Synthesis of New 6-Aroylpyrido[2,3-*d*]pyrimidines

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The synthesis of 6-dimethylaminomethylenaminopyrimidin-4(3*H*)-ones **2** and its reaction with β-dimethylaminopropiophenone hydrochloride **3** is discussed in this work. The reaction of 6-aminopyrimidin-4(3*H*)-ones **1** with an excess of dimethylformamide dimethyl acetal gives rise to the formation of 6-dimethylaminomethyleneaminopyrimidines **2**. The heating of equimolecular quantities of **2** and **3** in dimethylformamide leads to the 6-aroylpyrido[2,3-*d*]pyrimidines derivatives **4**. The structures of compounds **2** and **4** were determined on the basis of nmr measurements.

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Introduction.

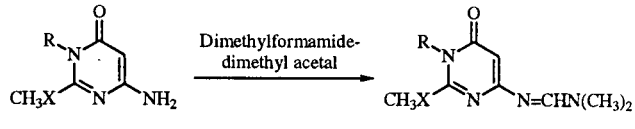
The pyrido[2,3-*d*]pyrimidines, deazaanalogs of pteridines, and their oxo derivatives have been of interest for their potential biological activities [1-5]. Thus, there have been ample precedents on the synthesis of these fused pyrimidines [1,6-11]. Our recent work has provided a convenient method for preparation of pyrido[2,3-*d*]pyrimidines by reactions of 6-aminopyrimidin-4-ones with chalcones [9,10], arylidene derivatives of Meldrum's acid [12], dimedone [13] and malonodinitrile [14].

In this work we studied the reaction of the 6-aminopyrimidin-4(3*H*)-ones **1** with dimethylformamide dimethyl acetal to synthesize 6-dimethylaminomethylenaminopyrimidin-4(3*H*)-ones **2** and its reaction with β-dimethylaminopropiophenones **3** with the purpose of obtaining new pyrido[2,3-*d*]pyrimidines.

Results and Discussion.

The 6-dimethylaminomethylenaminopyrimidines **2a-c** were easily prepared, in excellent yield, by the condensation reaction of 6-aminopyrimidines **1** with an excess of dimethylformamide dimethyl acetal (Scheme 1). Compounds **2a-c** were treated with stoichiometric amounts of β-dimethylaminopropiophenone hydrochloride in hot dimethylformamide to give the corresponding 6-aroylpyrido-[2,3-*d*]pyrimidines **4a-h** in good yields (Scheme 2).

Scheme 1

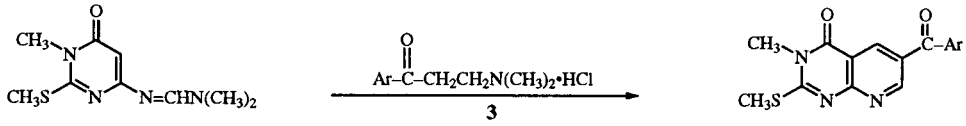


1a-c **2a-c**

	R	X	Mp °C	Yield %
2a	CH_3	S	112	85
2b	H	O	92	80
2c	CH_3	O	84	88

The formation of compounds **4** was confirmed by spectroscopy analysis. In the ^1H nmr spectra of compounds **4a-h** measured in dimethyl-d_6 sulfoxide (Table 1) besides the signal of CH_3X-group at 2.49-2.58 ppm for **4a-c**, the signal of the CH_3N-group at 3.27-3.43 ppm and the aromatic proton signals at 7.26-8.43 ppm, there are two doublets with ^{meta}J = 1.7 ±0.2 Hz at δ = 7.83-8.65 and 8.33-9.36 ppm with a 1:1 relationship, corresponding to the H-5 and H-7 protons of the pyrido[2,3-*d*]pyrimidine system.

