JOC*Note*

Basic Ionic Liquid as Catalysis and Reaction Medium: A Novel and Green Protocol for the Markovnikov Addition of *N*-Heterocycles to Vinyl Esters, Using a Task-Specific Ionic Liquid, [bmIm]OH

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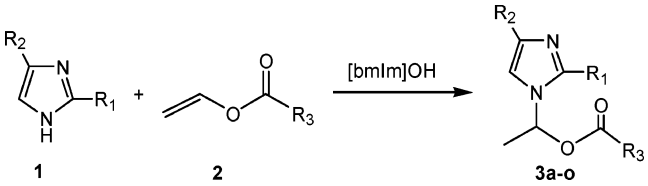
Received January 16, 2006



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A basic ionic liquid, 1-methyl-3-butylimidazolium hydroxide ([bmIm]OH), has been introduced as a catalyst and reaction medium for the Markovnikov addition of *N*-heterocycles to vinyl esters under mild conditions. The evidence for the role of this basic ionic liquid [bmIm]OH in promoting the Markovnikov addition has been given. On the basis of the evidence, a mechanism was postulated.

In recent times room temperature ionic liquids have attracted increasing interest in the area of green chemistry.[1] Although ionic liquid was initially introduced as an alternative green reaction medium,[1] today it has marched far beyond showing its significant role in controlling the reaction as catalyst.[2] Since the first successful use of ionic liquid, dialkylimidazolium chloroaluminate, as a catalyst in Friedel−Crafts acylations,[2a] a number of ionic liquids with unique properties have been developed and applied to catalyze many types of reactions. Some acidic ionic liquids, which exhibit a stable acidic anion, have been utilized to catalyze esterification reaction[3] and cleavages of ethers.[4] The neutral ionic liquids have also been successfully applied in the alkylation,[5] aldol condensation,[6] epoxidation,[7] and Michael addition.[8] Recently, basic ionic liquids have aroused unprecedented interest because they showed more advantages such as catalytic efficiency and recycling of the ionic liquid than the combination of inorganic base and ionic liquid for some base-catalyzed processes.[9] A basic ionic liquid [bmIm]OH has been successfully applied to catalyze the Michael addition of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles.[10] However, the catalytic mechanism of this basic ionic liquid was ambiguous and other catalytic reactions by this basic ionic liquid are worthy of exploration.

Markovnikov-type addition is among the most useful carbon−carbon, oxygen−carbon, or nitrogen−carbon bond-forming reactions. It is especially important to synthesize bioactive *N*-heterocycle derivatives with a nitrogen−carbon linkage, which could be achieved by an addition reaction. This reaction was traditionally promoted by harsh bases, strong acid, or high temperature,[11] which would lead to environmentally hazardous residues and unwanted byproducts. A lot of effort have been made in view of green synthesis. Recently, a new enzymatic strategy to perform Markovnikov addition was developed with use of penicillin G acylase as catalyst.[12] In this Note, we discovered that the basic ionic liquid [bmIm]OH[13] also could effectively promote this kind of addition reaction under mild conditions. Herein we employed this tailor-made ionic liquid in the Markovnikov addition of *N*-heterocycles to vinyl esters to synthesize a series of *N*-heterocycle derivatives, which are usually pharmacologically active and may be applied as potential

(1) (a) Wasserscheid, P. J.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772−3789. (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2083. (c) Blanchard, L. A.; Hancu, D.; Beckman, E. J.; Brennecke, J. F. *Nature* **1999**, *399*, 28−29. (d) Brown, R. A.; Pollet, P.; Mckoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254−1255. (e) Leitner, W. *Nature* **2003**, *423*, 930−931. (f) Yang, X. F.; Wang, M. W.; Li, C. J. *Org. Lett.* **2003**, *5*, 657−660. (g) Kumar, A.; Pawar, S. S. *J. Org. Chem.* **2004**, *69*, 1419−1420.

(2) (a) Boon, J. A.; Levinsky, J. A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480. (b) Sheldon, R. *Chem. Commun.* **2001**, 2399−2407. (c) Kim, Y. J.; Varma, R. S. *Tetrahedron Lett.* **2005**, *46*, 7447−7449. (d) Ranu, B. C.; Jana, R. *J. Org. Chem.* **2005**, *70*, 8621. (e) Zhu, A. L.; Jiang, T.; Wang, D.; Han, B. X.; Liu, L.; Huang, J.; Zhang, J. C.; Sun, D. H. *Green Chem.* **2005**, *7*, 514−517.

