Synthesis of *N*-(3-Arylmethyl-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)benzamides

Shujiang Tu,* Junyong Zhang, Runhong Jia, Bo Jiang, Yan Zhang, Changsheng Yao, and Hong Jiang
Department of Chemistry, Xuzhou Normal University, Key Laboratory of Biotechnology for Medicinal Plant, Xuzhou, Jiangsu 221116, P. R. China

(Received November 17, 2006; CL-061355; E-mail: laotu2001@263.net)

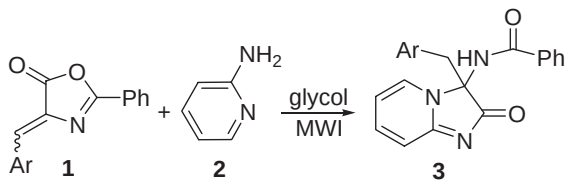
A new series of imidazo[1,2-*a*]pyridin-2-one derivatives were synthesized by the reaction of 4-arylidene-2-phenyl-5(4*H*)-oxazolones and pyridin-2-amine under microwave irradiation in ethylene glycol. The starting materials were easily obtained and the operation was very convenient.

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and unnatural products, many of which exhibit useful biological activity.[1] Imidazo[1,2-*a*]pyridines show anticytomegalo-zoster and antivaricella-zoster virus,[2a–2e] antibacterial,[3] antiinflammatory, analgesic, antipyretic,[4a–4c] hypnoselective and anxioselective activities.[5] They are β-amyloid formation inhibitors[6] and constitute a novel class of orally active nonpeptide bradykinin B2 receptor antagonists.[7] Some imidazo[1,2-*a*]pyridines are known to improve the cerebral function and may cure the cognitive and memory disorder such as Alzheimer's disease.[8] Even recently, bicyclic imidazo derivatives (imidazo[1,2-*a*]pyridine, imidazo-[2,1-*b*]thiazole) have been screened as new anti-HIV-1 compounds such as non-nucleosidereverse transcriptase (RT) inhibitors (NNRTIs).[9] Several imidazo[1,2-*a*]pyridines already on the market include zolimidine (an antiulcer drug),[3c] zolpidem (a hypnotic drug), and alpidem (a nonsedative anxiolytic).[10]

Due to their diverse biological activities, researchers have been interested in the synthesis of derivatives of this structural type. Several groups have described the synthesis of imidazo[1,2-*a*]pyridines derivatives.[2a,2b,11–19] However, the synthesis of the imidazo[1,2-*a*]pyridin-2-ones with benzyl- and benzamido-group simultaneously occupying 3-position has seldom been reported.

In the context of our interest in the design and development of useful tactics and strategies for the synthesis of nitrogen heterocycles,[20] in this paper, we wish to report a new route for the synthesis of a new imidazo[1,2-*a*]pyridin-2-one derivatives by a novel cascade reaction. The starting material 4-arylidene-2-phenyl-5(4*H*)-oxazolones (**1**) were easily prepared according to our reported procedure.[21] By the treatment of **1** and equimolar pyridin-2-amine (**2**) under microwave irradiation (MWI) in ethylene glycol, to our delight, the reaction proceeded smoothly and afforded a variety of *N*-(3-benzyl-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)benzamide (**3**) (Scheme 1).[22]

In order to search the optimum reaction condition, different organic solvents, such as ethanol, DMF, glacial acetic acid, ethylene glycol were tested in the synthesis of **3a** at 100 °C. We found that the reaction in ethylene glycol gave the best result.



Scheme 1.

