Tetrahedron Letters 49 (2008) 5943–5945

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of novel 5-amino-1-aroylpyrazoles

Jairo Quiroga [a,*], Jaime Portilla [b], Rodrigo Abonía [a], Braulio Insuasty [a], Manuel Nogueras [c], Justo Cobo [c]

[a] Heterocyclic Compounds Research Group, Department of Chemistry, Universidad del Valle, A. A. 25360, Cali, Colombia
[b] Bioorganic Compounds Research Group, Department of Chemistry, Universidad de los Andes, Carrera 1 N° 18A 10, Bogotá, Colombia
[c] Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain

ARTICLE INFO

Article history:
Received 8 July 2008
Revised 21 July 2008
Accepted 29 July 2008
Available online 3 August 2008

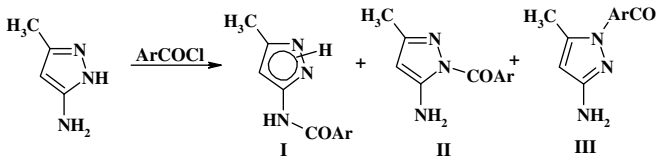
Keywords:
1-Aroyl-5-aminopyrazoles
7-Aminopyrazolo[1,5-*a*]pyrimidine
β-Aminocrotononitrile
Hydrazines

ABSTRACT

A series of 5-amino-1-aroylpyrazoles **3** are synthesized directly by the reaction of β-aminocrotononitrile **1** with some structures containing the hydrazine moiety (X-NHNH$_2$) **2** by refluxing ethanol in presence of sodium acetate. When semicarbazide **3i** was used (X = CONH$_2$), the reaction afforded the unexpected 7-aminopyrazolo[1,5-*a*]pyrimidine **4**.

Examples of natural products containing pyrazole nucleus are very scarce, but many synthetic pyrazoles are biologically active,[1] and some have shown pharmacological utility as antianxiety,[2] antipyretic, analgesic, and anti-inflammatory agents,[3] as well as for their antimicrobial properties, especially antibacterial[4] and antifungal activities.[5] Substituted pyrazoles are important synthetic targets in the pharmaceutical industry as the pyrazole structure forms part of numerous biologically active compounds,[6] including blockbuster drugs such as Celebrex®[7] and Viagra®.[8] The 5-aminopyrazoles having two or more adequate functional groups are potential intermediates of useful polyheterocycles.[9] Additionally, some pyrazole structures containing the aroyl group present an important elastase inhibitory activity.[10]

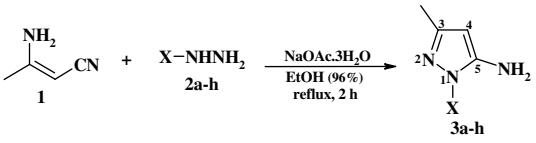
It is known that the acylation of N-unsubstituted aminopyrazoles gives a mixture of structures **I** (exocyclic amino group) or **II**, **III** (endocyclic amino group) (Scheme 1).[11] In the course of this work, some difficulties have been found in the structural determination, particularly for the N-unsubstituted compounds for which tautomerism may occur. The tautomerism of N-unsubstituted aminopyrazoles has been the subject of several studies.[12]



Scheme 1.

As part of our study using acrylonitriles as the starting material for the preparation of aminoderivatives of pyrazole,[12d,13] we have now designed a simple method for the synthesis of novel 5-amino-1-aroylpyrazoles by the reaction of β-aminocrotononitrile **1** with compounds containing the hydrazine moiety (X-NHNH$_2$) **2**. The reaction of **1** with **2a–h** in equimolecular amounts was carried out in refluxing ethanol in the presence of sodium acetate to afford the 1-aroyl-5-aminopyrazoles **3a–h** in good yields (Scheme 2).[14,15]

It is important to point out that when semicarbazide **2i** was used (X = H$_2$NCO) the reaction afforded the 7-aminopyrazolo[1,5-*a*]pyrimidine **4** (yield 38%). Compound **4** is probably formed through the intermediate pyrazole **3i**, which would suffer

