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Chitosan nanoparticles as a green and renewable catalyst in synthesis of 1,4-dihydropyridine under solvent-free conditions

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In the present study Chitosan nanoparticles were obtained based on the gelation of Chitosan by heptamolybdate anions and dried with dry CO_2 for 30 minutes. Chitosan nanoparticles efficiently proceeded Hantzsch reaction in 80 °C under metal and solvent free condition. The present method offers several advantages such as simple procedure, green condition, excellent yields and short reaction time.

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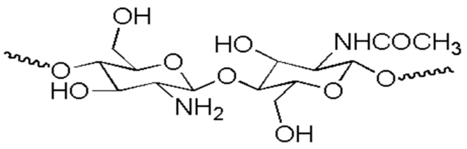
1. Introduction

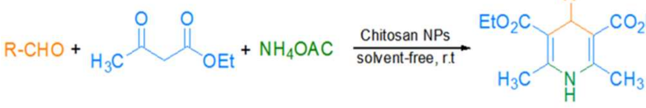
These are exciting times for renewable chemicals. Throughout history, humans have enlisted biological polymers especially proteins and polysaccharides to meet their needs for food, fuel, clothing and shelter. The development of renewable chemicals and polymers will significantly benefit from the previous advances in industrial chemistry. There is also increasing interest in obtaining chemicals from renewable resources and this has spurred a myriad of commercial activities. Chitin is the second most abundant natural polysaccharide on earth after cellulose [1]. Chitosan, a random copolymer of *N*-acetyl-*β*-D-glucosamine and *β*-D-glucosamine linked (1→4), is obtained after partial *N*-deacetylation of chitin [2] (Scheme 1). Literature survey shows that a wide range of applications have been reported for chitosan in different fields such as medicinal, drug delivery [3], food packaging [4], cosmetics [5], water treatment [6], membranes [7], fuel cells [8], hydrogels [9], adhesives [10], and surface conditioner [11].

Scheme 1. Chemical structure of chitosan



Chitosan is an antibacterial, biocompatible, environment friendly, biodegradable material and has great potential for surface modification due to amino and hydroxyl groups in its chemical structure [12]. chitosan is soluble in most mineral and organic acids and it's insoluble in the most of organic compounds and pure water [13]. Nano materials are expected to be a fruitful area for green catalysis due the increasing ability to design in the nano scales and the high surface areas found in nano materials.[14] Chitosan nanoparticles were first prepared by Alonso et al. that were based on the ionic gelation of chitosan with sodium tripolyphosphate (TPP) anions [15]. The number of active hydroxyl and amino groups existing on chitosan nanoparticles are more than chitosan and it can be modified chemically into many forms and can participate more effectively in different types of chemical reactions as a suitable support for different catalytic species [16]. The OH and NH_2 groups can activate the nucleophilic and electrophilic components of the reactions by hydrogen bonding and lone pairs, respectively. These requirements are fully exist in the multi component Strecker reaction of carbonyl compounds and amines with trimethylsilyl cyanide (TMSCN) [16]. The Hantzsch reaction is one of the most straightforward methods for the synthesis of 1,4-Dihydropyridines (DHPs). 1,4- DHPs, first synthesized by Arthur Hantzsch in 1882 [17]. DHPs are an important class of N-heterocyclic ring. Many DHPs are already commercial products such as: amlodipine [18], felodipine [19], isradipine [20], lacidipine [21], nicardipine [22], nitrendipine [23], nifedipine [24] and nemadipine B [25], of which nitrendipine and nemadipine B exhibit potent calcium channel blocking activities [26]. Realizing the importance of 1,4-dihydropyridine derivatives, several synthesis methods have been reported, like FeF_3[27], ionic liquid [28], organocatalysts [29], Microwave assisted [30], Cellulose sulfuric acid [31], nano-ZnO [32] and Heteropolyacid catalyst [33]. Although some reactions are satisfactory in terms of yield, the use of high temperatures, expensive metal precursors, catalysts that are harmful to the environment, and long reaction times, limits the use of these methods. This study investigates the role that chitosan and chitosan nanoparticles can play in the Hantszch reaction. herein we wish to report commercially available chitosan NPs, as a renewable and recoverable bifunctional heterogeneous catalyst, for the one-pot three-component Hantzsch reaction of aldehydes and ethyl acetoacetate and ammonium acetate under solvent-free conditions at 40 ºC temperature (Scheme 2).

