

Efficient Synthesis of Benzo[b]pyrans and Knoevenagel Products Using Magnetically Separable Nano TPPA-IL-Fe₃O₄

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A simple, efficient, and green practical approach to Knoevenagel condensation of malononitrile and different aldehydes has been developed using an ionic liquid functionalized on Fe₃O₄ magnetic nanoparticles as heterogeneous catalyst. This nanostructural catalyst has also been applied for the synthesis of 4H-benzo[b]pyran derivatives in water at room temperature in short reaction time. All of the products were obtained in good to excellent yields. The TPPA-IL-Fe₃O₄ catalyst was used at least seven times with comparable activities to the fresh catalyst.

Keywords: Ionic liquid, Fe₃O₄ magnetic nanoparticles, Knoevenagel condensation, 4H-benzo[b]pyran

INTRODUCTION

Ionic liquids play an important role in greening chemical protocols and sustainable chemistry. Nowadays, many types of ionic liquids are available with variable cations and anions. These liquids are a great candidate against volatile organic compounds (VOC), which are used for example as solvent. They are non-volatile, non-flammable, thermally stable, have excellent solvation properties [1-2], wide liquid range, higher ionic conductivity and excellent solubility [3-4]. The key step in ionic liquids is to support them to a solid surface to generate a recoverable and non-leachable and reusable catalyst or reagent [5-8].

Many works have focused on supported ionic liquids on different materials, such as silica and polymers. In the recent years, supported catalysts on the nanoparticles have attracted much attention in organic reactions. When the size of the support is decreased to the nanometer scale, the surface area is substantially increased and the support can be evenly dispersed in solution (forming a homogenous emulsion) [9-11]. The main drawbacks of these catalysts are their separation from reaction media; because nanoparticles

cannot be separated by conventional methods such as filtration techniques [12]. This drawback can be overcome using magnetic nanoparticles (MNPs) as a new type of soluble matrix, which can be easily recovered from the reaction mixture by external magnet [13-15]. MNPs are readily available with high-surface-area resulting in high catalyst loading capacity and outstanding stability [16]. The notable advantages of Fe₃O₄ MNPs are their simple synthesis procedure, readily available, low cost, high surface area, low toxicity, and its superparamagnetism properties [17].

Knoevenagel condensation is one of the most important carbon-carbon double-forming reactions in organic synthesis, which is reacted between carbonyl compounds and active methylene compounds and widely used in the synthesis of chemically, biologically, and pharmaceutically significant compounds [18]. Recently, several catalytic systems have been developed for this transformation [19-21]. Industrially, these reactions are indeed carried out in the homogeneous phase with KOH or NaOH [22-25].

Assembly of biologically important molecules based on molecular diversity by utilizing multi-component reactions has received great attention in drug architecture and organic synthesis. One-pot multi-component reactions are preferably simple, fast, and efficient [26-27]. 4H-

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benzo[b]pyrans and their derivatives have been attracted a lot of attention as important heterocyclic compounds because of their wide range of biological properties such as anti-cancer, anti-coagulant and anti-anaphylactic activates [28-29]. These compounds find extensive applications in different fields, such as cosmetics, pigments, and as potential biodegradable agrochemicals [30]. 4H-pyrans also constitute the structural unit of a series of natural products. Finally, a number of 2-amino-4H-pyrans are useful as photoactive materials [31]. Therefore, the synthesis of such compounds has attracted strong interest [32-34].

EXPERIMENTAL

Materials

Chemicals were purchased from Fisher and Merck chemical companies. The reagents and solvents were obtained from Sigma-Aldrich, Fluka or Merck and used without further purification.

1.1.

Preparation of Magnetic Fe₃O₄ Nanoparticles (MNPs)

The mixture of FeCl₃.6H₂O (5.838 g, 0.022 mol) and FeCl₂.4H₂O (2.147 g, 0.011 mol) were dissolved in 100 ml of deionized water in a three-necked bottom (250 ml) at 80 °C under N₂ atmosphere. Thereafter, 10 ml of aqueous NH₃ solution (32%) was added into the mixture within 30 min with vigorous mechanical stirring. The black precipitate solid was isolated by magnetic decantation, washed with double-distilled water until neutrality, and further washed twice with ethanol and dried at 80 °C in vacuum [13].

