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L-Tyrosine loaded nanoparticles: an efficient catalyst for the synthesis of dicoumarols and Hantzsch 1,4-dihydropyridines†

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Environmentally benign L-tyrosine loaded nanoparticles are fabricated and characterized by PCS, TEM, FT-IR and AFM studies. A novel straightforward green approach was applied for the synthesis of dicoumarols and Hantzsch 1,4-dihydropyridines using this catalyst. The structures and purity of these compounds were confirmed by FT-IR and NMR (^{1}H, ^{13}C and DEPT). The flexible and swelling properties of the polymer coating increase L-tyrosine dispersion and its high catalytic activity in organic reactions.

Introduction

Implementation of several transformations through a multi-component reaction strategy is highly compatible with the goal of green chemistry.[1] Use of environmentally benign solvents like water[2] and solvent-free reactions[3] offers a powerful and green protocol from both synthetic and economical points of view. It has several advantages like reduced pollution, simplicity of processing and low cost, which is useful to the industry as well as for the environment.

Dicoumarols and their derivatives are of interest because of their anticoagulant (Antivitamin K activity), spasmolytic and rodenticidal activities.[4] Chemically, it is designated as 3,3′-methylenebis[4-hydroxycoumarin]. Dicoumarol and its synthetic derivative warfarin sodium (Coumadin) help to decrease metastases in animal model.[5] Recently, Xian-Xing Luo and his co-workers reported the anti-bacterial activity of pyridine substituted dicoumarols.[6] Similarly, Hantzsch 1,4-dihydropyridines (1,4-DHPs) have remarkable pharmacological efficiency.[7] The ferrocene moiety is known to play an important role in organometallic drugs because of its high affinity towards amino acids, proteins, DNA and carbohydrates.[8] Therefore, the attempts to modify the conditions of Hantzsch reaction are still of growing importance. Dicoumarols have been synthesized using various catalysts such as Zn(proline)$_2$,[9] molecular iodine,[10] sulphated titania,[11] SDS,[12] $MnCl_2$,[13] Biodegradable Task-specific ionic liquid,[14] nano silica chloride[15] *etc.* For Hantzsch's 1,4-DHPs synthesis Several modified methods have been reported nowadays for example such as free nano Fe_2O_3,[16] Zn(L-proline)$_2$,[17] PPh_3,[18] L-proline under ultrasound condition[19] *etc.* Furthermore, ionic liquid such as glycine nitrate,[20] Ni^{2+} containing ionic liquid,[21a] Silica functionalized sulphonic acid coated with ionic liquid,[21b] enzymes such as Baker's yeast,[22] lipase B[23] demonstrated catalytic activity in 1,4-DHPs synthesis. Some heterogeneous catalysts have also been reported such as sulfonic acid supported γ-Fe_2O_3,[24] cellulose,[25] alginic acid.[26]

Two recent studies have established L-tyrosine as an efficient organocatalyst in multi-component reactions for green synthesis.[27] Thitherto, there was no report of any catalytic activity of this amino acid. Researchers in the past few years have investigated the pharmacological importance L-tyrosine loaded nanoparticles (LTNPs). It has been found to increase the antitumoural activity of direct electric current in a metastatic melanoma cell model.[28] Beside, L-tyrosine polyphosphate nanoparticles are also used in gene therapy.[29a] So these studies reveal that encapsulating L-tyrosine inside nano-sized polymeric coating possibly increases its pharmacological activity. Consequently, the next question that arises is whether this encapsulation of L-tyrosine affects its ability to catalyze organic reactions and if yes, in which direction. The fact that L-proline functionalized polymeric nanoreactors have been used as catalyst in Aldol reaction,[29b] makes the above question more pertinent. With this aim, LTNPs have been used as catalyst for preparation of dicoumarols and Hantzsch 1,4-DHPs following a fully green synthetic method. To the best of our knowledge, this is the first report of LTNPs acting as catalyst in any organic reaction. The products are fully characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, DEPT NMR and also by comparison with authentic samples (Scheme 1).

