Convenient Synthesis of 4-Amino-7-(dialkylamino)pyrido[2,3-*d*]pyrimidines from Polysubstituted Pyridines

Maria Teresa Cocco, Cenzo Congiu, Antonio Maccioni* and Valentina Onnis

Dipartimento Farmaco Chimico Tecnologico, Università,
Via Ospedale 72, I-09124 Cagliari, Italy
Received August 31, 1992

A convenient synthesis of 4-amino-7-(dialkylamino)pyrido[2,3-*d*]pyrimidines *via* cyclization of functionalized pyridines is reported. The preparation of the starting pyridines from 3-amino-3-(dialkylamino)propenenitriles and ethoxymethylenemalononitrile is described.

J. Heterocyclic Chem., **30**, 253 (1993).

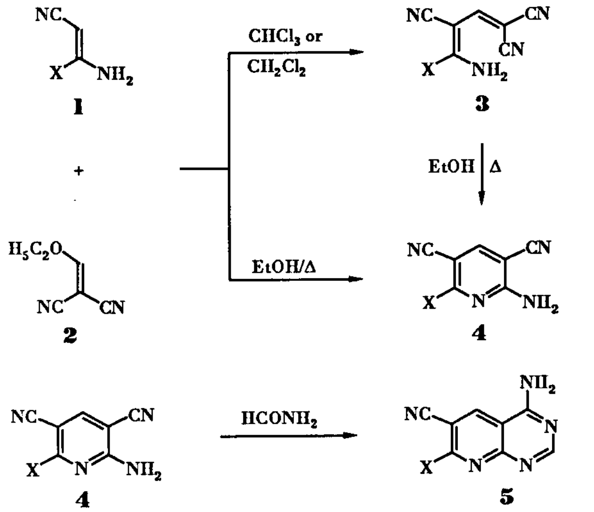
The pyrido[2,3-*d*]pyrimidine ring system has been the subject of numerous studies because of its structural similarity to folic acid. Particularly the oxo and amino derivatives of pyrido[2,3-*d*]pyrimidine stand out for their antibacterial [1,2], antitumor [3] and anticonvulsive [4] activity. With the aim of finding new chemotherapeutic agents, we have considered the 4,7-diaminopyrido[2,3-*d*]pyrimidine derivatives **5**.

Here we report an efficient method for the preparation of this ring system in which the 3-amino-3-(dialkylamino)-propenenitriles **1** are used as starting materials (Scheme).

We have found previously that enaminonitriles **1** are versatile and convenient reagents for the synthesis of nitrogen heterocycles [5-7] and that the reaction between the enaminonitriles **1** and the enol ethers containing electron-withdrawing groups leads to polysubstituted pyridine derivatives [8-9].

The reaction of **1** with ethoxymethylenemalononitrile (**2**) in chloroform or dichloromethane at temperatures between 0° and 5° for 24 hours, leads to dienaminonitriles **3** in good yields (Table 1). These adducts **3** are transformed into the pyridine derivatives **4** in almost quantitative yields (Table 3) when refluxed for a short time in ethanol. The pyridine derivatives **4** are also formed when equivalent amounts of **1** and **2** are refluxed in ethanol. By reacting **1** and **2** in ethanol at room temperature, mixtures of

Scheme

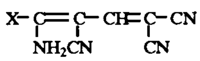


a, X = pyrrolidino
b, X = piperidino
c, X = morpholino
d, X = 4-methylpiperazino
e, X = 4-phenylpiperazino
f, X = 4-ethoxycarbonylpiperazino

adducts **3** and pyridine derivatives **4** are obtained, because the adducts **3** that are in solution undergo intramolecular cyclization. The reactions were monitored by thin layer chromatography (tlc) thus pointing out the greater reactivity of the enaminonitriles **1a-c**. In fact after

Table 1

Physical and Analytical Data of Compounds **3a-f**



Compound No.	X	Yield (%)	Mp (°C)	Molecular Formula	Analysis % Calcd.			Analysis % Found		
					C	H	N	C	H	N
3a	pyrrolidino	78	226	$C_{11}H_{11}N_5$	61.95	5.20	32.85	61.93	5.22	32.84
3b	piperidino	81	184	$C_{12}H_{13}N_5$	63.42	5.77	30.82	63.45	5.72	30.80
3c	morpholino	85	220	$C_{11}H_{11}N_5O$	57.63	4.84	30.55	57.67	4.82	30.52
3d	4-methylpiperazino	76	171	$C_{12}H_{14}N_6$	59.48	5.82	34.69	59.40	5.84	34.67
3e	4-phenylpiperazino	87	190	$C_{17}H_{16}N_6$	67.08	5.30	27.62	67.05	5.27	27.65
3f	4-ethoxycarbonylpiperazino	76	255	$C_{14}H_{16}N_6O_2$	55.99	5.37	27.99	55.95	5.35	28.00

