Synthesis of Novel 5-Aryl-6-Cyano-3*H*,8*H*-pyrido[2,3-*d*]pyrimidine-4,7-diones in the Reaction of 6-Amino-4-pyrimidinones with Benzaldehyde and Ethyl Cyanoacetate

Jairo Quiroga*, Mario Alvarado and Braulio Insuasty

Department of Chemistry, Universidad del Valle, A.A. 25360, Cali, Colombia

Manuel Nogueras, Adolfo Sánchez and M. Dolores López

Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain

Received June 18, 1998

The title compounds **4** and **5** have been prepared in one-step reaction from 6-amino-4-pyrimidinones **1**, the corresponding 4-substituted benzaldehyde **2** and ethyl cyanoacetate **3** in very good yields. The structure of the final compounds was determined on the basis of nmr measurements, especially by $^1H,^1H$-, $^1H,^{13}C$ COSY, and DEPT.

J. Heterocyclic Chem., **36**, 113 (1999).

Introduction.

Pyrido[2,3-*d*]pyrimidines present interesting biological properties [1-6], especially for their potential antibacterial [7,8] properties, and as for some recent applications, they have been used as dihydrofolate reductase inhibitors and as antitumor agents [9-11]; some of them have shown antimicrobial activity [12], diuretics properties [13] and activity against platelet aggregation [14].

In continuation of our previous studies of the synthesis of heterocyclic compounds from heterocyclic amines [15-20], in this work we studied the reaction of 6-amino-3,4-dihydro-4-pyrimidones **1a,b** with 4-substituted benzaldehydes **2** and ethyl cyanoacetate **3** in order to obtain novel pyrido[2,3-*d*]pyrimidine derivatives.

Results and Discussion.

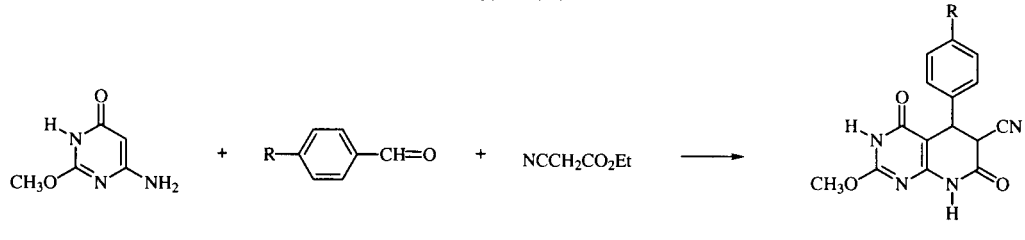
A solution of equimolar amounts of amine **1a**, benzaldehyde **2** and ethyl cyanoacetate **3** in ethanol, in the presence of catalytic amounts of triethylamine, was heated to reflux for 2.5-3 hours. After the reaction mixture was cooled, a precipitate was formed and removed by filtration to give the corresponding 5-(4-*R*-phenyl)-6-cyano-2-methoxy-5,6-dihydro-3*H*,8*H*-pyrido[2,3-*d*]pyrimidine-4,7-diones **4a-c** (Scheme 1) which were recrystallized from ethanol.

It is important to note that the reaction of compound **1b** (methylthio analogous of **1a**) with **2** and **3** under the same conditions leads to the formation of oxidized products, 5-(4-*R*-phenyl)-6-cyano-2-methylthio-3*H*,8*H*-pyrido[2,3-*d*]pyrimidine-4,7-diones **5a-c**, in this case, it was impossible to isolate the intermediate product, a dihydro derivative (Scheme 2).

The formation of **4** and **5** was confirmed by their spectroscopic analysis. Thus, the ir spectra of these compounds, measured in potassium bromide pellets, show two bands of the elongation vibrations of the C=O groups at 1638-1727 cm^{-1}, two bands for NH-groups at 3276-3435 cm^{-1} and one band for the CN group at 2220-2263 cm^{-1}.

In the ^1H-nmr spectra of compounds **4a-c** and **5a-c,** measured in dimethyl-d_6 sulfoxide (Table 1), besides the signal of CH_3X- group at 3.90-3.92 (methoxy) and 2.58-2.59 (methylthio) ppm and the aromatic proton signals at 7.21-8.31 ppm, for **4** two doublets were observed at δ = 4.42-5.15 ppm (^3J = 7.1 ±0.2 Hz) which were assigned to the H-5 and H-6 protons. These two doublets disappeared in the ^1H-nmr spectra of compounds **5**. For compounds **4** and **5** two singlets at δ = 12.45-13.09 and 11.25-13.09 ppm with a 1:1 relation, corresponding to the protons 3-NH and 8-NH of pyrido[2,3-*d*]pyrimidine system, were observed.

