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N-PEGylated Thiazolium Salt: A Green and Reusable Homogenous Organocatalyst for the Synthesis of Benzoins and Acyloins

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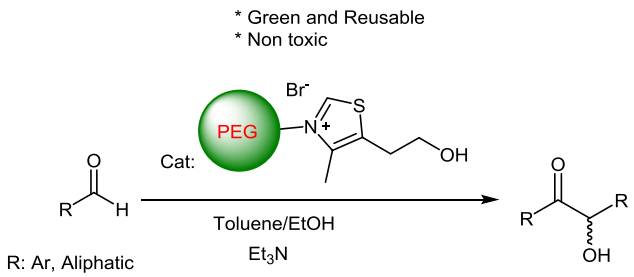
Abstract

N-PEGylated-thiazolium salt is used as efficient catalyst for the benzoin condensation. The catalyst was synthesized by reaction of activated polyethylene glycol 10,000 (PEG-10000) with 4-methyl-5-thiazoleethanol (sulfurol). Reaction mixture undergoes temperature-assisted phase transition and catalyst separated by simple filtration. After reaction course, catalyst can be recycled and reused without any apparent loss of activity which makes this process cost effective and hence ecofriendly. Synthesized benzoins and acyloins by this method have been characterized on the basis of melting point and ^{1}H-NMR spectral studies.

Graphic Abstract



Keywords *N*-PEGylated thiazolium salt · Benzoin condensation · Acyloins · Homogenous catalysis · Pegylation · Sulfurol

1 Introduction

The benzoin reaction is one of the oldest reactions in organic chemistry, found serendipitously by Liebig and Wohler in 1832 [l]. They discovered that the cyanide anion can catalyze the union of two molecules of aromatic aldehydes to afford α-hydroxy ketones [1]. More than a century later, Onium salts have been known to catalyze the benzoin reaction by Ukai et al. who discovered catalytic activity of 3-ethylthiazolium bromide [2]. This may be regarded as an early example of organocatalysis using an azolium salt. Breslow, in 1958, investigated the catalyst role of thiazolium salt for the self-condensation of benzadehyde to benzoin and proposed a mechanism, which generally admitted [3, 4]. He depicted the catalytically active species as a thiazolium zwitterion (the resonance structure of an NHC) and proposed that the reaction proceeds via an enaminol intermediate. However,

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in the recent years, many researchers have challenged this mechanism with evidence [5–7]. Almost three decades later Bertrand et al. used the *N*-heterocyclic carbene (NHC) as catalytically active species in the benzoin reaction with a stable phosphinocarbene [8]. Stetter's in 1976 used *N*-benzyl sulfurol chloride for benzoin condensation and may be regarded as the first report of an NHC-catalysed benzoin reaction on a synthetically useful scale [9].

