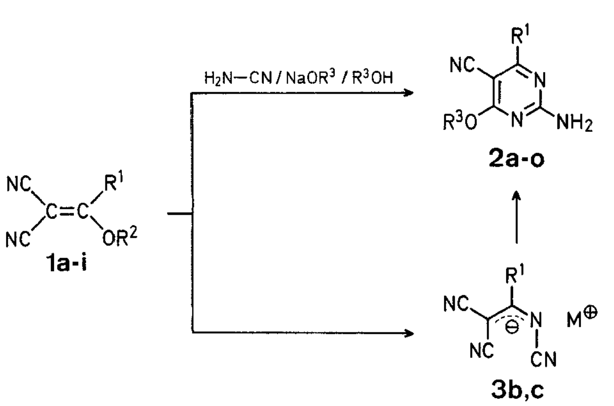
Synthesis of 6-Alkoxy-2-amino-5-cyanopyrimidines through Sodium Alkoxide-Induced Regiospecific Cyclization of 1,3-Dicarbonitriles

Miguel A. PEREZ, José L. SOTO*

Department of Organic Chemistry, Facultad de Química, Universidad Complutense, Madrid-3, Spain

Although the cyclization of α,ω-dicarbonitriles under acidic conditions is well documented[1], the addition of oxygen nucleophiles followed by cyclization has received scant attention[2]. We have applied this procedure to the synthesis of pyridines[3] and then attempted to generalize this reaction to other heterocycles. We now report the specific synthesis of the hitherto unknown 4-alkoxy-2-amino-5-cyanopyrimidines **2** through sodium alkoxide-induced cyclization of 1,3-dicarbonitriles.

As educts, we selected the readily accessible 3-alkoxy-3-aryl (or alkyl)-2-cyanopropenenitriles **1** (Table 1), prepared in a manner similar to the reported procedures[4,5,6].

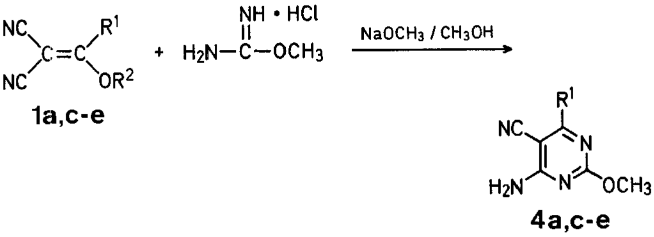


Scheme **A**

By refluxing equimolar amounts of the propenenitriles **1** and cyanamide in alcohols in the presence of two molar equivalents of the respective sodium alkoxides, the 6-alkoxy-2-amino-4-aryl (or alkyl)-5-cyanopyrimidines **2** (Table 2) can be isolated pure in moderate yields by simply pouring the reaction mixture into water and collecting the precipitate by filtration. By using a small amount of alcohol and only one molar equivalent of sodium alkoxide at room temperature, the salts **3b**[7], **c** ($R^1=CH_3$, C_6H_5, respectively; M = Na) precipitated after a few minutes and can be obtained in high yields upon dilution with diethyl ether. The 3-cyanamino-2-cyano-3-phenylpropenenitrile tetraphenylarsonium salt [**3c**, $M=(C_6H_5)_4As$], prepared from its potassium salt by cation exchange, gave a correct analysis. Its spectroscopic data are similar to those reported for other related salts[8]. On treating these salts with one molar equivalent of sodium methoxide, the pyrimidines **2b, c** are obtained.

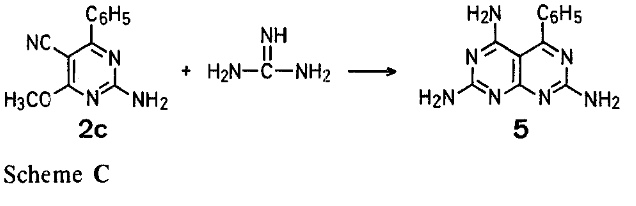
In this cyclization reaction, the alkoxide ($R^2O^\ominus$) used is incorporated into the formed pyrimidine **2** after specifically attacking the C-bonded carbonitriles of the conjugation-stabilized salt **3**, with probable formation of an intermediate imidate, and subsequent cyclization with the N-bonded carbonitrile. No trace of the 6-aminopyrimidines **4**, proceeding from attack of the alkoxide on the N-bonded carbonitrile, could be detected in the mother liquors either in the course of different work-ups or by following the reaction by T.L.C.

For comparison purposes, several pyrimidines **4** were prepared as depicted in Scheme **B**. These 6-aminopyrimidines **4** (Table 3) have higher melting points than their positional isomers **2**. Further evidence for the structure of the pyrimidines **2** was achieved through a condensation reaction and an independent synthesis.