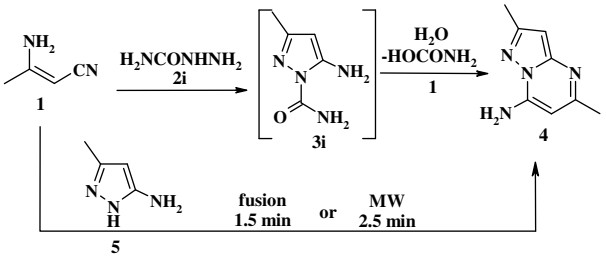


3	X	Yield (%)
a	$C_6H_5C(O)$	94
b	$(2\text{-}O_2NC_6H_4)C(O)$	97
c	$(4\text{-}O_2NC_6H_4)C(O)$	96
d	$(2\text{-}FC_6H_4)C(O)$	97
e	$(2\text{-}ClC_6H_4)C(O)$	98
f	$(4\text{-}ClC_6H_4)C(O)$	85
g	$(4\text{-}CH_3OC_6H_4)C(O)$	90
h	$H_2NC(S)$	80

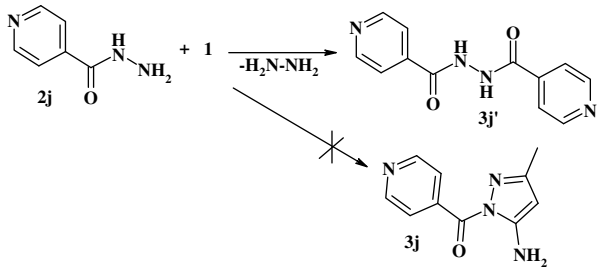
Scheme 2.

* Corresponding author. Fax: +57 2 33392440.
E-mail address: jaiquir@univalle.edu.co (J. Quiroga).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.07.166



Scheme 3.



Scheme 4.

hydrolysis and later cyclocondensation with a second molecule of **1** (Scheme 3).

In order to corroborate the formation of unexpected compounds **4** according to the above suggestion and based on our studies on the application of solvent-free cyclocondensation procedures in the synthesis of fused pyrazoles,[16] we carried out the reaction between **1** and 5-amino-1H-pyrazoles **5** in equimolecular amounts by fusion method heating in an oil-bath at 150 °C for 1.5 min or irradiated in a microwave oven for 2.5 min (at 600 W), that successfully afforded the desired 7-aminopyrazolo[1,5-*a*]pyrimidine **4** (Scheme 3).[17]

It is also important to mention that when isoniazid **2j** was used in this reaction, under the same conditions described above, a new product was formed, whose molecular weight did not correspond to the expected pyrazole **3j**. The spectroscopic results enabled us to propose a structure that is consistent with mass spectral findings, and corresponding to *N,N′*-bis(isonicotinoyl)hydrazine **3j′**, the product formed by reaction of two molecules of isoniazid **2j** with elimination of a hydrazine molecule (Scheme 4).[18,19]

The structures of all new compounds were appropriately established by the usual spectroscopic methods. Single crystal X-ray diffraction analysis of some selected compounds was used to corroborate the postulated structures.[15,17,19]

In summary, we have established a short, practical, and simple method for the synthesis of novel 1-aroyl-5-aminopyrazoles **3a-h** from β-aminocrotononitrile **1**, resulting in promising substrates for drug design. The chemical and biological interest of the aminoaroylpyrazoles mainly obtained in these experiments are under investigation.

Acknowledgments

Authors are grateful to COLCIENCIAS, to Universidad del Valle, to Universidad de los Andes, to the Spanish 'Consejería de Innovación, Ciencia y Empresa, Junta de Andalucía', and 'Servicios Técnicos de la Universidad de Jaén' for financial support, and Fabio Zuluaga for reviewing this manuscript.

