Enaminouraciles as Precursors for Synthesis of Pyrimido[4,5-*d*]pyrimidine-2,4-diones

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The reaction of 6-aminouracil **1** with formaldehyde and secondary amines in ethanol at room temperature gave the corresponding 5-alkylaminomethyl derivatives (**2**a-c) and bis(4-pyrimidyl)methane (**4**). Also, Mannich reaction with primary aliphatic and aromatic amines at room temperature afforded pyrimido[4,5-*d*]pyrimidine (**5** and **6**).

Treatment of **1** with *o*-phenylenediamine through transamination gave compound **7** which cyclized through intramolecular Mannich reaction with formalin to yield pyrimido[4,5-*e*]-[1,4]diazepine (**8**).

Introduction

The importance of uracile and its annelated substrates is well recognized by synthetic [1] as well as biological chemists [2]. With the development of clinically useful anticancer [3], antiviral [4], antiallergic [5], and antitumor [6] drugs, there has recently been remarkable interest in the synthetic manipulations of enamino amide in which the 6-amino-1,3-dimethyluracil is considered to be a heterocyclic enamino amide [7,8]. Chemotherapeutically valuable compounds in this class such as pyrimidopyrimidinedione derivatives are reported in the patent literature [5]. Recently, the synthesis of pyrimidine Mannich bases has been reported [9].

Although, the Mannich of 3(5)-arylaminopyrazoles with primary amines has been reported [10] as a route to pyrazolo[3,4-*d*]pyrimidine, no attention has been paid to the similar reaction with 6-amino-1,3-dimethyluracil, which can be used as a key intermediates for the synthesis of pyrimido[3,4-*d*]pyrimidine-2,4-dione derivatives.

Results and Discussion

The objective of the present work was to investigate the behaviour of the Mannich reaction towards 6-amino-1,3-dimethyluracile (**1**) as a bifunctional nucleophile with both secondary and primary amines.

The Mannich reaction of **1** with morpholine, N-methylpiperazine or piperazine and formalin afforded the Mannich bases **2a-c** which revealed that the C-5 center is more nucleophilic than the amino group at C-6 [8]. The IR spectra of **2a-c** displayed the NH_2 stretching bands at 3484–3152 cm^{-1}. The ^1H NMR spectra of **2a-c** lacked the 5-H proton (at δ 4.76 ppm) [8]; however, compound **4** was isolated as the main product on heating the reaction mixture for a short time (30 min) due to the condensation of **1** with formalin. The structure of **4** was established by its analytical and spectral data. On using dimethylamine in the Mannich reaction with compound **1**, compound **4** was isolated as a sole product instead of the expected Mannich base **3**. The formation of **4**, may be rationalized in terms of the formation [11,12] of **3** as an intermediate which undergoes deamination to give **4**. On the other hand, treatment of **1** with primary aliphatic and aromatic amines and formalin in a molar ratio (1:1:2) gave the pyrimido[4,5-*d*]pyrimidine ring systems (**5** and **6**) *via* a double Mannich reaction. The involvement of both C-5 and amino group in this reaction is in line with our work [13,14] and the work of Roth and Hagen [15].

Furthermore, the interesting psychopharmacological activity of benzodiazepine [16,17], pursued us to synthesize the pyrimido[4,5-*e*][1,4]diazepine derivative **8**. Compound **8** has been obtained through transamination of **1** with *o*-phenylenediamine to give **7** followed by intramolecular Mannich type cyclization with formalin to afford **8**. The above reaction sequence is similar to some reported cases [18,19] in which the diazepine ring system has been obtained.