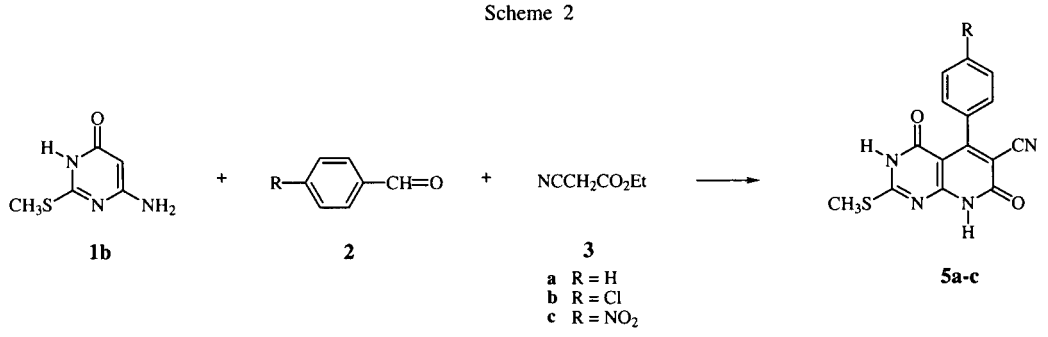
Scheme 1



1a **2** **3** **4a-c**

a R = H
b R = Cl
c R = NO_2

Scheme 2



1b **2** **3**

a R = H
b R = Cl
c R = NO_2

5a-c

Table 1

^{1}H-NMR Data for **4** and **5** (δ values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide, 300 MHz)

Compound	CH_3X	5-H	6-H	3-NH	8-NH		5-Ar	
	s	d	d	s	s	o	m	p
4a	3.90	5.01	4.42	12.45	11.25	7.21	7.32	7.28
4b	3.90	5.03	4.46	12.45	11.25	7.23	7.41	–
4c	3.92	5.15	4.70	12.50	11.35	7.51	8.21	–
5a	2.58	–	–	12.91	12.91	7.20	7.34	7.27
5b	2.59	–	–	13.00	13.01	7.34	7.50	–
5c	2.59	–	–	13.09	13.09	7.63	8.31	–

Table 2

^{13}C-NMR Data for **4** and **5** (δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide 75 MHz)

Compound		**4a**	**4b**	**4c**	**5a**	**5b**	**5c**
CH_3X		54.9	55.0	55.1	12.9	13.06	13.01
C-2		157.7	157.8	158.0	159.9	159.8	158.8
C-4		161.3	161.3	161.3	161.0	160.0	160.0
C-4a		96.1	95.7	95.0	98.9	99.0	98.9
C-5		40.9	40.8	40.3	102.2	102.3	101.9
C-6		36.8	36.2	36.5	157.8	157.9	158.0
C-7		163.8	163.6	163.5	166.8	167.0	167.5
C-8a		138.0	137.2	147.1	136.1	135.2	147.5
-CN		115.7	115.6	115.4	115.2	115.3	115.1
Ar	C_i	154.1	154.2	154.4	155.4	155.5	155.6
	$C_{o,m}$	127.4	128.7	123.9	127.1	127.6	123.1
		128.6	129.3	128.9	127.6	129.0	128.9
	C_p	132.5	133.4	145.8	128.7	133.4	143.3

The final elucidation of structure of compounds **4** and **5** was carried out by analysis of the ^{13}C-nmr spectra (Table 2). In the ^{13}C-nmr spectra of compounds **4a-c** two carbon signals at δ = 36.2-36.8 and 40.3-40.9 ppm were observed, corresponding to carbon atoms C-6 and C-5, respectively. The ^{1}H, ^{13}C COSY (HMQC and HMBC) reveal that the proton signal at 5.01-5.15 ppm belongs to the carbon atom C-6 at highest field.

EXPERIMENTAL

Melting points were taken on a Büchi Melting Point Apparatus and are uncorrected. The ^{1}H-and ^{13}C nmr spectra were run on a Bruker DPX 300 spectrometer operating at 300 MHz and 75 MHz respectively, in dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as 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. The elemental analyses have been obtained using a LECO CHNS-900 equipment.

General Procedure for the Preparation of the Substituted Pyrido[2,3-*d*]pyrimidines **4** and **5**.

A solution of the 6-aminopyrimidine **1a,b** (1.5 mmoles), the corresponding 4-substituted benzaldehyde (**2**) (1.5 mmoles) and ethyl cyanoacetate (**3**) (1.5 mmoles) in 10 ml of absolute ethanol and 1 ml of triethylamine was heated to reflux for 2.5-3 hours. The reaction mixture was cooled. The cyclized products **4** and **5** were collected by filtration, washed with ethanol, dryed and recrystallized from ethanol.

