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Short communication

SHORT COMMUNICATION

Synthesis of some 3,5-diaryl-2-isoxazoline derivatives in ionic liquids media

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Abstract: Biologically active isoxazoline derivatives were efficiently synthesized in excellent yields and in smaller reaction times using mild, effective and environmentally friendly butylmethylimidazolium bromide as the solvent and catalyst. By use of this catalyst, isoxazoline derivatives were produced *via* cyclization reaction of a chalcone and hydroxylamine hydrochloride in the ionic liquid media. The separation of the product was facile and the catalyst could be separated and recycled. The method is very rapid, safe and avoids the use of hazardous and expensive reagents and solvents.

Keywords: isoxazoline; cyclization reaction; ionic liquids; butylmethylimidazolium bromide; multi-component reactions; biological activities.

INTRODUCTION

Compounds incorporating heterocyclic ring systems continue to attract considerable interest due to the wide range of their biological activities. Amongst them, five-membered heterocyclic compounds occupy a unique place in the realm of natural and synthetic organic chemistry. Isoxazolines as heterocyclic compounds have found wide application as pharmaceutical and agrochemical agents. For instance, isoxazolines possess biological activities,[1–8] such as insecticidal, antibacterial, antibiotic, antitumour, antifungal, antimicrobial activity, and anti-inflammatory and analgesic. In addition, isoxazoline derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis.[9,10] Consequently, much attention has been paid to the development of new methodologies for their preparation. Several methods have been reported for the synthesis of isoxazoline derivatives. The synthetic routes for the preparation of isoxazoline derivatives mainly are cyclization reaction of chalcones,[11–14] 1,3-dipolar cycloaddition of oximes to alkenes,[15,16]

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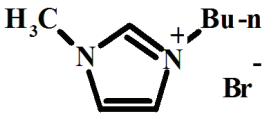
direct transformation of 3-arylpropargyl hydroxylamines hydrochlorides,[17] reaction of alkenes or alkynes with ketones,[18] 1,3-dipolar cycloaddition of nitrile oxides to vinylic compounds[19] and cyclization of *O*-propargylic hydroxylamines.[20]

In accordance with the significance of the application these compounds, a mild and efficient route to the synthesis of isoxazoline derivatives in ionic liquid media is reported herein.

In the past decade, ionic liquids have received substantial attention in organic synthesis because of their environmentally benign nature, high polarity, and good thermal stability. Often shorter reaction times, high yields, cleaner reaction products and high selectivity are obtained from ionic-liquid reaction media.[21,22] Ionic liquids (ILs) have attracted increasing interest recently in the context of green organic synthesis. Although ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of non-volatility, non-inflammability, negligible vapor pressure, reusability and high thermal stability, today they have marched far beyond this boundary, showing their significant role in controlling reactions as solvents or catalysts.[23,24]

There are many reports concerning the applications of ionic liquids as solvents and catalysts in organic reactions, such as Friedel–Crafts reaction,[25] Diels–Alder reaction,[26,27] Biginelli reaction,[28] Beckmann rearrangement,[29] Michael reaction,[30] reduction of aldehydes,[31] electophilic substitution of aromatic rings,[32,33] 1,3-dipolar cycloaddition[34,35] and other reactions.[36–38]

In the continuation of ongoing studies on the application of IL media, it was found that dialkylimidazolium halide derivatives have many advantages over conventional solvents.[39–42] These reagents are safe, easy to handle, environmentally benign and present fewer disposal problems. Therefore, butylmethylimidazolium bromide ([bmim]Br) (Scheme 1) could be an excellent candidate for employment in organic reactions. The advantage of these methods over conventional methods is that they provide greater selectivity, enhanced reaction rates, cleaner products and manipulative simplicity. According to the development of methods that consist of using environmentally friendly reagents and in continuation of our ongoing program to develop environmentally benign methods, the use of an ionic liquid in the synthesis of isoxazoline derivatives in a mild, facile and clean manner is reported herein.



Scheme 1. 1-Butyl-3-methylimidazolium bromide ([bmim]Br).

EXPERIMENTAL

Butylmethylimidazolium bromide ([bmim]Br) was purchased from Fluka. All melting points are uncorrected and were determined in a capillary tube using a Boetius melting point

microscope. The Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Magna 550 spectrometer (KBr). The ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker 400 MHz spectrometer in $CDCl_3$ as solvent using tetramethylsilane (TMS) as an internal standard. All reactions were monitored and checked by thin layer chromatography (TLC) using hexane/ /ethyl acetate (8:2) and the spots were examined using a UV lamp. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. The mass spectra were recorded on a Joel D-30 instrument at an ionization potential of 70 eV.

