Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4195–4198

A novel, one-pot, three-component synthesis of 4*H*-pyrido[1,2-*a*]pyrimidines

Mehdi Adib,[a,*] Mohammad Hosein Sayahi,[a] Meisam Nosrati[a] and Long-Guan Zhu[b]

[a]*School of Chemistry, University College of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran*
[b]*Chemistry Department, Zhejiang University, Hangzhou 310027, PR China*

Received 20 February 2007; revised 5 April 2007; accepted 16 April 2007
Available online 20 April 2007

Abstract—A novel, one-pot, three-component synthesis of 4*H*-pyrido[1,2-*a*]pyrimidines is described. The reactive 1:1 zwitterionic intermediate, formed by the addition of isocyanides to dialkyl acetylenedicarboxylates, was trapped by *N*-(2-pyridyl)amides to produce the title compounds under mild reaction conditions in good yields.

Multi-component reactions (MCRs), by virtue of their convergence, productivity, facile execution and generally high yields of products, have received a great deal of attention in organic and medicinal chemistry. MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area.[1]

The development of simple synthetic routes for widely used organic compounds from readily available reagents is a challenging problem in organic synthesis.[2] Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[3,4] The interest in bicyclic 6–6 systems with one ring junction and one extra nitrogen atom, stems from the occurrence of saturated and partially saturated pyrido[1,2-*a*]pyrimidines in many biologically active compounds and natural products.[4] Compounds containing the pyrido[1,2-*a*]pyrimidine ring system have been used as analgesics (e.g. rimazolium, **1**; Fig. 1),[5] antiallergics,[6] antiasthmatics (e.g. pemirolast, **2**; Fig. 1), antipsychotics (e.g. risperidone, **3**; Fig. 1, a unique full antagonist of the LSD interoceptive effects),[7] gastrointestinal protective,[8] neurotropic and stress-protecting agents.[9] Moreover, some examples are key intermediates for the synthesis of rutaecarpine alkaloids and several are neutral hydrogen chloride acceptors in organic synthesis.[4]

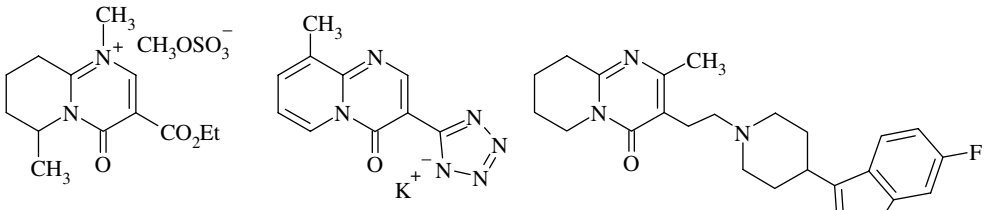
So far, the most common synthetic methods reported for the preparation of pyrido[1,2-*a*]pyrimidine ring systems involve (i) transformation of an existing heterocycle and (ii) cyclizations, classified on the basis of the number of ring atoms in each of the components being cyclized: (iia) single bond formation, α, β or γ to the ring junction nitrogen atom; (iib) formation of two bonds, from [5+1], [4+2] or [3+3] atom fragments; (iic) formation of three bonds, from [4+1+1], [3+2+1] or [2+2+2] atom fragments; (iid) formation of four bonds, from [3+1+1+1] or [2+2+1+1] atom fragments.[4]

Due to the unique pharmacological properties of pyrido[1,2-*a*]pyrimidines, the development of synthetic methods, enabling facile access to this fused heterocycle, are desirable.[4,10] As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds,[11] herein we report a novel synthesis of functionalized 4*H*-pyrido[1,2-*a*]pyrimidines from [1+2+3] atom fragments using simple starting materials and involving the formation of three bonds. Thus, a mixture of an isocyanide **4**, a dialkyl acetylenedicarboxylate **5** and an *N*-(2-pyridyl)amide **6** undergoes a smooth 1:1:1 addition reaction in dry CH_2Cl_2 at ambient temperature to produce 2-amino-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylates **7a–j** in 82–92% yields (Scheme 1).