Preparation of Fe₃O₄-(3-aminopropyl)-triethoxysilane

The obtained magnetic nanoparticles (MNPs) powder (1.5 g) was dispersed in a mixture of ethanol and water (250 ml, 1:1 by volume) by sonication for 30 min. Then, 3-aminopropyl (triethoxy) silane (99%, 3 ml) was added to the mixture, and then kept under mechanical stirring under N₂ atmosphere at room temperature for 8 h. At the end of the reaction, the resulted product was washed with copious amounts of deionized water and ethanol under magnetic decantation, and dried under vacuum at room temperature overnight [8].

Preparation of TPPA-IL-Fe₃O₄

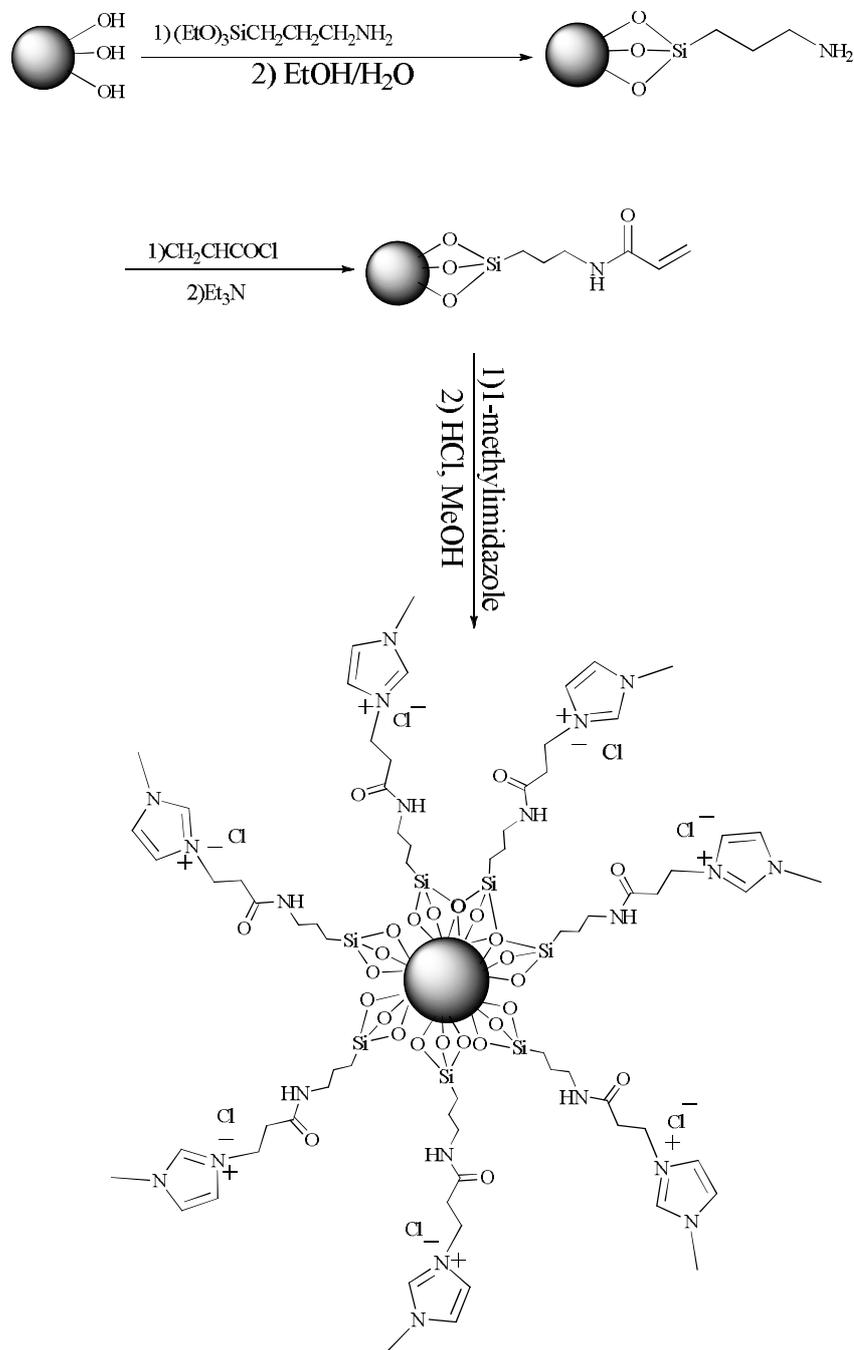
The amino-functionalized MNPs (1 g) were dispersed in dry CH₂Cl₂ (3 ml) by ultrasonic bath for 10 min, and the flask was cooled in an ice-water bath. Triethylamine (3.2 ml) was added and stirred for 30 min. Subsequently, acryloyl chloride (0.8 ml, 9.84 mmol) was added drop wise over a period of 30 min at room temperature. The mixture was stirred at room temperature for 48 h. Then, the prepared functionalized MNPs nanoparticles were separated by magnetic decantation and washed three times with acetone and deionized water to remove the unattached substrates. The resulting product was dispersed in methanol (10.0 ml), and stirred with 1-methylimidazole (2.0 mmol, 0.164 g). Subsequently, a stoichiometric amount of concentrated HCl (97%, 0.2 ml) was added drop wise and the mixture stirred for 1 h at 0 °C and then stirred for 1 week at room temperature. The solids were separated by a magnetic field and washed with acetone. The resulting product was dried under vacuum for 12 h [13].

