# An Improved Synthesis of Pyrido[2,3-*d*]pyrimidines



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An improved and efficient synthesis of 1,3-dialkylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones from 6-methylaminouracils and methyl propiolate or diethyl ethoxymethylenemalonate is described.

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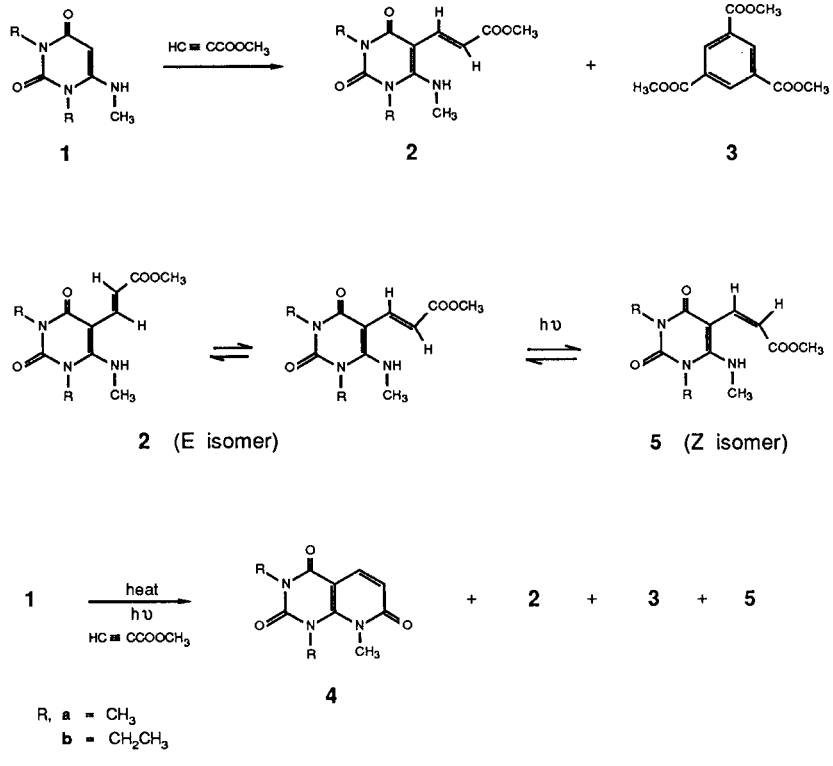
Previously, we reported the novel synthetic procedures of 1,3-dialkylpyrido[2,3-*d*]pyrimidines by the oxidative cyclization of 6-allylamino-1,3-dialkyluracils using the $PdCl_2$-$CuCl$-$O_2$ system and by the treatment of 1,3-dialkyl-6-alkylaminouracils with dimethyl acetylenedicarboxylate (DMAD) [1,2]. Recently, we developed an even simpler and more convenient approach to the pyrido[2,3-*d*]pyrimidine system which we describe herein.

Treatment of 1,3-dimethyl-6-methylaminouracil (**1a**) with methyl propiolate gave a mixture from which the adduct 1,3-dimethyl-5-(*E*)-(2-methoxycarbonylvinyl)-6-methylaminouracil (**2a**, mp 177-179°) and trimethyl benzene-1,3,5-tricarboxylate (**3**) were isolated in 49% yield and trace, respectively [3].

A similar reaction of **1b** and methyl propiolate afforded the adduct 1,3-diethyl-5-(*E*)-(2-methoxycarbonylvinyl)-6-methylaminouracil (**2b**, mp 149°) in 23% yield. Formation of bicyclic product **4** was not observed in either reaction apparently due to the *E* configuration around the double bond of $\alpha,\beta$-unsaturated carboxylate in **2** which had prevented cyclization between the ester and amine functions. The corresponding *Z* isomer **5**, however, is expected to cyclize to the pyrido[2,3-*d*]pyrimidine derivative **4**. In order to isomerize **2** into **5** followed by cyclization to **4** in a one-pot synthesis, a mixture of **1a** and methyl propiolate, after refluxing for 1 hour, was irradiated in ace-

Scheme 1



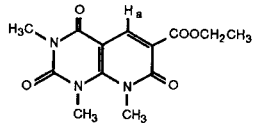
tone with 400 W high pressure mercury lamps with a pyrex filter for 13 hours under nitrogen. From the reaction mixture, **2a** (13% yield), 1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**4a**, mp 217°, 6% yield) and 1,3-dimethyl-5-(*Z*)-(2-methoxycarbonylvinyl)-6-methylaminouracil (**5a**, oil, 8% yield), in addition to trimethyl benzene-1,3,5-tricarboxylate (**3**) were isolated (Scheme 1).

