



5-Cyanoacetylpyrimidines as intermediates for 7-aryl-6-cyanopyrido[2,3-*d*]pyrimidin-5-ones

Jairo Quiroga^{a,*}, Jorge Trilleras^b, Jaime Gálvez^a, Braulio Insuasty^a, Rodrigo Abonía^a, Manuel Nogueras^{c,*}, Justo Cobo^c

^a Grupo de Investigación de Compuestos Heterocíclicos, Department of Chemistry, Universidad del Valle, A. A. 25360 Cali, Colombia

^b Grupo de Investigación de Compuestos Heterocíclicos, Programa de Química, Universidad del Atlántico, Km 7 vía antigua Puerto Colombia Barranquilla, Colombia

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

ARTICLE INFO

Article history:

Received 16 April 2009

Revised 20 August 2009

Accepted 20 August 2009

Available online 26 August 2009

Keywords:

Pyrimidin-5-yl-3-oxopropanenitriles
N-(Pyrimidin-4-yl)-2-cyanoacetamides
Pyrido[2,3-*d*]pyrimidin-2,4,5-triones
Cyclocondensation

ABSTRACT

The reactions of *N*⁴- and 5-cyanoacetyl derivatives of 4-aminopyrimidines with aromatic aldehydes have yielded the *N*-(pyrimidin-4-yl)-3-arylacrylamides and the dihydropyrido[2,3-*d*]pyrimidines, respectively. The first reaction was a Claisen–Schmidt reaction catalysed by base, and the second one proceeded via thermal cyclocondensation.

© 2009 Elsevier Ltd. All rights reserved.

Pyrimidine-fused heterocycles are important targets in chemical biology or medicinal chemistry, and among them, pyrido[2,3-*d*]pyrimidine derivatives have attracted much attention because they are deazapteridines which have shown interesting bio-activities.^{1–3} The preparation of this kind of fused pyrimidines has been extensively investigated and well documented.^{1,4} They usually require forcing conditions,⁵ long reaction times,⁶ and complex synthetic pathways.⁷ Thus, the search for new and simple synthetic routes of these molecules still attracts considerable attention in order to develop high-throughput methods.^{2c,8}

As a matter of fact, we have already reported the regioselective synthesis of several 5-aryl-6-cyanopyrido[2,3-*d*]pyrimidines by the multicomponent reaction of 6-aminopyrimidines, aryl aldehydes, and ethyl cyanacetate^{8e} or 3-oxo-3-phenylpropanenitrile analogues.^{8f} On the other hand, the cyanoacetyl group has been used as methylene active residue to prepare diverse and versatile precursors and heterocyclic products.⁹

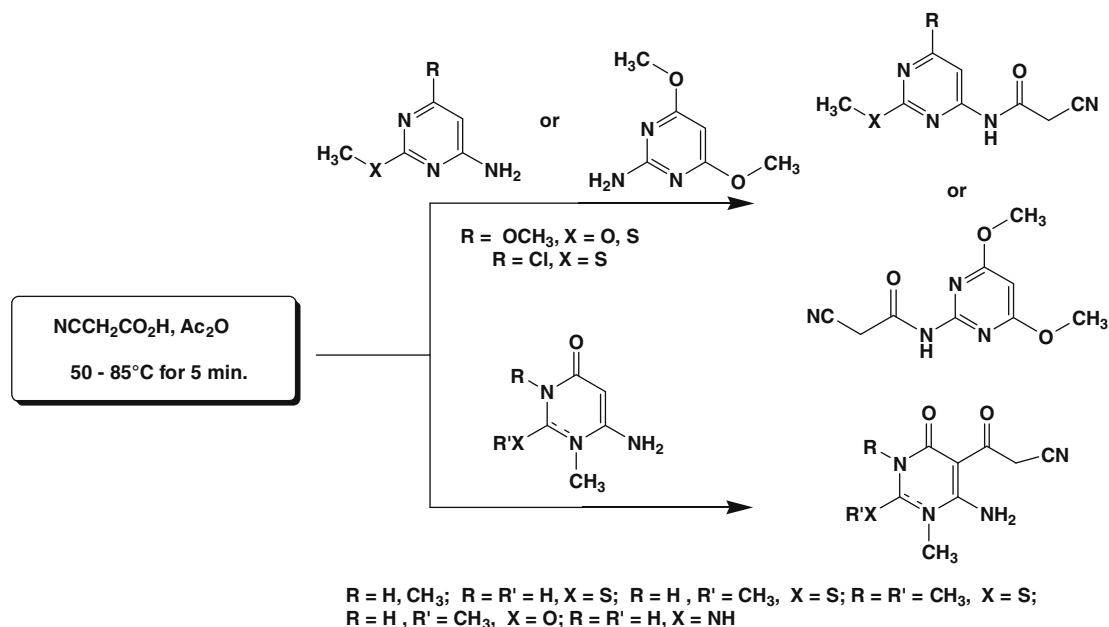
Accordingly, we consider that cyanoacetyl-substituted 6-aminopyrimidines constitute good precursors for the preparation of versatile functionalized pyrido[2,3-*d*]pyrimidines. In fact, we have recently reported the regioselective preparation of 3-pyrimidin-5-yl-3-oxopropanenitriles and *N*-(pyrimidin-4-yl)-2-cyanoacetamides¹⁰ through the reaction of 6-aminopyrimidines with

