

PYRIMIDINES. PART 57.¹ A VERSATILE SYNTHESIS OF PYRIMIDO-
[4,5-d]PYRIMIDINE-2,4,5-TRIONE DERIVATIVES

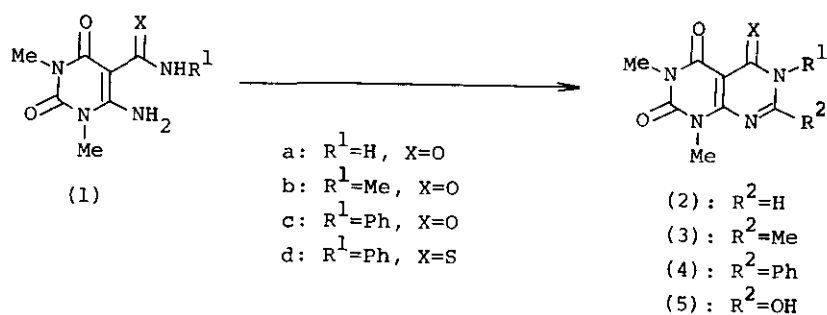
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Abstract - Synthesis of pyrimido[4,5-d]pyrimidine derivatives (2-5) was effected by cyclization of 6-amino-5-carbamoyluracil derivatives (1) with one-carbon reagents such as dimethylformamide dimethylacetal, acid anhydrides, and N,N'-carbonyldiimidazole.

Bicyclic fused pyrimidine derivatives have been received much attention in connection with the biologically significant system such as purines and pteridines.³ The synthesis of pyrimido[4,5-d]pyrimidine-2,4-dione derivatives, 5-deaza and 6-aza analogue of pteridines, has been accomplished by the cyclization of 6-aminouracil derivatives⁴ and the ring transformation of other fused pyrimidine-2,4-diones.⁵ Recently, we have also reported a convenient synthetic method of the pyrimido[4,5-d]pyrimidine-2,4-diones from 6-aminouracil derivatives.⁶ The present paper describes a versatile synthesis of pyrimido[4,5-d]pyrimidine-2,4,5-triones, involving the cyclization of 6-amino-5-carbamoyl(or 5-thiocarbamoyl)uracils (1) with one-carbon reagents such as dimethylformamide dimethylacetal (DMF-DMA), acid anhydrides, and N,N'-carbonyldiimidazole.

6-Amino-5-carbamoyl-1,3-dimethyluracil (1a), employed here as a starting material, was prepared by the reaction of 6-amino-5-ethoxycarbonyl-1,3-dimethyluracil^{5a} with ammonia. 6-Amino-5-(N-substituted carbamoyl)-1,3-dimethyluracil derivatives (1b-d) were synthesized upon treatment of 6-amino-1,3-dimethyluracil with methyl isocyanate, phenyl isocyanate, and phenyl isothiocyanate according to the previously reported procedure.⁷

After the reaction of the 5-carbamoyluracils (1a-d) with DMF-DMA in DMF at 80-90°C, dilution of the reaction mixture with ethanol allowed with easy deposition of 7-unsubstituted pyrimido[4,5-d]pyrimidines (2a-d). In the above reaction, when (1a) was heated at high temperature (140-150°C), the resulting product was (2b) rather than (2a), which can be formed by further N-methylation of (2a) with the excess DMF-DMA.



Scheme 1

Table 1 Preparation of Pyrimido[4,5-d]pyrimidine-2,4,5-trione Derivatives

Starting compound No.	Reagent	Reaction time	Product				Recryst. solvent	mp (°C)	Yield (%)
			No.	R^1	R^2	X			
(1a)	DMF-DMA	3h	(2a)	H	H	O	MeOH	>300	81
(1b)	DMF-DMA	2h	(2b)	Me	H	O	EtOH	217-218	70
(1c)	DMF-DMA	10min	(2c)	Ph	H	O	EtOH	245-246	66
(1d)	DMF-DMA	2h	(2d)	Ph	H	S	MeCN	282-284	95
(1a)	Ac ₂ O	1h	(3a)	H	Me	O	DMF	>300	83
(1b)	Ac ₂ O	3h	(3b)	Me	Me	O	AcOEt	220-221	91
(1c)	Ac ₂ O	23h	(3c)	Ph	Me	O	MeCN	298-300	83
(1d)	Ac ₂ O	5h	(3d)	Ph	Me	S	MeCN	289-291	76
(1a)	(PhCO) ₂ O	4h	(4a)	H	Ph	O	DMF	>300 ^{a)}	88
(1b)	(PhCO) ₂ O	9h	(4b)	Me	Ph	O	MeOH	203-204	83
(1b)	() ₂ CO	1h	(5b)	Me	OH	O	AcOH	>300	80
(1c)	() ₂ CO	4h	(5c)	Ph	OH	O	EtOH-H ₂ O	>300	85