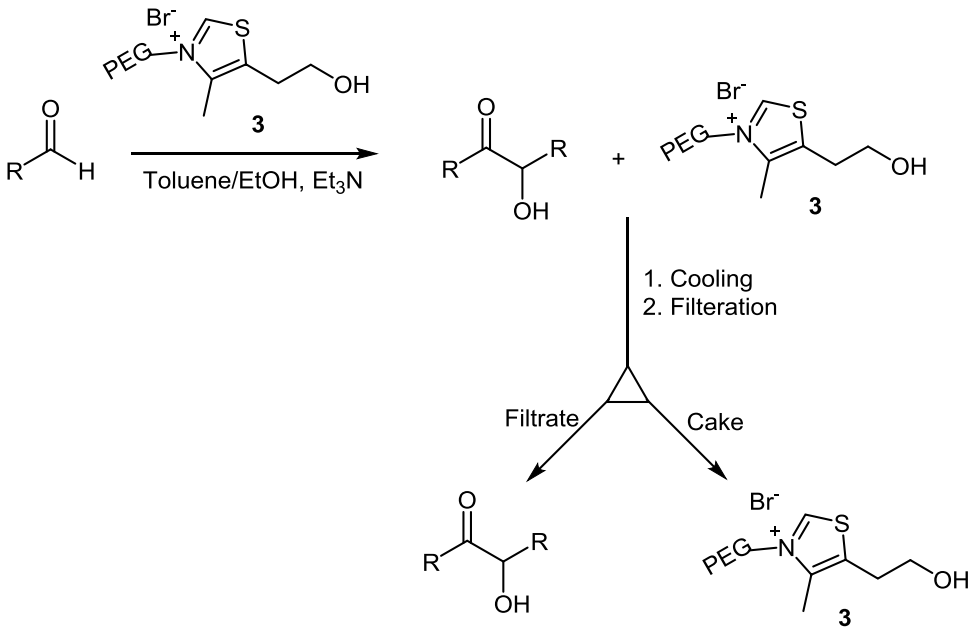
Since the first thiazolium salt catalyzed benzoin condensation [2] a continuous research for a new and efficient thiazolium salts catalyst for the benzoin condensation has been carried out. To name a few, this includes the use of 3-ethylbenzothiazolium bromide [10], 3-mesyl cycloheptathiazolium perchlorate [11], *N*-ethylsulfurol bromide [12], 3-(2,6-diisopropylphenyl)thiazolium perchlorate [13] and etc. However, all of these reports have significant drawbacks such as separation and recyclability of the catalyst, low isolated yields and long reaction time. Difficulties associated with the recovery of the catalyst from the reaction mixture have prevented the application of thiazolium salts to the benzoin condensation on a preparative scale. In fact, a few research article in application of the polymer-supported thiazolium salt and recovery of the catalyst in the benzoin condensation have been made [14–18]. Our group in 1984 used chloromethylated-polystyrene copolymer-bound thiazolium salt as efficient catalyst in the benzoin condensation [17]. This and the amazing number of diverse chemical transformation catalyzed by thiazolium salt [4] and using of PEGylated resolving agent for the resolution of racemic mixtures by our group [19] encouraged us to evaluate the prospects of *N*-PEGylated thiazolium salt as catalyst in the benzoin condensation due to phase transition property of PEG in the low temperature and as a result, easily separation of catalyst from the reaction mixture (Scheme 1).

2 Experimental Section

PEG was obtained from Kimiagaran Emrouz Ltd., Iran. Thiamine Mononitrate or Vitamin B_1 for the synthesis of 4-methyl-5-thiazoleethanol was obtained from Nokam Pharmaceutical Co., Iran. Aldehydes and solvents were obtained from commercially available sources such as Sigma–Aldrich and Merck without any purification. ^{1}H-NMR spectra were measured ($CDCl_3$) with a Bruker DRX-500 AVANCE spectrometer at 500.13. Melting points were measured on an Electrothermal 9100 apparatus.

2.1 Activation of PEG-10000

The process of Bückmann et al. [20] was used with minor modification. PEG (10,000) (5 g, 0.5 mmol) was dissolved in 150 ml of toluene, followed by the distillation of 50 ml of the solvent to remove traces of moisture. After cooling to 35 °C, freshly distilled anhydrous triethylamine (0.375 ml, 2.7 mmol) was added. Freshly phosphorus tribromide (0.15 ml, 2.1 mmol), dissolved in 10 ml of dry toluene, and was then added dropwise over 1 h at 35 °C under a dry nitrogen atmosphere with continuous stirring. The mixture was refluxed for 1 h and triethylammonium chloride was removed by passing the hot solution through a bed of Celite. The solution was treated with 0.5 g of decolorizing carbon at 50 °C and filtrated over Celite. The filtrate was stored at 4 °C overnight, affording activated PEG, which was filtered at 4 °C. The solid



Scheme 1 Synthesis of benzoins and acyloins catalyzed by of *N*-PEGylated thiazolium salt

product was further purified by dissolving in 0.5 L of absolute ethanol at 60 °C and treating with 0.25 g of decolorizing carbon, followed by filtration over Celite. The ethanolic filtrate was stored overnight at 4 °C to recrystallize the product. The solid material was separated by filtration and washed with cold ethanol and then ether. After drying in a vacuum desiccator 4.9 g of a pale yellow product was obtained (97%).

2.2 Preparation of *N*-PEGylated Thiazolium Bromide

4-methyl-5-thiazoleethanol (sulfurol) (0.6 g, 4 mmol) and activated PEG (10,000) (20 g, 2 mmol) was dissolved in 200 ml of acetonitrile. Thereafter, the resulting pale yellow solution was stirred at reflux for 24 h. The solvent was evaporated under reduced pressure and toluene was added to oily crude product. The reaction mixture was then cooled to 0–5 °C to crystallize the product. The solid material was separated by filtration and washed with cold toluene and then ether. After drying in a vacuum desiccator 18 g of a pale yellow product was obtained (88%). The product was characterized ^{1}H-NMR spectra. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.87 (bs, 1H, OH), 3.04 (t, J = 6.5 Hz, 2H, CH_2), 3.66 (bs, n CH_2), 3.86 (t, J = 6.5 Hz, 2H, CH_2), 8.62 (bs, CH).

