

Green and mild protocol for hetero-Michael addition of sulfur and nitrogen nucleophiles in ionic liquid

Yogesh O. Sharma, Mariam S. Degani*

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, N. Parekh Marg, Matunga, Mumbai - 400019, India

Received 7 May 2007; received in revised form 10 July 2007; accepted 28 July 2007

Available online 8 August 2007

Abstract

2-Hydroxyethylammonium formate was used as cost-effective ionic liquid to develop a mild and environmentally friendly hetero-Michael reaction. The ionic liquid works both as reaction medium as well as catalyst and can be recycled efficiently without significant loss in activity. The reaction is applicable to various aromatic sulfur nucleophiles, secondary nitrogen nucleophiles and different activated olefins. © 2007 Elsevier B.V. All rights reserved.

Keywords: Hetero-Michael reaction; Nitrogen and sulfur nucleophiles; α,β -Unsaturated carbonyl and nitrile compounds; Ionic liquid

1. Introduction

Conjugate addition of nitrogen and sulfur nucleophiles to unsaturated carbonyl or nitrile compounds by Michael reaction is one of the most convenient methods for the construction of C–N and C–S bonds in organic synthesis. Various β -amino carbonyl compounds such as β -amino acids and their derivatives are important intermediates for many potent drugs or antibiotics like β -lactams and anticancer agents [1–5]. The reaction is particularly useful for sulfur nucleophiles such as thiols and substituted thiols where analogous Mannich or aldol reactions do not exist [6]. Conjugate addition of thiols to α,β -unsaturated compounds to form C–S bond is a key reaction in many organic processes including synthesis of biologically active calcium antagonist diltiazem [7–14].

Several alternative procedures for aza-Michael and thia-Michael addition have been reported over the past few years to overcome various disadvantages. These methods generally utilize metal catalysts such as $\text{Yb}(\text{OTf})_2$, InCl_3 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{Bi}(\text{NO}_3)_3$, $\text{Al}_2\text{O}_3/\text{KF}$, $\text{Cu}(\text{OTf})_2$, $\text{FeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{Co}(\text{OAc})_2$, LiClO_4 , SnCl_4 [15–24]. However, some metal catalysts require harsh conditions and excess of reagents. Few publications report the reaction in green solvents like water,

but some of them suffer from disadvantages like greater reaction times and require additives like quaternary ammonium salts [25], boric acid [26] and β -cyclodextrin [27]. The need for an environmentally benign, cheaper and mild protocol still exists.

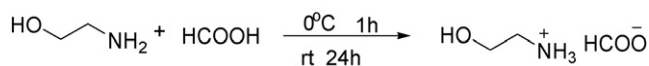
Currently, ionic liquids are extensively being used as green solvents for laboratory as well as industrial use due to their desirable properties such as good solvating ability, variable polarity, negligible vapor pressure, and ease of recyclability [28]. In spite of these advantages, there are few publications utilizing ionic liquids as green solvents for Michael reaction. Moreover the ionic liquids reported so far for Michael reaction are mostly limited to salts of 1,3-disubstituted imidazoles [8,25,29–31]. Recently Nazira Karodia and co-workers reported Michael reaction in ionic liquids incorporating phosphorus based cations [32].

While considering ionic liquids as reaction media and their use in industrial processes, one major concern is cost. The cost of the ionic liquid would be directly dependent on the price of the cations and anions that are used for their production [28]. Thus, the currently popular ionic liquids incorporating expensive cations such as alkyl methyl imidazolium and dialkyl imidazolium are likely to remain expensive. Similarly the anions that are frequently used in ionic liquids such as tetrafluoro borate and hexafluoro phosphate are also expensive. This indicates that there is a need to develop and explore simple and cost-effective ionic liquids.

In our research, focusing towards a mild, economical and green route to β -amino and β -thio carbonyl compounds, we proposed to make use of an easily synthesizable low cost ionic

* Corresponding author. Tel.: +91 22 24145616; fax: +91 22 24145614.

E-mail addresses: msdegani@udct.org, m.degani@yahoo.com (M.S. Degani).



Scheme 1. Synthesis of ionic liquid 2-hydroxyethylammonium formate.

liquid. For the first time, 2-hydroxyethylammonium formate was utilized to replace the imidazolium based ionic liquids for hetero-Michael reaction. This seemed to be a promising ionic liquid due to its high conductivity and powerful solvating ability. Its low melting point (-82°C) makes it an appropriate solvent for low temperature reactions [33]. It can easily be synthesized from commercially available low cost chemicals (Scheme 1).