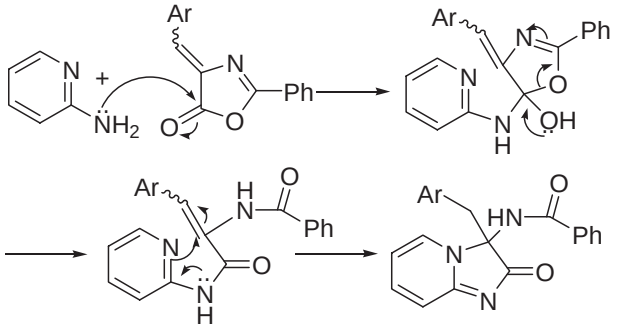
Moreover, to further optimize the reaction temperature, reaction of 4-(4-fluorobenzyliden)-2-phenyl-5(4*H*)-oxazolone (**1a**) and **2** was carried out at the temperatures ranging from 100 to 140 °C in increments of 10 °C each time in ethylene glycol. When the temperature was increased from 100 to 120 °C, the yield of *N*-(3-(4-fluorobenzyl)-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)benzamide (**3a**) was improved. However, no significant increase in the yield of product **3a** was observed as the reaction temperature was raised from 120 to 140 °C. Therefore, the temperature of 120 °C was chosen for all further microwave-assisted reactions. Under these optimized reaction conditions [120 °C, ethylene glycol], a series of products **3** were synthesized with this simple reaction procedure. The results are summarized in Table 1.

For comparison, the synthesis of **3a** under classical heating conditions at 120 °C was performed. The yield of **3a** was only 35% and the reaction time was 5 h. Therefore, microwave irradiation exhibited advantages over the conventional heating by reducing the reaction time and improving the reaction yield. The electronic effect of aryl was investigated. Under our reaction conditions, both electron-withdrawing and electron-donating substituents readily provided imidazo[1,2-*a*]pyridin-2-ones in good yields (Table 1), as highlighted by chloro-containing compound **3d**, which was obtained in 78% yield. It is worth noting that there is no literature precedent for the synthesis of *N*-(3-arylmethyl-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)-benzamides.

The assigned molecular structures of new compounds **3** are based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, COSY, DEPT135), and elemental analysis.

Table 1. Synthesis of compounds **3**

Entry	Product	Ar	Time /min	Yield /%	Mp/°C
1	**3a**	4-FC_6H_4	4	74	>300
2	**3b**	4-ClC_6H_4	4	76	>300
3	**3c**	4-BrC_6H_4	4	75	>300
4	**3d**	2,4-$Cl_2C_6H_3$	5	78	281–282
5	**3e**	4-$NO_2C_6H_4$	4	73	295–296
6	**3f**	2-ClC_6H_4	5	61	280–282
7	**3g**	4-$(CH_3)_2NC_6H_4$	6	63	>300
8	**3h**	4-$CH_3OC_6H_4$	6	67	>300
9	**3i**	3,4-$(OCH_2O)C_6H_3$	7	68	>300
10	**3j**	3,4-$(CH_3O)_2C_6H_3$	6	58	290–292
11	**3k**	C_6H_5	6	62	296–298
12	**3l**	4-$CH_3C_6H_4$	5	70	>300



Scheme 2.

Regarding the structure of **3** the assignment of **3e** was described. ^{1}H NMR showed two methylene protons at δ 3.69 (d, 1H, $J = 13.2$ Hz, CH_2), 3.46 (d, 1H, $J = 13.2$ Hz, CH_2), respectively. DEPT135 at δ 41.49 ppm, ^{13}C NMR spectrum at δ 41.49 and δ 77.51 ppm were consistent with the existence of one secondary carbon and one quaternary carbon. Furthermore, the C–H correlated spectra also suggested the presence of methylene.

Although we have not established the mechanism of this reaction in an experimental manner, to explain the formation of products **3** from the corresponding materials, a possible explanation is proposed in Scheme 2.

In summary, we have provided a new route for the synthesis of a series of imidazo[1,2-*a*]pyridin-2-one derivatives by a novel cascade reaction. The starting materials were easily obtained and the operation was convenient. Most importantly, the series of imidazo[1,2-*a*]pyridin-2-one derivatives may provide a classes of biological active compounds for biomedical screening. An extension of this work is currently under investigation.