cyanoacetic acid and acetic anhydride (Scheme 1).¹¹ Our synthetic strategy is based on the nucleophilic character of methylene carbon in cyanoacetylated compounds.¹ These compounds may be used as intermediates to prepare (via aryl aldehyde through a Claisen–Schmidt cyclocondensation) the regioisomers 7-aryl-6-cyanopyrido[2,3-*d*]pyrimidin-5-ones or 5-aryl-6-cyanopyrido[2,3-*d*]pyrimidin-7-ones.¹²

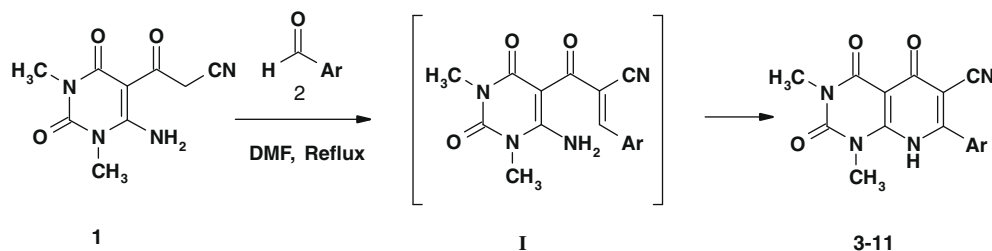
First, we have used the compound 3-(6-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidin-5-yl)-3-oxo-propanenitrile **1** in the reaction with aromatic aldehydes **2** by heating in DMF for 15 h to render the desired cyclocondensation products **3–11** in acceptable to good yields. The formation of pyrido[2,3-*d*]pyrimidines **3–11** is assumed initially to proceed by the formation of the corresponding heterocyclic cyanochalcone **I** as intermediate,¹³ that would suffer an intramolecular Michael addition via the amino group, followed by an oxidative process which is favored under reaction conditions (Scheme 2).¹⁴ The reactions proceeded quite well with different substituted aldehydes with electron-donating/electron-withdrawing groups giving moderate to good yields. These results are given in Table 1.

Next, the 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-acetamide **12** was put to react with aromatic aldehydes **2** in similar conditions in order to prepare the regioisomeric pyrido[2,3-*d*]pyrimidines. In turn, the 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-3-arylacrylamides **13–24** were isolated in moderate to good yields by a simple condensation reaction (Scheme 3). Formation of pyridopyrimidines was not observed.¹⁵ After reaction optimization, the compounds

* Corresponding authors. Fax: +57 2 33392440 (J.Q.); +34 618907111 (M.N.).
E-mail addresses: jaiquir@univalle.edu.co (J. Quiroga), mmontiel@ujaen.es (M. Nogueras).



Scheme 1.



Scheme 2.

Table 1
Results for the preparation of pyrido[2,3-*d*]pyrimidines by conventional method

Product	Ar	Mp °C	Yield (%)
3	C ₆ H ₅	220–222	60
4	4-ClC ₆ H ₄	229–231	50
5	4-BrC ₆ H ₄	248–250	90
6	4-FC ₆ H ₄	230–232	58
7	4-H ₃ CC ₆ H ₄	255–257	50
8	4-H ₃ COC ₆ H ₄	227–229	42
9	3-Pyridyl	319–321	70
10	3,4,5- <i>tri</i> -H ₃ COC ₆ H ₂	260–262	73
11	4-F ₃ CC ₆ H ₄	267–269	95

