Synthesis of Pyrido[2,3-*d*]pyrimidinones by the Reaction of Aminopyrimidin-4-ones with Benzylidene Meldrum's Acid Derivatives

Jairo Quiroga*, Angelina Hormaza and Braulio Insuasty

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

Manuel Nogueras and Adolfo Sánchez

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

Norbert Hanold and Herbert Meier

Institute of Organic Chemistry, University of Mainz, D-55099 Mainz, Germany

Received July 12, 1996

A series of pyrido[2,3-*d*]pyrimidine-4,7-diones **5a-h** were prepared from 6-amino-4-pyrimidones **1** and benzylidene Meldrum's acid derivatives **2** by cyclization reactions in boiling nitrobenzene. The structure of **5**, determined by nmr measurements, reveals a selective orientation of **1** and **2** in the addition step.

J. Heterocyclic Chem., **34**, 521 (1997).

Pyrido[2,3-*d*]pyrimidines and their oxo derivatives deserve interest for their biological and pharmacological activities [1-5], especially for their potential antitumor [6,7] and antibacterial [8,9] properties. Thus, there have been ample precedents for the synthesis of these fused heterocycles [1,10-14]. Our recent study provided a convenient method for the preparation of pyrido[2,3-*d*]pyrimidines by reactions of 6-amino-4-pyrimidones with chalcones [13,14].

In the present work we studied the reaction of 6-amino-3,4-dihydro-4-pyrimidones **1** with benzylidene derivatives of Meldrum's acid (**2**). A solution of equimolar amounts of **1** and **2** was refluxed in nitrobenzene for 2.5 hours. After cooling the generated precipitate was filtered off, to give the corresponding 5-aryl-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidine-4,7-diones **5a-i**. (Scheme 1)

Table 1

^{1}H NMR Data of **5a-h** (δ Values in DMSO-d_6, TMS as Internal Standard)

5	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
2-SCH_3	2.50	2.56	---	2.49	2.56	---	2.51	2.59
2-OCH_3	---	---	3.88	---	---	3.98	---	---
3-CH_3	---	3.35	---	---	3.35	3.24	---	3.37
5-H	4.19	4.22	4.18	4.19	4.22	4.35	4.35	4.38
6-H	2.52	2.54	2.51	2.51	2.54	2.57	2.57	2.58
	3.02	3.03	3.01	3.03	3.03	3.10	3.12	3.13
8-H	10.53	10.56	10.53	10.58	10.59	10.63	10.66	10.69
5-Ar								
o	7.13	7.15	7.17	7.16	7.16	7.44	7.43	7.45
m	7.26	7.27	7.34	7.33	7.33	8.15	8.16	8.15
p	7.19	7.18	---	---	---	---	---	---

