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Amino-functionalized ionic liquid as an efficient and recyclable catalyst for Knoevenagel reactions in water

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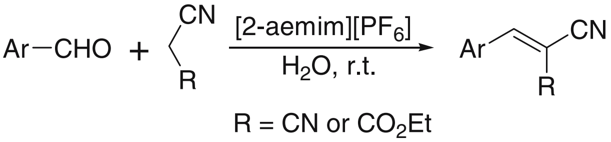
The Knoevenagel condensation of aromatic aldehydes with malononitrile and ethyl cyanoacetate using amino-functionalized ionic liquid, 1-aminoethyl-3-methylimidazolium hexafluorophosphate as catalyst was successfully performed in aqueous media. The catalyst can be recycled and reused at least six times without apparently loss of activity.



KEY WORDS: functional ionic liquid; Knoevenagel reaction; catalyst; aqueous synthesis.

1. Introduction

The Knoevenagel condensation reaction, which was discovered many years ago, is one of the most important C–C bonds forming reactions in organic chemistry. In general, this type of condensation reaction performs in homogeneous solution in the presence of organic bases [1]. This method has its limitations, namely, it has difficulties in catalyst separation and recycling. In order to reduce effluents to environmentally acceptable limits, this transformation has been studied by using various heterogeneous solid bases [2a], for example, hydrotalcite [2b], Cs-MCM-41 [2c], MCM-41 [2d], modified silica gel [2e], Ga/Al-containing layered double hydroxides [2f], $Zr(O_3POK)_2$ [2g], modified expanded corn starches [2h], amino-immobilized MCM-48 [2i] and so on. More recently, Knoevenagel reactions have been performed using functional ionic liquids, e.g., ethylammonium nitrate [3a], ethylenediammonium diacetate [3b], Lewis acidic ionic liquids [3c], as both the catalysts and solvents. In these processes, however, products were isolated by extraction or water dilution, thus the use of large amounts of volatile solvents or tedious distillation work-up was unavoidable. Also some approaches have been reported that Knoevenagel reaction could be performed in water [4], even in the absence of catalyst [5]. Unfortunately, they are efficient only with highly activated substrates. For example, Bigi and co-workers have described the aqueous catalyst-free Knoevenagel reaction between aromatic aldehydes and malononitrile (a highly activated methylene compound). However, this protocol is time consuming and need to be performed at heating condition [5].

Nowadays there is an urgent need to develop green chemistry process, where the use of noxious substance and the generation of waste can be avoided. From both environmental and economical points of view, using aqueous media to perform organic reactions has attracted considerable interest because water is considered to be the most environmentally acceptable, safe and inexpensive solvent [6]. Recently, work has focused on the preparation and application of functionalized ionic liquids [7] with special tasks, such as carrying hydroxyl [8], amino [9], sulfonic acid [10], or carboxyl [11] and so on [12–19]. Recently, we have also reported the use of functional ionic liquids as catalyst [20] and recoverable ligand [21] for organic synthesis. Herein we describe an eco-friendly and economical approach to Knoevenagel condensation reaction in water catalyzed by amino-functionalized ionic liquid, 1-aminoethyl-3-methylimimidazolium hexafluorophosphate ([2-aemim][PF_6]) or 1-aminoethyl-3-methylimidazolium tetrafluoborate ([2-aemim][BF_4]) (scheme 1). With minimal amount of catalysts (0.8 mol%), reactions were completed at room temperature with high yields of desired products. In

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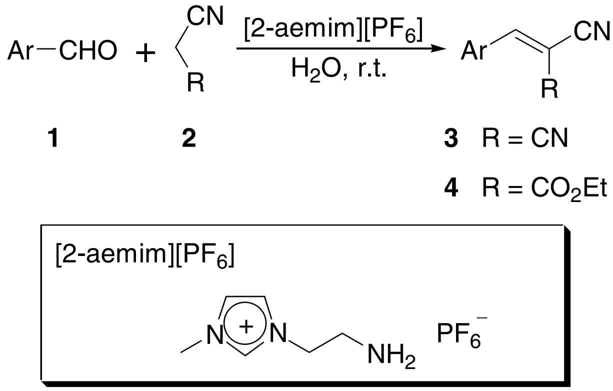

Scheme 1.

addition, the recyclability of the catalyst is also well established.

2. Experimental

Reagents are obtained from commercial resource. Products are all known compounds and were identified by comparing of their physical and spectra data with those reported in the literature.