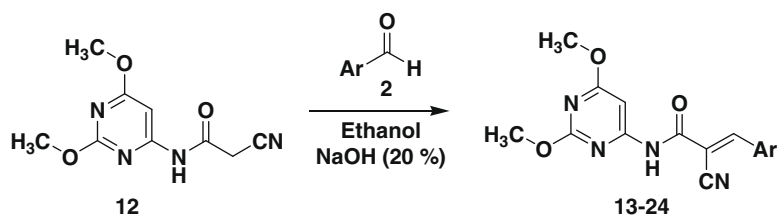
could be prepared in 56–95% in ethanol with base catalyst at room temperature for 2–3 h. Applying this new set of conditions the cyclocondensation between **1** and **2** did not proceed even under heating.

It is important to point out that this method allowed us to obtain the regioisomeric pyrido[2,3-*d*]pyrimidin-5-one while the previous three-component reactions among 6-amino-4-pyrimidinones, benzaldehydes, and cyanoacetyl derivatives led to the formation of the pyrido[2,3-*d*]pyrimidin-7-one.^{8e}

It follows from [Tables 1 and 2](#) that although the yields of all products ranging from good to excellent, nevertheless no relationship was found between them and the nature of the substituents of the aldehydes.

The structures of all new compounds were determined from analytical and spectral data, NMR 1D and 2D mainly, MS, and elemental analysis.

In conclusion, we have described the preparation of novel 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-3-arylacrylamides (in moderate to good yields) as products from the reaction of 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-acetamide and aromatic aldehydes and the preparation of new 7-aryl-6-cyano-1,



Scheme 3.

Table 2

Synthesis of 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-3-arylacrylamides derivatives by condensation reaction between 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-acetamide **12** and aldehydes using NaOH as catalyst

Product	Ar	Mp °C	Yield (%)
13	C ₆ H ₅	148–150	60
14	4-ClC ₆ H ₄	229–231	60
15	4-BrC ₆ H ₄	238–240	56
16	2-FC ₆ H ₄	165–167	61
17	4-FC ₆ H ₄	218–220	73
18	4-H ₃ CC ₆ H ₄	221–223	82
19	4-H ₃ COC ₆ H ₄	211–213	56
20	3,4-OCH ₂ O-C ₆ H ₃	227–229	72
21	4-O ₂ NC ₆ H ₄	252–254	80
22	2-HOCC ₆ H ₄	211–213	95
23	4-(H ₃ C) ₂ NC ₆ H ₄	253–255	76
24	3-Pyridyl	174–176	93

3-dimethyl-1,2,3,4,5,8-hexahydro-pyrido[2,3-*d*]-pyrimidin-2,4,5-triones. This is an efficient, simple, and regioselective alternative via cyclocondensation reactions from the isomeric precursor 3-(6-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxypyrimidin-5-yl)-3-oxopropanenitrile.

The chemical and biological properties of the new compounds obtained in these experiments are under investigation.

Acknowledgments

The authors thank Universidad del Valle, COLCIENCIAS, the Universidad de Jaén (project reference UJA-07-16-33), 'Servicios Técnicos de Investigación de Universidad de Jaén' and the staff for data collection, the Consejería de Innovación, Ciencia y Empresa (Junta de Andalucía, Spain) and Ministerio de Ciencia e Innovación (project reference SAF2008-04685-C02-02) for financial support, and Walter Torres for reviewing this manuscript.

References and notes

- Lunt, E.; Newton, C. C. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Boulton, A. J., Mc Killop, A., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, pp 199–232. and pp 260–261.
- (a) Tu, S.; Li, C.; Shi, F.; Zhou, D.; Shao, Q.; Cao, L.; Jiang, B. *Synthesis* **2008**, 369–376; (b) Bagley, M. C.; Hughes, D. D.; Lloyd, R.; Powers, V. E. C. *Tetrahedron Lett.* **2001**, 42, 6585–6588; (c) Devi, I.; Kumar, B. S. D.; Bhuyan, P. J. *Tetrahedron Lett.* **2003**, 44, 8307–8310; (d) Devi, I.; Borah, H. N.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, 45, 2405–2408.
- (a) Kanth, S. R.; Reddy, G. V.; Kishore, K. H.; Rao, P. S.; Narsaiah, B.; Murthy, U. S. N. *Eur. J. Med. Chem.* **2006**, 41, 1011–1016; (b) Bulicz, J.; Bertarelli, D. C. G.; Baumert, D.; Fülle, F.; Müller, C. E.; Heber, D. *Bioorg. Med. Chem.* **2006**, 14, 2837–2849; (c) Tu, S.; Zhang, J.; Zhu, X.; Xu, J.; Zhang, Y.; Wang, O.; Jia, R.; Jiang, B.; Zhang, J. *Bioorg. Med. Chem. Lett.* **2006**, 16, 3578–3581.
- Tamura, G.; Sakaguchi, T.; Klawasaki, T.; Kita, Y. *Heterocycles* **1975**, 3, 183–186.
- Hirota, K.; Kuki, H.; Maki, Y. *Heterocycles* **1994**, 37, 563–570.
- (a) Srivastava, P.; Saxena, A. S.; Ram, V. J. *Synthesis* **2000**, 541–544; (b) Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem.* **1976**, 41, 1095–1099.
- Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1980**, 23, 327–329.

