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Original Research Article

Preparation and characterization of polyethylene glycol-bis(*N*-methylimidazolium) dihydroxide as a basic phase-transfer catalyst and its application in Knoevenagel condensation under aqueous media

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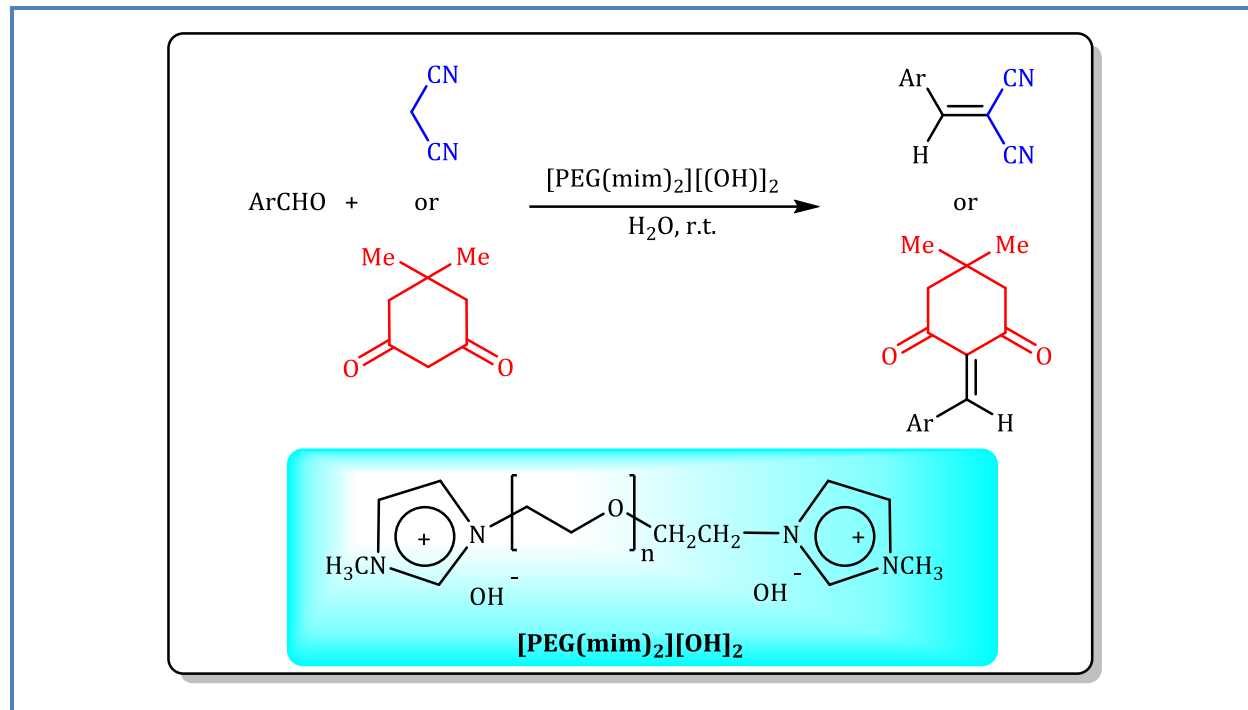
KEYWORDS

Green chemistry
Phase-transfer catalysis
Polyethylene glycol-bis(*N*-methylimidazolium)dihydroxide
Knoevenagel condensation

ABSTRACT

A basic phase-transfer catalyst ([PEG(mim)₂][OH]₂) was prepared from the reaction of polyethylene glycol-bis(*N*-methylimidazolium) dibromide and sodium hydroxide dissolved in water at ambient temperature. The obtained white solid was used as an efficient basic phase-transfer catalyst in Knoevenagel condensation reactions between aromatic aldehydes and active methylene compounds in water at room temperature. The reaction is done without side products and in the presence of trace amounts of the catalyst gives the corresponding products with high yields. The phase-transfer catalyst could be successfully reused without significant decrease in its activity for at least five cycles.

Graphical Abstract



Introduction

Phase-transfer catalysts (PTCs), as very active compounds, are widely used in organic synthesis. In particular, this method is very useful for performing organic reactions in water. Since most of the organic reactants don't dissolve in water, the use of phase-transfer catalysts can resolve this problem. Both homogeneous and heterogeneous phase-transfer catalysts improve the intimate contact between inorganic reagents and organic substrates, but in most cases the use of homogeneous PTCs increase the reactivity [1].