In the same manner, treatment of **1b** and methyl propiolate afforded **2b** (mp 149°, 8% yield) and 1,3-diethyl-8-methylpyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*,3*H*,8*H*)-trione (**4b**, oil 7% yield). Product **5b** was observed by tlc and nmr, but could not be isolated because of an unstable intermediate. These experiments provided evidence that the *cis* configuration of the pyrimidine and carboxylic ester moieties in the adduct **5** is required for cyclization to the pyrido[2,3-*d*]pyrimidine derivative **4**.

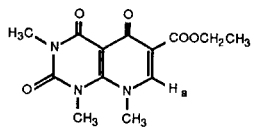
Furthermore, we investigated the synthesis of pyrido-[2,3-*d*]pyrimidines from **1a** with diethyl ethoxymethylenemalonate. A solution of **1a** in diethyl ethoxymethylenemalonate was stirred with heating at 200-230° in an oil bath for 8 hours to give 6-ethoxycarbonyl-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*,3*H*,8*H*)-trione (**7**, mp 223-226°, 39% yield). The structure of **7'** which is one of two possible products (**7**, and **7'**) was excluded by the comparison of the signal of its $^1$H-nmr spectrum to that of **8**. The signal of Ha of the product in the $^1$H-nmr spectrum appeared at $\delta$ 8.77. On the other hand, the signal of Ha of compound **8** which has an analogous partial structure to **7'**, was observed at $\delta$ 9.70-9.83 [4] (Figure).

In spite of several attempts to isolate the intermediate (**6**) by the various reaction conditions, **6** could not be obtained. It is presumed that the compound (**6**) immediately cyclizes to **7** on our reaction conditions.

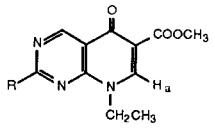
Figure



**7**



**7'**



**8**

The elimination of ethoxycarbonyl group from **7** was performed by refluxing of a solution of **7** in acetic acid and hydrochloric acid in 56% yield. This compound was perfectly in accord with structure **4a** (Scheme 2).

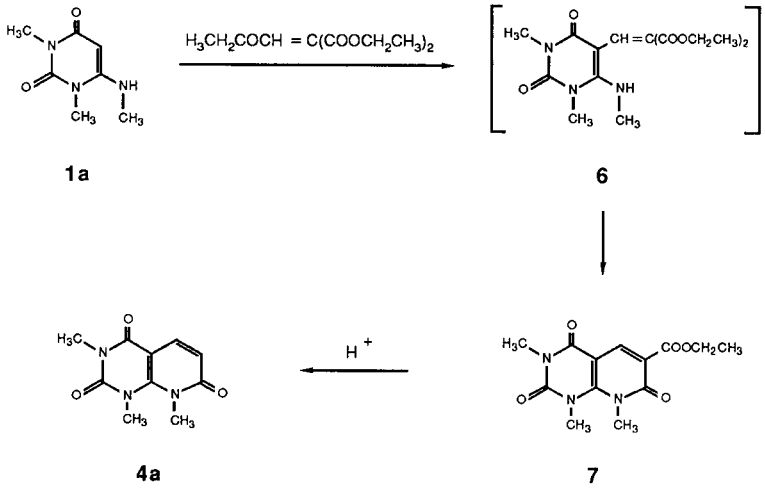
## EXPERIMENTAL

All melting points were determined by using a Yamato MP-1 cappillary melting point apparatus and are uncorrected. Mass spectra (ms) were recorded on a JEOL-D-100 instrument. The uv spectra were measured with a Hitachi 340 spectrometer. The $^1$H-nmr spectra were recorded on a Varian EM-390-NMR spectrometer and the $^{13}$C-nmr spectra were measured on a JNM-FX 100 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in $\delta$ value. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Microanalyses were performed by the staff in the Microanalytical Laboratory of this school. Preparative thin-layer chromatography (tlc) was done with Merck precoated Silica gel 60 $F_{254}$ plates, 20 × 20 cm, with a thickness of 0.5 mm.

