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Polymer-supported benzimidazolium based ionic liquid: an efficient and reusable Brønsted acid catalyst for Biginelli reaction

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A polymer-supported benzimidazolium based ionic liquid (PSBIL) was synthesized by reaction of poly(vinylbenzyl chloride) and benzimidazole followed by ring opening of 1,4-butane sultone and acidification with sulphuric acid. The resulting Brønsted acid heterogeneous organocatalyst is very competent for the Biginelli reactions under mild conditions in high yields of 3,4-dihydropyrimidine-2(1H)-one/thiones (DHPMs). Since poly(vinylbenzyl chloride) makes the catalyst bed, the sulphonic acid catalyst will have high loading level of acidic groups compare to other heterogeneous acid catalysts. In spite of conventional heterogeneous ionic liquid catalysts, current PSBIL shows thermal stability up to 334 °C and recyclability up to 5 cycles. This PSBIL signifies a new class of heterogeneous catalyst which is particularly noticeable in green chemistry. The present protocol highlights the easy separation of products without further purification. Furthermore, the effectiveness of this protocol has demonstrated by synthesis of mitotic Kinesin EG5 inhibitor, Monastrol under optimized conditions.

Introduction

Dihydropyrimidinone (DHPM) products are commonly used in various applications such as biological, calcium channel blockers, α-adrenergic antagonists, antihypertensive agents, inhibitors of the fatty acid transporter and mitotic kinesin inhibition.[1] Batzelladine alkaloids were recently found to be effective HIV gp-120-CD4 inhibitors among all the alkaloids obtained from the oceanic sources which constitute the DHPM core unit.[2] The DHPM was first synthesized by the Italian chemist Pietro Biginelli in 1893 from the reaction of aldehydes, β-ketoester and urea under strongly acidic conditions. The major disadvantages related with acid-catalyzed reactions were lower yields from 26% to 60%, mainly for tri and tetra-substituted aldehydes of aromatic and aliphatic origins and longer duration of reactions from 24 to 36 h. The developing significance in this class of compound leads to the upgrading of other synthetic multistep approaches with alternate catalysts in slightly better yields.[3]

On the contrary, multicomponent reactions (MCR) are convenient tools in organic synthesis giving direct, neat and simple access to bioactive compound libraries. Combining multi-reagents in one pot is noticeable practice, and important as the ecological point of view but still suffers from several limitations.[4] Therefore, the reaction for the synthesis of DHPMs has attracted better

attention and several procedures have been illustrated.

Some of these methods employ catalysts such as polystyrenesulfonic acid,[5] polystyrene-poly(ethylene glycol) resin supported sulphonic acid,[6] mesoporous silica MCM-41,[7] silica sulphuric acid,[8] sulphonated carbon material[9] and silica gel supported L-pyrrolidine-2-carboxylic acid-4-hydrogen sulphate.[10] However, in spite of their potential ability, many of these methods include expensive and/or toxic catalysts, non-stoichiometric amount of catalyst, poor yields, tedious workup procedures and inconsistency with certain functional groups.[11]

In recent years, the use of non-aqueous room temperature ionic liquids (RTILs) and task-specific ionic liquids (TSILs) have executed as a powerful alternative to green solvents or catalysts in organic synthetic processes due to their undetectable vapour pressure, wide liquid range, solvating ability as well as the ease of recovery and reuse.[12-20] Moreover, TSILs have been widely used in the past few years for the synthesis of DHPMs.[21-29]

Conversely, RTILs and TSILs with imidazole moiety are relatively expensive, which hampers their industrial applications. Also, specific ILs consist of halogen-containing anions such as $[PF_6]^-$, $[BF_4]^-$, $[CF_3SO_3]^-$ and $[(CF_3SO)_2N]^-$ which in some respect limit their greenness.[30-32] At the edge between heterogeneous and homogeneous catalysis, there is a great opportunity for the expansion of novel materials that combine the benefits and minimize drawbacks related with each of these classes. The main difficulty of the homogeneous catalysts is the concern of their recovery from the reaction mixture. The product is separated from the reaction medium either by precipitation and extraction using other solvent or distillation with subsequent recovery. Such work-up operations may deactivate the catalyst. Opposite, leaching can occur in the reaction medium during

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Electronic Supplementary Information (ESI) available: [¹H, ¹³C NMR of PSBIL, Physical data of DHPMs and copies of ¹H, ¹³C, FT-IR and GC-MS spectra's of DHPMs]. See DOI: 10.1039/x0xx00000x

extraction on the one hand and requests further struggle to upgrade the extracted compound.

