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Efficient Knoevenagel Condensation Catalyzed by 2-Hydroxyethylammonium Acetate Under Solvent-Free Conditions at Room Temperature

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Abstract: An efficient method for Knoevenagel condensation of aromatic aldehydes with malononitrile or ethyl cyanoacetate has been developed using the inexpensive and environmentally friendly ionic liquid 2-hydroxyethylammonium acetate as catalyst. The reactions were carried out under solvent-free conditions at room temperature in short periods with simple workup procedure and good to excellent yields.

Keywords: Aromatic aldehydes, ionic liquid, Knoevenagel condensation, methylene compounds

The Knoevenagel condensation is a very useful reaction and has been widely employed for the generation of double bonds from a carbonyl compound and an active methylene compound. This reaction is usually catalyzed by organic bases.[1] In the past two decades, the use of Al_2O_3,[2] $ZnCl_2$,[3] CdI_2,[4] I_2–K_2CO_3,[5] K_3PO_4,[6] KF–Al_2O_3,[7] $AlPO_4$–Al_2O_3,[8] H_2O/cetyltriethylammonium bromide (CTMAB),[9] montmorillonite K10–$ZnCl_2$,[10] zinc acetate,[11] diammonium hydrogen phosphate,[12] USY zeolite,[13] xonotlite,[14] silica gel,[15] silica gel functionalized with

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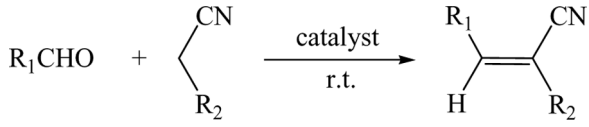
amino groups,[16] aminopropyl–functionalized MCM-41,[17] ionic liquid–functionalized silica gel,[18] ionic liquid–functionalized SBA-15,[19] basic ionic liquid,[20] and others[21–32] have been reported. In spite of their potential utility, some of these methods are limited by low yields, long reaction times, harsh conditions, expensive reagents, and use of toxic solvents. Thus, there is an increasing interest in the development of new catalysts under mild reaction conditions with cleaner reaction profiles, good yields, less catalyst load, and simple experimental and isolation procedures.

Solvent-free organic synthesis has received considerable attention as a result of growing worldwide concerns about chemical wastes and future resources.[33] Ionic liquids have attracted increasing interest in recent years because of their properties of nonvolatility, nonflammability, thermal stability, low toxicity and reusability. A variety of catalytic reactions have been successfully conducted with ionic liquids as catalysts or solvents.[34,35] In this article, we report a simple and very efficient Knoevenagel condensation reaction of aromatic aldehydes with active methylene compounds catalyzed by 2-hydroxyethylammonium acetate ionic liquid under solvent-free conditions at room temperature (Scheme 1).

2-Hydroxyethylammonium acetate ionic liquid was easily prepared from cheaply available acetic acid and 2-aminoethanol by a simple acid–base reaction.[36] Initially, we examined the effects of catalyst load on the condensation of benzaldehyde and ethylcyanoacetate. The results are summarized in Table 1. The yield increased with the increase of catalyst load, and the optimum molar ratio of 2-hydroxyethylammonium acetate to the substrate was about 20% (entry 3). Further increasing the amount of 2-hydroxyethylammonium acetate did not led to greater yield (entry 4). Subsequently, Knoevenagel condensation of ethylcyanoacetate and malononitrile with a variety of aromatic aldehydes with 20 mol % of 2-hydroxyethylammonium acetate as catalyst was investigated. Results listed in Table 1 show efficient Knoevenagel condensation of aromatic aldehydes with active methylene compounds in the presence of 2-hydroxyethylammonium acetate. Aromatic aldehydes with electron-donating or electron withdrawing substituents could react very well with malononitrile, and good to excellent yields were achieved in a very



Scheme 1. Knoevenagel condensation of aromatic aldehydes with ethyl cyanoacetate and malononitrile.

