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A novel and highly efficient protocol for Markovnikov's addition using ionic liquid as catalytic green solvent

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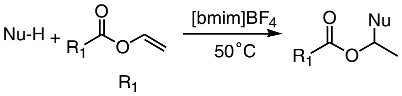
Abstract—A novel and highly efficient protocol for Markovnikov's addition using ionic liquid as a catalytic green solvent is described. The strategy is especially useful in the synthesis of N-heterocycle derivatives with biological activity. This reaction widens largely the applicability of ionic liquid in organic synthesis.

Markovnikov's addition is an effective method to form C–C, C–N, and C–S bonds and has wide applications in organic chemistry and pharmaceutical synthesis. This reaction was generally promoted by harsh bases, strong acid or high temperature,[1] which would lead to environmentally hazardous residues and undesirable by-products. Recently, a new enzymatic strategy to perform Mrakovnikov's addition was developed using penicillin G acylase as the catalyst.[2] Although the reaction was conducted under mild and neutral conditions, the polar solvent DMSO was used as reaction medium, which resulted in complex isolation and recovery procedures. Thus, the development of simple, more convenient and environmentally friendly approaches for Markovnikov's addition poses a great challenge to organic chemists.

During the past few years, ionic liquids[3,4] have been demonstrated as efficient and practical alternatives to organic solvents for many important organic transformations. Recently ionic liquids are attracting more attention due to their significant role in controlling the reaction as a catalyst. A variety of ionic liquids have been successfully applied in many types of reactions such as Friedel–Crafts acylations[5] and alkylations.[6] However, the relevant reports about addition reaction are relatively scarce. A molten cinchonidine-derived bifluoride salt was developed to catalyze enantioselective aldol addition reactions.[7] Recently, molten tetrabutylammonium bromide[8] and ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF$_6$) and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF$_4$)[9] have been demonstrated as an efficient catalyst for Michael addition in a solventless system. Considering these elegant discoveries of addition activity of ionic liquid, we envisage that other types of addition could also be catalyzed by ionic liquid. Herein we report for the first time the use of ionic liquid as a novel and recyclable reaction media, as well as an efficient catalyst for Markovnikov's addition of N-heterocyclic compounds to vinyl esters to afford corresponding N-heterocycle derivatives in high yields under mild and neutral conditions (Scheme 1). The Markovnikov's adducts obtained provided therapeutical and pharmaceutical alternatives.[10]

An initial experiment on the reaction of 4-nitroimidazole and vinyl acetate was carried out in different conditions,[11] which was shown in Table 1. The results indicated that ionic liquid containing a BF$_4^-$ anion exhibited excellent catalytic activity (entries 1 and 3). In contrast, no reaction was observed in the ionic liquid containing a PF$_6^-$ anion (entries 2 and 4). This was probably attributed to the poor solubility of 4-nitroimidazole in hydrophobic ionic liquid [bmim]PF$_6$. It is interesting to note that ionic liquids with longer cationic carbon chain exhibited higher Markovnikov's addition activity (entries 1 and 3). At room temperature, Markovnikov's



Scheme 1.

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Table 1. Markovnikov's addition of 4-nitroimidazole to vinyl acetate promoted by ionic liquid under various reaction conditions[a]

Entry	Ionic liquid	Vinyl acetate (equiv)	Time (h)	Yield (%)[b]
1	[bmim]BF_4	6	12	98
2	[bmim]PF_6	6	48	n.d.[c]
3	[emim]BF_4	6	48	96
4	[emim]PF_6	6	48	n.d.[c]
5	[bmim]BF_4	4	24	95
6	[bmim]BF_4	2	48	96
7[d]	[bmim]BF_4	6	96	97
8[e]	Solventless	—	96	n.d.[c]
9	DMSO	6	96	0.3

[a] All reactions were run on a 1.0 mmol scale of 4-nitroimidazole in 1 mL of ionic liquid at 50 °C.

[b] Isolated yields.

[c] n.d. = no product detected.

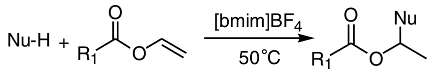
[d] Reaction was carried out at 25 °C.

