Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2689–2691
Tetrahedron Letters

Regioselective formylation of pyrazolo[3,4-*b*]pyridine and pyrazolo[1,5-*a*]pyrimidine systems using Vilsmeier–Haack conditions

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

[a] *Heterocyclic Compounds Research Group, Department of Chemistry, Universidad del Valle, A. A. 25360 Cali, Colombia*
[b] *Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain*

Received 18 January 2008; revised 19 February 2008; accepted 29 February 2008
Available online 4 March 2008

Abstract

Regioselective formylation behavior has been found in the reaction of pyrazolo[3,4-*b*]pyridines and pyrazolo[1,5-*a*]pyrimidines via Vilsmeier–Haack conditions. While the 4,5- and 6,7-dihydro derivatives afforded pyrazolo[3,4-*b*]pyridine-5-carbaldehydes and 4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3,6-dicarbaldehydes, respectively, the aromatic analogs rendered the pyrazolo[1,5-*a*]pyrimidine-3-carbaldehyde only, and no reaction took place at the pyrazolopyridine derivatives.

Keywords: 5-Aminopyrazole; Formylation; Dihydropyrazolo[3,4-*b*]pyridines; Dihydropyrazolo[1,5-*a*]pyrimidines; Vilsmeier–Haack reaction

Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs. Pyrazole compounds can provide privileged scaffolds for the generation of target compounds for drug discovery.[1] Hence, the synthesis and study of pyrazolo-fused compounds have been of interest due to their wide variety of biological and pharmacological properties.[1a,d–f]

The structural diversity and biological importance of pyridines and pyrimidines have made them attractive targets for synthesis over many years.[2] The 4,5-dihydropyrazolo[3,4-*b*]pyridine and 6,7-dihydropyrazolo[1,5-*a*]-pyrimidine systems are a convenient models for investigating the reactivity, chemical stability, and tautomerism of partially hydrogenated azoloazines. As a result, these compounds have become interesting targets for further modifications aimed at preparing new fused or substituted derivatives. There is a growing interest in formylation as an interesting strategy to form intermediate carboxaldehydes, due to their intrinsic pharmacological properties and chemical reactivity.[3] Formylation reactions have been described for pyrido[2,3-*d*]pyrimidines as a key step to the introduction of functionalities via the intermediate carboxaldehydes.[2]

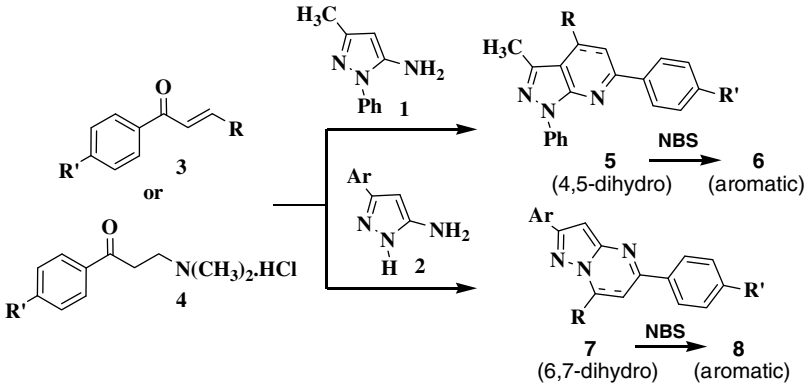
We have already reported some procedures for the synthesis of aromatic and dihydro pyrazolo[3,4-*b*]pyridines and pyrazolo[1,5-*a*]pyrimidines by the reaction of 5-aminopyrazoles **1** and **2** with α,β-unsaturated ketones **3** (chalcones) or their precursors, such as β-dimethyl-aminopropiophenones **4** (Mannich bases)[4,5] (Scheme 1). We report here a specific formylation on the pyridine and pyrimidine rings, which render pyrazolopyridine- and pyrazolopyrimidine-carbaldehydes, respectively, only when starting from their dihydro-derivatives **5** and **7**.

Both 4,5-dihydro- and aromatic pyrazolo[3,4-*b*]-pyridines were synthesized according to the reported procedure. The dihydro-derivatives were prepared and then readily oxidized to their aromatic form with *N*-bromosuccinimide in ethanol.[4a]

To functionalize the pyridine residue by inserting a one-carbon fragment, the formylation via Vilsmeier–Haack

* 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.2008.02.166



Scheme 1.

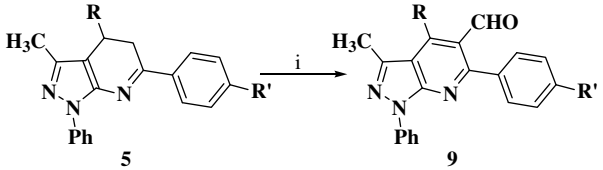
conditions was attempted, affording the expected formylation along with the aromatization of the pyridinic ring to yield **9** (Scheme 2 and Table 1).[6]

In the case of the aromatic pyrazolopyridines **6**, the formation of any formylated product was not observed and the starting material was always recovered unchanged.