The reactions were carried out by first mixing acetylenic ester **5** and *N*-(2-pyridyl)amide **6** in dry CH_2Cl_2. Then, a

Keywords: *N*-(2-Pyridyl)amides; Acetylenic esters; Isocyanides; 4*H*-Pyrido[1,2-*a*]pyrimidines; Three-component synthesis.
* Corresponding author. Tel./fax: +98 21 66495291; e-mail: madib@khayam.ut.ac.ir

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.068

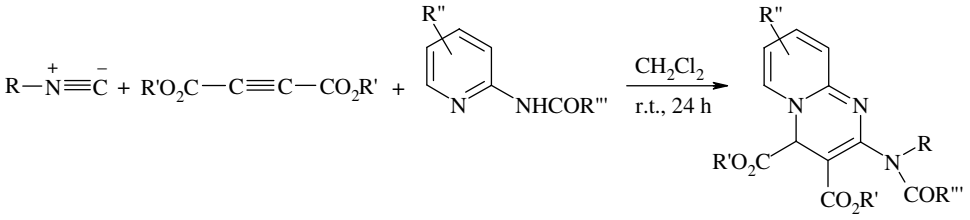


Rimazolium,**1**
an analgesic agent

Pemirolast, **2**
an orally-active antiallergic-antiasthmatic agent

Risperidone, **3**
an antipsychotic agent

Figure 1. Examples of biologically active pyrido[1,2-*a*]pyrimidines.



4 **5** **6** **7**

7	R	R'	R''	R'''	% Yield
a	Cyclohexyl	Me	H	CO_2Et	92
b	Cyclohexyl	Me	8-Me	CO_2Et	87
c	Cyclohexyl	Me	7-Me	CO_2Et	90
d	Cyclohexyl	Me	H	OEt	83
e	Cyclohexyl	Et	H	CO_2Et	88
f	Cyclohexyl	Et	7-Me	CO_2Et	85
g	^{t}Bu	Me	H	CO_2Et	89
h	^{t}Bu	Me	7-Me	CO_2Et	82
i	^{t}Bu	Et	H	CO_2Et	85
j	^{t}Bu	Et	7-Me	CO_2Et	87

Scheme 1.

solution of isocyanide **4** in dry CH_2Cl_2 was added to the reaction mixture. The reaction proceeded spontaneously at ambient temperature and was complete within 24 h. ^{1}H NMR analysis of the reaction mixtures clearly indicated the formation of pyrido[1,2-*a*]pyrimidines **7** in good yields.[12]

The structures of the isolated products were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **7a** displayed the molecular ion (M^+) peak at *m*/*z* 445, which was consistent with the 1:1:1 adduct of cyclohexyl isocyanide, dimethyl acetylenedicarboxylate and ethyl 2-oxo-2-(2-pyridylamino)acetate. The ^{1}H NMR spectrum of **7a** exhibited three sharp singlets, arising from the two CH_3O (δ 3.64 and 3.69 ppm) and methine (δ 6.01 ppm) groups along with characteristic signals with appropriate chemical shifts and coupling constants for the 16 protons of the ethoxy and cyclohexyl functions, as well as characteristic multiplets for the four alkene protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **7a** showed 22 distinct resonances, in agreement with the proposed structure.[12] Single-crystal X-ray analysis conclusively confirmed the structure of the isolated products. An ORTEP diagram of **7a** is shown in Figure 2.[13]

