



## Research Article

# Silver Nanoparticles Supported on Chitosan as a Green and Robust Heterogeneous Catalyst for Direct Synthesis of Nitrogen Heterocyclic Compounds under Green Conditions

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## Abstract

The catalytic efficiency of silver nanoparticles supported on chitosan as a green, robust, and efficient nanocatalyst for the direct synthesis of biologically active compounds, such as: imidazole derivatives as well as pyrazine scaffolds through multi-component reactions strategy, have been demonstrated. In this work, imidazole derivatives were achieved *via* pseudo four-component reactions by utilization of benzaldehydes, benzils, anilines, and ammonium acetate under solvent-free conditions. Moreover, pyrazine scaffolds were synthesized through a three-component reaction of phenylenediamine derivatives, isocyanides and various ketones in water. The main advantages of this protocol are the reusability of the catalyst, operational simplicity, mild reaction conditions, and high-yielding. Copyright © 2019 BCREC Group. All rights reserved

**Keywords:** Chitosan; Silver nanoparticles; Heterogeneous catalyst; Heterocyclic compounds; Green chemistry

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## 1. Introduction

Green chemistry directs synthetic chemists to obtain chemicals from renewable resources. In this regard, the extraction of chitin which is the second most abundant natural polymer in the world after cellulose, from the exoskeletons of arthropods, such as: crustaceans (e.g., crabs,

lobsters and shrimps), is industrialized [1]. Chitosan (Cs), the most abundant natural amino polysaccharide, is produced by the deacetylation of chitin and displays hydrophilic, non-toxic, antibacterial, biodegradable, and biocompatible properties [2]. Due to the complex molecular structure of chitosan which contains multiple functional groups, such as: amino and hydroxyl moieties, chitosan and its derivatives, have been applied in several fields, for instance, drug de-

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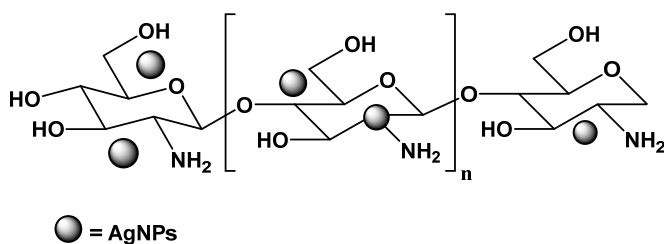
livery [3], biosorbent [4], adhesives [5], membranes [6], and especially, in catalysis fields [7,8]. In particular, its reactive amino, primary hydroxyl, and secondary hydroxyl functional groups can be used to induce covalently or non-covalently chemical modifications and makes this polymer a great solid candidate for immobilizing different metal-nanoparticles which can be explored as an efficient heterogeneous catalyst in the chemical reactions.

Silver nanoparticles (Ag NPs) possess favorable characteristics, such as: small size, high surface-to-volume ratio, antibacterial, and catalytic activities [9]. Since it is difficult to separate the Ag nanoparticles catalysts from the reacting mixtures, they had been immobilized onto the various supports, such as: silica [10], carbon nanotubes [11], alumina [12], and polymeric materials [13], to simply reuse the catalysts and enhance their catalytic activities. Although, silver catalysts have become important in the catalytic oxidation and reduction procedures [13,14], the few reports are available on