Both 6,7-dihydro- and aromatic pyrazolo[1,5-*a*]pyrimidines (**7** and **8**, respectively), synthesized according to a previously reported procedure,[5a] were subjected to the same formylation conditions described above for pyrazolopyridines **5** and **7**. Thus, when we started from the 6,7-dihydro-derivatives **7**, a double formylation at positions 3 and 6 at the pyrazolopyrimidine system occurred to yield pyrazolo[1,5-*a*]pyrimidine-3,6-dicarbaldehyde **10** (Scheme 3 and Table 2).[7]

On the other hand, the formylation of pyrazolopyrimidines **8** (obtained by the oxidation of dihydroderivative **7**[5a]) under Vilsmeier conditions (DMF–$POCl_3$) took place only at position 3 of the pyrazole ring, leading to the formation of the pyrazolopyrimidine-3-carbaldehyde **11** (Scheme 3 and Table 2).[8] Reaction of electrophilic substitution on this position of the pyrazole ring is widely referenced in the literature.[9]

The structure of all new compounds was determined on the basis of their analytical and spectral data, 1D and 2D-NMR mainly, MS and elemental analysis, which are in agreement with their proposed structures. Single crystal X-ray diffraction analysis of compound **10** ($R = C_6H_5$, $R' = CH_3$, $Ar = p\text{-}CH_3\text{-}C_6H_4$) was used to corroborate the postulated structures.[10] Based on X-ray findings, the short intramolecular hydrogen bond interaction between the oxygen of formyl group at C-3 and N(4)–H provides

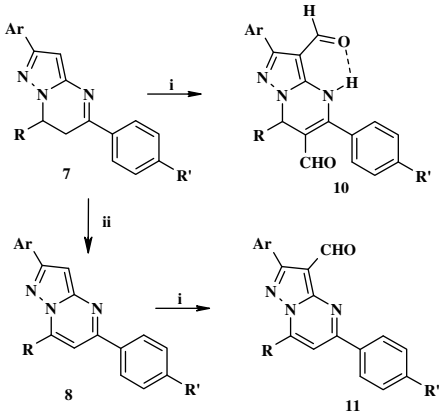


i) $POCl_3$/DMF; R = H, C_6H_5,

Scheme 2.

Table 1
Formylation of pyrazolo[3,4-*b*]pyridines systems

	Compound **9**							
R	H	H	H	H	H	C_6H_5	C_6H_5	C_6H_5
R′	H	OCH_3	Cl	Br	NO_2	H	Br	NO_2
Yield (%)	65	67	65	75	78	66	65	68



i) $POCl_3$/DMF; ii) NBS/Ethanol;

Scheme 3.

Table 2
Formylation of dihydropyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]-pyrimidines systems

R	R′	Ar	Yield (%)	
			Comp. **10**	Comp. **11**
H	NO_2	4-ClC_6H_4	65	54
H	OCH_3	4-ClC_6H_4	60	60
H	Cl	4-ClC_6H_4	70	63
H	Cl	4-$H_3CC_6H_4$	81	50
C_6H_5	CH_3	4-$H_3CC_6H_4$	65	60
C_6H_5	CH_3	4-$O_2NC_6H_4$	65	60
4-ClC_6H_4	OCH_3	4-ClC_6H_4	70	70

a higher stability to compound **10** with respect to the dihydro analog of **9**, and so precludes the further oxidation step to the aromatic derivative.

In conclusion, the formylation on the pyridine or pyrimidine rings only takes place when there is a dihydroderivative on the appropriate pyrazolo-fused systems. The use of the Vilsmeier–Haack conditions has permitted us to develop a fast and efficient method for the formation of pyrazolo[3,4-*b*]pyridine-5-carbaldehydes, dihydropyrazolo[1,5-*a*]pyrimidine-3,6-dicarbaldehydes, and pyrazolo[1,5-*a*]pyrimidine-3-carbaldehydes. These novel formylderivatives provide access to a great number of structures for the introduction of functionalities via the intermediate carbaldehydes.

Acknowledgments

The authors are grateful to COLCIENCIAS, to Universidad del Valle, to the Spanish 'Consejería de Innovación, Ciencia y Empresa, Junta de Andalucía', and 'Servicios Técnicos de Investigación' of 'Universidad de Jaén' for financial support.