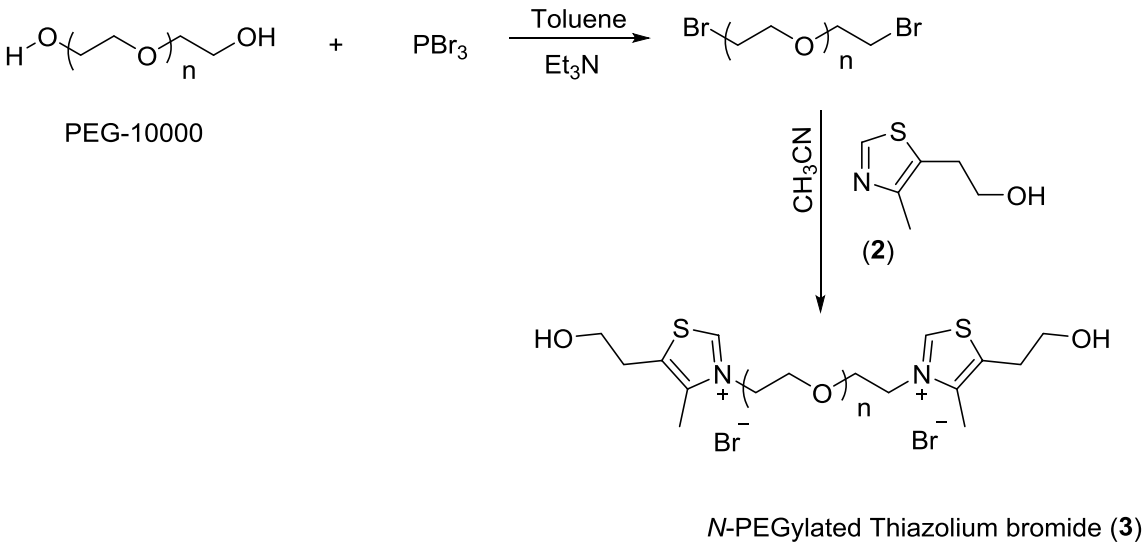
2.3 Catalytic Activity of *N*-PEGylated Thiazolium Salt in the Benzoin and Acyloin Condensation

To a mixture of PEGylated thiazolium bromide (0.25 g, 0.025 mmol) and Et_3N (5 mg, 0.05 mmol) in toluene (5 ml) and EtOH (2 ml), aldehyde (1 mmol) was added and the resulting mixture was heated at reflux for 12 h. After completion of the reaction (monitored by TLC) reaction mixture was cooled to 0–5 °C, the resulting precipitate was filtered and washed by cold toluene (5 ml). Then, the filtrate was evaporated under reduced pressure and oily product was purified by column chromatography (silica gel, n-hexane/EtOAc) to afford benzoin and acyloin 5a–h. structure of all product was characterized by melting point and ^{1}H-NMR spectra (See supporting information).

3 Result and Discussion

The present work is the result of endowment of known thiazolium salt catalyst with physico-chemical properties of polyethylene glycol (PEG). We used polyethylene glycol (PEG) to N-PEGylate the thiazole for two reasons. First, PEG dissolves in aqueous and most organic solvents, providing a soluble catalyst in a variety of solvent systems. Second, PEG is endowed with unique physico-chemical properties allowing it to undergo temperature-dependent as well as ionic strength-dependent phase transition from a soluble chemical entity to a semisolid or a solid. Therefore, in organic reaction medium the soluble *N*-PEGylated thiazolium salt catalyst precipitates by cooling the reaction mixture (Scheme 1). With the above assumption, we have synthesized the catalyst three and investigated their catalytic activity in the benzoin and acyloin condensation.

For the synthesis of catalyst, 4-methyl-5-(2′ -hydroxyethyl)thiazole (2) was used as thiazole source which easily obtained from the sulfite cleavage of thiamine [16]. Firstly, Polyethylene glycol-10000 (PEG-10000) is activated using phosphorus tribromide and then reaction of thiazole two with activated PEG gives *N*-PEGylated thiazolium bromide (3) (Scheme 2). The resulting catalyst is a new class of thiazolium salt which facilitates the benzoin condensation and



Scheme 2 Synthesis of *N*-PEGylated thiazolium salt

separation of the catalyst from the reaction mixture. Structure of the catalyst confirmed by ^{1}H-NMR spectra (see supporting information).