(3) (a) Gui, J. Z.; Cong, X. H.; Liu, D.; Zhang, X. T.; Hu, Z. D.; Sun, Z. L. *Catal. Commun.* **2004**, *5*, 473−477. (b) Joseph, T.; Sahoo, S.; Halligudi, S. B. *J. Mol. Catal. A: Chem.* **2005**, *234*, 107−110. (c) Zhu, H. P.; Yang, F.; Tang, J.; He, M. Y. *Green Chem.* **2003**, *5*, 39−39. (d) Fraga-Dubreuil, J.; Bourahla, K.; Rahmouni, M.; Bazureau, J. P.; Hamelin, J. *Catal. Commun.* **2002**, *3*, 185−190.

(4) (a) Driver, G.; Johnson, K. E. *Green Chem.* **2003**, *5*, 163−169. (b) Kemperman, G. J.; Roeters, T. A.; Hilberink, P. W. *Eur. J. Org. Chem.* **2003**, *9*, 1681−1686.

(5) (a) McNulty, J.; Cheekoori, S.; Nair, J. J.; Larichev, V.; Capretta, A.; Robertson, A. J. *Tetrehedron Lett.* **2005**, *46*, 3641−3644. (b) Jorapur, Y. R.; Lee, C. H.; Chi, D. Y. *Org. Lett.* **2005**, *7*, 1231−1234. (c) Shen, H. Y.; Judeh, Z. M. A.; Ching, C. B. *Tetrehedron Lett.* **2003**, *44*, 981−983. (d) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13 000−13001.

(6) Horikawa, M.; Busch-Peterson, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843−3846.

(7) Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1*, 1287−1290.

(8) (a) Yadav, J. S.; Reddy, B. V. S.; Baishya, G.*J. Org. Chem.* **2003**, *68*, 7098−7100. (b) Ranu, B. C.; Dey, S. S. *Tetrehedron* **2004**, 60, 4183−4188. (c) Xu, L. W.; Li, J. W.; Zhou, S. L.; Xia, C. G. *New J. Chem.* **2004**, *28*, 183−184. (d) Zhang, F. Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097−1100.

(9) (a) Formentin, P.; Garcia, H.; Leyva, A. *J. Mol. Catal. A*: *Chem.* **2004**, *214*, 137. (b) Chen, H.; Justes, D. R.; Cooks, R. G. *Org. Lett.* **2005**, *7*, 3949−3952.

(10) Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049−3052.

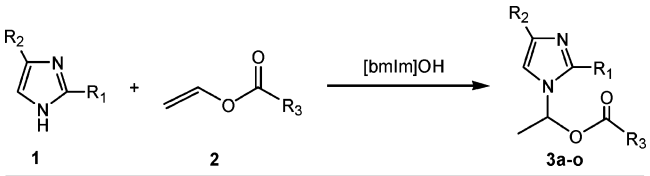
(11) (a) Attaryan, O. S.; Asratyan, G. V.; Darbinyan, E. G.; Matsoyan, S. G. *Zh. Org. Khim.* **1988**, *24*, 1339. (b) Belousov, A. M.; Gareev, G. A.; Kirillova, L. P.; Vereshchagin, L. I. *Zh. Org. Khim.* **1980**, *16*, 2622−2623. (c) Timokhin, B. V.; Golubin, A. I.; Vysotskaya, O. V.; Kron, V. A.; Oparina, L. A.; Gusarova, N. K.; Trofimov, B. A. *Chem. Heterocycl. Compd.* **2002**, *38*, 981−985.

(12) Wu, W. B.; Wang. N.; Xu, J. M.; Wu, Q.; Lin, X. F. *Chem. Commun.* **2005**, *18*, 2348−2350.

(13) For the preparation of 1-butyl-3-methylimidazolium hydroxide [bmIm]OH, see: (a) Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049−3052. (b) Mehnert, C. P.; Dispenziere, N. C.; Cook, R. A. *Chem. Commun.* **2002**, *15*, 1610.