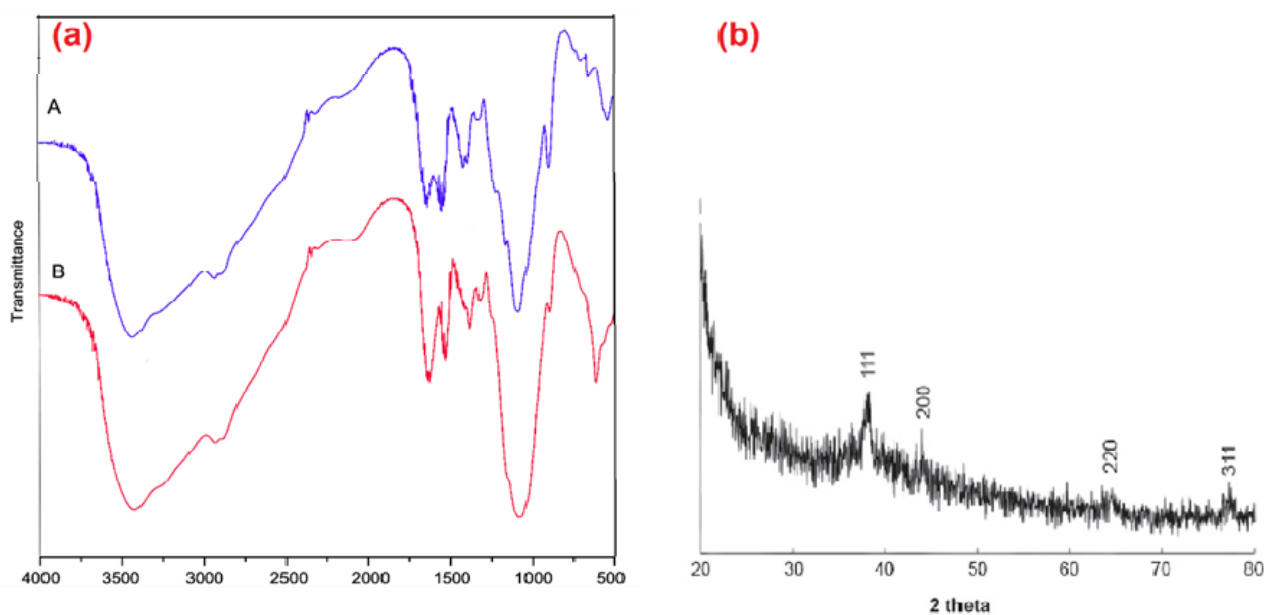
the utilization of Ag NPs for multicomponent heterocyclic synthesis [15].

Multicomponent reactions (MCRs) are very efficient synthetic methods [16,17]. These strategies offer significant advantages over classical stepwise approaches allowing the formation of several bonds and the construction of complex molecular architectures from simple precursors in a single synthetic operation without the need for isolation of intermediates [18,19]. MCRs, particularly those performed under solvent-free condition or in water, have become increasingly useful tools for the synthesis of chemically and biologically important compounds because of their environmentally friendly atom economy and green characteristics [20].

Heterocyclic rings have a rich chemistry with wide spectrum applications related to all areas of pharmaceutical, medicinal, and industrial fields [21]. These remarkable molecules widely present in various natural products, for instance, hormones and vitamins as well as dyes and mainly use for the development of many outstanding drugs [22]. Among the top 25 best-selling pharmaceuticals in the year 2014, there have been small molecule drugs with heterocyclic moieties, which generally contain nitrogen and account for more than 50 billion USD in annual revenue [23]. In this context, imidazole scaffolds as remarkable nitrogen-containing heterocyclic compounds exist in many natural products which possess a wide range of biological activities covering anti-inflammatory [24], anti-allergic [25], and glu-