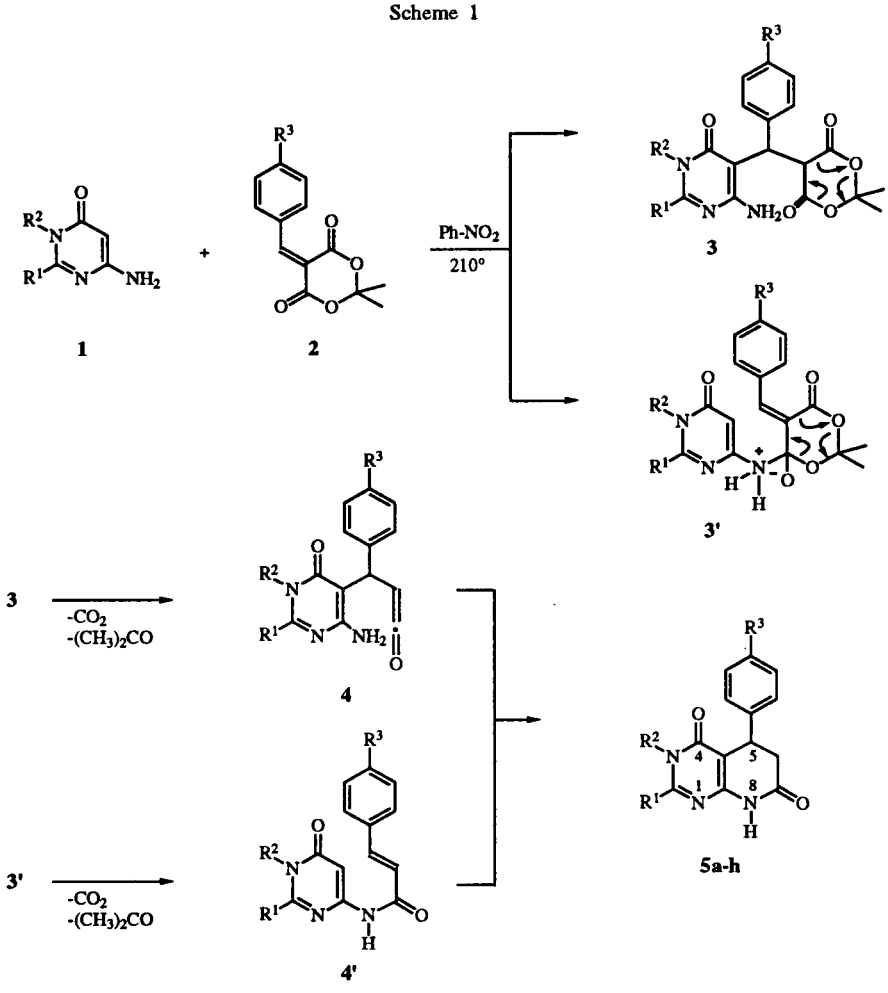
Table 2

^{13}C NMR Data of **5a-h** (δ Values in DMSO-d_6, TMS as Internal Standard)

5	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
C-2	161.6	162.3	157.5	161.6	162.5	156.6	161.2	162.9
C-4	161.7 [a]	160.3	162.0	162.2 [a]	160.2	160.8	161.2 [a]	160.7
C-4a	98.2	97.3	95.7	97.8	96.9	94.2	97.1	96.1
C-5	33.0	33.7	32.3	32.4	33.2	33.8	33.1	33.8
C-6	38.0	38.0	37.9	37.8	37.8	37.5	37.4	37.4
C-7	170.3	170.3	170.2	170.0	170.0	169.8	169.7	169.7
C-8a	154.7	152.7	155.2	154.2	152.8	153.6	154.0	153.0
2-OCH_3	---	---	54.7	---	---	55.8	---	---
2-SCH_3	12.6	14.3	---	12.6	14.3	---	12.6	14.3
3-CH_3	---	29.9	---	---	29.9	27.4	---	29.9
5-Ar								
C_i	142.5	142.5	141.7	141.4	141.4	150.7	150.4	150.3
C_o,C_m	126.4	126.4	128.3	128.3	128.3	123.6	123.7	123.7
	128.5	128.5	128.4	128.4	128.4	127.8	127.8	127.9
C_p	126.6	126.6	131.1	131.1	131.2	146.3	146.3	146.4

[a] Broad signal (tautomeric exchange of protons).

Scheme 1



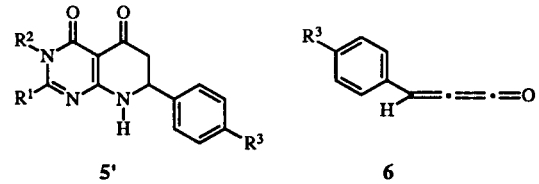
5	a	b	c	d	e	f	g	h
R^1	SCH_3	SCH_3	OCH_3	SCH_3	SCH_3	OCH_3	SCH_3	SCH_3
R^2	H	CH_3	H	H	CH_3	CH_3	H	CH_3
R^3	H	H	Cl	Cl	Cl	NO_2	NO_2	NO_2
Yield [%]	70	68	76	77	78	72	84	82

In principal the enamines **1** can attack on the carbonyl carbon atom or on the β-C atom of the α,β-unsaturated cyclic ester **2**. We assume for the initial step either a CC or a CN bond formation leading to **3** and **3'**, respectively. In the second step one molecule of acetone and carbon dioxide are split off and finally the tetrahydropyridine ring can be closed *via* the ketene **4** or the unsaturated amide **4'**. Related processes with Meldrum's acids are well-known [15,16], particularly a recent publication [17] on the preparation of 2,4,7-trioxo- and 4,7-dioxo-2-thioxooctahydropyrido[2,3-*d*]pyrimidines prompted us to report our results.

The formation of **5** was confirmed by spectroscopical data. Thus, the ir spectra of **5** measured in potassium bromide pellets show typical amide absorptions (Experimental) and no vibrations which would prove the structures of unsaturated ketones **5'**. (Scheme 2)

The ^1H nmr spectra of the compounds **5** measured in DMSO-d_6 exhibit besides the signals for the aromatic protons (7.13-8.16 ppm) an AMX spin pattern for the CH_2-CH segment. The coupling constants amount to ^2J =

Scheme 2



-(16.5 ± 0.5) Hz, $^3J_{trans}$ = (7.8 ± 0.5) Hz and $^3J_{cis}$ = (1.3 ± 0.5) Hz. The final proof of structure **5** is based on the ^{13}C nmr spectra.