We are grateful to the financial support from the National Science Foundation of China (No. 20672090) and Natural Science Foundation of the Jiangsu Province (No. BK2006033).

References and Notes

1 J. Pastor, J. Siro, J. L. Garcia-Navio, M. M. Rodrigo, M. Ballesteros, J. Alvarez-Builla, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3043.

2 a) A. Elhakmaoui, A. Gueiffier, J.-C. Milhavet, Y. Blache, J.-P. Chapat, O. Chavignon, J.-C. Teulade, R. Snoeck, G. Andrei, E. De Clercq, *Bioorg. Med. Chem. Lett.* **1994**, *16*, 1937. b) A. Gueiffier, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J.-C. Teulade, A. Kerbal, E. M. Essassi, J.-C. Debouzy, M. Witvrouw, Y. Blache, J. Balzarini, E. De Clercq, J.-P. Chapat, *J. Med. Chem.* **1996**, *39*, 2856. c) L. B. Townsend, J. C. Drach, WO 27 205, **1997**; *Chem. Abstr.* **1997**, *127*, 190983j. d) A. Gueiffier, S. Mavel, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J.-C. Teulade, M. Witvrouw, J. Balzarini, E. De Clercq, J.-P. Chapat, *J. Med. Chem.* **1998**, *41*, 5108. e) S. Mavel, J. L. Renou, C. Galtier, R. Snoeck, G. Andrei, J. Balzarini, E. De Clercq, A. Gueiffier, *Arzneim.-Forsch.* **2001**, *51*, 304; *Chem. Abstr.* **2001**, *135*, 131730s.

3 J. C. Teulade, G. Grassy, J. P. Girard, J. P. Chapat, M. Simeon De Buochberg, *Eur. J. Med. Chem.* **1978**, *13*, 271.

4 a) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, W. Murmann, *J. Med. Chem.* **1965**, *8*, 305. b) E. Abignente, F. Arena, E. Luraschi, C. Saturnino, F. Rossi, E. Lampa, M. Cazzola, E. Brandinelli, R. Marrazzo, E. Marmo, *Rend. Atti Accad. Sci. Med. Chir.* **1985**, *139*, 313; *Chem. Abstr.* **1986**, *105*, 126822z. c) E. Abignente, *Actual. Chim. Ther.* **1991**, *18*, 193; *Chem. Abstr.* **1991**, *115*, 256028n.

5 G. Bartholini, *L.E.R.S. Monogr. Ser.* **1993**, *8*, 1; *Chem. Abstr.* **1996**, *124*, 164079n.

6 K. Fuchs, M. Romig, K. Mendla, H. Briem, K. Fechteler, WO 14 313, **2002**; *Chem. Abstr.* **2002**, *136*, 183824r.

7 Y. Abe, H. Kayakiri, S. Satoh, T. Inoue, Y. Sawada, K. Imai, N. Inamura, M. Asano, C. Hatori, A. Katayama, T. Oku, H. Tanaka, *J. Med. Chem.* **1998**, *41*, 564.

8 Y. Yamaguchi, T. Matsuno, S. Kawashima, *Brain Res.* **2002**, *945*, 259.

9 C. Moog, A. Wick, P. Le Ber, A. Kirn, A.-M. Aubertin, *Antiviral Res.* **1994**, *24*, 275.

10 S. Z. Langer, S. Arbilla, J. Benavides, B. Scatton, *Adv. Biochem. Psychopharmacol.* **1990**, *46*, 61.

11 a) E. S. Hand, W. W. Paudler, *J. Org. Chem.* **1978**, *43*, 2900. b) R. Rydzkowski, D. Blondeau, H. Sliwa, *Tetrahedron Lett.* **1985**, *26*, 2571. c) S. Löber, H. Hübner, P. Gmeiner, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97. d) H. Tomoda, T. Hirano, S. Saito, T. Mutai, K. Araki, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1327. e) T. Ikemoto, M. Wakimasu, *Heterocycles* **2001**, *55*, 99.

