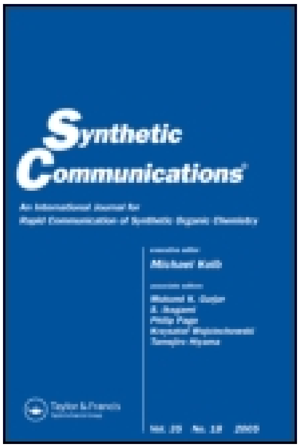

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Organic Reactions in Ionic Liquids: Ionic Liquids Ethylammonium Nitrate Promoted Knoevenagel Condensation of Aromatic Aldehydes with Active Methylene Compounds

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Organic Reactions in Ionic Liquids: Ionic Liquids Ethylammonium Nitrate Promoted Knoevenagel Condensation of Aromatic Aldehydes with Active Methylene Compounds

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Abstract: The Knoevenagel condensation of aromatic aldehydes with active methylene compounds proceeded efficiently in a reusable ionic liquid, ethylammonium nitrate, at room temperature in the absence of any catalyst with high yields.

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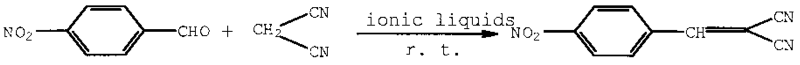
INTRODUCTION

Knoevenagel condensation is one of the elemental reactions in organic chemistry. Traditionally, it was carried out in the presence of a base, acid, or surfactant catalyst in organic solvents.[1] Additionally, Knoevenagel condensation could also be performed by infrared[2] or microwave irradiation[3] under solvent-free conditions, but these techniques usually require the use of catalysts, organic solvents for the extraction of product from the solid supports and do not yield pure product so that further solvents are used for purifying work-up.

In recent years ionic liquids (ILs) are emerging as potential "greener" alternatives to volatile organic solvents[4] and they have been used as environmentally benign media for many important organic reactions.[5] To date, some reports have shown the Knoevenagel condensation could be performed more efficiently in ionic liquids than the traditional methods. For example, Forbes et al. reported glycine-promoted Knoevenagel condensation of benzaldehyde with malononitrile in ionic liquid [6-mim]PF_6 (1-hexyl-3-methyl imidazolium hexafluorophosphate).[6] Meanwhile, Salunkhe et al. reported the reaction conducted in Lewis acidic ionic liquids [Bmim]$Cl \cdot xAlCl_3$ and [Bpy]$Cl \cdot xAlCl_3$.[7] Most recently, Garcia et al. reported the reaction was run in ionic liquid [Bmim]PF_6 catalyzed by KOH,[8] and Khan et al. reported this condensation reaction could be efficiently proceeded in [Bmim]BF_4 or [Bmim]PF_6 using hydrotalcite as a heterogeneous catalyst.[9] Previously, we also reported an effective Knoevenagel condensation catalyzed by ethylenediammonium diacetate in ionic liquids [Bmim]BF_4 or [Bmim]PF_6.[10] In continuation of our interest in using ionic liquids as a recyclable, eco-friendly reaction medium in the Knoevenagel condensation, we found that Knoevenagel reaction of aromatic aldehydes with active methylene compounds could occur in ionic liquid ethylammonium nitrate (EAN) without a catalyst.[11] Obviously, the new methods described here are more convenient than are those reported in the literatures in which other ionic liquids were used as reaction media.[6–10]

In fact, simple stirring of a mixture of *p*-nitrobenzaldehyde with malononitrile in ethylammonium nitrate for three hours at room temperature gave, after directly filtering, the corresponding condensation product in high yield with practical purity (see Scheme 1).



Scheme 1.

Table 1. Condensation of *p*-nitrobenzaldehyde with malononitrile in different ionic liquids

Entry[a]	Ionic liquids	Time (h)	Yields (%)[b]
1	EAN	3	94
2	$[\text{Bmim}]PF_6$	6	Trace
3	$[\text{Bmim}]BF_4$	6	Trace

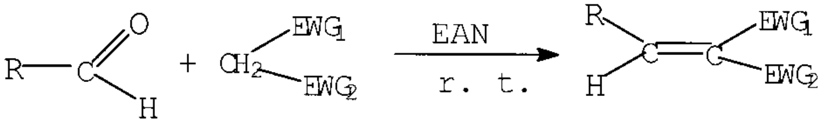
[a] All reactions were run with *p*-nitrobenzaldehyde (2 mmol) and malononitrile (2 mmol) in 2 mL ionic liquid at room temperature.

[b] Isolated yields.

We investigated the efficacy of EAN compared to the most commonly used ionic liquids, $[\text{Bmim}]PF_6$ and $[\text{Bmim}]BF_4$ by the model condensation between *p*-nitrobenzaldehyde and malononitrile. The experimental results summarized in Table 1 showed the reaction could hardly take place in the absence of catalyst in $[\text{Bmim}]PF_6$ and $[\text{Bmim}]BF_4$, which is different from the results obtained by Khan et al.[12] The results showed that the ionic liquid, EAN, plays a dual role as solvent and promoter in this reaction.

Next, the scope of the Knoevenagel condensation of a variety of aromatic aldehydes **1** and different active methylene compounds **2** in ionic liquid EAN was investigated (Scheme 2). The results are summarized in Table 2. The products were characterized by ^1H nuclear magnetic resonance (NMR), infrared (IR), and melting points, that were consistent with the literature data.