2. Experimental

2.1. General

The ionic liquid was prepared by the previously reported method without any modifications (Scheme 1), and characterized by IR and ^1H NMR spectroscopy and physical constants like density (1.20 g/cm^3) and viscosity ($\eta = 105\text{ cP}$ at 25°C) [33]. All reactions were carried out with efficient stirring in a round bottom flask at room temperature, unless otherwise stated, and monitored by TLC. The reagents and solvents are commercially available. The products were purified using column chromatography wherever needed. Methyl vinyl ketone was distilled before use. All reactions with methyl vinyl ketone were carried out in nitrogen atmosphere. All synthesized compounds are known, and identified by spectroscopic data and by comparison with available standards. FTIR spectra were obtained on a Perkin-Elmer infrared spectrometer with KBr discs and ^1H NMR spectra were recorded on a 500 MHz Bruker AM500 spectrometer with TMS as internal standard.

2.2. Typical procedure for Michael addition of sulfur nucleophile

To 2 ml of 2-hydroxyethylammonium formate (the ionic liquid) in a 10 ml round bottom flask, thiophenol (1.0 g, 0.009 mol) was added and stirred. Ethyl acrylate (1.36 g, 0.013 mol) was then added to the solution dropwise over a period of 1 min and allowed to stir. During the reaction an exotherm was observed. The reaction was monitored by TLC. After the completion of reaction, reaction mixture was extracted thrice with diethyl ether and passed over anhydrous sodium sulphate. Evaporating the solvent under vacuum gave the product ethyl 3-(phenylthio) propanoate (1.78 g, 93%). The ionic liquid could be reused for further reaction by washing with solvent.

2.3. Typical procedure for Michael addition of nitrogen nucleophile

To 2 ml 2-hydroxyethylammonium formate (the ionic liquid) in a 10 ml round bottom flask, imidazole (1.0 g, 0.014 mol) was added and stirred. Ethyl acrylate (2.205 g, 0.022 mol) was then added to the solution drop wise over a period of 1 min and allowed to stir. The reaction was monitored by TLC. After

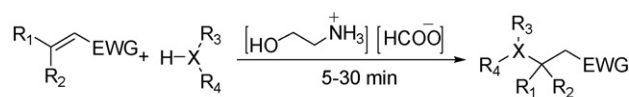
the completion of reaction, reaction mixture was extracted thrice with diethyl ether and passed over anhydrous sodium sulphate. Evaporating the solvent under vacuum gave ethyl 3-(1H-imidazole-1-yl) propanoate (2.074 g, 84%).

3. Results and discussions

Reactions of various structurally diverse sulfur and nitrogen nucleophiles were carried out with different activated olefins such as methyl vinyl ketone, ethyl acrylate, *n*-butyl acrylate, acrylonitrile and cyclic α,β -unsaturated ketone as shown in Scheme 2. The results are described in Table 1.

It was found that, in case of sulfur nucleophiles, thiophenol reacted readily with ethyl acrylate and acrylonitrile with shorter reaction times of 5 and 10 min, respectively, with excellent yields (entries 1, 2), whereas substituted thiophenol such as 4-methyl thiophenol required comparatively longer times (up to 30 min) for completing the reaction (entries 4, 5). Reactions of thiophenols with *n*-butyl acrylate and 2-cyclohexen-1-one required extended times such as 20–30 min to complete the reaction (entries 7–10). This indicates that the rate of reaction is dependent on nature of nucleophiles as well as α,β -unsaturated compounds. Thiophenol and 4-methylthiophenol also react with methyl vinyl ketone which is a typical Michael acceptor (entries 3, 6). However, no product formation was observed when the Michael reaction of aliphatic thiol such as phenylmethanethiol with ethyl acrylate was carried out even in presence TBAB as phase transfer catalyst at 80°C (entry 11). The results obtained for Michael reaction of aromatic thiols are comparable to those obtained for thia-Michael reaction in presence of ethyltri-*n*-butylphosphonium tosylate ionic liquid [32]. The time required for thia-Michael reaction in 2-hydroxyethylammonium formate is less as compared to reaction using 1-pentyl-3-methylimidazolium bromide as ionic liquid in which case the similar reaction required 1 to 1.5 h to complete [31].