General Procedure for the Knoevenagel Condensation

TPPA-IL-Fe₃O₄ (8 mg) was added to a mixture of 4-chlorobenzaldehyde (1 mmol) and malononitrile (1 mmol) at room temperature in water (3 ml). Then the mixture was stirred for the appropriate time. The progress of reaction was monitored by TLC. After completion of the reaction, the catalyst was separated by magnetic decantation and the mixture was washed with CH₂Cl₂ (5 × 2 ml), then, the product was extracted with CH₂Cl₂ (4 × 5 ml). The organic layer was dried over anhydrous Na₂SO₄ (1.5 g). Finally, the organic solvent was evaporated, and products were obtained in good to high yield.

General Procedure for the Synthesis 4H-benzo[b]pyrans

A solution of an aldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol) and water (2 ml) in the presence of TPPA-IL-Fe₃O₄ (8 mg) was heated at 60 °C, with stirring for 15-60 min. The progress of the reaction was followed by TLC. After completion of the reaction, the catalyst was separated by magnetic decantation and the mixture was washed with CH₂Cl₂ (5 × 2 ml), then, the product was extracted with CH₂Cl₂ (4 × 5 ml). The organic



Scheme 1. Synthesis of TPPA-IL- Fe_3O_4

layer was dried over anhydrous Na_2SO_4 (1.5 g). Finally, the organic solvent was evaporated, and resulting solid products were recrystallized in ethanol and products were obtained in good to high yield.

RESULTS AND DISCUSSION

The process for the preparation of 3-((3-(triethoxysilyl)propyl)propionamide)-1-methyl-