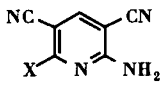
Table 2

Spectroscopic Data of Compounds **3a-f**

Compound No.	IR (cm^{-1})	^{1}H-NMR δ (ppm)
3a	3320, 3180, 2200, 2180, 1660, 1585	1.87 (m, 4H, $(CH_2)_2$), 3.30, 3.50 (m, 4H, CH_2NCH_2), 7.19 (s, 1H, =CH), 8.01 (br s. 2H, NH_2)
3b	3330, 3190, 2205, 2180, 1660, 1585	1.56 (m, 6H, $(CH_2)_3$), 3.42 (m, 4H, CH_2NCH_2), 7.16 (s, 1H, =CH), 8.09 (s, 1H, NH), 8.43 (s, 1H, NH)
3c	3330, 3190, 2210, 2190, 1670, 1575	3.48 (m, 4H, CH_2NCH_2), 3.61 (m, 4H, CH_2OCH_2), 7.20 (s, 1H, =CH), 8.22 (s, 1H, NH), 8.57 (s, 1H, NH)
3d	3530, 3300, 3090, 2210, 2190, 1690, 1565	2.25 (s, 3H, CH_3), 3.49 (m, 8H, $(CH_2NCH_2)_2$), 7.19 (s, 1H, =CH), 8.22 (s, 1H, NH), 8.58 (s, 1H, NH)
3e	3410, 3320, 3220, 2200, 2180, 1635, 1600, 1560	3.22, 3.63 (m, 8H, $(CH_2NCH_2)_2$), 6.78, 6.93, 7.20 (m, 5H Ar), 7.24 (s, 1H, =CH), 8.28 (s, 1H, NH), 8.61 (s, 1H, NH)
3f	3430, 3310, 3230, 2210, 2180, 1680, 1640, 1565	1.15 (t, 3H, CH_3), 3.44, 3.48 (m, 8H, $(CH_2NCH_2)_2$), 4.02 (q, 2H, CH_2), 7.20 (s, 1H, =CH), 8.24 (s, 1H, NH), 8.60 (s, 1H, NH)

Table 3

Physical and Analytical Data of Compounds **4a-f**



Compound No.	X	Yield (%) Method A	Yield (%) Method B	Mp (°C)	Molecular Formula	Analysis % Calcd. C	H	N	Analysis % Found C	H	N
4a	pyrrolidino	96	72	223 [a]	$C_{11}H_{11}N_5$	61.95	5.20	32.85	61.93	5.22	32.87
4b	piperidino	92	59	132 [a]	$C_{12}H_{13}N_5$	63.42	5.77	30.82	63.47	5.75	30.80
4c	morpholino	97	61	229 [b]	$C_{11}H_{11}N_5O$	57.63	4.84	30.55	57.60	4.86	30.54
4d	4-methylpiperazino	93	65	180 [b]	$C_{12}H_{14}N_6$	59.48	5.82	34.69	59.44	5.86	34.71
4e	4-phenylpiperazino	98	58	170 [b]	$C_{17}H_{16}N_6$	67.08	5.30	27.62	67.12	5.28	27.60
4f	4-ethoxycarbonylpiperazino	95	59	266 [a]	$C_{14}H_{16}N_6O_2$	55.99	5.37	27.99	56.02	5.35	27.97

[a] From acetonitrile. [b] From ethanol.

Table 4

Spectroscopic Data of Compounds **4a-f**

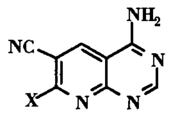
Compound No.	IR (cm^{-1})	^{1}H-NMR δ (ppm)
4a	3420, 3330, 3230, 2220, 2200, 1645, 1610	1.84 (m, 4H, $(CH_2)_2$), 3.59 (m, 4H, CH_2NCH_2), 7.18 (s, 2H, NH_2), 7.99 (s, 1H, H-4)
4b	3420, 3330, 3230, 2220, 2200, 1645, 1600	1.53 (m, 6H, $(CH_2)_3$), 3.67 (m, 4H, CH_2NCH_2), 7.31 (s, 2H, NH_2), 8.05 (s, 1H, H-4)
4c	3390, 3320, 3220, 2200, 1640, 1595	3.63 (m, 4H, CH_2NCH_2), 3.67 (m, 4H, CH_2OCH_2), 7.42 (s, 2H, NH_2), 8.10 (s, 1H, H-4)
4d	3520, 3410, 3320, 3200, 2200, 1650, 1600	2.14 (s, 3H, CH_3), 2.33 (m, 4H, CH_2NCH_2), 3.68 (m, 4H, CH_2NCH_2), 7.37 (s, 2H, NH_2), 8.07 (s, 1H, H-4)
4e	3460, 3320, 3210, 2200, 1630, 1600	3.21. 3.86 (m, 8H, $(CH_2NCH_2)_2$), 6.75, 6.91, 7.18 (m, 5H Ar), 7.43 (s, 2H, NH_2), 8.12 (s, 1H, H-4)
4f	3400, 3320, 3220, 2200, 1695, 1640, 1600	1.14 (t, 3H, CH_3), 3.43, 3.69 (m, 8H, $(CH_2NCH_2)_2$), 4.01 (q, 2H, CH_2), 7.42 (s, 2H, NH_2), 8.10 (s, 1H, H-4)