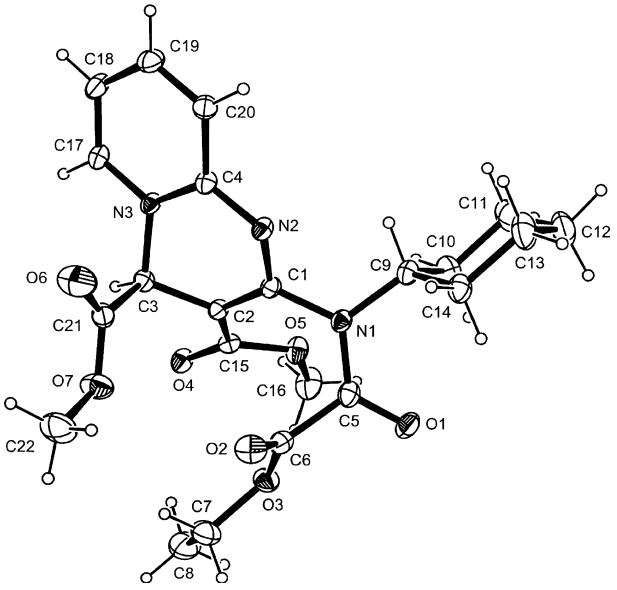
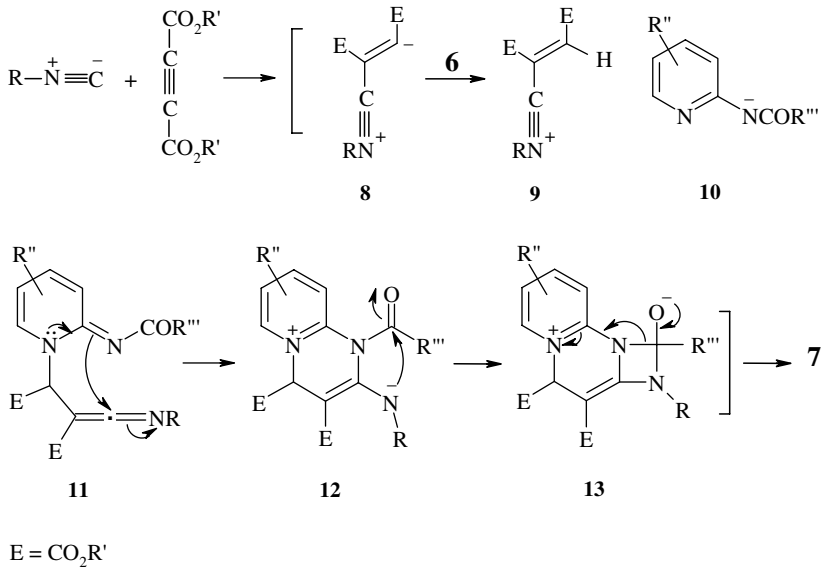


Figure 2. Molecular structure of **7a**, with 50% probability displacement ellipsoids, H atoms with arbitrary radii.

A mechanistic rationalization for this reaction is provided in Scheme 2. On the basis of the well-established chemistry of isocyanides,[1,14–17] it is reasonable to assume that pyrido[1,2-*a*]pyrimidines **7** result from the initial addition of the isocyanide to the acetylenic ester and subsequent protonation of the 1:1 zwitterionic



Scheme 2.

adduct **8** by *N*-(2-pyridyl)amide **6**, followed by conjugate addition of anion **10** to the α,β-unsaturated nitrilium ion **9** to form ketenimine intermediate **11**. The ketenimine may undergo intramolecular cyclization to bicyclic zwitterion **12**. Intramolecular nucleophilic addition of the nitrogen to the adjacent carbonyl group would yield tricyclic system **13**. Subsequent ring opening produces the fused heterocyclic system **7** (Scheme 2).

In summary, we have developed a novel, one-pot, three-component synthesis of 4*H*-pyrido[1,2-*a*]pyrimidines of potential synthetic and pharmacological interest. The good yields of the products, the mild reaction conditions and use of simple starting materials are the main advantages of this method.

Acknowledgement

This research was supported by the Research Council of the University of Tehran as research project (6102036/1/02).

