Tetrahedron Letters 49 (2008) 5672–5675

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

C- and N-cyanoacetylation of 6-aminopyrimidines with cyanoacetic acid and acetic anhydride

Jairo Quiroga [a,*], Jorge Trilleras [a], Jaime Gálvez [a], Braulio Insuasty [a], Rodrigo Abonía [a], Manuel Nogueras [b,*], Justo Cobo [b], Antonio Marchal [b]

[a] Grupo de Investigación de Compuestos Heterocíclicos, Department of Chemistry, Universidad del Valle A. A. 25360 Cali, Colombia
[b] Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain

ARTICLE INFO

Article history:
Received 6 June 2008
Revised 14 July 2008
Accepted 15 July 2008
Available online 19 July 2008

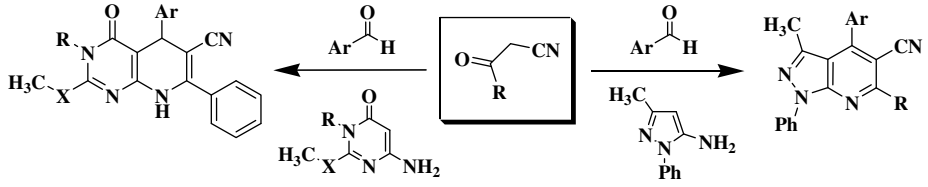
Keywords:
Cyanoacetylation
6-Aminopyrimidines
3-Pyrimidinyl-3-oxopropanenitriles

ABSTRACT

A series of 6-aminopyrimidines are cyanoacetylated with a mixture of cyanoacetic acid and acetic anhydride. When pyrimidin-4(3*H*)-ones are used as substrates, the substitution occurs at C-5, however, when the substrates are substituted pyrimidines at the C-2 and C-4, the cyanoacetylation takes place at the exocyclic amino group.

Simple nitrogenated heteroaromatic compounds have received much attention in the literature over the years. These compounds can be considered as potential building blocks in synthesis and are found in a wide variety of pharmacologically and biologically active compounds. The pyrimidine is a widespread heterocyclic moiety, which is present in numerous natural products as well as synthetic pharmacophores with biological activities.[1] Substituted pyrimidines, particularly with amino-groups at 2 and 4 positions, are known pharmacophores in several structure-based drug design approaches in medicinal chemistry.[2]

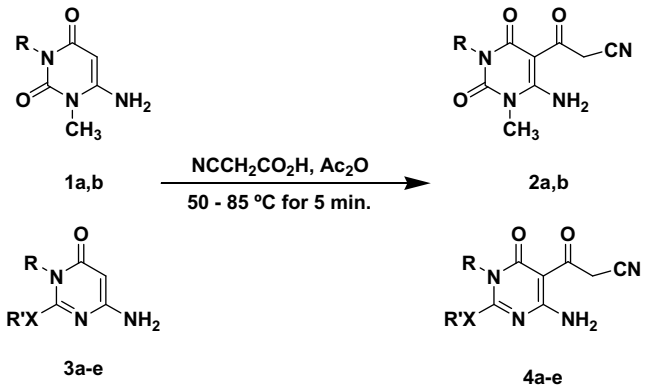
Heterocycles containing a cyanoacetyl group are relatively unexplored, most of reported preparations to get them involved nucleophilic displacement of halide in haloacetyl derivatives by cyanide,[3] or from an alkyl carboxylate using acetonitrile in the presence of a strong base, like sodium amide.[4] The cyanoacetylating reagent (acetic anhydride and cyanoacetic acid under heating) has been used in the synthesis of 6-aminouracils via urea,[5] by N-acetylation and C-acetylation of enamines.[6] Other activation procedures, such as conversion to cyanoacetyl chloride, have also been described, although this reagent is typical for its tendency to self-polymerize (particularly when heated).[7] Generation of the cyanoacetylation reagent from cyanoacetic acid and acetic anhydride has somehow been forgotten, and instead other less convenient reagents such as pyrazole derivative have been used.[8] The systems containing 3-oxopropanenitrile moiety are used as a building block in various reactions such as cyclizations[9] or



Scheme 1.

