A Facile Synthesis of 7-Substituted Pyrimido[4,5-*d*]-pyrimidine-2,4-diones

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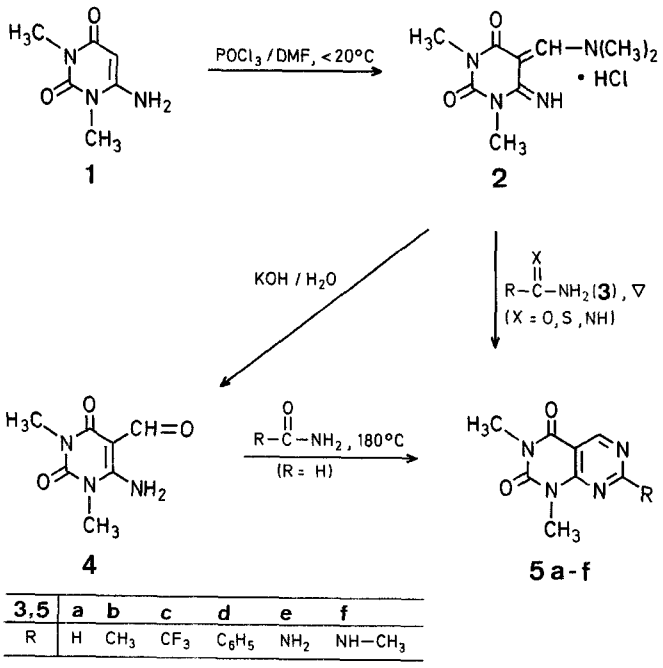
Synthetic studies on the fused pyrimidines have been extensively in connection with the biologically important purines and pteridines. However, only a few methods for the synthesis of 7-substituted pyrimido[4,5-*d*]pyrimidine-2,4-diones are known[1,2,3]. In the course of our investigations on the reactions of 6-amino-1,3-dimethyluracil (**1**), we have found a versatile and convenient method for the preparation of pyrimido[4,5-*d*]pyrimidines, involving the use of 6-imino-1,3-dimethyl-5-[(dimethylamino)-methylene]-5,6-dihydrouracil hydrochloride (**2**)[4] prepared in quantitative yield by treatment of **1** with phosphoryl chloride in dimethylformamide. Compound **2** is easily hydrolyzed to 6-amino-5-formyl-1,3-dimethyluracil (**4**)[2,5] upon treatment with aqueous potassium hydroxide. The reaction of **2** with the amides **3a-d** (X = O) at higher temperature affords 1,3-dimethylpyrimido[4,5-*d*]pyrimidin-2,4-dione (**5a**)[1], and the 7-substituted derivatives **5b-d**, respectively, in good yields. Similarly, heating of compound **4** with formamide (**3a**, X = O) results in the formation of **5a**.

Whereas analogous treatment of **2** with thiourea (**3e**, X = S) fails to produce the 7-amino derivative **5e**, this compound is obtained by heating the reactants in ethanolic sodium ethoxide. Similarly, the *N*-methyl product **5f** is formed. Compound **5e** can also be prepared by reaction of **2** with guanidine (**3g**, X = NH). All new compounds give satisfactory microanalyses and exhibit spectra completely in accord with the assigned structures (Table).



3,5	a	b	c	d	e	f
R	H	CH_3	CF_3	C_6H_5	NH_2	NH–CH_3

6-Imino-1,3-dimethyl-5-[(dimethylamino)-methylene]-5,6-dihydrouracil Hydrochloride (2):

To a suspension of **1** (20 g, 129 mmol) in dimethylformamide (550 ml) is added dropwise at < 20 °C phosphoryl chloride (21.6 g, 141 mmol). The mixture is stirred for 30 min. The precipitate is collected by filtration and washed with acetone to give **2**; yield: 30 g (95%); m.p. 206–210 °C. This product is used for the next step without further purification.

$C_9H_{15}ClN_4O_2$	calc.	C 43.82	H 6.13	N 22.71
(246.7)	found	43.30	6.16	22.66

^{1}H-N.M.R. (DMSO-d_6): δ = 3.12 (s, 3H); 3.27 (s, 3H); 3.37 (s, 3H); 3.62 (s, 3H); 8.63 (s, 1H); 9.00 ppm (br. s, 2H).

M.S.: *m/e* = 210 (M^+—HCl).

Hydrolysis of 2:

A mixture of **2** (1 g, 4 mmol) and potassium hydroxide (0.23 g, 41 mmol) in water (20 ml) is stirred for 30 min. The precipitate is collected by filtration and recrystallized form ethanol to give **4**; yield: 0.55 g (74%); m.p. 199–201 °C (Lit. m.p. 198 °C[2], 194–196 °C[5]); which is identical with an authentic sample prepared according to Ref.[2].