As can be seen from Table 2, the reaction was found to be general and applicable to the aromatic aldehydes bearing various substituents such as nitro, chloro, methyl, methoxyl, hydroxyl, and N,N′-dimethylamino, etc. The reaction of 2-furancarboxaldehyde (Entry 6, 20) and the aromatic α, β-unsaturated aldehyde, cinnamic aldehyde (Entry 7, 15) also could proceed smoothly under the reaction conditions. The experimental results show aromatic aldehydes bearing electron-withdrawing groups reacted more easily compared with those containing electron-donating groups. Besides, in the case of 2-hydroxybenzaldehyde, the reaction led to the formation of



1 **2** **3**

Scheme 2.

Table 2. Knoevenagel condensation of aromatic aldehydes with active methylene compounds

Entry	Product	R	EWG$_1$	EWG$_2$	Time (h)	Yield (%)[a]	Mp °C (lit.)
1	**3a**	C_6H_5	CN	CO_2Et	8	86	47–48(47–48)[10]
2	**3b**	*p*-$CH_3C_6H_4$	CN	CO_2Et	10	90	92–93(94–95)[3c]
3	**3c**	*p*-ClC_6H_4	CN	CO_2Et	6	91	91–92(91–92)[3c]
4	**3d**	*o*-$NO_2C_6H_4$	CN	CO_2Et	5	92	101–102(102–103)[13]
5	**3e**	*p*-$NO_2C_6H_4$	CN	CO_2Et	4	94	169–170(170–171)[10]
6	**3f**	2-furfuraly	CN	CO_2Et	8	84	93–94(93–94)[10]
7	**3g**	$C_6H_5CH{=}CH$	CN	CO_2Et	10	87	107–108(107–108)[3c]
8	**3h**	*o*-OHC_6H_4	CN	CO_2Et	12	85	134–135(134–136)[10]
9	**3i**	*p*-$Me_2NC_6H_4$	CN	CN	8	95	179–180(185–185.5)[2a–2b]
10	**3j**	*p*-$MeOC_6H_4$	CN	CN	8	83	114–115(114–115)[10]
11	**3k**	*p*-$NO_2C_6H_4$	CN	CN	3	94	160–161(159–160)[3b]
12	**3k**	*p*-$NO_2C_6H_4$	CN	CN	3	95[b]	—
13	**3k**	*p*-$NO_2C_6H_4$	CN	CN	3	93[c]	—
14	**3l**	*p*-ClC_6H_4	CN	CN	5	89	161–162(162–163)[3b]
15	**3m**	$C_6H_5CH{=}CH$	CN	CN	8	91	127–128(126)[14]
16	**3n**	C_6H_5	CN	CN	6	84	83–84(82–84)[1b]
17	**3o**	*p*-$NO_2C_6H_4$	CN	$CONH_2$	6	89	236–237(237–238)[3b]
18	**3p**	*p*-$MeOC_6H_4$	CN	$CONH_2$	12	88	213–214(214–215)[3b]
19	**3q**	*p*-$MeOC_6H_4$	–(CONHCONHCO)–		0.2	95	275–276(276–277)[2b]
20	**3r**	2-furfuraly	–(CONHCONHCO)–		0.2	94	261–262(264)[15]
21	**3s**	*p*-$Me_2NC_6H_4$	–$(COOC(CH_3)_2OCO)$–		0.5	97	163–164(162)[1b]
22	**3t**	*p*-OHC_6H_4	–$(COOC(CH_3)_2OCO)$–		1.0	95	194–195(193)[1b]

[a] Isolated yields.

[b–c] Second and third recycling of EAN.

3-substituted coumarin derivatives in good yield (3**h**, Entry 8). Several active methylene compounds such as malononitrile, ethyl cyanoacetate, cyanoacetamide, bartituric acid, and meldrum's acid, etc. were successfully reacted and all unsymmetric active methylene compounds gave E-isomers as described in the literature.[1,2,10] Disappointing, we did not obtain satisfactory result when the same methods are applied to aliphatic aldehydes and ketones under the same reaction conditions. In addition, the ionic liquid could be typically recovered and reused with no appreciable decrease in yields and reaction rates (Table 2, Entries 11–13).

In conclusion, we have demonstrated that the Knoevenagel condensation between aromatic aldehydes with active methylene compounds can be effectively performed at room temperature in the ionic liquid EAN. The present method has many obvious advantages compared to previous methods, including there is no need for the use of any catalyst, the method is environmentally more benign, the ease of product isolation, the simplicity of methodology, the high yield, the generality, the convenience of preparing ionic liquid EAN using much cheaper starting material, and the potential for recycling of ionic liquid. We have shown that the ionic liquid, EAN, can replace the organic solvents, other ionic liquids, and the catalysts, and is a simpler system—a good example of green chemistry.

EXPERIMENTAL

Melting points were determined on digital melting point apparatus and were not corrected. Infrared spectra were recorded on a VECTOR-22 Infrared Spectrophotometer. ^{1}H NMR spectra were recorded on a BRUKER-400MHz spectrometer using $CDCl_3$ or DMSO-d_6 (for **3o–3t**) as the solvent with tetramethylsilane (TMS) as an internal standard. The ionic liquids [Bmim][PF_6] and [Bmim][BF_4] were synthesized as lit,[16] ethylammonium nitrate was synthesized according to the literature.[17]

General Procedure for the Preparation of 3a–3t.

Aromatic aldehyde **1** (2 mmol), active methylene compound **2** (2 mmol) were dissolved in ionic liquid EAN (2 mL). The reaction mixture was stirred at room temperature for an appropriate time, reaction was monitored by thin layer chromatography (TLC). Upon completion of the reaction, after filtering the solid directly from the reaction mixture and washing with water gave the desired products **3** in high yields with essential purity. After isolation of the product, the remainder of the ionic liquids EAN was dried for 4 h under vacuum at 50°C. The next run was performed under identical reaction conditions.

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