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A simple, efficient, and green protocol for Knoevenagel condensation in a cost-effective ionic liquid 2-hydroxyethlammonium formate without a catalyst

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Abstract Knoevenagel condensation of aromatic aldehydes with active methylene compounds such as malononitrile, ethylcyanoacetate, and cyanoacetamide proceeded very smoothly in reusable and cheap ionic liquid 2-hydroxyethylammonium formate at room temperature in the absence of a catalyst. Compared to other reported ionic liquids, the ionic liquid 2-hydroxyethylammonium formate shows better potential in the applications on the industrial scale with its low cost and viscosity.

Keywords Knoevenagel condensation · Ionic liquid · Recyclability · Cost-effectiveness

Introduction

Knoevenagel condensation plays an important role in the formation of C=C bond reactions in of organic synthesis [1]. It has been used for the preparation of natural products [2], cosmetics, perfumes, several therapeutic drugs [3], and fine chemicals [4]. In general, Knoevenagel condensation is performed in organic solvents in the presence of the bases or acids, mainly including DMAP [5], *N*-methylpiperazine [6], potassium fluoride mixture [7], guanidines [8], $ZnCl_2$ [9], and $LaCl_3$ [10]. Recently, some novel heterogeneous catalysts, basic Si-MCM-41 [11], nitrogen-doped carbon materials [12], Ni-SiO_2-supported catalysts [13], and modified SBA-1 materials [14] have been exploited as catalysts for the Knoevenagel reaction. However, many of the above procedures have some or one of the drawbacks such as a long reaction time, harsh reaction conditions, stoichiometric amount of catalysts, or a large amount of organic solvent as the reaction medium.

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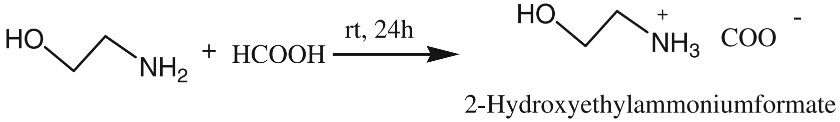
On the other hand, ionic liquids (ILs), possessing advantages such as undetectable vapor pressure and excellent reusability, have been investigated extensively in organic transformations as solvents or catalysts [15–17]. Thus, various ILs have been used as reaction solvents as well as catalysts for Knoevenagel condensation [18–21]. While considering the applications of ILs in industrial processes, one major concern is cost. Almost all reported ILs used in the Knoevenagel reaction are imidazolium ILs, which are relatively expensive. Thus, the need to explore simple and cost-effective ILs for Knoevenagel condensation still exists.

Ionic liquid 2-hydroxyethylammonium formate was simply prepared by neutralization reaction of 2-hydroxyethylamine and formic acid (Scheme 1) [22]. Compared to traditional imidazolium ILs, 2-hydroxyethylammonium formate has much lower cost, melting points, and viscosity [22]. Considering these advantages of the IL 2-hydroxyethylammonium formate, Degani and Sharma [23] utilized 2-hydroxyethylammonium formate as a reaction solvent as well as the catalyst in hetero-Michael addition, and satisfactory results were observed. With our continuous research in organic transformations using ILs as both catalyst and green solvent [24–27], herein we first reported a simple and environmentally benign methodology for the Knoevenagel condensation of aromatic aldehydes with active methylene compounds using 2-hydroxyethylammonium formate as reaction solvent without any catalyst.

Results and discussion

The reaction of benzaldehyde with ethyl cyanoacetate without any catalyst was selected as the model to establish the rational reaction conditions. As shown in Table 1, the reaction in organic solvents, acetonitrile, methanol, and toluene proceeded very slowly (entries 1–3). We then investigated the efficiency of IL 2-hydroxyethylammonium formate compared to the most commonly used ILs, [Bmim]BF_4 and [Bmim]PF_6 by the model condensation (entries 4–6). The results showed that the reaction in the absence of catalyst with the two imidazolium ILs as reaction solvents proceeded very slowly and the reaction could react smoothly in the presence of the novel IL 2-hydroxyethylammonium formate. The results summarized in Table 1 show that the IL 2-hydroxyethylammonium formate plays a dual role as both a catalyst and a solvent in the reaction. The volume of the IL was also tested with the same reaction as model (Table 1, entries 7–9). The suitable solvent amount is 2 mL. As a result, we adopted the optimal reaction conditions



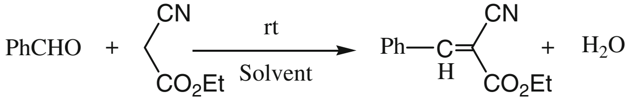
Scheme 1 Preparation of ionic liquid 2-hydroxyethylammonium formate

(aldehydes:1 mmol, active methylene compounds: 1 mmol, 2 mL 2-hydroxyethylammonium formate, rt) for further examinations.

