Task-Specific Basic Ionic Liquid: A Reusable and Green Catalyst for One-Pot Synthesis of Highly Functionalized Pyrroles in Aqueous Media

Issa Yavari,* Elaheh Kowsari

Chemistry Department, Tarbiat Modares University, PO Box 14115-175, Tehran, Iran
Fax +98(21)88006544; E-mail: yavarisa@modares.ac.ir

Received 27 December 2007

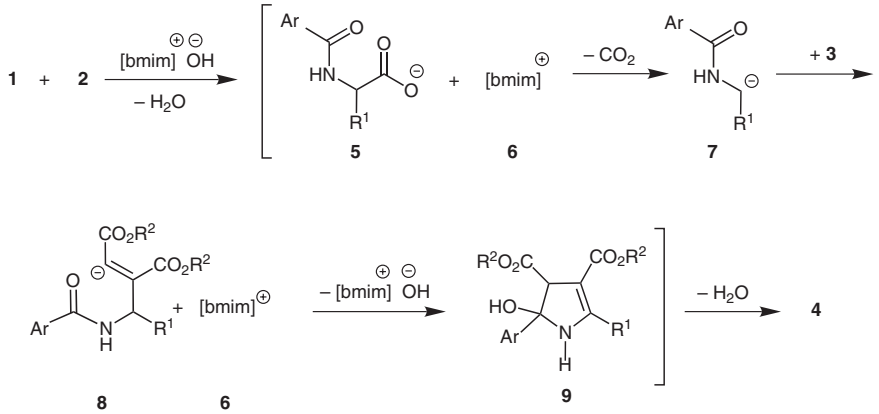
Abstract: A basic functionalized ionic liquid, 1-butyl-3-methylimidazolium hydroxide ([bmim]OH), catalyzed the three-component condensation reaction of acid chlorides, amino acids, and dialkyl acetylenedicarboxylates in water to afford functionalized pyrroles in high yields.

Key words: functional ionic liquid, pyrrole synthesis, aqueous media, green catalyst

Room-temperature ionic liquids (IL) have attracted intensive interests in recent years due to their wide applications in synthesis, catalysis, and chemical separations.[1,2] In comparison with conventional molecular solvents, the IL are advantageous because they are nonvolatile, thermally stable over a wide temperature range, and recyclable. Reactions in aqueous media offer many advantages such as simple operation and high efficiency in many organic reactions that involve water-soluble substrates and reagents.[3] These advantages become even more attractive if such reactions can be conducted using IL in aqueous media.

Pyrroles represent an important class of N-heterocycles that display remarkable pharmacological activities.[4] Many synthetic methods are known for the construction of the pyrrole structure.[5] The most frequently used methods include the classical Hantzsch procedure,[6] the cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal–Knorr synthesis),[7] and various cycloaddition strategies.[8] Multicomponent strategies offer significant advantages over classical linear syntheses by combining a series of reactions from easily available and simple precursors without the need for isolation of the intermediates. Such reactions are thus economically and environmentally attractive and have become an important area of research in organic chemistry. Herein we report an efficient reaction of acid chlorides **1**, amino acids **2**, and dialkyl acetylenedicarboxylates **3** in aqueous medium in the presence of a task-specific basic IL, [bmim]OH,[9] as a catalyst (Table 1).[10] The catalyst can be recycled for subsequent reactions without appreciable loss of efficiency.

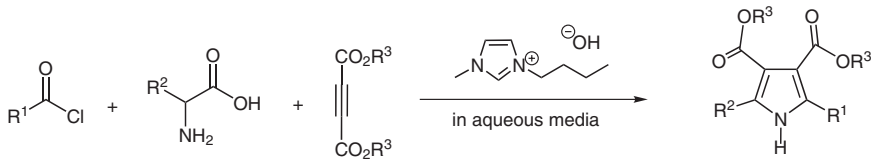
The three-component, one-pot condensation of **1**, **2**, and **3** proceeded smoothly in [bmim]OH–H_2O system to give the functionalized pyrroles **4** in high yields. When benzoyl chlorides with electron-withdrawing groups (such as NO_2) are employed, the reaction time is shorter than those with electron-donating groups. Results obtained under optimized conditions were compared with those using inorganic or organic alkali catalysts. The [bmim]OH–H_2O system was found to be a much better catalytic medium for this reaction. Non-imidazolium-based ILs such as [EtPy][BF_4] or [bmim][BF_4] were found to be less effective catalysts for reaction of **1**, L-phenylalanine, and **3**. These results confirm the vital role of the hydroxy counterion of the [bmim]OH–H_2O system.