- (a) Mohamed, N. R.; El-Saidi, M. M.; Mahmoud Ali, Y.; Elnagdi, M. H. *Sci. Pharm.* **2007**, 75, 9–28; (b) Wang, X.; Zeng, Z.; Shi, D.; Wei, X.; Zong, Z. *Synth. Commun.* **2004**, 34, 4331–4338; (c) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Noguerras, M.; Cobo, J. *Tetrahedron Lett.* **2006**, 47, 27–30; (d) Quiroga, J.; Cisneros, C.; Insuasty, B.; Abonía, R.; Cruz, S.; Noguerras, M.; de la Torre, J. M.; Sortino, M.; Zaccchino, S. J. *Heterocycl. Chem.* **2006**, 43, 299–306; (e) Quiroga, J.; Alvarado, M.; Insuasty, B.; Noguerras, M.; Sánchez, A.; López, M. D. *J. Heterocycl. Chem.* **1999**, 36, 113–115; (f) Quiroga, J.; Cisneros, C.; Insuasty, B.; Abonía, R.; Noguerras, M.; Sánchez, A. *Tetrahedron Lett.* **2001**, 42, 5625–5627.
- (a) Gálvez, J.; Quiroga, J.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr., Sect. C* **2008**, 64, 385–387; (b) Sánchez, A.; Trilleras, J.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr., Sect. C* **2007**, 63, 287–291; (c) Elmaati, T. *Acta Chim. Slov.* **2002**, 49, 721–732; (d) Jachak, M.; Taktak, C.; Toche, R.; Badgujar, N. *Monatsh. Chem.* **2004**, 135, 1529–1538; (e) Radwan, M.; El-Sherbiny, M. *Bioorg. Med. Chem.* **2007**, 15, 1206–1211; (f) Sun, C.; Ji, S.; Liu, Y. *Tetrahedron Lett.* **2007**, 48, 8987–8989; (g) Radwan, M. A. A.; Ragab, E. A.; Sabry, N. M.; El-Shenawy, S. M. *Bioorg. Med. Chem.* **2007**, 15, 3832–3841; (h) Zhu, S.; Ji, S.; Su, X.; Sun, C.; Liu, Y. *Tetrahedron Lett.* **2008**, 49, 1777–1781; (i) Ibrahim, H. M.; Makhseed, S.; Abdel-Motaleb, R. M.; Makhlof, A.-M. A.-S.; Elnagdi, M. H. *Heterocycles* **2007**, 71, 1951–1966.
- (a) Quiroga, J.; Trilleras, J.; Gálvez, J.; Insuasty, B.; Abonía, R.; Noguerras, M.; Cobo, J. *Tetrahedron Lett.* **2008**, 49, 5672–5675; (b) Trilleras, J.; Low, J.; Cobo, J.; Marchal, A.; Glidewell, C. *Acta Crystallogr., Sect. C* **2008**, 64, 149–154.
- (a) Slätt, J.; Janosik, T.; Wahlström, N.; Bergman, J. *J. Heterocycl. Chem.* **2005**, 42, 141–145; (b) Slätt, J.; Romero, I.; Bergman, J. *Synthesis* **2004**, 2760–2765; (c) Kappe, T.; Stelze, H. P.; Ziegler, E. *Monatsh. Chem.* **1983**, 114, 953–963.
- (a) Berghot, M. A.; Moawad, E. B. *Eur. J. Pharm. Sci.* **2003**, 20, 173–179; (b) Powers, D. G.; Casebier, D. S.; Fokas, D.; Ryan, W. J.; Troth, J. R.; Coffen, D. L. *Tetrahedron* **1998**, 54, 4085–4096.
- (a) Kolosov, M. A.; Orlov, V. D.; Kolos, N. N.; Shishkin, O. V.; Zubatyuk, R. I. *ARKIVOC* **2007**, xvi, 187–194; (b) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Noguerras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *J. Heterocycl. Chem.* **2001**, 38, 53–60; (c) Quiroga, J.; Cobo, D.; Insuasty, B.; Abonía, R.; Noguerras, M.; Cobo, J.; Vázquez, Y.; Gupta, M.; Derita, M.; Zaccchino, S. *Arch. Pharm.* **2007**, 400, 603–606.