Table. 7-Substituted Pyrimido[4,5-*d*]pyrimidine-2,4-diones (**5a–f**) prepared

Product	Reagent **3**		Reaction conditions		Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	^{1}H-N.M.R. (solvent/TMS) δ [ppm]
	R	x	time [h]	temp. [°C]				
5a	H	O	4	160°	92	145–146° (H_2O)	148–149°[1]	($CDCl_3$): 3.49 (s, 3H); 3.71 (s, 3H); 9.16 (s, 1H); 9.30 (s, 1H)
5b	CH_3	O	1.3	reflux	71	113–115° (C_2H_5OH)	$C_9H_{11}N_4O_2$ (206.2)	($CDCl_3$): 2.81 (s, 3H); 3.48 (s, 3H); 3.70 (s, 3H); 9.23 (s, 1H)
5c	CF_3	O	7	120°	64	135–139° (C_2H_5OH)	$C_9H_7F_3N_4O_2$ (260.2)	($CDCl_3$): 3.51 (s, 3H); 3.76 (s, 3H); 9.45 (s, 1H)
5d	C_6H_5	O	2	170°	71	279–281° (C_2H_5OH)	268°[2]	(CF_3COOH): 3.60 (s, 3H); 3.97 (s, 3H); 7.50–8.10 (m, 3H); 8.25–8.55 (m, 2H); 9.63 (s, 1H)
5e	NH_2	S	18	reflux[b]	52	> 300° (CH_3OH)	$C_8H_9N_5O_2$ (207.2)	(DMSO-d_6): 3.25 (s, 3H); 3.45 (s, 3H); 7.66 (br. s, 2H); 8.69 (s, 1H)
5e	NH_2	NH	2	reflux[c]	81			
5f	H_3C-NH	S	15	reflux[b]	70	260.5° (C_2H_5OH)	$C_9H_{11}N_5O_2$ (221.2)	(CF_3COOH): 3.22 (d, 3H, *J* = 4 Hz); 3.48 (s, 3H); 3.72 (s, 3H); 8.05 (br. s, 1H); 8.99 (s, 1H)

[a] Satisfactory microanalysis obtained; C ± 0.17, H ± 0.11, N ± 0.26.
[b] In ethanolic sodium ethoxide.
[c] In ethanol.

7-Substituted 1,3-Dimethylpyrimido[4,5-*d*]pyrimidine-2,4-diones 5a-d, General Procedure:

A mixture of **2** (0.495 g, 2 mmol) and the amide **3** (20 mmol) is heated (Table). For the isolation of **5d**, the resulting mixture is dissolved in ethanol (20 ml) and the precipitate is separated by filtration. Compounds **5a-c** are obtained by dissolving the resulting mixture in water (20 ml) and extraction of the solution with chloroform (100 ml). The extract is dried with magnessium sulfate and the solvent is removed under reduced pressure. Recrystallisation from an appropriate solvent gives an analytically pure sample of **5** (Table).

Reaction of 4 with Formamide:

A mixture of **4** (0.549 g, 3 mmol) and formamide (**3a**, X = O; 1.35 g, 30 mmol) is heated at 180 °C for 5 h. The mixture is dissolved in water (20 ml) and the solution is extracted with chloroform (100 ml). The extract is dried with magnesium sulfate and the solvent is removed under reduced pressure to give **5a**, which is identical with the compound prepared above; yield: 0.41 g (71%).

7-Amino-1,3-dimethylpyrimido[4,5-*d*]pyrimidines 5e,f; General Procedure:

A mixture of **2** (0.74 g, 3 mmol) and the corresponding thiourea (32 mmol) in ethanolic sodium ethoxide [prepared from sodium (0.21 g, 9 mmol) in dry ethanol (50 ml)] is refluxed (Table). The solvent is removed under reduced pressure and the residue is dissolved in water (20 ml). The precipitate is collected by filtration. Recrystallization from an appropriate solvent gives an analytically pure sample (Table).

Reaction of 2 with Guanidine:

Guanidine nitrate (3.8 g, 32 mmol) is stirred in ethanolic sodium ethoxide [prepared from sodium (0.51 g, 22 mmol) in dry ethanol (50 ml)] for 10 min. After the insoluble sodium nitrate formed is removed by filtration compound **2** (0.74 g, 3 mmol) is added. The mixture is refluxed for 2 h and the precipitate is collected by filtration. Recrystallization from methanol gives analytically pure **5e** which is identical with the compound prepared above; yield: 0.50 g (81%).

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[4] For convenience, only one of the possible tautomeric formulae for compound **2** is given.
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