Table 1. Knoevenagel condensation catalyzed by 2-hydroxyethylammonium acetate[a]

Entry	R_1	R_2	Time (min)[b]	Yield (%)[c]
1[d]	C_6H_5	–COOEt	180	63
2[e]	C_6H_5	–COOEt	30	76
3	C_6H_5	–COOEt	25	80
4[f]	C_6H_5	–COOEt	25	80
5	4-$CH_3OC_6H_4$	–COOEt	30	90
6	4-ClC_6H_4	–COOEt	2	85
7	4-$CH_3C_6H_4$	–COOEt	2	95
8[g]	4-$CH_3C_6H_4$	–COOEt	2	95
9[h]	4-$CH_3C_6H_4$	–COOEt	2	95
10[i]	4-$CH_3C_6H_4$	–COOEt	3	95
11	4-$(CH_3)_2NC_6H_4$	–COOEt	60	90
12	4-$NO_2C_6H_4$	–COOEt	1	93
13	2-Furyl	–COOEt	2	84
14	$C_6H_5CH{=}CH$	–COOEt	2	85
15	C_6H_5	–CN	1	96
16	4-$CH_3OC_6H_4$	–CN	1	94
17	4-ClC_6H_4	–CN	1	92
18	4-$CH_3C_6H_4$	–CN	1	91
19	4-$(CH_3)_2NC_6H_4$	–CN	2	95
20	$C_6H_5CH{=}CH$	–CN	1	85

[a]Unless otherwise indicated, the reaction was carried out using 2-hydroxyethylammonium acetate (3 mmol), aldehyde (15 mmol), and active methylene compound (15 mmol). All the products are known compounds and were identified by comparison of their melting points and spectral data with those reported.

[b]The mixture was stirred at room temperature. After the mixture solidified, the workup was performed.

[c]Isolated yield.

[d]The amount of 2-hydroxyethylammonium acetate is 0.75 mmol.

[e]The amount of 2-hydroxyethylammonium acetate is 1.5 mmol.

[f]The amount of 2-hydroxyethylammonium acetate is 4.5 mmol.

[g]The second run.

[h]The third run.

[i]The fourth run.

short reaction time. The less-active methylene compounds such as ethylcyanoacetate also reacted with the aldehydes to give the corresponding products with good to excellent yields in short periods. The reuse of 2-hydroxyethylammonium acetate was studied, and 4-methylbenzaldehyde and ethyl cyanoacetate were chosen as the substrates. It was shown that

ionic liquid retained strong catalytic activity for four runs (entries 7–10). In this methodology; reactions were completed in a short time and with excellent yields; workup procedure is simple. In addition, all the reactions were carried out at room temperature with constant stirring (i.e., using mild reaction conditions). Another attractive feature of this methodology is the use of recyclable ionic liquid as catalyst under solvent-free conditions, primarily avoiding toxic organic solvent in the whole procedure and thus decreasing both the cost of the synthesis and the amount of waste flow.

In summary, we have demonstrated a simple and very efficient Knoevenagel condensation reaction of one aromatic aldehyde with each active methylene compounds to obtain condensation products in good to excellent yields under mild reaction conditions using the inexpensive and environmentally friendly ionic liquid 2-hydroxyethylammonium acetate as catalyst. The workup is simple, and 2-hydroxyethylammonium acetate can be used at least four runs without noticeable loss of catalytic activity.

EXPERIMENTAL

Melting points were uncorrected. Fourier transform–infrared (FT-IR) spectra were obtained on a Nexus 470 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Mercury 300 spectrometer.

In a round-bottomed flask, 2-hydroxyethylammonium acetate (3 mmol) was added to a stirring mixture of 4-methylbenzaldehyde (15 mmol) and ethyl cyanoacetate (15 mmol) at room temperature. After completion of the reaction, the crude product was purified by recrystallization from 95% ethanol to give pure ethyl (E)-2-cyano-3-(4-methylphenyl)-2-propenoate (3.1 g, 95%) as white crystals, mp 89–91°C (lit.[32] 88–89°C). The mother liquor was concentrated under reduced pressure to give the ionic liquid. The ionic liquid was washed with a small amount of ethyl acetate and dried under vacuum. A second run using the recovered ionic liquid was performed under the identical conditions.

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