In recent years, the use of heterogeneous catalysis has received universal attention that offers a clarification for the major drawback of homogeneous catalysis. From both an industrial and an environmental point of view, this method is very interesting, since it allows the upcoming application of heterogeneous catalysts in the synthesis of cost-effective products, leading to rapid, clean and selective green industrial processes.[33] Supported ILs catalysis is an idea which combines the benefits of ILs with those of heterogeneous support materials. The feasibility of this model has been established by several studies which have effectively restrained various ionic phases to the surface of support materials and discovered their prospective catalytic uses. The majority of the evaluated supports were silica based and several studies focused on polymeric materials including Merrifield resin and polystyrene. These materials were prepared by two different immobilization methodologies. First method includes the covalent attachment of IL to the support surface while another merely links the ILs phases with catalytically active species on the peripheral of the support.

However, only a few protocols have been reported using polymer supported ionic liquid for the synthesis of DHPM derivatives. Wang et al.[34] have reported PsMImBF$_4$ or PsMImPF$_6$ by immobilizing 1-methyl-1H-imidazole on polystyrene-based chloromethyl resin followed by ion exchange with NaBF$_4$ or NH$_4$PF$_6$. This heterogeneous polymer supported ionic liquid catalyst was found efficient for the synthesis of 1,2,3,4-tetrahydro-2-oxopyrimidine-5-carboxylates. Pourjavadi et al.[35] have synthesized a dual acidic heterogeneous organocatalyst by copolymerization of acidic IL monomer (vinyl-3-(3-sulfopropyl)imidazolium hydrogen sulfate [VSim][HSO$_4$] and IL crosslinker (1,4-butanediyl-3,3-bis-vinyl imidazolium dihydrogen sulfate) and used successfully for the Biginelli reaction. Moreover, methods using ultrasound[36] and microwave-assisted dry media technology containing TiO$_2$ nanoparticles supported on multi-walled carbon nanotubes crystalline carbon materials TiO$_2$–MWCNTs[37] have also been reported.

Prompted by the above effective themes and as part of our persistent effort to develop new heterogeneous catalyst, we have decided to synthesize metal-free polymer-supported benzimidazolium based ionic liquid. On the basis of our experience in the synthesis of ILs[38] and concern in catalytic processes in this ionic media. Herein we report the PSBIL is an excellent heterogeneous catalyst with admirable results for the Biginelli reaction. The efficiency of the developed catalyst has been tested for the Biginelli reaction by varying all the starting materials. Also, the thermal stability and recyclability of the PSBIL has been examined, which shows the promising results compared to the other reported catalysts.

Experimental

Materials

4-vinylbenzyl chloride (90%) and 1, 4-butane sultone were purchased from Sigma-Aldrich (India). Azobisisobutyronitrile (AIBN) and sulphuric acid were obtained from Avra synthesis, India. Sodium hydride (60% suspension in paraffin oil), benzimidazole and all the substituted aromatic aldehydes, urea, thiourea, ethyl acetoacetate, acetylacetone, anhydrous sodium sulphate and all the solvents were purchased from S D Fine chemicals India. TLC plate silica gel GF-254 was procured from Merck and Co.

Characterization techniques

NMR spectra were recorded in DMSO-d$_6$ and CDCl$_3$ on Bruker spectrometer operating at 400 MHz and the chemical shifts are given in ppm downfield from TMS (δ = 0.00). The molecular weight of the DHPM derivatives was determined using Perkin Elmer GC modal-Clarus 680 (EI). Elemental analysis (C, H, N, O and S) of the PSBIL was performed on EURO VECTOR EA 3000 elemental analyzer. Thermal stability of PSBIL was tested using TG/DTA thermoanalyser SII, 7200 (Seiko, Japan). FT-IR spectra of the PSBIL and DHPM derivatives were obtained from IR affinity-1 Shimadzu FT-IR spectrophotometer using KBr pellet method.