5-Phenyl-6-cyano-2-methoxy-5,6-dihydro-3*H*,8*H*-pyrido[2,3-*d*]-pyrimidine-4,7-dione **4a**.

This compound was obtained according to the general procedure as white crystals, mp 319°, yield 65%; ir (potassium bromide): ν 1638, 1717 (C=O), 2260 (CN), 3279, 3390 (NH) cm^{-1}; ms: (70 eV) m/z (%) 297 (23), 296 (100, molecular ion), 295 (23), 270 (17), 269 (72, M^+-HCN), 268 (14), 267 (28), 228 (19), 219 (23, M^+-$C_6H_5^•$), 194 (28), 128 (13), 77 (15, $C_6H_5^•$), 58 (23), 51 (21), 44 (10), 39 (13).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.95; H, 4.13; N, 18.80.

5-(4-Chlorophenyl)-6-cyano-2-methoxy-5,6-dihydro-3*H*,8*H*-pyrido[2,3-*d*]pyrimidine-4,7-dione **4b**.

This compound was obtained according to general procedure as white crystals, mp 323°, yield 68%; ir (potassium bromide): ν 1638, 1717 (C=O), 2263 (CN), 3276, 3435 (NH) cm^{-1}; ms: (70 eV) m/z (%) 332 (27), 331 (19), 330 (87, molecular ion), 329 (13), 305 (34), 304 (25), 303 (100, M^+-HCN), 302 (12), 301 (24), 295 (15), 262 (12), 221 (7), 220 (9), 219 (31, M^+-4-Cl-$C_6H_4^•$), 111 (7, 4-Cl-$C_6H_4^•$), 75 (13), 69 (10), 68 (14), 67 (13), 58 (37), 50 (10), 44 (12), 43 (10), 39 (8).

Anal. Calcd. for $C_{15}H_{11}N_4O_3Cl$: C, 54.47; H, 3.35; N, 16.94. Found: C, 54.35; H, 3.51; N, 16.82.

5-(4-Nitrophenyl)-6-cyano-2-methoxy-5,6-dihydro-3*H*,8*H*-pyrido[2,3-*d*]pyrimidine-4,7-diones **4c**.

This compound was obtained according to general procedure as white crystals, mp 303°, yield 70%; ir (potassium bromide): ν 1641, 1718 (C=O), 2263 (CN), 1337, 1513 (NO_2), 3350, 3510 (NH) cm^{-1}; ms: (70 eV) m/z (%) 342 (22), 341 (100, molecular ion), 340 (16), 324 (33), 315 (15), 314 (66, M^+-HCN), 312 (14), 294 (14), 266 (13), 227 (18), 219 (32, M^+-4-NO_2-$C_6H_4^•$), 194 (39), 187 (11), 180 (13), 176 (10), 127 (12), 115 (10), 101 (18), 100 (11), 89 (13), 88 (10), 83 (11), 77 (16), 76 (22), 75 (23), 74 (11), 69 (24), 68 (23), 67 (18), 64 (17), 63 (22), 58 (98), 57 (10), 55 (10), 44 (25), 43 (23), 42 (11), 39 (24).

Anal. Calcd. for $C_{15}H_{11}N_5O_5$: C, 52.79; H, 3.25; N, 20.52. Found: C, 52.65; H, 3.13; N, 20.80.

5-Phenyl-6-cyano-2-methylthio-3*H*,8*H*-pyrido[2,3-*d*]pyrimidine-4,7-dione **5a**.

This compound was obtained according to general procedure as white crystals, mp 345°, yield 65%; ir (potassium bromide): ν 1637, 1721 (C=O), 2220 (CN), 3390, 3420 (NH) cm^{-1}; ms: (70 eV) m/z (%) 312 (15), 311 (24), 310 (100, molecular ion), 309 (58), 263 (15), 236 (19), 221 (25), 165 (35), 154 (10), 153 (15), 140 (13), 128 (18), 127 (19), 77 (38), 69 (29), 68 (52), 63 (61), 51 (39), 44 (45), 43 (45), 41 (35), 39 (37).

Anal. Calcd. for $C_{15}H_{10}N_4O_2S$: C, 58.06; H, 3.25; N, 18.05. Found: C, 58.16; H, 3.15; N, 18.13.

5-(4-Chlorophenyl)-6-cyano-2-methylthio-3*H*,8*H*-pyrido[2,3-*d*]-pyrimidine-4,7-dione **5b**.

