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ARTICLE

Polymer grafted layered double hydroxides (LDHs-g-POEGMA): a highly efficient reusable solid catalyst for the synthesis of chromene incorporated dihydroquinoline derivatives under solvent-free conditions

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In this study, a novel poly(oligoethylene glycol methacrylate)-*g*-supported layered double hydroxides (LDHs-*g*-POEGMA) with high surface area with easy accessibility of active sites was successfully prepared for the first time *via* an efficient sequential synthetic procedure and characterized by FT-IR spectroscopy, XPS spectra, thermogravimetric analysis (TGA), powder X-ray diffraction (XRD), scanning electron microscopy (SEM) and NMR spectroscopy. The obtained green catalyst was used as an effective, inexpensive, environmentally friendly and highly active reusable heterogeneous solid catalyst for the synthesis of chromene incorporated dihydroquinoline derivatives *via* a one-pot three-component condensation of 4-hydroxy-2*H*-chromen-2-one, aromatic amines and various aldehydes under solvent-free conditions. The notable features of this “green” reaction contain good to excellent yields, shorter reaction time, avoid toxic solvent and endure the substrate diversity. Herein we also observed that the LDHs-*g*-POEGMA is highly stable at reaction condition, easily separated from reaction mixture and can be reused for several consecutive runs without any apparent loss of its catalytic activity.

Introduction

Now-a-days the environmental protection is one of the major and important increasing recognition of green and sustainable chemistry. Therefore, to the development of environmentally benign alternatives for traditional environmentally unfriendly processes the synthetic chemists have been devoted more and more. According to the green chemistry principles, when going to plan the synthetic strategy of a reaction must be considered into account different factors (like, multi-component one-pot reactions, either solvent-free or in an ionic liquid/ PEGs/ water medium, and heterogeneous catalysts, *etc.*)¹ to make sure is it environmentally friendly and cost-efficient. Among them to overcome the problems of various biologically active compounds synthesis in green

chemistry, first and best eco-friendly methodology is the multi-component one-pot syntheses under solvent-free conditions. Herein, greatly removing the flammable and ecologically harmful organic solvents which are create a large quantity of wastage and using fewer or no toxic substances.² Secondly, another extremely important one in green chemistry is the catalysis which decreases reaction period with enhancing favorable reaction rates and resulted either decrease or eliminate the pollution at source.³ In addition, solid/polymer-supported catalysis is another attractive of current interest branch in green chemistry due to combination of advantages of heterogeneous catalysis enables environmentally friendly and sustainable catalytic processes.⁴ Because of their inherent advantages in synthetic organic chemistry and chemical industries, the polymer-supported catalysts are have gained considerable importance in the recent decades due to their easy work-up, excellent product yields, high selectivity, non-corrosiveness and thermal stability.⁵

On the other hand, because of an increasing public concern on the environment and the human body now-a-days the organic chemists showing an important attention on harmful effects of organic solvents. In addition in the respect of organic reactions the role of a solvent is still complex, because, it has the power to increase or decrease the speed of a reaction (sometimes extremely), can

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influence the rate of reaction by changing the solvent and sometimes it may also alter the course of reaction, yields and ratios of product. Therefore, through the solvation of the reactants, transition state, or other intervening species a solvent can be deeply and inseparably associated with the process of an organic reaction. Herein, the solvent-free reactions are having been playing an important role in the designing and development of molecular synthesis. Therefore, in the field of green chemistry one of the most significant research themes is the development of solvent-free reactions⁶. Because they offer several advantages with simple and amazing versatile less labor-intensive methodologies, simpler equipment, less energy consumption, and more efficient product yields with faster reaction rates by minimization of formation of other waste. Since, with their essential advantages of solvent-free reactions are particularly welcome polymer-supported heterogeneous reactions⁷ in green chemistry for environmentally benign efficient synthetic methodology.

Brucite-like layered general structure based layered double hydroxides (LDHs), also known as hydrotalcite-like compounds, are ionic lamellar materials, a class of host-guest layered solids, with octahedrally surrounded M^{2+}/M^{3+} by six hydroxy anions which belonging to the group of anionic clays with the general formula $[M^{2+}_{1-x}M^{3+}_x(OH)_2]^{x+}[A^{n-}]_{x/n} \cdot mH_2O$.⁸ Where, M^{2+} and M^{3+} are di- and tri-valent metal cations respectively and A^{n-} is an organic or inorganic interlayer n-valent anion and x values has usually between 0.20 and 0.33. The properties of LDHs have been tailored over the past two decades in a wide variety of fields like, electrochemistry, photochemistry and pharmaceuticals to produce materials to fulfil specific requirements for practical applications, such as adsorption materials, additives in polymers, and precursors for functional materials.⁹ Therefore, in recent years, the LDHs have received much attention because of their extensive applications at various fields, like, adsorption, catalysis, as organic-inorganic nanocomposites, and electrochemicals *etc.*¹⁰ They also have attracted considerable attention in the areas of drug delivery and gene therapy because of their biocompatibility.¹¹ In addition they have been widely used in catalytic fields and as catalyst support and wider applications has received a vigorous attention.¹² Therefore, these can act as good candidates for polymer supporting application by various strategies, like, through surface modification, grafting and self-assembly for constructing recoverable heterogeneous catalysts and therefore, in organic transformations they were applied for the preparation of various solid-supported reagents.¹³

Therefore, we focused to develop an efficient and highly active reusable heterogeneous solid catalyst, poly(oligoethylene glycol methacrylate)-*g*-layered double hydroxides (LDHs-*g*-POEGMA) by combining of these two materials (LDHs and poly(oligo(ethylene glycol) methacrylate) (POEGMA)) as composite. So these LDHs-*g*-POEGMA catalyst show noticeable advantages of their inexpensiveness, analytical simplicity, non-volatile, lack of diffusion phenomena, reusability, high thermal stability and good structural stability. Therefore, from simple and easily available starting materials it would be straightforward and ideal to adopt a "green chemistry" procedure.

On the other hand, natural heterocycles as well as synthetic heterocycles with nitrogen and oxygen atoms are composing an important classes of organic compounds because of their availability in a wide range of interesting drug molecules, drug-like scaffolds, agricultural industries, and as well as advanced materials.¹⁴ Some examples of them which are proved various biological activities are shown in Figure 1. Compound **A** (Lamellarin D) has cytotoxicity for a wide range of cancer cell lines and is also potent inhibitor of human topoisomerase,¹⁵ compound **B** and its analogues display Alzheimer's activity,¹⁶ compound **C** has found to be an anti-cancer drug candidate,¹⁷ and compound **D** has found to be potent anti-tubercular activity.¹⁸ Some of these derivatives were also identified as anti-hypertensive agents and important building blocks for the synthesis of selective V1b receptor antagonists (Figure 1, E).¹⁹ These are also reported as Parkinson's drug candidates, anti-TMV, anti-tumor, anti-inflammatory, anti-metabolic and antimalarial agents.²⁰ Moreover, they can be used as dyes, biosensors, for visualization of biomolecules as pH-sensitive fluorescent material and also utilized in laser technologies.²¹

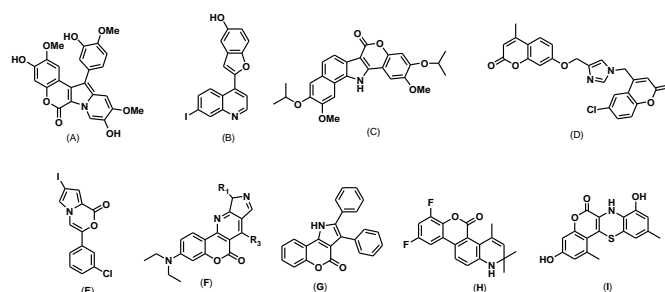
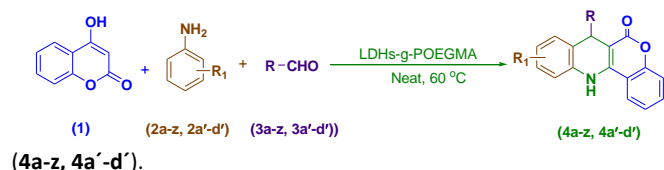


Figure 1 Some of biologically important nitrogen and oxygen containing heterocyclic compounds.

