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Synthesis of Pyrido[2,3-*d*]pyrimidines from 6-Amino-1,3-dimethyluracil and Aldehydes

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Abstract—6-Amino-1,3-dimethyluracil reacted with aliphatic aldehydes on heating in formic acid to give mixtures of 1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetraone and the corresponding 5,6-dialkyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones. The reaction of 6-amino-1,3-dimethyluracil with 3-phenylprop-2-enal under analogous conditions afforded 6-benzyl-1,3-dimethyl-5-[(*E*)-2-phenylvinyl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione and 1,3-dimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. 1,3-Dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione was obtained in the reaction of the title compound with 3-phenylpropynaldehyde diethyl acetal.

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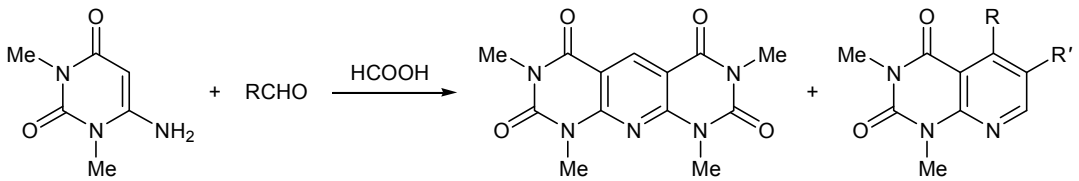
Pyrido[2,3-*d*]pyrimidine derivatives were found to exhibit a broad spectrum of biological activity [1–3]. A number of pyrimido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones were synthesized from 6-amino-5-formyl-1,3-dimethyluracil which can be prepared by reaction of 6-amino-1,3-dimethyluracil with acetic formic anhydride [4] or Vilsmeier reagent [5, 6]. 6-Amino-1,3-dimethyluracil reacts with aldehydes in water to give heteroaryl-substituted bis(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methanes [7]. 7-Amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione was synthesized by condensation of 6-amino-1,3-dimethyl-5-formyluracil with malononitrile. Likewise, reactions of the latter with ethyl cyanoacetate, ethyl acetoacetate, and cyanoacetic acid afforded pyrido[2,3-*d*]pyrimidine derivatives containing a carboxy or ethoxycarbonyl group in the 6-position [8]. 6-Amino-1,3-dimethyluracil was reported [9] to react with cinnamaldehyde in acetic acid with formation of 1,3-dimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.

We recently described [10] reactions of 6-amino-1,3-dimethyluracil (**1**) with aliphatic aldehydes **2a** and **2b** in formic acid, which led to the formation of mixtures of 1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetraone (**3**) and the corresponding 5,6-dialkyl-1,3-dimethylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-diones **4a** and **4b** (Scheme 1). The structure of **4a** and **4b** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, including 2D ^{1}H–^{13}S HSQC and HMBC data for **4a** [10]. A probable mechanism of formation of bicyclic compounds **4** (from butanal as

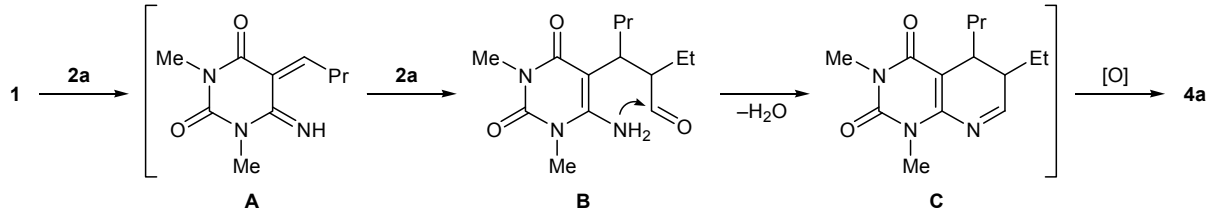
Scheme 1.