Polyethylene glycol (PEG) and its derivatives are known to be inexpensive, nontoxic, almost negligible vapor pressure, thermally persistent, recyclable and environmentally benign media for chemical reactions. The properties of PEG offer the possibility for immobilizing and recycling a homogeneous catalyst [2]. One of the ways to increase efficiency of polyethylene glycol as a phase-transfer catalyst in organic synthesis is the covalently bonding of quaternary ammonium salts [3–5].

The Knoevenagel condensation of aldehydes with active methylene compounds is an important and widely applied method for carbon-carbon bond formation in organic synthesis with numerous applications in the synthesis of various pharmaceutically and biologically active compounds [6]. A literature survey shows that several methods for the Knoevenagel reaction using different catalysts have been reported [7–17]. However, many proposed methods for this transformation suffer

disadvantages including the use of toxic organic solvents or catalysts containing transition metals, high temperature reaction conditions, need for an excessive amounts of the reagent, tedious work-up procedure, troublesome waste discarding, long reaction times, low yields of products and non-recyclability of the catalyst. Therefore, introducing simple, efficient and mild procedures with easily separable and reusable catalysts to overcome these problems is still in demand.

In the framework of our continuous effort on synthesis of novel catalysts [18–20], herein, we prepared polyethylene glycol-bis(*N*-methylimidazolium) dihydroxide, [PEG(mim)₂][OH]₂ as a recyclable homogeneous basic phase-transfer catalyst which catalyzed the Knoevenagel condensation between aryl aldehydes and malononitrile or dimedone under aqueous conditions at room temperature.

Experimental

Materials and methods

All materials and reagents were purchased from Fluka and Merck and used without further purification. Polyethylene glycol 400 was heated at 80 °C under vacuum for 30 min before use to remove traces of moisture. Products were characterized by comparing their physical data, IR, ¹H NMR and ¹³C NMR spectra with known samples. NMR spectra were recorded in CDCl₃ on a Bruker Advance DPX 400 MHz instrument spectrometer using TMS as internal standard. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrometer. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates.

Synthesis of polyethylene glycol dibromide, [PEG]Br₂

Polyethylene glycol dibromide was prepared according to the reported method [21]. To a solution of polyethylene glycol 400 (20 g, 0.1 mol OH) and pyridine (7.9 g, 0.1 mol) in 500 mL of toluene, thionyl chloride (16 g, 0.14 mol) was added slowly with stirring over a period of half an hour. The mixture was then refluxed for about 6 h. After cooling and filtering off the pyridine hydrochloride, the solvent was removed in vacuo. The residue was dissolved in dichloromethane and treated with activated alumina. The process was repeated twice. The dichloromethane solution was filtered and evaporated to obtain polyethylene glycol dichloride. A mixture of polyethylene glycol dichloride (10 g, 0.015 mol) and sodium bromide (10.3 g, 0.1 mol) was heated in an oil bath at 120 °C overnight. After cooling, dichloromethane was added, the solution was filtered, and the solvent was removed in vacuo in order to obtain polyethylene glycol dibromide.

Synthesis of polyethylene glycol-bis(N-methylimidazolium) dibromide, [PEG(mim)₂]Br₂

A mixture of polyethylene glycol dibromide (5 g, 0.01 mol) and *N*-methylimidazole (4.1 g, 0.05 mol) in acetonitrile (50 mL) was stirred at reflux for 48 h in a two necked round bottom flask equipped with water condenser. Then, the reaction mixture was cooled to room temperature. The solvent was evaporated under reduced pressure using a rotary evaporator. The reaction mixture was washed with ethyl acetate (3×10 mL) to remove unreacted starting materials and the resulting quaternized polyethylene glycol-bis(*N*-methylimidazolium) dibromide was obtained as a thick liquid.