Among them, diversified and highly functionalized numerous synthetic or naturally occurring molecules of chromeno-quinoline derivatives (Figure 1, F-I) have gotten tremendous importance in drug discovery due to their broad range of biological and pharmacological activities because of unique and selective binding abilities with the biological targets.^{22,23} In addition, these derivatives are also explored their fluorescence properties in the design of fluorescent sensors.²⁴ Therefore, these structures are important synthetic targets for organic chemists.

Herein, we are motivated by the above two areas of findings and continuation of our ongoing efforts endowed with finding of new synthetic protocols under principles of green chemistry.²⁵ So we focused our attention on the simple, green, and an efficient method for preparation of poly(oligoethylene glycol methacrylate)-*g*-supported layered double hydroxides (LDHs-*g*-POEGMA), as a novel recyclable polymeric heterogeneous catalyst, and established it on the basis of FT-IR, XPS spectra, powder X-ray diffraction (XRD), scanning electron microscopy (SEM) and NMR spectroscopy. Subsequently it was successfully applied for the synthesis of chromene incorporated dihydroquinoline derivatives (**4a-z**, **4a'-d'**) by the condensation reactions of 4-hydroxy-2H-chromen-2-one (**1**) with various aromatic amines (**2a-z**, **2a'-d'**) and various aldehydes (**3a-z**, **3a'-d'**) under solvent-free thermal conditions (Scheme-1). To the best of our knowledge, such as an environmentally benign and

sustainable reaction system was explored by us first time for the expeditious synthesis of chromene incorporated dihydroquinolines

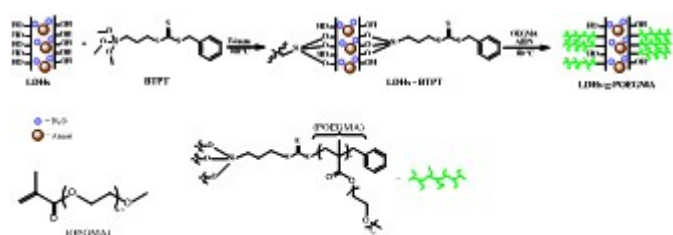


Scheme 1 Synthesis of chromene incorporated dihydroquinoline derivatives (4a-z, 4a'-d').

Results and discussion

Synthesis of LDHs-g-POEGMA

In the course of finding of green catalysts we first went to the syntheses of LDHs-g-POEGMA via a simple and convenient reversible addition-fragmentation chain-transfer (RAFT) polymerization using grafting reaction. Initially, surface of LDHs was functionalized with *S'*-(3-trimethoxysilyl) propyltrithiocarbonate (BTPT) by silane condensation reaction in dry toluene followed by RAFT process using poly(oligo(ethylene glycol) methacrylate) (POEGMA) in the presence of 2, 2'-azobis (2-methylpropionitrile) (AIBN) in the next step and obtained in good yield (Scheme 2). The formed LDHs-g-POEGMA was confirmed by FT-IR and XRD pattern. And a thermal property and surface morphologies of the catalyst were also analyzed by XPS, TGA, SEM and PMR experiment.



Scheme 2 Schematic presentation of synthesis of poly(oligoethylene glycol methacrylate)-g-layered double hydroxides (LDHs-g-POEGMA).

GPC analysis of POEGMA cleavage

The POEGMA brushes were cleaved from the LDHs using aminolysis reaction for GPC analysis.²⁶ To a glass tube was added 100 mg of POEGMA grafted LDHs, five mL of THF, and one drop of a dilute aqueous solution of $\text{Na}_2\text{S}_2\text{O}_4$. After degassing the mixture with nitrogen for 15 min, 0.1 mL of degassed *n*-hexylamine was injected into the mixture. Stirring at 50 °C for overnight, the mixture was filtered off, and the recovered POEGMA was subjected to GPC analysis. As expect, the GPC result proved that BTPT had a good control for polymerization of OEGMA (M_n , GPC = 4500 g/mol, PDI = 1.39) (Figure 1).

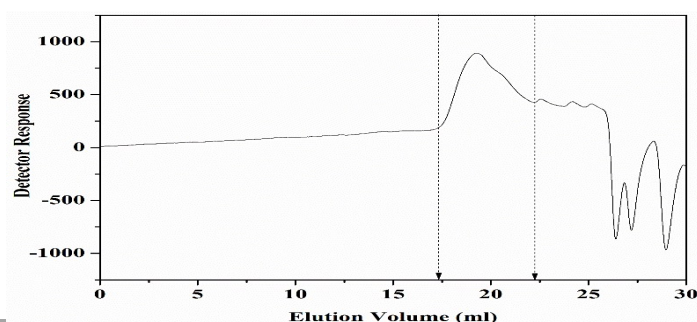


Figure 1 GPC result of cleaved POEGMA brushes.

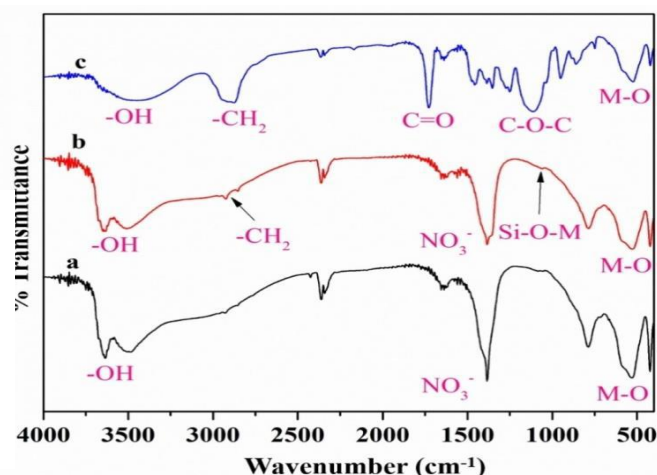
FT-IR spectra of LDHs-g-POEGMA

Figure 2 depicts the FT-IR spectra of catalyst and precursors composites. In all the spectrum of LDHs, LDHs-BTPT, and LDHs-g-POEGMA (Figure 2a-c respectively) observed a broad band peak at 3400-3700 cm^{-1} due to the Al-OH/ H_2O stretching vibration. Whereas the broad peaks from 788 to 530 cm^{-1} were implied to metal to oxygen (M-O) and O-M-O vibrations in all composites structures. The strong peak at 1384 cm^{-1} was attributed to the interlayer NO_3^- anion. The chemical bond of RAFT agent on the surface of the LDHs showed the characteristic peaks at 2924 cm^{-1} and 1060 cm^{-1} owing to methylene and Si-O-Si group, respectively (Figure 2b). As expected, the LDHs-g-POEGMA exhibit new absorption bands at 1729, 1251, and 1114 cm^{-1} indicating the stretching vibration of C=O and C-O-C of POEGMA moieties (Figure 2c).