Reaction of 1,3-Dimethyl (or Diethyl)-6-methylaminouracil with Methyl Propiolate by Heating.

a) A solution of 1,3-dimethyl-6-methylaminouracil (**1a**, 845 mg, 5

Scheme 2



mmoles) in methyl propiolate (2.62 g, 30 mmoles) was refluxed for 3 hours. The reaction mixture was concentrated *in vacuo*, the residue was subjected to silica gel column chromatography with chloroform to afford a product **2a** and trimethyl benzene-1,3,5-tricarboxylate.

1,3-Dimethyl-5-(*E*)-(2-methoxycarbonylvinyl)-6-methylaminouracil (**2a**).

This compound was obtained as white crystals, mp 177-179°, yield 217 mg (17%); ms: m/z 253 ($M^+$); $^1$H-nmr (deuteriochloroforom): 3.07 (3H, d, J = 5 Hz, NHC$H_3$), 3.31 (6H, s, $NCH_3$ × 2), 3.79 (3H, s, ester $CH_3$), 4.94 (1H, d, J = 5 Hz, N*H*$CH_3$), 6.87 (1H, d, J = 15 Hz, -CH=CH-, *trans*); uv (ethanol): λ max nm (log ε 285 (4.73), 319 (4.78).

*Anal.* Calcd. for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 25.27. Found: C, 51.96; H, 5.81; N, 25.03.

Trimethyl benzene-1,3,5-tricarboxylate (yield 89 mg, mp 144-145°, lit mp 143-144° [3]) was confirmed by ms and $^1$H-nmr spectral data.

1,3-Diethyl-5-(*E*)-(2-methoxycarbonylvinyl)-6-methylaminouracil (**2b**).

b) A solution of 1,3-diethyl-6-methylaminouracil (**1b**, 394 mg, 2 mmoles) in methyl propiolate (2 ml) was refluxed for 3 hours. The reaction mixture was concentrated *in vacuo* to give a pale brown oil which was subjected to silica gel column chromatography to afford **2b**, mp 149°, yield 123 mg (23%); ms: m/z 289 ($M^+$); $^1$H-nmr (deuteriochloroform): 1.22, 1.30 (each 3H, t, -$CH_2CH_3$ × 2), 3.15 (3H, d, J = 6 Hz, NHC$H_3$), 3.77 (3H, s, ester $CH_3$), 3.90, 4.07 (each 2H, q, -$CH_2CH_3$), 6.80, 7.67 (each 1H, d, J = 15 Hz, -CH=CH-, *trans*); uv (ethanol): λ max nm (log ε) 281 (4.88), 327 (4.95).

*Anal.* Calcd. for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.38; H, 6.68; N, 15.11.

Reaction of 1,3-Dimethyl (or Diethyl)-6-methylaminouracil with Methyl Propiolate by Heating and Irradiation.

a) After a solution of 1,3-dimethyl-6-methylaminouracil (**1a**, 1.69 g, 10 mmoles) and methyl propiolate (5.04 g, 60 mmoles) in dichloromethane (10 ml) was refluxed for 1 hour, the reaction mixture in acetone (300 ml) was irradiated with 400 W high pressure mercury lamp covered with a pyrex filter for 13 hours under nitrogen. The reaction mixture was evaporated to dryness *in vacuo* at room temperature and the residue was separated by preparative tlc (deuteriochloroform) to give **2a** (330 mg 13%), **4a** (133 mg, 6%), **5a** (177 mg, 7%) and trimethyl benzene-1,3,5-tricarboxylate (**3**, 28 mg).

1,3,8-Trimethylpyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*,3*H*,8*H*)-trione (**4a**).

This compound had mp 217°; ms: m/z 221 ($M^+$); $^1$H-NMR ($CDCl_3$), 3.37 (3H, s, $NCH_3$), 3.55 (3H, s, $NCH_3$), 3.58 (3H, s, $NCH_3$), 6.35 (1H, d, J = 11 Hz, -CH=CH-, *cis*), 7.94 (1H, d, J = 11 Hz, -CH=CH-, *cis*); $^{13}$C-nmr (deuteriochloroform): 28.42, 37.22, 38.92, 98.10, 114.42, 136.73, 151.18, 152.59, 159.75, 164.21; uv (ethanol): λ max nm (log ε) 283 (4.67), 334 (4.74).