Scheme **B**

The reaction of the pyrimidine **2c** with guanidine affords the expected 2,5,7-triamino-4-phenylpyrimido[4,5-*d*]pyrimidine (**5**) in good yield (Scheme **C**).



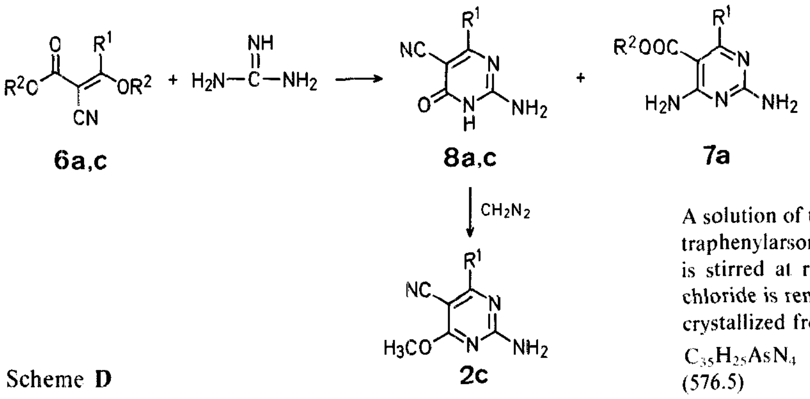
Scheme **C**

An independent synthesis of the pyrimidine **2c** was performed as depicted in Scheme **D**. The cyclization of **6a** ($R^1=H$, $R^2=C_2H_5$)[10] with guanidine afforded 2,6-diamino-5-ethoxycarbonylpyrimidine (**7a**; $R^1=H$, $R^2=C_2H_5$)[11] as the major product. However, with methyl (*E*)-2-cyano-3-methoxy-3-phenylpropenoate (**6c**; $R^1=C_6H_5$, $R^2=CH_3$), isolated from its (*E,Z*)-mixture[12] by recrystallization from methanol, the 2-amino-5-cyano-6-phenyl-4(3*H*)-pyrimidinone (**8c**; $R^1=C_6H_5$) was obtained. Methylation of **8c** with diazomethane led to **2c** in good yield.

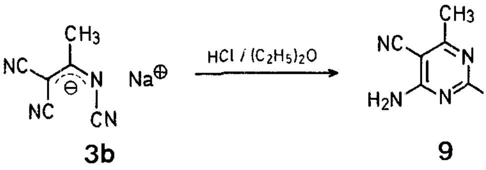
To correlate their structures, **2j** and **2m** were also obtained from **2c** and **2g** by refluxing with one molar equivalent of sodium ethoxide in ethanol.

The specificity of this dicarbonitrile cyclization seems to be also present under acidic conditions. In this instance however, the N-bonded carbonitrile is being attacked. Thus, by suspending the salt **3b** (M = Na) in dry diethyl ether and bubbling dry hydrogen chloride through it only the formation of the 2-chloropyrimidine **9**[7] is observed (Scheme **E**).

0039-7881/81/1232-0955 $ 03.00



Scheme D



Scheme E

6-Alkoxy-2-amino-4-aryl(or alkyl)-5-cyanopyrimidines 2; General Procedure:

A solution of sodium alkoxide (20 mmol), cyanamide (10 mmol), and propenenitrile **1** (10 mmol) in dry alcohol (50 ml) is heated under reflux for 4 to 48 h and poured into water. The precipitate thus formed is collected and recrystallized to yield the pyrimidine **2** (Table 2).

6-Amino-4-aryl(or alkyl)-5-cyano-2-methoxypyrimidines 4; General Procedure:

A solution of sodium methoxide (20 mmol) and methyl carbamimidate hydrochloride (22 mmol) in dry methanol (50 ml) is stirred with ice cooling for 15 min. The precipitated sodium chloride is filtered out and propenenitrile **1** (20 mmol) is added to the filtrate. The mixture is stirred at room temperature for 1 h, then refluxed for 1 h, and cooled. The precipitate is collected and recrystallized to afford the pyrimidine **4** (Table 3).

3-Cyanamino-2-cyano-3-phenylpropenenitrile, Tetraphenylarsonium Salt [3c; M = $(C_6H_5)_4As$]:

A mixture of potassium methoxide (0.106 mol), cyanamide (4.45 g, 0.106 mol), and 2-cyano-3-methoxy-3-phenylpropenenitrile (**1c**; 19.51 g, 0.106 mol) in dry methanol (140 ml) is stirred at room temperature for 30 min. After dilution with dry diethyl ether (600 ml), the precipitate is collected and dried in vacuo to give crude **3c** (M = K); yield: 23.51 g (95%).

