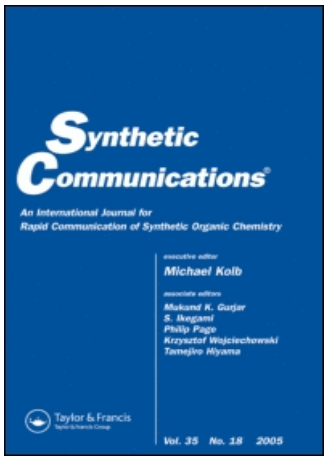

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Synthesis of Novel Classes of Pyrido[2,3-*d*]-pyrimidines, Pyrano[2,3-*d*]pyrimidines, and Pteridines

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Abstract: 6-Amino-5-formyluracils **1** and 5-formyl-6-hydroxyuracils **4** react with Meldrum's acid **2** in the presence of piperidine as catalyst under thermolytic conditions to afford 6-carboxy-2,4,7-trioxopyrido[2,3-*d*]pyrimidines **3** and 6-carboxy-2,4,7-trioxopyrano[2,3-*d*]pyrimidines **5** in good yield. Under identical conditions, 6-amino-5-nitrosouracils **6** react with **2** to afford pteridine-6-carboxylic acids **7** in good yields.

Keywords: Meldrum's acid, pteridines, pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines, uracil

The importance of uracil and its annelated substrates is well recognized by synthetic and biological chemists.[1] Pyrido[2,3-*d*]pyrimidines, pyrano[2,3-*d*]pyrimidines, and pteridines represent broad classes of annelated uracils and have received considerable attention over the past years because of their wide range of biological activities. A number of compounds with these ring systems have diverse pharmacological activity such as antibacterial,[2] antitumor,[3] cardiotonic,[4] hepatoprotective,[4a] antihypertensive,[4a] and anti-bronchits.[5] Some of them exhibit antialergic,[6] antimalerial,[7] analgesic,[8] and antifungal[9] properties. Therefore, large efforts have been directed toward the synthetic manipulation of uracils for the preparation of these molecules.[10] In this regard, the synthetic exploitation of the nucleophilic double bond of uracil is an important reaction strategy.[11]

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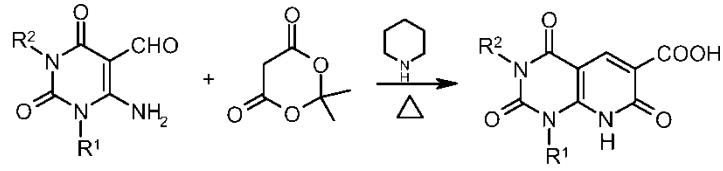
Meldrum's acid appears to be an attractive reagent in organic synthesis because of its high acidity, steric rigidity, and high reactivity.[12]

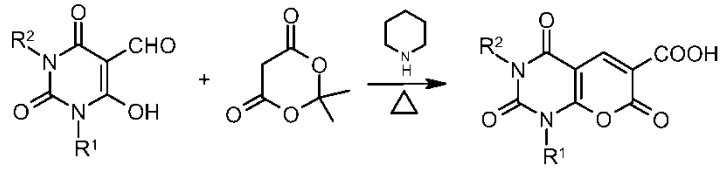
As a part of our continued interest in the development of highly expedient methods for the synthesis of annelated uracils of biological significance,[13] we recently utilized 6-amino-5-formyluracils and 5-formyl-6-hydroxyuracils as 1,4-dienes in a [4 + 2] cycloaddition reaction.[14] In the present article, we report the synthesis of novel classes of 6-carboxy-2,4,7-trioxopyrido[2,3-*d*]-pyrimidines, 6-carboxy-2,4,7-trioxopyrano[2,3-*d*] pyrimidines, and pteridine-6-carboxylic acids (lumazines) from 6-amino-5-formyluracils, 5-formyl-6-hydroxyuracils, and 6-amino-5-nitroso-uracils based on the cyclocondensation reaction, which allows access to a range of structural variation (Scheme 1).



1. a : R^1=R^2=CH_3
b : R^1=R^2=H
c : R^1=C_2H_5, R^2=H

2

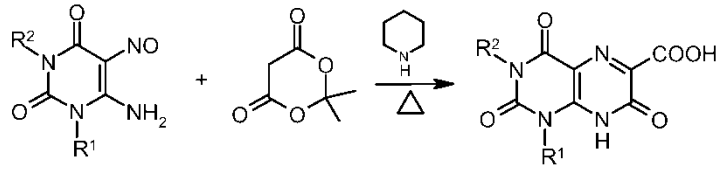
3a-c



4. a : R^1=R^2=CH_3
b : R^1=CH_3,R^2=H
c : R^1=C_2H_5, R^2=H

2

5a-c



6. a : R^1=R^2=CH_3
b : R^1=R^2=H
c : R^1=C_2H_5, R^2=H

2

7a-c

Scheme 1.

