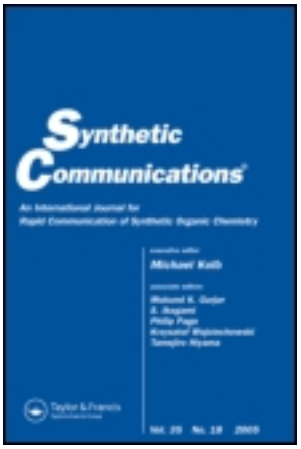


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Three-Component, One-Pot Synthesis of Benzo[b][1,4]oxazines in Ionic Liquid 1-Butyl-3-methylimidazolium Bromide

Ebrahim Soleimani [a], Mohammad Mehdi Khodaei [a] & Afsaneh Taheri Kal Koshvandi [a]

[a] Department of Chemistry, Razi University, Kermanshah, Iran

Accepted author version posted online: 21 Oct 2011. Version of record first published: 11 Jan 2012

To cite this article: Ebrahim Soleimani, Mohammad Mehdi Khodaei & Afsaneh Taheri Kal Koshvandi (2012): Three-Component, One-Pot Synthesis of Benzo[b][1,4]oxazines in Ionic Liquid 1-Butyl-3-methylimidazolium Bromide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:9, 1367-1371

To link to this article: http://dx.doi.org/10.1080/00397911.2010.540056

Synthetic Communications®, 42: 1367–1371, 2012

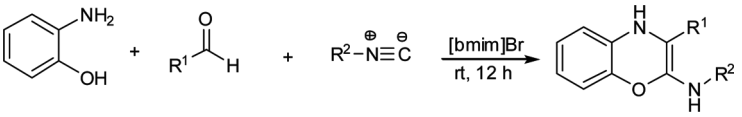
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.540056

Taylor & Francis
Taylor & Francis Group

THREE-COMPONENT, ONE-POT SYNTHESIS OF BENZO[*b*][1,4]OXAZINES IN IONIC LIQUID 1-BUTYL-3-METHYLIMIDAZOLIUM BROMIDE

Ebrahim Soleimani, Mohammad Mehdi Khodaei, and Afsaneh Taheri Kal Koshvandi
Department of Chemistry, Razi University, Kermanshah, Iran

GRAPHICAL ABSTRACT



Abstract *Benzo[*b*][1,4]oxazines have been synthesized in good to excellent yields in the presence of the ionic liquid 1-butyl-3-methylimidazolium bromide [bmim]Br under relatively mild conditions without any added catalyst, The method offers the advantages of good yields and short reaction times, and the ionic liquid can be easily separated from the product and reused.*

Keywords Benzo[*b*][1,4]oxazines; [bmim]Br; ionic liquid; isocyanide; multicomponent reactions

INTRODUCTION

Heterocyclic skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs.[1] This is especially true for six-member ring heterocyclic compounds, which are core components of a large number of substances that possess a wide range of interesting biological activities.[2] In this respect, the utility of the benzo[*b*][1,4]oxazin scaffold as a privileged structure for the generation of drug-like libraries in drug-discovery programs has been amply demonstrated. Benzo[*b*][1,4]oxazin derivatives have been used as the basic framework for substances of interest in numerous therapeutic areas, such as anti-Candina albicans agents,[3] antifungals,[4] and kinase inhibitors.[5]

Multicomponent reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion.[6] Devising MCRs that achieve the formation of multiple bonds in a single operation is one of the major

Received November 10, 2010.
Address correspondence to Ebrahim Soleimani, Department of Chemistry, Razi University, Kermanshah, Iran. E-mail: e_soleimanirazi@yahoo.com

challenges in modern organic synthesis.[7] As such processes avoid time-consuming and costly purification processes, as well as protection–deprotection steps, they are inherently more environmentally benign and atom economical.[8] They provide a powerful tool for the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles.[9] MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds.[6,10]

In recent years, studies of low-waste routes and reusable reaction media for enhanced selectivity and energy minimization are key interests of synthetic organic chemists the world over.[11] In this context, in recent times, the use of room-temperature ionic liquids as green solvents in organic synthetic processes has gained considerable importance because of their solvating ability, negligible vapor pressure, and easy recyclability.[12] We have recently shown that they can also promote and catalyze isocyanide-based MCRs under ambient conditions without the need for any added catalyst or ligand.[13]

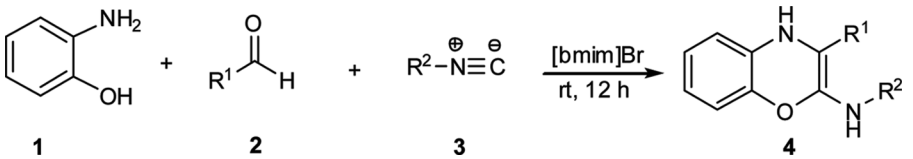
RESULTS AND DISCUSSION

Proceeding along the same lines, we chose to evolve an efficient and ecofriendly process for the preparation of benzo[*b*][1,4]oxazines **4** by the three-component condensation of 2-aminophenole **1,** an aldehyde **2**, and isocyanide **3** in the presence of 1-butyl-3-methylimidazolium bromide ([bmim]Br) as reaction media as well as promoters, in the absence of any added catalyst, at ambient temperature (Scheme 1).