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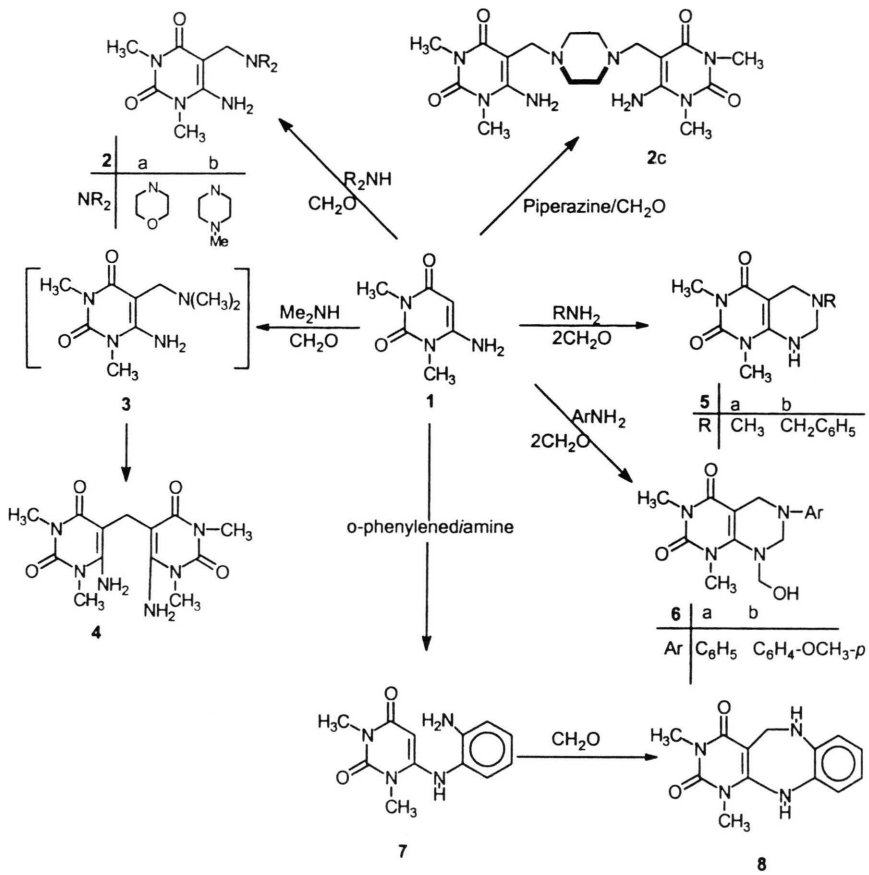

Experimental

Melting points (uncorrected) were taken in an open capillary tubes by the use of a Gallenkamp electric melting points apparatus. Infrared spectra were recorded on a Mattson 500 FTIR spectrometer using KBr wafer technique. ^{1}H NMR spectra were measured on Varian-Gemini 200 MHz in $CDCl_3$ or DMSO-d_6 as solvent unless stated otherwise and with TMS as internal standard. Mass spectra were determined on GC-MSHP Model 5988.

4-Amino-1,3-dimethyl-5-(N-morpholinomethyl)-2,6-dioxo-1,2,3,4-tetrahydro-pyrimidine (**2a**), *4-amino-1,3-dimethyl-5-(N-methylpiperazino-methyl)-2,6-dioxo-1,2,3,4-tetrahydropyrimidine* (**2b**) *and N,N'-bis(4-amino-1,3-dimethyl-2,6-dioxo-pyrimidin-5-ylmethyl)-piperazine* (**2c**)

A solution of the enaminone (**1**) (6.5 mmol) in ethanol (30 ml) was added to a stirred solution of morpholine (6.5 mmol), methylpiperazine (6.5 mmol) or piperazine (3.25 mmol) and formalin (6.5 mmol, 40% solution) in ethanol (20 ml). The reaction mixture was stirred for 2 h then left at room temperature for 3 days. The resulting precipitate was collected by filtration and crystallized from ethanol to give the corresponding Mannich bases **2a-c** in moderate yield (Table I).

Bis-(4-amino-1,3-dimethyl-2,6-dioxopyrimidine)-methane (**4**)

A mixture of **1** (3.3 mmol) and formalin (3.3 mmol, 40% solution) was heated in ethanol (25 ml) at 80 °C for 30 min. The resulting precipitate was collected by filtration and crystallized from acetic acid to give **4** in good yield (Table I).

1,3,6,8-Tetrasubstituted-4,5,6,7-tetrahydro-2,4-dioxopyrimido[4,5-d]pyrimidine **5a,b** *and* **6a,b**

A solution of **1** (6.5 mmol) in ethanol (30 ml) was added to a solution of primaryamines

Table I. Analytical data of the compounds **2,4,5,6,7,** and **8**.