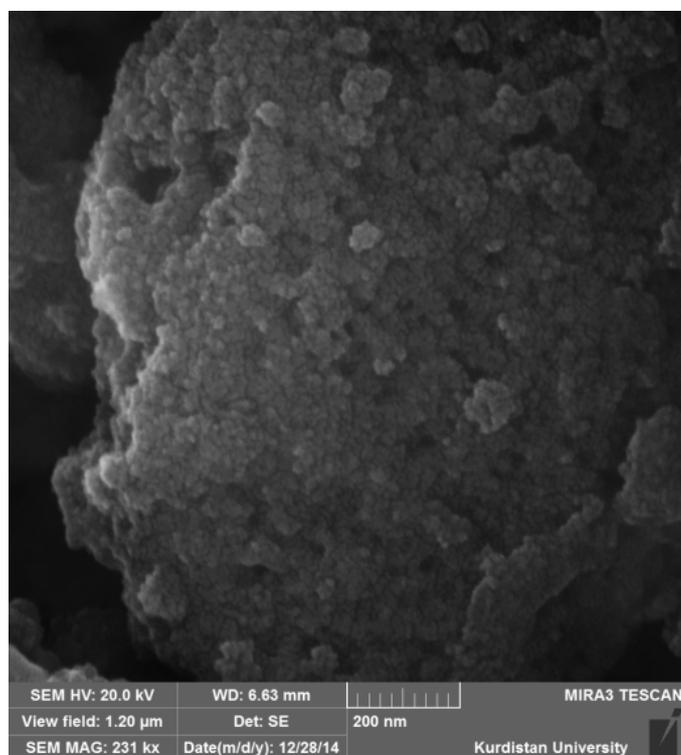
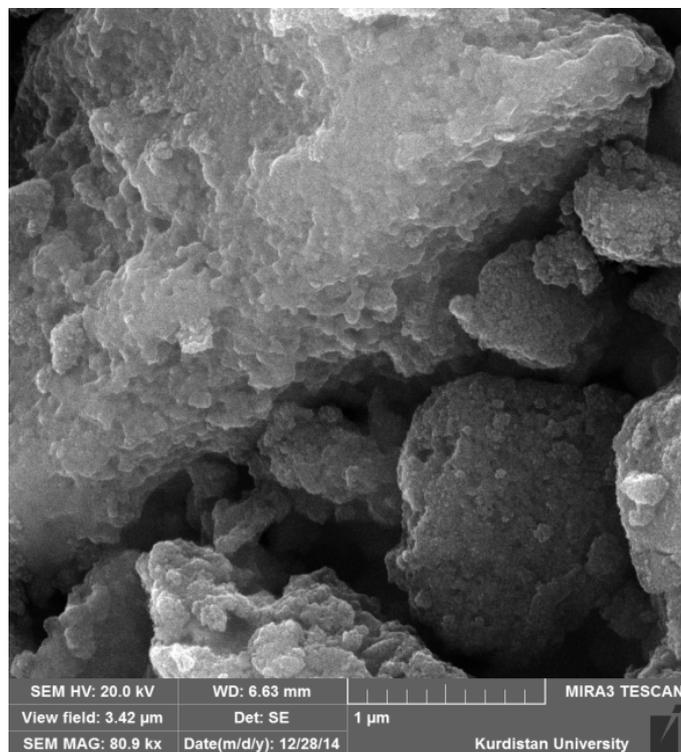
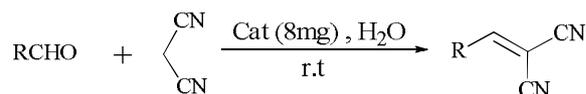


Fig. 1. SEM images of TPPA-IL-Fe₃O₄ with different magnifications (a, b).

