Synthesis of 6-Cyanopyrido[2,3-*d*]pyrimidinones in the Reaction of 6-Amino-4-pyrimidinones with Arylidene Derivatives of Malonodinitrile

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This paper describes the synthesis of a new series of 7-amino-5-aryl-6-cyano-5,8-dihydropyrido-[2,3-*d*]pyrimidin-4(3*H*)-ones **3** from the reaction of 6-amino-4-pyrimidinones **1** with arylidene derivatives of malonodinitrile **2**. The structure of the final compounds was determined on the basis of nmr measurements, especially by ^{1}H, ^{1}H-, ^{1}H, ^{13}C COSY, DEPT, HMBC and HMQC experiments.

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Introduction.

The pyrido[2,3-*d*]pyrimidines (deaza-analogs of pteridines) and their oxo derivatives deserve great interest for their potential biological and pharmacological activities [1-6], especially for their potential antitumor [7,8] and antibacterial [9,10] properties.

We have previously reported the reaction of 6-amino-4-pyrimidones with chalcones [11,12] and benzylidene derivatives of Meldrum's acid [13] as an efficient method for the synthesis of pyrido[2,3-*d*]pyrimidines. It has been our interest to examine this method and its application to the synthesis of new pyrido[2,3-*d*]pyrimidine derivatives from arylidene malonodinitrile as α,β-unsaturated component.

In this work, we studied the extension of the above reaction to 6-amino-3,4-dihydropyrimidines **1** and the benzylidene derivatives of malononitrile **2**.

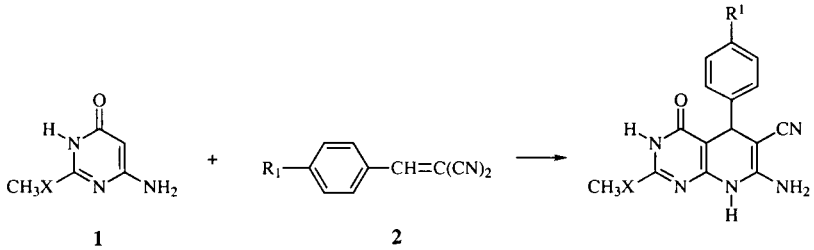
Results and Discussion.

A solution of equimolar amounts of 6-amino-3,4-dihydro-4-pyrimidones **1** and **2** was refluxed in ethanol, in the presence of catalytic amounts of triethylamine, for 1-1.5 hours. After cooling the generated precipitate was filtered off to give the corresponding 7-amino-5-aryl-6-cyano-5,8-dihydropyrido[2,3-*d*]pyrimidines **3a-f**. The new compounds were obtained in good yields (Scheme 1) as stable crystalline solids and were easily purified by recrystallization from ethanol.

The structure of compounds **3** was confirmed by spectroscopy analysis. Thus, the ir spectra of **3** measured in potassium bromide pellets show three bands for NH groups at 3240-3270 cm^{-1} and the typical nitrile absorption at 2173-2200 cm^{-1}.

The ^{1}H-nmr spectra of compounds **3a-f** measured in dimethyl sulfoxide-d_6 (Table 1) exhibit the signals of the methyl group at 2.42-3.85 ppm and the aromatic proton signals at 7.16-8.15 ppm. There are also singlets at δ 4.43-4.75, 9.20-9.24 and 5.86-7.30 ppm respectively with a 1:1:2 relation, corresponding to 5-H, 8-NH protons of the pyrido-[2,3-*d*]pyrimidinic system and the amino group (in **3a**, **3d** and **3f**, signals for 3-NH and 8-NH were not observed).

Scheme 1



1 **2** **3a-f**

	3a	**3b**	**3c**	**3d**	**3e**	**3f**
R^1	H	Cl	NO_2	H	Cl	NO_2
X	O	O	O	S	S	S
mp °C	245	250	278	>360	335	260
Yield, %	72	72	75	68	70	70

Table 1

^{1}H-NMR Data of **3a-f** (δ values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide, 300 MHz)

Compound	CH_3X s	5-H s	3-NH [a] s	8-NH [a] s	NH_2 [a] s	5-Ar dd
3a	3.76	4.51	[b]	[b]	7.10	7.19-7.33
3b	3.85	4.43	12.02	9.23	5.85	7.17-7.34
3c	3.77	4.72	[b]	[b]	7.27	7.46-8.22
3d	2.47	4.43	12.40	9.20	5.86	7.16-7.26
3e	2.48	4.45	12.38	9.24	5.92	7.18-7.34
3f	2.42	4.61	11.75	9.32	5.99	7.43-8.15

[a] Deuterium oxide-exchangeable. [b] Not observed.