Synthesis of PSBIL

Synthesis of poly(vinylbenzyl chloride) (1)

Prior to polymerization of 4-vinylbenzyl chloride, inhibitor i. e. tert-butyl catechol was removed by dissolving 4-vinylbenzyl chloride in chloroform and extracted three times in 0.5% aqueous NaOH solution followed by the water. Anhydrous Na$_2$SO$_4$ was added for drying, filtered and chloroform was removed under rotary evaporator to get the inhibitor free 4-vinylbenzyl chloride monomer. The monomer (7.6 g, 50 mmol) was taken in two-necked round bottom flask with 150 mL chloroform and AIBN (0.164 g) and refluxed at 70 °C for 48 h under N$_2$ atmosphere. After 48 h, chloroform was removed by rotary evaporator and methanol was added to the viscous liquid to get white solid polymer, which was repeatedly washed with methanol (3 × 20 mL) to remove unreacted monomer and dried under high vacuum to get the fine white powder of poly(vinylbenzyl chloride). Yield: 6.3 g, 82.89%.

Synthesis of poly-1-(4-vinylbenyl)-1H-benzimidazole (2)

The synthesis of compound (2) was carried out based on the literature.[39] THF solution of poly(vinylbenzyl chloride) (6.08 g, 40 mmol) was added dropwise to a stirred solution of benzimidazole (4.72 g, 40 mmol) and sodium hydride (1.6 g, 40 mmol). The above reaction mixture was refluxed at 60 °C for 48 h. Precipitated NaCl was removed by filtration from the reaction mixture and THF was removed by rotary evaporator under vacuum. Chloroform (150 mL) added to dark brown viscous oil and the organic layer was washed with deionized water (5 × 150 mL). The reaction mixture was dried using anhydrous Na$_2$SO$_4$, filtered and chloroform was removed by rotary evaporator and polymer was washed with acetone, dried in hot air oven for overnight to obtain a yellowish powder of poly-1-(4-vinylbenyl)-1H-benzimidazole (2).

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Synthesis of poly-(4-(1-(4-vinylbenzyl)-1H-benzimidazol-3-ium-3-yl)-butane-1-sulfonate (3)

The synthesis of compound (3) was carried out according to literature.[40] The ring opening reaction of 1,4-butane sultone (2.58 g, 19 mmol) with poly-1-(4-vinylbenzyl)-1H-benzimidazole (7 g) at 50 °C for 48 h in 150 mL chloroform was performed. The reaction mixture was concentrated using rotary evaporator and diethyl ether was added. The off-white polymer (3) was precipitate which was washed repeatedly with diethyl ether (3 × 40 mL) to remove unreacted starting materials. Finally, it was dried overnight at 50 °C in a hot air oven to afford off-white powder of poly-(4-(1-(4-vinylbenzyl)-1H-benzimidazol-3-ium-3-yl)-butane-1-sulfonate (3).

Synthesis of PSBIL (4) from poly-(4-(1-(4-vinylbenzyl)-1H-benzimidazol-3-ium-3-yl)-butane-1-sulfonate

Compound (3) (4 g) was taken in minimum amount of water in RB flask and stirred in cool condition using ice-crush bath and added slowly 2 equivalent of conc. H_2SO_4. The reaction mixture was stirred under same condition for half an hour followed by at 70-80 °C for 12 h. The obtained yellowish solid was constantly washed with deionized water until the pH of washed water gets neutral. Further, the polymer was filtered under high vacuum and dried in an oven for 12 h at 60 °C to get yellowish crystalline PSBIL as a product (Scheme 1). Resulting PSBIL was insoluble in almost all organic solvents except DMSO showing solubility at 90 °C.