Table 1. Optimization of the Knoevenagel Condensation

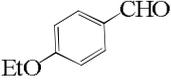
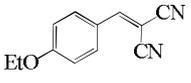
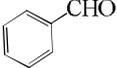
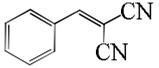
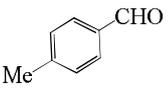
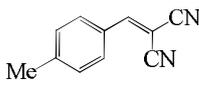
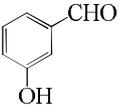
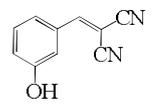
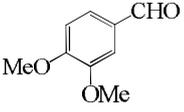
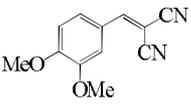
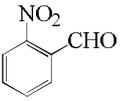
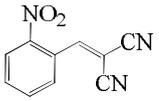
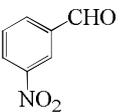
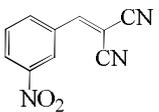
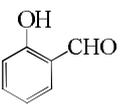
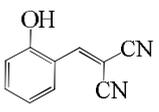
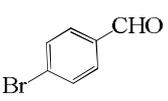
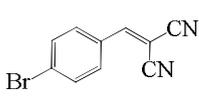
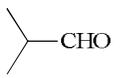
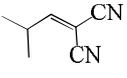
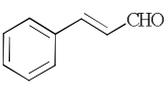
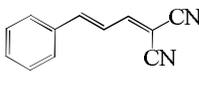
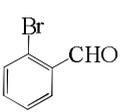
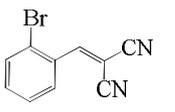
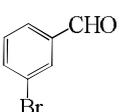
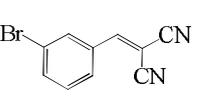
Entry	Solvent	Catalyst (mg)	Time (min)	Yield (%) ^b
1	EtOH	8	120	54
2	CH ₂ Cl ₂	8	120	60
3	n-Hexane	8	120	trace
4	Acetone	8	120	48
5	EtOAc	8	120	62
6	H ₂ O	2	12	54
7	H ₂ O	4	12	60
8	H ₂ O	6	12	85
9	H ₂ O	8	12	99
10	H ₂ O	10	12	99
11	H ₂ O	No catalyst	360	35

^aReaction conditions: 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol), room temperature. ^bIsolated yields.

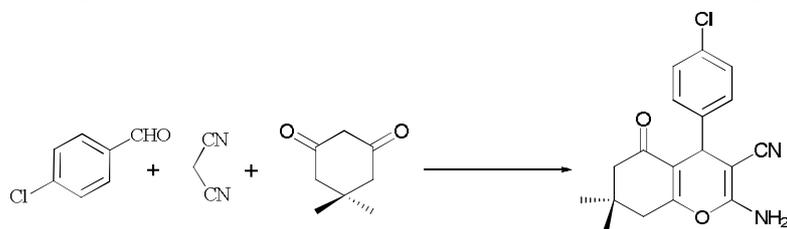
Table 2. Knoevenagel Condensation of Different Aldehydes

Entry	Substrate	Product	Time (min)	Yield (%) ^b
1			17	97
2			12	99
3			5	100
4			17	99

Table 2. Continued

5			23	98
6			14	100
7			12	90
8			4	98
9			8	95
10			8	90
11			7	92
12			11	99
13			8	97
14			5	91
15			4	96
16			10	98
17			5	98

^aReaction conditions: substrate (1 mmol), malononitrile (1 mmol), catalyst 8 mg, room temperature. ^bIsolated yields.

Table 3. Optimization of Reaction Conditions for Synthesis of 4H-benz [b]pyrans^a

Entry	Solvent	Catalyst (mg)	Time (min)	Yield (%) ^b
1	H ₂ O	No catalyst	360	Trace
2	H ₂ O	2	120	54
3	H ₂ O	4	120	60
4	H ₂ O	6	120	85
5	H ₂ O	8	35	98
6	H ₂ O	10	35	98
7	EtOH	8	120	54
8	CH ₃ CN	8	120	75
9	EtOAc	8	120	62

^aReaction conditions: 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol), ^bIsolated yields.

imidazolium chloride ionic liquid supported on magnetic nanoparticle (TPPA-IL-Fe₃O₄) is schematically outlined in Scheme 1. The preparation and characterization of TPPA-IL-Fe₃O₄ have been reported in our newly published work [13].

The morphological and size of the catalyst was evaluated by SEM analysis (Fig. 1). According to Figs. 1a-b, most of the particles were obtained in quasi-spherical form with an average diameter about 8-18 nm.

In continuing our research about catalytic properties of TPPA-IL-Fe₃O₄ and its ability to act as organocatalyst, herein we wish to report TPPA-IL-Fe₃O₄ as a potential catalyst for the Knoevenagel condensation.