Figure 2 FT-IR results: (a) LDHs, (b) LDHs-BTPT, (c) LDHs-g-POEGMA.

XPS spectra of LDHs-g-POEGMA

The surface modification of LDHs was investigated by the XPS analysis (Figure 3). The elemental peaks are dominated by O, Ca and



Al of LDHs (Fig. 3a,b,c). The presence of C, Si, and S in LDHs-BTPT sample was confirmed due to the characteristic peaks for C 1s at the binding energy (BE) of about 284.8 eV, Si 2p at the BE of about 102.5 eV and S 2p at the BE of about 164.02 eV, respectively (Figure 4). In the Fig. 3c, the strong C and O signals (associated with the grafted POEGMA) were also observed, suggesting the successful formation of LDHs-g-POEGMA. In comparison with the LDHs surface, the Al and Ca signals of LDH-g-POEGMA were reduced significantly. In addition, the characteristic peaks for C 1s included 3 peaks at 284.8 eV (C-C bonding), 286.7 eV (C-O-C bonding) and 288.6 eV (O-C=O bonding) indicated that the polymer was successfully introduced onto the LDH surface by covalent linkages (Figures 4&5).

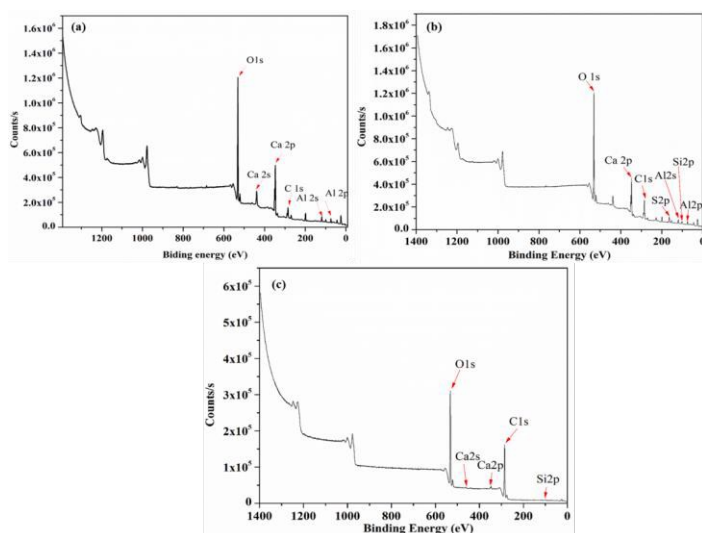


Figure 3 XPS spectra of (a) as-synthesized LDHs, (b) LDHs-BTPT and (c) LDHs-g-POEGMA.

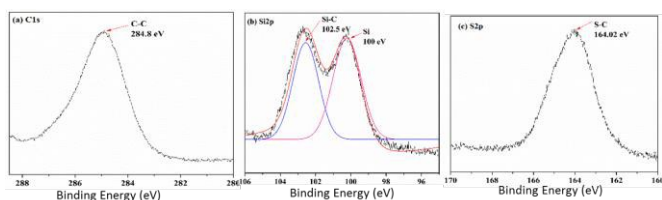


Figure 4 XPS wide-scan spectra of C1s (a), Si2p (b) and S2p (c) of LDHs-BTPT.

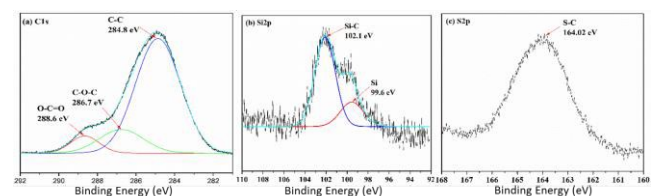


Figure 5 XPS wide-scan spectra of C1s (a), Si2p (b) and S2p (c) of LDHs-g-POEGMA.

XRD spectra of LDHs-g-POEGMA

Figure 6 shows the XRD patterns of LDHs, synthesized LDHs, LDHs-BTPT, and LDHs-g-POEGMA composites. To confirm the successful syntheses of CaAl-layered double hydroxides, we used the Ca-Al-Cl hydrocalumite $\text{Ca}_4\text{Al}_2\text{O}_6\text{Cl}_2 \cdot 10\text{H}_2\text{O}$ as a reference with the reference code is 00-031-0245. In detail, the synthesized LDHs were identified by the main peaks at 11.56 degree, two overlapped peaks at the 2θ values of 23.05, and 23.72, and the single peak at 31.36 degree (Fig. 6 a,b). It can be clearly seen that the peaks of the LDHs-BTPT (Figure 6c) and the LDHs-g-POEGMA (Figure 6d) are perfectly indexed to tetragonal phase of the LDHs with 2θ values of 11, 22.5, 23.3, and 31.1 corresponding to the crystal planes of (002), (004), (112) and (020), respectively (Figure 6a,b). These XRD result revealed the grafting of polymer did not alter the crystallinity of the LDHs.

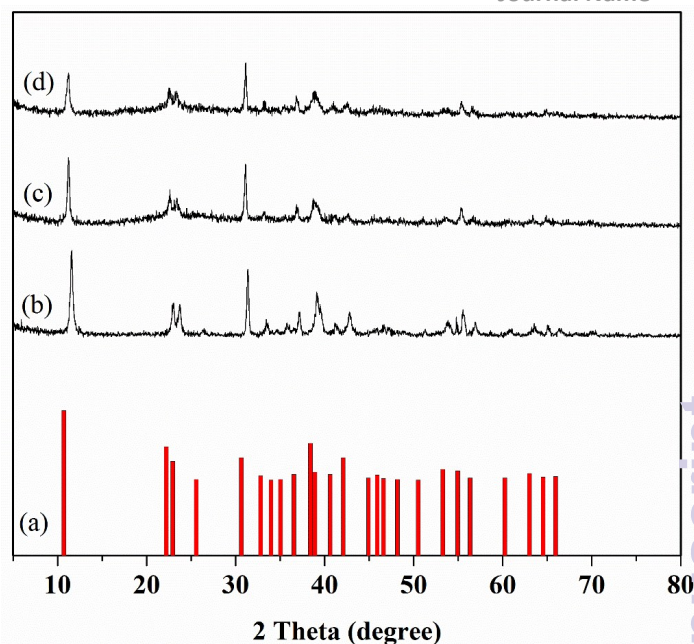


Figure 6 X-ray diffraction patterns of (a) Ca-Al-Cl hydrocalumite as a reference (b) as-synthesized LDHs (c) LDHs-BTPT (d) LDHs-g-POEGMA.

