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A Simple Synthesis of 1,3-Dialkylpyrido[2,3-*d*]pyrimidines[1)]

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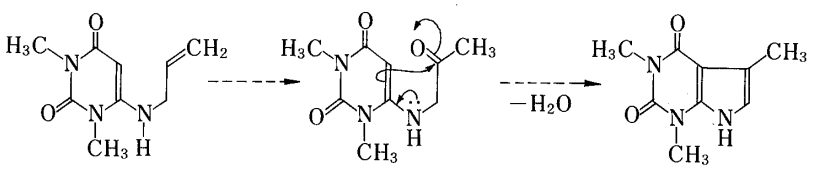
A new and convenient synthesis of 1,3-dialkylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones from 6-allylamino- and 6-(substituted allyl)aminouracils by $PdCl_2$–$CuCl$–O_2-catalyzed oxidative cyclization is described. Further, 1,3-dimethylpyrido[2,3-*d*]pyrimidine 2,4(1*H*,3*H*)-dione (**4a**) was prepared by the reaction of 6-allylamino-1,3-dimethyluracils (**3a**) with $(AcO)_2Pd$ and by the thermal cyclization of **3a**.

Keywords——substituted allylamine; 6-(substituted allyl)aminouracil; 1,3-dialkylpyrido-[2,3-*d*]pyrimidine; $PdCl_2$–$CuCl$–O_2 complex; palladium (II) acetate; oxidative cyclization; fused uracil; Claisen rearrangement

Recently many synthetic reactions utilizing palladium compounds have been reported, but their applications to heterocyclic compounds are limited. During the course of our studies on uracil derivatives,[2)] we became interested in attempting to synthesize 7-deazacaffeine from 6-allylaminouracil by using a palladium complex. Tsuji *et al.*[3)] reported a method to prepare methyl ketones from terminal olefins by using the $PdCl_2$–$CuCl$–O_2 combination, and we

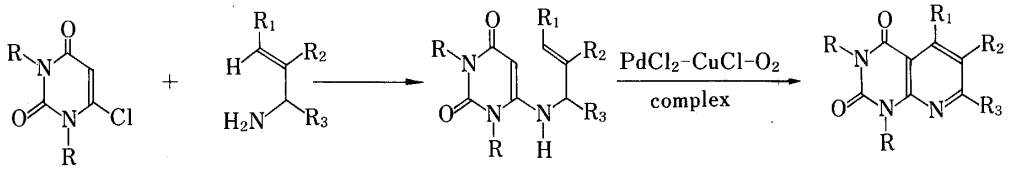


3a A B

Chart 1

hoped that application of this reagent combination to **3a** might afford A *via* a π-allylpalladium complex, and then intramolecular dehydrative cyclization of A might give the desired B. Oxidation of **3a** proceeded very smoothly in the $PdCl_2$–$CuCl$–O_2 system in aqueous dimethylformamide (DMF). The product isolated, however, was not the desired B, but 1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4a**).

In order to determine the scope and limitations of this reaction, we attempted to prepare several 1,3-dialkyl-6-(substituted allyl)aminouracils (**3b—h**). Compounds **3b—h** were prepared from 6-chloro-1,3-dialkyluracils (**1a—b**) and substituted allylamines (**2a—d**) in good yields, and were subjected to oxidation by the $PdCl_2$–$CuCl$–O_2 combination. In all cases, the corresponding pyrimidines (**4b—h**) were obtained as the only isolable product in fair to low yield. Treatment of **3a** with palladium (II) acetate also gave pyridopyrimidine (**4a**) in good