Compound	Yield (%)	M.p (°C)	Solvent of cryst.	Molecular Formula, (g/mol)	Microanalysis Calcd/Found C	H	N
2a	56	104	EtOH	$C_{11}H_{18}N_4O_3$ (254.3)	51.96 51.89	7.13 7.06	22.04 22.00
2b	52	128	EtOH	$C_{12}H_{21}N_5O_2$ (267.3)	53.91 53.84	7.92 7.84	26.20 26.12
2c	41	231	EtOH	$C_{18}H_{28}N_8O_4$ (420.5)	51.42 51.31	6.71 6.65	26.65 26.59
4	70	320	AcOH	$C_{13}H_{18}N_6O_4$ (322.3)	48.44 48.22	5.63 5.58	26.08 26.01
5a	75	170	EtOH	$C_9H_{14}N_4O_2$ (210.2)	51.42 51.29	6.71 6.59	26.65 26.71
5b	60	116	EtOH	$C_{15}H_{18}N_4O_2$ (286.3)	62.92 62.81	6.34 6.22	19.57 19.63
6a	73	196	EtOH	$C_{15}H_{18}N_4O_3$ (302.3)	59.59 59.64	6.00 6.02	18.53 18.50
6b	80	158	EtOH	$C_{16}H_{20}N_4O_4$ (332.4)	57.82 57.76	6.07 6.01	16.86 16.80
7	30	205	EtOH	$C_{12}H_{14}N_4O_2$ (246.3)	58.52 58.60	5.73 5.79	22.75 22.78
8	80	235	EtOH	$C_{13}H_{14}N_4O_2$ (258.3)	60.45 60.36	5.46 5.40	21.69 21.59

Table II. Mass spectra and IR spectra of compounds **2,4,5,6,7,** and **8**.

Compound	IR (KBr) (cm^{-1})	MS, *m/e* (%)
2a	3484, 3188 (NH_2); 2958, 2803 (CH aliph.); 1702 (CO lactam)	255 (M^++1)(1); 207(2); 185(3); 166(7); 149(21); 111(14); 81(44); 69(100); 56(55)
2b	3407, 3152 (NH_2); 2950, 2810 (CH aliph), 1702 (CO lactam)	269 (M^++2)(3); 264(14); 252(8); 239(19); 205(10); 164(17); 159(13); 129(16); 98(31); 97(85); 83(100); 69(48)
2c	3305, 3149 (NH_2); 2940, 2816 (CH aliph); 1695 (CO lactam)	420(M^+)(1); 411(2); 407(29); 368(9); 285(6); 238(28); 196(100); 169(55); 98(45); 83(75); 67(25)
4	3395, 3127 (NH_2); 2944 (CH aliph); 1661 (CO lactam)	323(M^++1)(37); 209(M^+-1)(36); 167(37); 149(100); 105(41); 82(42); 57(75).
5a	3436 (NH); 2934 (CH aliph); 1705 (CO lactam)	210(M^+)(37); 209(M^+-1)(36); 167(37); 149(100); 105(41); 82(42); 57(75)
5b	3289 (NH); 3090 (CH arom); 2984 (CH aliph); 1692 (CO lactam)	286(M^+)(9); 285 (M^+-1)(17); 237(20); 180(15); 165(16); 124(29); 96(37); 72(19); 57(100)
6a	3510 (OH); 3298 (NH); 3120 (CH arom); 2943 (CH aliph); 1684 (CO lactam)	305(M^++2) (33); 304 (M^++1) (14); 303 (M^+)(13); 273(33); 180(26); 157(35); 118(38); 106(64); 72(46); 59(100)
6b	3504 (OH); 3294 (NH); 3120 (CH arom); 2965 (CH aliph); 1690 (CO lactam)	332(M^+) (8); 275 (23); 184(21); 152(32); 115(35); 101(60); 71(22); 57(100)
7	3400 (NH_2); 3254 (NH); 3150 (CH arom); 2984 (CH aliph); 1665 (CO lactam)	243(M^+-3) (3); 239(12); 236(19); 215(23); 183(17); 165(18); 130(39); 111(48); 97(100); 57(88)
8	3259 (NH); 3059 (CH arom); 2910 (CH aliph); 1655 (CO lactam)	257(M^+-1)(4); 256(M^+-2) (5); 250 (15); 247(19); 237(24); 209(16); 183(24); 161(36); 147(39); 104(30); 97(36); 84(39); 68(31); 57(100)

Table III. ^{1}H NMR of the compounds **2a, 2c, 4, 5a, 6a** and **8**.