References and notes

1. (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (b) Bagley, M. C.; Dale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682–1683; (c) Mont, N.; Teixidó, J.; Borrell, J. I.; Kappe, C. O. *Tetrahedron Lett.* **2003**, *44*, 5385–5387; (d) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, *24*, 4957–4980; (e) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866–2869; (f) Huang, Y. J.; Yang, F. Y.; Zhu, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387; (g) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634; (h) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.
2. Laszlo, P. *Organic Reactions: Simplicity and Logic*; Wiley: New York, 1995.
3. Swinbourne, J. F.; Hunt, H. J.; Klinkert, G. *Adv. Heterocycl. Chem.* **1987**, *23*, 103.
4. Hermecz, I.; Vasvari-Debreczy, L.; Matyus, P. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds.; Pergamon Press: London, 1996, Chapter 8.23, pp 563–595 and references cited therein.
5. Hermecz, I.; Mészáros, Z. *Med. Res. Rev.* **1988**, *8*, 203–230.
6. (a) Doria, G.; Passarotti, C.; Magrini, R.; Forgione, A.; Sberze, P.; Corno, M. T. M. L.; Cruzzola, G.; Cadelli, G. *Eur. J. Med. Chem.* **1983**, *18*, 227–232; (b) Devos, C.; Dessy, F.; Hermecz, I.; Meszaros, Z.; Breining, T. *Int. Arch. Allergy Imm.* **1982**, *67*, 362–368.
7. Colpaert, F. C. *Nat. Rev. Drug Disc.* **2003**, *2*, 315–320.
8. Knoll, J.; Gyires, K.; Hermecz, I. *Drugs Exp. Clin. Res.* **1987**, *13*, 253–258.
9. Kozlovskaya, M. M.; Inozemtsev, A. N.; Nikitin, S. V.; Gochmuradov, A. G.; Yakushev, R. A.; Chabakgorbach, R. *Bull. Exp. Biol. Med.* **1995**, *119*, 291–293.
10. Cebasek, P.; Bevk, D.; Pirc, S.; Stanovnik, B.; Svete, J. *J. Comb. Chem.* **2006**, *8*, 95–102; Adib, M.; Yavari, H.; Mollahosseini, M. *Tetrahedron Lett.* **2004**, *45*, 1803–1805; Harriman, G. C. B.; Chi, S.; Zhang, M.; Crowe, A.; Bennett, R. A.; Parsons, I. *Tetrahedron Lett.* **2003**, *44*, 3659–3662; Djerrari, B.; Essassi, E. M.; Fifani, J.; Garrigues, B. *C.R. Chim.* **2002**, *5*, 177–183; Bibas, H.; Moloney, D. W. J.; Neumann, R.; Shtaiwi, M.; Bernhardt, P. V.; Wentrup, C. *J. Org. Chem.* **2002**, *7*, 619–2631; Bernad, D. J.; Esteruelas, M. A.; Lopez, A. M.; Olivan, M.; Onate, E.; Puerta, M. C.; Valerga, P. *Organometallics* **2000**, *19*, 4327–4335; Berges, D. A.; Ridges, M. D.; Dalley, N. K. *J. Org. Chem.* **1998**, *63*, 391–392; Kappe, C. O.; Peters, K.; Peters, E.-M. *J. Org. Chem.* **1997**, *62*, 3109–3118; Mellor, J. M.; Merriman, G. D.; Rataj, H.; Reid, G. *Tetrahedron Lett.* **1996**, *37*, 2615–2618; Huang, Z.-T.; Wang, X.-J. *Tetrahedron Lett.* **1987**, *28*, 1527–1528.
11. Adib, M.; Sheibani, E.; Mostofi, M.; Ghanbary, K.; Bijanzadeh, H. R. *Tetrahedron* **2006**, *62*, 3435–3438; Adib, M.; Tahermansouri, H.; Aali Koloogani, S.; Mohammadi, B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 5957–5960; Adib, M.; Mahdavi, M.; Mahmoodi, N.; Pirelahi, H.; Bijanzadeh, H. R. *Synlett* **2006**, 1765–1767; Adib, M.;

Haghighat Jahromi, A.; Tavoosi, N.; Mahdavi, M.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 2965–2967; Adib, M.; Ghanbary, K.; Mostofi, M.; Bijanzadeh, H. R. *Tetrahedron* **2005**, *61*, 2645–2648.

