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Henry and Knoevenagel Reactions Catalyzed by Methoxyl Propylamine Acetate Ionic Liquid[1]

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Abstract—Henry reactions and Knoevenagel reactions, used to prepare substituted olefins, have been limited by complex catalyst separation. In this article, methoxyl propylamine acetate ionic liquid was used as an environmentally benign catalyst for these reactions under solvent-free condition for the first time. This ionic liquid was shown to effectively catalyze Henry reactions and Knoevenagel reaction of active nitromethane compounds with various aldehydes. Yields from the catalyzed reactions were over 99% under solvent free condition. The process is highly effective, environmentally benign, and very selective. Furthermore, methoxyl propylamine acetate ionic liquid was conveniently separated with the products and easily recycled to catalyze Knoevenagel reaction again with excellent yields.

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1. INTRODUCTION

In recent years, ionic liquids (ILs) have attracted increasing interest and been successfully used in variety of catalytic reactions as environmentally benign solvents and catalysts due to their relatively low viscosities, low vapor pressure, and high thermal and chemical stability, etc. Much attention has currently been focused on the organic reactions with ILs as catalysts or solvents and many organic reactions were performed in ILs with high performances [1, 2].

Henry reaction, i.e., nitroaldol condensation, is one of the most convenient direct carbon-carbon bond forming reactions and widely used in synthetic applications. Due to the versatile chemistry of the nitro group, this reaction provides access to valuable structural motifs, such as 1,2-amino alcohols and α-hydroxy acids by reduction to amines or by the Nef reaction, respectively [3]. Jiang et al. first reported to utilize ILs to accelerate Henry reaction. They employed 1,1,3,3-tetramethyl guanidine based IL as catalyst and the system produced good yields with efficient recycling [4, 5].

Knoevenagel reactions of aldehydes with active methylene compounds have been commonly employed in the synthesis of specialty chemicals and chemical intermediates. The conventional Knoevenagel reactions under homogeneous conditions or in the presence of excess solvents were catalyzed by amines, ammonia salts, or catalysts containing both acid-base sites in a liquid phase system with pronounced solvent dependency [6, 7], which generated a large amount of undesired wastes. There is a need to develop an effective process for Knoevenagel reaction both economically and environmentally [8]. Using ILs as catalysts or solvents is very promising. For instance, Knoevenagel reactions proceeded efficiently in [Bmim]BF_4 or [Bmim]PF_6 [9], and was catalyzed by glycine with microwave heating in ILs [10]. To the best of our knowledge, there is no literature about using methoxyl propylamine acetate IL as catalyst for Henry reactions and Knoevenagel reactions.

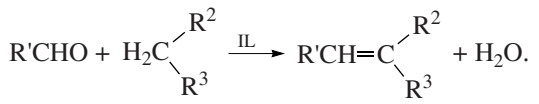
In this article, methoxyl propylamine acetate IL (Scheme 1) was first synthesized and used to catalyze Henry reactions and Knoevenagel reactions of active methane compound with various aldehydes at low tem-

$$CH_3–O–CH_2–CH_2–CH_2–NH_2 + CH_3COOH \longrightarrow CH_3–O–CH_2–CH_2–CH_2–NH_3^+–OOCCH_3$$

Scheme 1. Preparation of the methoxyl propylamine acetate IL.

$$R'CHO + CH_3–NO_2 \xrightarrow{IL} R'CH{=}CH–NO_2 + H_2O$$

Scheme 2. Henry reactions with methoxyl propylamine acetate IL as catalyst.



Scheme 3. Knoevenagel reactions with methoxyl propylamine acetate IL as catalyst.

[1] The article is published in the original.

Table 1. Henry reaction of benzaldehyde with nitromethane under different conditions

Entry	Molar ratio of benzaldehyde and nitromethane	Reaction temperature, °C	Reaction time, h	Amount of IL, mol	Yield, %
1	1 : 1	50	3	0.008	85.5
2	1 : 1.5	50	3	0.008	91.8
3	1 : 2	50	3	0.008	94.5
4	1 : 3	50	3	0.008	97.6
5	1 : 5	50	3	0.008	99.5
6	1 : 2	rt	48	0.008	81.6
7	1 : 2	40	8	0.008	91.2
8	1 : 2	50	3	0.008	94.5
9	1 : 2	60	3	0.008	77.6
10	1 : 2	50	1	0.008	51.1
11	1 : 2	50	2	0.008	78.8
12	1 : 2	50	3	0.008	94.5
13	1 : 2	50	4	0.008	95.4
14	1 : 2	50	4	0.001	60.7
15	1 : 2	50	4	0.003	92.4
16	1 : 2	50	4	0.005	94.3
17	1 : 2	50	4	0	0