about 5 minutes both dienaminonitrile **3** and its cyclic product **4** could be observed in solution, while the enaminonitriles **1d-f** as well as their products, the dienaminonitriles, are less reactive.

A tlc examination of the reaction mixture shows that dienaminonitrile forms after about 3 hours and its cyclic

Table 5

Physical and Analytical Data of Compounds **5a-f**



Compound No.	X	Yield (%)	Mp (°C)	Molecular Formula	Analysis % Calcd. C	H	N	Analysis % Found C	H	N
5a	pyrrolidino	98	310 [a]	$C_{12}H_{12}N_6$	59.98	5.03	34.98	59.95	5.00	34.97
5b	piperidino	65	268 [a]	$C_{13}H_{14}N_6$	61.40	5.55	33.05	61.43	5.52	33.03
5c	morpholino	98	280 [a]	$C_{12}H_{12}N_6O$	56.24	4.72	32.80	56.20	4.74	32.82
5d	4-methylpiperazino	98	253 [a]	$C_{13}H_{15}N_7$	57.97	5.61	36.41	57.94	5.63	36.44
5e	4-phenylpiperazino	65	264 [a]	$C_{18}H_{17}N_7$	65.24	5.17	29.59	65.20	5.15	29.62
5f	4-ethoxycarbonylpiperazino	65	272 [a]	$C_{15}H_{17}N_7O_2$	55.03	5.23	29.96	55.00	5.25	29.95

[a] From ethanol.

Table 6

Spectroscopic Data of Compounds **5a-f**

Compound No.	IR (cm^{-1})	^{1}H-NMR δ (ppm)
5a	3500, 3300, 3050, 2210, 1670, 1650	1.91 (m, 4H, $(CH_2)_2$), 3.70, (m, 4H, CH_2NCH_2), 7.83 (s, 2H, NH_2), 8.27 (s, 1H, H-5), 8.86 (s, 1H, H-2)
5b	3390, 3340, 3050, 2210, 1670, 1600	1.61 (m, 6H, $(CH_2)_3$), 3.70 (m, 4H, CH_2NCH_2), 7.93 (s, 2H, NH_2), 8.32 (s, 1H, H-5), 8.91 (s, 1H, H-2)
5c	3520, 3300, 3060, 2200, 1680, 1600	3.25 (m, 4H, CH_2NCH_2), 3.71 (m, 4H, (CH_2OCH_2)), 7.98 (s, 2H, NH_2), 8.36 (s, 1H, H-5), 8.97 (s, 1H, H-2)
5d	3430, 3320, 3050, 2200, 1670, 1600	2.18 (s, 3H, CH_3), 2.41, 3.72 (m, 8H, $(CH_2NCH_2)_2$), 7.98 (s, 2H, NH_2), 8.34 (s, 1H, H-5), 8.94 (s, 1H, H-2)
5e	3320, 3050, 2210, 1670, 1600	3.30. 3.88 (m, 8H, $(CH_2NCH_2)_2$), 6.76, 6.95, 7.19 (m, 5H Ar), 8.00 (s, 2H, NH_2), 8.37 (s, 1H, H-5), 8.97 (s, 1H, H-2)
5f	3600, 3380, 3050, 2220, 1685, 1670 1600	1.16 (t, 3H, CH_3), 3.50, 3.74 (m, 8H, $(CH_2NCH_2)_2$), 4.03 (q, 2H, CH_2), 8.00 (s, 2H, NH_2), 8.36 (s, 1H, H-5), 8.97 (s, 1H, H-2)

product after 24 hours. Moreover a ^{1}H nmr study of the reaction between enaminonitrile **1c** and the enol ether **2** in DMSO-d_6 shows that immediately after mixing the signal of the olefinic proton of dienaminonitrile **3c** appears at 7.20 ppm and that after 40 minutes the signal of the H-4 of pyridine **4c** already appears at 8.20 ppm.