1 2 3 4

1a: R=CH_3
1b: R=CH_2CH_3

2a: $R_1=R_2=R_3=H$
2b: $R_1=CH_3$, $R_2=R_3=H$
2c: $R_1=R_3=H$, $R_2=CH_3$
2d: $R_1=R_2=H$, $R_3=CH_3$

3a: R=CH_3, $R_1=R_2=R_3=H$
3b: R=CH_2CH_3, $R_1=R_2=R_3=H$
3c: R=$R_1=CH_3$, $R_2=R_3=H$
3d: R=CH_2CH_3, $R_1=CH_3$, $R_2=R_3=H$
3e: R=$R_2=CH_3$, $R_1=R_3=H$
3f: R=CH_2CH_3, $R_2=CH_3$, $R_1=R_3=H$
3g: R=$R_3=CH_3$, $R_1=R_2=H$
3h: R=CH_2CH_3, $R_1=R_2=H$, $R_3=CH_3$

4a: R=CH_3, $R_1=R_2=R_3=H$
4b: R=CH_2CH_3, $R_1=R_2=R_3=H$
4c: R=$R_1=CH_3$, $R_2=R_3=H$
4d: R=CH_2CH_3, $R_1=CH_3$, $R_2=R_3=H$
4e: R=$R_2=CH_3$, $R_1=R_2=H$
4f: R=CH_2CH_3, $R_1=R_3=H$, $R_2=CH_3$
4g: R=$R_3=CH_3$, $R_1=R_2=H$
4h: R=CH_2CH_3, $R_1=R_2=H$, $R_3=CH_3$

Chart 2

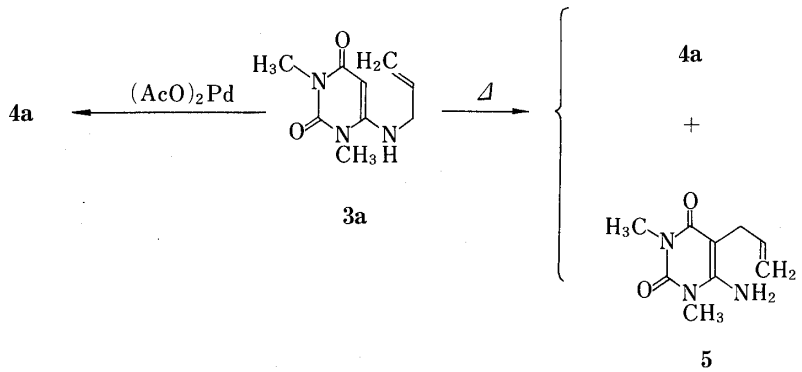


Chart 3

yield. Moreover, we investigated the thermal reaction of **3a**. Treatment of **3a** in tetralin under reflux gave **4a** and 5-allyl-6-amino-1,3-dimethyluracil (**5**), formed by the Claisen rearrangement, in 6.5% and 17% yields, respectively, while **5** afforded **4a** in poor yield under the same reaction conditions. It is reasonable to suppose that **4a** was formed *via* intermediate **5** as shown in Chart 3. Thus, it was found that **4a** was produced not only by the reaction of **3a** using $PdCl_2$–$CuCl$–O_2 complex and palladium (II) acetate but also by the thermal reaction.

The mass and proton nuclear magnetic resonance (^{1}H-NMR) spectral data and elemental analyses were consistent with the indicated structures of the products. The ^{1}H-NMR spectra of the products were clarified on the basis of the chemical shifts and aromatic *ortho* and *meta* couplings as detailed in the experimental section. The ^{1}H-NMR spectra of **4c** and **4g** were identical with those reported[4] for 1,3,5-trimethyl- and 1,3,7-trimethylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione, respectively. Compound **4a** has been synthesized[5] but the yield and ^{1}H-NMR data were not reported.

The method for the preparation of alkylated pyridopyrimidines by using the $PdCl_2$–$CuCl$–O_2 combination described herein is quite simple and versatile. Though the yields of the

products are fair to low, they might be improved upon by the optimization of the reaction conditions.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus. Mass spectra (MS) were recorded on a JEOL D-100 instrument. ^{1}H-NMR spectra were recorded on a Varian EM-390-NMR spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ values. The following abbreviations are used; s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad. Microanalyses were performed by Mrs. Ueno in the Microanalytical Laboratory of this school.