10.1021/jo0600914 CCC: $33.50
Published on Web 04/13/2006

TABLE 1. Markovnikov Addition of Imidazoles to Vinyl Esters Promoted by [bmIm]OH[a]

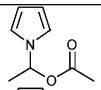
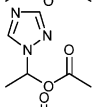
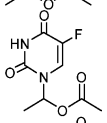
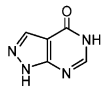
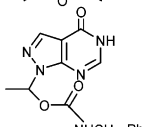
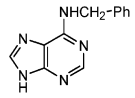
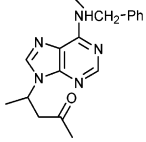


1 2 3a-o

entry	R_1	R_2	R_3	time (h)	yield[b] of **3** (%)
1	H	NO_2	CH_3	2	**3a** (93)
2	H	NO_2	$CH_3(CH_2)_2$	8	**3b** (82)
3	H	NO_2	$(CH_3)_2CH$	8	**3c** (75)
4	H	NO_2	$CH_3(CH_2)_3$	12	**3d** (79)
5	H	NO_2	$CH_3(CH_2)_4$	12	**3e** (76)
6[c]	H	NO_2	Ph	12	**3f** (81)
7	H	H	CH_3	4	**3g** (91)
8	H	H	$CH_3(CH_2)_2$	8	**3h** (80)
9	H	H	$CH_3(CH_2)_4$	12	**3i** (78)
10[c]	H	H	Ph	12	**3j** (84)
11	H	CH_3	CH_3	4	**3k** (88)
12	CH_3	H	CH_3	4	**3*l*** (73)
13	CH_3	NO_2	CH_3	12	**3m** (85)

[a] Reactions were carried out on 1.0 mmol scale of substrate with 4 equiv of vinyl ester in 1 mL of ionic liquid at 50 °C. [b] Isolated yields. [c] Reaction was performed at 100 °C.

TABLE 2. Markovnikov Addition of Other *N*-Heterocycles with Vinyl Acetate Promoted by [bmIm]OH[a]

entry	Substrate	Product	Time (h)	Yield[b] **5** (%)
1			8	**5a** (81)
2			4	**5b** (91)
3			4	**5c** (95)
4			24	**5d** (35)
5			6	**5e** (90)
6			24	**5f** (70)

[a] Reactions were carried out on 1.0 mmol scale of substrate with 4 equiv of vinyl ester in 1 mL of ionic liquid at 50 °C. [b] Isolated yields.

therapeutic alternatives.[14] On the basis of the experimental facts, we proposed a mechanism for the Markovnikov addition catalyzed by [bmIm]OH and designed some experiments to support the postulated mechanism.

In view of the observation, we first examined the Markovnikov addition of 4-nitroimidazole to vinyl acetate. When the reaction was carried out with 4 equiv of vinyl acetate at 50 °C in [bmIm]OH for 2 h, a single product was prepared in 93% isolated yield after flash chromatography. The structure of this compound was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HR-MS. We also monitored the formation of product by TLC and HPLC. It is worthwhile to mention that no byproduct was detected resulting from anti-Markovnikov addition, acylation reaction, hydrolytic reaction, or other reactions.

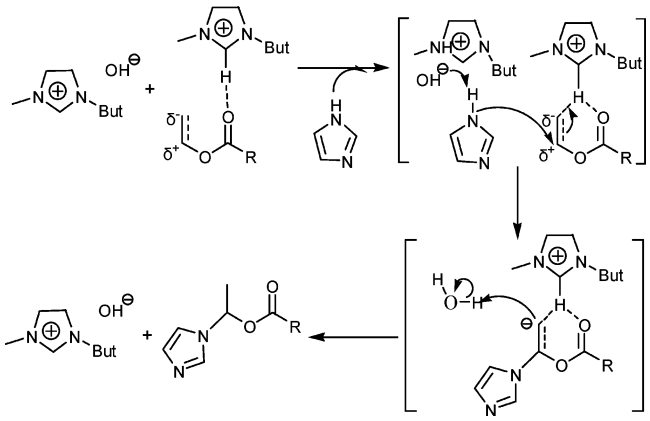
A variety of structurally diverse imidazoles and vinyl esters also underwent Markovnikov additions smoothly without any other catalyst to afford the corresponding imidazole derivatives in moderate to high yields. The results are summarized in Table 1. Generally, the Markovnikov addition of 4-nitroimidazole to a series of vinyl esters proceeded favorably. When the chain of the vinyl ester increased, the Markovnikov addition activity decreased dramatically (entries 1−5, Table 1). More sterically hindered vinyl ester provided relatively lower yield (entries 2 and 3, Table 1). The reactivity of vinyl benzoate is rather low compared to that of the fatty acid vinyl esters (entry 6, Table 1) because the aromatic group of the vinyl ester would decrease the basicity of the vinyl group. Accordingly, higher temperature (100 °C) was required to afford good yields. Comparable behavior was observed with imidazole as substrate (entries 7−10, Table 1). The four substituted imidazoles examined underwent Markovnikov addition with vinyl acetate favorably and all substituted imidazoles could be obtained in good yields in short reaction times (entries 1, 7, 11, 12, and 13, Table 1). The reactivity decreased by the following order: 4-nitroimidazole, imidazole, 4-methylimidazole, in agreement with their acidity. Sterically hindered imidazole underwent Markovnikov addition much more slowly (entry 12, Table 1).