The structural assignments of **3** are confirmed by ir and ^{1}H nmr spectroscopic data (Table 2) and by the conversion of **3** into **4**. The ^{1}H nmr spectra of the compounds **3** show a singlet between 7.16 and 7.24 due to the olefinic proton, and two NH signals that can be assigned to chelated and free NH groups.

In the ^{1}H nmr spectra of compounds **4** (Table 4), two singlets appear in the aromatic region: the downfield singlet (8.12-7.99 ppm) is due to the H-4 while the other (7.43-7.18), that disappears after deuteration, is attributable to the NH_2 group.

The pyridine derivatives **4** are a versatile intermediary for the synthesis of fused pyridines. The reaction of compounds **4** with formamide lead to pyrido[2,3-*d*]pyrimidine derivatives **5** (Table 5) in 65-98% yields.

The structure of compounds **5** was established through analytical and spectral data (Table 6) and especially by the presence of the signals of the H-2 proton at 8.36-8.27 and by the H-5 proton at 8.97-8.86.

EXPERIMENTAL

Melting points were determined on Köfler hot stage and are uncorrected. The ir spectra were obtained in Nujol with a Perkin-Elmer 398 spectrophotometer. The ^{1}H nmr spectra were recorded in hexadeuteriodimethyl sulphoxide solution with a Varian Unity 300 spectrometer; chemical shifts are reported in ppm from hexamethyldisiloxane as an internal standard and are given in δ units. The elemental analyses (C,H,N) were carried out with a Carlo Erba model 1106 Elemental Analyzer. The reaction mixtures were monitored by tlc on DC-Alufolien Kieselgel 60-F254 (Merck) using ethyl acetate-petroleum ether 2:1 as eluant.

General Procedure for the Preparation of Dienaminonitriles **3a-f**.

A solution of compound **2** (0.61 g, 5 mmoles) in 10 ml of dry chloroform was added to a solution of enaminonitrile **1** (5 mmoles) in 10 ml of dry chloroform. The mixture was kept at 0-5° for 24 hours. The formed precipitate was filtered off and washed with chloroform (3 x 10 ml) to give dienaminonitriles **3a-f** in 76-87% yields.

General Procedure for the Preparation of Pyridines **4a-f**.

Method A.

A suspension of dienaminonitrile **3** (2 mmoles) in 20 ml of ethanol was refluxed for 2 hours. After removal of the solvent *in vacuo* the residue was collected and recrystallized to give pyridines **4a-f** in almost quantitative yields.

Method B.

A mixture of compound **2** (5 mmoles) and enaminonitrile **1** (5 mmoles) in 30 ml of anhydrous ethanol was heated under reflux. In the case of compounds **1a-c** the mixture was refluxed for 0.5 hour and in the case of **1d-f** for 4 hours. After evaporation of the solvent the corresponding pyridines were obtained and elaborated as shown in Method A.

General Procedure for the Preparation of Pyrido[2,3-*d*]pyrimidines **5a-f**.

A mixture of compound **4** (5 mmoles) in 5 ml of formamide was refluxed for 15 minutes. After cooling the formed precipitate was filtered off, washed with water, dried and recrystallized to give compounds **5**.

Acknowledgments.

This work was supported by a grant from the Ministero della Università e Ricerca Scientifica.

REFERENCES AND NOTES

[1] B. S. Hurlbert, R. Ferone, T. A. Herrmann, G. H. Hitchings, M. Barnett and S. R. M. Bushby, *J. Med. Chem.*, **11**, 711 (1968).

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

[3] E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch and C. A. Nichol, *J. Med. Chem.*, **23**, 327 (1980).

[4] E. Kretzchmar, *Pharmazie*, **35**, 253 (1980).

[5] M. T. Cocco, C. Congiu, A. Plumitallo, M. L. Schivo and G. Palmieri, *Farmaco Ed. Sci.*, **42**, 347 (1987).

[6] M. T. Cocco, C. Congiu, V. Onnis and A. Maccioni, *Synthesis*, 529 (1991).

[7] M. T. Cocco, C. Congiu, A. Maccioni and V. Onnis, *Synthesis*, 371 (1992).

[8] M. T. Cocco, C. Congiu, A. Maccioni and A. Plumitallo, *J. Heterocyclic Chem.*, **26**, 1859 (1989).

[9] M. T. Cocco, C. Congiu and A. Maccioni, *J. Heterocyclic Chem.*, **27**, 1143 (1990).