Materials——α-Methyl- and β-methylallylamine and crotylamine were prepared by the method reported by Roberts and Hazur.[6] Palladium (II) acetate was purchased from Tokyo Kasei Kogyo Co., Ltd.

General Procedure for the Synthesis of 1,3-Dialkyl-6-(substituted allyl)aminouracils (3a—h)——A gently stirred solution of 6-chloro-1,3-dialkyluracil (0.02 mol) and a substituted allylamine (0.07 mol) was refluxed for 3 h. The reaction mixture was concentrated *in vacuo*, then the residue was extracted with 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.

6-Allylamino-1,3-dimethyluracil (3a)——According to the general procedure, the crude product was obtained from 6-chloro-1,3-dimethyluracil (**1a**) and allylamine (**2a**), and recrystallized from MeOH to give colorless needles, mp 164—165 °C. Yield 2.22 g (57%). ^{1}H-NMR ($CDCl_3$): 3.26, 3.43 (each 3H, s, NCH_3), 3.77 (2H, br, $NHC\underline{H}_2$), 4.78 (1H, s, H-5), 5.13—5.40 (2H, m, $-CH=C\underline{H}_2$), 5.63—6.08 (1H, m, $-C\underline{H}=CH_2$ and N$\underline{H}$). MS *m/z*: 195 (M^+). *Anal.* Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.42; H, 6.67; N, 21.31.

6-Allylamino-1,3-diethyluracil (3b)——According to the general procedure, the crude product was obtained from 6-chloro-1,3-diethyluracil (**1b**) and allylamine (**2a**), and recrystallized from AcOEt to give colorless needles, mp 205—206 °C. Yield 2.67 g (60%). ^{1}H-NMR ($CDCl_3$): 1.20, 1.27 (each 3H, t, $-CH_2C\underline{H}_3$), 3.73 (2H, br, $NHC\underline{H}_2$), 3.93, 3.96 (each 2H, q, $NC\underline{H}_2CH_3$), 4.77 (1H, s, H-5), 5.02 (1H, br, NH), 5.13—5.40 (2H, m, $-CH=CH_2$), 5.63—6.08 (1H, m, $-C\underline{H}=CH_2$). MS *m/z*: 223 (M^+). *Anal.* Calcd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.13; H, 7.68; N, 18.63.

6-Crotylamino-1,3-dimethyluracil (3c)——According to the general procedure, the crude product was obtained from **1a** and crotylamine (**2b**), and recrystallized from MeOH to give colorless needles, mp 163—164 °C. Yield 2.38 g (57%). ^{1}H-NMR ($CDCl_3$): 1.70 (3H, d, J=6 Hz, $=CHC\underline{H}_3$), 3.25, 3.55 (each 3H, s, NCH_3), 3.67 (2H, br, $-NHC\underline{H}_2$), 4.77 (1H, s, H-5), 5.37 (1H, br, NH), 5.50—5.90 (2H, m, $-C\underline{H}=C\underline{H}-$), MS *m/z*: 209 ($M^+$). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.22; N, 20.08. Found: C, 57.18; H, 7.19; N, 20.33.

6-Crotylamino-1,3-diethyluracil (3d)——According to the general procedure, the crude product was obtained from **1b** and crotylamine (**2b**), and recrystallized from MeOH to give colorless needles, mp 145—146 °C. Yield 2.51 g (53%). ^{1}H-NMR ($CDCl_3$): 1.22, 1.31 (each 3H, t, $CH_2C\underline{H}_3$), 1.74 (3H, d, J=6 Hz, CH_3), 3.68, 3.98 (each 2H, q, $-CH_2$), 4.60 (1H, br, NH), 4.84 (1H, s, H-5), 5.40—5.96 (2H, m, $-C\underline{H}=C\underline{H}-$). MS *m/z*: 237 ($M^+$). *Anal.* Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.56; H, 8.06; N, 17.58.