Scheme 2. The Hantzsch reaction of carbonyl compounds and ammonium acetate catalyzed by chitosan NPs



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2. Exprimental method

2.1. General

All chemicals were purchased from Merck or Aldrich. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellets on a Shimadzu FT IR-8400S spectrometer. ^{1}H NMR (400 MHz) spectra were obtained using a Bruker DRX-400 AVANCE spectrometer. Analytical thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck) or neutral alumina oxide gel 60F 254 (Merck). Morphological characteristics of the nano-conjugates were observed by scanning electron microscope (SEM, EVO LS 10, Zeiss, Carl Zeiss Inc., Germany) operating at an accelerating voltage of 20 KV under high vacuum. Freshly prepared nano-conjugate sample was fixed to aluminum stubs with double-sided carbon adhesive tape, sputter-coated with conductive gold–palladium and observed using SEM.

2.2. Procedure for preparation of chitosan NPs

Chitosan was modified to nano-Chitosan by an ionic-gelation method with Ammonium heptamolybdate. 0.5 g Chitosan was dissolved in 2% acetic acid solution under constant magnetic stirring at room temperature and dropwise 5 ml Ammonium heptamolybdate tetrahydrate with the concentration of 2 g/l to 50 ml of Chitosan solution. The product were extensively rinsed with distilled water to remove any ammonium heptamolybdate and then Chitosan NPs were obtained by centrifugation at 16,000 rpm after dried with dried CO_2 for 30 min.

2.3. Morphology and structure characterization of chitosan NPs

FT-IR of Chitosan and Chitosan NPs were taken with KBr pellets (Figure 1). The characterization peaks in the Chitosan spectrum are 3000-3800 cm^{-1} (–OH and –NH_2 stretching), 2877 cm^{-1} (C-H stretching) 1656 cm^{-1} (amide I band), 1640 cm^{-1} (N–H deformation) and 1079 cm^{-1} (C–O stretching). The FT-IR spectrum of Chitosan NPs shows the characteristic absorption peak of OH and NH_2 at 3000–3800 cm^{-1}. The characteristic absorption peaks of N– H, –CH_3 and the second hydroxyl (OH) absorption peak (bending) appear at 1631, 1382 and 1337 cm^{-1} respectively. The OH bending appears as a broad and weak peak and here obscured by the CH_3 bendings. The absorption bands at 1080 cm^{-1} (asymmetric stretching of the C–O–C bridge) was characteristic absorption bands of the polysaccharide structure of Chitosan.

In Fig. 3 the X-ray diffraction(XRD) patterns of Chitosan NPs were shown. Original Chitosan (see Electronic Supplementary Information (ESI)) gives two characteristic peaks at and 2θ=10° (weak diffraction peak) and 20° (strong diffraction peak) indicating the high degree of crystallinity of chitosan. However, there are not Comparable peak in the diffractograms of chitosan NPs. The reason for broad peaks is attributed to the increased amorphous nature of Chitosan NPs. The XRD of chitosan NPs is characteristic of an amorphous polymer.

SEM micrograph of synthesized Chitosan NPs is shown in Fig. 2 As can be seen in Fig. 2 the particles are nearly spherical with an average diameter 50 nm.

2.4. Procedure for preparation of 1,4-dihydropyridin by chitosan NPs

In a 25 ml round bottom flask equipped with a magnetic bar, a mixture of aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1 mmol) and 0.05 g Chitosan NPs was stirred under solvent-free conditions at 80 °C. After completion of the reaction (monitored by TLC, Petroleum: Ethyl acetate, 3:2), 5 ml EtOH 96% was added to mixture reaction and was heated to 60 ˚C. The products were solved in EtOH and isolated from Chitosan NPs and in crystalline form by cooling in an ice-bath and need no further crystallization.