Spectral Data of PSBIL

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (br, 1H), 9.19 (br, 1H), 7.61 (br, 4H), 7.11(br, 4H), 6.20 (br, 5H), 5.51 (br, 2H), 4.53 (br, 2H), 2.66 (br, 2H), 2.05 (br, 2H), 1.68 (br, 2H), 1.59 (br, 1H) 1.23 (br, 2H). Anal. Calcd for $C_{22}H_{30}N_2O_7S_2$ (%): C, 52.99, H, 6.06, N, 5.6, O, 22.46, S, 12.86; Found: C, 60.796, H, 5.895, N, 8.036, O, 15.762, S, 5.670.
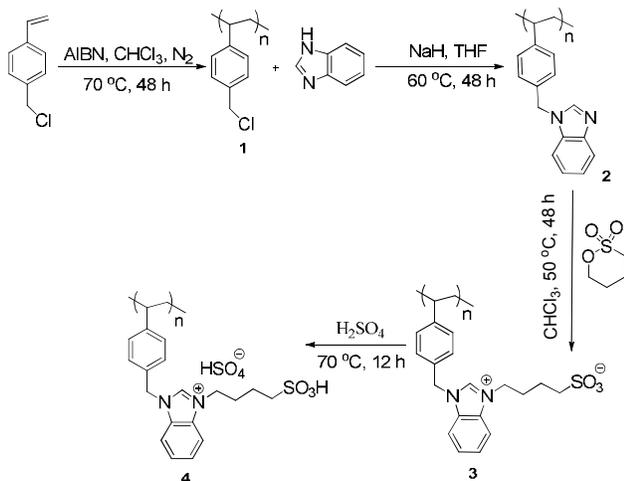
**Scheme 1.** Schematic representation of the synthesis of PSBIL.

Typical Biginelli reaction

The mixture of benzaldehyde (0.106 g, 1 mmol), ethyl acetoacetate (0.156 g, 1.2 mmol), urea (0.09 g, 1.5 mmol) and PSBIL (50 mg) in ethanol (5 mL) were successively charged into a 50 mL single neck round bottom flask (RBF) with magnetic stirring bar. The reaction mixture was refluxed at 110 °C for the period of 18 h. The progress

of reaction was monitored by TLC using ethyl acetate: hexane (1:1) as mobile phase till the disappearance of reactants. After completion of reaction, the solid DHPM was separated from the wall of RBF by simply scraping out with a spatula (Fig. S8; see the ESI†), washed with water and dried in an oven at 50 °C. Moreover, the ethanol containing DHPMs from the reaction mixture poured onto the crushed ice, filtered and dried. The recovered catalyst was washed with ethanol, followed by water and dried in an oven at 50 °C for 12 h to reuse for the next experiment.

Results and discussion

Catalytic studies

Sulphonic acid functionalized ionic liquids containing HSO_4^- counter anion enhances the Brønsted acidity of the catalyst.[41] Accordingly, herein we would like to report the synthesis of polymer-supported Brønsted acid ionic liquid containing sulphonic acid functionality with HSO_4^- as a counter anion for Biginelli reaction. A range of aldehydes comprising substituted aromatic aldehydes, aliphatic aldehyde, heterocyclic aldehydes and aldehyde containing polycyclic aromatic hydrocarbon were selected and condensed with ethyl acetoacetate, acetylacetone, urea and thiourea towards the synthesis of 3,4-dihydropyrimidine-2(1H)-ones/thiones.
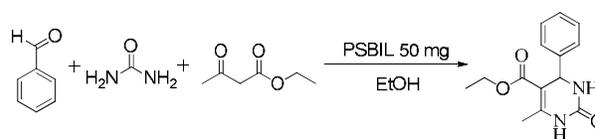
Scheme 2 Biginelli reaction of benzaldehyde, urea and ethylacetoacetate to get the 5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

We initially assessed the use of different amounts of PSBIL for the model reaction of benzaldehyde (1 mmol), ethyl acetoacetate (1.2 mmol) and urea (1.5 mmol) to produce DHPM under classical conditions (Table 1). From the data presented in Table 1, it is clear that the high yield of product (91%) (Table 1, entry 6) was perceived using 50 mg of catalyst while with 0 to 40 mg of catalyst, yields were not good (Table 1, entries 1-5). From these results, it was obvious that the amount of catalyst plays a vital role to advance the result to a larger extent. It was also found that there is no greater alteration in yields of product greater than 50 mg of catalyst (Table 1, entry 7).

Use of benzaldehyde, ethyl acetoacetate and urea in 1:1.2:1.5 equivalent ratio with the proposed PSBIL (50 mg) at 110 °C gave 5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one 91% yield in 18 h. The greater yield in this reaction is in accordance with atom economy concept.

