vinyl ether (**4f**), which is consistent with that of the palladium-catalyzed reaction of the aryl halide with styrene and *tert*-butyl vinyl ether.[8] In the case of electron-deficient olefins (**4a-e**), the regioselectivity is in good accord with that reported by Hirota.[7]

The reaction of **3** with olefins (**4a-e**) gave one product respectively according to TLC. However, the reaction of **3** with olefins (**4f-h**) gave two products respectively. In the reaction with *tert*-butyl vinyl ether (**4f**), two regioisomers (**5f**) and (**5f'**) (4:1 according to ^1H NMR) are formed. Several attempts (recrystallization and chromatography) for the separation of these two isomers were failed. The reaction of **3** with fumarate (**4g**) and maleate (**4h**) gave two products respectively: one is decarboxylated pyridopyrimidines (**5g'**, **5a**) and the other pyridopyrimidinedicarboxylic acid esters (**5g**, **5h**). The formation mechanism of these pyridopyrimidines (**5g'**, **5a**) is not clear. These decarboxylated products did not seem to be formed by the decarboxylation of pyridopyrimidines (**5g**, **5h**) respectively because the amount of decarboxylated products did not increase during the extended reaction time. However, the decarboxylation seemed to proceed before the formation of coupling products (**6**).

In conclusion, we developed an efficient synthetic route to pyrido[2,3-*d*]pyrimidines using a catalytic amount of palladium reagent. The reactions go through palladium-catalyzed coupling followed by electrocyclization and elimination. This method allows an access to a range of structural variations of the C-5 or/and C-6 positions of pyridopyrimidine by the reaction of uracil (**3**) with olefins having the various functional groups (electron donating and withdrawing).

EXPERIMENTAL

All reactions were run under a nitrogen atmosphere. Flash chromatography was performed with Kiesel 60 (230-400 mesh) silica gel. NMR spectra were recorded on a Varian Gemni 200 MHz. Mps were determined on Electrothermal IA9000 Series Digital Melting Point Apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu FT-IR spectrophotometer. HRMSs were recorded on a VG70-VSEQ Mass Spectrometer.

6-(Dimethylaminomethylene)amino-1,3-dimethyluracil (2). To a solution of 6-amino-1,3-dimethyluracil (1.55 g, 0.01 mol) in anhydrous methanol (30 mL) was added DMF-DMA (1.59 mL, 0.012 mol) at rt. The resulting solution was stirred at rt for 24 h under argon. The reaction was concentrated under reduced pressure and the formed yellow solid was recrystallized using ethyl acetate to give yellow crystals in 81.5% yield (1.81 g); mp 102-103 °C; IR (KBr) 1700 and 1650 (CO), 1630 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.07 and 3.13 (each s, each 3H, $N(CH_3)_2$), 3.34 and 3.41(each s, each 3H, 2 x NCH_3), 5.07(s, 1H, 5-H), 7.67(s, 1H, 8-H). *Anal.* Calcd for $C_9H_{14}N_4O_2$: C, 51.42; H, 6.71; N, 26.65. Found: C, 51.08; H, 6.90; N, 26.50.

5-Iodo-6-(dimethylaminomethylene)amino-1,3-dimethyluracil (3). The solution of compound (**2**) (444 mg, 2 mmol) and NIS (540 mg, 2.4 mmol) in anhydrous methylene chloride (20 mL) was refluxed for 30 min. The solution was washed with water (20 ml x 3), dried with anhydrous $MgSO_4$ and concentrated to give a product (brown crystals) (**3**) in 93 % yield (650 mg); mp 108-110 °C; IR (KBr) 1700 and 1651 (CO), 1620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 and 3.14 (each s, each 3H, $N(CH_3)_2$), 3.40 and 3.41 (each s, each 3H, 2 x NCH_3), 7.72 (s, 1H, 8-H). *Anal.* Calcd for $C_9H_{13}N_4O_2I$: C, 32.16; H, 3.90; N, 16.67; I, 37.75. Found: C, 32.38; H, 3.71; N, 16.55.

General procedure for the synthesis of pyridopyrimidines (5a-h). To the solution of compound (**3**) (100 mg, 0.287 mmol) in anhydrous DMF (8 mL) were added $Pd(OAc)_2$ (3.2 mg, 0.014 mmol), CuI (1.37 mg, 0.007 mmol), anhydrous K_2CO_3 (60 mg, 0.34 mmol), and an olefin (1.2 eq.). The resulting solution was stirred at 100 °C for several hours (3-6 h) under dry argon atmosphere, concentrated under reduced pressure, and chromatograped on silica gel using a solution of ethyl acetate and hexane (1:4) as eluent. The concentration gave the pyridopyrimidines (**5a-h**) in moderate to high yield respectively.