The alternative structure **5'** could be ruled out, because neither signals for saturated carbon atoms adjacent to nitrogen atoms nor signals for carbonyl carbon atoms of ketones could be detected. The ^{1}H and ^{13}C nmr data are listed in the Tables 1 and 2.

Summarizing the reaction of **1** and **2**, one can point out that the Meldrum's acid derivatives **2** behave as synthetic equivalents of the heterocummulene **6**. Irrespective of the decision, which bond (CC or CN) is formed initially, the cyclization process is highly selective (**5** ← **1** + **2** ↛ **5'**).

EXPERIMENTAL

Melting points were taken on a Büchi 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 AM 400 in DMSO-d_6. The mass spectra were recorded on a Varian MAT 711 and Finnigan M 95 operating at 70 eV. The elemental analysis have been obtained using a LECO CHNS-900 equipment.

General Procedure for the Preparation of the 5-Aryl-3,4,5,6,7,8-hexahydropyrido[2,3-*d*]pyrimidine-4,7-diones **5a-h**.

A solution of 6-aminopyrimidone **1** (1.0 mmole) and a derivative of Meldrum acid **2** [18] in 5 ml of nitrobenzene was refluxed for 2.5 hours. The products **5a-h** were isolated by cooling, followed by filtration, washing with ethanol, drying and recrystallization from ethyl acetate/hexane (1:1).

3,4,5,6,7,8 -Hexahydro-2-methylthio-5-phenylpyrido[2,3-*d*]-pyrimidine-4,7-dione (**5a**).

The compound, obtained in 70% yield, forms colorless crystals, mp 303°; ir (potassium bromide): ν 1650, 1715, 3160, 3240 cm^{-1}. The mass spectrum shows the following peaks: ei ms (70 eV) m/z (%) = 287 (100) [M$^+$], 210 (50), 77 (32).

Anal. Calcd. for $C_{14}H_{13}N_3O_2S$: C, 58.54; H, 4.53; N, 14.63. Found: C, 58.63; H, 4.73; N, 14.46.

3,4,5,6,7,8-Hexahydro-3-methyl-2-methylthio-5-phenyl-pyrido[2,3-*d*]pyrimidine-4,7-dione (**5b**).

The compound, obtained in 68% yield, forms colorless crystals, mp 237°; ir (potassium bromide): ν 1670, 1738, 3230 cm^{-1}. The mass spectrum shows the following peaks: ei ms (70 eV) m/z (%) = 301 (100) [M$^+$], 224 (45).

Anal. Calcd. for $C_{15}H_{15}N_3O_2S$: C, 59.80; H, 4.98; N, 13.95. Found: C, 59.87; H, 4.82; N, 13.89.

5-(4-Chlorophenyl)-3,4,5,6,7,8-hexahydro-2-methoxypyrido-[2,3-*d*]pyrimidine-4,7-dione (**5c**).

The compound, obtained in 76% yield, forms colorless crystals, mp 287°; ir (potassium bromide): ν 1655, 1713, 3115, 3210 cm^{-1}. The mass spectrum shows the following peaks: ei ms (70 eV) m/z (%) = 307 (33) / 305 (100) [M$^+$], 304 (94), 270 (51), 194 (72), 123 (39), 77 (75).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_3$: C, 54.44; H, 3.93; N, 13.75. Found: C, 54.56; H, 3.96; N, 13.68.

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

This compound, obtained in 77% yield, forms colorless crystals, mp 307-8°; ir (potassium bromide): ν 1650, 1715, 3130, 3200 cm^{-1}. The mass spectrum shows the following peaks: ei ms (70 eV) m/z (%) = 321 (100) [M$^+$], 286 (31).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_2S$: C, 52.25; H, 3.73; N, 13.06. Found: C, 52.34; H, 3.78; N, 13.12.

5-(4-Chlorophenyl)-3,4,5,6,7,8-hexahydro-3-methyl-2-methylthiopyrido[2,3-*d*]pyrimidine-4,7-dione (**5e**).

The compound, obtained in 78% yield forms colorless crystals, mp 262°; ir (potassium bromide): ν 1670, 1735, 3220 cm^{-1}. The mass spectrum shows the following peaks: ei ms (70 eV) m/z (%) = 337 (38) / 335 (100) [M$^+$], 300 (41), 224 (60), 88 (22).