Note: All reactions were run using 0.05 mol benzaldehyde.
The reaction of nitromethane and aldehyde without IL was run at 50°C.
rt— room temperature.

perature (Schemes 2 and 3). The reactions proceeded smoothly in the presence of catalytic amount of methoxyl propylamine acetate IL to afford the desired E-isomers of the corresponding alkenes with excellent yields. No organic solvent was used and therefore purification of final products was fairly simple. Furthermore, this IL was conveniently separated from the products and easily recycled for another round of Knoevenagel reaction. This will significantly reduce the effects of these reactions on environment and thus pave a way for the large scale applications.

2. EXPERIMENTAL

2.1. Preparation of Methoxyl Propylamine Acetate IL

Under vigorous stirring with magnetic stirring bar, 0.25 mol of acetic acid was added dropwise into a 250 ml three-neck flask with 0.2 mol of methoxyl propylamine for about 1 h at room temperature. The mixture was continuously stirred at 60°C for 8 h. The mixture was distilled under vacuum for 2 h to remove redundant acetic acid, and then cooled to room temperature. The transparent yellow methoxyl propylamine acetate IL was obtained. Conductivity of this IL is 2.5 mS/cm at 50°C and the weigh loss at 150°C.

Methoxyl propylamine acetate IL: ^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ 2.13 (t, 2H, J = 6.0 Hz), 2.473 (t, 2H, J = 5.0 Hz), 3.31 (s, 3H), 3.46 (s, 3H), 3.65 (t, 2H, J = 5.0 Hz), 8.25 (bs, 3H).

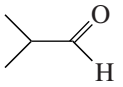
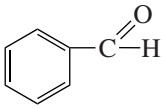
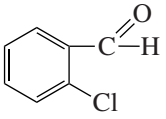
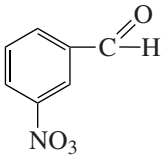
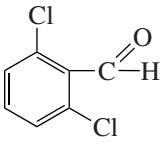
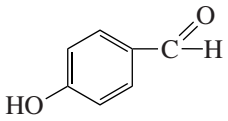
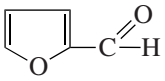
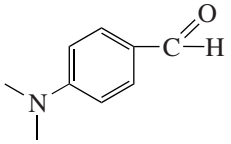
2.2. Henry Reactions

In a typical reaction, aldehyde, nitromethane and methoxyl propylamine acetate ionic liquid as catalyst were added successively into a 100 mL round flask equipped with a thermometer, a magnetic stirrer, and a N_2-inlet valve. The mixture was kept in a water bath under stirring at certain temperature. The reaction proceeded at the temperature ranging from 20 to 60°C for a period of time ranging from 1 to 12 h with vigorous stirring. After the reaction, the mixture was placed for a while for the formation of two phases. The IL phase was simply separated through separation funnel. The upper organic phase was decanted and monitored by GC-MS (Agilent 6890 Series/5973N). Conversion and selectivity were calculated according to the chromatograph peak areas given by chemstations.

2.3. Knoevenagel Reactions

Knoevenagel reactions (Scheme 3) of various aldehydes with active methylene compounds using methoxyl propylamine acetate IL as catalyst were investigated. Typical procedure of Knoevenagel reaction was similar to that of Henry reaction as described above except that nitromethane used in Henry reaction was replaced with an active methylene compound. After reaction, the product was isolated via filtration, washed with H_2O and dried under vacuum. The separated prod-

Table 2. Henry reactions of a variety of aldehydes and nitromethane under different conditions

Entry	Carbonyl compound	Molar ratio of Carbonyl compound and nitromethane	Temperature, °C	Reaction time, h	Yield, %
1		1 : 3	50	3	96.7
2		1 : 3	50	3	97.6
3		1 : 3	50	3	99.0
4		1 : 3	40	3	99.2
5		1 : 3	50	8	83.5
6		1 : 3	60	6	28.3
7		1 : 3	rt	8	81.3
8		1 : 10	50	6	79.2

Note: All reactions were run using 0.05 mol aldehyde and 0.008 mol IL.
rt— room temperature.

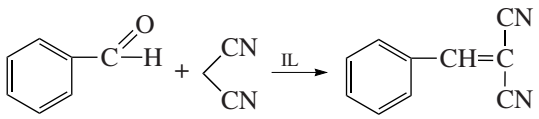
uct was then tested by ^{1}H NMR and results agreed well with that of authentic samples [10, 11]. Therefore further purification was not necessary.