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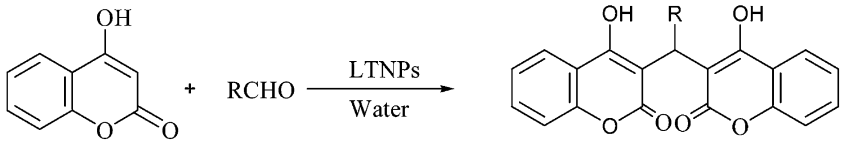
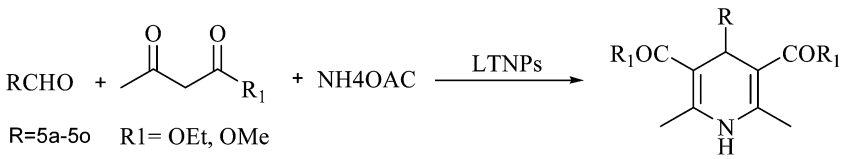


Scheme 1 Synthesis of dicoumarols using LTNPs as catalyst.

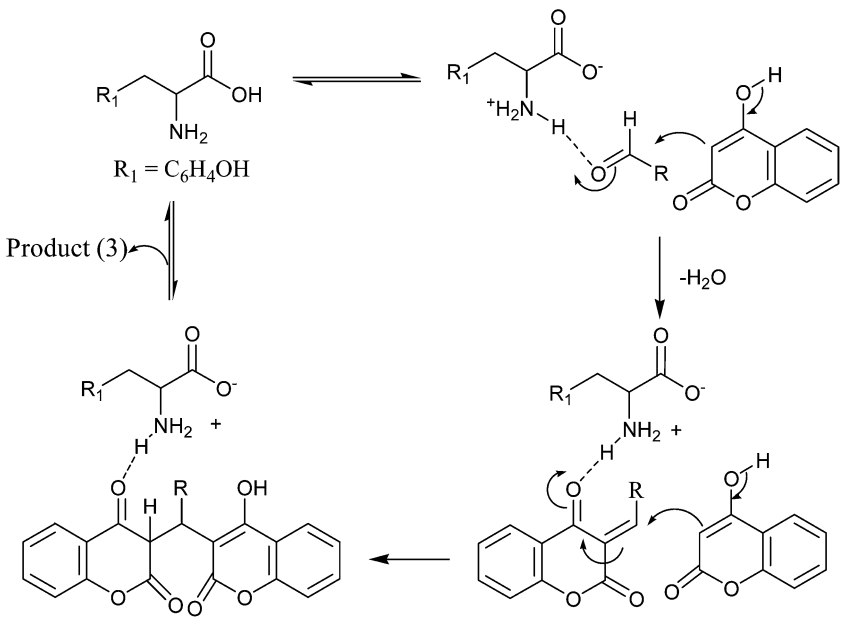
Results and discussions

LTNPs were prepared with polymer Eudragit® RS100 using the solvent evaporation (single emulsion) technique with slight modification as previously reported by Jana *et al.*[30] Eudragit is the co-polymer of poly(ethylacrylate, methylmethacrylate and chlorotrimethyl-ammonioethyl methacrylate) containing quaternary ammonium group.[30] The ammonium groups are present as salts and make the polymers permeable. This polymer has high permeability and pH independent swelling properties. The prepared nanoparticles (ESI-1,† for details) are characterized by particle size analysis, TEM (average size 50 nm), FT-IR and AFM studies (ESI-2†) (Scheme 2).

The C-3 position of 4-hydroxycoumarin (1) ring is highly reactive as it is flanked by electron donating hydroxyl group C-4 and electron withdrawing carbonyl group at C-2. As the carbon–carbon double bond and lone pair of electrons present on the oxygen atom of the OH group is in conjugation, this make coumarin ring very convenient at position 3 to react with carbonyl carbon of the aldehydes. In Scheme 3 we have mentioned the plausible mechanism for the synthesis of various dicoumarols using LTNPs as catalyst. At the outset, we tried the condensation of 4-methoxy benzaldehyde and 4-hydroxy coumarin as a model reaction to synthesize the dicoumarol (**3a**) using LTNPs catalyst in water at 70 °C in a water bath. A broad range of dicoumarols (**3a–3j**) have been synthesized. In a comparative study a large number of catalysts were used to show the effectiveness of LTNPs over other catalysts (Table 1). Increment in the amount of LTNPs catalyst to 0.05 g did not show any improvement in the yield (Table 1, Entry-7) whereas, the yield was found to be



Scheme 2 Synthesis of 1,4-DHPs using LTNPs as catalyst.



Scheme 3 Plausible mechanism for the synthesis of dicoumarols using LNTPs (LTNPs dispersed through Eudragit coating).