1,3-Dimethyl-6-(β-methylallyl)aminouracil (3e)——According to the general procedure, the crude product was obtained from **1a** and β-methylallylamine (**2c**), and recrystallized from MeOH to give colorless needles, mp 135—136 °C. Yield 1.87 g (45%). ^{1}H-NMR ($CDCl_3$): 1.73 (3H, s, $-CH_3$), 3.23, 3.43 (each 3H, s, NCH_3), 3.67 (2H, d, J= 6 Hz, $NHCH_2-$), 4.70 (1H, s, H-5), 4.86 (2H, d, J=3 Hz, $C=CH_2$), 6.20 (1H, t, J=6 Hz, NH). MS *m/z*: 209 (M^+). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.22; N, 20.08. Found: C, 57.21; H, 7.42; N, 19.88.

1,3-Diethyl-6-(β-methylallyl)aminouracil (3f)——According to the general procedure, the crude product was obtained from **1b** and **2c**, and recrystallized from ether–CH_2Cl_2 to give colorless needles, mp 151—152 °C. Yield 2.37 g (50%). ^{1}H-NMR ($CDCl_3$): 1.27, 1.29 (each 3H, t, $-CH_2C\underline{H}_3$), 1.75 (3H, s, CH_3), 3.33 (2H, d, J=6 Hz, $NHC\underline{H}_2$), 3.94, 3.96 (each 2H, q, $-C\underline{H}_2CH_3$), 4.70 (1H, s, H-5), 4.90 (2H, d, J=3 Hz, $C=CH_2$), 5.32 (1H, t, J= 6 Hz, NH). MS *m/z*: 237 (M^+). *Anal.* Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.59; H, 8.02; N, 17.56.

1,3-Dimethyl-6-(α-methylallyl)aminouracil (3g)——According to the general procedure, the crude product was obtained from **1a** and α-methylallylamine (**2d**), and recrystallized from MeOH to give colorless needles, mp 112—113 °C. Yield 2.35 g (56%). ^{1}H-NMR ($CDCl_3$): 1.37 (3H, d, J=6 Hz, $CHC\underline{H}_3$), 3.23, 3.42 (each 3H, s, NCH_3), 3.90 (1H, m, $-NHC\underline{H}CH_3$), 4.90 (1H, s, H-5), 5.00—5.30 (2H, m, $-CH=C\underline{H}_2$), 5.37 (1H, br, NH), 5.40—6.00 (1H, m, $-C\underline{H}=CH_2$). MS *m/z*: 209 (M^+). *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.22; N, 20.08. Found: C, 57.36; H, 6.92; N, 19.88.

1,3-Diethyl-6-(α-methylallyl)aminouracil (3h)——According to the general procedure, the crude product was obtained from **1b** and **2d**, and recrystallized from MeOH to give colorless needles, mp 76—78 °C. Yield 2.50 g (53%). ^{1}H-NMR ($CDCl_3$): 1.20, 1.31 (each 3H, t, $CH_2C\underline{H}_3$), 1.25 (3H, d, J=6 Hz, CH_3), 3.83 (1H, m, $NHC\underline{H}CH_3$), 3.96, 4.14 (each 2H, q, $C\underline{H}_2CH_3$), 4.80 (1H, s, H-5), 5.00 (1H, br, NH), 5.60—5.15 (1H, m, $-C\underline{H}=CH_2$). MS *m/z*: 237

(M^+). *Anal.* Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.84; H, 8.02, N, 17.52.

General Procedure for the Synthesis of 1,3-Dialkylpyrido[2,3-*d*]pyrimidines (4a—h)——A mixture of CuCl (10 mmol) and $PdCl_2$ (2 mmol) in DMF (10 ml) and water (1 ml) was stirred in a stream of oxygen at room temperature for 3 h. Compound **3** (10 mmol) was added and the mixture was stirred under oxygen overnight, then diluted with 3 N HCl (5 ml), extracted with five 5 ml portions of ether, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by recrystallization or column chromatography.