12. The procedure for the preparation of dimethyl 2-[cyclohexyl(2-ethoxy-2-oxoacetyl)amino]-4*H*-pyrido[1,2-*a*]pyrimidine 3,4-dicarboxylate **7a** is described as an example. To a magnetically stirred solution of ethyl 2-oxo-2-(2-pyridylamino)acetate (0.194 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise a solution of cyclohexyl isocyanide (0.109 g, 1 mmol) in dry CH_2Cl_2 (2 mL) at 25 °C for 10 min. The reaction mixture was then stirred for 24 h. The solvent was removed and the residue was purified by column chromatography using hexane–ethyl acetate (1:2) as eluent. The solvent was removed and the product was obtained as yellow crystals, mp 167–169 °C, 0.41 g, yield 92%. IR (KBr) (υ_{max}/cm^{-1}): 1742, 1730 and 1672 (C═O), 1564, 1487, 1396, 1330, 1219, 1146, 1094, 989, 770. MS, *m*/*z* (%): 445 (M^+, 6), 417 (4), 386 (98), 372 (13), 344 (18), 304 (28), 290 (27), 230 (90), 205 (100), 170 (22), 78 (21). Anal. Calcd for $C_{22}H_{27}N_3O_7$ (445.47): C, 59.32; H, 6.11; N, 9.43. Found: C, 59.1; H, 6.3; N, 9.2. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.02–2.13 [13H: 3H, t, $J = 7.0$ Hz, OCH_2CH_3 and 10H, m, $CH(CH_2)_5$], 3.64 and 3.69 (6H, 2s, $2OCH_3$), 3.99–4.25 [3H, m, OCH_2CH_3 and $NCH(CH_2)_5$], 6.01 (1H, s, NCH), 6.76 (1H, t, $J = 6.4$ Hz, CH), 7.13 (1H, d, $J = 8.3$ Hz, CH), 7.38 (1H, d, $J = 6.2$ Hz, CH), 7.56 (1H, t, $J = 7.6$ Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.83 (OCH_2CH_3), 25.65, 26.10, 26.11, 28.57 and 31.98 ($5CH_2$), 51.64 and 52.92 ($2OCH_3$), 56.77 and 61.44 (2NCH), 62.32 (OCH_2), 87.28 ($N_2C{=}C$), 114.51, 123.84, 136.97 and 139.08 (4CH), 152.66 and 153.48 (2C), 161.88, 162.36, 164.75 and 168.18 (4C═O).
13. *Selected X-ray crystallographic data for compound* **7a**: $C_{22}H_{27}N_3O_7$, triclinic, space group = *P*-1 (No. 2), $a = 11.353(2)$ Å, $b = 13.700(3)$ Å, $c = 15.132(3)$ Å, $V = 2245.1(7)$ Å^3, $T = 295(2)$ K, $Z = 4$, $D_{calcd} = 1.318$ g cm^{-3}, μ(Mo Kα) = 0.099 mm^{-1}, 17002 reflections measured, 8265 unique reflections ($R_{int} = 0.0705$), 4016 observed reflections, final $R_1 = 0.074$, $wR_2 = 0.150$ and for all data $R_1 = 0.158$, $wR_2 = 0.188$. CCDC 636589 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
14. Nair, V.; Vinod, A. U.; Nair, J. S.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett.* **2000**, *41*, 6675–6679; Nair, V.; Deepthi, A. *Tetrahedron Lett.* **2006**, *47*, 2037–2039.
15. Walborsky, H. M.; Periasamy, M. P. In *The Chemistry of Functional Groups, Supplement C*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1983, Chapter 20, pp 835–837.
16. Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810–819.
17. Ugi, I. *Isonitrile Chemistry*; Academic Press: London, 1971.