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Green synthesis of a nano salt and its application as multifunctional organocatalyst for Knoevenagel condensation

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Abstract 1,2-Ethanediammonium 3-hydroxypropane-1-sulfonate [(EDA)(HPS)] as a novel nano multifunctional organosalt was synthesized via a simple and green chemical route and characterized using various techniques such as proton nuclear magnetic resonance (^{1}H NMR), thermogravimetric analysis (TGA), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and elemental analysis. [(EDA)(HPS)] was successfully applied as a multifunctional organocatalyst in Knoevenagel reaction of aryl/heteroaryl/alkyl aldehydes or ketones with active methylene compounds. The hydroxyl and ammonium groups in the structure of [(EDA)(HPS)] showed interesting effects on its catalytic efficiency. [(EDA)(HPS)] was also recovered and reused five times without significant decrease in activity. TEM and elemental analysis of the recovered catalyst after five reaction cycles confirmed its durability and high stability under the applied reaction conditions.

Keywords Nano · Multifunctional · Organocatalyst · Knoevenagel condensation

Introduction

Over the past decade, much research has focused on nanostructured materials, because of their unique structural and textural properties [1, 2]. Different synthetic techniques have been applied for preparation of nanostructured materials, including sonochemical, sol–gel, precipitation, solid-state reaction,

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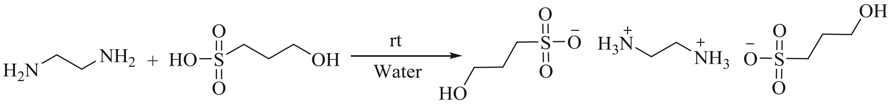
microwave irradiation, alcohothermal, and electrochemical methods [3, 4]. Although these protocols are valuable, most of them suffer from one or more disadvantage such as long reaction time, high temperature, harsh reaction conditions, low yield, or use of expensive, toxic, and hazardous stabilizers or solvents. To overcome these drawbacks, much attention has been paid to development of green and ecofriendly methods for synthesis of nanostructured materials. Green synthetic protocols are generally simple and use nontoxic and safe solvents.

Ammonium salts are well known as nerve-blocking agents in brain surgery, disinfectants, sterilants, and surfactants [5]. In recent years, ammonium salts have attracted considerable attention as organocatalysts owing to their negligible vapor pressure, good solvating capability, tunable polarity, excellent thermal stability, and ease of recyclability [6, 7]. Recently, Kumari et al. [8] synthesized nano ammonium perchlorate, albeit by a harsh and time-consuming chemical route. Thus, it would be preferable to introduce a green and simple method (not using expensive and hazardous solvents, stabilizers, or high-temperature calcination) for synthesis of nano ammonium salts.

Knoevenagel condensation is one of the most important reactions for synthesis of valuable compounds that are widely used to prepare fine chemical intermediates, herbicides, insecticides, cosmetics, perfumes, polymers, and therapeutic drugs [9–11]. In Knoevenagel condensation, carbon–carbon double bonds form through the reaction of carbonyl compounds with activated methylenes in presence of different catalysts [12–15]. However, most reported protocols suffer from inherent drawbacks related to use of organic solvents and expensive catalysts, laborious and complex reaction workup, difficult catalyst recovery, and environmental pollution. Therefore, the search for new catalysts for Knoevenagel condensation reaction remains a topic of interest in synthetic organic chemistry.

In continuation of our research work on use of new catalysts for organic reactions [16–19], we present herein, for the first time, synthesis of 1,2-ethanediammonium 3-hydroxypropane-1-sulfonate [(EDA)(HPS)] as a nano organosalt via a simple and green chemical route (Scheme 1). To explore the catalytic activity of [(EDA)(HPS)], we used it as a novel, green, and reusable nanocatalyst for Knoevenagel condensation. [(EDA)(HPS)] is a suitable catalyzing agent due to the hydroxyl groups on the anionic moieties and ammonium groups on the cationic moiety and can act as a multifunctional organocatalyst.