1,3-Dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a)——The crude product obtained from **3a** according to the general procedure was recrystallized from MeOH to give colorless prisms, mp 164—164.5 °C (lit.[5] 164—165 °C). Yield 0.96 g (50%). Spectral data for the known compound were not given in the literature,[5] so they are reported here. ^{1}H-NMR ($CDCl_3$): 3.63, 3.70 (each 3H, s, NCH_3), 7.17 (1H, dd, H-6), 8.43 (1H, dd, H-7), 8.66 (1H, dd, H-5), $J_{5,6}=7.69$ Hz, $J_{5,7}=1.83$ Hz, $J_{6,7}=4.76$ Hz. MS *m/z*: 191 (M^+).

1,3-Diethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4b)——The crude product obtained from **3b** according to the general procedure was recrystallized from MeOH to give colorless needles, mp 210—211 °C. Yield 0.79 g (36%). ^{1}H-NMR ($CDCl_3$): 1.23, 1.33 (each 3H, t, $-CH_2C\underline{H}_3$), 4.13, 4.40 (each 2H, q, $-C\underline{H}_2CH_3$), 7.17 (1H, dd, H-6), 8.45 (1H, dd, H-7), 8.65 (1H, dd, H-5), $J_{5,6}=7.69$ Hz, $J_{5,7}=1.83$ Hz, $J_{6,7}=4.76$ Hz. MS *m/z*: 219 (M^+). *Anal.* Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.11; H, 5.82; N, 19.31.

1,3,5-Trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4c)——The crude product obtained from **3c** according to the general procedure was recrystallized from MeOH to give colorless needles, mp 158—159 °C (lit.[4] 159—160.5 °C). Yield 0.30 g (14%).

1,3-Diethyl-5-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4d)——The crude product obtained from **3d** according to the general procedure was recrystallized from MeOH to give colorless needles, mp 96—97 °C. Yield 0.51 g (22%). ^{1}H-NMR ($CDCl_3$): 1.30, 1.33 (each 3H, t, $-CH_2C\underline{H}_3$), 2.80 (3H, s, $-CH_3$), 4.12, 4.42 (each 2H, q, $-C\underline{H}_2CH_3$), 6.97 (1H, d, $J_{6,7}=5.20$ Hz, H-6), 8.43 (1H, d, $J_{6,7}=5.20$ Hz, H-7). MS *m/z*: 233 (M^+). *Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.52; H, 6.57; N, 18.16.

1,3,6-Trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4e)——The crude product obtained from **3e** according to the general procedure was recrystallized from MeOH to give colorless needles, mp 159 °C. Yield 0.26 g (13%). ^{1}H-NMR ($CDCl_3$): 2.40 (3H, s, CH_3), 3.46, 3.67 (each 3H, s, NCH_3), 8.25 (1H, d, $J_{5,7}=1.80$ Hz, H-7), 8.48 (1H, d, $J_{5,7}=1.80$ Hz, H-5). MS *m/z*: 205 (M^+). *Anal.* Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.47. Found: C, 58.38; H, 5.36; N, 20.37.

1,3-Diethyl-6-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4f)——The crude product obtained from **3f** according to the general procedure was recrystallized from MeOH to give colorless needles, mp 210—210.5 °C. Yield 0.49 g (22%). ^{1}H-NMR ($CDCl_3$): 1.30, 1.33 (each 3H, t, $-CH_2C\underline{H}_3$), 2.43 (3H, s, $-CH_3$), 4.16, 4.43 (each 2H, q, $-C\underline{H}_2CH_3$), 8.27 (1H, d, $J_{5,7}=1.83$ Hz, H-7), 8.47 (1H, d, $J_{5,7}=1.83$ Hz, H-5). MS *m/z*: 233 (M^+). *Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.56; H, 6.23; N, 17.98.