The final elucidation of the structure of compounds **3a-f** was carried out by analysis of the ^{13}C-nmr spectra (Table 2). In the ^{13}C-nmr spectra of **3a-f**, a carbon signal at δ = 35.1-37.5 ppm was observed. ^{1}H,^{13}C-COSY reveals that the proton signal belongs to the carbon atom C-5 at highest field. 2-D experiments as HMQC were very useful for the complete assigning of the carbon spectra.

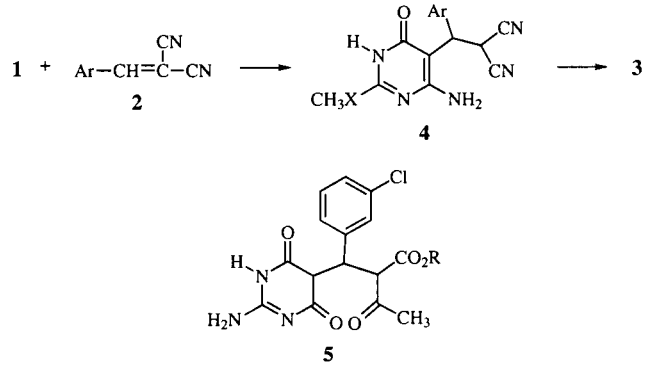
Table 2

^{13}C-NMR Data of **3a-f** (δ values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide, 75 MHz)

Compound		**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
	CH_3X	54.4	54.7	54.0	12.7	12.6	13.3
	C-2	164.0	157.0	163.6	151.5	151.4	161.8
	C-4	164.1	161.6	163.8	161.0	161.0	169.4
	C-4a	89.8	92.9	88.2	95.5	95.0	90.4
	C-5	35.6	37.1	35.0	37.5	37.0	35.1
	C-6	58.2	56.2	56.4	56.5	56.0	56.4
	C-7	160.0	151.4	159.7	151.5	151.4	159.8
	C-8a	162.3	152.2	162.0	151.9	151.7	160.8
	-CN	120.4	121.4	119.5	121.7	121.3	119.6
Ar	C_i	144.3	145.5	146.4	146.5	145.3	146.6
	$C_{o,m}$	127.4	128.0	123.8	126.9	128.1	124.0
		128.9	128.7	128.3	128.3	128.6	128.4
	C_p	127.3	130.7	151.2	126.4	130.8	151.0

The formation of **3** in this reaction is assumed to proceed *via* a sequence similar to that discussed in [13-15]. These reactions must occur by Michael addition of the nucleophilic carbon atom C-5 of the pyrimidine ring towards the α,β-unsaturated system of **2** followed by cyclization of the Michael intermediate **4** (Scheme 2). The attempts of authors to work [15] to condense the 2-amino-4,6-dihydroxypyrimidine with methyl 2-(3'-chlorophenyl-methylene)acetoacetate resulted in nucleophilic C-5 attack and gave a product **5** with structure similar to intermediate **4**. Likewise, aminopyrimidines **1** also yield Michael adducts with α,β-unsaturated carbonyl systems as dimethyl acetylenedicarboxylate and ethyl propiolate [16].

Scheme 2



EXPERIMENTAL

Melting points were taken on a Buchi Melting Point Apparatus and are uncorrected. The ir spectra were obtained in potassium bromide pellets with a Perkin-Elmer 599B spectrometer. The ^{1}H and ^{13}C-nmr spectra were run on a Bruker DPX 300 spectrometer operating at 300 MHz and 75 MHz respectively, using dimethyl sulfoxide-d_6 as the solvent and tetramethylsilane as the internal standard. The mass spectra were scanned on a Hewlett Packard HP Engine-5959 spectrometer (equipped with a direct inlet probe) operating at 70 eV or 30 eV. The elemental analysis have been obtained using a LECO CHNS-900 equipment.

General Procedure for the Preparation of the Substituted Pyrido[2,3-d]pyrimidines **3**.

A solution of 6-aminopyrimidine **1** (1.5 mmoles) and the corresponding arylidene derivative of malonodinitrile **2** (1.5 mmoles) in 10 ml of absolute ethanol and 1 ml of triethylamine, was stirred at reflux for 1-1.5 hours. The cycled products **3** were isolated by cooling, followed by filtration, washed with cool ethanol, dried and recrystallized from ethanol.

7-Amino-6-cyano-5.8-dihydro-2-methoxy-5-phenylpyrido-[2,3-*d*]pyrimidin-4(3*H*)-one **3a**.