References and notes

1. (a) Elguero, J.; Goya, P.; Najerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst.* **2002**, *6*, 52–98; (b) Dressen, D.; Garofalo, A. W.; Hawkinson, J.; Hom, D.; Jagodzinski, J.; Marugg, J. L.; Neitzel, M. L.; Pleiss, M. A.; Szoke, B.; Tung, J. S.; Wone, D. W. G.; Wu, J.; Zhang, H. *J. Med. Chem.* **2007**, *50*, 5161–5167; (c) Wustrow, D. J.; Capiris, T.; Rubin, R.; Knobelsdorf, J. A.; Akunne, H.; Davis, M. D.; MacKenzie, R.; Pugsley, T. A.; Zoski, K. T.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2067–2070; (d) Hardy, C. R. *Adv. Heterocycl. Chem.* **1984**, *36*, 343–409; (e) Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. E. H. *Adv. Heterocycl. Chem.* **1987**, *41*, 319–376; (f) Elnagdi, M. H.; Elmoghayar, M. R. H.; Sadek, K. U. *Adv. Heterocycl. Chem.* **1990**, *48*, 223–280.
2. Girreser, U.; Heber, D.; Schütt, M. *Tetrahedron* **2004**, *60*, 11511–11517.
3. (a) Vovk, M. V.; Mel'nichenko, N. V.; Sukach, V. A.; Chubaruk, N. G. *Chem. Heterocycl. Compd.* **2004**, *40*, 1485–1489; (b) Lipson, V. V.; Desenko, S. M.; Shirobokova, M. G.; Borodina, V. V.; Musatov, V. I. *Chem. Heterocycl. Comp.* **2005**, *41*, 492–495.
4. (a) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonía, R.; Hernandez, P.; Bolaños, A.; Moreno, R. *J. Heterocyclic Chem.* **1998**, *35*, 333–338; (b) Orlov, V. D.; Quiroga, J.; Kolos, N. N. *Khim. Geterosikl. Soedin.* **1987**, 1247–1251. C. A.: *88*, 167373.
5. (a) Orlov, V. D.; Quiroga, J.; Kolos, N. N.; Desenko, S. M. *Khim. Geterosikl. Soedin.* **1988**, 962–965; (b) Quiroga, J.; Insuasty, B.; Rincón, R.; Larrahondo, M.; Hanold, N.; Meier, H. *J. Heterocyclic Chem.* **1994**, *31*, 1333–1335; (c) Quiroga, J.; Insuasty, B.; Hormaza, A.; Gamenara, D.; Domínguez, L.; Saldaña, J. *J. Heterocyclic Chem.* **1999**, *36*, 11–13.
6. *Preparation of pyrazolo[3,4-b]pyridine-5-carbaldehydes* **9**: To a suspension of 1.0 mmol of **5** in 2 mL of DMF was added dropwise 200 μL (0.33 g, 2.1 mmol) of $POCl_3$ while cooling with an ice/water bath. The reaction mixture was stirred for 30 min at rt, then the reaction mixture was heated to 80 °C for 3 h. After cooling, 15 g of ice was added and the mixture was stirred vigorously. The precipitate was filtered, dried, and recrystallized from DMF. Data for 6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde **9** (R = H, R′ = Cl): White solid, mp 210–212 °C (65%) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.72 (s, 3H), 7.26–7.53 (m, 5H), 7.63–8.30 (dd, 4H, $J = 8.81$ Hz), 8.76 (s, 1H), 10.10 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.6 (CH_3), 116.6 (C-3a), 124.5 (C-5), 132.0 (C-4), 145.2 (C-7a), 151.0 (C-3), 160.8 (C-6), 190.5 (C=O). EI MS: *m/z*: 349/347 (M^+, 37/100), 321/319 (M^+−CO, 6/18), 318 (19), 304 (6), 77 (5). HR-MS (EI): $C_{20}H_{14}ClN_3O$ calcd 347.0825, found 347.0815. Anal. Calcd for $C_{20}H_{14}ClN_3O$: C, 69.07; H, 4.06; N, 12.08. Found: C, 69.24; H, 4.39; N, 12.26.
