A Novel and Expedient Synthesis of 7-Pyrimidinylpyrimido[4,5-*d*]pyrimidinones

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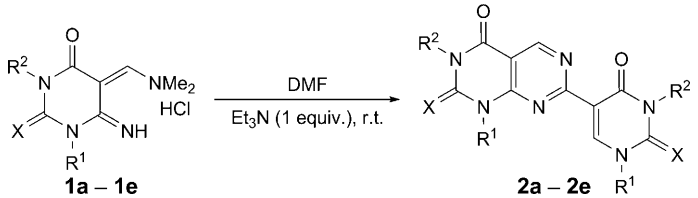
A novel and efficient procedure for the synthesis of new 7-pyrimidinylpyrimido[4,5-*d*]pyrimidinone derivatives was elaborated *via* the base-promoted cyclodimerization reaction of 5-[(dimethylamino)-methylidene]-6-iminopyrimidine-2,4(1*H*,3*H*)-dione hydrochlorides. In an analogous manner, a 2-thioxo analog was prepared starting with the corresponding 2-thioxopyrimidin-4-one.

Introduction. – N-containing heterocycles have attracted considerable attention as they are integral components of many natural products, dyes, agrochemicals, and pharmaceuticals. Among the condensed N-heterocycles, pyrimido[4,5-*d*]pyrimidines represent an attractive target due to their interesting pharmacological activities regarding the modulation of antitumor drug acitivity [1], antioxidant (lipid peroxidation inhibitors) [2], and antiviral activities [3], and potent inhibitory action on the tyrosine kinase domain of epidermal growth factor receptor [4], 5-phosphoribosyl-1-pyrophosphate synthetase [5], and dihydrofolate reductase [6]. Some of them are used clinically as effective cardiovascular [7] and antineoplastic agents [8]. The most promising methods up to now for the synthesis of pyrimido[4,5-*d*]pyrimidines are derived from multistep cyclocondensation reactions of pyrimidine and uracil derivatives [9][10] and usually required drastic conditions, long reaction times, and complex synthetic pathways.

Results and Discussion. – 5-[(Dimethylamino)methylidene]-6-imino-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride (**1a**) was previously synthesized from the reaction of 6-amino-1,3-dimethyluracil and $SOCl_2$ in DMF and used frequently as precursor for efficient syntheses of various pyrimidine fused heterocycles [9a][11]. In continuation of our studies and the development of highly expedient methods for the synthesis of annulated uracils of potentially biological importance [12], we report herein a novel and simple method for the efficient synthesis of some new 7-pyrimidinylpyrimido[4,5-*d*]pyrimidinone derivatives in excellent yields within a few minutes (*Table*).

The experimental procedure for this reaction is remarkably simple and does not require the use of vigorous conditions or inert atmospheres. When a solution of the salt

Table. *Synthesis of New Derivatives of 7-Pyrimidinylpyrimido[4,5-*d*]pyrimidinones* **2a**–**2e**



1a – **1e** **2a** – **2e**

2[a])	R^1	R^2	X	Yield[b])
a	Me	Me	O	95
b	Me	H	O	90
c	Ph	H	O	80
d	$PhCH_2$	H	O	88
e	Me	Me	S	95

[a]) The structures of the products **2a**–**2e** were fully characterized by NMR and mass spectroscopy. [b]) Refers to isolated pure products.

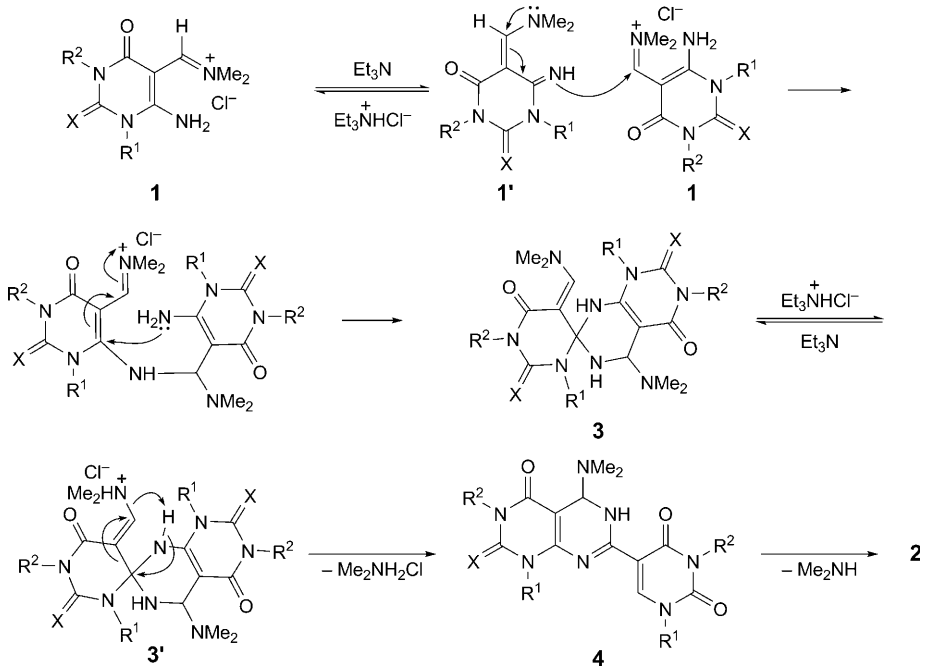
1 in DMF was treated with Et_3N, 7-pyrimidinylpyrimido[4,5-*d*]pyrimidinone derivatives **2** were produced and simply isolated by addition of H_2O to the mixture and filtration of the product. The reactions proceeded rapidly under mild conditions and the results were excellent in terms of yields and product purity. However, in the absence of Et_3N, the products were obtained in low yields after long reaction times. This indicates that a basic catalyst is required for this reaction. The results are summarized in the *Table*.