TGA analysis of LDHs-g-POEGMA

TGA analyses were performed in order to check the thermal degradation property as shown in Figure 7. LDHs started to decompose at 78 °C and lost 13 and 23% of weight at 214 and 348 °C due to the release of absorbed water and interlayer anions respectively (Figure 7a). The LDHs-BTPT started to degrade at 80 °C and showed the 24% weight loss upto 458 °C, since in addition to water the encapsulating organic molecules decomposed at this high temperature (Figure 7b). The grafting prepared LDHs-g-POEGMA were significantly degraded between 280-430 °C and lost 90% at 800 °C (Figure 7c). LDHs-g-POEGMA showed the higher starting degradation temperature in comparison to LDHs and LDHs-BTPT due to the coverage of polymer layers which prevented the escape of absorbed water and interlayer anions. TGA results demonstrated that the brush polymers were successfully decorated onto the LDHs and they are more stable at higher temperature.

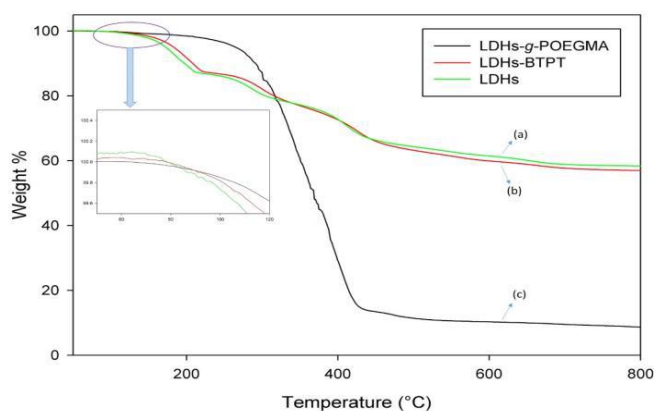


Figure 7 TGA spectra of (a) LDHs, (b) LDHs-BTPT, and (c) LDHs-g-POEGMA.

NMR Analysis of LDHs-g-POEGMA

In addition to the above identification analytical data we were also checked the NMR spectral data for the final conformation of the catalyst formation (Figure 8). Herein, we compare the synthesized LDHs-g-POEGMA catalyst with the BTPT and monomer unit of LDHs. Both the reactant's peaks (Figure 8a&b) are disappeared in the final catalyst, LDHs-g-POEGMA. It clearly shows that the disappearance of the two double bonded protons peaks of monomer unit at near 6 ppm indicating that the grafting was successfully achieved (Figure 8c).

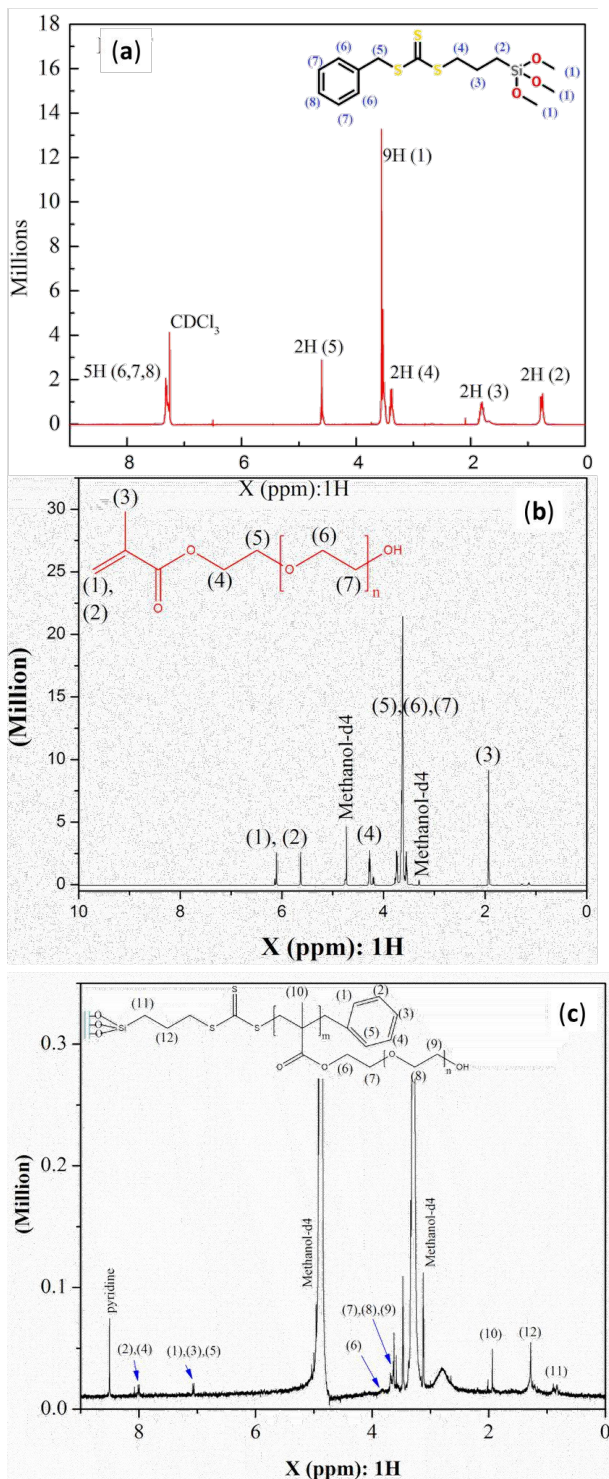


Figure 8 PMR spectra of (a) BTPT, (b) LDHs, and (c) LDHs-g-POEGMA.

Surface morphologies of LDHs-g-POEGMA

The surface morphologies of pristine LDHs and LDHs-g-POEGMA could be visualized by using SEM characterization. The morphology of LDHs displays distinct separation as shown in Figure 9a. After RAFT grafting polymerization, LDHs-g-POEGMA image demonstrates relatively irregular shape having the polymer layer due to coverage of POEGMA chains as brushes (Figure 9b).

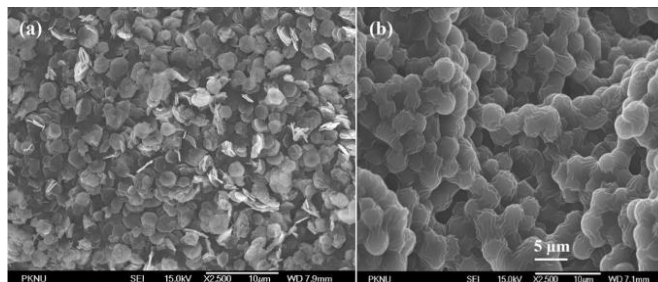


Figure 9 SEM images of (a) LDHs and (b) LDHs-g-POEGMA.