Table 1 Optimization of amount of catalyst, temperature and time on the Biginelli reaction.[a]

Entry	Catalyst amount (PSBIL) (mg)	Solvent	Temperature (°C)	Time (h)	Yields[b] (%)
1	-	Ethanol	110	24	36
2	10	Ethanol	110	24	52
3	20	Ethanol	110	24	60
4	30	Ethanol	110	24	69
5	40	Ethanol	110	24	74
6	50	Ethanol	110	24	91
7	60	Ethanol	110	24	91
8	50	Ethanol	70	24	60
9	50	Ethanol	80	24	64
10	50	Ethanol	90	24	69
11	50	Ethanol	100	24	77
12	50	Ethanol	110	24	91
13	50	Ethanol	120	24	71
14	50	Ethanol	110	4	20
15	50	Ethanol	110	12	65
16	50	Ethanol	110	18	89
17	50	Ethanol	110	24	91
18	50	Ethanol	110	28	88

[a]Reaction conditions: benzaldehyde (1 mmol), urea (1.2 mmol), ethyl acetoacetate (1.5 mmol) and ethanol (5 mL).
[b]Isolated yield of products.

The increase of reaction temperature above 110 °C had no marginal effect on the yield of condensation product (Table 1, entry 13). Prolonging the time further up to 28 h (Table 1, entry 18) had practically no effect on the yield showing that, reaction is complete in 18 h (Table 1, entry 16). Finally, the effect of solvent on model reaction was studied using different polar and non-polar solvents at their respective reflux temperatures for 18 h. As can be seen, in (Table 2) the condensation reaction proceeded smoothly in the presence of ethanol (Table 2, entry 4) and gave the desired product in excellent yield.

Table 2 Effect of solvent on Biginelli reaction.[a]

Entry	Catalyst amount (PSBIL) (mg)	Solvent	Temperature (°C)	Time (h)	Yields[b] (%)
1	50	Acetonitrile	Reflux	18	41
3	50	Toluene	Reflux	18	44
4	50	Water	Reflux	18	45
5	50	Ethanol	Reflux	18	72
6	50	THF	Reflux	18	39
7	50	Methanol	Reflux	18	32
8	50	n-hexane	Reflux	18	20

[a]Reaction conditions: Aldehydes (1 mmol), ethylacetoacetate or acetylacetone (1.2 mmol), urea or thiourea (1.5 mmol) and PSBIL (50 mg) refluxing for 18 h.
[b]Isolated yield of products.

With the optimized reaction conditions in hand, we then studied the scope and constraints of this strategy for other diverse substrates using combination of ethyl acetoacetate/acetylacetone, a series of aldehydes comprising substituted aromatic aldehydes, aliphatic aldehyde, heterocyclic aldehydes and aldehyde containing polycyclic aromatic hydrocarbon and urea/thiourea in ethanol medium at 110 °C for 18 h and the results are summarized in Table 3. All the reactions progressed well to afford good to admirable yields with PSBIL as a catalyst. Aldehydes with the electron-donating group (Table 3, entries 2-9) gave much higher yields than those with an electron-attracting group. Then we vary the aldehydes with electron withdrawing group keeping urea and ethyl acetoacetate constant (Table 3, entries 10-12) to give the corresponding products in 80% to 68% yields. An important advantage of this protocol is that it shows an excellent group tolerance capacity towards nitrobenzaldehyde.