12 A. J. Hubert, H. Reimlinger, *Chem. Ber.* **1970**, *103*, 3811.

13 H. Galons, I. Bergerat, C. Combet Farnoux, M. Miocque, *Synthesis* **1982**, 1103.

14 H.-J. Knölker, R. Boese, R. Hitzemann, *Chem. Ber.* **1990**, *123*, 327.

15 M. P. Groziak, S. R. Wilson, G. L. Clauson, N. J. Leonard, *J. Am. Chem. Soc.* **1986**, *108*, 8002.

16 K. Groebke, L. Weber, F. Mehlin, *Synlett* **1998**, 661.

17 L. Cai, C. Brouwer, K. Sinclair, J. Cuevas, V. W. Pike, *Synthesis* **2006**, 113.

18 A. V. Dolzhenko, N. V. Kolotova, V. O. Kozminykh, W. Chui, P. W. S. Heng, V. N. Khrustalev, *Heterocycles* **2004**, *63*, 55, and references therein.

19 C. Plorac, M. Baudy-noćh, A. Robert, *Tetrahedron* **1990**, *46*, 445.

20 a) S. Tu, T. Li, F. Shi, Q. Wang, J. Zhang, J. Xu, X. Zhu, X. Zhang, S. Zhu, D. Shi, *Synthesis* **2005**, 3045. b) S. J. Tu, B. Jiang, R. H. Jia, J. Y. Zhang, Y. Zhang, C. S. Yao, F. Shi, *Org. Biomol. Chem.* **2006**, *4*, 3664. c) S. J. Tu, B. Jiang, J. Y. Zhang, R. H. Jia, Y. Zhang, C. S. Yao, *Org. Biomol. Chem.* **2006**, *4*, 3980.

21 S. J. Tu, H. Jiang, Q. Y. Zhuang, C. B. Miao, D. Q. Shi, X. S. Wang, Y. Gao, *Chin. J. Org. Chem.* **2003**, *23*, 491.

22 General procedures for the synthesis of **3** are as follows: A mixture of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (**1**) (1 mmol) and pyridin-2-amine (**2**) (1 mmol) was added to a 10-mL reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to react under microwave irradiation at 240 W power and 120 °C in ethylene glycol (2 mL) for 4–7 min. The reaction mixture was cooled to room temperature, then poured into water (50 mL), filtered to give crude product, which was further purified by recrystallization from EtOH (**3a–3l**). Compound **3e**: IR (KBr): 3241, 3014, 2987, 1679, 1664, 1567, 1532, 868, 809, 786, 724, 591 cm^{-1}; ^{1}H NMR (DMSO-d_6) (δ, ppm): δ 9.69 (s, 1H, NH), 8.30 (d, 1H, $J =$ 6.4 Hz, ArH), 8.04 (d, 2H, $J = 8.4$ Hz, ArH), 7.92 (d, 2H, $J =$ 7.6 Hz, ArH), 7.65–7.52 (m, 4H, ArH), 7.15 (d, 2H, $J = 8.4$ Hz, ArH), 6.82–6.74 (m, 2H, ArH), 3.69 (d, 1H, $J = 13.2$ Hz, CH_2), 3.46 (d, 1H, $J = 13.2$ Hz, CH_2); ^{13}C NMR (DMSO-d_6) (δ, ppm): δ 183.05, 166.46, 165.93, 147.03, 143.03, 140.01, 134.22, 132.62, 132.46, 131.52, 128.61, 128.06, 123.15, 114.59, 112.19, 77.51, 41.49; DEPT 135: δ 143.03, 134.22, 132.46, 131.52, 128.61, 128.06, 123.15, 114.59, 112.19, 41.49. Anal. calcd for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.15; N, 14.43%. Found: C, 65.12; H, 4.20; N, 14.28%.

Published on the web (Advance View) December 26, 2006; doi:10.1246/cl.2007.222