Application of LDHs-g-POEGMA for the synthesis of chromene incorporated dihydroquinoline derivatives

After confirmation of the LDHs-g-POEGMA we investigated its catalytic activity in the synthesis of diversified and highly functionalized chromene incorporated dihydroquinoline derivatives. Firstly we performed a reaction of 4-hydroxy-2H-chromen-2-one (**1**, 1 mmol), 4-methoxybenzamine (**2a**, 1 mmol), and 2-methylbenzaldehyde (**3a**, 1 mmol) as a model reaction, which was conducted at room temperature (RT) in solvent-free and catalyst-free conditions. Unexpectedly herein we observed the undesired bis-chromene derivative (**5a**) instead of desired chromeno-quinoline derivative (**4a**) even after 5 h of reaction time (Table 1, entry 1). Therefore, we investigated the reaction by using LDHs-g-POEGMA as catalyst and performed it at various conditions to set the suitable reaction conditions. At beginning we used 2 mg of LDHs-g-POEGMA at RT under solvent-free condition. To our gratifyingly the reaction occurred to afford the desired product **4a** in moderate yield (70%) within 60 min (Table 1, entry 2). In our endeavor to further improve the yield, the experiment was carried out using 5 mg of LDHs-g-POEGMA at RT but there was no gratifying success and observed only marginal increment in yield which is 73% (Table 1, entry 3). While tuning the reaction conditions a tremendous and rapid reaction rate was observed when the reaction temperature increased from RT to 60 °C and offered excellent product yield even within 10 min with 5 mg of LDHs-g-POEGMA (Table 1, entry 4). This result encouraged us to improve the yield furthermore and to fix the higher limit of catalyst amount. So we increased its amount from 5 mg to 8 mg but didn't find significant increment in yield (Table 1, entry 5). On the other hand to find the minimal limit of catalyst amount we carried out the same reaction using 3 mg of catalyst and observed the decrease in the product yield (Table 1, entry 6). After that we regulated the temperature on model reaction with 5 mg of LDHs-g-POEGMA under solvent-free condition to find the optimum reaction temperature. Herein, we didn't obtain further better yield even after 15 min of reaction time at 80 °C (Table 1, entry 7).

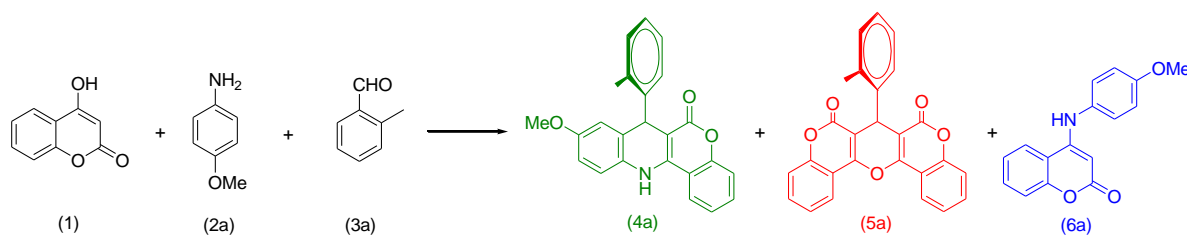
Subsequently, we examined the effect of solvent on model reaction with 5 mg of LDHs-*g*-POEGMA catalyst at 60 °C using ethanol, THF, toluene, DMF and DCM as solvents (Table 1, entries 8-12). Under these solvent mediums found that the rate of reactions were slower and resulted moderate yields of **4a** in mixture even after prolonged reaction times. But the model reaction already showed better result under solvent-free condition (Table 1, entry 4) and didn't require the chromatographic separation of product in this procedure. Therefore, this solvent-free protocol with an increment in safety and reduction effect of cost leads to a clean and economical technology in green chemistry.

To merit the catalytic activity of LDHs-*g*-POEGMA a comparison study was conducted with available acid and base catalysts and polymer supported catalysts at various reaction conditions. At first the model reaction was performed in ethanol using *p*-toluenesulphonic acid (PTSA) as catalyst at 80 °C. Even though 4-hydroxy-2*H*-chromen-2-one (**1**) and 2-methylbenzaldehyde (**3a**) were almost consumed (by TLC test) after 30 min, **4a** could not be observed but 85% of by-product, **5a** could be isolated from the reaction mixture (Table 1, entry 13). After that we performed the model reaction with various solvents, such as, DMF, EtOH, CH₃CN, and H₂O using various acid catalysts, such as, Cu(OTf)₃, Zn(OTf)₃, InCl₃, FeCl₃, H₃BO₃ and Cu(OAc)₂ at different reaction conditions. But, in addition to promote the desired product (**4a**) significantly in all these reaction conditions, only the by-product (**6a**) was observed predominantly (Table 1, entries 14-19).

After that replaced the acid catalysts with some available base catalysts, such as, dibutylamine (DBA), tetramethylguanidine (TMG), L-proline and triethylamine (Et₃N) in solvent and solvent-free conditions at different temperature, which were resulted into still the by-product (**6a**) and another by-product (**5a**) as predominates. But the desired product (**4a**) was observed in lower yields (Table 1, entries 20-28). Then the model reaction was carried out using polymer supported (PS) catalysts like, PS/PTSA, PS/AlCl₃ and PS/GaCl₃ under neat condition at 60 °C and obtained desired product in moderate yields within reduced reaction times (Table 1, entries 29-31) as mixture. Finally to merit the catalytic activity of LDHs-*g*-POEGMA we were also tested the catalytic nature of the precursors of it by individually each and as mixture both. Herein, the LDH and POEGMA are individually couldn't shown desired catalytic activity towards titled compound, **4a** (Table 1, entries 32,33). But in mixture form they could shown some what extend product yield (Table 1, entry 34).

With these overall results demonstrated that LDHs-*g*-POEGMA is the best heterogeneous solid catalyst for the multi-component fusion of 4-hydroxy-2*H*-chromen-2-one (**1**), 4-methoxybenzylamine (**2a**), and 2-methylbenzaldehyde (**3a**). It gives the desired target chromene incorporated dihydroquinoline **4a** in excellent yield and in short reaction time by avoiding the by-products.

Table 1 Optimization of reaction conditions for the synthesis of **4a**^a



Entry	Solvent	Catalyst (%)	Tem (°C)	Time (min)	Yield (%) ^b		
					4a	5a	6a
1	Neat	Neat	RT	300	-	92	-
2	Neat	LDHs- <i>g</i> -POEGMA (2 mg)	RT	60	70	10	-
3	Neat	LDHs- <i>g</i> -POEGMA (5 mg)	RT	60	73	10	-
4	Neat	LDHs- <i>g</i> -POEGMA (5 mg)	60	10	95, 94, 92, 90, 89	-	-
5	Neat	LDHs- <i>g</i> -POEGMA (8 mg)	60	10	95	-	-
6	Neat	LDHs- <i>g</i> -POEGMA (3 mg)	60	25	83	-	-
7	Neat	LDHs- <i>g</i> -POEGMA (5 mg)	80	15	95	-	-
8	Ethanol	LDHs- <i>g</i> -POEGMA (5 mg)	60	45	65	-	20