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Table 3 Biginelli reaction catalyzed by PSBIL.[a]
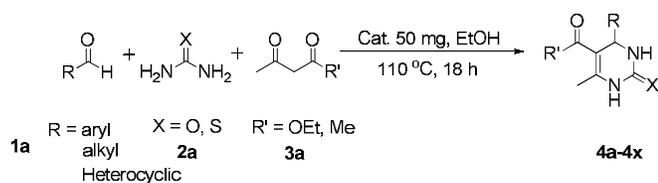
Entry	Aldehyde	X	R'	Product	Yield (%)[b]
1	C_6H_5	O	OEt	4a	91
2	4-$MeOC_6H_4$	O	OEt	4b	92
3	2-MeO C_6H_4	O	OEt	4c	90
4	3,4- $MeOC_6H_4$	O	OEt	4d	86
5	4-$CH_3C_6H_4$	O	OEt	4e	89
6	4-OH C_6H_4	O	OEt	4f	88
7	4-BrC_6H_4	O	OEt	4g	81
8	2-BrC_6H_4	O	OEt	4h	80
9	4-ClC_6H_4	O	OEt	4i	88
10	4-FC_6H_4	O	OEt	4j	80
11	4-$O_2NC_6H_4$	O	OEt	4k	78
12	3-$O_2NC_6H_4$	O	OEt	4l	68
13	1-Naphthyl	O	OEt	4m	88
14	2-Furanyl	O	OEt	4n	84
15	2-Thienyl	O	OEt	4o	82
16	n-$CH_3(CH_2)_2$	O	OEt	4p	56
17	4-ClC_6H_4	O	Me	4q	88
18	C_6H_5	O	Me	4r	89
19	C_6H_5	S	Me	4s	85
20	4-ClC_6H_4	S	Me	4t	84
21	4-$MeOC_6H_4$	S	Me	4u	88
22	C_6H_5	S	OEt	4v	85
23	4-ClC_6H_4	S	OEt	4w	84
24	4-$OMeC_6H_4$	S	OEt	4x	87

[a]Reaction condition: Aldehydes (1 mmol), ethyl acetoacetate or acetylacetone (1.2 mmol), urea or thiourea (1.5 mmol) and PSBIL (50 mg) in 5 mL ethanol refluxing at 110 °C for 18 h.
[b]Isolated yield of the products.

The optimized conditions were then employed to assess the generalization of the method. The PSBIL was found to be compatible with various substrates and the products were obtained in good to excellent yields (Table 3). The various aldehydes like 1-naphthyl aldehyde, 2-furanyl aldehyde and 2-thianyl aldehyde were also reacted well under the same conditions to give their respective products (Table 3, entries 13–15). However, lower yield were obtained in the case of aliphatic aldehyde (Table 3, entry 16). Encouraged by these favourable results we next studied the multicomponent reaction using 1,3-diketones instead of β-ketoesters (Table 3, entries 17 and 18). In both the cases, the reactions were complete in 18 h to furnish DHPMs with good yields. Finally, the catalytic activity of PSBIL was examined for the Biginelli reaction by using thiourea instead of urea that yields 84 to 88% DHPMs demonstrating the excellent catalytic activity of catalyst (Table 3, entries 19-24).

It is found that, most of the metal-based catalysts for the Biginelli reaction were in solvent-free conditions.[42-44] But, the post-treatment requires more volume of organic solvents and thus the methodology not only made the work-up procedure complicated but also brought more difficulty in separating the catalysts for their recycling. Hence, it is opposite of the principle of green chemistry. On the contrary, synthesis of DHPMs via the PSBIL catalyst in ethanol requires neither tedious workup procedure nor column chromatographic purification.

A plausible mechanism for the Biginelli reaction catalyzed by PSBIL is shown in (Scheme 3). Initially, PSBIL facilitates the formation of intermediate I via Knoevenagel condensation of β-ketoester 1 and aldehyde 2. An intermediate I undergo the dehydration to give olefin II. Then, the conjugate addition of NH_2 group in urea or thiourea 3 at the β-carbon of α, β-unsaturated carbonyl group to form compound III which tautomerizes to more stable keto form followed by cyclization via nucleophilic attack of NH_2 on electrophilic carbonyl carbon. Finally elimination of another water molecule with regeneration of catalyst yields the DHPMs.
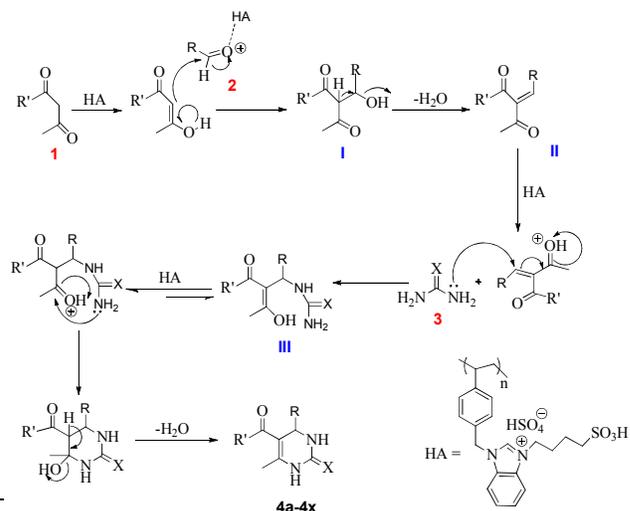
Scheme 3 Possible reaction pathway for the synthesis of DHPMs.