Anal. Calcd. for $C_{15}H_{14}ClN_3O_2S$: C, 53.65; H, 4.15; N, 12.52. Found: C, 53.85; H, 4.11; N, 12.34.

3,4,5,6,7,8-Hexahydro-2-methoxy-3-methyl-5-(4-nitrophenyl)-pyrido[2,3-*d*]pyrimidine-4,7-dione (**5f**).

The compound, obtained in 72% yield, forms almost colorless crystals, mp 251-252°; ir (potassium bromide): ν 1660, 1715, 3260 cm^{-1}. The mass spectrum shows the following peaks: ei ms (70 eV) m/z (%) = 330 (100) [M$^+$], 208 (69), 72 (13).

Anal. Calcd. for $C_{15}H_{14}N_4O_5$: C, 54.54; H, 4.24; N, 16.96. Found: C, 54.72; H, 4.08; N, 16.82.

3,4,5,6,7,8-Hexahydro-2-methylthio-5-(4-nitrophenyl)pyrido-[2,3-*d*]pyrimidine-4,7-dione (**5g**).

The compound, obtained in 84% yield, forms almost colorless crystals, mp 333-334°; ir (potassium bromide): ν 1650, 1700, 3100, 3220 cm^{-1}. The mass spectrum shows the following peaks: ei ms (70 eV) m/z (%) = 332 (100) [M$^+$], 210 (69).

Anal. Calcd. for $C_{17}H_{12}N_4O_4S$: C, 50.60; H, 3.61; N, 16.86. Found: C, 50.82; H, 3.24; N, 16.56.

3,4,5,6,7,8-Hexahydro-3-methyl-2-methylthio-5-(4-nitro-phenyl)pyrido[2,3-*d*]pyrimidine-4,7-dione (**5h**).

The compound, obtained in 82% yield, forms almost colorless crystals, mp 255°; ir (potassium bromide): ν 1670, 1720, 3390 cm^{-1}. The mass spectrum shows the following peaks: ei ms (70 eV) m/z (%) = 346 (100) [M$^+$], 271 (18), 224 (89), 88 (53).

Anal. Calcd. for $C_{15}H_{14}N_4O_4S$: C, 52.02; H, 4.05; N, 16.18. Found: C, 52.10; H, 4.11; N, 16.11.

Acknowledgment.

The authors thank COLCIENCIAS for the financial support. J. Q. and B. I. thank the German Academic Exchange Service (DAAD) for the award of a fellowship.

REFERENCES AND NOTES

[1] E. Lunt and C. C. Newton, in Comprehensive Heterocyclic Chemistry, Vol. 3, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, pp 199-232 and pp 260-261.

[2] L. K. A. Rahman and S. R. Chhabra, *Med. Res. Rev.*, **8**, 95 (1988); *Chem. Abstr.*, **108**, 105720m (1988).

[3] B. S. Hurlbert, R. Ferone, T. A. Herrmann, G. H. Hitchings,

M. Barnett and S. R. M. Bushby, *J. Med. Chem.*, **11**, 711 (1968); *Chem. Abstr.*, **69**, 25839t (1968).

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

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

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

[7] E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch and C. A. Nichol, *J. Med. Chem.*, **23**, 327 (1986); *Chem. Abstr.*, **92**, 121712s (1980).

[8] J. Matsumoto and S. Minami, *J. Med. Chem.*, **18**, 74 (1975); *Chem. Abstr.*, **82**, 132772f (1975).

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

[10] H. Wamhoff, J. Dzenis and K. Hirota, *Adv. Heterocyclic Chem.*, **55**, 129 (1992).

[11] T. J. Delia in The Chemistry of Heterocyclic Compounds, Vol **24**, Pt **4**. E. C. Taylor ed, Interscience Publishers, New York, 1992.

[12] J. A. García, A. Sánchez and M. Nogueras, *J. Heterocyclic Chem.*, **26**, 1089 (1989).

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

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

[15] H. McNab, *Chem. Soc. Rev.*, **7**, 345 (1978).

[16] R. F. C. Brown, F. W. Eastwood, K. J. Harrington, *Austr. J. Chem.*, **27**, 2373 (1974).

[17] R. Rodríguez, M. Suárez, E. Ochoa, A. Moráles, L. Gonzalez, N. Martin, M. Quinteiro, C. Seoane, and J. L. Soto, *J. Heterocyclic Chem.*, **33**, 45 (1996).

[18] D. Prajapati and J. S. Sandhu, *J. Chem. Soc., Perkin Trans. 1*, 739 (1993).