3. RESULTS AND DISCUSSION

3.1. Henry Reactions

Henry reaction of benzaldehyde with nitromethane using methoxyl propylamine acetate IL as catalyst was first investigated. Effects of experimental conditions on Henry reaction were studied. Main factors included molar ratio between benzaldehyde and nitromethane, amount of IL, reaction time and reaction temperature. The experimental results are summarized in Table 1.

As shown in the Table 1, molar ratio between benzaldehyde and nitromethane, amount of IL, reaction time and reaction temperature all have significant effects on the reaction. Effect of different molar ratios between benzaldehyde and nitromethane was firstly examined. It could be seen that with the increase of the molar ratio from 1 : 1 to 1 : 5, reaction yield was significantly improved (entries 1–5, Table 1). Based on economic considerations, molar ratio of 1 : 2 was chosen to examine effects of other factors. As shown in the table (entries 6–8, Table 1), increasing reaction temperature accelerated the reaction dramatically. However, reaction yield decreased when reaction temperature was employed because this reaction is essentially exothermic (entry 9, Table 19). The highest yield was obtained



Scheme 4. Knoevenagel reaction of benzaldehyde and malononitrile.

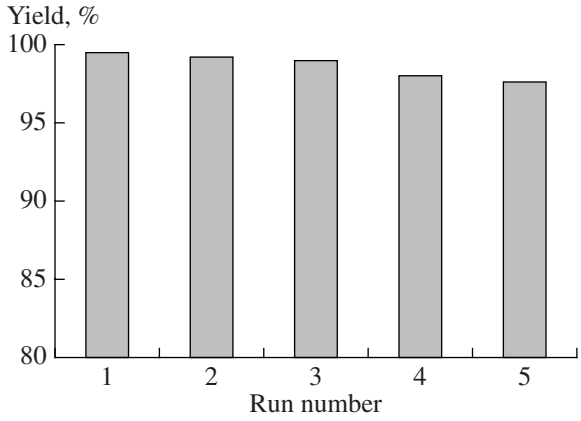
when the reaction proceeded at 50°C (entry 8, Table 1). As expected, increasing the reaction time (entries 10–13, Table 1) and the amount of IL (entries 13–17, Table 1) accelerated the reaction and led to higher yield. Under the chosen conditions, the reaction was almost complete after 3 h. Reactions of nitromethane and aldehyde at 50°C were conducted without IL to study the effect of IL. No product was detected after 4 h no matter what the molar ratio of nitromethane and aldehyde (entry 17, Table 1).

Secondly, IL was also used as catalyst for Henry reactions of nitromethane with a variety of aldehydes and the results are shown in Table 2.

The results demonstrated that reactions with aromatic and aliphatic aldehydes achieved excellent yields. The structural properties of reactants in Table 2 were carefully examined and it was determined that the nitroaldol condensation was strongly affected by electronic and steric factors. Aromatic aldehydes with electron withdrawing groups offered excellent yields and the reactions were almost complete with 97.8–99.2% yield in short time (entries 2–4, Table 2). However, lower yield was obtained when 2,6-dichlorobenzaldehyde was used as substrate due to steric hindrance (entry 5, Table 2). Lower yields were observed when electron donating groups are present in the reactants and more reaction time was required (entries 7, 8, Table 2). Moreover, very low yield was obtained with 4-hydroxybenzaldehyde as substrate due to both electro donating group and steric hindrance (entry 6, Table 2).

3.2. Knoevenagel Reactions

Knoevenagel reactions of different aldehydes and active methylene compounds were performed with



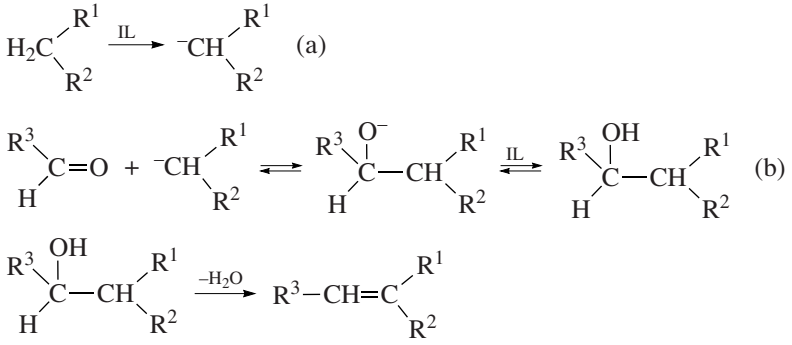
Recycling of methoxyl propylamine acetate IL as catalyst. All reactions were run using 0.05 mol benzaldehyde, 0.05 mol malononitrile, and 0.008 mol IL. Reaction temperature: rt. Reaction time: 0.05 h.

methoxyl propylamine acetate IL as catalyst and the results were shown in Table 3.