*Anal.* Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.12; H, 4.81; N, 18.73.

1,3-Dimethyl-5-(*Z*)-(2-methoxycarbonylvinyl)-6-methylaminouracil (**5a**).

This compound was obtained as an oil; ms: m/z 253 ($M^+$); $^1$H-nmr (deuteriochloroform): 3.02 (3H, d, J = 6 Hz, -NHC$H_3$), 3.15 (3H, s, $NCH_3$), 3.31 (3H, s, $NCH_3$), 3.73 (3H, s, ester $CH_3$), 5.83 (1H, d, J = 11 Hz, -CH=CH-, *cis*), 6.98 (1H, d, J = 11 Hz, -CH=CH-, *cis*), 11.55 (1H, br, -N*H*$CH_3$); uv (ethanol): λ max nm (log ε) 285 (4.93), 316 (4.97).

*Anal.* Calcd. for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.02; H, 5.91; N, 16.36.

b) A reaction mixture of 1,3-diethyl-6-methylaminouracil (**1b**, 304 mg, 2 mmoles) and methyl propiolate (2 ml) was treated by heating and irradiating under the similar condition described above and **2b** (44 mg, 8%) and **4b** (35 mg, 7%) together with traces of starting material **1b** were isolated by preparative tlc from the resulting residue.

1,3-Diethyl-8-methylpyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*,3*H*,8*H*)-trione (**4b**).

This compound was obtained as an oil; ms: m/z 249 ($M^+$); $^1$H-nmr (deuteriochoroform): 1.23 (3H, t, -$CH_2CH_3$), 1.38 (3H, t, -$CH_2CH_3$), 3.57 (3H, s, -$NCH_3$); 4.00, 4.08 (each 2H, q, $CH_2CH_3$), 6.32 (1H, d, J = 9 Hz, -CH=CH-, *cis*), 7.92 (1H, d, J = 9 Hz, -CH=CH-, *cis*); uv (ethanol) λ max nm (log ε), 284 (4.65), 315 (4.69).

*Anal.* Calcd. for $C_{11}H_{15}N_3O_3$: C, 55.68; H, 6.37; N, 17.71. Found: C, 55.42; H, 6.21; N, 17.65.

Reaction of 1,3-Dimethyl-6-methylaminouracil with Diethyl Ethoxymethylenemalonate.

A reaction mixture of **1a** (3.5 g, 0.02 mole) and diethyl ethoxymethylenemalonate (2.5 g, 0.115 mole) was heated for 8 hours with stirring at a bath temperature of 200-230°. After allowing to stand at room temperature overnight, the precipitate (2.34 g, 39%) was collected by suction and washed with ether. Recrystallization from methanol was repeated several times to give pure analytical sample.

6-Ethoxycarbonyl-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4,7-[1*H*,3*H*,8*H*]-trione (**7**).

This compound had mp 223-226° (white needles); ms: m/z 393 ($M^+$); $^1$H-nmr (deuteriochloroform): 1.38 (3H, t, J = 7 Hz, -$CH_2CH_3$), 3.42 (3H, s, $NCH_3$), 3.61 (3H, s, $NCH_3$), 3.64 (3H, s, $NCH_3$), 4.36 (2H, q, J = 7 Hz, -$CH_2CH_3$), 8.77 (1H, s, -CH=); $^{13}$C-nmr (deuteriochloroform): 14.27, 28.47, 37.63, 38.92, 61.18, 97.22, 114.25, 141.90, 152.12, 153.41, 159.04, 160.45, 163.27.

*Anal.* Calcd. for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.16; N, 14.33. Found: C, 53.17; H, 5.11; N, 14.26.

Elimination of the Ethoxycarbonyl Group from **7**.

A solution of **7** (153 mg, 0.5 mmole) in acetic acid (10 ml) and concentrated hydrochloric acid (10 ml) was refluxed for 2 days until the strating material **7** disappeared in reaction mixture. After evaporation of solvent, the residue was treated by preparative tlc (chloroform:methanol = 9:1) to give **4a** (65.0 mg, 56% yield) which was in accord with presynthesized **4a** by direct comparison.

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