*General procedures for the synthesis of chalcones **1a–j***

Chalcone derivatives have been prepared by condensation of various aromatic aldehydes and acetophenones in alkaline ethanol according to the procedure reported by Nielsen *et al*.[43]

To a mixture of NaOH (2.5 g) in 20 ml water and 15 ml EtOH, was added 0.050 mol of the required acetophenone derivative and the solution was stirred at 0–5 °C for 10 min, then 0.050 mol of the required aromatic aldehyde was added and the reaction mixture was refluxed for an appropriate time. After completion of reaction, as indicated by TLC using hexane/ethyl acetate (7:3) the residue was filtered, washed with water and recrystallyzed from ethanol.

*Typical procedures for the synthesis of isoxazolines **3a–j***

Conventional heating. Hydroxylamine hydrochloride (0.010 mol) was dissolved in water (5 ml) and added to a solution of chalcone (0.01 mol) in pyridine (10 ml). The reaction mixture was refluxed (magnetic stirring) on oil bath for 3 h. After completion of the reaction, observed by TLC using hexane/ethyl acetate (8:2), the mixture was cooled to room temperature, poured into ice-cold water and then acidified with dilute acetic acid. The obtained solid was filtered, washed with water and recrystallyzed from ethanol.

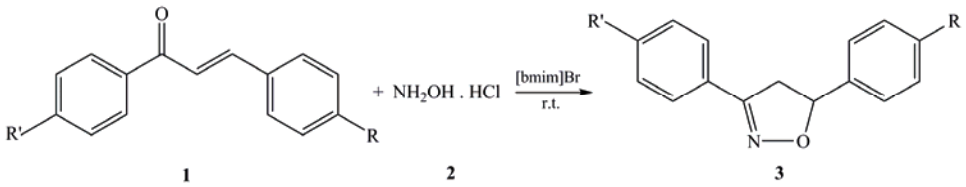
[Bmim]Br method. A mixture of chalcone (0.010 mol), hydroxylamine hydrochloride (0.010 mol) and [bmim]Br (0.76 g, 0.0035 mol) was stirred at room temperature for the appropriate period After completion of the reaction, as indicated by TLC using hexane/ethyl acetate (8:2), the reaction mixture was extracted with diethyl ether (3×10 ml). The organic layer was evaporated under reduced pressure and the solid residue was recrystallyzed from ethanol. The immiscible ionic liquid phase was recovered and heated for 3 h under vacuum for further use. The best results were obtained with a molar ratio of 1:1:0.35 of chalcone, hydroxylamine hydrochloride and [bmim]Br.

Data of synthesized compounds are are given in Supplementary material.

RESULTS AND DISCUSSION

In this research, the ring closure reaction of chalcone **1** and hydroxylamine hydrochloride **2** occurred under I) conventional and II) in the presence of [bmim]Br to afford the isoxazoline derivatives **3** (Scheme 2). The reactions were performed using α,β-unsaturated carbonyl compounds with diverse substituents. The results of the experiments are summarized in Table I.

A possible mechanism for this reaction, proposed based on our experimental results together with some literature data for the cyclization reaction of chalcone, is that it is realized in two steps; first nucleophilic attack of the carbonyl group by the NH_2 moiety occurs, which is followed by oxime formation and then intramolecular cyclization leads to the five-membered ring products.[12,13]



Scheme 2. Preparation of isoxazolines **3** in [bmim]Br.

TABLE I. One-pot synthesis of substituted isoxazolines catalyzed by ([bmim]Br)

Entry	R	R'	Product	M.p., °C	
				Found	Reported
1	H	H	**3a**	150–152	151–152[11]
2	CH_3	H	**3b**	167–168	168[11]
3	Cl	H	**3c**	174–175	175[11]
4	OCH_3	H	**3d**	149–150	148–151[12]
5	NO_2	Br	**3e**	150–151	150–151[15]
6	OH	H	**3f**	149–150	–[a]
7	OH	CH_3	**3g**	140–142	–[a]
8	NO_2	CH_3	**3h**	121–123	122–123[15]
9	Br	CH_3	**3i**	142–143	142–143[15]
10	OCH_3	Br	**3j**	168–170	–[a]