Synthesis of polyethylene glycol-bis(N-methylimidazolium) dihydroxide, [PEG(mim)₂][OH]₂

A mixture of polyethylene glycol-bis(*N*-methylimidazolium) dibromide (1.2 g, 2.0 mmol) and sodium hydroxide (0.5 g, 12.5 mmol) in water (20 mL) was stirred at room temperature for 3 h. The solution was placed in air overnight to evaporate the water. Then, a white precipitate formed which was washed with ethyl acetate (10 mL) to give the quaternized polyethylene glycol-bis(*N*-methylimidazolium) dihydroxide in 92% yield. The pH of the catalyst determined by pH meter was 10.38 for 0.01 g of the solid base at 25 °C. IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3463, 3078, 2871, 1574, 1453, 1170, and 1105. ¹H NMR (400 MHz, D₂O): δ 3.63 (m, 22H, O-CH₂-CH₂-O), 3.84 (t, 4H, *J* = 2.4 Hz, O-CH₂-CH₂-N), 4.31 (s, 6H, N-CH₃), 4.70 (t, 4H, *J* = 2.4 Hz, N-CH₂-CH₂-O), 7.37-7.47 (m, 4H, C(4,5)-H), 8.36-8.38 (m, 2H, C(2)-H).

General procedure for the Knoevenagel condensation reaction

The basic PTC, [PEG(mim)₂][OH]₂, (5.6 mg, 0.01 mmol) was added to a mixture of aromatic aldehydes (1 mmol) and active methylene compounds (1 mmol) in water (3 mL). The reaction mixture was stirred at ambient temperature for the appropriate time shown in Table 2. After completion of the reaction according to TLC analysis (*n*-hexane/ethyl acetate, 5:2), the mixture was filtered off and the filtrate was washed with water and the solid products were purified by recrystallization from ethanol.

*Selected spectroscopic data**2-(Phenylmethylene)malononitrile (1a)*

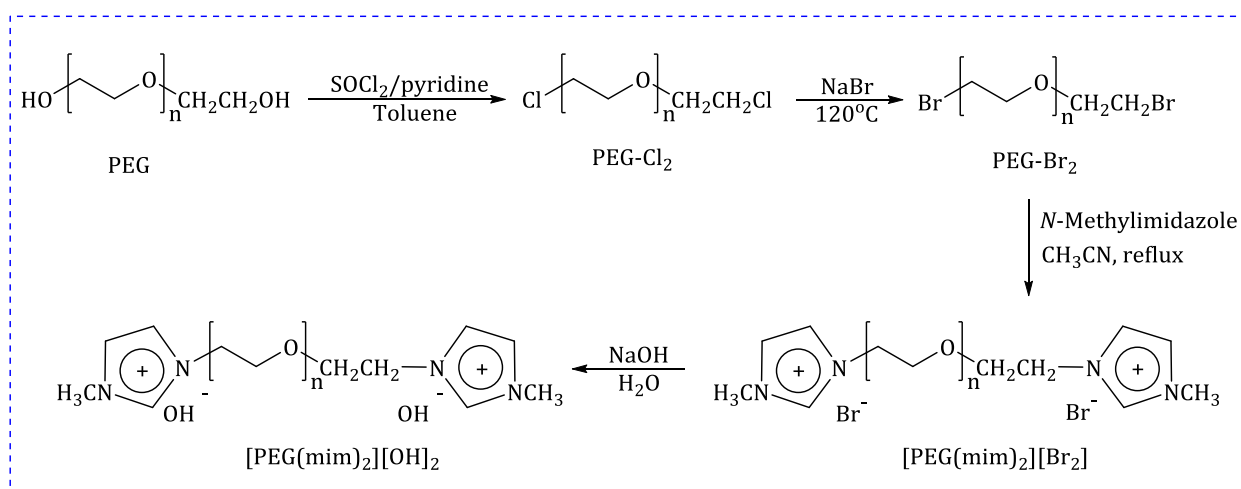
IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3037, 2222, 1594, and 761. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.70 (t, *J* = 7.6 Hz, 2H), 7.78 (m, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 8.64 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 81.6, 113.2, 114.2, 129.5, 130.5, 131.3, 134.4, 161.6.

2-(Furylmethylene)malononitrile (**10a**)

IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3041, 2952, 2224, 1600, 1448, and 759. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.01 (dd, $J = 2.0, 3.6$ Hz, 1H), 7.54 (d, $J = 3.6$ Hz, 1H), 8.29 (d, $J = 2.0$ Hz, 1H), 8.39 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 74.9, 113.3, 114.5, 114.8, 125.9, 144.5, 148.1, 151.2.

2-(2-Chlorophenylmethylene)-5,5-dimethylcyclohexane-1,3-dione (**2b**)

IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3428, 1718, 1595, 1301, and 1122. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 0.92 (s, 3H), 1.03 (s, 3H), 2.41-2.58 (m, 4H), 6.94-7.10 (m, 3H), 7.31 (m, 1H), 7.80 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 28.7, 33.4, 58.7, 125.7, 126.8, 128.4, 131.1, 132.0, 132.5, 140.8, 147.3, 195.8, 199.6.