Scheme 2



2a **4a-c**

	Ar	Mp °C	Yield %
4a	*p*-ClC_6H_4	339	55
4b	*p*-BrC_6H_4	342	58
4c	*p*-$O_2NC_6H_4$	338	66

Table 1

^{1}H-NMR Data of **4a-h** (δ values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide)

Compound	R	CH_3X	1-NH	H-5	H-7	Ar
4a	3.43	2.52	---	8.62	9.18	7.69-7.83
4b	3.36	2.49	---	8.63	9.36	7.44-7.67
4c	3.38	2.58	---	8.65	9.22	7.75-8.30
4d	3.37	---	11.90	7.83	8.33	7.26-8.14
4e	---	---	11.49	7.87	8.35	7.62-8.18
4f	---	---	10.91	8.03	8.47	7.75-8.36
4g	3.27	---	11.99	7.85	8.35	7.37-8.17
4h	3.27	---	12.22	8.49	8.97	7.99-8.43

The final elucidation of the structure of compounds **4** was carried out by analysis of the ^{13}C nmr spectra. The number of quaternary, tertiary and secondary carbon atoms for compounds **4**, which are consistent with the spectroscopic analysis above, were determined by ^{13}C nmr (DEPT experiment) spectroscopy.

It is important to point out that the thermal cyclization of compounds **2b,c** under the same conditions, leads to the formation of compounds **4d-h** by the loss of the methyl group of the C-2 atom of the pyrimidine ring. In similar reactions we have also observed this loss as a consequence of the reaction conditions [8,15,16] (Scheme 3).

EXPERIMENTAL

Melting points were taken on a Buchi Melting Point Apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were run on a Bruker DRX 300 spectrometer at 300 MHz and 75 MHz respectively, using dimethyl-d_6 sulfoxide as the solvent and tetramethylsilane as the internal standard. The mass spectra were scanned on a Fison MD-LC 800 (EI) operating at 70 eV. The elemental analysis have been obtained using a LECO CHNS-900 equipment.

Synthesis of 6-Dimethylaminomethylenaminopyrimidin-4(3*H*)-ones **2a-c**.

General Procedure.

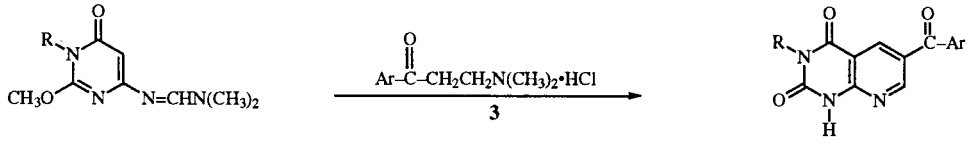
A solution of 6-aminopyrimidin-4(3*H*)-one **1** (1 mmole) and dimethylformamide dimethyl acetal (3 mmoles) was heated to reflux for 2 hours. The precipitated products **2** were isolated by filtration, washing with ethanol, drying and recrystallized from ethanol.

6-Dimethylaminomethylenamino-3-methyl-2-methylthiopyrimidin-4(3*H*)-one **2a**.

This compound was obtained by the general procedure as white crystals; ^{1}H nmr (dimethyl-d_6 sulfoxide, ppm): 2.96 and 3.09 [$N(CH_3)_2$], 2.54 (CH_3S), 3.31 (NCH_3), 5.36 (H-5) and 8.60 (N=CH); ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 14.3 (CH_3S), 29.0 (CH_3N), 34.3 and 40.4 [$N(CH_3)_2$], 94.1 (C-5), 156.5 (N=CH), 160.8 (C-6), 162.6 (C-2), 162.9 (C-4). The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 226 (8, M^+), 182 (14), 181 (100), 99 (9), 44 (7).

Anal. Calcd. for $C_9H_{14}N_4OS$: C, 47.77; H, 6.24; N, 24.76. Found: C, 47.65; H, 6.33; N, 24.59.