Scheme 1 Synthesis of [(EDA)(HPS)]

Experimental

General information

Chemicals were purchased from Merck Chemical Company and used as received. NMR spectra were recorded on a Bruker Avance DPX-400 using deuterated dimethylsulfoxide (DMSO)-d_6 and D_2O as solvent and tetramethylsilane (TMS) as internal standard. Melting points were determined using a Büchi 510 apparatus and are uncorrected. Product purity and reaction progress were assessed by thin-layer chromatography (TLC) on silica gel POLYGRAM SIL G/UV254 plates. Elemental analysis was carried out using an ECS4010 CHNSO analyzer. A Shimadzu thermogravimetric analyzer (TG-50) was applied to characterize the gravimetric (TG) behavior of the [(EDA)(HPS)] nano salt. TEM analysis was performed using a Philips CM30. Product morphology was investigated by scanning electron microscopy (SEM, model s4160; Hitachi, Japan) at accelerating voltage of 15 kV.

Large-scale synthesis of [(EDA)(HPS)]

Solution of 3-hydroxypropyl sulfonic acid (100 mmol, 14.00 g) in water (60 mL) was added dropwise to aqueous solution of ethylenediamine (100 mmol, 7.412 g) at room temperature. Stirring of the resultant solution was continued for another 20 h at the same condition, then water was removed by distillation under reduced pressure and the residue was dried at room temperature to obtain [(EDA)(HPS)] as white solid (m.p. 298 °C).

Knoevenagel condensation reaction using [(EDA)(HPS)] organocatalyst

[(EDA)(HPS)] (10 mol%, 0.0340 g) was added to stirred mixture of aldehyde (1 mmol) and active methylene compounds (1.2 mmol) at 60 °C under solvent-free condition. The reaction mixture was stirred for appropriate time (Table 2). Reaction progress was monitored by TLC. After reaction completion, warm ethanol (5 mL) was added to the reaction mixture. The organocatalyst was filtered and completely washed with warm ethanol (2 × 10 mL), then dried at room temperature. Solvent in the remaining solution was evaporated under reduced pressure to give crude products. Pure products were obtained by recrystallization in aqueous ethanol.

2-(Phenylmethylene)malononitrile M.p. 83–84 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (2H, t, $J = 8.0$ Hz, Ar), 7.64 (1H, t, $J = 7.6$ Hz, Ar), 7.79 (1H, s, CH=), 7.92 (2H, d, $J = 7.6$ Hz, Ar).

Recovery of [(EDA)(HPS)] organocatalyst after Knoevenagel condensation reaction

[(EDA)(HPS)] (10 mol%, 0.170 g) was added to a stirred mixture of benzaldehyde (5 mmol) and malononitrile (5.2 mmol) at 60 °C under solvent-free condition. The reaction mixture was stirred for 50 min. After reaction completion, warm ethanol

(5 mL) was added to the reaction mixture. The organocatalyst was filtered and completely washed with ethanol (2 × 10 mL), then dried at room temperature. [(EDA)(HPS)] organocatalyst was then reused in the same condition as above for at least five reaction runs, delivering the corresponding Knoevenagel product in high yield.

Results and discussion

Synthesis and characterization of 1,2-ethanediammonium 3-hydroxypropane-1-sulfonate [(EDA)(HPS)] as nano multifunctional organosalt

1,2-Ethanediammonium 3-hydroxypropane-1-sulfonate [(EDA)(HPS)] was synthesized as novel nano multifunctional organosalt from cheap and readily available starting materials. An important advantage of this nanocatalyst is the safe and simple procedure for its preparation. The synthesized [(EDA)(HPS)] was characterized by ^{1}H NMR, elemental analysis, TGA, SEM, and TEM.

The ^{1}H NMR spectra of [(EDA)(HPS)] in DMSO-d_6 and D_2O are shown in Fig. 1. Hydrogens of methylene groups in anionic moieties appeared at $\delta = 1.77$–1.84, 2.51–2.57, and 3.37–3.45 ppm. Presence of a singlet peak at $\delta = 3.08$ ppm was attributed to C–H hydrogens of cationic moiety. Two broad singlets at $\delta = 3.37$ and 8.01 ppm were assigned to OH and NH_3 protons, respectively. The latter assignment was confirmed by D_2O exchange, which showed a missing peak due to NH_3 protons. Peaks were exchanged at 3.37 and 3.54 ppm, related to exchange of OH protons in presence of D_2O (Fig. 2b). These results are in good agreement with the elemental analysis data (anal. calcd. for $C_8H_{24}N_2O_8S_2$: $N = 8.23$, $C = 28.23$, $H = 7.11$, $S = 18.84$ %; found: $N = 8.27$, $C = 28.20$, $H = 7.15$, $S = 18.89$ %).