Table 1 Screening of various catalysts on the synthesis of **3a** using water as solvent[a]

Entry	Catalyst	Catalyst loading (g)	Time	Yield[b] (%)
1	PTS	0.02	No reaction	NA
2	Glycine	0.02	1.5 h	65
3	L-Proline	0.02	2 h	50
4	L-Serine	0.02	20 min	72
5	L-Tyrosine	0.02	15 min	75
6	LTNPs	0.02	5 min	90
7	LTNPs	0.05	5 min	90
8	LTNPs	0.01	15 min	78

[a] Reaction temperature: 70 °C; molar ratio of aldehydes : 4-hydroxycoumarin: 1 : 2. [b] Isolated yields.

Table 2 Effect of various solvents on the synthesis of **3a** using LTNPs[a]

Entry	Solvent	ε_r	Time	Yield[b] (%)
1	H_2O	80	5 min	90
2	MeOH	32	15 min	86
3	CH_3COOH	6	20 min	65
4	CH_2Cl_2	9	20 h	30
5	CH_3CN	37	NA	NA

[a] Reaction conditions: molar ratios of aldehydes : 4-hydroxycoumarin = 1 : 2; ε_r is the dielectric constant; catalyst loading: 0.02 g. [b] Isolated yields.

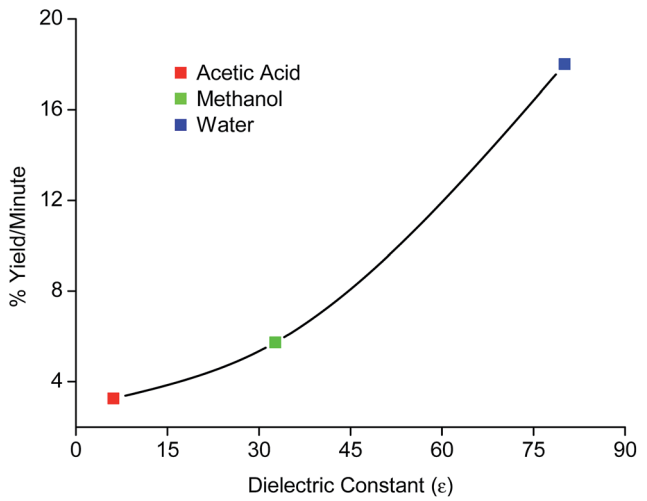


Fig. 1 Relative efficiency of three protic solvents as reaction medium for dicoumarol (**3a**) synthesis using LTNPs.

lesser when the catalyst loading reduced to 0.01 g (Table 1, Entry-8).

The next aim was to look for a suitable medium in which the chosen catalyst, *i.e.* LTNPs provides high yield in short reaction time. Both protic as well as aprotic solvents were tried and the former type proved to be way more effective (Table 2) both in terms of product yield and reaction time.

Among the three protic solvents tried, an interesting trend was observed which made our choice of reaction medium very easy and straightforward. With increment in the dielectric constant of solvents the catalyst was found to give higher yield in lesser time, and when the yield to time ratio was plotted against the dielectric constants of the solvents, it showed a monotonic relationship between the two (Fig. 1).

The highest yield (90%) in shortest period (5 minutes) was obtained for the solvent with highest dielectric constant among the three solvents tried, water. Considering the undeniable importance of water as solvent in organic reactions when the primary goal is search for a green synthetic protocol, it was promptly chosen as the solvent for dicoumarol synthesis. A range of dicoumarols were synthesized using the various aldehydes and 4-hydroxycoumarin. The results are summarized in Table 3.

Regardless of substitution (electron withdrawing and electron donating) of the aromatic aldehydes, the products were obtained in good yields. Similar results were also obtained with the heterocyclic aldehydes. The excellent catalytic performance of this catalyst prompted us to explore its further applications toward the synthesis of various substituted 1,4-DHPs under solvent-free condition at room temperature stirring.

Here too, a number of different catalysts were tried and LTNPs was easily the best of the lot in terms of both yields and time (Table 4).