Compound	^{1}H NMR (solvent) δ ppm
2a	($CDCl_3$): δ = 2.4 [t, 4H, -N(CH_2)$_2$]; 3.2 [s, 3H, CONCH_3]; 3.3[s, 3H, (CO)$_2$N-CH_3]; 4.3 [s, 2H, C=C-CH_2-N]; 3.6[q, 6H (4H, O(CH_2)$_2$ and 2H, NH_2), became triplet after deuteration]
2c	(DMSO-d_6): δ = 2.3 [m, 8H, N(CH_2)$_4$], 3.10 [s, 6H, (CONCH_3)$_2$]; 3.14 [s, 4H, (C=C-CH_2N)$_2$]; 3.2[s, 6H, ((CO)$_2$NCH_3)$_2$]; 3.7[s, 4H, (NH_2)$_2$, exchangeable with D_2O]
4	(DMSO-d_6): δ = 3.1 [s, 6H, (CO-NCH_3)$_2$]; 3.2 [s, 8H (6H, ((CO)$_2$NCH_3)$_2$ and 2H, CH_2-(C=C)$_2$]; 3.3 [s, 4H, (NH_2)$_2$, exchangeable with D_2O]
5a	(DMSO-d_6): δ = 2.8 [s, 3H, N-CH_3]; 3.1 [s, 3H, CON-CH_3]; 3.3 [(s, 3H, (CO)$_2$N-CH_3]; 3.4 [brs, 1H, NH, exchangeable with D_2O]; 3.9 [s, 2H, CH_2-N]; 4.5 [d, 2H, N-CH_2-N]
6a	($CDCl_3$): δ = 3.2 [s, 3H, CON-CH_3]; 3.3 [s, 3H, (CO)$_2$NCH_3]; 4.2 [s, 2H, N-CH_2-C=C]; 4.7 [s, 2H, NCH_2N], 4.8 [s, 2H, NCH_2O]; 5.4 [s, 1H, OH, exchangeable with D_2O]; 6.8–7.2 [m, 5H, arom-H]
8	(DMSO-d_6): 3.2[s, 3H, CON-CH_3]; 3.3 [s, 3H, (CO)$_2$NCH_3]; 3.5 [s, 2H, N-CH_2-C=C]; 4.4 [s, 1H, NH, exchangeable with D_2O]; 5.2 [s, 1H C=C-NH-C=C, exchangeable with D_2O]; 7.1–7.5 [m, 4H,arom-H]

(6.5 mmol) and formalin (13 mmol, 40% solution) in ethanol (20 ml) and the reaction mixture was stirred for 2 h, then left at room temperature for 3 days. The resulting precipitate was collected by filtration, then purified by crystallization from ethanol to give the corresponding pyrimido[4,5-*d*]pyrimidine derivatives in good yield.

4-(o-Aminoanilino)-1,3-dimethyl-2,6-dioxo-1,2,3,4-tetrahydropyrimidine (**7**)

A mixture of **1** (6.5 mmol) and o-phenylenediamine (6.5 mmol) in glacial acetic acid (20 ml), was heated for 2 h on a steam bath, kept overnight at room temperature, diluted with water then basified to pH 8 by ammonia. The precipitated product was crystallized from ethanol to give **7** in low yield (Table I).

6,10-Dihydro-1,3-dimethyl-2,4-dioxopyrimido-[4,5-e][1,4]diazepine (**8**)

To a solution of (4 mmol) of **7** in ethanol (10 ml) was added formalin (6 mmol, 40% solution), and the mixture was refluxed for 0.5 h. The deposited crystals were collected by filtration and crystallized from ethanol to give **8** in good yield (Table I).

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