Thermogravimetric (TG) analysis was applied to determine the thermal stability of [(EDA)(HPS)] (Fig. 2). According to the TGA results, [(EDA)(HPS)] was very stable and showed no evident weight loss below 301 °C.

The size, shape, and morphology of [(EDA)(HPS)] nano organosalt were studied by scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

SEM of [(EDA)(HPS)] revealed the morphology of the organosalt (Fig. 3). Considering the TEM image (Fig. 4), [(EDA)(HPS)] had spherical morphology with relatively good monodispersity. The particle size of [(EDA)(HPS)] was evaluated based on the TEM results and found to be about 10 nm.

Catalytic activity of [(EDA)(HPS)] nano multifunctional organosalt in Knoevenagel condensation reaction

After characterization, we studied application of [(EDA)(HPS)] nano multifunctional organosalt as catalyst for Knoevenagel condensation reaction of benzaldehyde and malononitrile as model reaction under different conditions. Systematic

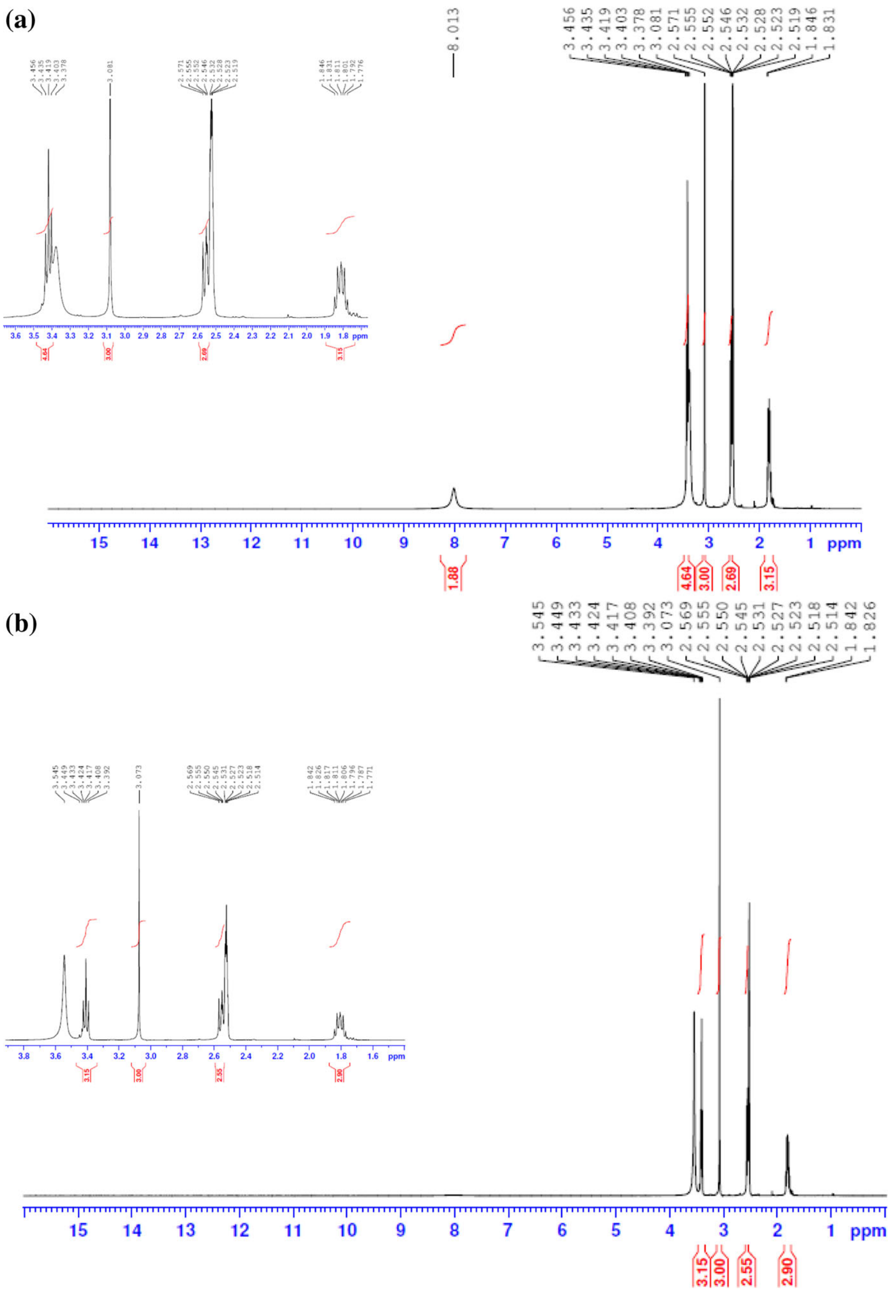
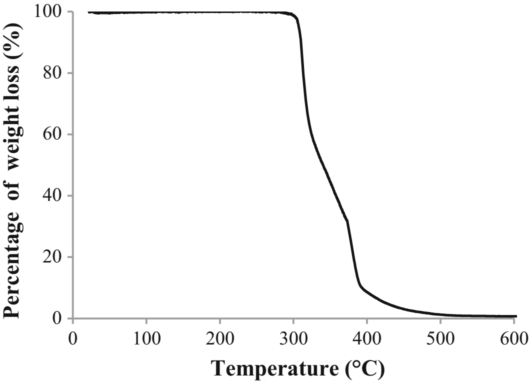