With the optimal reaction system in hand, we then investigated the Knoevenagel condensation of various aromatic aldehydes with malononitrile, ethyl cyanoacetate, and cyanoacetamide. It can be observed from Table 2 that three active methylene ingredients could successfully react with various aromatic aldehydes and all products (3a–3o) obtained were *E*-geometry exclusively and no subsequent Michael adduct was detected. The effects of substituents at the aromatic ring on the Knoevenagel reaction were also studied, and the reaction time of electron-withdrawing group (such as nitro group) substituted aromatic aldehydes was shorter than that of electron-donating group (such as methoxyl, methyl, or 4-(*N,N*)-dimethyl group) substituted aromatic aldehydes (Table 2, entries 2–5, 14, 15). The hindrance of substituents such as chloro could retard the reaction and decreased the product yields (Table 2, entries 11–13). In addition, Knoevenagel condensation of hetero aromatic aldehydes such as 2-furaldehyde and 3-pyridinecarboxaldehyde with active methylene compounds also underwent smoothly at room temperature (Table 2, entries 7, 8).

Finally, in order to demonstrate the industrial applicability of this methodology, the Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate was carried out on a larger scale (Table 3). The reaction was completed in 3 h. An excellent yield of 92% for the condensational product was achieved. On the same scale, the recyclability of the catalytic system was investigated using the same reaction as model reaction. Upon the completion of the reaction, the product was isolated via filtration, washed with water, and then dried under vacuum without further separation, while the filtrate IL 2-hydroxyethylammonium formate was dried to

Table 1 Effects of various reaction solvents and their quantities on the Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate at room temperature

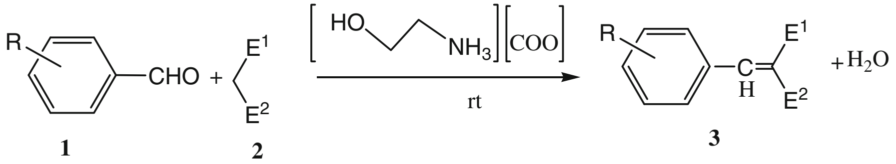


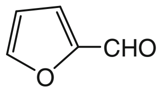
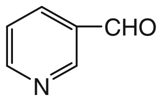
Entry	Solvents (mL)	Yields[a] (%)
1	Acetonitrile (2)	33
2	Methanol (2)	29
3	Toluene (2)	22
4	[Bmim]BF_4 (2)	9
6	[Bmim]PF_6 (2)	16
7	2-hydroxyethylammonium formate (2)	90
8	2-hydroxyethylammonium formate (5)	91
9	2-hydroxyethylammonium formate (1)	58

Reaction conditions: benzaldehyde (1.0 mmol), ethyl cyanoacetate (1.0 mmol), reaction time (3 h), rt

[a] Isolated yields of products

Table 2 Results of Knoevenagel condensation between various aromatic aldehydes and methylene active compounds at room temperature in ionic liquid 2-hydroxyethylammonium formate



Entry	R	E^1	E^2	Time (h)	Product	Yields[a] (%)
1	H	CN	CN	5	3a	88
2	4-Me	CN	CN	6	3b	94
3	4-MeO	CN	CN	5	3c	94
4	2-MeO	CN	CN	7	3d	90
5	4-NO_2	CN	CN	2	3e	88
6	4-(*N,N*)-dimethyl	CN	CN	8	3f	96
7		CN	CN	4	3g	93
8		CN	CN	4	3h	92
9	4-Me	CN	CO_2Et	8	3i	98
10	4-NO_2	CN	CO_2Et	4	3j	92
11	3,4-Dichloro	CN	CO_2Et	6	3k	82
12	2,4-Dichloro	CN	CO_2Et	8	3l	75
13	4-Chloro	CN	CO_2Et	6	3m	95
14	4-NO_2	CN	$CONH_2$	5	3n	90
15	4-MeO	CN	$CONH_2$	8	3o	91

Reaction conditions: aromatic aldehydes (1 mmol), active methylene compounds (1 mmol) stirred in ionic liquid (2 mL) 2-hydroxyethylammonium formate without a catalyst at room temperature

[a] Isolated yields of desired products

remove water at 60 °C under vacuum. The recovered IL was reused in subsequent reactions. As shown in Table 3, the IL 2-hydroxyethylammonium formate can be recycled five times without a considerable decrease of activity.

Table 3 Reuse of catalyst for Knoevenagel condensation between benzaldehyde (100 mmol) and ethyl cyanoacetate (100 mmol) in 200 mL ionic liquid 2-hydroxyethylammonium formate in the absence of a catalyst at room temperature within 3 h

Cycles	1	2	3	4	5
Product[a] (%)	92	89	92	89	86

[a] Isolated yields

Conclusions

The use of IL 2-hydroxyethylammonium formate as a solvent without a catalyst allows Knoevenagel condensation of aromatic aldehydes with active methylene compounds to be performed both simply and highly efficiently. Compared to the reported methods, the present protocol has many obvious advantages, including low cost of IL, no need for the use of a catalyst, ease of work-up, high product yields, as well as good recyclability of IL 2-hydroxyethylammonium formate.