References and notes

1. (a) Katritzky, A.; Rees, C.; Scriven, E. In *Comprehensive Heterocyclic Chemistry II*; Pergamon Press: Oxford, 1996; Vol. 3; pp 1–75; (b) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 3505–3508; (c) Singh, P.; Paul, K.; Holzer, W. *Bioorg. Med. Chem.* **2006**, *14*, 5061–5071; (d) Foote, K. M.; Mortlock, A. A.; Heron, N. M.; Jung, F. H.; Hill, G. B.; Pasquet, G.; Brady, M. C.; Green, S.; Heaton, S. P.; Kearney, S.; Keen, N. J.; Odedra, R.; Wedgea, S. R.; Wilkinson, R. W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1904–1909; (e) Moura, S.; Flores, A. F. C.; Paula, F. R.; Pinto, E.; Machado, P.; Martins, M. A. P. *Lett. Org. Chem.* **2008**, *5*, 91–97.
2. (a) Haufel, J.; Breitmaier, E. *Angew. Chem.* **1974**, *13*, 604; (b) Wustrow, D.; Capris, T.; Rubin, R.; Knobelsdorf, J.; Akunne, H.; Davis, M.; MacKenzie, R.; Pugsley, T.; Zoski, K.; Heffner, T.; Wise, L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2067–2070.
3. (a) Eid, A.; Kira, M.; Fabmy, H. *J. Pharm. Belg.* **1978**, *33*, 303–305; (b) Penning, T.; Talley, J.; Bertenshaw, S.; Carter, J.; Collins, P.; Doctor, S.; Graneto, M.; Lee, L.; Malecha, J.; Miyashiro, J.; Rogers, S.; Rogier, D.; Yu, S.; Anderson, G.; Burton, E.; Cogburn, J.; Gregory, S.; Koboldt, C.; Perkins, W.; Seibert, K.; Veenhuizen, W.; Zhang, Y.; Isakson, P. *J. Med. Chem.* **1997**, *40*, 1347–1365.
4. (a) Habib, N.; Tawil, G. *Sci. Pharm.* **1981**, *49*, 42–43; (b) Daidone, G.; Maggio, B.; Plescia, S.; Raffa, D.; Musiu, C.; Milia, C.; Perra, G.; Marongiu, M. *Eur. J. Med. Chem.* **1998**, *33*, 375–378; (c) El-Emary, T.; Bakbite, E. *Pharmazie* **1999**, *54*, 106–110.
5. (a) Devi, S.; Mitro, P.; Mishra, S.; Mitra, A. *J. Indian Chem. Soc.* **1983**, *60*, 679–681; (b) Vicentini, C.; Forlani, G.; Manfrini, M.; Romagnoli, C.; Mares, D. *J. Agric. Food Chem.* **2002**, *50*, 4839–4843; (c) Mares, D.; Romagnoli, C.; Tosi, B.; Benvegnu, R.; Bruni, A.; Vicentini, C. *Fangal Genet. Biol.* **2002**, *36*, 47–51.
6. Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. *Targets Heterocycl. Syst.* **2002**, *6*, 52–98.
7. Penning, T.; Talley, J.; Bertenshaw, S.; Carter, J.; Collins, P.; Docter, S.; Graneto, M.; Lee, L.; Malecha, J.; Miyashiro, J.; Rogers, R.; Rogier, D.; Yu, S.; Anderson, G.; Burton, E.; Cogburn, J.; Gregory, S.; Koboldt, C.; Perkins, W.; Seibert, K.; Veenhuizen, A.; Zhang, Y.; Isakson, P. *J. Med. Chem.* **1997**, *40*, 1347–1365.
8. Terrett, N.; Bell, A.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824.
9. (a) Bauer, L.; Mahajanshetti, S. *J. Heterocycl. Chem.* **1967**, *4*, 325–327; (b) Tominaga, Y.; Yoshioka, N.; Kataoka, S.; Aoyama, N.; Masunari, T.; Miike, A. *Tetrahedron Lett.* **1995**, *36*, 8641–8644.
10. (a) Schepetkin, I. A.; Khlebnikov, A. I.; Quinn, M. T. *J. Med. Chem.* **2007**, *50*, 4928–4938; (b) Khlebnikov, A. I.; Igor, A.; Schepetkin, I. A.; Quinn, M. T. *Bioorg. Med. Chem.* **2008**, *16*, 2791–2802.
11. (a) Michon, V.; Hervk du Penhoat, C.; Tombret, F.; Gillardin, J. M.; Lepage, F.; Berthon, L. *Eur. J. Med. Chem.* **1995**, *3*, 147–155; (b) Ege, G.; Franz, H. *J. Heterocycl. Chem.* **1984**, *21*, 689–695.
12. (a) Gonzalez, E.; Faure, R.; Vincent, E. J.; Espada, M.; Elguero, J. *J. Org. Magn. Res.* **1979**, *12*, 587–592; (b) Dorn, H. *J. Prakt. Chem.* **1973**, *315*, 382–418; (c) Catalan, J.; Menendez, M.; Laynez, J.; Claramunt, R. M.; Bruix, M.; de Mendoza, J.; Elguero, J. *J. Heterocycl. Chem.* **1985**, *22*, 997–1000; (d) Quiroga, J.; Insuasty, B.; Foces-Foces, C.; Infantes, L.; Claramunt, R. M.; Cabildo, P.; Jiménez, J. A.; Elguero, J. *Tetrahedron* **1997**, *53*, 10783–10802; (e) Portilla, J.; Mata, E.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr., Sect. C* **2007**, *63*, 510–513.