Fig. 1 ^{1}H NMR spectra of [(EDA)(HPS)] in **a** DMSO-d_6 and **b** D_2O

investigation of temperature was performed in the range of 25–70 °C in presence of 10 mol% [(EDA)(HPS)] under solvent-free condition. The results are presented in Table 1. As can be seen from Table 1, the best yield and conversion rate were

Fig. 2 Thermogravimetric (TG) analysis of [(EDA)(HPS)]



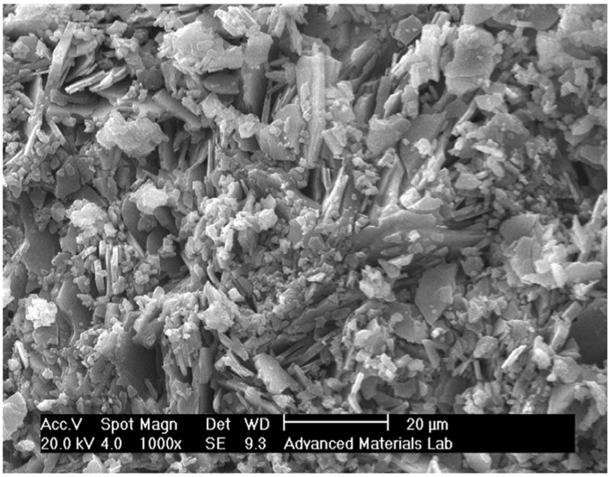


Fig. 3 SEM of [(EDA)(HPS)]

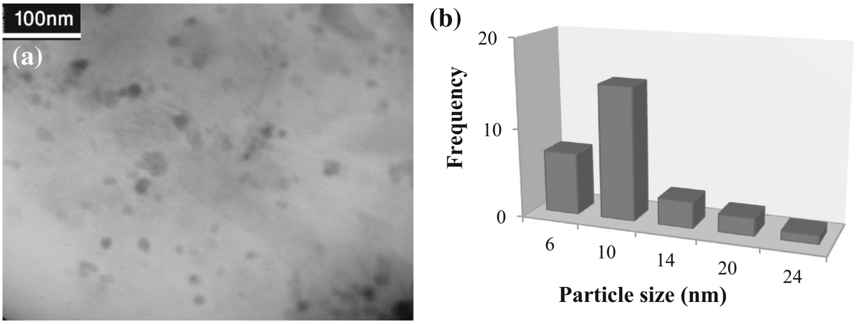


Fig. 4 **a** TEM and **b** particle size distribution of [(EDA)(HPS)]

Table 1 Knoevenagel condensation reaction of benzaldehyde and malononitrile under different condition

Entry	Catalyst	Amount of catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)[a]
1	[(EDA)(HPS)]	10	25	6	82
2	[(EDA)(HPS)]	10	50	4	87
3	[(EDA)(HPS)]	10	60	50 min	95
4	[(EDA)(HPS)]	10	70	50 min	95
5	[(EDA)(HPS)]	5	60	3	91
6	[(EDA)(HPS)]	2.5	60	4	90
7	–	–	60	12	19