Figure 2. FT-IR spectra of Chitosan (red line) and Chitosan NPs (blue line)

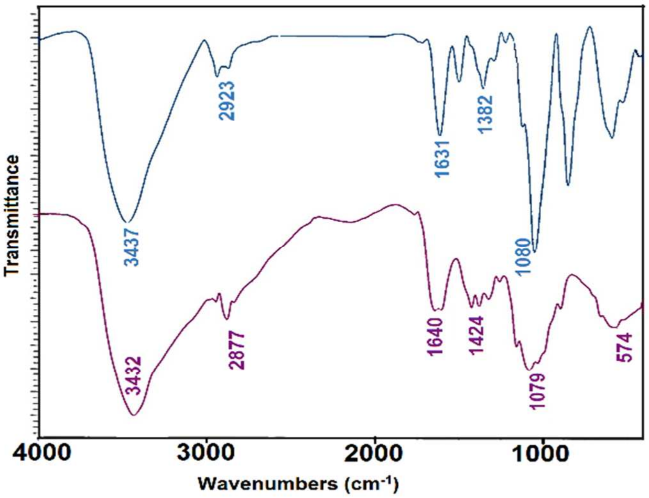
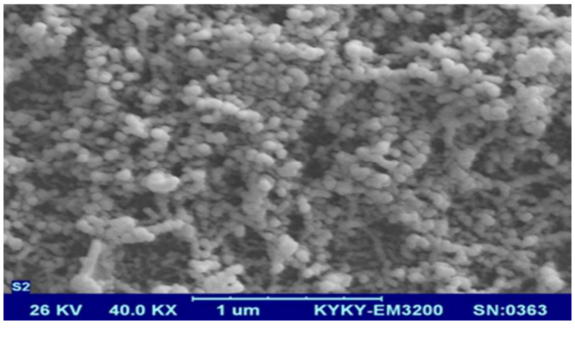


Figure 2. SEM micrograph of synthesized chitosan NPs



3. Results and discussion

In order to compare Chitosan and Chitosan NPs catalytic properties, a reaction model was carried out. The results were indicated, Chitosan NPs have better efficiency than bulk

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Chitosan (Table 1, Entry 9). Hence, Chitosan NPs were selected as main catalyst and all reactions were carried out using Chitosan NPs. According to our studies, the Hantzsch reaction has a poor yield in organic solvents and water. To achieve the best conditions, various solvents and amount of catalyst were employed and results listed in Table 1. The results were proposed that the solvent-free condition is more efficient than solvents such as EtOH or CCl_4. The varying amounts of Chitosan NPs were tested and 0.1 g was used as optimized catalyst amount under the reaction conditions (Table 1, Entry 9).

Figure 3. X-ray diffraction patterns of Chitosan NPs

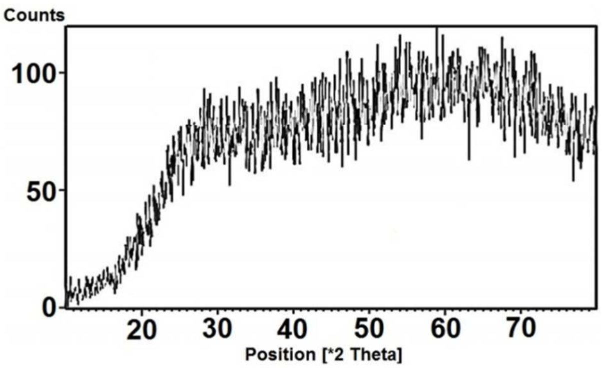


Table 1. Optimization of the Reaction Conditions

Entry	Catalyst (g)	Solvent	Time	Yield (%)*
1	-	-	18 h	Trace
2	Chitosan NPs (0.05)	EtOH	3 h	65
3	Chitosan NPs (0.1)	EtOH	3 h	70
4	Chitosan NPs (0.15)	EtOH	3 h	70
5	Chitosan NPs (0.05)	CCl_4	4 h	55
6	Chitosan NPs (0.1)	CCl_4	4 h	55
7	Chitosan NPs (0.15)	CCl_4	4 h	55
8	Chitosan NPs (0.05)	-	1 h	80
9	**Chitosan NPs (0.1)**	**-**	**20 m**	**90**
10	Chitosan (0.1)	-	3 h	90
11	Sulfonated Chitosan (0.1)	-	2 h	90
12	Chitosan NPs (0.15)	-	40 m	90

*Reaction condition: benzaldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1 mmol) and catalyst stirred at 80 °C.