[e] 1.0 mmol 4-nitroimidazole in 1.0 mL of vinyl acetate at 50 °C.

addition reaction could also proceed smoothly and good yield was obtained but required longer reaction time (entry 7). Systematically reducing the number of equivalents of vinyl acetate led to somewhat longer reaction times but still provided good isolated yield of Markovnikov's adduct (entries 1, 5, and 6).

Some blank experiments were also carried out to demonstrate the catalysis of [bmim]BF_4. When the reaction was performed in a solventless system, no product was detected after 4 days due to the poor solubility of 4-nitroimidazole in vinyl acetate (entry 8). When DMSO was used as solvent, only 0.3% of Markovnikov's adduct was formed even after 4 days (entry 9). The results showed that ionic liquid [bmim]BF_4 played the role of catalyst as well as a reaction medium during the reaction process.

Table 2. Markovnikov's addition of N-heterocycles to vinyl esters promoted by [bmim]BF_4[a]



1 2 3a-3o

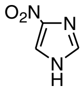
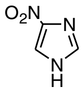
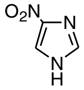
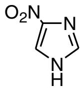
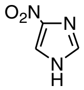
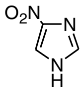
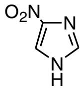
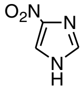
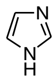
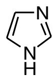
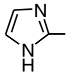
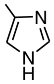
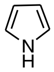
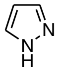
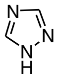
Entry	Nu–H	R_1	Time (h)	Yield **3** (%)[b]
1		CH_3	12	**3a** (98)
2		$CH_3(CH_2)_2$	48	**3b** (90)
3		$(CH_3)_2CH$	48	**3c** (86)
4		$CH_3(CH_2)_3$	72	**3d** (91)
5		$CH_3(CH_2)_6$	72	**3e** (89)
6		$CH_2{=}CHOOC(CH_2)_2$	36	**3f** (93)
7		$CH_2{=}CHOOC(CH_2)_4$	60	**3g** (94)
8[c]		Ph	48	**3h** (92)
9		CH_3	24	**3i** (97)
10		$CH_2{=}CHOOC(CH_2)_2$	48	**3j** (93)

Table 2 (*continued*)

Entry	Nu–H	R_1	Time (h)	Yield **3** (%)[b]
11		CH_3	72	**3k** (97)
12		CH_3	48	**3l** (96)
13		CH_3	72	**3m** (80)
14		CH_3	72	**3n** (86)
15		CH_3	48	**3o** (94)

[a] All reactions were run on a 1.0 mmol scale of N-heterocycles with 6.0 equiv of vinyl ester in 1 mL of ionic liquid at 50 °C.

[b] Yields refer to those of pure isolated products characterized by ^1H and ^{13}C NMR spectroscopic data.

[c] Reaction was carried out at 100 °C.

With optimal conditions in hand, we then examined the generality of these conditions to other substrates. The results are summarized in Table 2. All the reactions proceeded smoothly in $[bmim]BF_4$ without the need of any other catalyst. Interestingly, no by-product generated from anti-Markovnikov's addition, acylation or other reaction was detected by TLC and HPLC. All novel Markovnikov's adducts obtained were characterized by ^1H NMR, ^{13}C NMR, and HRMS and the results indicated that all adducts were N-1-alkylated.

The Markovnikov's addition of 4-nitroimidazole with vinyl acetate proceeded smoothly at 50 °C and almost quantitative yield was obtained after 12 h (entry 1). In addition to vinyl acetate, the reaction also took place with other fatty acid vinyl esters and aromatic acid vinyl esters (entries 2–8). The activity of vinyl esters was dependent on the structure of acid moiety. As the chain length of fatty acid vinyl ester increased, the reactivity decreased (entries 1, 2, 4, and 5). When the chain length was comparable, divinyl dicarboxylate proceeded faster than mono-acid vinyl ester (entries 2, 5, 6, and 7). The sterically hindered fatty acid vinyl ester exhibited slightly lower Markovnikov's addition activity (entries 2 and 3). The reactivity of vinyl benzoate was rather low in comparison with the fatty acid vinyl esters (entry 8) because the aromatic group of vinyl ester decreased the nucleophilicity of the double bond. Accordingly, higher temperature (100 °C) was required in order to afford good yield.