Having obtained favorable results with imidazoles, we then examined the addition of other *N*-heterocycles to vinyl acetate. Other five-membered *N*-heterocycles such as pyrrole, pyrazole, and triazole also exhibited high Markovnikov addition activity. Among them, triazole reacted fastest due to its strong acidity (entry 3, Table 2). However, pyrrole showed relatively lower Markovnikov addition activity compared to pyrazole and triazole (entries 1−3, Table 2). More complicated *N*-heterocycles, such as pyrimidines and purines, also can be used as substrate to obtain the corresponding Markovnikov adducts. The similar reaction of fluorouracil with vinyl acetate provided a relatively low yield of Markovnikov adduct (35%) after 1 day, since the N−H of amide is much less acidic than that of amine (entry 4, Table 2). Although the reactivity of pyrimidine derivatives was low, excellent regioselective was achieved and only *N*-1 adducts were prepared (also monitored by TLC and HPLC). The Markovnikov addition of allopurinol and 6-benzylaminopurine also proceeded smoothly to give Markovnikov adducts at the *N*-9 position in moderate to high yields (entries 5 and 6, Table 2).

The ionic liquid remained intact (^{1}H NMR) and was used for subsequent runs without any difficulty. It has been observed that the Markovnikov addition of 4-nitroimidazole to vinyl acetate did not proceed in some molecular solvents such as THF, DMF, and DMSO. Thus the ionic liquid [bmIm]OH played the role of catalyst during the reaction process, as well as reaction medium. The Markovnikov addition of *N*-heterocycles to vinyl

(14) (a) Geen, G. R.; Kincey, P. M.; Choudary, B. M. *Tetrehedron Lett.* **1992**, *33*, 4609−4612. (b) Kato, K.; Ohkawa, S.; Terec, S.; Terashita, Z.; Nishikawa, K. *J. Med. Chem.* **1985**, *28*, 287−294. (c) Butters, M.; Ebbs, J.; Green, S. P.; MacRae, J.; Morland, M. C.; Murtiashaw, C. W.; Pettman, A. J. *Org. Process Res. Dev.* **2001**, *5*, 28−36. (d) Bando. T.; Jida, H.; Tao, Z. F.; Narita, A.; Fukuda, N.; Yamon, T.; Sugiyama, H. *Chem. Biol.* **2003**, *10*, 751−758. (e) Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M.; Iwai, N.; Hiyama, Y.; Suzuki, K.; Ito, H.; Terauchi, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J. *J. Med. Chem.* **2004**, *47*, 3693−3696.

SCHEME 1. Proposed Mechanism for the Markovnikov Addition Promoted by [bmIm]OH



esters proceeded smoothly to obtain corresponding adducts. However, none of the products were observed for the Markovnikov addition of *N*-heterocycles to vinyl ethers. This indicated that the carboxyl group in vinyl ester was considerably significant in the addition reaction. With all these results in hand, we proposed a mechanism for the Markovnikov addition reaction promoted by [bmIm]OH (Scheme 1). Owing to the electron-withdrawing effect of the carboxyl group, the α-carbon of the vinyl group carries partial positive charge. When the substrate was added, hydroxyl anion deprived the *N*-proton and the nucleophile simultaneously adds to the partial positively charged α-C position. The resulting negative charge at the *β*-C carbon could be stabilized by C2−H of [bmIm]OH. Finally, the H_2O formed would deliver the proton to obtain the Markovnikov adduct.