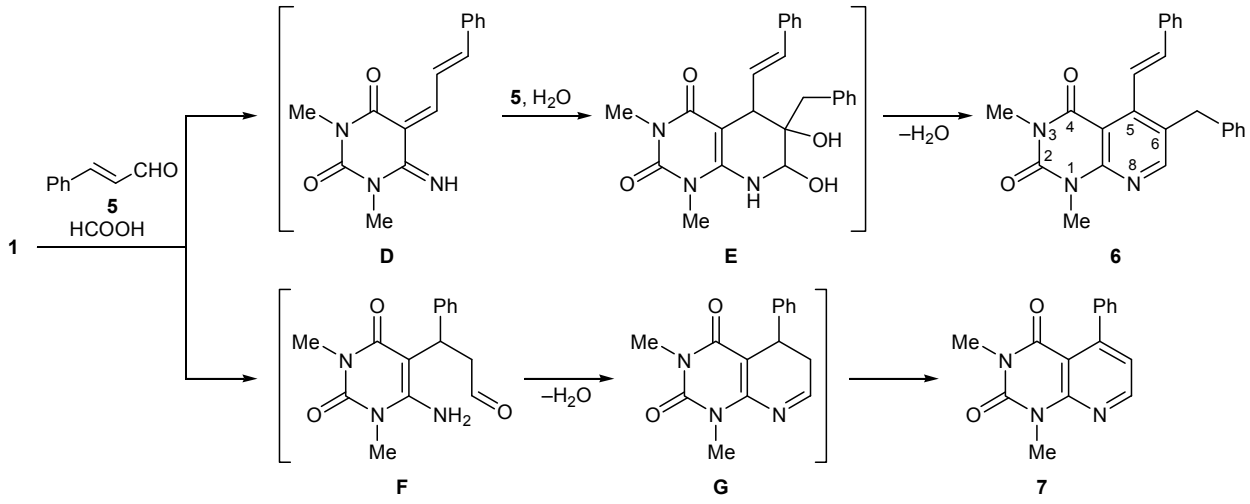
1 **2a**, **2b** **3** **4a**, **4b**

2, R = Pr (**a**), Bu (**b**); **4**, R = Pr, R′ = Et (**a**); R = Bu, R′ = Pr (**b**).

Scheme 2.



Scheme 3.

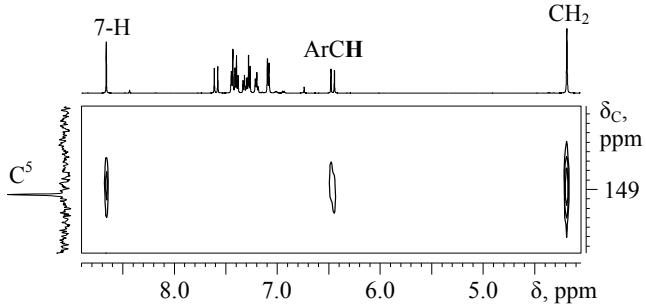


an example) is shown in Scheme 2. According to that scheme, Knoevenagel condensation product **A** reacts with the second butanal molecule at the exocyclic C=C bond to give intermediate **B** which undergoes intramolecular cyclization to **C**, and aromatization (oxidation) of the latter yields pyridopyrimidine **4a**. The oxidation of **C** may be effected by atmospheric oxygen or components of the reaction mixture. The oxidation process is likely to be accompanied by generation of formaldehyde which is necessary for the formation of dipyrimidine **3**. In fact, compound **3** [8] was synthesized by heating uracil **1** with formaldehyde in formic acid.

In continuation of our studies on the transformations of 6-amino-1,3-dimethyluracil (**1**), in the present work we examined its reactions with α,β-unsaturated aldehydes with the aim to develop new methods of synthesis of pyrido[2,3-*d*]pyrimidine derivatives. By heating aminouracil **1** with 3-phenylprop-2-enal **5** in formic acid we obtained a mixture of 6-benzyl-1,3-dimethyl-5-[(*E*)-2-phenylvinyl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**6**) and known [9] 1,3-dimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**7**) (Scheme 3).

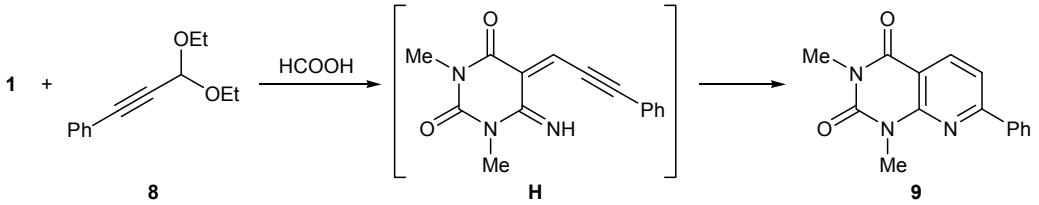
The structure of **6** was determined on the basis of ^{1}H and ^{13}C NMR spectra and two-dimensional NMR experiments. Methine carbon atoms were identified by cross-peaks with the corresponding protons in the 2D ^{1}H–^{13}C HSQC spectrum. Analysis of cross-peaks in the ^{1}H–^{13}C HMBC spectrum of **6** allowed us to assign quaternary carbon signals and determine the position of the substituents. Figure shows the most informative HMBC cross-peaks, which unambiguously confirm the structure of **6**. In fact, simultaneous correlations between C^5, on the one hand, and ArCH, 7-H, and CH_2 protons, on the other, are possible only for structure **6**.