Scheme 3. Chitosan NPs catalyzed synthesis of 1,4-dihydropyridines

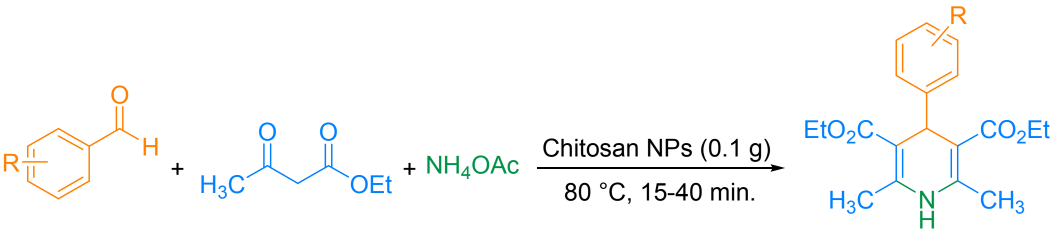
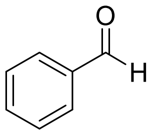
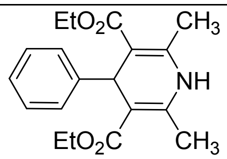
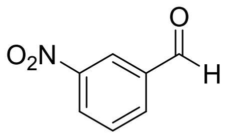
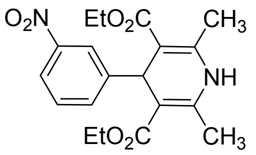
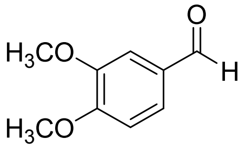
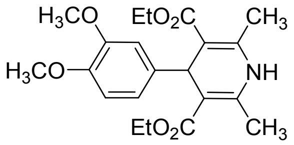


Table 3. Chitosan NPs catalyzed synthesis of 1,4-dihydropyridines

Entry	Aldehyde	Product	Time (min)	Yield (%)	M. p.	M. p.^{ref}
1			20	90	157-158	157-159
2			15	95	162-164	162-164
3			40	80	147-148	146-149

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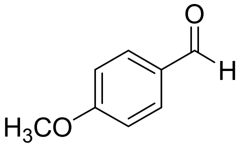
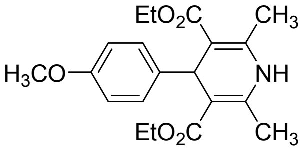
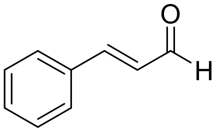
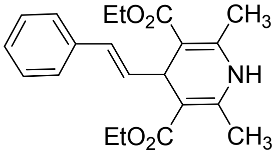
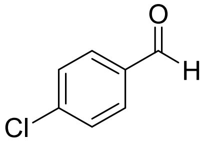
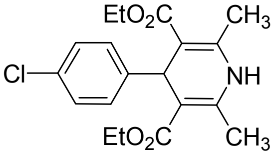
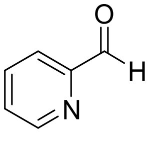
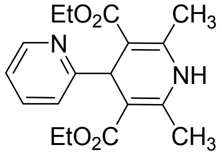
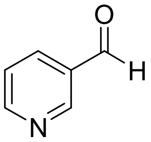
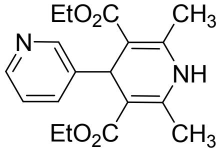
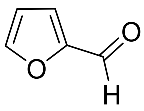
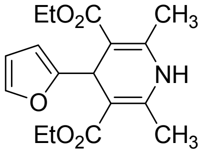
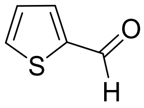
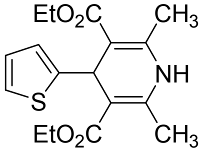
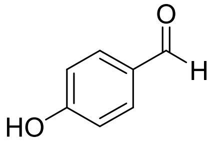
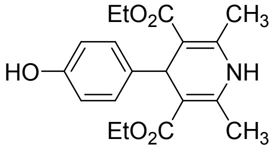
4			40	80	157-159	156-159
5			30	80	145-146	147-149
6			30	90	144-146	146-148
7			30	95	192-194	190-192
8			30	95	192-194	190-192
9			20	95	149-152	148-150
10			20	98	169-171	172-174
11			40	80	210-212	205-212