The evidence from ^{13}C NMR spectroscopy also supported the proposed mechanism. Imidazole and vinyl butyrate were used as a representative example. Comparing the ^{13}C NMR spectra ($CDCl_3$) of imidazole (neat) with a mixture of imidazole and 1 equiv of [bmIm]OH, it could be observed that there is an upfield shift of C2 (0.27 ppm) and C4 (0.55 ppm) of imidazole in the mixture, indicating the deprivation of the *N*-proton of imidazole by the hydroxyl anion of [bmIm]OH. We also compared the ^{13}C NMR spectra ($CDCl_3$) of butyrate (neat) with a mixture of butyrate and 1 equiv of [bmIm]OH to verify the interaction of C2−H and vinyl ester. An upfield shift of 0.13 ppm for the carbonyl carbon was found. Repeating the above experiment with ionic liquid [bmIm]BF_4, a 0.04 ppm downfield shift was observed. The results indicated the existence of hydrogen bond of the imidazolium cation with the vinyl ester as shown in Scheme 1. The 0.13 ppm upfield shift for the carbonyl carbon probably resulted from the coordination effect of the hydroxide anion with the carbonyl carbon of the vinyl butyrate. In fact, the chemical shift of the C-2 proton of [bmIm]-OH is 10.24 ppm, which could form a hydrogen bond as in Scheme 1. Much literature has verified the existence of the hydrogen bond on the C-2 proton by some methods such as NMR, IR, and quantum calculation.[15] Our ^{13}C NMR data also demonstrated the existence of the hydrogen bond. Therefore, the proton of the C2 position of the ionic liquid [bmIm]OH interacted with the carbonyl group and then first activated the α-C partially.

(15) (a) Aggarwal. A.; Lancaster, N. L.; Sethi, A. R.; Welton, T. *Green Chem.* **2002**, *4*, 517. (b) Ross, J.; Xiao, J. L. *Chem. Eur. J.* **2003**, *9*, 4900−4906. (c) Huang, J. F.; Chen, P. Y.; Sun, I. W.; Wang, S. P. *Inorg. Chim. Acta* **2001**, *320*, 7−11.

To trace the transfer process of C2−H, [2-D]-imidazolium ionic liquid was also synthesized. However, hydroxide anion was also deuterated because the hydrogen of the hydroxide anion was more active. The deuterated ionic liquid was used to catalyze the Markovnikov addition of 4-nitroimidazole and vinyl acetate. The corresponding Markovnikov adduct **3a** was isolated and characterized by ^1H NMR spectroscopy and ESI-MS. The ^1H NMR and ESI-MS figures were showed in the Supporting Information. The proton number at *β*-C was about 2.6 according to the ^1H NMR data, indicating that the Markovnikov adduct was partially deuterated and the ratio of **3a** and deuterated **3a** was about 6:4. ESI-MS data also demonstrated that the Markovnikov adduct was the mixture of **3a** and deuterated **3a**. According to the proposed mechanism, the hydroxide anion first deprived the *N*-proton to form HDO. The nucleophilic anion was added to the partial positive charged α-C position. The resulting negative charge at the *β*-C carbon was stabilized by C2−H. Finally, HDO would deliver the proton to the *β*-C carbon. Considering the similar probability of H and D, the proton number at *β*-C was about 2.5. This was almost in accordance with the experimental result. Therefore, the proton of C2 just stabilized the negative charge at the *β*-C carbon as the proposed mechanism.

In conclusion, the present procedure with a basic ionic liquid [bmIm]OH provides an efficient and convenient protocol for Markovnikov addition of *N*-heterocycles to vinyl esters without the requirement of any other catalyst and organic solvent. This strategy is quite general and it works with a broad range of *N*-heterocycles as addition substrates, including five-membered *N*-heterocycles, pyrimidines, and purines. Furthermore, this method exhibits a simple and green procedure, mild conditions, and general applicability and avoids hazardous organic solvent and toxic catalysts. The catalytic mechanism was postulated and supported by experimental facts. More applications (forming C−O, C−S, and C−C bonds) of the Markovnikov addition reaction promoted by this new tailor-made task specific ionic liquid [bmIm]OH are in progress in our laboratories.

Experimental Section

Materials and General Methods. ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz in $CDCl_3$ or DMSO-d_6, respectively. Chemical shifts are reported in ppm (*δ*), relative to the internal standard of tetramethylsilane (TMS). All chemicals were obtained from commercial suppliers and used without further purification.

The ionic liquid remaining in the conical flask was further washed with ether, dried under vacuum at 90 °C for 2 h to eliminate any water trapped from moisture, and reused for subsequent reactions. This can be used for the reactions for up to five runs without any appreciable loss of efficiency. After five runs, about 50% fresh ionic liquid was added and the mixture was found to be good for several more reactions.

Acknowledgment. This investigation has enjoyed financial support from the Natural Science Foundation of China (No. 20572099).

Supporting Information Available: Experimental procedures, characterization data of all compounds, and the ^{13}C NMR spectroscopy for the mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0600914