The structure of the N-heterocycles also affected the results of the Markovnikov's addition reaction. The four substituted imidazoles examined underwent Markovnikov's addition with vinyl acetate favorably and all substituted imidazole could be obtained in good yield (entries 1, 9, 11, and 12). The reactivity decreased by the following order, 4-nitroimidazole, imidazole, and 4-methyl-imidazole, in agreement with their nucleophilicity. The reaction activity dramatically decreased for sterically hindered imidazole (entry 11). Apart from imidazole derivatives, other N-heterocycles such as pyrrole, pyrazole, and triazole also exhibited high Markovnikov's addition activity, and triazole reacted fairly faster due to its strong nucleophilicity (entry 15). However, pyrrole showed relatively lower Markovnikov's addition activity compared to pyrazole and triazole (entries 13–15).

With the success of the above reactions, we continued our study by exploring the recyclability of the ionic liquid. The remaining ionic liquid $[bmim]BF_4$ was recovered and recycled in subsequent reactions five times without loss of activity (Fig. 1).

In summary, an efficient and environmentally friendly method for aza-Markovnikov's addition was developed using recyclable ionic liquid $[bmim]BF_4$ as the reaction

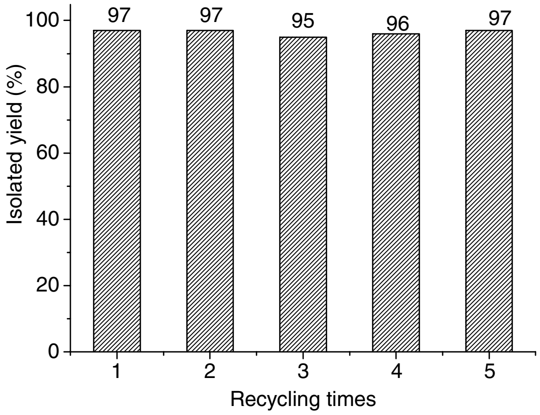


Figure 1. Recycling of $[bmim]BF_4$ in Markovnikov's addition of imidazole with vinyl acetate. Conditions: 1.0 mmol scale of imidazole and 6.0 equiv of vinyl acetate in 1 mL of $[bmim]BF_4$ at 50 °C for 24 h.

media. It is noteworthy that our procedure does not require any catalyst. This method is quite general and it works with a series of N-heterocycles and vinyl esters. More applications (forming C–O, C–S, and C–C bonds) of Markovnikov's addition reaction promoted by ionic liquid [bmim]BF$_4$ are in progress in our laboratories.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.001.

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11. Representative experimental procedure for the Markovnikov's addition of 4-nitroimidazole with vinyl acetate (**3a**). 4-Nitroimidazole (113 mg, 1 mmol) and vinyl acetate (512 mg, 6 mmol) were added to a 10 mL conical flask containing 1 mL [bmim]BF$_4$ and the mixture was shaken at 200 rpm and 50 °C for 12 h. The reaction mixture was extracted from the ionic liquid phase with ethyl ether (10.0 mL × 5). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel) to obtain 1-(1-(4-nitroimidazole))-ethyl acetate (196 mg) as a white solid. The ionic liquid left 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. 1-(1-(4-Nitroimidazole))-ethyl acetate: white solid, mp 82–83 °C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ, ppm): 8.68 (s, 1H), 8.11 (s, 1H), 6.77 (q, 1H, $J = 6.20$ Hz), 2.05 (s, 3H), 1.78 (d, 3H, $J = 6.20$ Hz). ^{13}C NMR (DMSO-d_6, 125 MHz, δ, ppm): 169.8, 147.8, 137.2, 120.1, 77.3, 21.1, 20.1. HRMS (ESI) m/z calcd for [M+Na] $C_7H_9N_3O_4Na$ 222.0485, found 222.0476.