This compound was obtained according to general procedure as white crystals, mp >360°, yield 70%; ir (potassium bromide): ν 1650, 1720 (C=O), 2240 (CN), 3445, 3565 (NH) cm^{-1}; ms: (70 eV) m/z (%) 346 (11), 345 (31), 344 (100, molecular ion), 343 (38), 255 (11), 89 (10), 47 (13), 46 (11), 45 (12).

Anal. Calcd. for $C_{15}H_9N_4O_2SCl$: C, 52.26; H, 2.63; N, 16.25. Found: C, 52.18; H, 2.52; N, 16.34.

5-(4-Nitrophenyl)-6-cyano-2-methylthio-3*H*,8*H*-pyrido[2,3-*d*]-pyrimidine-4,7-dione **5c**.

This compound was obtained according to general procedure as white crystals, mp 350°, yield 68%; ir (potassium bromide): ν 1642, 1721 (C=O), 2226 (CN), 1347, 1516 (NO_2), 3300, 3440 (NH) cm^{-1}.

Anal. Calcd. for $C_{15}H_9N_5O_4S$: C, 50.70; H, 2.55; N, 19.71. Found: C, 50.64; H, 2.43; N, 19.79.

Acknowledgment.

The authors thank The Colombian Institute for Science and Research (COLCIENCIAS, Project 1106-05-411-95) and UNIVERSIDAD DEL VALLE for financial support.

REFERENCES AND NOTES

[1] W. J. Irwin and D. G. Wibberley, *Adv. Heterocyclic Chem.*, **10**, 149 (1969).

[2] B. S. Herbert, R. Ferone, T. A. Herman, G. H. Hitchings, M. Barnelt and S. R. Bushby, *J. Med. Chem.*, **11**, 711 (1968).

[3] G. L. Anderson and A. D. Broom, *J. Org. Chem.*, **42**, 997 (1977).

[4] L. Prakash, M. Shaihla and R. L. Mital, *Pharmazie*, **44**, 490 (1989).

[5] E. Lunt and C. C. Newton, Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees, Vol **3**, A. J. Boulton and A. Mc Killop, eds, Pergamon Press, Oxford, 1984, pp 199-232 and pp 260-261.

[6] L. K. A. Rahman and S. R. Chhabra, *Med. Res. Rev.*, **8**, 95 (1988).

[7] J. Matsumoto and S. Minami, *J. Med. Chem.*, **18**, 74 (1975).

[8] N. Suzuki, *Chem. Pharm. Bull.*, **28**, 761 (1980).

[9] G. L. Anderson, J. L. Shim and A. D. Broom, *J. Org. Chem.*, **41**, 1095 (1976).

[10] E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch and C. A. Nichol, *J. Med. Chem.*, **23**, 327 (1987).

[11] A. Gangjee, A. Vasudevan, F. Queener and R. Kisliuk, *J. Med. Chem.*, **38**, 1778 (1995); A. Gangiee, U.S. Patent 5,508,281 (1996); *Chem. Abstr.*, **125**, 33667a, (1996); A. Gangjee, A. Vasudevan, F. Queener and R. Kisliuk, *J. Med. Chem.*, **39**, 1438 (1996).

[12] S. A. K. Sharma and L. Prakash, *Heterocyclic Commun.*, **1**, 89 (1994).

[13] A. Monge, V. Martinez, C. San Martín and M. A. Simon, Spanish Patent ES 2,056,742 (1994); *Chem. Abstr.*, **122**, 105912q (1995).

[14] G. Hou, D. Gravier, F. Casadebaig, J. Dupin, H. Bernard and M. Boiseau, *Pharmazie*, **50**, 719 (1995).

[15] J. Quiroga, B. Insuasty, A. Sánchez, M. Nogueras and H. Meier, *J. Heterocyclic Chem.*, **29**, 1045 (1992).

[16] J. Quiroga, J. García, B. Insuasty, N. L. Mendoza, M. Pungo and H. Meier, *An. Quim.*, **90**, 3-4C, 300 (1994).

[17] J. Quiroga, A. Hormaza, B. Insuasty, A. Sánchez, M. Nogueras, N. Hanold and H. Meier, *J. Heterocyclic Chem.*, **34**, 521 (1997).

[18] B. Insuasty, J. Quiroga, H. Meier, *Trends Heterocyclic Chem.*, **5**, 83 (1997).

[19] J. Quiroga, A. Hormaza, B. Insuasty, A. J. Ortíz, A. Sánchez and M. Nogueras, *J. Heterocyclic Chem.*, **35**, 231 (1998).

[20] J. Quiroga, M. Alvarado, B. Insuasty, A. Sánchez, M. Nogueras and J. Cobo, *J. Heterocyclic Chem.*, (1998), in press.