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9	THF	LDHs- <i>g</i> -POEGMA (5 mg)	60	60	55	30	-
10	Toluene	LDHs- <i>g</i> -POEGMA (5 mg)	60	65	53	-	41
11	DMF	LDHs- <i>g</i> -POEGMA (5 mg)	60	48	69	-	22
12	DCM	LDHs- <i>g</i> -POEGMA (5 mg)	60	60	55	40	-
13	Ethanol	PTSA (10 mol%)	80	30	-	85	
14	Ethanol	Cu(OTf) ₃ (10 mol%)	80	300	30	-	52
15	DMF	Zn(OTf) ₃ (10 mol%)	120	240	35	-	55
16	CH ₃ CN	InCl ₃ (10 mol%)	80	240	29	-	51
17	H ₂ O	FeCl ₃ (10 mol%)	70	180	38	-	43
18	Neat	H ₃ BO ₃ (10 mol%)	60	300	33	-	57
19	H ₂ O	Cu(OAc) ₂ (10 mol%)	100	180	37	-	42
20	DMF	DBA (10 mol%)	120	240	25	35	20
21	Ethanol	TMG (10 mol%)	80	300	20	50	22
22	CH ₃ CN	L-proline (10 mol%)	80	240	32	60	-
23	Water	L-proline (10 mol%)	100	300	15	-	70
24	Neat	DBA (10 mol%)	60	240	22	62	-
25	Ethanol	DBA (10 mol%)	80	300	20	45	18
26	Neat	TMG (10 mol%)	60	255	21	18	40
27	CH ₃ CN	TMG (10 mol%)	80	240	22	23	35
28	Ethanol	Et ₃ N (10 mol%)	80	270	23	55	10
29	Neat	PS/PTSA (10 mg)	60	90	62	25	-
30	Neat	PS/ AlCl ₃ (10 mg)	60	88	58	32	-
31	Neat	PS/ GaCl ₃ (10 mg)	60	100	63	30	-
32	Neat	POEGMA (10 mg)	60	120	25	65	-
33	Neat	LDH (10 mg)	60	55	55	-	30
34	Neat	POEGMA+ LDH (10 mg)	60		60	30	-

^aReaction of 4-hydroxy-2*H*-chromen-2-one1 (**1**, 1 mmol), 4-methoxybenzenamine (**2a**, 1 mmol), and 2-methylbenzaldehyde (**3a**, 1 mmol);

^bIsolated yield; ^cCatalyst was reused five times.

In any catalytic reaction processes in view of green chemistry, the recyclability of the catalyst is an important issue for industrial and commercial use. In this connection, herein, we studied the LDHs-*g*-POEGMA reusability on the model reaction (Figure 10). At the end of the reaction the catalyst was isolated by simple filtration using 10

mL of ethyl acetate (EA) as solvent and washed the precipitated catalyst with acetone and dried in an oven. After that the dried catalyst could be reused for the model reaction and we delighted to note that the catalytic activity of LDHs-*g*-POEGMA has no significant loss up to five runs (Table1, entry 4). Furthermore we observed that it didn't show any significant change even after its exposure to air

at room temperature for one week. It's indicating that the exceptional stability and catalytic activity of LDHs-*g*-POEGMA. In addition to this reusable catalytic activity the LDHs-*g*-POEGMA has another remarkable feature of its insensitivity to air and moisture.

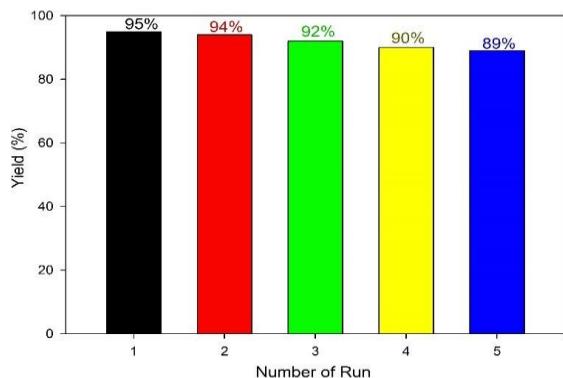


Figure 10 Reusability of the LDHs-*g*-POEGMA catalyst.

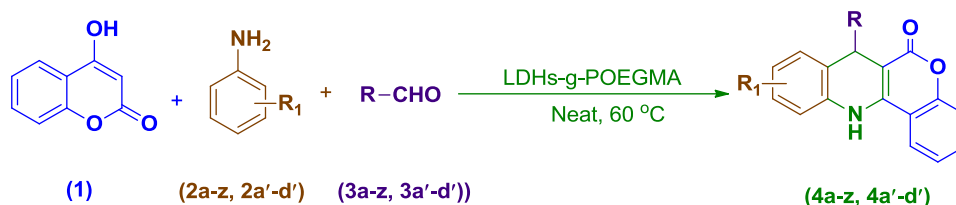
With the optimized conditions of green" catalytic system LDHs-*g*-POEGMA in hand, we employed a wide range of amines (**2a-z**, **2a'-d'**) and aldehydes (**3a-z**, **3a'-d'**) to establish the extend and limitations of this protocol and synthesized (Scheme-1) a series of chromene incorporated dihydroquinoline derivatives in good to excellent yields (Table 2). Firstly, we examined the effect of electron donating/ withdrawing groups on aldehydes. It was found that the

groups either, good electron donating (such as, -Me, -OMe, etc.) or strong electron withdrawing (such as, -CN and -NO₂, etc.) at either position of aromatic ring of an aldehyde were proceed the reaction smoothly and resulted the corresponding titled chromene incorporated dihydroquinoline derivatives in excellent yields. On the other hand we couldn't observed any differences in yields and reaction time with halogen (such as, -Br, -Cl and -F) substituted aldehydes at either position of the aromatic ring and also heterocyclic aldehyde of thiophenecarboxaldehyde provided desired product in very good yield.

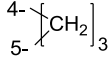
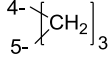
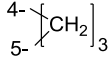
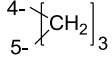
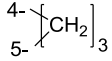
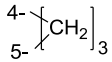
After that we examined the reaction with a diversity of substituted anilines and couldn't observe any remarkable differences in their reactivity and product yields even aniline with any type of substituent on aromatic ring. Similarly, also used the poly-substituted anilines and delivered their expected products in excellent product yields.

In addition, the green chemistry metric calculations were carried out to measure aspects of a chemical process, such as the atom economy, E-factor, and reaction mass efficiency for the LDHs-*g*-POEGMA catalyzed model reaction according to A.P. Dicks, *et al.*²⁷ reported general equation. The smaller E-factor (0.15), high atom economy (91.11%), and best operative reaction mass efficiency (86.63%) proves the significant environmentally benign green approach of this catalytic reaction system (see supplemental information for calculations).

Table 2 Synthesis of chromene incorporated dihydroquinoline derivatives (**4a-z**, **4a'-d'**)^a



Entry	R ₁	R	Product	Time (min)	Yield ^b (%)	mp (°C)
1	4-OMe	2-Me-C ₆ H ₄	4a	10	95	274-276
2	4-F	3-Cl-C ₆ H ₄	4b	11	92	326-328
3	3-5-OMe	4-Cl-C ₆ H ₄	4c	12	94	279-281
4	4-OMe	2-Cl-C ₆ H ₄	4d	9	93	278-280
5	4-F	2-Me-C ₆ H ₄	4e	11	95	287-289
6	4-OMe	3-Cl-C ₆ H ₄	4f	10	91	265-267
7	4-OMe	3-F-C ₆ H ₄	4g	11	91	255-257
8	4-OMe	2-NO ₂ -C ₆ H ₄	4h	10	93	263-265
9	4-OMe	2-Br-C ₆ H ₄	4i	12	90	302-304