2.1. General procedure for the synthesis of ionic liquid [2-aemim][PF_6] and [2-aemim][BF_4]

A mixture of 1-methylimidazole (8.20 g, 0.10 mol) and 2-bromoethylamine hydrobromide (20.50 g, 0.10 mol) in 50 ml of acetonitrile was heated with stirring at 80 °C for 4 h. On completion, the solvent was removed by distillation and the residue was washed with ethanol (10 ml × 3), and then added 40 ml of CH_3CN/H_2O (1:1, v/v) and KPF_6 (18.40 g, 0.10 mol) or $NaBF_4$ (10.98 g, 0.10 mol). The mixture was left for 24 h at room temperature and added NaOH (4.00 g, 0.10 mol) for neutralization. Solvents were then evaporated *in vacuo* followed by adding $CHCl_3$ (20 ml) and methanol (2 ml), salts thus separated were filtered and solvents were evaporated. The obtained yellow oil was washed successively with chloroform (10 ml × 3) and ether (10 ml × 3). After dried 6 h under vacuum at 80 °C, the expected ionic liquid was obtained ([2aemim][PF_6], 21.70 g, 80%; [2aemim][BF_4], 17.31 g, 81%). 1-Aminoethyl-3-methylimimidazolium hexafluoro-phosphate ([2-aemim][PF_6]): IR (KBr): 3430, 3086, 2896, 1581, 1452, 1175, 847 cm^{-1}. ^1H NMR (D_2O, 500 MHz): δ_H 3.25 (t, $J_1 = 6.18$ Hz, $J_2 = 5.63$ Hz, 2H, NH_2–CH_2), 4.12 (s, 3H, CH_3), 4.49 (t, $J_1 = 6.19$ Hz, $J_2 = 5.66$ Hz, 2H, N–CH_2), 7.68 (s, 1H, NC*H*), 7.75 (s, 1H, NC*H*), 8.63 (s, 2H, NH_2), 8.99 (s, 1H, N (*H*) CN). MS (ESI) *m*/*z*: 126.1 (100%) $[M\text{-}PF_6]^+$, 397.2 (100%) $[2M\text{-}PF_6]^+$. 1-Aminoethyl-3-methylimimidazolium fluoborate ([2-aemim][BF_4]): IR (KBr): 3404, 3101, 2953, 2855, 1575, 1396, 1174, 1085 cm^{-1}. ^1H NMR (D_2O, 500 MHz): δ_H 3.12 (t, $J_1 = 5.74$ Hz, $J_2 = 5.68$ Hz, 2H, NH_2–CH_2), 3.99 (s, 3H, CH_3), 4.37 (t, $J_1 = 5.90$ Hz, $J_2 = 5.56$ Hz, 2H, N–CH_2), 7.56 (s, 1H, NC*H*), 7.62 (s, 1H, NC*H*), 8.50 (s, 2H, NH_2), 8.61 (s, 1H, N (*H*) CN). MS (ESI) *m*/*z*: 169.2 (100%) $[M\text{-}CH_2CH_2NH_2 + H]^+$, 126 (20%) $[M\text{-}BF_4]^+$, 339 (25%) $[2M\text{-}BF_4]^+$.

2.2. Knoevenagel condensation of aromatic aldehydes with malononitrile

In a typical experiment, a solution of benzaldehyde (0.53 g, 5 mmol), malononitrile (0.33 g, 5 mmol) and [2-aemim][PF_6] (0.01 g, 0.8 mol%) in water (10 ml) was stirred at room temperature for 20 min (monitored by TLC). After completion, the precipitates were collected by filtration and washed with water (10 ml × 3). After drying, 0.71 g (92%) of **3a** was obtained (mp: 87–88 °C; lit. [22]: 87 °C). ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.55 (t, $J = 8.0$ Hz, 2H, ArH), 7.64–7.72 (m, 1H, ArH), 7.78 (s, 1H, CH =), 7.91 (d, $J = 7.6$ Hz, 2H, ArH) ppm. IR (KBr): 3031, 2221, 1591, 1560, 1454, 1217, 968, 754, 684 cm^{-1}. MS (GC/MS) *m*/*z*: 154 ($M^{+\cdot}$), 127, 103.