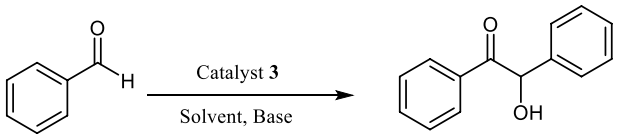
We commenced our investigation with the benzaldehyde for the optimization of reaction condition. As shown in Table 1, the yield proved invariant to the either base, but nature of solvent greatly effects the yield of the reaction. Different solvents such as EtOH, THF, toluene, CH_2Cl_2 and mixture of toluene/EtOH (3:1) were used. As shown in Table 1, best result was obtained when mixture of toluene and ethanol were used (entries 19–21, 26 and 31). As expected, the reaction in the abovementioned solvents and at room temperature either did not lead to the formation of the product or had a very low yield. But as shown in Table 1, the yield increased with increasing temperature, and the desirable results were obtained in a mixture of toluene and ethanol (3:1). There are two possible reasons for this phenomenon; a. increasing the temperature (due to the high boiling point of toluene) increases the reaction rate and b. solubility of the catalyst increases due to the hydrogen bonds formation with ethanol. One of the most important advantages of using toluene-ethanol mixture is that at high temperatures the catalyst is completely soluble and the reaction mixture is homogeneous, but with decreasing the temperature to 5 °C the catalyst becomes insoluble and easily separated by filtration and more than 90% of the catalyst (by weight) is recovered, while the product is soluble at this condition. However, in other solvents (THF and CH_2Cl_2), both at high and low temperatures, the catalyst is completely soluble, and as a result, separating the catalyst is difficult and costly.

To explore the effect of different bases on reaction, three bases including Et_3N, N(*i*Pr)$_2$Et and DBU were used (Table 1), but the results did not show significant change. Therefore, triethylamine was used due to its availability.

Our results with changing amount of catalyst shown that the catalytic loading no significant impact on the yield (entries 20, 21). So, with optimization reaction condition in hand (entry 19) we next turned to the question of substrate scope, an issue that has limited the utility of the benzoin condensation reaction in the past. We evaluated the performance of catalyst 3 in benzoins and acyloins condensation of substituted aromatic aldehydes with different electronic and steric characters. As a shown in Table 2, the yield of the reaction depends on the electron-donating or withdrawing nature of the substituents. Aldehydes with electron-releasing group (entries 2–5) afford good yields compared to withdrawing group (entry 6).

In the case of 4-nitrobenzaldehyde (Table 2, entry 6), the imine α-carbanion (6, Scheme 3), the 4-nitro group provides additional stability to imine α-carbanion by electron-withdrawing group contribution, rendering it a weaker nucleophile for C–C bond formation with the second aldehyde [6, 21]. But in the case of electron-releasing group such

Table 1 Optimization of reaction conditions



4a **5a**

Entry	Base	Catalyst loading (mol %)	Solvent	T (°C)	Yield[a] (%)
1	Et_3N	2.5	EtOH	rt	5
2	Et_3N	2.5	THF	rt	-
3	Et_3N	2.5	Toluene	rt	5
4	Et_3N	2.5	CH_2Cl_2	rt	-
5	Et_3N	2.5	Toluene/ EtOH (2:1)	rt	15
5	N(*i*Pr)$_2$Et	2.5	EtOH	rt	Trace
6	N(*i*Pr)$_2$Et	2.5	THF	rt	-
7	N(iPr)$_2$Et	2.5	Toluene	rt	5
8	N(iPr)$_2$Et	2.5	CH_2Cl_2	rt	-
9	N(iPr)$_2$Et	2.5	Toluene/ EtOH (2:1)	rt	10
10	DBU[b]	2.5	EtOH	rt	-
11	DBU	2.5	THF	rt	-
12	DBU	2.5	Toluene	rt	-
13	DBU	2.5	CH_2Cl_2	rt	-
14	DBU	2.5	Toluene/ EtOH (2:1)	rt	10
15	Et_3N	2.5	EtOH	reflux	41
16	Et_3N	2.5	THF	reflux	35
17	Et_3N	2.5	Toluene	reflux	54
18	Et_3N	2.5	CH_2Cl_2	reflux	15
19[d]	**Et_3N**	**2.5**	Toluene/ EtOH (2:1)	**reflux**	**80**
20	Et_3N	5	Toluene/ EtOH (2:1)	reflux	79
21	Et_3N	10	Toluene/ EtOH (2:1)	reflux	80
22	N(*i*Pr)$_2$Et	2.5	EtOH	reflux	35
23	N(*i*Pr)$_2$Et	2.5	THF	reflux	38
24	N(iPr)$_2$Et	2.5	Toluene	reflux	52
25	N(iPr)$_2$Et	2.5	CH_2Cl_2	reflux	20
26	N(iPr)$_2$Et	2.5	Toluene/ EtOH (2:1)	reflux	76
27	DBU[c]	2.5	EtOH	reflux	44
28	DBU[c]	2.5	THF	reflux	34
29	DBU	2.5	Toluene	reflux	53
30	DBU	2.5	CH_2Cl_2	reflux	21
31	DBU	2.5	Toluene/ EtOH (2:1)	reflux	75