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

0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.07.084



1a-b: R = H, CH_3; 3a : R = R' = H, X = S; 3b: R = H , R' = CH_3, X = S; 3c: R = R' = CH_3, X = S; 3d: R = H , R' = CH_3, X = O; 3e: R = R' = H, X = NH

Scheme 2.

synthesis of the other heterocyclic systems which have exciting biological properties.[5a,7,10]

Recently, we have reported synthesis of pyrazolopyridines derivatives[11] in the reaction of aminopyrazoles with 3-oxopropanenitrile derivatives or with its precursors, and aldehydes. Also we have reported synthesis of dihydropyrido[2,3-*d*]pyrimidines starting from readily available aminopyrimidin-4-ones, benzoylacetonitrile and benzaldehydes (Scheme 1).[12]

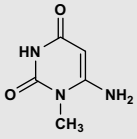
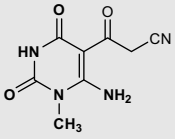
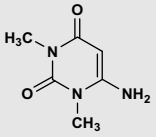
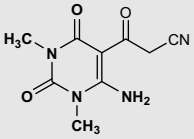
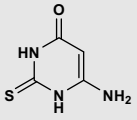
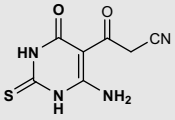
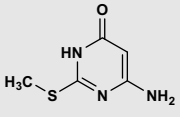
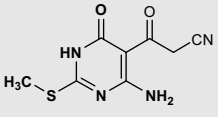
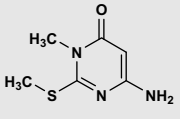
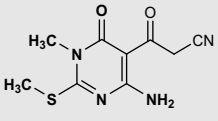
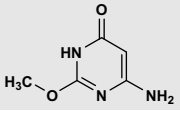
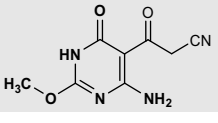
To demonstrate the generality of cyanoacetic acid-acetic anhydride reagent in order to get cyanoacetylation, we have investigated its scope on diverse 6-aminopyrimidines to develop a route to functionalize the C-5 position at pyrimidines. So, to render the cyanoacetylation the pyrimidines, were poured onto a solution of the cyano-acetylating reagent and heated to 85 °C for 5 min, 3-oxopropanenitrile pyrimidine derivatives were isolated as solid products by simple filtration.[13]

Two main different behaviours were observed depending on the pyrimidine frame, so when pyrimidin-4(3*H*)-ones are used as substrates, substitution does indeed occur at C-5 to provide 5-cyanoacetylpyrimidine derivatives (Scheme 2, Table 1, entries 2–4). Interestingly, various substrates such as pyrimidines substituted at the N-1, C-2 and N-3 position reacted efficiently with cyanoacetylating reagent in good yields.

However, when the substrates used were formal aromatic pyrimidines, no ring substitution occurs. Instead, acetylation occurred at the exocyclic amino group giving N-acetylated pyrimidines (Scheme 3, Table 1, entries **5a–d**).

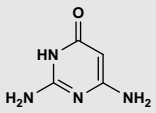
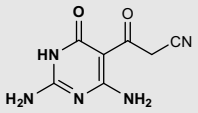
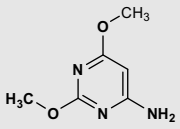
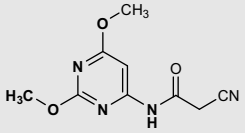
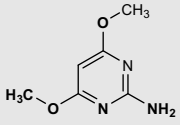
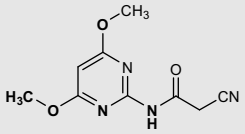
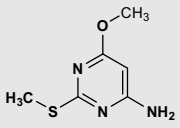
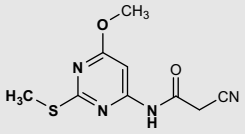
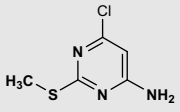
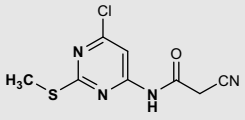
In C-cyanoacetylated compounds, the exocyclic carbonyl group is nearly coplanar with the ring, with a deviation of carbonyl atom O from the mean plane of the ring; this is probably associated both with the polarization of the molecular–electronic structure and with an intramolecular N–H···O hydrogen bond, which is

Table 1
Cyanoacetylated 6-aminopyrimidines with cyanoacetic acid and acetic anhydride to yield 3-pyrimidinyl-3-oxopropanenitrile derivatives

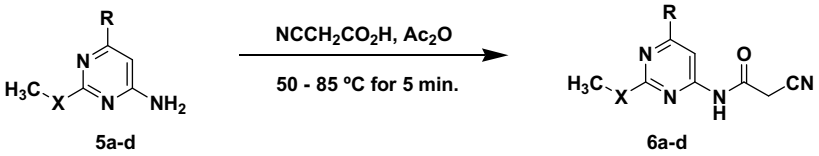
Entry	Pyrimidine	Product	Mp (°C)	%	Recrystallization solvent
2a			213–215	95	DMF/ethanol (5/3)
2b			260–262 (260)[a] (250–251)[b]	87 (99)[a] (95)[b]	DMF
4a			>300	68	DMF/ethanol (5/3)
4b			283–285	70	DMF/ethanol (5/3)
4c			246–248	60	DMF
4d			272–274	60	DMF

(*continued on next page*)