[a]Compounds **3f**, **3g** and **3j** are new products

The one-pot condensation of *α*,*β*-unsaturated carbonyl compounds and hydroxylamine hydrochloride proceeded in the presence of the ionic liquid smoothly to give the corresponding products in high yields and shorter reaction times in comparison to thermal heating method; the results are summarized in Table II. It was found that [bmim]Br is a fairly good catalytic medium for this reaction. Compared with traditional catalysts, such as AcOH, KOH and NaOH, [bmim]Br not only gives higher yields but also takes much less time and can be easily recycled. Compared with traditional solvents, ionic liquids can be easily reused.

TABLE II. Comparison of the two methods for the synthesis of 3,5-diaryl-2-isoxazolines

Product	Conventional conditions		Stirred in [bmim]Br	
	Time, h	Yield, %	Time, min	Yield, %
3a	3.5	35	52	63
3b	3.5	45	50	70
3c	3	50	48	78
3d	3	52	46	80
3e	3	60	45	87
3f	3	60	44	82
3g	3	55	52	75
3h	3	60	42	84
3i	3	52	44	82
3j	3	50	45	80

As mentioned earlier, one of the goals in the use of ionic liquids is to identify and exploit the advantages these compounds can offer over conventional organic solvents besides their greener nature. It has been documented that, compared with classical organic solvents, reactions carried out in ionic liquids often offer enhanced reactivity, better yields and simpler operational process. These advantages were confirmed in the present paper for the synthesis of 3,5-diaryl-2--isoxazoline. The obtained results can be explained by the better catalytic and coordinative properties[44,45] of this kind of ionic liquids in comparison to other methods.

CONCLUSIONS

In conclusion, the ionic liquid promoted one-pot annulation reactions of chalcones and hydroxylamine hydrochloride and was proved an efficient medium for the synthesis of isoxazoline derivatives. Compared with conventional organic solvents, the use of [bmim]Br had several advantages, *i.e.*, high yields, mild conditions and simpler procedure in shorter reaction times. In addition, the ionic liquid used can be easily recovered and effectively reused at least 5 times more without any significant loss in efficiency.

SUPPLEMENTARY MATERIAL

Spectral data of the compounds are available electronically from http:// //www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

СИНТЕЗА НОВИХ ДЕРИВАТА 3,5-ДИАРИЛ-2-ИЗОКСАЗОЛИНА У ЈОНСКИМ ТЕЧНОСТИМА

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Биолошки активни деривати изоксазолина синтетисани су у одличном приносу, у присуству бутилметилимидазолијум-бромида као растварача и катализатора. Производи су добијени реакцијом циклизације халкона и хидроксиламин-хидрохлорида. Производи су лако раздвојени, а катализатор је могуће одвојити и поновно користити. Описани поступак је кратак и омогућава да се избегне употреба опасних и скупих реагенаса и растварача.

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REFERENCES

1. R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **2** (1963) 565
2. P. Caramella, P. Grunanger, *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, Wiley, New York, USA, 1984
3. V. M. Barot, *Oriental J. Chem.* **16** (2000) 177