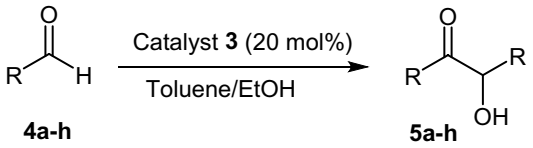
[a]Based on quantitative TLC

[b]1,8- Diazabicyclo[5.4.0]undec-7-ene

[c]Reaction conditions: Aldehyde (1 mmol), Base (2 mmol), Time: 12 h

[d] Optimization reaction condition

Table 2 Evaluation of catalyst scope [a]



4a-h **5a-h**

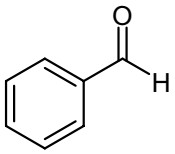
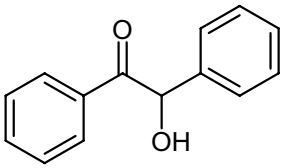
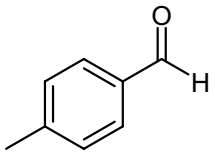
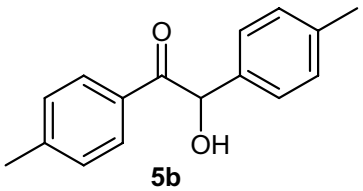
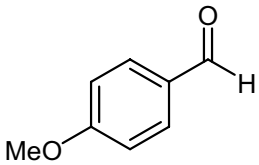
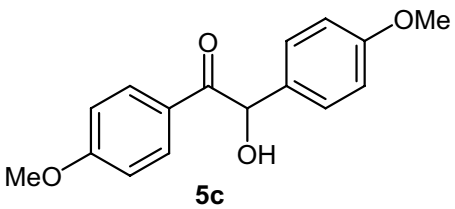
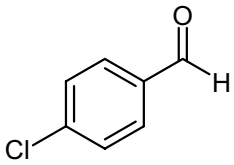
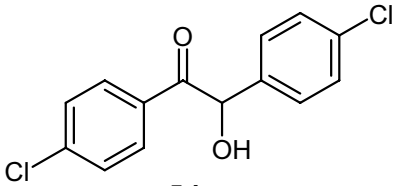
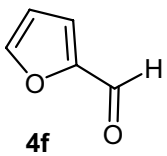
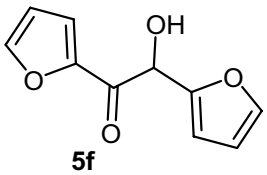
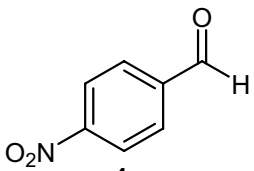
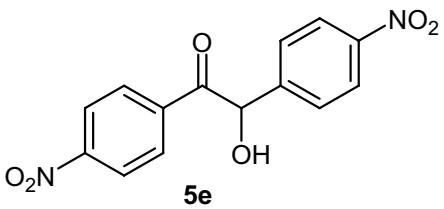
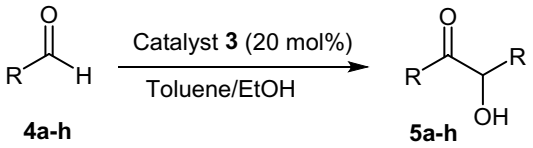
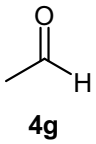
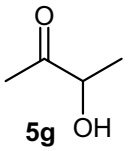
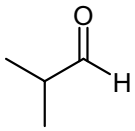
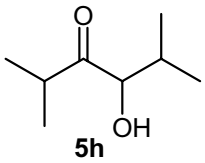
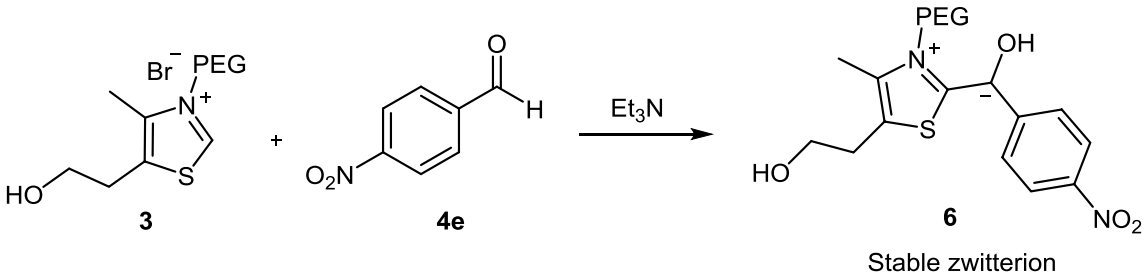
Entry	Aldehyde	Product	Yield
1	 **4a**	 **5a**	80
2	 **4b**	 **5b**	79
3	 **4c**	 **5c**	82
4	 **4d**	 **5d**	78
5	 **4f**	 **5f**	79
6	 **4e**	 **5e**	Trace [b]