13. (a) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *J. Heterocycl. Chem.* **2001**, *38*, 53–60; (b) Quiroga, J.; Mejía, D.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *Tetrahedron* **2001**, *57*, 6947–6953; (c) Portilla, J.; Mata, E.; Nogueras, M.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr., C* **2007**, *63*, 21–25; (d) Portilla, J.; Quiroga, J.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr., C* **2007**, *63*, 26–28.
14. *Preparation of 5-amino-1-aroylpyrazoles* **3a-g** *and 5-amino-1-thiocarbamoylpyrazole* **3h**: A mixture of β-aminocrotononitrile **1** (2 mmol), arylhydrazides **2a–g** or thiosemicarbazide 2 h (2 mmol), and sodium acetate trihydrate (2 mmol) was refluxed in ethanol (50 mL) for 2 h. After the solution was cooled, the reaction mixture was poured into water (50 mL) with vigorous stirring for 20 min. The deposited products were collected by filtration and recrystallized from ethanol. Data for 5-amino-1-(4-methoxybenzoyl)-3-methyl-pyrazole **3g**: White crystals. Mp 81–82 °C, yield 90%. IR (KBr): 1618 cm^{-1} (C=N), 1672 (C=O), 3426, 3293 cm^{-1} (NH_2); RMN ^1H (DMSO-d_6, 400 MHz) δ 2.06 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.29 (s, 1H, H4), 6.61 (s, 2H, NH_2), 7.04 (d, 2H, Ho, J = 8.00 Hz), 8.07 (d, 2H, Hm, J = 8.00 Hz); RMN ^{13}C (DMSO-d_6, 100 MHz) δ 13.9 (CH_3), 55.4 (OCH_3), 87.9 (C4), 113.1 (Co), 125.2 (Ci), 133.3 (Cm), 152.6 (C5), 152.8 (C3), 162.4 (Cp), 168.2 (C=O); MS: (30 eV) m/z (%) = 231 (16, M^+), 135 (100), 107 (13), 77 (20). HRMS: calcd for $C_{12}H_{13}N_3O_2$: m/z = 231.1008; found: 231.1008.
15. Quiroga, J.; Portilla, J.; Low, J. N.; Cobo, J.; Glidewell, C. *Acta Crystallogr.* **2008**, *64*, 76–79.
16. (a) Quiroga, J.; Cisneros, C.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A. *Tetrahedron Lett.* **2001**, *42*, 5625–5627; (b) Quiroga, J.; Rengifo, A.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A. *Tetrahedron Lett.* **2002**, *43*, 9061–9063; (c) Quiroga, J.; Portilla, J.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sortino, M.; Zacchino, S. *J. Heterocycl. Chem.* **2005**, *42*, 61–66; (d) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2006**, *47*, 27–30; (e) Quiroga, J.; Portilla, J.; Serrano, H.; Abonía, R.; Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2007**, *48*, 1987–1990; (f) Quiroga, J.; Portilla, J.; Abonía, R.; Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2007**, *48*, 6352–6355; (g) Portilla, J.; Quiroga, J.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr., Sect. B* **2008**, *64*, 72–83.
17. Portilla, J.; Quiroga, J.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr.* **2006**, *62*, 186–189.
18. *Preparation of N,N′-bis(isonicotinoyl)hydrazine* **3j′**: A mixture of isoniazid **2j** (2 mmol) and sodium acetate trihydrate (2 mmol) was refluxed in ethanol

(50 mL) for 2 h. Data for *N*,*N*′-bis(isonicotinoyl)hydrazine **3j**′: This compound was obtained as white crystals according to above described procedure. Mp; 267–8 °C, yield 90%. IR (KBr) 1605 cm^{-1} (C=N), 1685 (C=O), 3352 cm^{-1} (NH); RMN ^{1}H (DMSO-d_6, 400 MHz) δ (ppm): 7.82 (d, 4H, H3, J = 8.12 Hz), 8.79 (d. 2H, H2, J = 8.12 Hz), 10.95 (s, 2H, NH); RMN ^{13}C (DMSO-d_6, 100 MHz) δ (ppm): 121.3 C3, 139.3 C4, 150.5 C2, 164.3 C=O; MS: (70 eV) m/z (%) = 242 (4, M^+), 106 (100), 78 (32), 51 (10). HRMS: calcd for $C_{12}H_{10}N_4O_2$: m/z = 242.2334; found: 242.2335.

19. Portilla, J.; de la Torre, J.; Cobo, J.; Low, J.; Glidewell, C. *Acta Crystallogr., Sect. E* **2007**, *63*, 1687–1690.