Secondary nitrogen nucleophiles like imidazole, *N*-methyl piperazine, and piperidine were reacted with ethyl acrylate at room temperature with reaction times of 20–30 min to generate Michael adduct (entries 12, 14 and 18). Reactions of imidazole with acrylonitrile and typical Michael acceptor methyl vinyl ketone gave good to average yields of respective Michael adducts (entries 16, 17). A general trend was observed in which the reactivity decreased with increase in chain length of the acrylates. The long chain butyl acrylate reacted sluggishly with nitrogen nucleophiles at room temperature with lower conversions and required extended time of 8–10 h. In an attempt to accelerate the reaction of long chain acrylates, catalytic amount of tetra-



$\text{R}_1, \text{R}_2 = \text{H}, \text{Alkyl}$ $\text{X} = \text{N}, \text{S}$ When $\text{X} = \text{N}$; $\text{R}_3, \text{R}_4 = \text{Alkyl}$

When $\text{X} = \text{S}$; $\text{R}_3 = \text{aryl}$

Scheme 2. Hetero-Michael addition of sulfur and nitrogen nucleophiles to α,β -unsaturated compounds.

Table 1
Results for hetero Michael reaction of sulfur and nitrogen nucleophiles with activated olefins

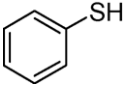
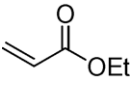
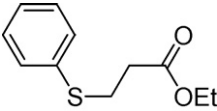
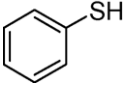

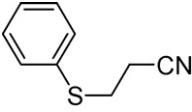
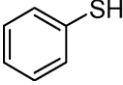

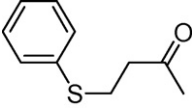
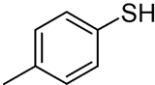
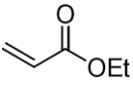
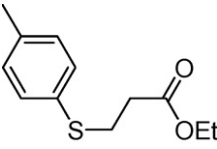
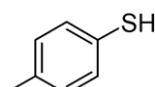

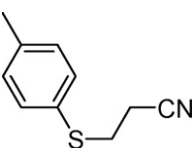
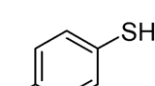

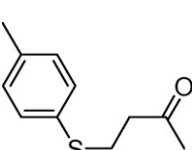
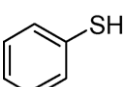
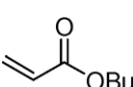
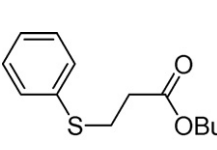
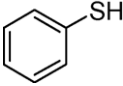
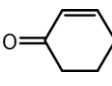
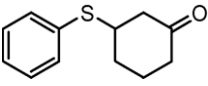
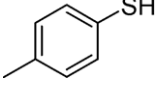
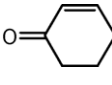
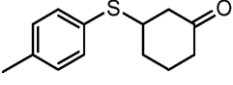
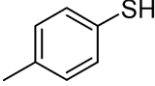
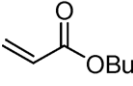
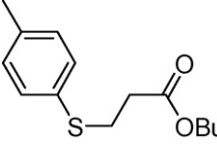
Entry	Nucleophile	Olefin ^a	Product	Time (min)	Isolated yield (%) ^b
1				5	93
2				10	90
3				25	82
4				25	87
5				30	84
6				25	77
7				20	88 ^c
8				20	92
9				30	87
10				30	85 ^c

Table 1 (Continued)

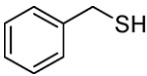
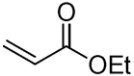
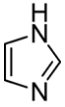
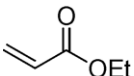
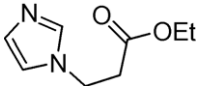
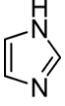
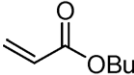
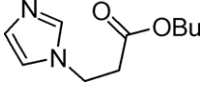
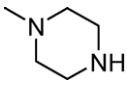
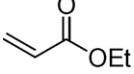
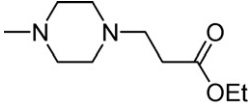
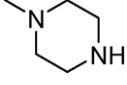
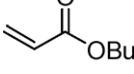
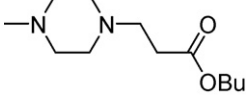
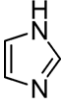
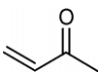
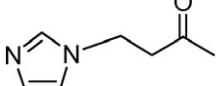
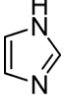