Table 2 (continued)



Entry	Aldehyde	Product	Yield
7	 4g	 5g	73
8	 4h	 5h	74

[a]Reaction conditions: Aldehydes (1 mmol), catalyst (2.5 mol%), Et_3N (5 mol%), Toluene (5 mL), EtOH (2 ml), 50 °C, Time: 2 h.[b] by TLC



Scheme 3 Formation of stable zwitterion in case of 4-nitrobenzaldehyde

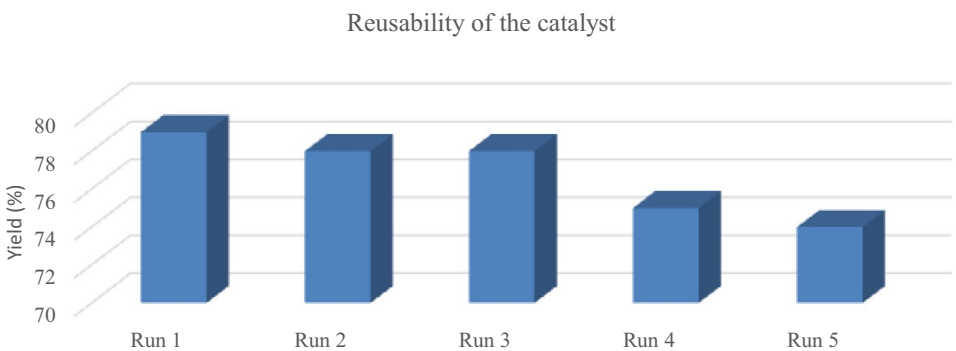


Fig. 1 Reusability of the catalyst for benzoin condensation of benzaldehyde

as 4-methoxy group, the imine α-carbanion intermediate is very strong nucleophile and led to desired product.

Reusability of catalysts is of paramount importance in their application and are important issues to be reviewed. To address these issues, the catalyst was recovered by simple filtration and washed with cold toluene and dried at room temperature. The recovered catalyst was reused for benzoin condensation of benzaldehyde. The result indicates that the PEG-thiazolium salt catalyst can be used for several cycles successfully with minimal loss of activity (Fig. 1).

4 Conclusion

In conclusion, we have studied the simple and effective method for the preparation of benzoins and acyloins by N-PEGylated thiazolium salt as reusable catalyst. Regards to the significant catalytic activity of the N-PEGylated thiazolium Salt, a range of aromatic and aliphatic aldehydes with electron-releasing and electron with-drawing group converted to the corresponding benzoin and acyloins rapidly with good to excellent yields. The major advantage of this method is due to the simple recovery of the catalyst by temperature-dependent phase transition of PEGylated thiazolium salt. Further studies on other useful application of PEGylated catalysts and development of its catalytic scope are in progress and would be presented in the future.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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