Scheme 1 Plausible mechanism for the formation of functionalized pyrroles **4**

SYNLETT 2008, No. 6, pp 0897–0899
Advanced online publication: 11.03.2008
DOI: 10.1055/s-2008-1042912; Art ID: D41007ST

Table 1 Synthesis of Compounds **4a**–**q**[10]



1 **2** **3** **4**

Entry	Product	R^1	R^2	R^3	Yield (%)
1	**4a**	Ph	Ph	Me	95
2	**4b**	4-MeC_6H_4	Ph	Me	91
3	**4c**	4-ClC_6H_4	Ph	Me	93
4	**4d**	4-$O_2NC_6H_4$	Ph	Me	96
5	**4e**	Ph	Bn	Me	92
6	**4f**	4-MeC_6H_4	Bn	Me	94
7	**4g**	4-ClC_6H_4	Bn	Me	87
8	**4h**	4-$O_2NC_6H_4$	Bn	Me	95
9	**4i**	Ph	*i*-Bu	Me	87
10	**4j**	4-MeC_6H_4	*i*-Bu	Me	89
11	**4k**	4-ClC_6H_4	*i*-Bu	Me	84
12	**4l**	4-$O_2NC_6H_4$	*i*-Bu	Me	88
13	**4m**	Ph	Ph	Et	91
14	**4n**	4-MeC_6H_4	Ph	Et	90
15	**4o**	4-ClC_6H_4	Ph	Et	89
16	**4p**	4-$O_2NC_6H_4$	Ph	Et	87
17	**4q**	Ph	*i*-Bu	Et	96

The structures of **4a**–**q** were deduced from their high-field ^1H NMR and ^{13}C NMR spectra, and IR spectral data.

Although the mechanistic details of the reaction are not clearly known, it is reasonable to assume that intermediate **5** results from the reaction of acid chloride **1** with amino acid **2**. Subsequent decarboxylation of **5** in the presence of [bmim]OH leads to intermediate **7**, which is attacked by **3** to produce **8**. Cyclization of **8** leads to **9**, which is converted to **4** by elimination of H_2O (Scheme 1).

In conclusion, we have described a convenient route to functionalized pyrroles from the three-component reaction of benzoyl chlorides, amino acids, and dialkyl acetylenedicarboxylates in a [bmim]OH–H_2O system. The attractive features of this protocol are: simple procedure, short reaction time, use of cheap and benign solvent, the reuse of the reaction medium, and its adaptability for synthesis of a diverse set of pyrroles.

References and Notes

(1) (a) Rantwijk, F.; Sheldon, R. A. *Chem. Rev.* **2007**, *107*, 2757. (b) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615. (c) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363.
(2) (a) Binnemans, K. *Chem. Rev.* **2007**, *107*, 2592. (b) Yavari, I.; Kowsari, E. *Tetrahedron Lett.* **2007**, *48*, 3753.
(3) (a) Grieco, P. A. *Organic Synthesis in Water*; Blackie: London, **1998**. (b) Wei, W.; Li, C. J.; Varma, R. S. *Clean Tech. Environ. Policy* **2005**, *7*, 62. (c) Narayan, S.; Muldoon, J.; Finn, M. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.
(4) Jacobi, P. A.; Coults, L. D.; Guo, J. S.; Leung, S. I. *J. Org. Chem.* **2000**, *65*, 205.
(5) For reviews on pyrrole synthesis, see: Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*, Vol. 2; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 119.
(6) For examples of the Hantzsch synthesis, see: Trautwein, A. W.; Süßmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381.

(7) For recent examples of the Paal–Knorr synthesis, see: (a) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (b) Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z. *Synlett* **2003**, 75. (c) Tracey, M. R.; Hsung, R. P.; Lambeth, R. H. *Synthesis* **2004**, 918.