a) Lit.^{5a} mp >300°C

The reaction of (1) with acid anhydrides such as acetic anhydride and benzoic anhydride caused the cyclization leading to 7-methyl- (3a-d) and 7-phenyl-pyrimido[4,5-d]pyrimidines (4a,b), respectively, in high yields. Treatment of 5-(N-phenylcarbamoyl)uracils (1c,d) with benzoic anhydride, however, did not give the expected 6,7-diphenyl products (4c,d) and resulted in the recovery of the starting materials, which could be ascribed to the steric reason.

Table 2 Spectral and Analytical Data of Pyrimido[4,5-d]pyrimidines (2)-(5)

Compound No.	UV (EtOH) λ max, nm(ϵ)	NMR ^a (δ)	Formula	Calcd. (found)		
				C	H	N
(2a)	232(27100), 267(3000) 294(3100)	8.73(A) C ₇ -H	C ₈ H ₈ N ₄ O ₃	46.15 (46.27)	3.87 3.86	26.92 27.14
(2b)	232(31100), 270(6100) 292(4400)	8.76(B) C ₇ -H	C ₉ H ₁₀ N ₄ O ₃	48.65 (48.45)	4.57 4.75	25.22 25.22
(2c)	234(34200) 274(9000)	8.60(A) C ₇ -H	C ₁₄ H ₁₂ N ₄ O ₃	59.15 (59.11)	4.26 4.21	19.71 19.75
(2d)	222(15400) 263(15900) 318(15400)	8.96(B) C ₇ -H	C ₁₄ H ₁₂ N ₄ O ₂ S 1/2H ₂ O	54.36 (54.51)	4.24 3.91	18.11 18.34
(3a)	232(29200) 263(3500) 293(5300)	2.75(A) C ₇ -Me	C ₉ H ₁₀ N ₄ O ₃	48.65 (48.78)	4.54 4.54	25.22 25.31
(3b)	233(31100) 267(5600) 295(5200)	2.63(B) C ₇ -Me	C ₁₀ H ₁₂ N ₄ O ₃	50.84 (50.83)	5.12 5.15	23.72 23.72
(3c)	234(36100) 266(6600) 297(4600)	2.21(B) C ₇ -Me	C ₁₅ H ₁₄ N ₄ O ₃	60.39 (60.28)	4.73 4.74	18.78 18.78
(3d)	226(13400) 257(12200) 318(12000)	2.24(B) C ₇ -Me	C ₁₅ H ₁₄ N ₄ O ₂ S	57.13 (57.57)	4.49 4.47	17.82 18.09
(4a)	238(18300) 278(8400) 314(8500)		C ₁₄ H ₁₂ N ₄ O ₃	59.15 (59.16)	4.26 4.25	19.71 19.61
(4b)	235(30600) 271(7400) 306(7900)		C ₁₅ H ₁₄ N ₄ O ₃	60.39 (60.36)	4.73 4.76	18.78 18.84
(5b)	227(30100) 274(15500)		C ₉ H ₁₀ N ₄ O ₄	45.38 (45.23)	4.23 4.26	23.52 23.49
(5c)	228(37800) 276(15100)		C ₁₄ H ₁₂ N ₄ O ₄	56.00 (56.18)	4.03 4.03	18.66 18.75

a) Solvent: A = CF₃COOH; B = DMSO-d₆

7-Oxo derivatives (5b and 5c) were obtained with easy by the reaction of 5-(N-substituted carbamoyl)uracils (1b and 1c) with N,N'-carbonyldiimidazole in DMF at 110-120°C. The reaction of 5-(N-unsubstituted carbamoyl)- (1a) and 5-thio-carbamoyluracils (1d), however, afforded an intractable mixture and the expected products (5a and 5d) could not be isolated in pure form.

These results are summarized in Table 1 and 2.

In conclusion, the reaction of 6-amino-5-carbamoyluracils with one-carbon reagents serves as a convenient method for the preparation of 7-substituted pyrimido[4,5-d]pyrimidine-2,4,5-triones.

EXPERIMENTAL

Melting points were taken on a Yanagimoto melting-point apparatus and are uncorrected. Ultraviolet spectra (UV) were obtained from ethanol solution on a Shimadzu 260 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined with a Hitachi Perkin-Elmer R-20B (60MHz) instrument for solutions in $(\text{CD}_3)_2\text{SO}$ and CF_3COOH , using sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard.