Table 1 (*continued*)

Entry	Pyrimidine	Product	Mp (°C)	%	Recrystallization solvent
4e			>300	75	Ethanol
5a			209–211	80	Ethanol
5b			200–202	74	Ethanol
5c			156–158	60	Ethanol
5d			256–258	70	Ethanol

[a,b] Mp and yield reported in the literature.[7,15]



5a-d **6a-d**

5a,c : R = OCH_3, X = O, S; 5b: R = OCH_3 on position 4 and 6, X = NH_2; 5d: R = Cl, X = S

Scheme 3.

charge-assisted as a consequence of the polarization.[13] This behaviour is observed in ^1H NMR spectra, two signals to exocyclic NH_2 were observed as a result of the difference between these two protons.[14]

The structure of all new compounds was determined on the basis of their analytical, 1D and 2D-NMR spectra and HR-MS, which agree with the proposed structures. Single crystal X-ray diffraction analysis of compounds **2b**, **4c**, **5c** and **5d** was used to corroborate the postulated structures. The crystal structure of compound **2b** shows the formation of a hydrogen-bond.[13]

In summary, cyanoacetylation by combination of cyanoacetic acid and acetic anhydride is presented as a convenient method for preparation of cyanoacetylated pyrimidines. We have demonstrated a simple and efficient approach to obtained 3-(pyrimidin-5-yl)-3-oxopropane-nitrile derivative and *N*-(pyrimidin-4yl)-2-cyano-acetamide in a regioselective fashion depending on the nature of the pyrimidine precursor. The activated methylene group in the obtained compounds (see Table 1) can take part in numerous reactions providing access to more complex molecules. Thus, new derivatives may be used as intermediates to construct novel heterocyclic compounds that incorporate pyrimidines moieties into a molecule, and may potentially have enhanced biological activities. This work is currently in progress and the results will be reported in due course.

Acknowledgements

The authors thank 'Servicios Técnicos de Investigación of Universidad de Jaén' and the staff for data collection, and the Consejería de Innovación, Ciencia y Empresa (Junta de Andalucía, Spain), the Universidad de Jaén, Universidad del Valle and COLCIENCIAS for financial support. J.T. thanks COLCIENCIAS for supporting a research visit to the Universidad de Jaén.

References and notes

1. (a) Choudhury, A.; Chen, H.; Nilsen, C. N.; Sorgi, K. L. *Tetrahedron Lett.* **2008**, *49*, 102–105; (b) Brndvang, M.; Gundersen, L. L. *Tetrahedron Lett.* **2007**, *48*, 3057–3059; (c) Peng, Z.-H.; Journet, Michel; Humphrey, G. *Org. Lett.* **2006**, *8*, 395–398; (d) Girreser, U.; Heber, D.; Schutt, M. *Tetrahedron* **2004**, *60*, 11511–11517.
2. (a) Baudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, 3737–3740; (b) Baraldi, P. G.; Bovero, A.; Fruttarolo, F.; Romagnolo, R.; Tabrizi, M. A.; Preti, D.; Varani, K.; Borea, P. A.; Moorman, A. R. *Bioorg. Med. Chem.* **2003**, *11*, 4161–4169.
3. Hayashi, H.; Ohmoto, S.; Somei, M. *Heterocycles* **1997**, *45*, 1647–1650.
4. Eby, C. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1957**, *79*, 723–725.