This compound was obtained according to general procedure as white crystals; ir (potassium bromide): ν 3497, 3383, 3300, 3152, 2195 (CN), 1661 (CO) cm^{-1}. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) 295 (11, M$^+$), 230 (10), 219 (12), 218 (100, M$^+$-phenyl), 77 (18, phenyl), 69 (10), 58 (26), 52 (10), 51 (22), 44 (23), 43 (17), 39 (12).

Anal. Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 61.05; H, 4.53; N, 23.80.

7-Amino-5-(4-chlorophenyl)-6-cyano-5,8-dihydro-2-methoxy-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **3b**.

This compound was obtained according to general procedure as white crystals; ir (potassium bromide): ν 3480, 3381, 3290, 3203, 2173 (CN), 1655 (CO) cm^{-1}. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) 329 (7, M$^+$), 328 (11), 327 (14), 326 (20), 312 (16), 232 (13), 218 (17, M$^+$-*p*-chlorophenyl), 111 (8, *p*-chlorophenyl), 84 (14), 75 (12), 73 (10), 70 (10), 69 (18), 66 (29), 58 (10), 55 (31), 53 (12), 51 (10), 50 (15), 44 (100), 43 (76), 39 (23).

Anal. Calcd. for $C_{15}H_{12}N_5O_2Cl$: C, 54.64; H, 3.67; N, 21.24. Found: C, 54.71; H, 3.62; N, 21.31.

7-Amino-6-cyano-5,8-dihydro-2-methoxy-5-(4-nitrophenyl)-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **3c**.

This compound was obtained according to general procedure as white crystals; ir (potassium bromide): ν 3500, 3380, 3250, 3200, 2200 (CN), 1685 (CO) cm^{-1}. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) 340 (M^+, 5), 308 (1), 293 (1), 276 (2), 275 (13), 235 (1), 219 (12), 218 (100, M^+-*p*-nitrophenyl), 201 (2), 175 (7), 161 (8), 127 (6), 106 (9), 76 (13), 58 (44), 57 (43), 43 (85).

Anal. Calcd. for $C_{15}H_{12}N_6O_4$: C, 52.94; H, 3.55; N, 24.70. Found: C, 52.87; H, 3.52; N, 24.77.

7-Amino-6-cyano-5,8-dihydro-2-methylthio-5-phenyl-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **3d**.

This compound was obtained according to general procedure as white crystals; ir (potassium bromide): ν 3480, 3456, 3346, 3208, 2173 (CN), 1643 (CO) cm^{-1}. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) 311 (13, M^+), 309 (16), 308 (10), 235 (16), 234 (100, M^+-phenyl), 186 (43), 140 (11), 77 (21, phenyl), 74 (17), 68 (14), 51 (29), 50 (10), 45 (14), 44 (28), 43 (42), 39 (12).

Anal. Calcd. for $C_{15}H_{13}N_5OS$: C, 57.86; H, 4.21; N, 22.49. Found: C, 57.79; H, 4.13; N, 22.56.

7-Amino-5-(4-chlorophenyl)-6-cyano-5,8-dihydro-2-methyl-thiopyrido[2,3-*d*]pyrimidin-4(3*H*)-one **3e**.

This compound was obtained according to general procedure as white crystals; ir (potassium bromide): ν 3400, 3350, 3250, 3200, 2190 (CN), 1660 (CO) cm^{-1}. The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) 347 (3), 345 (12), 329 (9), 296 (8), 271 (3), 254 (3), 236 (7), 235 (13), 234 (100, M^+-*p*-chlorophenyl), 186 (34), 161 (6), 131 (4), 74 (10), 43 (12).

Anal. Calcd. for $C_{15}H_{12}N_5OSCl$: C, 52.10; H, 3.50; N, 20.25. Found: C, 52.19; H, 3.43; N, 20.16.

7-Amino-6-cyano-5,8-dihydro-2-methylthio-5-(4-nitrophenyl)-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **3f**.

This compound was obtained according to general procedure as white crystals; ir (potassium bromide): ν 3463, 3347, 3237, 3160, 2181 (CN), 1630 (CO) cm^{-1}. The mass spectrum shows the following peaks: ms: (30 eV) m/z (%) 357 (3), 356 (14), 291 (12), 236 (6), 235 (16), 234 (100, M^+-*p*-nitrophenyl), 201 (2), 186 (2), 161 (17), 144 (6), 106 (12), 91 (4), 74 (25), 43 (17).

Anal. Calcd. for $C_{15}H_{12}N_6O_3S$: C, 50.56; H, 3.39; N, 23.58. Found: C, 50.48; H, 3.33; N, 23.50.

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