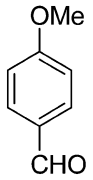
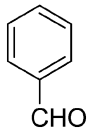
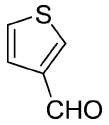
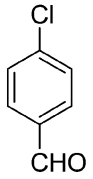
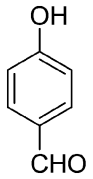
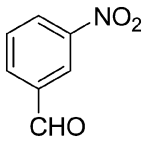
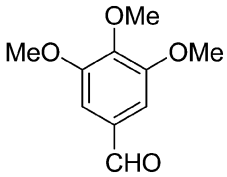
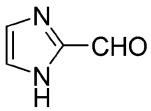
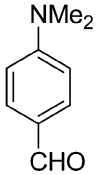
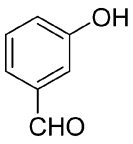
Once the reaction condition was established, the scope of this reaction was investigated with various aldehydes and β-ketoesters yielding a variety of highly functionalized 1,4-DHPs (Table 5, **5a–5o**). In Scheme 4 we have mentioned the plausible mechanism for the synthesis of various 1,4-DHPs using LTNPs as catalyst.

When reaction was carried out with ferrocenyl aldehydes to synthesize their corresponding 1,4-DHPs using free L-tyrosine as catalyst, it resulted in moderate yields (72%) in relatively longer time (25 min). Replacing it with LTNPs showed striking improvements in both yield and time (**5d** and **5e**). Owing to the potential of ferrocene moiety to be used in drugs, a fast, easy and green method for synthesizing 1,4-DHPs possessing ferrocenyl side chains can lead up to much easier synthetic protocols for large scale production of important drug molecules. The reduced particle size and improved surface area of the L-tyrosine loaded polymeric nanoparticulate system increase the penetrability of L-tyrosine in the reaction mixture which in turns gives the high yields. Moreover the polymer Eudragit® RS100 has the ability of swelling, which represents the good material for L-tyrosine dispersion.

Experimental

All commercially available chemicals were obtained from Merck and Aldrich, and used without further purifications.

Table 3 Reaction of 4-hydroxycoumarin with aromatic/hetero-aromatic aldehydes catalyzed by LTNPs in water (**3a–3j**)

Entry	Aldehydes	Product	Time[a] (min)	Yield[b] (%)
1		**3a**	5	90
2		**3b**	10	88
3		**3c**	10	91
4		**3d**	10	87
5		**3e**	10	93
6		**3f**	10	89
7		**3g**	15	91
8		**3h**	10	85
9		**3i**	15	90
10		**3j**	10	92

[a] All reactions are monitored by TLC. [b] Isolated yields.

Table 4 Effect of various catalysts on the synthesis of **5a** using LTNPs as catalyst

Entry	Catalyst	Catalyst loading (g)	Time[a]	Yield[b] (%)
1	PTS	0.02	10 h	70
2	Glycine	0.02	1.5 h	63
3	L-Proline	0.02	2 h	68
4	l-Serine	0.02	30 min	72
5	l-Tyrosine	0.02	20 min	75
6	LTNPs	0.02	10 min	91
7	LTNPs	0.05	10 min	91
8	LTNPs	0.01	25 min	80

[a] All reactions were monitored by TLC. [b] Isolated yields.

Melting points were uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 782 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra in DMSO were run on a Bruker AM-300L instrument operating at 300 MHz and 75 MHz respectively.

a. Materials

L-Tyrosine and Lutrol® F-68 (Poloxamer 188) were obtained from Sigma, Mumbai. Eudragit® RS100 (Evonik Industries AG, Germany) was obtained from Sandoz Ltd. Mumbai. Distilled-deionized water was prepared with Milli-Q plus System (Elix 10, Millipore corp. India). All other chemicals used were of the highest available grade.

b. Catalyst preparation

The L-tyrosine loaded-polymeric nanoparticles were prepared with polymer Eudragit® RS100 using the solvent evaporation (single emulsion) technique with slight modification.[30] In brief, the polymeric solution was prepared by adding 100 mg of Eudragit® RS100 in the mixture of methanol and acetone (20 : 80 v/v) at room temperature. Weighed quantity of L-tyrosine (equivalent to 10% w/w dry weight of polymer) was dissolved in 1(N) HCl and added to the polymeric solution. The resultant solution was poured into 25 ml of aqueous phase containing 1% (w/v) of poloxamer-188 with a constant flow rate of 1 ml min^{-1}. The mixture was then homogenized using a probe homogenizer (VIRTIS, Cyclone IQ, USA), at constant agitation speeds of 10 000 rpm in an ice bath. The formed emulsion was kept at room temperature under gentle stirring for 24 h to evaporate the organic solvents. The prepared polymeric nanoparticles were centrifuged at 18 000 rpm, for 15 min (Sorvall Ultracentrifuge, USA). The nanoparticle was recovered and freeze dried for 2 days (−80 °C and <10 mm mercury pressure, Freezone 6lt, Labconco Corp., MO) to get powdered nanoparticles and stored in freeze.