5. (a) Abdel-Motaleb, R. M.; Abdel-Salam Makhloof, Abdel -Monein.; Ibrahim, H. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 109–114; (b) Isobe, Y.; Tobe, M.; Inoue, Y.; Isobe, Y.; Tsichiya, M.; Hayashi, H. *Bioorg. Med. Chem.* **2003**, *11*, 4933–4940; (c) Papesch, V.; Schroeder, E. *J. Org. Chem.* **1951**, 1879–1890; (d) Muller, T.; Augustin, M.; Werchan, H. G. *Z. Chem.* **1989**, *29*, 281–283.
6. Kappe, T.; Stelze, H. P.; Ziegler, E. *Monatsh. Chem.* **1983**, *114*, 953.
7. Slätt, J.; Romero, I.; Bergman, J. *Synthesis* **2004**, *16*, 2760–2765.
8. Slätt, J.; Janosik, T.; Wahlström, N.; Bermang, J. *J. Heterocycl. Chem.* **2005**, *42*, 141–145.
9. (a) Lim, H. N.; Song, Y. S.; Lee, K. J. *Synthesis* **2007**, *21*, 3376–3384; (b) Ryabukhin, S. V.; Volochnyuk, D. M.; Plaskon, A. S.; Naumchik, V. S.; Tolmachev, A. A. *Synthesis* **2007**, *8*, 1214–1224; (c) Vildan Burgaz, E.; Yılmaz, M.; Tarık Pekela, A.; ktemera, A. O. *Tetrahedron* **2007**, *63*, 7229–7239.
10. (a) Zhu, S.-L.; Ji, S.-J.; Su, X.-M.; Sun, C.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 1777–1781; (b) Radwan, M. A. A.; Ragab, E. A.; Sabrya, N. M.; El-Shenawy, S. M. *Bioorg. Med. Chem.* **2007**, *15*, 3832–3841; (c) Sun, C.; Ji, S.-J. ; Liu, Y. *Tetrahedron Lett.* **2007**, *48*, 8987–8989; (d) Zhuang, B.-R. ; Hsu, G.-J. ; Sung, K. *Bioorg. Med. Chem.* **2006**, *14*, 3399–3404; (e) Berghot, M. A.; Moawad, E. B. *Eur. J. Pharm. Sci.* **2003**, *20*, 173–179.
11. (a) Quiroga, J.; Trilleras, J.; Sánchez, A. I.; Insuasty, B.; Abonía, R.; Nogueras, M.; Cobo, J. *Lett. Org. Chem.*, submitted for publication.; (b) Low, J. N.; Cobo, J.; Sánchez, A.; Trilleras, J.; Glidewell, C. *Acta Crystallogr., Sect. C* **2007**, *63*, 287–291; (c) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *J. Heterocycl. Chem.* **2001**, *38*, 53–60; (d) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R. *Heterocycl. Commun.* **2000**, *6*, 275–282.
12. Quiroga, J.; Cisneros, C.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A. *Tetrahedron Lett.* **2001**, *42*, 5625–5627.
13. Trilleras, J.; Low, J. N.; Cobo, J.; Marchal, A.; Glidewell, C. *Acta Crystallogr., Sect. C* **2008**, *64*, 149–154.
14. *General procedure for the reaction of pyrimidines with the cyanoacetylating reagent*: The pyrimidines were added to a solution of cyanoacetic acid (50 mmol) in acetic anhydride (50 ml) at 50 °C. The mixture was heated to 85 °C for 5 min, whereupon the products started to crystallize. After a further 5 min, the mixture was allowed to cool to ambient temperature, and the resulting solid products were collected by filtration, washed with methanol, dried in air and recrystallized. *Data for 3-(6-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)-3-oxopropanenitrile (entry* **2b**): Yellow solid, yield 87%, mp 260–262 °C. ^{1}H NMR (400 MHz DMSO-d_6) δ: 3.13 (*s*, 3H, N_1–CH_3); 3.30 (*s*, 3H, N_3–CH_3) 4.36 (*s*, 2H, CH_2); 7.67 (*s*, 1H, CH-5); 8.51 (s, 1H, NH_2); 10.66 (s, 1H, NH_2). ^{13}C NMR (100 MHz DMSO-d_6) δ: 27.6 (N_3–CH_3); 29.7 (N_1–CH_3); 33.2 (CH_2); 89.3 (C-5); 116.5 (CN); 149.3 (C-2); 158.1 (C-6); 161.2 (C-4); 186.5 (C=O). IR (KBr) cm^{-1} 3451–3162 (NH *st*); 2247 (CN *st*) 1715, 1654, 1603 (C=O *st*). HR-MS calcd for $C_9H_{10}N_4O_3$ 222.0742, found 222.0753. Anal. Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.21. Found: C, 48.92; H, 4.98; N, 25.61. *Data for N-(6-chloro-2-(methylthio)pyrimidin-4-yl)-2-cyanoacetamide (entry* **5d**): Yellow solid, yield 70%, mp 256–258 °C. ^{1}H NMR (400 MHz DMSO-d_6) δ: 2.48 (s, 3H, S–CH_3) overlap with DMSO-d_6 signal; 4.02 (s, 2H, CH_2); 7.67 (s, 1H, H-5); 11.44 (s, 1H, NH). ^{13}C NMR (100 MHz DMSO-d_6) δ: 13.5 (CH_3); 27.3 (CH_2); 104.0 (C-5); 115.0 (CN); 158.2 (C-6); 160.5 (C-4); 164.0 (C=O); 172.0 (C-2). IR (KBr) cm^{-1}3313 (NH *st*); 2262 (CN *st*); 1720 (C=O *st*); 1321–1261 (SCH_3 δ). HR-MS calcd for $C_8H_7ClN_4OS$ 242.0024, found 242.0029. Anal. Calcd for $C_8H_7ClN_4OS$: C, 39.59; H, 2.91; N, 23.09. Found: C, 39.76; H, 3.33; N, 22.99.
15. Smirnova, N. M.; Cherdantseva, N. M.; Burova, O. A.; Nesterov, V. M.; Safonova, T. S. *Chem. Heterocycl. Compd.* **1990**, 811–815.