Presumably, the scheme of formation of **6** involves intermediates **D** and **E**. The addition of the second



A fragment of the 2D ^{1}H–^{13}C HMBC spectrum of 6-benzyl-1,3-dimethyl-5-[(*E*)-2-phenylvinyl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**6**).

Scheme 4.



phenylpropenal molecule to the exocyclic C=C double bond of Knoevenagel condensation product **D** in aqueous formic acid gives intermediate **E** which loses two water molecules, yielding final pyridopyrimidine **6**. Alternatively, initial addition of uracil **1** through C^5 to the C=C double bond of phenylpropenal (intermediate **F**) and subsequent cyclization and aromatization of intermediate **G** lead to the formation of structure **7** (Scheme 3).

The reaction of **1** with 3-phenylpropynal diethyl acetal (**8**) in formic acid afforded 1,3-dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9**) which is isomeric to **7** (Scheme 4). The ^{1}H NMR spectrum of **9** displayed signals at δ 3.51 and 3.84 ppm due to methyl protons, aromatic multiplets at δ 7.50–7.54 (3H) and 8.10–8.15 ppm (2H), and doublets at δ 8.50 and 7.67 ppm due to 5-H and 6-H, respectively. Presumably, the reaction of uracil **1** with acetal **8** involves replacement of the ethoxy groups in the latter by C-nucleophile, followed by intramolecular addition–cyclization to the triple bond of intermediate **H**.

In summary, we have revealed a novel transformation where 6-aminouracil reacts successively with two aliphatic aldehyde molecules, so that the latter eventually act as a 1,3-dicarbonyl reagent. The reaction makes it possible to obtain 5,6-substituted pyrido[2,3-*d*]pyrimidines in one step. The reaction of aminouracil **1** with 3-phenylpropenal follows a similar path, i.e., two aldehyde molecules are involved with formation of 5,6-disubstituted pyridopyrimidine derivative in one step. However, in reactions with α,β-unsaturated aldehydes, condensation of **1** with one aldehyde molecule is also possible to give monosubstituted pyrido[2,3-*d*]pyrimidine.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-400 (400 and 100 MHz, respectively) and Avance-500 spectrometers (500 and 126 MHz). The mass spectra (electron impact, 75 eV) were obtained on a Shimadzu GCMS-QP2010 Ultra instrument (ion source temperature 200°C).

Reaction of 6-amino-1,3-dimethyluracil (1) with aldehydes 2a and 2b (*general procedure*). A mixture of 0.5 g (3.2 mmol) of aminouracil **1** and 12.8 mmol of butanal (**2a**) or pentanal (**2b**) in 5 mL of formic acid was stirred for 5 h at 50°C and was then evaporated by 3/4 under reduced pressure. The residue was treated with 3 mL of ethanol, and the precipitate was filtered off and washed with 2 mL of ethanol. Yield of 1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetraone (**3**) 25–30%, mp 321–323°C [8]. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 3.51 s (6H, CH_3), 3.76 s (6H, CH_3), 9.18 s (1H, 5-H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 28.53 (3-Me, 7-Me), 30.02 (1-Me, 9-Me), 106.41 (C^{4a}, C^{5a}), 140.88 (C^5), 151.15 (C^{9a}, C^{10a}), 153.59 (C^2, C^8), 159.86 (C^4, C^6). Mass spectrum, *m/z* (I_{rel}, %): 303 (100) $[M]^+$, 275 (23), 218 (12), 191 (77).

The mother liquor was diluted with an equal volume of water, and the precipitate was filtered off and recrystallized from high-boiling petroleum ether.

6-Ethyl-1,3-dimethyl-5-propylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (4a). Yield 55–60%, mp 109–110°C [10].

5-Butyl-1,3-dimethyl-6-propylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (4b). Yield 55–60%, mp 85–86°C [10].

Reaction of 6-amino-1,3-dimethyluracil (1) with formaldehyde. A mixture of 0.05 g (0.3 mmol) of aminouracil **1** and 0.1 mL (1.2 mmol) of formaldehyde solution in 3 mL of formic acid was stirred for 5 h at 50°C and was then evaporated by 3/4 under reduced pressure. The residue was treated with 3 mL of ethanol, and the precipitate was filtered off and washed with 2 mL of ethanol. Yield of **3** 0.032 g (67%).