c. Characterization of nanoparticles

Determination of particle size. Particle size analysis was performed by Photon Correlation Spectroscopy (PCS) with

Table 5 LTNPs catalyzed synthesis of Hantzsch 1,4-DHPs scaffolds (**5a–5o**)[a]

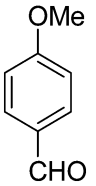
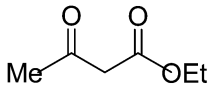
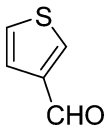
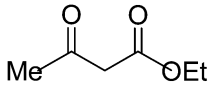
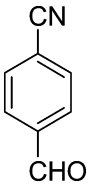
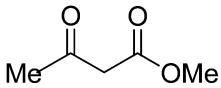
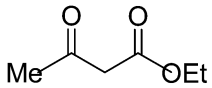
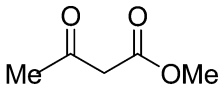
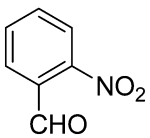
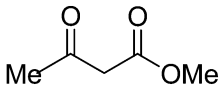
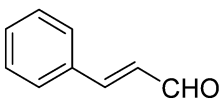
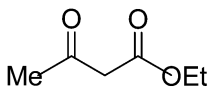
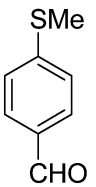
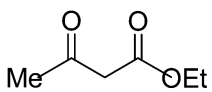
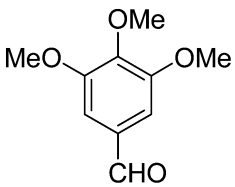
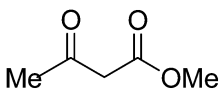
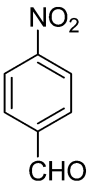
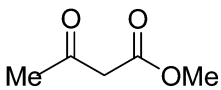
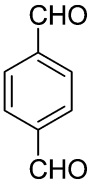
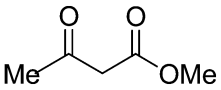
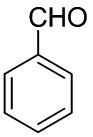
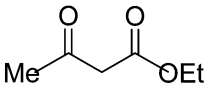
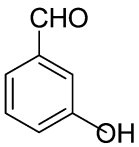
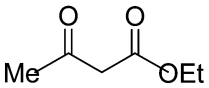
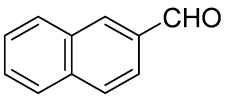
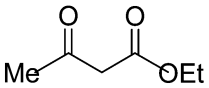
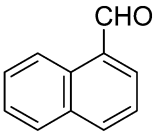
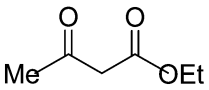
Entry	Aldehyde	1,3-Diketone	Product	Time[b] (min)	Yield[c] (%)
1			**5a**	10	91
2			**5b**	15	85
3			**5c**	5	89
4	Ferrocene-3-carboxaldehdye		**5d**	15	91
5	Ferrocene-3-carboxaldehyde		**5e**	15	90
6			**5f**	10	91
7			**5g**	12	94
8			**5h**	15	85
9			**5i**	10	87
10			**5j**	5	93

Table 5 (*Contd.*)

Entry	Aldehyde	1,3-Diketone	Product	Time[b] (min)	Yield[c] (%)
11			**5k**	10	89
12			**5l**	7	92
13			**5m**	10	90
14			**5n**	15	86
15			**5o**	15	85

[a] Reaction conditions – aldehyde : 1,3-diketone : ammonium acetate = 1 : 2 : 1; catalyst loading = 0.02 g. [b] Reaction progress monitored by TLC. [c] Isolated yields.

Zetasizer 3000 (Malvern Instruments). The freeze dried powdered samples were suspended in Milli-Q water (1 mg ml^{-1}) at 25 °C and sonicated for 30 s in an ice bath before measurement to prevent clumping. The mean particle diameter and size distribution of the suspension were assessed. Analysis was carried out for three times for each batch of sample under identical conditions and mean values were reported.