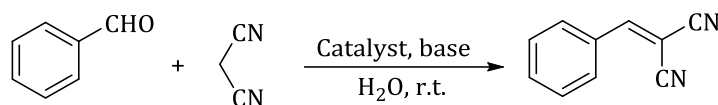
Scheme 1. Preparation of the polyethylene glycol-bis(*N*-methylimidazolium) dihydroxide

Results and discussion

Polyethylene glycol-bis(*N*-methylimidazolium) dihydroxide was prepared as shown in [Scheme 1](#). Polyethylene glycol dibromide was prepared according to the literature method [21]. Then, polyethylene glycol dibromide was treated with two equivalent of *N*-methylimidazole in acetonitrile under reflux conditions to afford the dicationic PTC with bromide anion. Ultimately, the stirring of the PTC in aqueous NaOH at room temperature led to the formation of polyethylene glycol-bis(*N*-methylimidazolium) dihydroxide, [PEG(mim)₂][OH]₂ as a white solid with basic characteristic.

Following the preparation of the catalyst, it was decided to consider the catalytic activity of [PEG(mim)₂][OH]₂ as an effective basic phase-transfer catalyst for the Knoevenagel condensation reaction. The reaction of benzaldehyde (1 mmol) with malononitrile (1 mmol) was chosen as a model reaction, and the reaction was evaluated in various conditions ([Scheme 2](#) and [Table 1](#)).

The results showed that the reaction in the presence of NaOH and K₂CO₃ (10 mol%) without PTC did not complete even in longer time and gave the corresponding product in 40% and 55% yields,



Scheme 2. Knoevenagel condensation of benzaldehyde with malononitrile in water at room temperature

Table 1. Optimization of the reaction conditions^a

Entry	Catalyst (mol%)	Base (mol%)	Time (min)	Yield (%) ^b
1	-	NaOH (10)	120	40
2	-	K ₂ CO ₃ (10)	120	55
3	PEG 400 (10)	K ₂ CO ₃ (10)	120	70
4	[PEG(mim) ₂]Cl ₂ (10)	K ₂ CO ₃ (10)	120	75
5	[PEG(mim) ₂]Br ₂ (10)	K ₂ CO ₃ (10)	120	80
6	[PEG(mim) ₂][OH] ₂ (1)	K ₂ CO ₃ (10)	15	93
7	[PEG(mim) ₂][OH] ₂ (1)	-	18	92

^a Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), required amounts of the catalysts and bases, water (3 mL), room temperature

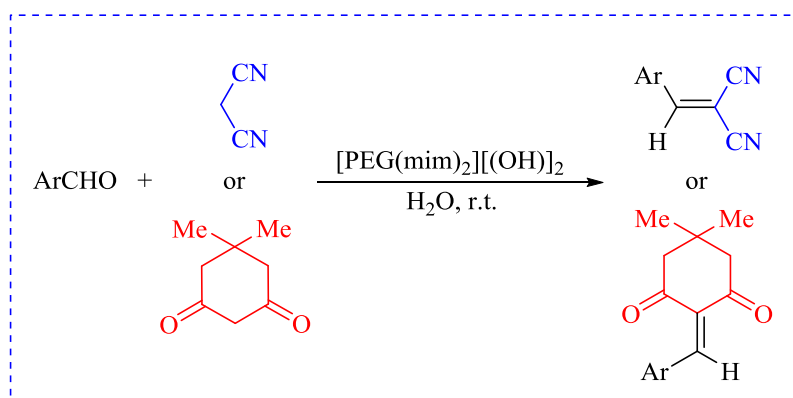
^b Isolated yield

respectively (Table 1, entries 1 and 2). The reaction in the presence of K₂CO₃ (10 mol%) and PEG 400, [PEG(mim)₂]Cl₂ or [PEG(mim)₂]Br₂ (Each, 10 mol%) gave the corresponding product in higher yields at the same reaction times; but, it is worth mentioning that the reactions did not complete (Table 1, entries 3–5). Although this condensation was performed in the presence of K₂CO₃ (10 mol%) and [PEG(mim)₂][OH]₂ (1 mol%) in less time (Table 1, entry 6) the best condition was the use of [PEG(mim)₂][OH]₂ (1 mol%) in the absence of any base.