It is shown that aldehydes were converted into corresponding olefins with different yields without forming any main side products. All reactions investigated were almost complete in 0.05 to 8 h duration to produce corresponding electrophilic alkenes. Reaction of aromatic aldehydes and malononitrile offered good yields and the reaction was complete in short time (entries 1, 2, Table 3). because malononitrile easily produce stable C^- with strong electron withdrawing character. The low yield of 4-hydroxybenzaldehyde reaction was due to both electro donating property and steric hindrance (entry 7, Table 3). Similarly, aliphatic aldehydes also took more reaction time due to their lower reactivity (entry 9, Table 3).

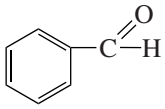
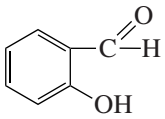
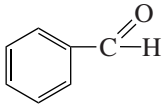
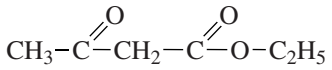
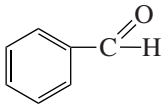
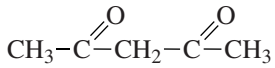
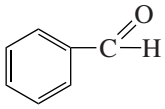
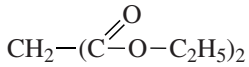
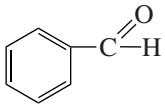
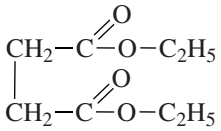
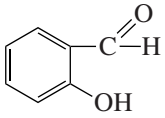
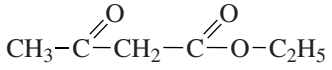
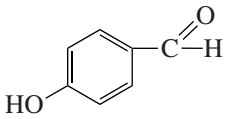
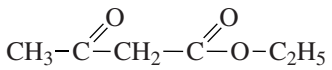
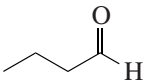
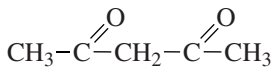
From previous experiments, best results were achieved for reaction between benzaldehyde and malononitrile, as shown in Scheme 4. Thus this reaction was chosen reaction to test the recyclability of IL. After reaction was complete, IL was separated and utilized for another batch of the same reaction.

Results from different runs were plotted in figure. Yields from different runs remained nearly the same up



Scheme 5. Mechanism of Henry and Knoevenagel reactions catalyzed by methoxyl propylamin acetate IL.

Table 3. Knoevenagel reactions of a variety of aldehydes and active methylene compounds under different conditions

Entry	Aldehyde	Active methylene compound	Reaction temperature, °C	Reaction time, h	IL, mol	Yield, %
1			rt	0.05	0.005	99.5
2			rt	0.05	0.005	99.3
3			50	4	0.008	95.3
4			50	4	0.008	91.2
5			50	8	0.008	92.4
6			50	8	0.008	89.7
7			50	8	0.008	51.2
8			rt	3	0.008	92.6
9			rt	8	0.008	84.2

Note: Isolated yields.
All reactions were run using 0.05 mol aldehyde and 0.05 mol active methylene compound.
rt— room temperature.

to five cycles. This indicated that methoxyl propylamine acetate IL was highly efficient and recyclable for Knoevenagel reaction (figure).

3.3. Discussion of the Mechanism

The possible mechanism of Henry reaction and Knoevenagel reaction catalyzed by methoxyl propylamine acetate IL was shown in Scheme 5.

As to the possible mechanism of this reaction, the synergism combination of two active sites (N^+ and COO^-) in the methoxyl propylamine acetate IL should be the key. It is shown that methoxyl propylamine acetate IL is not only as the acceptor of proton (Scheme 5a), but also as the donator of proton (Scheme 5b). They would to promote the formation of product. So, the reaction obtained good yield using methoxyl propylamine acetate IL as catalyst.

4. CONCLUSIONS

In summary, methoxyl propylamine acetate IL was successfully prepared and utilized as an effective catalyst for Henry reactions and Knoevenagel reactions under solvent-free conditions. The product was easily separated with high yields. Catalyst was readily recycled and reused to produce almost identical results. No organic solvent was used, resulting in eco-friendly process. This process will pave a way for large scale applications of Henry reaction and Knoevenagel reaction. Further applications for other reaction systems are currently under investigation.

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