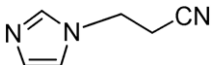

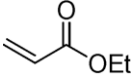
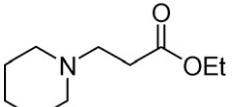

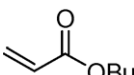
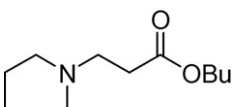
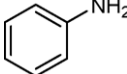
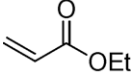
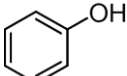
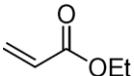

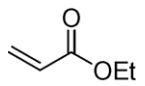
Entry	Nucleophile	Olefin ^a	Product	Time (min)	Isolated yield (%) ^b
11			No reaction ^c	180	–
12				25	84
13				30	87 ^c
14				25	90
15				15	86 ^c
16				30	75
17				30	72
18				20	90
19				25	85 ^c
20			No reaction ^c	180	–
21			No reaction ^c	180	–

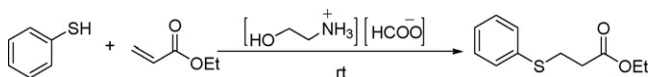
Table 1 (Continued)

Entry	Nucleophile	Olefin ^a	Product	Time (min)	Isolated yield (%) ^b
22			No reaction ^c	180	–

^a 1.5 eq. activated olefin used.

^b Yields based on quantity of nucleophile used.

^c Cat. TBAB was added. Reaction was carried out at 80 °C.



Scheme 3. Example for recyclability of ionic liquid for Michael addition of thiophenol and ethyl acrylate.

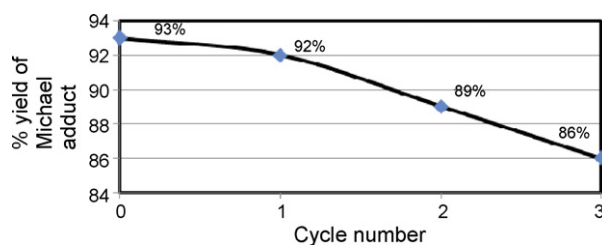


Fig. 1. Results for recyclability of ionic liquid for Michael addition of thiophenol and ethyl acrylate.

butylammonium bromide (TBAB) was added as phase transfer catalyst and reaction temperature was increased up to 80 °C. This significantly enhanced the rate of reaction of both nucleophiles with butyl acrylate (entries 7, 10, 13, 15 and 19). Michael reaction of phenol, aromatic amine (aniline) and aliphatic alcohol (ethanol) with ethyl acrylate were carried out at 80 °C in presence of TBAB as catalyst, but no product was formed even after 180 min (entries 20–22).

Isolation of the product was convenient and did not need aqueous workup. Extraction of product with a suitable solvent under efficient stirring and then evaporating solvent under vacuum resulted in isolation of the product. The ionic liquid was recovered by washing repeatedly with diethyl ether and reused without significant loss of activity. As reactions were performed on small scale, this led to about 10% decrease in ionic liquid per run, which was suitably compensated for. The reusability of ionic liquid was quantified by performing a set of experiments (Scheme 3) using thiophenol and ethyl acrylate. The ionic liquid was recovered and reutilized three times without addition of extra ionic liquid; the results are shown in Fig. 1.

4. Conclusion

A mild and green process was developed for hetero-Michael reaction of sulfur and nitrogen nucleophiles utilizing relatively novel and cost-effective ethanolamine based ionic liquid. The reactions proceeded within minutes in most cases. In case of

long chain acrylates which usually react sluggishly, faster reactions occurred when combination of ionic liquid and TBAB (as phase transfer catalyst) was used. Isolation of the product was simple and did not require aqueous workup. The reaction is compatible with various secondary nitrogen nucleophiles, aromatic sulfur nucleophiles and activated olefins; however it does not work in similar conditions with alcohols, aliphatic thiols and aromatic amines. The ionic liquid seems a promising reaction medium for various other organic reactions which are being investigated.

Acknowledgements

The financial support from WHO funded Technical Education Quality Improvement Program (TEQIP), Govt. of India, is acknowledged by the author Yogesh O. Sharma.