4. M. D. Ankhiwala, M. V. Hathi, *J. Indian Chem. Soc.* **71 (**1994) 587
5. C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananhan, V. S. Bhadti, *J. Heterocycl. Chem.* **18** (1981) 43
6. B. L. Varma, *Indian. J. Heterocycl. Chem.* **13** (2003) 111
7. R. P. Tangallapally, S. D. Rakesh, N. Budha, B. Meibohm, *Bioorg. Med. Chem. Lett*. **17 (**2007) 6638
8. A. G. Habeeb, P. N. Praveen, R. E. Knaus, *J. Med. Chem.* **44** (2001) 2921
9. Y. V. Tomilovi, G. P. Okonnishnikova, E. V. Shulishov, O. M. Nefedov, *Russ. Chem. Bull.* **44** (1995) 2114
10. E. I. Klimova, M. Marcos, T. B. Klimova, A. T. Cecilio, A. T. Ruben, R. R. Lena, *J. Organomet. Chem.* **106** (1999) 585
11. M. Venugopal, P. T. Perumal, *Proc. Indian Acad. Sci. (Chem. Sci.)*. **105** (1993) 19
12. M. Kidwai, P. Misra, *Synth. Commun*. **29** (1999) 3237
13. A. Voskienė, V. Mickevičius, *Chem. Heterocycl. Compd*. **45** (2009) 1485
14. T. Shah, V. Desai, *J. Serb. Chem. Soc*. **72** (2007) 443
15. A. Tavares, O. M. S. Ritter, U. B. Vasconcelos, B. C. Arruda, A. Schrader, P. H. Schneider, A. A. Merlo, *Liquid Cryst*. **37** (2010) 159
16. R. Maurya, A. Ahmad, P. Gupta, K. Chand, M. Kumar, P. Rawat, N. Rasheed, G. Palit, *Med. Chem. Res*. **20** (2011) 139
17. L. Pennicott, S. Lindell, *Synlett* **3** (2006) 463
18. K. I. Itoh, H. Sakamaki, N. Nakazato, A. Horiuchi, E. Horn, C. A. Horiuchi, *Synthesis* **20** (2005) 3541
19. I. N. N. Namboothiri, N. Rastogi, *Top. Heterocycl. Chem.* **12** (2008) 1
20. D. W. Knight, A. J. Proctor, J. M. Clough, *Synlett* **4** (2010) 628
21. H. Olivier-Bourbigou, L. Magna, *J. Mol. Catal*. **419** (2002) 182
22. D. Zhao, M. Wu, Y. Kou, E. Min, *Catal. Today* **74** (2002) 157
23. P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH Verlag, Stuttgart, Germany, 2002
24. A. P. M. Martins, P. F. Clarissa, N. M. Dayse, N. Zanatta, G. H. Bonacorso, *Chem. Rev*. **108** (2008) 2015
25. A. Stark, B. L. MacLean, R. D. Singer, *J. Chem. Soc., Dalton Trans. 1* (1999) 63
26. T. Fischer, A. Sethi, T. Welton, J. Woolf, *Tetrahedron Lett*. **40** (1999) 793
27. P. Ludley, N. Karodia, *Tetrahedron Lett*. **42** (2001) 2011
28. J. J. Peng, Y. Q. Deng, *Tetrahedron Lett.* **42** (2001) 5917
29. R. X. Ren, L. D. Zueva, W. Ou, *Tetrahedron Lett*. **42** (2001) 8441
30. B. C. Ranu, S. S. Dey, *Tetrahedron* **60** (2004) 4183
31. G. W. Kabalka, R. R. Malladi, *Chem. Commun*. **22** (2000) 2191
32. K. K. Laali, V. J. Gettwert, *J. Org. Chem*. **66** (2001) 35
33. F. Zulfiqar, T. Kitazume, *Green Chem*. **2** (2000) 296
34. J. F. Dubreuil, J. P. Bazureau, *Tetrahedron Lett*. **41** (2000) 7351
35. D. Conti, M. Rodriquez, A. Sega, M. Taddei, *Tetrahedron Lett*. **44** (2003) 5327
36. A. R. Hajipour, Z. Nasreesfahani, A. E. Ruoho, *Org. Prep. Proc. Int*. **40** (2008) 385
37. A. Zare, A. Hasaninejad, M. Shekouhy, A. R. M. Zare, *Org. Prep. Proc. Int.* **40** (2008) 457
38. A. R. Williams, A. J. Angel, K. L. French, D. R. Hurst, D. D. Beckman, C. F. Beam, *Synth. Commun*. **29** (1999) 1977
39. J. Safaei-Ghomi, A. R. Hajipour, *J. Chin. Chem. Soc*. **56** (2009) 416

40. J. Safaei-Ghomi, M. Taheri, M. A. Ghasemzadeh, *Org. Prep. Proc. Int.* **42** (2010) 485
41. J. Safaei-Ghomi, A. R. Hajipour, M. Esmaeili, *Dig. J. Nanomater. Bios.* **5** (2010) 865
42. J. Safaei-Ghomi, A. R. Hajipour, *Org. Prep. Proc. Int.* **43** (2011) 372
43. A. T. Nielsen, W. J. Houlihan, *Org. React.* **16** (1968) 1
44. Y. Chen, Y. Zu, Y. Fu, X. Zhang, P. Yu, G. Sun, T. Efferth, *Molecules* **15** (2010) 9486
45. S. Kantevari, M. V. Chary, A. P. Rudra Das, S. V. N. Vuppalapati, N. Lingaiah, *Catal. Commun.* **9** (2008) 1575.