In order to ascertain the feasibility of this transformation, 4-chlorobenzaldehyde and malononitrile were selected as model substrates, and conversion to 2-(4-chlorobenzylidene)malononitrile was studied under a

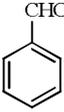
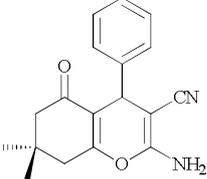
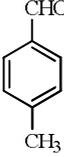
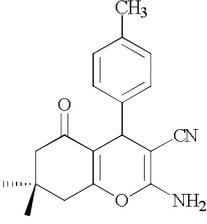
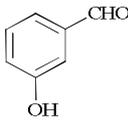
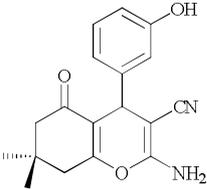
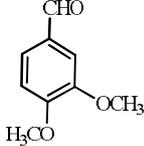
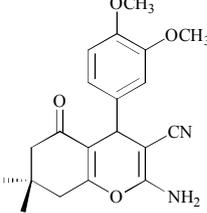
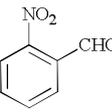
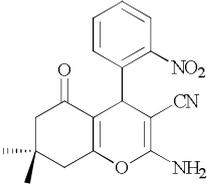
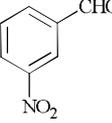
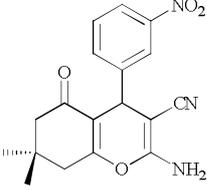
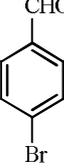
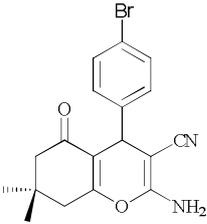
variety of conditions. Initially, the solvent effect was examined, and a significant solvent effect was observed. Different solvents such as water, ethanol, dichloromethane, ethyl acetate, and acetone were tested (Table 1). Among them, water afforded the best yield of product.

In order to determine the appropriate amount of the catalyst, we examined the model reaction using varied concentrations of TPPA-IL-Fe₃O₄ such as 2, 4, 6, 8 and 10 mg. In this study, formation of the product was observed in 64%, 60%, 85%, 99% and 99% yield, respectively. These results indicated that 8 mg of TPPA-IL-Fe₃O₄ is sufficient to carry out efficiently the condensation reaction. In order to prove the catalytic role of TPPA-IL-Fe₃O₄ the reaction was performed in the absence of this material. Doing reaction in this conditions leads to production of 2-(4-chlorobenzylidene)malononitrile only in 35% yield after 360 min (Table 1, entry 11). Thus TPPA-IL-Fe₃O₄ was

Table 4. Synthesis of 4H-benzo[b]pyran Derivatives Using TPPA-IL-Fe₃O₄

Entry	Substrate	Product	Time (min)	Yield (%) ^b	M.p. (°C)[Ref.]
1			25	96	199-201 [24]
2			35	98	214-216 [24]
3			15	94	223-225 [24]
4			35	91	200-202 [24]
5			15	95	233-235 [29]

Table 4. Continued

6			20	96	232-233 [30]
7			22	98	214-216 [30]
8			35	93	231-232 [30]
9			25	96	181-182 [30]
10			60	90	224-226 [26]
11			50	93	177-178 [24]
12			32	96	198-200 [24]

^aReaction conditions: substrate (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol), catalyst 8 mg^bIsolated yields.