6-Amino-5-carbamoyl-1,3-dimethyluracil (1a): A solution of 6-amino-5-ethoxycarbonyl-1,3-dimethyluracil^{5a} (500mg, 2.2 mmole) and 30% NH_4OH (10ml) in DMF (10ml) was heated in a sealed tube at 100°C for 6 h. The reaction mixture was evaporated under reduced pressure and the residue was triturated with water. The resulting precipitate was collected by filtration and recrystallized from ethyl acetate to give 305mg (70%) of (1a), mp 267-268°C. Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{N}_4\text{O}_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.45; H, 5.07; N, 28.30.

6-Amino-1,3-dimethyl-5(N-methylcarbamoyl)uracil (1b) and 6-amino-1,3-dimethyl-5-(N-phenylcarbamoyl)uracil (1c) were prepared by the reaction of 6-amino-1,3-dimethyluracil with methyl isocyanate and phenyl isocyanate.^{7b}

6-Amino-1,3-dimethyl-5-(N-phenylthiocarbamoyl)uracil (1d): A solution of 6-amino-1,3-dimethyluracil (500mg, 3.2 mmole) and phenyl isothiocyanate (1.3g, 9.6 mmole) in dry DMF (10ml) was stirred at 90°C for 9 h. The solvent was removed by distillation under reduced pressure. The residue was washed fully with hot ethanol. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 860mg (93%) of (1d), mp 218-219°C. Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$: C, 53.79; H, 4.86; N, 19.30. Found: C, 54.07; H, 4.90; N, 19.14.

1,3-Dimethylpyrimido[4,5-d]pyrimidine-2,4,5-triones (2a-c) and 1,3-Dimethylpyrimido[4,5-d]pyrimidine-2,4-dione-5-thione (2d) (Table 1 and 2): A solution of (1a-d) (1.8 mmole) and DMF-DMA (2.7 mmole) in dry DMF (1ml) was heated at 80-90°C until the starting material disappeared. After cooling, the reaction mixture was triturated with ethanol. The resulting precipitate was collected by filtration to give the products (2a-d).

1,3,6-Trimethylpyrimido[4,5-d]pyrimidine-2,4,5-trione (2b): A solution of (1a) (250 mg, 1.3 mmole) and DMF-DMA (300 mg, 2.5 mmole) in dry DMF (1 ml) was heated at 140-150°C for 2.5 h. The reaction mixture was treated as described above to give 245 mg (90%) of (2b), which was identical with the compound obtained above by the reaction of (1b) with DMF-DMA.

1,3,7-Trimethylpyrimido[4,5-d]pyrimidine-2,4,5-triones (3a-c) and 1,3,7-Trimethylpyrimido[4,5-d]pyrimidine-2,4-dione-5-thione (3d) (Table 1 and 2): A mixture of (1a-d) (1.1 mmole) and acetic anhydride (3 ml) was heated under reflux* until the starting material disappeared. After cooling, the reaction mixture was triturated with ether. The resulting precipitate was collected by filtration and recrystallized to give the products (3a-d).

* When the 5-(N-phenylthiocarbamoyl)uracil (1d) was employed, the reaction was carried out at 100°C.

1,3-Dimethyl-7-phenylpyrimido[4,5-d]pyrimidine-2,4,5-trione (4a) (Table 1 and 2): A mixture of (1a) (320mg, 1.5 mmole) and benzoic anhydride (3.4g, 15 mmole) was heated at 170-190°C. After cooling, the reaction mixture was dissolved in CHCl_3 . The solution was washed with aqueous solution of NaHCO_3 and dried over MgSO_4 . The chloroform was removed by evaporation and the residue was triturated with ether. The resulting precipitate was collected by filtration and recrystallized from DMF to give the product (4a).

1,3,6-Trimethyl-7-phenylpyrimido[4,5-d]pyrimidine-2,4,5-trione (4b) (Table 1 and 2): A mixture of (1b) (0.9g, 4.2 mmole) and benzoic anhydride (6.0g, 26.5 mmole) was heated at 170-190°C. After cooling, the reaction mixture was washed fully with ether and then the ether was removed by decantation. The residue was recrystallized from MeOH to give (4b).

1,3-Dimethylpyrimido[4,5-d]pyrimidine-2,4,5,7-tetrones (5b and 5c) (Table 1 and 2): A mixture of (1b,c) (1.8 mmole) and N,N'-carbonyldiimidazole (2.4 mmole) in dry DMF (5 ml) was heated at 110-120°C. After cooling, the resulting precipitate was collected by filtration and recrystallized to give the products (5b and 5c).

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