Except for **2a**, which has also been synthesized independently *via* condensation reaction of 6-amino-1,3-dimethyl-5-thioformyluracil derivatives with enamines [13], all other products **2** are new and were characterized on the basis of their elemental analyses and IR, ^{1}H-NMR, ^{13}C-NMR, and MS data. For example, the ^{1}H-NMR spectrum of **2d** exhibited two sharp *singlet*s at δ(H) 4.38 and 5.21, readily recognized as arising from two $PhCH_2$ groups along with *singlet*s at δ(H) 8.05 and 8.79 for the uracil and pyrimidopyrimidine =CH groups, respectively. Additional signals for ten aromatic H-atoms are located as *mutiplet*s in the range of δ(H) 7.25–7.33, and two NH groups resonated at δ(H) 10.78 and 11.66. The ^{1}H-decoupled ^{13}C-NMR spectrum of **2d** showed 20 distinct resonances in agreement with the proposed structure. The signals at δ(C) 43.0 and 44.0 ppm correspond to the benzylic CH_2 groups. The mass spectrum of **2d** revealed a strong molecular ion peak at *m*/*z* 454, which confirmed the proposed molecular formula for this compound.

A reasonable mechanism for the formation of the product **2** is outlined in the *Scheme*. The reaction occurs *via* an initial formation of the spiro[pyrimidine-4,2′-pyrimido[4,5-*d*]pyrimidine] derivative **3**, *via* cyclocondensation of **1** as shown in the *Scheme*. The intermediate **3** can take a H-atom to form **3′**, which suffers a rearrangement together with elimination of dimethylammonium chloride to give the 5,6-dihydro-7-pyrimidinylpyrimido[4,5-*d*]pyrimidine **4**. The latter then undergoes subsequent Me_2NH elimination to afford the fully aromatized product **2**. Probably, the most important role of Et_3N is the deprotonation of **1** to form the relatively

electron-rich species **1′**, which undergoes a faster cyclodimerization reaction with **1**, compared with the same dimerization reaction which slowly takes place in the absence of Et_3N.

Scheme. *Proposed Mechanism for the Base-Promoted Synthesis of 7-Pyrimidinylpyrimido[4,5-*d*]pyrimidinones* **2**



In conclusion, our results demonstrate a novel, simple, and efficient synthesis of new 7-pyrimidinylpyrimido[4,5-*d*]pyrimidinone derivatives of potential biological significance in excellent yields.

Experimental Part

General. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-470* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker 500 DRX AVANCE* at 500 and 125 MHz, resp.; δ in ppm. EI-MS: *Shimadzu QP 1100EX* mass spectrometer operating at an ionization potential of 14 eV. Elemental analyses (CHN) were performed using a *Heraeus CHN-O-Rapid* analyzer.

Compounds **1a**–**1e** were synthesized based on a published procedure [9a][11] and characterized by their ^{1}H-NMR spectra. Other chemicals were of commercial grade and used without further purification.

*7-Pyrimidinylpyrimido[4,5-*d*]pyrimidinones. General Procedure.* A mixture of *5-[(dimethylamino)-methylidene]-6-imino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione hydrochloride* (**1a**, 0.247 g, 1 mmol) and Et_3N (0.140 ml, 1 mmol) in DMF (5 ml) was stirred at r.t. for 30 min. Then, H_2O (20 ml) was added, the mixture was filtered, and the obtained precipitate was washed with hot H_2O (3×10 ml) to give the pure 1,3-dimethyl-7-(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**2a**) in 95% yield. All products were sufficiently pure for IR, NMR, and MS analysis. In the cases that more pure product was necessary (*i.e.*, CHN analysis) it could be recrystallized from a DMSO/H_2O (70:30) mixture.