In order to prove the industrial applicability of this method, the reaction of 3-hydroxy benzaldehyde, ethyl acetoacetate and thiourea was carried out for the synthesis of mitotic Kinesin EG5

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inhibitor Monastrol under optimized conditions which yielded in 20% (Scheme 4). Thus, the present PSBIL catalyst is extremely attractive for producing DHPMs of biological and pharmacological interest. Also, yields obtained for PSBIL towards Biginelli reaction is better than or comparable with the literature reports (Table 4).
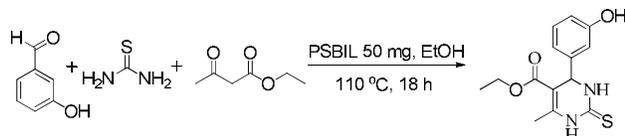
Scheme 4 Synthesis of 5-Ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (Monastrol).

In order to ascertain any fundamental changes in the PSBIL catalyst, we have verified FT-IR spectrum before and after condensation reaction. The FT-IR spectrum (Fig. 1A) of synthesized PSBIL makes clear that broad peak at 3452 cm^{-1} corresponds to the –OH stretching frequency of –SO$_3$H group.[45] The peaks at 2850 and 2922 cm^{-1} correspond to the aliphatic -C-H group while the peak at 3057 and 3126 cm^{-1} is appeared due to =C-H of the aromatic ring. The peak at 1035 and 1168 cm^{-1} is clearly observed in FT-IR spectrum due to the S=O asymmetric and symmetric stretching frequency of the –SO$_3$H group[46] whereas, peak at 615 cm^{-1} is due to the symmetric vibration of S-O of the –SO$_3$H group.[47] The stretching frequency of C-N and C=N appeared at 1382 and 1612 cm^{-1} respectively while the peak at 1492 and 1546 cm^{-1} is due to the C=C of aromatic ring which confirms the successful formation of PSBIL.

It was found that, FT-IR spectrum of PSBIL obtained before and after (Fig. 1, A and B) the Biginelli reaction shows no substantial changes.
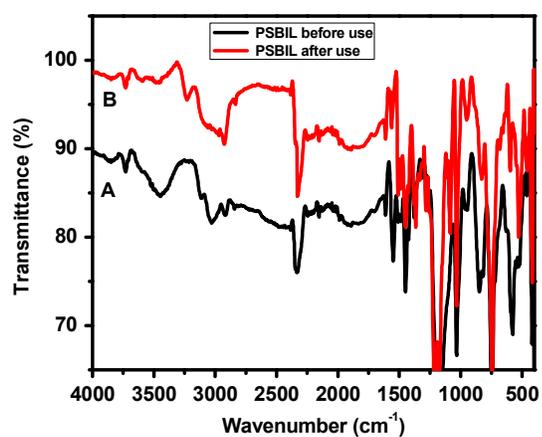

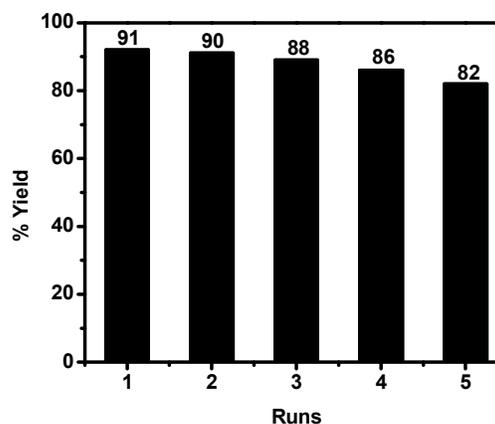**Fig. 1** FT-IR spectra of the PSBIL A) before reaction B) after the reaction.

Fig. 2 Recyclability of PSBIL in Biginelli reaction.