Scheme 3



2b,c **4d-h**

	R	Ar	Mp °C	Yield %
4d	H	C_6H_5	>360	48
4e	H	*p*-ClC_6H_4	>360	57
4f	H	*p*-$O_2NC_6H_4$	>360	70
4g	CH_3	C_6H_5	312	50
4h	CH_3	*p*-$O_2NC_6H_4$	345	68

The formation of **4** is assumed to proceed by a Michael type addition of the most basic ring atom in dimethylaminomethylenaminopyrimidines **2** to the activated double bond of an aryl vinyl ketone, resulting from the elimination of dimethylamine hydrochloride from **3**. The intermediate formed Michael adducts, by dimethylamine elimination and aromatization, give the 6-aroylpyrido[2,3-*d*]-pyrimidines **4**. The high regioselectivity of the reaction studied is in accordance with the increased nucleophilicity of C-5 due to the electron-donating effect of the dimethylamino substituent, compared to the azomethine carbon atom in **2** as shown in previous reports [17-19].

6-Dimethylaminomethylenamino-2-methoxypyrimidin-4(3*H*)-one **2b**.

This compound was obtained by the general procedure as white crystals; ^{1}H nmr (dimethyl-d_6 sulfoxide, ppm): 2.96 and 3.08 [$N(CH_3)_2$], 3.86 (CH_3O), 5.20 (H-5) and 8.53 (N=CH); ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 34.1 and 40.4 [$N(CH_3)_2$], 54.1 (CH_3O), 93.0 (C-5), 156.5 (N=CH), 158.1 (C-6), 164.0 (C-2), 164.1 (C-4). The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 196 (18, M^+), 181 (22), 140 (11), 126 (12), 111 (10), 97 (13), 82 (25), 38 (33), 57 (38), 44 (100).

Anal. Calcd. for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.16; N, 28.55. Found: C, 48.85; H, 6.23; N, 28.70.

6-Dimethylaminomethylenamino-2-methoxy-3-methylpyrimidin-4(3*H*)-one **2c**.

This compound was obtained by the general procedure as white crystals; ^{1}H nmr (dimethyl-d_6 sulfoxide, ppm): 2.96 and 3.08 [$N(CH_3)_2$], 3.17 (CH_3N), 3.94 (CH_3O), 5.30 (H-5) and 8.53 (N=CH); ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 26.7 (CH_3N), 34.3 and 40.4 [$N(CH_3)_2$], 55.2 (CH_3O), 92.5 (C-5), 156.4 (N=CH), 155.7 (C-6), 163.3 (C-2), 163.7 (C-4). The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 310 (100, M^+), 211 (11), 195 (57), 166 (10), 155 (17), 138 (21), 112 (10), 99 (13), 97 (12), 83 (11), 72 (42), 44 (26).

Anal. Calcd. for $C_9H_{14}N_4O_2$: C, 51.42; H, 6.71; N, 26.65. Found: C, 51.56; H, 6.76; N, 26.76.

Synthesis of 6-Aroylpyrido[2,3-*d*]pyrimidin-4-ones **4**.

General Procedure.

A solution of 6-dimethylaminomethylenaminopyrimidin-4(3*H*)-one **2** (1 mmole) and β-dimethylaminopropiophenone hydrochloride **3** (1 mmole) in 5 ml of dimethylformamide was heated to reflux for 20-30 minutes. The cyclized products **4** were isolated by cooling, followed by filtration, washing with ethanol, drying and recrystallized from a dimethylformamide-water mixture.

6-(4-Chlorobenzoyl)-3-methyl-2-methylthiopyrido[2,3-*d*]pyrimidin-4(3*H*)-one **4a**.

This compound was obtained by the general procedure as pale yellow crystals; ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 14.3 (CH_3S), 29.8 (CH_3N), 137.9 (C-5), 152.2 (C-7), 163.9 (C-4), 192.1 (C=O). The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 347/345 (36/64, M^+), 346 (17), 302 (34), 301 (28), 300 (100), 299 (12), 271 (12), 141 (12), 139 (34), 111 (27), 88 (21), 75 (15), 42 (11).

Anal. Calcd. for $C_{16}H_{12}N_3O_2SCl$: C, 55.57; H, 3.50; N, 12.15. Found: C, 57.45; H, 3.58; N, 12.31.