***Reaction condition:** benzaldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1 mmol), catalyst (0.1 g) stirred at 80 °

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By considering the optimal conditions we further investigated for more substrate derivatives, satisfactory results were observed that the results are summarized in Table 3. The reaction time for the Hantzsch reaction catalyzed by Chitosan NPs is generally shorter compared to previous methodologies that require a Bronsted or Lewis acid center in the structure of their catalysts. As we expect the aldehyde substrate containing electron donor groups (like OMe and OH, Entries 3, 4, 11), showed weaker results than cases containing electron withdrawing groups (like NO_2, Cl and Py. Entries 2, 6, 7, 8). The cases like furan-2-carbaldehyde and thiophene-2-carbaldehyde (Entry 9, 10) showed an excellent yield that probably could relate with less steric hindrance.

The proposed mechanism for the formation of the 1,4-dihydropyridines is shown in Scheme 3**.** As is clear from the structure of chitosan, it has many hydroxyl group and amine (or amide) groups. These OH and NH_2 groups in the structure of chitosan can activate the electrophilic components of the reactions like carbonyl group by hydrogen bonding. The hydrogen bonding between hydroxyl and amine groups and the substrates is key factor in Hantzsch reaction catalyzed by chitosan.

Figure 4. Recyclability study

Model reaction: benzaldehyde (1 mmol), ammonium acetate (1 mmol), ethylacetoacetate (2 mmol), 0.1 g catalyst, at r. t.

The reusability of the Chitosan NPs as catalyst for Hantzsch reaction was evaluated. The Chitosan NPs was separated after each reaction by filtration, washed 2-3 times by using ethanol and then heated at 60 °C (Fig. 4). The chemical structure of recovered chitosan NPs were verified using FT-IR spectroscopy. There are not significant difference between the FT-IR of fresh chitosan NPs and recovered chitosan NPs (see ESI).

4. Conclusions

In summary, various Lewis acids including $BF_3.OEt_2$, $NiCl_2.6H_2O$, $CeCl_3$, and other catalysts such as 1_2-tungstophosphoric acid, silicagel supported sodium hydrogensulfate, N-bromosuccinimide and iodine can also catalyze the reaction, however we attempted to find a biocompatible, recoverable and more efficient catalyst for 1,4-dihydropyridins synthesis. In comparison with other presented procedure, our method is very quick, avoid the use of expensive reagents or high temperature and leads to improved products yields by easy work up procedures at room temperature.

Acknowledgements

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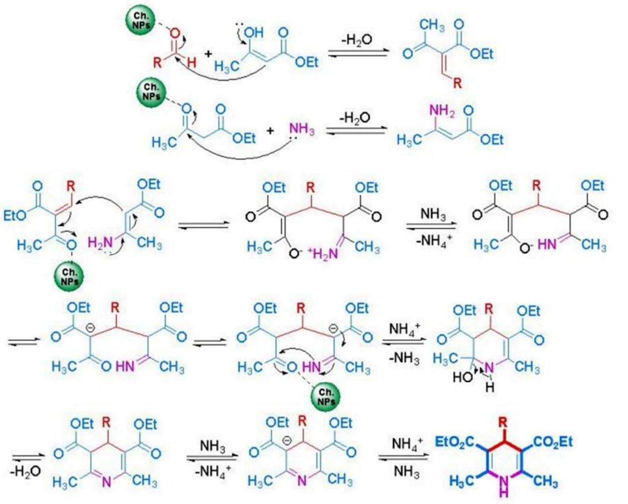
Scheme 4. Proposed mechanism for Chitosan NPs catalyzed Hantzsch synthesis



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