A solution of the potassium salt **3c** (M = K; 1.04 g, 4.44 mmol) and tetraphenylarsonium chloride (1.86 g, 4.44 mmol) in dry acetone (50 ml) is stirred at room temperature for 1 h. The precipitated potassium chloride is removed and the filtrate is concentrated. The residue is recrystallized from methanol; yield: 2.48 g (97%); m.p. 187-188 °C.

$C_{35}H_{25}AsN_4$	calc.	C 72.92	H 4.37	N 9.72
(576.5)	found	72.73	4.57	9.71

I.R. (KBr): $\nu = 2220, 2170\ cm^{-1}$.

^{13}C-N.M.R. (CD_3OD; measured as the crude **3c**, M = K): $\delta = 184.2$ (C-3); 137.0 (C-1′); 131.5, 129.3, 128.3 (C-2′, C-3′, C-4′); 120.6, 120.1, 118.4 (CN); 54.7 ppm (C-2).

2,5,7-Triamino-4-phenylpyrimido[4,5-*d*]pyrimidine (5):

A mixture of guanidinium sulfate (4.32 g, 20 mmol) and sodium ethoxide (40 mmol) in dry ethanol (50 ml) is stirred with ice cooling for 30 min. The precipitated sodium sulfate is removed and 2-amino-5-cyano-6-methoxy-4-phenylpyrimidine (**2c**; 2.26 g, 10 mmol) is added to the filtrate. The solution is heated under reflux for 20 h and cooled. The precipitate is collected and recrystallized from dimethylformamide; yield: 2.34 g (92%); m.p. 353-355 °C.

$C_{12}H_{11}N_7$	calc.	C 56.90	H 4.37	N 38.71
(253.3)	found	56.62	4.31	38.39

I.R. (KBr): $\nu = 3470, 3390, 3300, 3130, 1675, 1620\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 7.76$ (s, 5 H_{arom}); 6.8 ppm (br, 6 H, NH_2).

M.S.: *m/e* (relative intensity) = 253 (M^+, 90).

2-Amino-5-cyano-6-phenyl-4(3*H*)-pyrimidinone (8c):

A solution of free guanidine (22 mmol) and methyl (*E*)-2-cyano-3-methoxy-3-phenylpropenoate (**6c**; 4.34 g, 20 mmol) in dry ethanol (50 ml) is heated under reflux for 2 h. The mixture is diluted with water and some educt **6c** (1.51 g, 34%) is recovered. The filtrate is acidified with dilute hydrochloric acid. The precipitate thus formed is collected and recrystallized from acetic acid/water (1 : 1) to give **8c**; yield: 2.28 g (54%); m.p. 340-342 °C (dec.).

$C_{11}H_8N_4O$	calc.	C 62.26	H 3.80	N 26.41
(212.2)	found	62.02	3.75	25.95

I.R. (KBr): $\nu = 3400, 3140, 2220, 1680, 1625\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 11.8$ (br s, 1 H, OH), 7.5-8.0 ppm (m, 7 H, 5 H_{arom} + NH_2).

M.S.: *m/e* (relative intensity) = 212 (M^+, 97).

Table 1. 3-Alkoxy-3-aryl-2-cyanopropenenitriles **1**

Product	R^1	R^2	Yield [%]	m.p.[a] [°C]	Molecular formula or m.p. [°C] reported		I.R. (KBr) ν [cm^{-1}]
1a	H	C_2H_5	—[b]	—	—		—
1b	CH_3	C_2H_5	—[b]	—	—		—
1c	C_6H_5	CH_3	87	93-94[c]	93-94°[5]		—[c]
1d	2-H_3C—C_6H_4	CH_3	69	74-75[c]	$C_{12}H_{10}N_2O$	(198.2)	2220[d]
1e	3-Cl—C_6H_4	CH_3	71	91-92[c]	$C_{11}H_7ClN_2O$	(218.6)	2220[d]
1f	4-H_3CO—C_6H_4	CH_3	74	73-74[c]	$C_{12}H_{10}N_2O_2$	(214.2)	2220[d]
1g	4-Cl—C_6H_4	CH_3	79	122-123°	123°[5]		—[e]
1h	4-H_3C—C_6H_4	CH_3	71	102-103°	$C_{12}H_{10}N_2O$	(198.2)	2230, 2220
1i	4-O_2N—C_6H_4	CH_3	69	123-124°	$C_{11}H_7N_3O_3$	(229.2)	2235, 2220

[a] All compounds recrystallized from methanol; satisfactory microanalyses obtained for new products (C ±0.26, H ±0.13, N ±0.27, Cl ±0.12).