As indicated in Table 1, the reaction of aldehydes with 2-aminophenole and isocyanides afforded benzo[*b*][1,4]oxazines in [bmim]Br as a promoter in very good yields.

To optimize the reaction conditions, we conducted the condensation of benzaldehyde (1 mmol), 2-aminophenole (1 mmol), and cyclohexyl isocyanide (1 mmol) with stirring at room temperature in various ionic liquids (1 mmol) after 12 h. The results showed that the efficiency and the yield of the reaction in [bmim]Br was greater than those obtained in other ionic liquids. Also, to illustrate the need for [bmim]Br, the reaction was studied in the absence of [bmim]Br, in which no product was produce at room temperature after 12 h. Obviously, [bmim]Br is an important component of the reaction (Table 2).

One of the advantages of ionic liquids is their ability to function as a recyclable reaction medium. We were able to separate [bmim]Br from the reaction medium easily by washing with water and evaporating the solvent under vacuum, and reuse it for subsequent reactions.



Scheme 1. Synthesis of benzo[*b*][1,4]oxazines.

Table 1. Synthesis of benzo[*b*][1,4]oxazines in [bmim]Br

Product	R^1	R^2	Yield (%)
4a	Ph	Cyclohexyl	94[a]
4b	4-ClC_6H_4	Cyclohexyl	98[a]
4c	3-$NO_2C_6H_4$	Cyclohexyl	97[a]
4d	4-$NO_2C_6H_4$	Cyclohexyl	99[a]
4e	4-$CH_3C_6H_4$	Cyclohexyl	96[a]
4f	4-$CH_3OC_6H_4$	Cyclohexyl	95[a]
4g	4-HOC_6H_4	Cyclohexyl	95[a]
4h	Ph	*tert*-Butyl	91[a]
4i	4-$NO_2C_6H_4$	*tert*-Butyl	94[a]
4j	4-$CH_3OC_6H_4$	*tert*-Butyl	91[a]
4k	4-$NO_2C_6H_4$	1,1,3,3-Tetramethyl-butyl	98[b]

[a]Known compound.
[b]New compound.

Table 2. Synthesis of benzo[*b*][1,4]oxazines in the presence of various ionic liquids

Ionic liquid	Yield (%)
Tetrabutylammonium bromide	50
Tetrabutylphosphonium bromide	60
Tetrabutylphosphonium chloride	75
benzyltributylammonium chloride	Trace
1-Butyl-3-methylimidazolium bromide ([bmim]Br)	99
Without ionic liquid	Trace

CONCLUSION

In conclusion, we have introduced an efficient and environmentally friendly approach for the synthesis of benzo[b][1,4]oxazines via condensation of an aldehyde, 2-aminophenole, and an isocyanide using [bmim]Br in good to excellent yields at room temperature. The method offers easy experimental workup procedure and reuse of ionic liquid.

EXPERIMENTAL

All purchased solvents and chemicals were of analytical grade and used without further purification. Melting points and infrared (IR) spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. The ^1H and ^{13}C NMR spectra were obtained on a Bruker-200 Avance instrument using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard at 200 and 50 MHz, respectively. The mass spectra were recorded on a Finnigan-MAT 8430 instrument.

All products (except **4k**) are known compounds, which were characterized by IR and ^1H NMR spectral data, and their melting points were compared with literature reports.[14]

General Procedure

[bmim]Br (1.4 mmol) was added to a solution of 2-aminophenole (1 mmol), aldehyde (1.1 mmol), and isocyanide (1.1 mmol). The resulting mixture was stirred for 12 h at room temperature. After completion of the reaction, as indicated by thin-layer chromatography (ethyl acetate/*n*-hexane, 2:1), the reaction mixture was washed with water (10 cm^3) and the solid residue was crystallized from ethanol to give the pure product.

***N*-(2,4,4-Trimethylpentan-2-yl)-3-(4-nitrophenyl)-4H-benzo[b][1,4]oxazin-2-amine (4k).** Yellow crystals; yield 0.37 g (98%); mp 185–187 °C; IR (KBr) (ν_{max}, cm^{-1}): 3165, 3155;^{1}H NMR (200 MHz, $CDCl_3$): $\delta_H = 1.01$ [s, $C(CH_3)_3$], 1.41 [s, $C(CH_3)_2$], 1.71 (s, CH_2), 5.50 (brs, 2NH), 6.96–8.87 (8H, m, H-Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_C = 31.1$ [$C(CH_3)_2$], 31.4 (CH_2), 53.3 [$C(CH_3)_3$], 53.2 [$C(CH_3)_2$], 118.2, 124.3, 125.8, 127.8, 128.4, 130.3, 131.0, 132.4, 141.7, 147.9, 149.5, 159.1 (C-Ar and NH-C=C-NH) ppm; MS (70 eV): m/z (%) = 381 (M^+, 25), 268 (100), 253 (40), 57 (50). Anal. calcd. for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02;. Found: C, 69.50; H, 7.23; N, 11.00.