6-Ethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5a). Yield: 76%, mp 133-134 ℃; IR (KBr) 1720 and 1668 (CO), 1610 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (t, 3H, J = 7.1 Hz, ethoxy CH_3), 3.51 and 3.76 (each s, each 3H, 2 x NCH_3), 4.42 (q, 2H, J =

7.1 Hz, ethoxy CH_2), 9.02 and 9.24 (each d, each J = 2.2 Hz, each 1H). HRMS Calcd for $C_{12}H_{13}N_3O_4$ 263.0900, Found 263.0894. *Anal.* Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.977; N, 15.96. Found: C, 54.81; H, 4.99; N, 15.77.

6-*tert*-Butoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5b). Yield 80%; mp 203-204 ℃; IR (KBr) 1720 and 1682 (CO), 1610 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (s, 9H, $C(CH_3)_3$) 3.50 and 3.76 (each s, each 3H, 2 x NCH_3), 8.94 and 9.20 (each d, each J = 2.2 Hz, each 1H). HRMS Calcd for $C_{14}H_{17}N_3O_4$ 291.1219, Found 291.1220. *Anal.* Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.73; H, 5.92; N, 14.70.

6-Cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5c). Yield 91%; mp 172-173 ℃ (lit.,[7] mp 181-182 °C)

6-Acetyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5d). Yield 84%; mp 152-153 ℃ (lit.,[7] mp 167-168 °C)

1,3-Dimethyl-6-phenylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5e). Yield 94%; mp 120 ℃ (lit.,[7] mp 138-139 °C)

5-*tert*-Butoxy-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5f) and 6-*tert*-Butoxy-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5f') Yield 99%; mp 129-130 ℃; IR (KBr) 1701 and 1661 (CO), 1590 (C=N) cm^{-1}; ^1H NMR of **5f** ($CDCl_3$) δ 1.63 (s, 9H, $C(CH_3)_3$), 3.43 and 3.69 (each s, each 3H, 2 x NCH_3), 6.80 and 8.35 (each d, each J = 5.9 Hz, each 1H); ^1H NMR of **5f'** ($CDCl_3$) δ 1.62 (s, 9H, $C(CH_3)_3$), 3.49 and 3.73 (each s, each 3H, 2 x NCH_3), 8.48 and 8.67 (each d, each J = 2.0 Hz, each 1H). HRMS Calcd for $C_{13}H_{17}N_3O_3$ 263.1271, Found 263.1273. *Anal.* Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.55; H, 6.44; N, 16.09.

5,6-Dimethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5g) and 6-Methoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5g'). **5g**: Yield

61%; mp 152 ℃; IR (KBr) 1760, 1728 and 1672 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.46 and 3.78 (each s, each 3H, 2 x NCH_3), 3.95 and 4.09 (each s, each 3H, 2 x CO_2CH_3), 9.28 (s, 1H). HRMS Calcd for $C_{13}H_{13}N_3O_6$ 307.0804, Found 307.0805. *Anal.* Calcd for $C_{13}H_{13}N_3O_6$: C, 50.82; H, 4.26; N, 13.68. Found: C, 50.99; H, 4.51; N, 13.37. **5g'**: Yield 27%; mp 121-122 ℃; IR (KBr) 1738, 1716.5 and 1670 (CO), 1608.5 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.50 and 3.76 (each s, each 3H, 2 x NCH_3), 3.98 (s, 3H, CO_2CH_3), 9.03 and 9.24 (each d, each J = 2.2 Hz, each 1H). HRMS Calcd for $C_{11}H_{11}N_3O_4$ 249.0749, Found 249.0748. *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.31; H, 4.27; N, 16.65.

5,6-Diethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5h) and 6-Ethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(*1H,3H*)-dione (5a). **5h**: Yield 70%; mp 115-116 ℃; IR (KBr) 1737, 1715 and 1672 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, 6H, J = 7.0 Hz, 2 x ethoxy CH_3), 3.46 and 3.76 (each s, each 3H, 2 x NCH_3), 4.41 and 4.56 (each q, each 2H, J = 7.0 Hz, 2 x ethoxy CH_2), 9.29 (s, 1H). HRMS Calcd for $C_{15}H_{17}N_3O_6$ 335.1117, Found 335.1116. *Anal.* Calcd for $C_{15}H_{17}N_3O_6$: C, 53.73; H, 5.11; N, 12.53. Found: C, 53.61; H, 5.03; N, 12.55. **5a**: Yield 25%.

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