*1,3-Dimethyl-7-(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**2a**). Yield: 314 mg (95%). White powder. M.p. 310° [13]. IR (KBr): 1726, 1656. ^{1}H-NMR ((D$_6$)DMSO): 3.29 (*s*, Me); 3.34 (*s*, Me); 3.52 (*s*, Me); 3.63 (*s*, Me); 8.50 (*s*, =CH); 8.75 (*s*, =CH). ^{13}C-NMR ((D$_6$)DMSO): 28.7; 28.8; 29.7; 38.4; 106.0; 110.5; 149.1; 151.5; 156.7; 158.6; 160.2; 160.5; 165.0; 168.1.

1-*Methyl-7-(1,2,3,4-tetrahydro-1-methyl-2,4-dioxopyrimidin-5-yl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**2b**). Yield: 272 mg (90%). White powder. M.p. >315° (dec.). IR (KBr): 3309, 1705, 1651, 1581. ^{1}H-NMR ((D$_6$)DMSO): 3.30 (*s*, Me); 3.34 (*s*, Me); 8.20 (*s*, =CH); 8.75 (*s*, =CH); 10.79 (*s*, NH); 11.51 (br. *s*, NH). Because of low solubility in suitable NMR solvents, the ^{13}C-NMR spectra were not recorded. MS: 302 (50, M^+), 287 (40), 247 (100). Anal. calc. for $C_{12}H_{10}N_6O_4$ (302.25): C 47.69, H 3.33, N 27.81; found: C 47.77, H 3.20, N 27.75.

*1-Phenyl-7-(1,2,3,4-tetrahydro-2,4-dioxo-1-phenylpyrimidin-5-yl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**2c**). Yield: 341 mg (80%). White powder. M.p. >315°. IR (KBr): 3100, 3066, 1701, 1651, 1581. ^{1}H-NMR ((D$_6$)DMSO): 7.29–7.44 (*m*, 10 arom. H); 7.99 (*s*, =CH); 8.85 (*s*, =CH); 9.04 (*s*, NH); 10.79 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 107.7; 111.9; 120.1; 127.2; 128.8; 129.4; 129.8; 130.0; 130.1; 138.9; 139.5; 150.5; 151.9; 157.6; 158.8; 160.8; 161.0; 164.0. MS: 426 (25, M^+), 336 (60), 309 (100). Anal. calc. for $C_{22}H_{14}N_6O_4$ (426.39): C 61.97, H 3.31, N 19.71; found: C 61.92, H 3.39, N 19.50.

*1-Benzyl-7-(1-benzyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**2d**). Yield: 400 mg (88%).White powder. M.p. 227–228°. IR (KBr): 3400, 3250, 1710, 1650, 1580. ^{1}H-NMR ((D$_6$)DMSO): 4.38 (*s*, CH$_2$); 5.21 (*s*, CH$_2$); 7.25–7.33 (*m*, 10 arom. C); 8.05 (*s*, =CH); 8.79 (*s*, =CH); 10.78 (*s*, NH); 11.66 (*s*, NH). ^{13}C-NMR (CDCl$_3$): 43.0; 44.0; 101.1; 102.8; 127.3; 127.6; 128.01; 128.8; 137.4; 137.5; 139.8; 151.4; 151.5; 154.2; 155.1; 156.9; 156.7; 160.8; 168.3; 168.8. MS: 454 (85, M^+), 91 (100). Anal. calc. for $C_{24}H_{18}N_6O_4$ (454.44): C 63.43, H 3.99, N 18.49; found: C 63.40, H 3.80, N 18.56.

*2,3-Dihydro-1,3-dimethyl-7-(1,2,3,4-tetrahydro-1,3-dimethyl-4-oxo-2-thioxopyrimidin-5-yl)-2-thioxopyrimido[4,5-*d*]pyrimidin-4(1*H*)-one* (**2e**). Yield: 318 mg (95%). White powder. M.p. 312°. IR (KBr): 1705, 1651, 1581, 1554. ^{1}H-NMR (CDCl$_3$): 3.65 (*s*, Me); 3.66 (*s*, Me); 3.82 (*s*, Me); 4.01 (*s*, Me), 9.01 (*s*, =CH), 9.02 (*s*, =CH). Because of low solubility in suitable NMR solvents, the ^{13}C-NMR spectra were not recorded. MS: 362 (100, M^+), 347 (65), 318 (85), 288 (75). Anal. calc. for: $C_{14}H_{14}N_6O_2S_2$ (362.43): C 46.40, H 3.89, N 23.19; found: C 46.54, H 3.95, N 23.03.

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