1,3,7-Trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4g)——The crude product obtained from **3g** according to the general procedure was recrystallized from MeOH to give colorless prisms, mp 157—158 °C. (lit.[5] 157.5—159 °C). Yield 0.51 g (25%).

1,3-Diethyl-7-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4h)——The crude product obtained from **3h** according to the general procedure was recrystallized from MeOH to give colorless needles, mp 96—97 °C. Yield 0.83 g (36%). ^{1}H-NMR ($CDCl_3$): 1.27, 1.30 (each 3H, t, $-CH_2C\underline{H}_3$), 2.60 (3H, s, $-CH_3$), 4.13, 4.32 (each 2H, q, $-C\underline{H}_2CH_3$), 7.02 (1H, d, $J_{5,6}=7.50$ Hz, H-6), 8,37 (1H, d, $J_{5,6}=7.50$ Hz, H-5). MS *m/z*: 233 (M^+). *Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.52; H, 6.38; N, 18.15.

Thermal Reaction of 6-Allylamino-1,3-dimethyluracil (3a)——A solution of **3a** (0.50 g, 2.56×10^{-3} mol) in tetralin (5 ml) was refluxed for 45 h. The precipitate that resulted was filtered off and dissolved in CH_2Cl_2 (7 ml). The resulting mixture was extracted with five 3—4 ml portions of 0.01 N aqueous HCl, and the extract was neutralized with 20% aqueous NaOH. This solution was extracted with three 5 ml portions of $CHCl_3$, washed with water, and dried over $MgSO_4$. After removal of the solvent, the crystals that resulted were filtered off to give 5-allyl-6-amino-1,3-dimethyluracil (**5**), mp 111—112 °C, presumably formed by Claisen rearrangement. Yield 83 mg (17%). ^{1}H-NMR ($CDCl_3$): 3.19—3.28 (2H, m, $-CH_2-$), 3.36, 3.48 (each 3H, s, NCH_3), 4.82 (2H, br, NH_2), 5.02—5.16 (2H, m, $=CH_2$), 5.62—6.02 (1H, m, $-CH=CH_2$). MS *m/z*: 195 (M^+). *Anal.* Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.26, H, 6.56; N, 21.34.

On the other hand, the mother liquor was extracted with three 3 ml portions of 0.01 N aqueous HCl, and the extract was neutralized with 20% aqueous NaOH. This solution was extracted with three 3 ml portions of $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave **4a**, mp 155—158 °C. Yield 30 mg (6.2%).

Thermal Reaction of 5-Allyl-6-amino-1,3-dimethyluracil (5)——A solution of **5** (0.070 g, 0.3×10^{-3} mol) in tetralin (2.0 ml) was refluxed for 18 h. Then hexane (3 ml) was added, and the mixture was treated with 0.01 N aqueous HCl and 20% aqueous NaOH. The aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to leave a solid, mp 160—162 °C, yield 7.5 mg, which was shown [by mixed mp determination and comparison of ^{1}H-NMR spectra and thin

layer chromatography (TLC) behavior] to be identical with a authentic sample of **4a**.

Synthesis of 4a Using Palladium (II) Acetate——Palladium (II) acetate (0.224 g, 1×10^{-3} mol) was added to a solution of **3a** (0.195 g, 1×10^{-3} mol) in AcOH (20 ml). The resulting brown solution was refluxed for 6 h under an N_2 atmosphere. Distilled water was added to the reaction mixture, and the resulted solution was neutralized with 20% aqueous NaOH and saturated aqueous $NaHCO_3$, then extracted with AcOEt. The AcOEt extract was dried over $MgSO_4$ and evaporated *in vacuo* to leave colorless crystals, mp 155—158 °C, yield 90 mg (47%), which were shown (by comparison of ^{1}H-NMR spectra and TLC behavior) to be identical with an authentic sample of **4a**.

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