[b] Commercially available product.

[c] ^{13}C-N.M.R. ($CDCl_3$): $\delta = 185.3$ (C-3); 132.9, 129.3, 128.3 (C-2′, C-3′, C-4′); 127.9 (C-1′); 113.2, 111.7 (CN); 67.2 (C-2); 61.2 ppm (CH_3O).

[d] Double band.

[e] ^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.75$ (s, 4 H_{arom}); 3.92 ppm (s, 3 H, CH_3O).

Table 2. 6-Alkoxy-2-amino-4-aryl(or alkyl)-5-cyanopyrimidines **2a–o**

Product	R	R^2	Yield [%]	m.p.[a] [°C]	Molecular formula[b]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]	M.S. *m/e* (rel. intens. %)
2a	H	CH_3	22	207–208°	$C_6H_6N_4O$ (150.2)	3430, 3330, 3130, 2220, 1660	8.50 (s, 1 H_{arom}); 7.7 (br s, 2 H, NH_2); 3.97 (s, 3 H, CH_3O)	150 (M^+, 100)
2b	CH_3	CH_3	17	254–255°	$C_7H_8N_4O$ (164.2)	3410, 3320, 3110, 2210, 1660	7.5 (br s, 2 H, NH_2); 3.93 (s, 3 H, CH_3O); 2.33 (s, 3 H, CH_3)	—
2c	C_6H_5	CH_3	49	183°	$C_{12}H_{10}N_4O$ (226.2)	3500, 3300, 3160, 2225, 1640	8.0–7.5 (m, 7 H, H_{arom} + NH_2); 4.04 (s, 3 H, CH_3O)	226 (M^+, 100)
2d	2-H_3C—C_6H_4	CH_3	37	212–213°	$C_{13}H_{12}N_4O$ (240.3)	3360, 3320, 3160, 2220, 1650	7.8 (br s, 2 H, NH_2); 7.38 (s, 4 H_{arom}); 4.02 (s, CH_3O); 2.28 (s, CH_3)	240 (M^+, 83)
2e	3-Cl—C_6H_4	CH_3	23	192°	$C_{12}H_9ClN_4O$ (260.7)	3480, 3300, 3170, 2220, 1650	8.0–7.6 (m, 6 H, H_{arom} + NH_2); 4.03 (s, 3 H, CH_3O)	260 (M^+, 100)
2f	4-H_3CO—C_6H_4	CH_3	12	191–192°	$C_{13}H_{12}N_4O_2$ (256.3)	3520, 3400, — 2210, 1630	—	—
2g	4-Cl—C_6H_4	CH_3	46	202–203°	$C_{12}H_9ClN_4O$ (260.7)	3470, 3300, 3150, 2220, 1645	8.1–7.6 (m, 6 H, H_{arom} + NH_2); 4.04 (s, 3 H, CH_3O)	260 (M^+, 100)
2h	4-H_3C—C_6H_4	CH_3	21	189°	$C_{13}H_{12}N_4O$ (240.3)	3480, 3300, 3130, 2220, 1640	—	—
2i	4-O_2N—C_6H_4	CH_3	22	249–250°	$C_{12}H_9N_5O_3$ (271.2)	3450, 3350, 3220, 2220, 1660	8.5–7.8 (m, 6 H_{arom} + NH_2); 4.03 (s, 3 H, CH_3O)	—
2j	C_6H_5	C_2H_5	26	150–151°	$C_{13}H_{12}N_4O$ (240.3)	— 3300, 3160, 2220, 1660	8.0–7.5 (m, 7 H_{arom} + NH_2); 4.53 (q, 2 H, —CH_2O); 1.39 (t, CH_3—C)	240 (M^+, 100)
2k	2-H_3C—C_6H_4	C_2H_5	32	188–189°	$C_{14}H_{14}N_4O$ (254.3)	3440, 3300, 3170, 2220, 1640	—	—
2l	3-Cl—C_6H_4	C_2H_5	21	155–156°	$C_{13}H_{11}ClN_4O$ (274.7)	— 3360, 3160, 2230, 1660	—	—
2m	4-Cl—C_6H_4	C_2H_5	25	174–175°	$C_{13}H_{11}ClN_4O$ (274.7)	— 3330, 3170, 2210, 1650	8.0–7.5 (m, 6 H, H_{arom} + NH_2); 4.50 (q, 2 H, —CH_2O); 1.37 (t, CH_3—C)	—
2n	4-H_3C—C_6H_4	C_2H_5	16	157–158°	$C_{14}H_{14}N_4O$ (254.3)	— 3340, 3200, 2200, 1650	—	—
2o	C_6H_5	*n*-C_3H_7	32	131–132°	$C_{14}H_{14}N_4O$ (254.3)	— 3380, 3200, 2220, 1670	—	254 (M^+, 91)

[a] Products recrystallized from methanol **(2d, h, *i*)** or ethanol.