(8) (a) Katritzky, A. R.; Zhang, S.; Wang, M.; Kolb, H. C.; Steel, P. J. *J. Heterocycl. Chem.* **2002**, *39*, 759. (b) Bullington, J. L.; Wolff, R. R.; Jackson, P. F. *J. Org. Chem.* **2002**, *67*, 9439. (c) Washizuka, K. I.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 1296.

(9) [bmim]OH was prepared according to literature, see: Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049.

(10) **Dimethyl 2,5-Diphenyl-1*H*-pyrrole-3,4-dicarboxylate (4a); Typical Procedure**

A solution of the benzoyl chloride (**1a**, 0.14 g, 1 mmol), phenyl glycine (**2a**, 0.15 g, 1 mmol), and [bmim]OH (1.40 g, 0.01 mol) in H_2O (2 mL) was stirred at r.t. for 15 min. Then, **3** (0.14 g, 1 mmol) was added and the reaction mixture was refluxed for 3 h (monitored by TLC). The reaction mixture was cooled to r.t. and the solid mass was filtered, washed with Et_2O, and crystallized from *n*-hexane−EtOAc to give **4a** as colorless crystals; mp 150−151 °C; yield: 0.31 g (95%). IR (KBr): 3260 (NH), 1720 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.60 (s, 6 H, 2 OMe), 7.32–7.35 (m, 6 H, 6 CH), 7.50–7.52 (m, 4 H, 4CH), 8.85 (s, 1 H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 51.8 (2 OMe), 114.1 (2 C), 128.1 (2 CH), 128.5 (4 CH), 128.6 (4 CH), 130.8 (2 C), 137.8 (2 C), 165.8 (2 C=O). Anal. Calcd (%) for $C_{20}H_{17}NO_4$ (335.35): C, 71.56; H, 5.11; N, 4.18. Found: C, 71.70; H, 5.09; N, 4.21.

Dimethyl 2-Benzyl-5-phenyl-1*H*-pyrrole-3,4-dicarboxylate (4e)

Colorless crystals; mp 134–135 °C; yield 0.32 g (92%). IR (KBr): 3252 (NH), 1728 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 4.30 (s, 2 H, CH_2), 7.24–7.37 (m, 10 H, 2 C_6H_5), 8.38 (s, 1 H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.9 (CH_2), 51.3 (OMe), 52.0 (OMe), 112.5 (C), 114.5 (C), 127.0 (CH), 127.1 (CH), 128.1 (2 CH), 128.7 (2 CH), 128.8 (2 CH), 128.9 (2 CH), 130.7 (C), 131.5 (C), 137.2 (C), 137.4 (C), 164.8 (C=O), 166.9 (C=O). Anal. Calcd (%) for $C_{21}H_{19}NO_4$ (349.38): C, 72.19; H, 5.48; N, 4.01. Found: C, 72.13; H, 5.51; N, 4.05.

Dimethyl 2-Isobutyl-5-(4-methylphenyl)-1*H*-pyrrole-3,4-dicarboxylate (4j)

Colorless crystals; mp 141–143 °C; yield 0.29 g (89%). IR (KBr): 3225 (NH), 1681 (C=O) cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 0.90 (d, ^3J = 7.2, 6 H, $CHMe_2$), 1.92–1.97 (m, 1 H, CH), 2.32 (s, 3 H, Me), 2.70 (d, ^3J = 7.2 Hz, 2 H, CH_2), 3.77 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 7.11 (d, ^3J = 8.1 Hz, 2 H, 2 CH), 7.31 (d, ^3J = 8.1 Hz, 2 H, 2 CH), 8.87 (s, 1 H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.0 (Me), 22.2 (2 Me), 29.0 (CH), 35.6 (CH_2), 51.0 (OMe), 51.9 (OMe), 112.3 (C), 113.6 (C), 127.0 (2 CH), 128.0 (C), 129.2 (2 CH), 131.4 (C), 137.8 (C), 138.6 (C), 165.1 (C=O), 167.4 (C=O). Anal. Calcd (%) for $C_{19}H_{23}NO_4$ (329.39): C, 69.22; H, 7.00; N, 4.25. Found: C, 69.41; H, 7.03; N, 4.28.

All other compounds isolated possessed spectroscopic and analytical data in agreement with their proposed structures.