Reaction conditions: molar ratio of benzaldehyde:malononitrile: 1:1.2

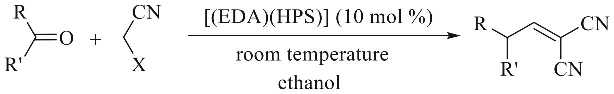
[a] Isolated yield

obtained at 60 °C (Table 1, entry 3). Increasing the reaction temperature to 70 °C had no effect on the product yield or reaction time (Table 1, entry 4). The impact of the amount of catalyst was also investigated (Table 1, entries 5, 6), revealing that the best result was obtained in presence of 10 mol% [(EDA)(HPS)] organosalt (Table 1, entry 3). To demonstrate the role of the catalyst, Knoevenagel condensation reaction of benzaldehyde and malononitrile was also examined in absence of catalyst at 60 °C. Under these conditions, the reaction led to formation of the desired product in low yield (19 %) after 12 h (Table 1, entry 7). The obtained results show that presence of catalyst and appropriate temperature together improved this reaction.

With the optimized conditions in hand (10 mol% catalyst at 60 °C under solvent-free condition), the scope of this novel organocatalyst was examined in Knoevenagel reaction of various aldehydes or ketones with active methylene compounds. The results of these studies are summarized in Table 2. Generally, all reactions were clean and the desired products were produced in excellent yields. Reaction of benzaldehyde with activated methylene compounds such as malononitrile, ethyl cyanoacetate, and cyanoacetamide proceeded well and produced the desired products in 91–95 % yields (Table 2, entries 1–3). [(EDA)(HPS)] was equally effective with substituted benzaldehydes bearing electron-releasing and electron-withdrawing groups, and the Knoevenagel reaction proceeded with excellent yield of the desired products (Table 2, entries 4–10). Interestingly, [(EDA)(HPS)] organosalt efficiently promoted Knoevenagel condensation reaction when using acid-sensitive aldehydes such as thiophene-2-carbaldehyde and furfural without polymerization or decomposition (Table 2, entries 11, 12). [(EDA)(HPS)] organosalt was also successfully applied for Knoevenagel reaction of malononitrile with *t*-butyraldehyde and 3-phenylpropionaldehyde as aliphatic aldehydes (Table 2, entries 13, 14). It is noteworthy that benzophenone and acetophenone reacted with malononitrile to produce the desired products in high yields (Table 2, entries 15, 16).

To investigate the effect of hydroxyl and amine functional groups in the structure of [(EDA)(HPS)] on the catalytic process, different organosalts with OH-free

Table 2 Knoevenagel condensation reaction of various aldehydes or ketones with activated methylene compounds in presence of [(EDA)(HPS)] organocatalyst



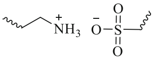
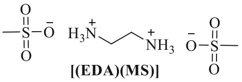
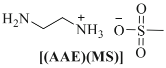
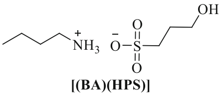
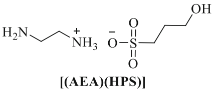
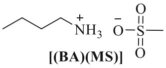
Entry	R	R′	X	Time (h)	Yield (%)[a]	M.p. (°C)/m.p. (°C) [References]
1	C_6H_5	H	CN	50 min	95	83–84/82–83 [21]
2	C_6H_5	H	CO_2Et	2	92	52–53/49–50 [23]
3	C_6H_5	H	$CONH_2$	2.5	91	121–122/123–124 [24]
4	2-$NO_2C_6H_4$	H	CN	20 min	96	142–143/140.2 [22]
5	4-$MeOC_6H_4$	H	CN	2.5	92	115–116/114–115 [23]
6	4-OHC_6H_4	H	CN	1.5	91	187/190 [22]
7	4-ClC_6H_4	H	CN	2.5	91	161/162.5–163.5 [24]
8	2-ClC_6H_4	H	CN	1	93	95–96/94–94.5 [24]
9	4-BrC_6H_4	H	CN	30 min	94	168/165–166 [25]
10	2-$MeOC_6H_4$	H	CN	3	91	84/79–80 [26]
11	2-Thienyl	H	CN	30 min	93	91–92/91–92 [23]
12	2-Furyl	H	CN	30 min	92	61–62/67–68 [23]
13	t-C_4H_9	H	CN	3	90	63/64–65 [25]
14	$C_6H_5(CH_2)_2$	H	CN	45 min	93	129–130/127–129 [27]
15	C_6H_5	C_6H_5	CN	2.5	90	141/143–144 [25]
16	C_6H_5	CH_3	CN	3	92	91–92/94–96 [25]