6-Amino-5-formyluracil **1a** was prepared from 6-amino-1,3-dimethyluracil[15] under the Vilsmeier–Haack formylation reaction condition.[16] In a typical experimental procedure, equimolar amounts of 6-amino-5-formyl uracil **1a** and Meldrum's acid **2** were refluxed in a mixture of methanol and chloroform (1:1) to afford 6-carboxy-2,4,7-trioxopyrido[2,3-*d*]pyrimidines **3a** in good yield. The structure of the compound **3a** was determined from the spectroscopic data and elemental analysis. The ^{1}H NMR spectrum showed the absence of the aldehyde proton and presence of a proton at δ 7.40 as a singlet and another broad peak for one proton at δ 8.95. The other signals appeared at δ 3.00 (s, 3H, N-CH_3) and 3.15 (s, 3H, NCH_3). The mass spectrum revealed a strong molecular ion peak at $(M+H)^+$ 252 (employing the positive ionization technique). The compound, on treatment with aqueous $NaHCO_3$ solution, evolves CO_2 with effervescence, which evidences the presence of a carboxylic acid group. Similarly, compounds **3b**,**c** were synthesized from the reaction of **1b**,**c** with **2** and characterized in Table 1.

Under identical conditions, 1,3-dimethyl-5-formyl-6-hydroxyuracil **4a**,[17] prepared from 1,3-dimethyl-6-hydroxyuracil, reacts with Meldrum's acid **2** to afford 6-carboxy-2,4,7-trioxo-pyrano[2,3-*d*]pyrimidine **5a** in good yields. The structure of the product was ascertained by spectroscopic and elemental analysis. The ^{1}H NMR spectrum showed the absence of the aldehyde proton and the presence of a proton at δ 7.95 as a singlet and a broad peak for one proton at δ 9.20. The other signals appeared at δ 3.05 (s, 3H, N-CH_3) and 3.10 (s, 3H, NCH_3). The mass spectrum exhibited a strong molecular ion peak at $(M+H)^+$ 253. Similarly, 6-carboxy-2,4,7-trioxopyrano[2,3-*d*]pyrimidines **5b**,**c** were synthesized from the reaction of **4b**,**c** with **2** and characterized in Table 1.

To explore the synthetic utility of the condensation process further, we studied the reactivity pattern of comparatively less reactive 6-amino-5-nitroso uracils **6** with Meldrum's acid **2** and found them to react moderately to afford

Table 1. Pyrido[2,3-*d*]pyrimidines **3**, pyrano[2,3-*d*]pyrimidines **5**, and pteridines **7**

Entry	Product	R^1	R^2	Reaction time (h)	Yield (%)	Mp (°C)
1	**3a**	CH_3	CH_3	18	61	345–347
2	**3b**	H	H	18	63	>350
3	**3c**	C_2H_5	H	18	57	>350
4	**5a**	CH_3	CH_3	20	63	278–280
5	**5b**	CH_3	H	20	60	337–339
6	**5c**	C_2H_5	H	20	56	>350
7	**7a**	CH_3	CH_3	21	70	326
8	**7b**	H	H	22	73	>330
9	**7c**	C_2H_5	H	21	69	>330

the ptridiene-6-carboxylic acid (lumazine) derivatives **7** in good yields. The structures of the compounds were confirmed from the spectroscopic data and elemental analysis (Table 1). The ^{1}H NMR of compound **7a** showed the presence of one proton at δ 9.10 as a singlet. The mass spectrum showed a strong molecular ion peak at $(M + H)^+$ 253. The IR spectrum showed the absence of the -NH_2 group and N═O group of the uracil derivative.

In conclusion, we have reported the synthesis of some novel classes of 6-carboxy-2,4,7-trioxo pyrido[2,3-*d*]pyrimidines, 6-carboxy-2,4,7-trioxo pyrano[2,3-*d*]pyrimidines, and lumazine derivatives by utilizing easily available organic synthones such as Meldrum's acid with suitably functionalized uracil derivatives.