7. *Preparation of 4,7-dihydropyrazolo[1,5-a]pyrimidine-3,6-dicarbaldehydes* **10**: To a suspension of 1.0 mmol of **7** in 2.0 mL of DMF was added dropwise 200 μL (0.33 g, 2.1 mmol) of $POCl_3$ while cooling with an ice/water bath. The reaction mixture was stirred for 30 min at rt, then the reaction mixture was heated to 80 °C for 3 h. After cooling, 15 g of ice was added and the mixture was stirred vigorously. The precipitate was filtered, dried, and recrystallized from DMF. Data for 2,5-di-(4-methylphenyl)-7-phenyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-3,6-dicarbaldehyde **10** (Ar = *p*-$CH_3C_6H_4$, R = C_6H_5, R′ = CH_3): Yellow solid, mp 271–273 °C (65%). ^{1}H NMR (400 MHz, DMSO) δ: 2.33 (s, 3H, CH_3, 2-aryl), 2.42 (s, 3H, CH_3, 5-aryl), 6.36 (s, 1H, H-7), 7.23 (d, 2H, H*m*, 2-aryl $J = 7.85$ Hz), 7.27 (t, 1H, H*p*, 7-aryl), 7.36 (d, 4H, 7-aryl), 7.43 (d, 2H, H*m*, 5-aryl, $J = 7.85$ Hz), 7.56 (d, 2H, H*o*, 5-aryl, $J = 8.07$ Hz), 7.64 (d, 2H, H*o*, 2-aryl, $J = 8.07$ Hz), 9.16 (s, 1H, C6-CHO), 9.95 (s, 1H, C3-CHO), 10.95 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO) δ: 20.8 (CH_3, 2-aryl), 21.0 (CH_3, 5-aryl), 57.1 (C-7), 104.6 (C-3), 110.6 (C-6), 126.8 (C*o*, 7-aryl), 127.7 (C*i*, 5-aryl), 128.1 (C*p*, 7-aryl), 128.3 (C*o*, 2-aryl), 128.6 (C*m*, 2-aryl), 128.8 (C*m*, 5-aryl), 129.2 (C*m*, 7-aryl), 130.2 (C*o*, 5-aryl), 138.5 (C*p*, 2-aryl), 141.1 (C*p*, 5-aryl), 141.2 (C*i*, 7-aryl), 141.5 (C-3a), 151,6 (C-2), 152.6 (C-5), 183.3 (3-C=O), 186.8 (6-C=O). EI MS: *m/z*: 433 (M^+, 92), 418 (23, M^+−CH_3), 405 (M^+−CO, 14), 356 (100), 91 (44), 65 (25). HR-MS (EI): $C_{28}H_{23}N_3O_2$ calcd 433.1790, found 433.1781. Anal. Calcd for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.35; N, 9.69. found: C, 77.46; H, 5.28; N, 9.89.
8. *Preparation of pyrazolo[1,5-a]pyrimidine-3-carbaldehyde* **11**: Carbaldehydes **11** were obtained from compounds **8** in the reaction under the same conditions as described above for **9**. Data for 2,7-bis(4-chlorophenyl)-5-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine-3-carbaldehyde **11** (Ar = R = *p*-ClC_6H_4, R′ = OCH_3): Yellow solid, mp >300 °C (dec) (60%). ^{1}H NMR (400 MHz, DMSO, 100 °C) δ: 3.90 (s, 3H, OCH_3), 7.14 (d, 2H, H*m*, 5-aryl, $J = 8.53$ Hz), 7.54 (d, 2H, H*m*, 7-aryl, $J = 8.03$ Hz), 7.69 (d, 2H, H*m*, 2-aryl, $J = 8.28$ Hz), 7.99 (s, 1H, 6-CH), 8.15 (d, 2H, H*o*, 2-aryl, $J = 8.28$ Hz), 8.27 (d, 2H, H*o*, 7-aryl, $J = 8.53$ Hz), 8.38 (d, 2H, H*o*, 5-aryl, $J = 8.28$ Hz), 10.48 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO, 373 K) δ: 54.9 (OCH_3), 106.2 (C-3), 106.9 (C-6), 113.9 (C*m*, 5-aryl), 127.6 (C*m*, 7-aryl), 127.8 (C*i*, 5-aryl), 127.9 (C*m*, 2-aryl), 129.0 (C*o*, 5-aryl), 129.7 (C*i*, 2-aryl), 130.1 (C*o*, 7-aryl), 131.0 (C*o*, 2-aryl) 134.1 (C*p*, 7-aryl), 135.7 (C*p*, 2-aryl), 145.1 (C-7), 152.2 (C-2), 158.3 (C-5), 161.8 (C*i*, 5-aryl), 181.6 (CHO). EI MS: *m/z*: 477/475/473 (M^+, 5/26/35), 449/447/445 (M^+−CO, 13/70/100), 336 (79), 220(19), 219 (74), 111 (29), 77(25), 75 (47). HR-MS (EI): $C_{26}H_{17}Cl_2N_3O_2$ calcd 473.0698, found 473.0694.
9. (a) Li, G.; Kakarla, R.; Gerritz, S. W. *Tetrahedron Lett.* **2007**, *48*, 4595–4599; (b) Stefani, H. A.; Pereira, C. M. P.; Almeida, R. B.; Braga, R. C.; Guzenb, K. P.; Rodrigo Cella, R. *Tetrahedron Lett.* **2005**, *46*, 6833–6837.
10. Low, J. N.; Cobo, J.; Trilleras, J.; Glidewell, C. *Acta Crystallogr., Sect. E* **2006**, *62*, 4930–4932.