6-(4-Bromobenzoyl)-3-methyl-2-methylthiopyrido[2,3-*d*]pyrimidin-4(3*H*)-one **4b**.

This compound was obtained by the general procedure as pale yellow crystals; ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 14.0 (CH_3S), 29.8 (CH_3N), 142.2 (C-5), 150.5 (C-7), 164.0 (C-4), 192.3 (C=O). The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 391/389 (82/88, M^+), 354 (84), 312 (30), 249 (28), 185 (35), 160 (20), 117 (18), 88 (100), 57 (23), 42 (26).

Anal. Calcd. for $C_{16}H_{12}N_3O_2SBr$: C, 49.24; H, 3.10; N, 10.77. Found: C, 49.16; H, 3.24; N, 10.90.

3-Methyl-2-methylthio-6-(4-nitrobenzoyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **4c**.

This compound was obtained by the general procedure as yellow crystals [20]. The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 356 (48, M^+), 354 (14), 343 (13), 341 (16), 326 (21), 312 (31), 311 (100), 310 (10), 282 (16), 281 (19), 150 (10), 120 (15), 104 (13), 88 (26), 76 (12).

Anal. Calcd. for $C_{16}H_{12}N_4O_4S$: C, 53.93; H, 3.39; N, 15.72. Found: C, 53.87; H, 3.45; N, 15.54.

6-Benzoylpyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione **4d**.

This compound was obtained by the general procedure as white crystals; ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 137.6 (C-5), 142.8 (C-7), 161.0 (C-4), 161.2 (C-2), 191.5 (C=O).

Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72. Found: C, 62.84; H, 3.53; N, 15.90.

6-(4-Chlorobenzoyl)pyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione **4e**.

This compound was obtained by the general procedure as pale yellow crystals; ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 129.8 (C-5), 137.5 (C-7), 159.1 (C-4), 162.1 (C-2), 192.5 (C=O).

Anal. Calcd. for $C_{14}H_8N_3O_3Cl$: C, 55.74; H, 2.67; N, 13.93. Found: C, 55.79; H, 2.57; N, 13.85.

6-(4-Nitrobenzoyl)pyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione **4f**.

This compound was obtained by the general procedure as yellow crystals; ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 130.6 (C-5), 142.8 (C-7), 163.7 (C-4), 165.7 (C-2), 191.9 (C=O).

Anal. Calcd. for $C_{14}H_8N_4O_5$: C, 53.85; H, 2.58; N, 17.94. Found: C, 53.79; H, 2.67; N, 17.86.

6-Benzoyl-3-methylpyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione **4g**.

This compound was obtained by the general procedure as pale yellow crystals; ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 27.2 (CH_3N), 130.6 (C-5), 137.8 (C-7), 160.4 (C-4), 161.6 (C-2), 192.5 (C=O). The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 281 (12, M^+), 180 (68), 266 (28), 265 (100), 258 (13), 257 (46), 254 (15), 253 (70), 242 (21), 196 (19), 166 (20), 105 (46), 104 (17), 77 (38).

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.22; H, 3.88; N, 14.90.

6-(4-Nitrobenzoyl)-3-methylpyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione **4h**.

This compound was obtained by the general procedure as yellow crystals; ^{13}C nmr (dimethyl-d_6 sulfoxide, ppm): 27.2 (CH_3N), 130.6 (C-5), 155.7 (C-7), 161.0 (C-4), 161.2 (C-2), 191.5 (C=O). The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 326 (54, M^+), 280 (11), 204 (100), 150 (17), 147 (35), 120 (22), 104 (13).

Anal. Calcd. for $C_{15}H_{10}N_4O_5$: C, 55.22; H, 3.09; N, 17.17. Found: C, 55.34; H, 3.13; N, 17.29.

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[20] Compound **4c** is barely soluble in dimethyl sulfoxide or any other solvent normally used for nmr spectroscopy. This made the registration of a high resolution ^{13}C nmr spectrum impossible.