Subsequently, the generality and synthetic scope of this protocol for the Knoevenagel condensation of various aryl aldehydes with malononitrile or dimedone were demonstrated under optimal conditions (Scheme 3 and Table 2). As shown in Table 2, yields of products are good to excellent for aromatic aldehydes bearing both electron-donating and electron-withdrawing groups.

Finally, the recyclability and reusability of the catalyst was studied for the reaction of benzaldehyde with malononitrile. After the reaction completion, the reaction mixture was filtered and the precipitate was washed with ethanol. The catalyst was recycled by evaporating the aqueous ethanolic phase in air and washing with ethyl acetate. After becoming air dried, the recycled catalyst could be reused as such in subsequent experiments (Up to five cycles) under similar reaction conditions. The yields of the product remained comparable in all experiments (92, 91, 89, 89, and 85 in cycles 1–5, respectively) indicating that the catalyst can be recycled at least five times with no considerable loss in its activity.

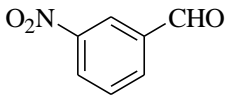

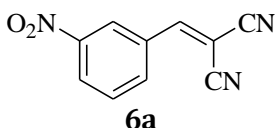
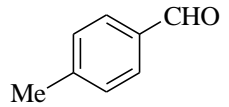
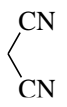
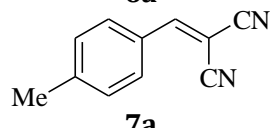
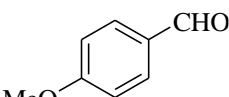

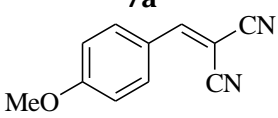
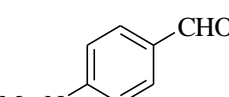

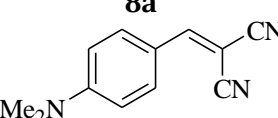
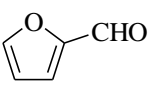
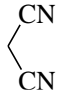
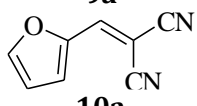
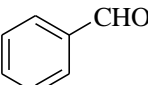
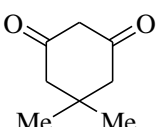
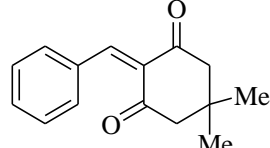
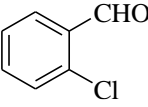
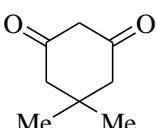
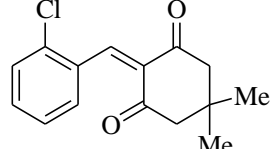
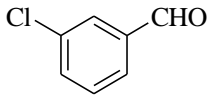
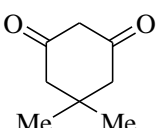
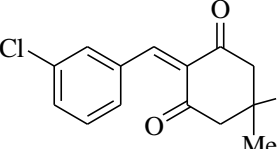
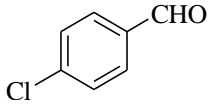
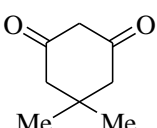
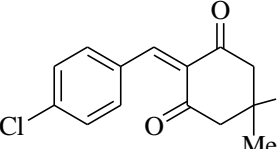
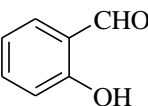
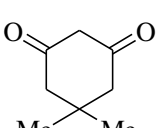
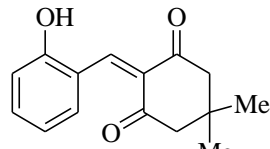
A comparison of the catalytic strength of $[\text{PEG}(\text{mim})_2][\text{OH}]_2$ in the Knoevenagel condensation between benzaldehyde and malononitrile with some of the methods reported in the literature is presented in [Tables 3](#). The results showed that our procedure provided high yields of products in short reaction times under mild and green conditions.