Journal Name		ARTICLE				
10	4-F	4-Isopropyl-C ₆ H ₄	4j	8	96	322-324
11	4-F	3-4-5-OMe C ₆ H ₂	4k	7	95	328-330
12	4-OMe	4-Cl-C ₆ H ₄	4l	8	93	274-276
13	4-OMe	4-OEt-C ₆ H ₄	4m	8	96	265-267
14	4-OMe	4-OMe-C ₆ H ₄	4n	9	95	279-281
15	4-F	4-Cl-C ₆ H ₄	4o	10	94	273-275
16	4-F	4-NO ₂ -C ₆ H ₄	4p	9	92	280-282
17	4-OMe	3-4-5-OMe C ₆ H ₂	4q	7	96	278-280
18		2-Me-C ₆ H ₄	4r	8	94	271-273
19	4-NO ₂	4-OMe-C ₆ H ₄	4s	12	92	246-248
20	4-OMe	4-CN-C ₆ H ₄	4t	11	93	283-285
21		3-Br-C ₆ H ₄	4u	9	92	281-283
22		3-OMe-C ₆ H ₄	4v	6	94	263-265
23	4-OMe	3-Br-C ₆ H ₄	4w	9	92	260-262
24	4-OMe	4-NO ₂ -C ₆ H ₄	4x	10	92	266-268
25		3-4-5-OMe C ₆ H ₂	4y	5	96	330-332
26		4-Cl-C ₆ H ₄	4z	7	92	241-243
27		C ₄ H ₃ S	4a'	9	90	280-282
28	4-OMe	4-OH-C ₆ H ₄	4b'	10	92	295-297
29	H	4-OEt-C ₆ H ₄	4c'	9	95	258-260
30	H	3-4-5-OMe C ₆ H ₂	4d'	7	96	337-339

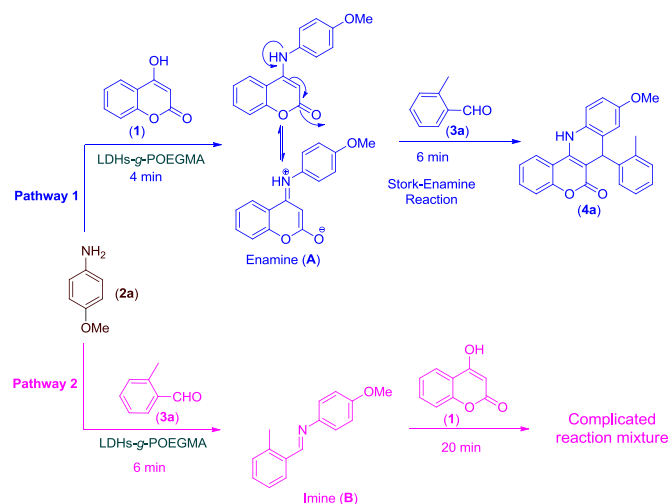
^aReaction of 4-hydroxy-2*H*-chromen-2-one1 (**1**, 1 mmol), amines (**2a-z**, **2a'-d'**, 1 mmol), and aldehydes (**3a-z**, **3a'-d'**, 1 mmol) catalyzed by 5 mg of LDHs-*g*-POEGMA under neat conditions at 60 °C; ^bIsolated yield.

Reaction Mechanism

We expected this reaction undergoes one of the two pathways (Scheme 3), either through an enamine (**A**) or an imine (**B**) as an intermediates. Therefore, in order to conclude the pathway of reaction mechanism we conducted some control experiments in this three-component reaction to gain some insight into the

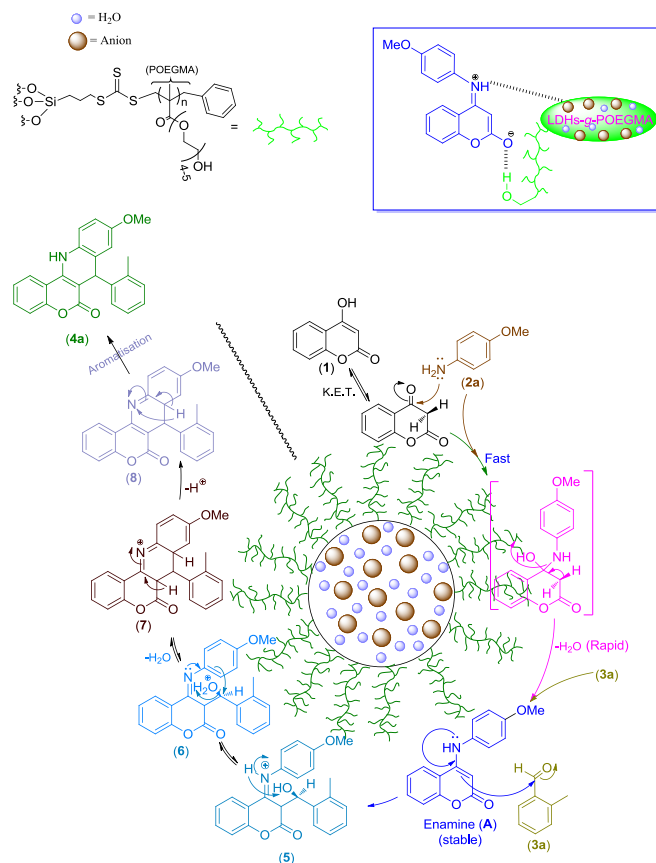
pathway of LDHs-*g*-POEGMA catalytic reactions. Herein, we carried out two parallel reactions using 5 mg of LDHs-*g*-POEGMA as catalyst, such as, pathway 1 [(**1** + **2a**) + **3a**]: treatment of **1** with **2a** gave an enamine intermediate (**A**) which was isolated in 90% yield after 5 min. Subsequently, **A** was treated with compound **3a** (Stork-enamine reaction) which led smoothly to expected product, **4a**, in 95% isolated yield. Pathway 2 [(**2a** + **3a**) + **1**]: Treatment of **2a** with

3a gave an imine intermediate (**B**) which was isolated in 85% yield after 6 min of reaction time. However, under identical experimental conditions, the reaction between **B** and compound **1** has not shown any amount of the desired product, **4a**. Herein, the catalyst played an important role at pathway 1 because due to its active surface and inner core shown high interactive/binding/chelating nature with the reacting components and as well with formed intermediate, enamine (**A**) (Scheme 4 sub-structure). It's attributing due to the combined activities of the starting LDH and POEGMA and also higher binding nature properties at a reaction center. Therefore, higher yield of product, **4a**. The obtained intermediates (**A** and **B**) at both pathways are further confirmed the structures by their PMR spectra (see supplemental information). Therefore, this controlled experiments clearly stated that the LDHs-*g*-POEGMA catalyzed three-component condensation reaction should proceed through pathway 1 [(**1** + **2**) + **3**] and giving the titled compounds (**4a-z**, **4a'-d'**).



Scheme 3 Schematic illustration of the control experiments for LDHs-*g*-POEGMA catalyzed synthesis of **4a**.

From the above experimental results we proposed a schematic illustration for the synthesis of titled compounds (Scheme 4). At first, herein, the chromene undergoes keto-enol tautomerisation and reacts with amine (**2a**) to give a stable enamine (**A**) intermediate at a fast rate. After then, this enamine can combine with an aldehyde (**3a**) as like Stork-enamine reaction and should be gone into some more intermediates (Scheme 4, 5-8) and at final given the titled compounds (**4a-z**, **4a'-d'**) by aromatization.