- 7-Aryl-6-cyano-1,3-dimethyl-1,2,4,5-trioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidines **3–11**. A solution of 3-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-3-oxopropanenitrile **1** (1.0 mmol) and aromatic aldehydes **2** (1.0 mmol) in DMF (1.0 mL) was heated during 15 h. The resulting precipitate was filtered, washed with ethanol, and recrystallized from a mixture of EtOH–DMF (7:3). Data for 6-cyano-1,3-dimethyl-7-phenyl-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidin-2,4,5-trione **3**: Yellow solid mp 220–222 °C. Yield 60%. IR (KBr, cm^{−1}): 3250 (NH), 2218 (C≡N), 1708, 1646 (C=O), 1600 (C=N). ¹H NMR (DMSO-*d*₆, 400 MHz, rt) δ (ppm): 3.24 (s, 3H, 3-NCH₃), 3.52 (s, 3H, 1-NCH₃), 7.53 (t, 1H, H_p), 7.60 (d, 2H, H_m, *J* = 8.42 Hz), 7.91 (d, 2H, H_o, *J* = 8.42 Hz), 8.65 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆ 100 MHz, rt) δ (ppm): 27.4 (3-NCH₃), 29.5 (1-NCH₃), 94.5 (C≡N), 95.8 (C9), 117.0 (C6), 128.3 (C_m), 130.4 (C_o), 135.2 (C_i), 136.3 (C_p), 150.7 (C2), 153.3 (C10), 162.0 (C7), 162.5 (C4), 172.8 (C5). The mass spectrum shows the following peaks: MS (30 eV) *m/z* (%): 308 (M⁺). Anal. Calcd for C₁₆H₁₂N₄O₃: C, 62.34; H, 3.92; N, 18.17. Found C, 62.26; H, 3.86; N, 18.09.
- 3-Aryl-2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)-acrylamides **13–24**. A solution of 2-cyano-*N*-(2,6-dimethoxypyrimidin-4-yl)acetamide **12** (1.0 mmol) and aromatic aldehyde **2** (1.0 mmol) in ethanol with a catalytic amount of NaOH (20%, 5 drops) was stirred during 2–3 h at room temperature. The resulting precipitate was filtered, washed with ethanol, and recrystallized from a mixture of DMF–ethanol. Data for 2-cyano-*N*-(2,6-dimethoxy-pyrimidin-4-yl)-3-phenylacrylamide **13**: Yellow solid, mp 148–150 °C. Yield 60 %. IR (KBr, cm^{−1}): 3335 (NH), 2219 (C≡N), 1697 (C=O). ¹H NMR (DMSO-*d*₆, 400 MHz, rt) δ (ppm): 3.91 (s, 6H, OCH₃), 7.10 (s, 1H, H-5), 7.60 (m, 3H, H_m and H_p), 7.98 (d, 2H, H_o, *J* = 8.00 Hz), 8.39 (s, 1H, H_p), 11.08 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆, 100 Hz, rt) δ (ppm): 53.9 (OCH₃), 54.1 (OCH₃), 88.5 (C5), 107.0 (C≡N), 129.2 (C_m), 130.2 (C_o), 131.8 (C_i), 132.6 (C_p), 151.8 (C_β), 164.4 (C6), 172.4 (C2). The mass spectrum shows the following peaks: MS (30 eV) *m/z* (%): 310 (M⁺, 100), 309 (23), 281 (32), 233 (25), 205 (55), 156 (30), 128 (65), 101 (36), 77 (58). Anal. Calcd for C₁₆H₁₄N₄O₃: C, 61.93; H, 4.55; N, 18.05. Found C, 61.82; H, 4.60; N, 18.11.