References

- [1] A. Graul, J. Castaner, *Drugs Future* 22 (1997) 956.
- [2] E. Juaristi, *Enantioselective Synthesis of β -Amino Acids*, John Wiley & Sons, New York, 1997.
- [3] N. Sewald, *Amino Acids* 11 (1996) 397.
- [4] G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* (1996) 117–128.
- [5] E. Juaristi, H. Lopez-Ruiz, *Curr. Med. Chem.* 6 (1999) 983–1004.
- [6] T.C. Wabnitz, J.B. Spencer, *Org. Lett.* 5 (2003) 2141–2144.
- [7] A.L. Fluharty, in: S. Patai (Ed.), *The Chemistry of the Thiol Group*, Part 2, John Wiley & Sons, London, 1974, pp. 589–668.
- [8] J.S. Yadav, B.V.S. Reddy, G. Baishya, *J. Org. Chem.* 68 (2003) 7098–7100.
- [9] J.H. Clark, *Chem. Rev.* 80 (1980) 429–452.
- [10] E. Fujita, Y.J. Nagao, *Bioorg. Chem.* 6 (1977) 287.
- [11] R. Budriesi, E. Carosati, A. Chiarini, B. Cosimelli, G. Cruciani, P. Ioan, D. Spinelli, R. Spisani, *J. Med. Chem.* 48 (2005) 2445–2456.
- [12] B.M. Trost, D.E. Keeley, *J. Org. Chem.* 40 (1975) 2013.
- [13] T. Shono, Y. Matsumura, S. Kashimura, K. Hatanaka, *J. Am. Chem. Soc.* 101 (1979) 4752–4753.
- [14] K. Nishimura, M. Ono, Y. Nagaoka, K. Tomioka, *J. Am. Chem. Soc.* 119 (1997) 12974–12975.
- [15] T.P. Loh, L.L. Wie, *Synlett* (1998) 975–976.
- [16] G. Bartoli, M. Bosco, E. Marcantoni, M. Petrini, L. Sambri, E. Torregiani, *J. Org. Chem.* 66 (2001) 9052–9055.
- [17] S. Matsubara, M. Yashioka, K. Utimoto, *Chem. Lett.* (1994) 827–828.
- [18] N. Srivastava, B.K. Banik, *J. Org. Chem.* 68 (6) (2003) 2109–2114.
- [19] T.C. Wabnitz, J.B. Spencer, *Tetrahedron Lett.* 43 (2002) 3891–3894.
- [20] L.-W. Xu, C.-G. Xia, *Tetrahedron Lett.* 45 (2004) 4507–4510.
- [21] G. Jenner, *Tetrahedron Lett.* 36 (1995) 233–236.
- [22] R. Varala, M.M. Alam, S.R. Adapa, *Synlett* (2003) 720–722.
- [23] N. Azizi, M.R. Saidi, *Tetrahedron* 60 (2004) 383–387.
- [24] L. Yang, L.-W. Xu, C.-G. Xia, *Tetrahedron Lett.* 46 (2005) 3279–3282.
- [25] L.-W. Xu, J.-W. Li, S.-L. Zhou, C.-G. Xia, *New J. Chem.* 28 (2004) 183–184.

- [26] M.K. Chaudhuri, S. Hussain, M.L. Kantam, B. Neelima, *Tetrahedron Lett.* 46 (2005) 8329–8331.
- [27] K. Surendra, N.S. Krishnaveni, R. Sridhar, K. Rama Rao, *Tetrahedron Lett.* 47 (2006) 2125–2127.
- [28] P. Wasserscheid, T. Welton, *Ionic Liquid in Synthesis*, Wiley-VCH, 2004.
- [29] J.S. Yadav, B.V.S. Reddy, A.K. Basak, A.V. Narsaiah, *Chem. Lett.* 32 (2003) 988–989.
- [30] M.L. Kantam, V. Neeraja, B. Kavita, B. Neelima, M.K. Chaudhuri, S. Hussain, *Adv. Synth. Catal.* 347 (2005) 763–766.
- [31] B.C. Ranu, S.S. Dey, *Tetrahedron* 60 (2004) 4183–4188.
- [32] N. Karodia, X. Liu, P. Ludley, D. Pletsas, G. Stevenson, *Tetrahedron* 62 (2006) 11039–11043.
- [33] N. Bicak, *J. Mol. Liq.* 116 (2005) 15–18.