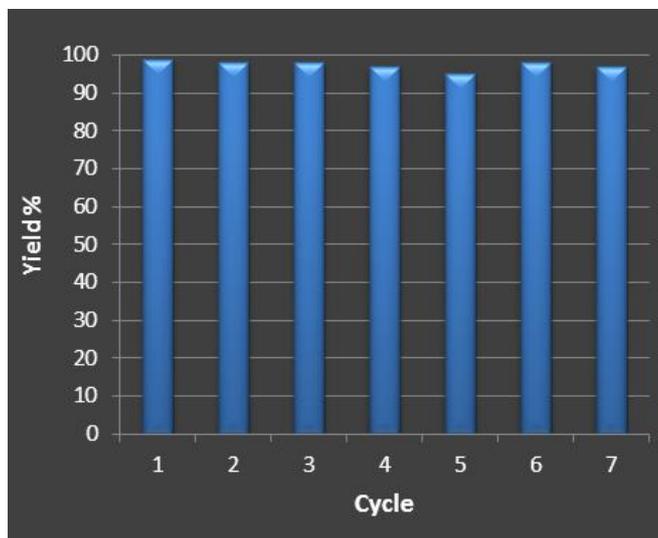


Fig. 2. Reusability of TPPA-IL-Fe₃O₄ for the preparation of 2-(4-chlorobenzylidene)malononitrile.

identified as an efficient and reusable catalyst for the present reaction at room temperature in water as solvent.

Table 1. Optimization of the Knoevenagel condensation

This observation encouraged us to expand the scope of this method. Therefore, a variety of aldehydes containing different acceptor and donor substituents were reacted with malononitrile in the presence of TPPA-IL-Fe₃O₄ under optimized conditions. The results of these condensation reactions are summarized in Table 2. The nitro, chloro, and bromo substituents were chosen as electron-withdrawing groups, and the methoxy, methyl, ethoxy substituents as a representative electron-donating group. Knoevenagel condensation of aliphatic aldehyde and cinnamaldehyde were carried and also afforded to the desired product in excellent yield (Table 2, entries 15 and 16).

As a part of our ongoing project devoted towards the development of a practical synthesis of biologically interesting heterocyclic molecules and explore the more activity of described catalyst, we wish to report here a simple and efficient method for the synthesis of 4H-Benzo[b]pyrans using TPPA-IL-Fe₃O₄ as catalyst. To obtain the optimum conditions, preparation of 4H-benzo[b]pyran was considered from the reaction of 4-chlorobenzaldehyde, dimedone and malononitrile as a model reaction in the

absence and presence of the TPPA-IL-Fe₃O₄ in order to establish the effectiveness of the catalyst. It was found that 4H-benzo[b]pyran was produced in trace amount after 6 h in the absence of TPPA-IL-Fe₃O₄; whereas 2 mg of catalyst led to 54% yield after 120 min (Table 3, entries 1 and 2). The best conditions to prepare the 4H-benzo[b]pyran was achieved by 8 mg of catalyst, and any excess of the catalysts did not lead to an increase in the conversion and yield of product (Table 1, entries 5 and 6).

Subsequently we screen various solvents in the presence of 8 mg of nanocatalyst. Among considered solvents, the reaction was found to proceed efficiently in water giving 98% yields in 35 min (Table 1, entries 5). Increasing interest of organic chemists for the use of water as a solvent of choice and its unique properties turned our attention to examine it for the present reaction.

With optimal conditions in hand, different aromatic aldehydes have been examined for described transformation. The results are summarized in Table 4. Both electron-rich and electron-deficient aldehydes are suitable substrates for this reaction to provide the corresponding 4H-benzo[b]pyran in good to excellent yields.

Table 4. Synthesis of 4H-benzo[b]pyran derivatives using TPPA-IL-Fe₃O₄

The most important aspect of the catalytic systems is the

reusability of the catalyst. Therefore, reusability of described catalyst was examined for the condensation of 4-chlorobenzaldehyde with malononitrile. After the first run, the catalyst was easily and rapidly separated from the reaction mixture using an external magnet and subsequently was used for the next run. As it can be seen from Fig. 2, the catalyst can be recycled at least for seven runs without any significant loss of its catalytic activity and efficient.

CONCLUSIONS

In summary, we have demonstrated that TPPA-IL-Fe₃O₄ acts as an efficient organocatalyst for the Knoevenagel condensation reaction and synthesis of 4H-benzo[b]pyrans under “green” reactions conditions. The present methodology shows very high atom economy with very high yields of the products. The catalyst is highly stable, environmentally benign, and recoverable. The product separation and catalyst recycling is easy and simple with the assistance of an external magnet. The catalyst can be reused at least 7 times without loss of its activity.

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