2.3. Reuse of [2-aemim][PF_6]

Ionic liquid [2-aemim][PF_6] used in benzaldehyde/ethyl cyanoacetate/water system was chosen as a representative example. In a typical procedure, on completion the first run, the precipitates were collected by filtration. After extraction with ethyl ether (10 ml × 3), the filtrate was added benzaldehyde (0.53 g, 5 mmol) and ethyl cyanoacetate (0.57 g, 5 mmol). Then the mixture was stirred at room temperature for 20 min (monitored by TLC). After standard procedure described above, 0.92 g (92% yield) of **4a** was obtained.

3. Results and discussion

Ionic liquid [2-aemim][PF_6] or [2-aemim][BF_4] was prepared by three steps reactions that first implied quaterisation of 1-methylimizole to 2-bromoethylamine hydrobromide, followed by anion exchange with KPF_6 or $NaBF_4$ and neutralization. The structure was indicated by IR, ^1H NMR and MS (ESI).

The as-synthesized ionic liquids were then tested as catalysts for the Knoevenagel condensation of malononitrile and aromatic aldehydes. In a representative experiment, benzenldehyde **1a** (5 mmol) and malononitrile (5 mmol) in water was stirred in the presence of [2-aemim][PF_6] (0.8 mol%) at room temperature. After 20 min, the benzaldehyde was consumed and the only detectable product was **3a**, the reaction mixture was cooled and the product thus precipitated was obtained in 92% yield. It is noteworthy that only 0.8 mol% of the catalyst was sufficient to push the reaction forward. In addition, no significant anion effect was observed as

Table 1
Knoevenagel condensation reactions of aromatic aldehydes with malononitrile

Product	Aldehydes	Time (min)	Yield (%)
3a	Benzaldehyde	20	92
3b	3-Nitrobenzaldehyde	15	92
3c	4-Chlorobenzaldehyde	20	89
3d	4-Cyanobenzaldehyde	15	91
3e	4-Dimethylaminobenzaldehyde	30	85
3f	4-Methoxybenzaldehyde	30	96
3g	Piperonal	20	90
3h	Furfural	120	95

both [2-aemim][PF_6] and [2-aemim][BF_4] could catalyze the reaction efficiently (20 min, 92% and 90% yield, respectively).

Using these optimized reaction conditions, various aromatic aldehydes **1** were treated with malononitrile **2** under optimal condition described above (table 1). In all cases, the reactions proceeded rapidly with high yield (85–96%). All products are well-known compounds and their structures were confirmed by melting point, IR and GC/MS. Interestingly, much longer reaction time (120 min) was needed for furfural **1h** than other aromatic aldehydes (15–30 min).

Encouraged by these results, we attempted the reaction of benzaldehyde with ethyl cyanoacetate in water in the presence of amino-functional ionic liquid. Typically, Knoevenagel condensation between these substrates is considered to be an equilibrium-limited reaction and the water thus formed should be continuously removed by azeotropic distillation [23]. Recently, Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate has been investigated using a membrane microreactor [24]. The presence of the miniature membrane enables continuous and selective removal of water during the reaction and resulted in an improved conversion over 85%. In our experiments, however, the ionic liquid-catalyzed model reaction would accomplish in 3 h with 92% yield of desired product even in water.

We next investigated the substrate generality with seven aromatic aldehydes (table 2). All of the reactions, including the case of using furfural accomplished in less than 3 h with high yield (91–98%).

Table 2
Knoevenagel condensation reactions of aromatic aldehydes with ethyl cyanoacetate

Product	Aldehydes	Yield (%)	Time (min)
4a	Benzaldehyde	91	180
4b	4-Hydroxybenzaldehyde	94	160
4c	Piperonal	92	155
4d	Vanillin	98	160
4e	3-Nitrobenzaldehyde	92	150
4f	Furfural	95	165
4g	4-Chlorobenzaldehyde	94	170

The recycle of catalyst was also investigated. On accomplishment of the model reaction between benzaldehyde and ethyl cyanoacetate, the product was isolated from aqueous media by filtration. The filtrate was washed with ether and then reused. The yields of product maintained at 91–94% in six cycles.

In summary, we have described a simple, green and efficient protocol for the aqueous Knoevenagel reactions catalyzed by functional ionic liquids, 1-aminoethyl-3-methylimidazolium hexafluorophosphate and 1-aminoethyl-3-methylimidazolium tetrafluoroborate. The combination of aqueous reaction media, room temperature reaction and the recyclability of ionic liquid catalyst with high yields and purities of products make this protocol to be efficient and eco-friendly.

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