Experimental section

All chemicals used were purchased from Aldrich or Fluka. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance DPX 400 spectrometer at 400 MHz and 100 MHz in $CDCl_3$ and D_2O, respectively. Chemical shifts were reported in parts per million (δ), relative to the internal standard of tetramethylsilane (TMS). Melting points were determined using a YRT-3 apparatus and were not corrected. Elemental analysis was carried out on a Carlo Erba 1160. All reactions were monitored by thin-layer chromatography (TLC). All condensation products were characterized by NMR analysis and measurement of melting points.

A typical experimental procedure for Knoevenagel condensation

Benzaldehyde (1 mmol) and ethyl cyanoacetate (1 mmol) were mixed together in the presence of 2 mL IL 2-hydroxyethylammonium formate, and then stirred at room temperature. Upon the completion of the reaction (monitored by TLC), the mixture was filtrated and the solid dried in vacuo at 60 °C for 10 h, was the condensational product with high purity, which did not need further purification. The filtrate (including IL and water) was dried to remove water at 60 °C under vacuum, and the recovered IL was reused for subsequent reactions. The product was analyzed by melting point, ^{1}H NMR and ^{13}C NMR.

Data for representative products

2-(Phenylmethylene)-malononitrile (product 3a)

White solid; mp 79–80 °C (Ref. [28]: 80–81 °C); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 7.91 (d, 2H, $J = 7.6$ Hz, ArH), 7.79 (s, 1H, C=CH), 7.64 (t, 1H, $J = 7.6$ Hz, ArH), 7.27 (t, 2H, $J = 7.6$ Hz, ArH), 7.27 (t, 2H, $J = 7.6$ Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm): 160.0, 134.6, 130.9, 130.7, 129.6, 113.7, 112.5, 82.7.

2-(4-Methyoxyphenylmethylene)malononitrile (product 3c)

Yellow solid; mp 110–112 °C (Ref. [28]: 110–111 °C); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 7.91 (d, 2H, $J = 8.8$ Hz, ArH), 7.66 (s, 1H, C=CH), 7.01 (d, 2H,

J = 8.8 Hz, ArH), 3.92 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm): 164.8, 158.9, 133.4, 123.9, 115.1, 114.4, 113.3, 78.4, 55.8.

2-(2-Furylmethylene)malononitrile (product 3g)

Pale yellow solid; mp 68–69 °C Ref. [28]: 68–69 °C); ^1H NMR (400 MHz, $CDCl_3$) (ppm): 7.81 (d, 1H, J = 1.6 Hz, furyl), 7.52 (s, 1H, C=CH), 7.37 (d, 1H, J = 3.6 Hz, furyl), 6.73–6.71 (m, 1H, furyl); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm): 149.6, 147.9, 143.0, 123.6, 114.4, 113.8, 112.6.

2-(3-Pyridylmethylene)malononitrile (product 3h)

White solid; mp 80–83 °C (Ref. [29]: 78–80 °C); ^1H NMR (400 MHz, $CDCl_3$) (ppm): 8.89 (d, 1H, J = 2 Hz, pyridyl), 8.83 (d, 1H, J = 3.6 Hz, pyridyl), 8.49-8.47 (m 1H, pyridyl), 7.55–7.52 (m, 1H, pyridyl); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm): 158.5, 154.6, 152.3, 135.6, 126.9, 124.2, 112.9, 111.9, 85.5.

Ethyl (E)-2-cyano-3-(4-nitrophenyl)-2-propenoate (product 3j)

Pale yellow solid; mp 168–171 °C (Ref. [28]: 169–170 °C); ^1H NMR (400 MHz, $CDCl_3$) (ppm): 8.35 (d, 2H, J = 8.4 Hz, ArH), 8.31 (s,1H, C=CH), 8.14 (d, 2H, J = 8.4 Hz, ArH), 4.43 (q, 2H, J = 7.2 Hz, CH_2), 1.42 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm): 161.4, 151.7, 149.6, 136.9, 131.1, 124.3, 114.5, 107.3, 63.3, 14.1.

Ethyl (E)-2-cyano-3-(4-chlorophenyl)-2-propenoate (product 3m)

White solid; mp 89–90 °C (Ref. [28]: 91–92 °C); ^1H NMR (400 MHz, $CDCl_3$) (ppm): 8.20 (s, 1H, C = CH), 7.94 (d, 2H, J = 8.8 Hz, ArH), 7.48 (d, 2H, J = 8.8 Hz, ArH), 4.39 (q, 2H, J = 7.2 Hz, CH_2), 1.40 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm): 162.2, 153.4, 139.5, 132.2, 129.8, 129.6, 115.2, 103.4, 62.8, 14.1.

Ethyl (E)-2-cyano-3-(4-methoxyphenyl)-2-acrylamide (product 3o)

White solid; mp 213–214 °C (Ref. [28]: 214–215 °C); ^1H NMR (400 MHz, $CDCl_3$) (ppm): 8.10 (s, 1H, C=CH), 7.96 (d, 2H, J = 8.4 Hz, ArH), 7.56 (br, s, 2H, NH_2), 7.16 (d, 2H, J = 8.4 Hz, ArH), 4.02(S, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm): 162.3, 151.4, 137.5, 136.8, 131.2, 129.5, 127.6, 115.2, 103.4, 61.8.

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