Scheme 4 Schematic illustration of LDHs-*g*-POEGMA catalyzed synthesis of titled compounds (**4a-z**, **4a'-d'**)

Conclusion

In conclusion, we have described first time the highly active, air stable and recyclable LDHs-*g*-POEGMA solid catalyst for the synthesis of chromene incorporated dihydroquinoline derivatives under solvent-free and mild reaction conditions. Main highlights/promising points of this methodology are variety of ways, such as, simplicity in the catalyst preparation from inexpensive materials, non-corrosive nature of the catalyst leads benefits to human health, and environment, easy work-up procedure at reactions, shorter reaction times, higher reaction rates, a variety of desirable products synthesized and the reusability of catalyst leads economic goals. Since, our research group is attempting to expand the applications of this successful catalyst system for other organic synthesis/transformations are in progress.

Experimental

Material and methods

Chemicals were purchased from Aldrich and Alfa Aesar Chemical Companies and used without further purification. NMR spectra were recorded in parts per million (ppm) in DMSO-*d*₆ on a Jeol JNM ECP 400 NMR instrument using TMS as internal standard. Standard abbreviations were used to denote signal multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m =

multiplet). Mass spectra were recorded on a Jeol JMS-700 mass spectrometer. All melting points were determined using open capillaries on an Electrothermal-9100 (Japan) instrument and are uncorrected. Fourier transform infrared (FTIR) spectra were measured on a JASCO FT/IR-4100 spectrometer with DLATGS detector. The crystallographic state of the nanocomposites was studied by a Philips X'pert-MPD system diffractometer. Thermogravimetric analysis (TGA) was conducted with Perkin-Elmer Pyris 1 analyzer (USA). The morphology analyzes of the hybrids were carried out by using scanning electron microscopy (SEM) images (Hitachi JEOL-JSM-6700F system, Japan). Surface composition was investigated using an X-ray photoelectron spectroscopy (XPS; Thermo VG Multilab 2000) in ultra-high vacuum with Al K α radiation. Gel permeation chromatography (GPC) was performed using an Agilent 1200 Series equipped with PLgel 5 μ m MIXED-C columns, with THF as the solvent at 30 °C. The solution flow rate was 1 mL/min. Calibration was carried out using PS standard.

Synthesis of Layered double hydroxides (LDHs)

LDHs were synthesized *via* co-precipitation method by one-pot reaction.²⁸ In a typical run, to an aqueous solution containing a calcium salt (Ca(NO₃)₂·4H₂O) and an aluminum salt (Al(NO₃)₃·9H₂O) with the Ca/Al molar ratio of 2.0 was added dropwise to the 2M NaOH aqueous solution in a 250 mL RB flask at 65 °C under vigorous stirring. The metal concentration and pH of the solution were adjusted to 0.66 mol·L⁻¹ and 11.5±0.1 respectively. The slurry solution was aged for 18 h at 65 °C and then filtered, washed with deionized water several times and dried overnight at 100 °C. Then the LDHs was obtained as white powder.

Anchoring of BTPT onto LDHs surface (LDHs-BTPT)

The mixture of 0.7g of LDHs and 20 mL of dry toluene was stirred at 100 °C. Then, 0.724 g (2 mmol) of BTPT in 10 mL dry toluene was injected into the flask under N₂. The reaction was conducted for 24 h. The crude product was filtered off and washed with DCM for three times to remove all unreacted BTPT. The final product was dried under vacuum overnight.

Preparation of LDHs-g-POEGMA by RAFT polymerization

2 g of PEGMA, 0.3 g of LDHs-BTPT, 20 mg of AIBN, and 4 mL of dry toluene were placed in a round bottom flask. The polymerization reaction was performed at 80 °C for 24 h under N₂. The mixture was precipitated in diethyl ether and washed three times with methanol. The product was dried under vacuum at 40 °C overnight (yield, 60%).

General Procedure for the synthesis of 9-methoxy-7-o-tolyl-7H-chromeno[4,3-b]quinolin-6(12H)-one (4a)

LDHs-g-POEGMA (5 mg) was added to a mixture of 4-hydroxy-2H-chromen-2-one (**1**, 1 mmol), 4-methoxybenzylamine (**2a**, 1 mmol), and 2-methylbenzaldehyde (**3a**, 1 mmol), was stirred at 60 °C under solvent-free conditions for 10 min (Table 2, entry **4a**). After the completion of the reaction (confirmed by TLC), and cooled to RT, then EA (15 mL) was added and the reaction mixture was filtered. The solid catalyst was washed with acetone (2 × 10 mL) and dried under vacuum before reuse. Pure **4a** was afforded by evaporation of the solvent followed by recrystallization from ethanol.

Supporting Information

Analytical and spectral data and NMR spectra were provided as supplementary data for all Compounds.

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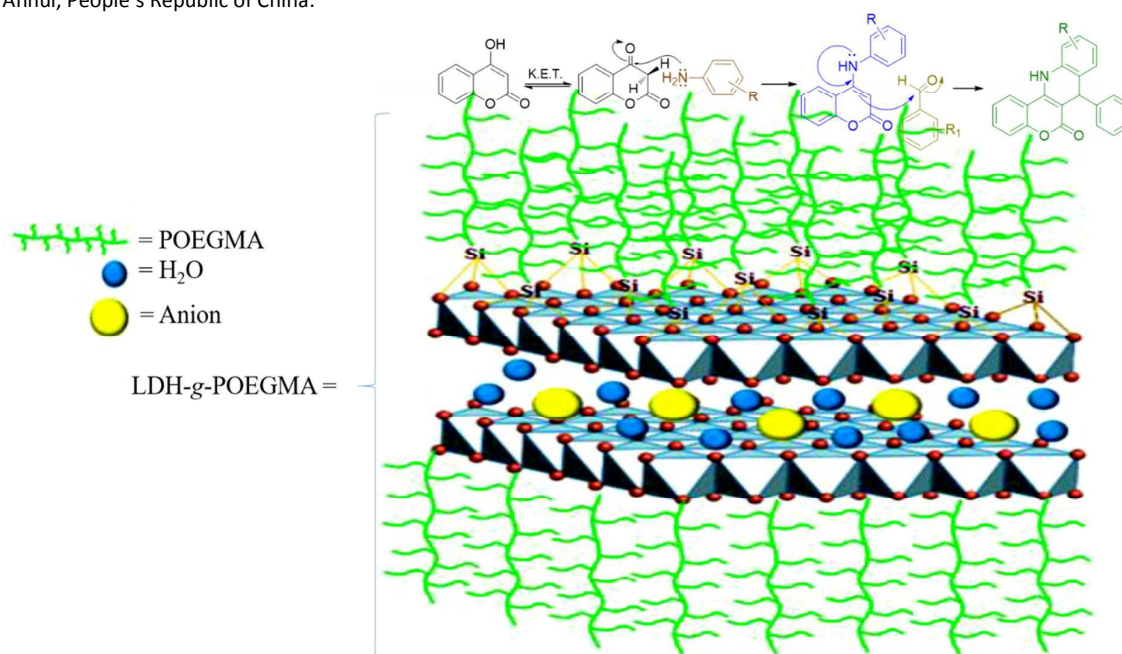
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Polymer grafted layered double hydroxides (LDHs-g-POEGMA): a highly efficient reusable solid catalyst for the synthesis of chromene incorporated dihydroquinoline derivatives under solvent-free conditions

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Syntheses of highly active air stable and recyclable LDHs-g-POEGMA solid catalyst and successfully applied as reusable heterogeneous solid catalyst for the synthesis of chromene incorporated dihydroquinoline derivatives under solvent-free conditions at room temperature.