Reaction of 6-amino-1,3-dimethyluracil (1) with 3-phenylprop-2-enal (5). A mixture of 0.5 g (3.2 mmol) of aminouracil **1** and 1.0 g (7.5 mmol) of aldehyde **5** in 5 mL of formic acid was stirred for 5 h at 50°C. The mixture was evaporated under reduced pressure, the residue was treated with 5 mL of ethanol, the mixture was stirred for 1.5–2 h, and the precipitate of 6-benzyl-1,3-dimethyl-5-[(*E*)-2-phenylethenyl]-

pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**6**) was filtered off and washed with 2.0 mL of cold (10°C) ethanol. Yield 0.38 g (30%), mp 139–140°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 3.25 s (3H, 3-Me), 3.58 s (3H, 1-Me), 4.19 s (2H, CH_2), 6.46 d (1H, 5-CH=C**H**, J = 16.8 Hz), 7.08 d (2H, *o*′-H,* J = 8.4 Hz), 7.20 t (1H, *p*′-H, J = 7.4 Hz), 7.26–7.33 m (3H, *m*′-H, *p*-H), 7.39 t (1H, *m*-H, J = 7.6 Hz), 7.44 d (2H, *o*-H, J = 8.4 Hz), 7.59 d (1H, 5-CH, J = 16.8 Hz), 8.66 s (1H, 7-H). ^{13}C NMR spectrum (126 MHz, DMSO-d_6) δ_C, ppm: 28.16 (3-Me), 29.55 (1-Me), 35.32 (CH_2), 107.98 (C^{4a}), 125.89 (5-CH), 126.13 ($C^{p'}$), 126.52 (C^{o}), 128.14 (C^{p}), 128.38 ($C^{o'}$), 128.51 ($C^{m'}$), 128.74 (C^{m}), 129.22 (C^{6}), 132.62 (5-CH=**C**H), 136.47 (C^{i}), 140.71 ($C^{i'}$), 149.05 (C^{5}), 150.10 (C^{8a}), 150.60 (C^{2}), 154.89 (C^{7}), 161.11 (C^{4}). Mass spectrum, m/z (I_{rel}, %): 383 (91) $[M]^+$, 305 (47), 292 (100). Found, %: C 75.00; H 5.62; N 10.68. $C_{24}H_{21}N_3O_2$. Calculated, %: C 75.18; H 5.52; N 10.96. M 383.45.

The alcoholic filtrate was evaporated under reduced pressure to a volume of 2–3 mL and cooled, and the precipitate was filtered off and recrystallized from a small amount of ethanol. Yield of of 1,3-dimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**7**) 0.10 g (12%), mp 169–170°C [8]. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 3.20 s (3H, 3-Me), 3.62 s (3H, 1-Me), 7.08 d (1H, 6-H, J = 4.9 Hz), 7.31 m (2H, H_{arom}), 7.39–7.43 m (3H, H_{arom}), 8.67 d (1H, 7-H, J = 4.9 Hz). ^{13}C NMR spectrum (100 MHz, DMSO-d_6) δ_C, ppm: 27.88, 29.63, 107.49, 121.55, 127.31 (2C), 127.58, 127.89 (2C), 139.08, 150.62, 151.50, 152.00, 153.05, 159.75. Mass spectrum, m/z (I_{rel}, %): 267 (65) $[M]^+$, 155 (100). $C_{15}H_{13}N_2O_2$. Calculated: M 267.28.

1,3-Dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9). A mixture of 0.155 g (1.0 mmol) of aminouracil **1** and 0.5 g (2.3 mmol) of 3-phenylpropynal (**8**) in 5 mL of formic acid was stirred for 5 h at 50°C. The mixture was evaporated under reduced pressure, the residue was stirred for 1.5–2 h in 3 mL of ethanol, the mixture was cooled to 10–15°C, and the precipitate was filtered off and washed with 2 mL of cold ethanol. Yield 0.05 g (25%), mp 172–173°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 3.51 s (3H, 3-Me), 3.84 s (3H, 1-Me), 7.50–7.54 m (3H, H_{arom}), 7.67 d (1H, 6-H, J = 8.0 Hz), 8.10–8.15 m (2H, H_{arom}), 8.50 d (1H, 5-H, J = 8.0 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 28.40, 29.39, 109.01, 115.12, 127.48 (2C), 128.93 (2C), 130.65, 137.48, 138.32, 150.72, 151.66, 161.20, 161.32. Mass spectrum, m/z (I_{rel}, %): 267 (100) $[M]^+$, 239 (55), 155 (70). Found, %: C 67.41; H 4.90; N 15.72. $C_{15}H_{13}N_2O_2$. Calculated, %: C 67.36; H 4.79; N 15.41. M 267.28.

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* Primed locants refer to the benzyl substituent on C^6.

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