EXPERIMENTAL SECTION

1,3-Dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*] pyrimidine-6-carboxylic Acid 3

In a typical experimental procedure, equimolar amounts of 1,3-dimethyl-6-amino-5-formyl uracil **1a** (2 mmol, 366 mg) and Meldrum's acid **2** (2 mmol, 288 mg) in the presence of piperidine (2 drops) were refluxed in a mixture of methanol and chloroform (1:1, 15 ml) for 18 h. The solvent was evaporated under reduced pressure, and the obtained solid compound was purified by preparative thin-layer chromatography (TLC) using chloroform–ethyl acetate (1:5) as eluent. The product **3a** was obtained in 61% yield (305.5 mg). Mp 345–347°C. ^{1}H NMR (300 MHz, $CDCl_3 + CH_3OD$) δ 3.00 (s, 3H), 3.15 (s, 3H), 7.40 (s, 1H), 8.95 (s, br, 1H). ^{13}C NMR (75 MHz) δ 28.5 (N-Me), 36.8 (N-Me), 107.20 (C-10), 142.15 (C-6), 143.00 (C-7), 144.50 (C-5), 150.20 (C-2), 154.00 (C-9), 157.25 (C-4), 168.00 (-COOH). IR KBr ν_{max} cm^{-1} 3400 (br), 1705, 1690, 1655. MS: $(M + H)^+$ 252. Anal. calcd. for $C_{10}H_9N_3O_5$ C, 47.80; H, 3.58; N, 16.73. Found C, 47.75; H, 3.45; N, 16.70.

1,3-Dimethyl-2,4,7-trioxo-1,2,3,4-tetrahydro-2*H*-pyrano[2,3-*d*] pyrimidine-6-carboxylic Acid 5

In a simple experimental procedure, equimolar amounts of 1,3-dimethyl-5-formyl-6-hydroxyuracil **4** (2 mmol, 368 mg) and Meldrum's acid **2** (2 mmol, 288 mg) in the presence of piperidine (2 drops) were refluxed in 15 ml of ethanol for 20 h. The solvent was evaporated under reduced pressure, and the solid compound obtained was purified by preparative TLC using chloroform–ethyl acetate (1:3) as eluent. The product **5a** was obtained in 63% yield (317 mg). Mp 278–280°C. ^{1}H NMR (300 MHz, $CDCl_3 + CH_3OD$) δ 3.05 (s, 3H), 3.10 (s, 3H), 7.95 (s, 1H), 9.20 (s, br, 1H). ^{13}C NMR (75 MHz) δ 29.18 (N-Me), 36.53 (N-Me), 107.00 (C-10),

144.23 (C-6), 145.00 (C-5), 151.10 (C-2), 153.80 (C-9), 156.75 (C-4), 169.17 (-COOH), 171.00 (C-7). IR KBr ν_{max} cm^{-1} 3450 (br), 1750, 1705, 1690, 1660. MS: $(M + H)^+$ 253. Anal. calcd. for $C_{10}H_8N_2O_6$ C, 47.61; H, 3.17; N, 11.11. Found C, 47.58; H, 3.14; N, 11.05.

1,3-Dimethyl-2,4,7-trioxo-1,2,3,4,7,8 hexahydropteridine-6-carboxylic Acid 7

In a typical experimental procedure, equimolar amounts of 1,3-dimethyl-6-amino-5-nitroso uracil **6a** (2 mmol, 368 mg) and Meldrum's acid 2 (2 mmol, 288 mg) and 0.25 mmol of NaOH were refluxed in water for 21 h. The solvent was evaporated under reduced pressure, and the solid compound obtained was purified by column chromatography using chloroform–ethyl acetate (1:3) as eluent. The product **7a** was obtained in 70% yield (401 mg). Mp 326°C. ^{1}H NMR (300 MHz, $CDCl_3 + CH_3OD$) δ 3.00 (s, 3H), 3.10 (s, 3H), 8.10 (s, 1H). ^{13}C NMR (75 MHz) δ 29.00 (N-Me), 36.50 (N-Me), 108.50 (C-10), 142.50 (C-6), 143.00 (C-7), 149.50 (C-2), 155.00 (C-9), 157.50 (C-4), 168.00 (-COOH). IR KBr ν_{max} cm^{-1} 3430, 1735, 1695, 1660. MS: $(M + H)^+$ 253. Anal. calcd. for $C_{15}H_{17}N_3O_3$ C, 62.71; H, 5.92; N, 14.63. Found: C, 62.68; H, 5.87; N, 14.70.

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