ACKNOWLEDGMENT

We gratefully acknowledge financial support from the Research Council of Razi University.

REFERENCES

1. (a) Hermakens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. Solid-phase organic reactions II: A review of the literature Nov 95–Nov 96. *Tetrahedron* **1997**, *53*, 5643; (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Foder, S. P. A.; Gallop, M. A. Applications of combinatorial technologies to drug discovery, 2-Combinatorial organic synthesis, library screening strategies, and future directions. *J. Med. Chem.* **1994**, *37*, 1385.
2. (a) Avendano, C.; Menendez, J. C. *Medicinal Chemistry of Anticancer Drugs*; Elsevier: Amsterdam, 2008; (b) Doherty, A. M. *Annual Reports in Medicinal Chemistry*; Academic Press: San Diego, CA, 2000; p. 35; (c) Patrick, G. L. *An Introduction to Medicinal Chemistry*; Oxford University Press: Oxford, UK, 1995.
3. Fringuelli, R.; Pietrella, D.; Schiaffella, F.; Guarrac, I. A.; Perito, S.; Bistoni, F.; Vecchiarelli, A. *Anti–Candida albicans* properties of novel benzoxazine analogues. *Bioorg. Med. Chem.* **2002**, *10*, 1681.
4. Macchiarulo, A.; Costantino, G.; Fringuelli, F.; Vecchiarelli, A.; Schiaffella, F.; Fringuelli, R. 1,4-Benzothiazine and 1,4-benzoxazine imidazole derivatives with antifungal activity: A docking study. *Bioorg. Med. Chem.* **2002**, *10*, 3415.
5. Adams, N. D.; Darcy, M. G.; Dhanak, D.; Duffy, K. J.; Fitch, D. M.; Knight, S. D.; Newlander, K. A.; Shaw, A. N. WO Int. Patent 2006113432, 2006. *Chem. Abstr.* **2006**, *145*, 438652.
6. (a) Dömling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem. Rev.* **2006**, *106*, 17; (b) Hulme, C.; Gore, V. Multi-component reactions: Emerging chemistry in drug discovery from xylocain to crixivan. *Curr. Med. Chem.* **2003**, *10*, 51; (c) Dömling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

7. (a) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005; (b) Ngouansavanh, T.; Zhu, J. Alcohol in isonitrile-based multicomponent reaction: Passerini reaction of alcohol in the presence of O-iodoxybenzoic acid (IBX). *Angew. Chem., Int. Ed.* **2007**, *46*, 5775; (c) Kaim, L. E.; Gizolme, M.; Grimaud, L.; Oble, J. Direct access to heterocyclic scaffolds by new multicomponent Ugi–Smiles couplings. *Org. Lett.* **2006**, *8*, 4019.
8. Trost, B. M. Atom economy, a challenge for organic synthesis: Homogeneous catalysis leads the way. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
9. Weber, L. The application of multicomponent reactions in drug discovery. *Curr. Med. Chem.* **2002**, *9*, 2085–2093.
10. Dömling, A. Recent advances in isocyanide-based multicomponent chemistry. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306.
11. Kitazume, T.; Ishizuka, T.; Takedu, M.; Itoh, K. A low-waste route to large-scale enzymatic resolution of a chiral dopant of ferroelectric liquid crystals. *Green Chem.* **1999**, *1*, 221.
12. (a) Welton, T. Room-temperature ionic liquids: Solvents for synthesis and catalysis. *Chem. Rev.* **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. Ionic liquids: New "solutions" for transition-metal catalysis. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; (c) Sheldon, R. Catalytic reactions in ionic liquids. *Chem. Commun.* **2001**, 2399.
13. (a) Shaabani, A.; Soleimani, E.; Maleki, A. Ionic liquid–promoted one-pot synthesis of 3-aminoimidazo[1,2-*a*]pyridines. *Tetrahedron Lett.* **2006**, *47*, 3031; (b) Shaabani, A.; Soleimani, E.; Darvishi, M. Ionic liquid–promoted one-pot synthesis of furo[2,3-d]pyrimidine-2,4(1H,3H)-diones. *Monatsh. Chem.* **2007**, *138*, 43.
14. Heravi, M. M.; Baghernejad, B.; Oskooie, H. A. A novel three-component reaction for the synthesis of 3-aryl-4*H*-benzo[1,4]oxazin-2-amine. *Mol. Divers.* **2009**, *13*, 395.