Recyclability and stability of the PSBIL

In view of an environmentally benign process, the recyclability of the catalyst is an important benefit especially in the heterogeneous system for commercial applications. The reusability of the PSBIL was investigated in consecutive Biginelli reactions of benzaldehyde, ethyl acetoacetate and urea (mole ratio 1:1.2:1.5) under the optimized conditions. The reactions were carried out by following the usual method. At the end of each reaction, the heterogeneous catalyst was washed with ethanol followed by water and dried in an oven for the next run. The results of reuse of PSBIL are summarized in Fig. 2. As it is shown, the PSBIL can be used 5 times without significant loss of its catalytic activity. However, a slight decrease in the catalytic activity from fourth 86 to 82% in the fifth cycle could be due to the blocking of the active sites of the PSBIL catalyst. As compared to traditional catalysts, the PSBIL exhibits easy recovery from the reaction mixture which is a perceptible asset of the heterogeneous catalyst for ecological protection and cost-effective reasons.

Table 4 Comparison of the Biginelli reaction using different heterogeneous catalyst.

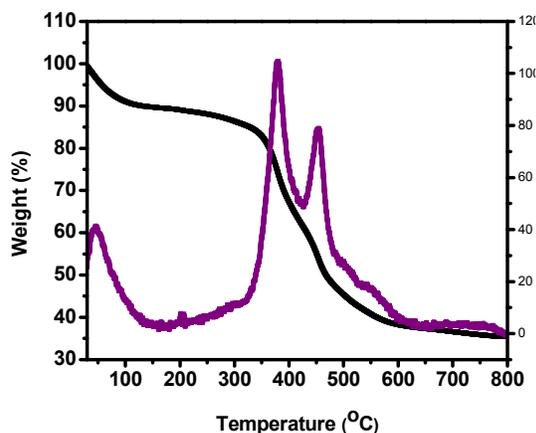| Entry	catalyst	Catalyst dosage (in mg)	Yield (%)	Ref.
1	PS-PEG-OSO$_3$H	300	79	6
2	Silica gel-supported L-pyrrolidine-2-carboxylic acid-4-hydrogen sulfate	212	98	10
3	(MCM-41-R-SO$_3$H)	100	94	48
4	PPF-SO$_3$H	250	89	49
5	PS-AFDPAT	650	94	50
6	PSBIL	50	92	Present work

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Fig. 3 The TG and DTG thermogram of PSBIL.

Thermogravimetric analysis was studied for defining the stability of synthesized PSBIL (Fig. 3). TG and DTG analysis of the PSBIL was examined in the range of 30 to 800 °C and the temperature was increased at the rate of 10 °C min^{-1} in a N$_2$ atmosphere. The thermogram shows the initial weight loss of 7.0305% at 98.2 °C due to the physically adsorbed water. The another weight loss of 42.4089% started from 334.1 °C to 474.9 °C and this weight loss is due to the alkyl sulphonic groups present in the PSBIL.

The final weight loss 25.3954% observed from 474.9 to 713.2 °C poly(1-(4-Vinylbenyl-1H-benzoimidazole) in the PSBIL. From TGA analysis it is observed that the weight loss is negligible up to 334.1 °C, therefore it is concluded that PSBIL catalyst is suitable for high-temperature reaction.

Conclusions

A polymer-supported benzimidazolium based ionic liquid was successfully synthesized by reaction of poly(vinylbenzyl chloride) and benzimidazole followed by ring opening of 1,4-butane sultone and acidification with sulphuric acid. The resulting PSBIL was found highly competent for the synthesis of DHPM derivatives via Biginelli reaction under mild conditions. The present PSBIL catalyst has been tolerate aliphatic, aromatic, heterocyclic aldehydes and affords good to excellent yields. Furthermore, the PSBIL catalyst exhibit excellent thermal stability and reproducibility. The PSBIL catalyst signifies a novel class of high loaded heterogeneous catalyst which is particularly promising in green chemistry and found to be effective in terms of the yield, catalyst dose, simple work-up procedure, separation and reusability of the catalyst. The DHPMs was separated easily from the reaction medium using a spatula, followed by washing with water and drying to get analytically pure products. Also, the industrial applicability of this protocol has demonstrated by the synthesis of mitotic Kinesin EG5 inhibitor Monastrol under optimized conditions.

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Polymer-supported benzimidazolium based ionic liquid: an efficient and reusable Brønsted acid catalyst for Biginelli reaction

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