Reaction conditions: molar ratio of carbonyl compound:malononitrile:catalyst = 1:1.2:0.1, 60 °C, solvent-free condition

[a] Isolated yield

anionic moieties and only a NH_3 group on the cationic moiety were synthesized. The catalytic activity of the synthesized organosalts was checked in Knoevenagel condensation reaction of benzaldehyde and malononitrile under the optimized reaction conditions. 1,2-Ethanediammonium methanesulfonate [(EDA)(MS)] and 1-ammonium 2-aminoethane methanesulfonate [(AAE)(MS)] as OH-free organosalts gave the desired product in 41 and 24 % yield after 12 h and 10 min, respectively (Table 3, entries 1, 2). These results indicate that the hydroxyl functional groups could affect the catalytic activity of the catalyst. On the other hand, the catalytic activity of butan-1-ammonium 3-hydroxypropane-1-sulfonate [(BA)(HPS)] and 2-aminoethane-1-ammonium 3-hydroxypropane-1-sulfonate [(AEA)(HPS)] as organosalts with only one NH_3 group was also studied, with the desired product being obtained in 41 and 55 % yield after 12 h and 10 min, respectively (Table 3, entries 3, 4). This low product yield in presence of [(AAE)(MS)] and [(AEA)(HPS)] is due to formation of byproduct. These results indicate that the catalytic activity of [(EDA)(HPS)] was affected by both ammonium functional groups in the structure of the organosalt. For further investigation, butan-1-aminium methanesulfonate [(BA)(MS)] as OH- and NH_2-free organosalt was synthesized and its catalytic activity examined. The Knoevenagel product was

Table 3 Knoevenagel condensation reaction of benzaldehyde and malononitrile in the presence of different organosalts

Entry		Time	Yield (%)[a]
1[b]	 **[(EDA)(MS)]**	12 h	35
2[c]	 **[(AAE)(MS)]**	10 min	24
3[d]	 **[(BA)(HPS)]**	12 h	41
4[e]	 **[(AEA)(HPS)]**	10 min	55
5[f]	 **[(BA)(MS)]**	12 h	23

Reaction conditions: molar ratio of benzaldehyde:malononitrile:catalyst = 1:1.2:0.1, 60 °C, solvent-free condition

[a] Isolated yield

[b] [(EDA)(MS)] as white solid

[c] [(AAE)(MS)] as white solid

[d] [(BA)(HPS)] as white semisolid

[e] [(AEA)(HPS)] as pale-yellow semisolid

[f] [(BA)(MS)] as white solid

synthesized in 23 % yield after 12 h (Table 3, entry 5). This result shows that the hydroxyl functional groups on the anionic moieties and both NH_3 groups on the cationic moiety in the organosalt have significant effects on the Knoevenagel reaction. Together, these results show that [(EDA)(HPS)] could act as a multifunctional organocatalyst in this reaction.

Based on these observations, a mechanism (supported by literature [20]) for the Knoevenagel reaction is outlined in Scheme 2. H-acidic malononitrile is activated by the hydroxyl groups of the catalyst, and the carbonyl group of aldehyde is activated by the ammonium groups of the catalyst. Then, malononitrile attacks the carbonyl group of benzaldehyde to gave intermediate *I*, which after appropriate rearrangements followed by dehydration gives the desired product.