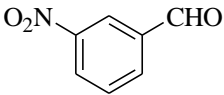
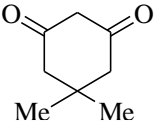
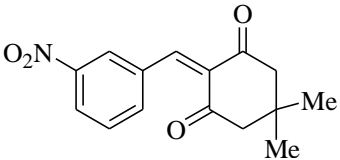
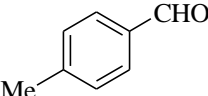
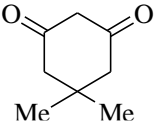
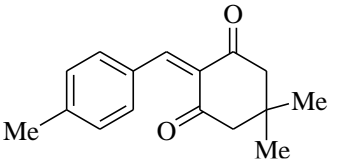
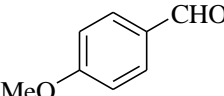
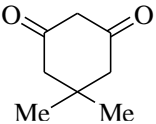
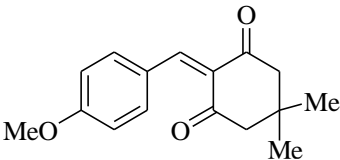
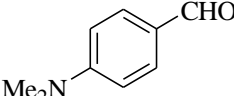
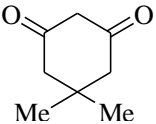
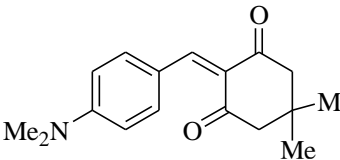
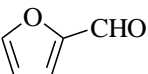
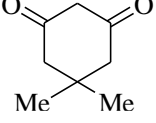
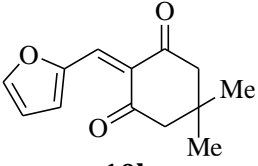


Scheme 3. Knoevenagel condensation of aryl aldehydes with active methylene compounds in the presence of $[\text{PEG}(\text{mim})_2][\text{OH}]_2$ in water at room temperature

Table 2. Knoevenagel condensation reaction of aromatic aldehydes and active methylene compounds catalyzed by $[\text{PEG}(\text{mim})_2][\text{OH}]_2^{\text{a}}$

Entry	Aromatic aldehydes	Active methylene compounds	Products	Time (h)	Yield (%) ^b
1				0.30	92
2				0.67	88
3				0.63	90
4				0.55	87
5				0.67	89

6			 6a	0.92	85
7			 7a	0.25	91
8			 8a	0.33	90
9			 9a	0.67	83
10			 10a	0.25	92
11			 1b	3	90
12			 2b	4	84
13			 3b	4	87
14			 4b	3	88
15			 5b	4	87

16				4	85
			6b		
17				3	89
			7b		
18				3	91
			8b		
19				4	83
			9b		
20				2	89
			10b		

^a Reaction conditions: aryl aldehyde (1 mmol), active methylene compound (1 mmol), PTC (1 mol%), water (3 mL), room temperature

^b Isolated yield

Table 3. Comparison of Knoevenagel condensation between benzaldehyde and malononitrile with different methods

Entry	Catalyst	Solvent	Condition	Time (min)	Yield (%)	Refs.
1	H ₃ PW ₁₂ O ₄₀	H ₂ O	reflux	15	91	[9]
2	Ni-nanoparticles	EtOH	r.t.	20	98	[11]
3	Calcined eggshell (CES)	H ₂ O	r.t.	15	92	[14]
4	[hmim][PF ₆]/glycine	-	55 °C	22 h	77	[22]
5	TiO ₂	CH ₂ Cl ₂	reflux	48 h	40	[23]
6	PMOV1	-	70 °C	45	86	[24]
7	MOF-Pd	DMSO- <i>d</i> ₆	r.t.	10	73.7	[25]
8	PdAlO(OH)	H ₂ O/MeOH	r.t.	35	85	[26]

9	RhPt@GO nanoparticles	H ₂ O/MeOH	r.t.	10	99	[27]
10	[PEG(mim) ₂][OH] ₂	H ₂ O	r.t.	18	92	This work

Conclusion

In conclusion, the present study describes the preparation of a homogeneous basic phase-transfer catalyst by the reaction of polyethylene glycol-bis(*N*-methylimidazolium) dibromide and sodium hydroxide in aqueous media at ambient temperature. Then, the catalytic activity of this green, recoverable and efficient catalyst was investigated in the Knoevenagel condensation reaction of aryl aldehydes with malononitrile or dimedone under aqueous media at room temperature. This catalytic method offers several advantages including environmental friendliness, high yield, short reaction time, the use of mild reaction conditions, a simple work-up procedure, ease of separation, and recyclability of the catalyst. So we think that this procedure could be considered as a new and suitable addition to the present methodologies in this area.

Disclosure statement

No potential conflict of interest was reported by the authors.

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