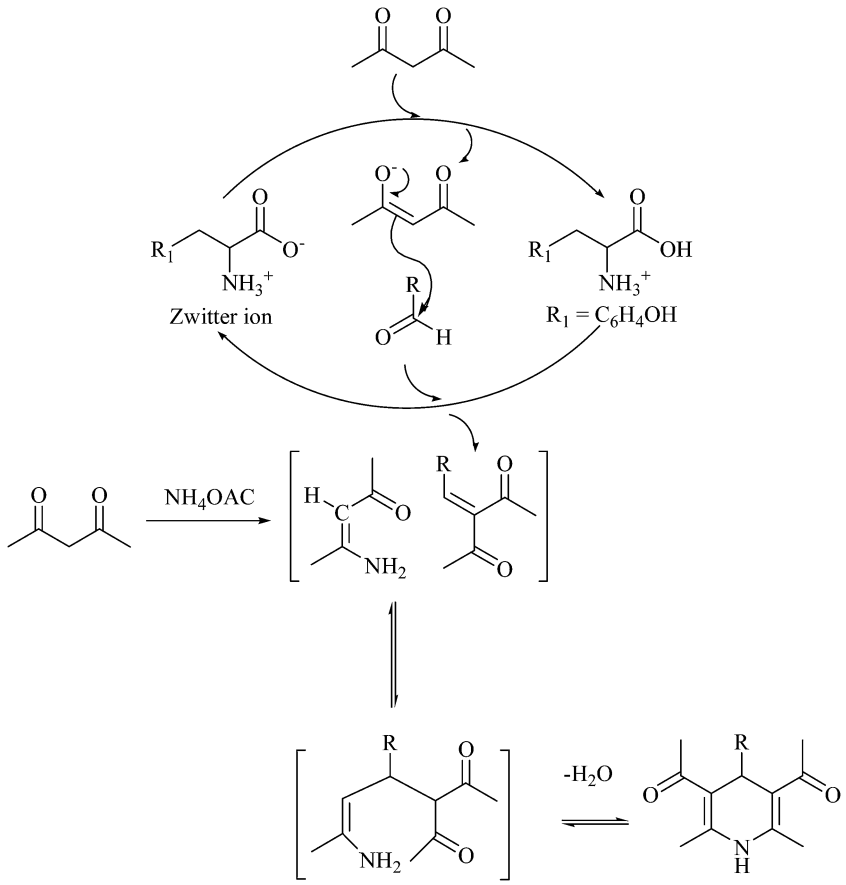
Atomic force microscopy (AFM). The surface morphology of prepared nanoparticles was carried out using atomic force microscopy (AFM). The nanoparticles suspension was prepared with milliQ water and dried overnight in air on a clean glass surface and observation was performed with AFM consisting of silicon probes with pyramidal cantilever having force constant of 0.2 N m^{-1}. To avoid damage of the sample surface, the tip to sample distance was kept constant. The scan speed of 2 Hz and 312 kHz resonant frequency was used for displaying amplitude, signal of the cantilever in the trace direction and to obtained images.

Transmission electron microscopy (TEM). Morphology of the particles was also examined using transmission electron microscope. A sample of particle suspension was diluted with 3% w/v phosphotungstic acid adjusted to pH 7.5 with potassium hydroxide corresponding to a 1 : 1 ratio before examination. One drop of sample was placed for one minute on a copper grid coated with a formvar carbon film. The excess of sample was wicked away with the aid of filter paper. The sample was then ready for analysis by TEM.

Fourier transforms infrared spectroscopy (FT-IR). The chemical integrity and possible chemical interaction between L-tyrosine and polymer can be determined by FTIR analysis (Perkin Elmer, FT-IR Spectrometer). Samples were mixed separately with potassium bromide (200–400 mg) and compressed by applying pressure of 200 kg cm^{-2} for 2 min in hydraulic press to prepare the pellets.

Conclusions

In summary, we have demonstrated that LTNPs as an organocatalyst in dicoumarols and 1,4-DHPs synthesis expecting advantages in (i) L-tyrosine can easily disperse through the flexible thin polymer coating (ii) increment in surface area (iii) easy separation of the catalyst (iv) fully green methodology and (v) very small catalyst loading is sufficient for reactions. Henceforth, this new catalyst works well in various organic transformations under green methodology.



Scheme 4 Plausible mechanism for the synthesis of 1,4-DHPs using LNTPs (LTNPs dispersed through Eudragit coating).

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