In addition to green nature, catalyst recovery is an important factor in green synthetic processes. Catalyst recovery was investigated using the reaction of benzaldehyde with malononitrile under standard reaction conditions. The reaction was very clean with no side-product formation, and the desired product was obtained in excellent yield. After reaction completion, warm ethanol was added to the reaction mixture and the organocatalyst was filtered, washed with ethanol, and dried at room temperature. It was then used in the above-mentioned reaction under

Scheme 2 Suggested mechanism for Knoevenagel reaction in presence of [(EDA)(HPS)]

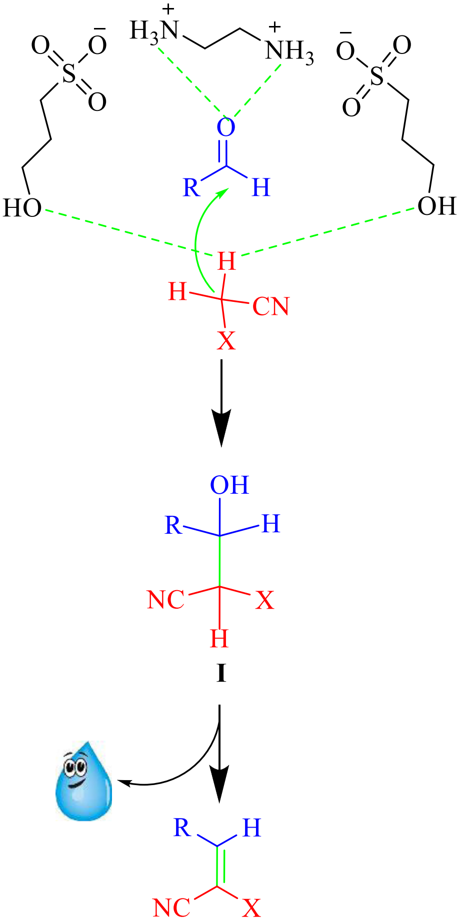
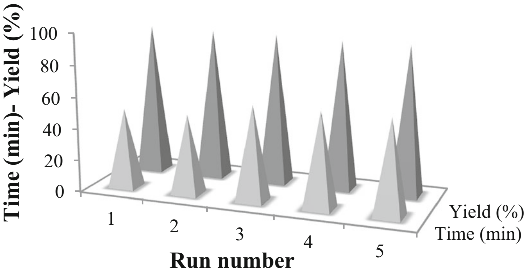


Fig. 5 Reusability of [(EDA)(HPS)] for synthesis of 2-benzylidenemalononitrile



the same conditions as before. The results illustrated that [(EDA)(HPS)] organocatalyst could be recovered and reused at least five times without significant loss of the initial catalytic activity (Fig. 5).

According to TEM analysis combined with elemental analysis of the recovered catalyst (Fig. 6) and comparison with the results obtained from fresh catalyst, it is

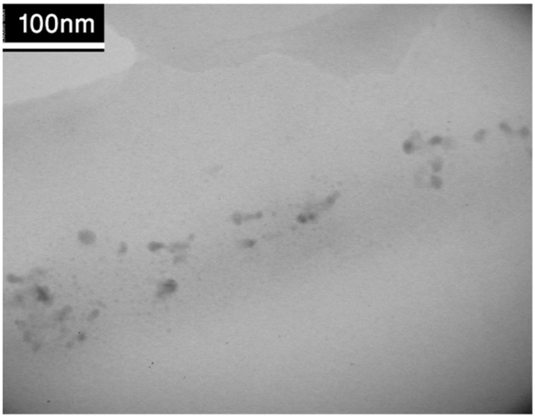


Fig. 6 TEM of [(EDA)(HPS)] after five recovery times

apparent that the [(EDA)(HPS)] organocatalyst exhibited remarkable morphological and structural stability during the reaction and the recycling experiments.

Conclusions

For the first time, 1,2-ethanediammonium 3-hydroxypropane-1-sulfonate [(EDA)(HPS)] was synthesized as a green and environmentally friendly nano organosalt from readily available starting materials. [(EDA)(HPS)] was characterized by various techniques. Spectral and analysis data confirmed successful formation of [(EDA)(HPS)]. TG analysis of [(EDA)(HPS)] showed that the synthesized organosalt had high thermal stability up to 301 °C. TEM revealed that [(EDA)(HPS)] had unique spherical morphology with size of 6–24 nm. Application of [(EDA)(HPS)] as catalyst for Knoevenagel condensation reaction was studied. The most important advantages of the presented approach are high yield, cleaner reaction profile, and easy workup, as well as excellent recyclability of this environmentally benign and cost-effective catalyst. Hence, our methodology exhibits high generality, making it appropriate for industrial application.

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