[b] Satisfactory microanalyses obtained (C ±0.33, H ±0.25, N ±0.28, Cl ±0.27).

Table 3. 6-Amino-4-aryl(or alkyl)-5-cyano-2-methoxypyrimidines **4**

Product	R	Yield [%]	m.p.[a] [°C]	Molecular formula[b] or Lit. m.p	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]	M.S. *m/e* (rel. intens. %)
4a	H	83	220–221°	221–222°[9]	3360, 3320, 3140, 2230, 1670	8.55 (s, 1 H_{arom}), 7.87 (br s, 2 H, NH_2), 3.90 (s, 3 H, CH_3O)	150 (M^+, 70)
4c	C_6H_5	92	217°	$C_{12}H_{10}N_4O$ (226.2)	3380, 3300, 3160, 2210, 1650	8.0–7.6 (m, 7 H, H_{arom} + NH_2), 3.97 (s, 3 H, CH_3O)	226 (M^+, 100)
4d	2-H_3C—C_6H_4	80	217–218°	$C_{13}H_{12}N_4O$ (240.3)	3420, 3330, 3100, 2220, 1640	—	240 (M^+, 100)
4e	3-Cl—C_6H_4	98	227°	$C_{12}H_9ClN_4O$ (260.7)	3450, 3300, 3120, 2220, 1655	—	260 (M^+, 91)

[a] Products recrystallized from methanol **(4d, e)** or ethanol.

[b] Satisfactory microanalyses obtained (C ±0.25, H ±0.24, N ±0.22, Cl ±0.17).

Pyrimidine 2c from Pyrimidinone 8c and Diazomethane:
A solution of diazomethane in diethyl ether (6.7 ml, 4 mmol) is allowed to drop in 30 min into a solution of pyrimidinone **8c** (0.848 g, 4 mmol) in ethyl acetate (200 ml) kept in an ice bath. The stirring is continued for 30 min and the solvent is removed in vacuo. The residue is purified by column chromatography on 20 g silica gel using benzene as eluent; yield: 0.72 g (80%), m.p. 183 °C (from ethanol); mixture m.p. with product **2c** from cyanamide: 183 °C.

6-Amino-2-chloro-5-cyano-4-methylpyrimidine (9):
A suspension of 3-cyanamino-2-cyano-3-methylpropenenitrile, sodium salt (**3b**, M = Na; 2.31 g, 15 mmol) in dry diethyl ether is stirred with ice cooling and dry hydrogen chloride is bubbled for 30 min. The mixture is kept in an ice-box for 12 h and the solvent is removed in vacuo. The residue is recrystallized from ethanol; yield: 2.07 g (81%); m.p. 252-253 °C (Lit.[7], m.p. 254 °C).

Received: June 2, 1981

---

* Author to whom correspondence should be adressed.

[1] H. Böhme, H. G. Viehe, *Adv. Org. Chem.* Vol. **9**, part 2, John Wiley & Sons, New York, 1979, p. 528.

[2] Z. Rappoport, *The Chemistry of the Cyano Group*, Wiley-Interscience, New York, 1970, p. 391.

[3] A. S. Alvarez-Insúa, M. Lora-Tamayo, J. L. Soto, *J. Heterocycl. Chem.* **7**, 1305 (1970).

[4] C. C. Cheng, R. K. Robins, *J. Org. Chem.* **21**, 1240 (1956).

[5] A. Dornow, E. Schleese, *Chem. Ber.* **91**, 1830 (1958).

[6] J. Fleury, B. Libis, *Bull. Soc. Chim. Fr.* **1964**, 413.

[7] H. Kristinsson, *J. Chem. Soc. Chem. Commun.* **1974**, 350.

[8] E. Allenstein, R. Fuchs, *Chem. Ber.* **101**, 1232 (1968).

[9] E. C. Taylor et al., *J. Am. Chem. Soc.* **82**, 5711 (1960).

[10] S. T. Ioffe et al., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, 1504; *Bull. Acad. Sci. USSR* **1970**, 1420.

[11] S. Nishigaki et al., *Chem. Pharm. Bull.* **18**, 1003 (1970).

[12] T. Hayashi, *J. Org. Chem.* **31**, 3253 (1966).

0039-7881/81/1232-0958 $ 03.00