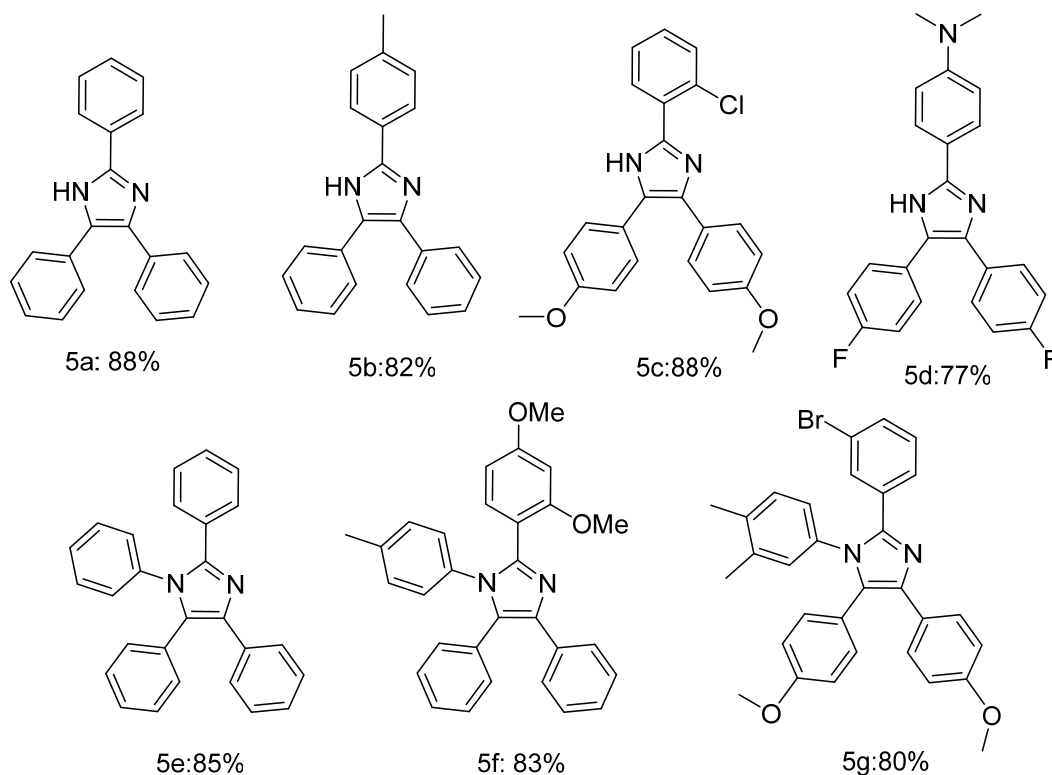
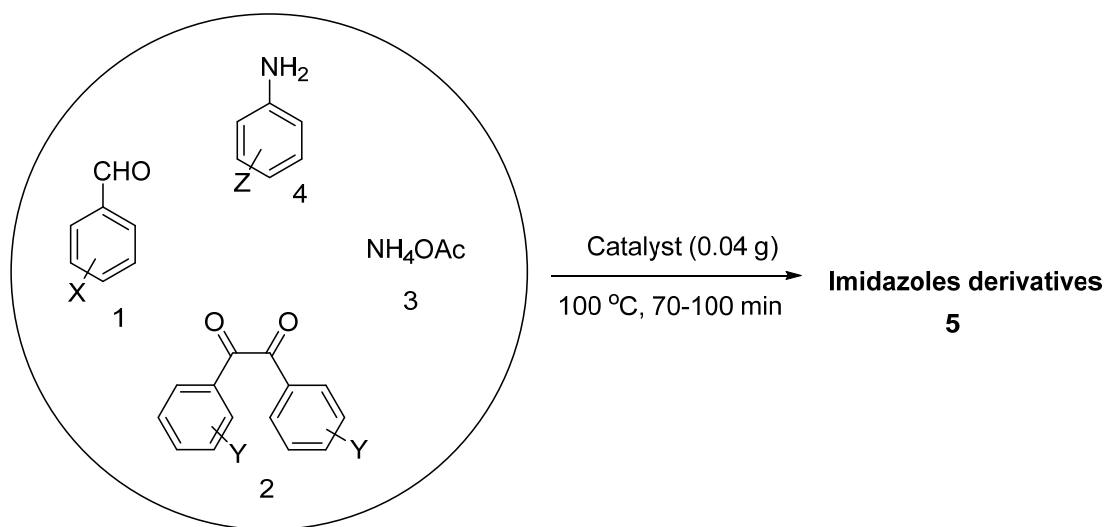
**Scheme 1.** Structure of silver nanoparticles on the surface of the chitosan



**Figure 1.** a) FT-IR of chitosan (A) and Ag NPs-Cs composite, b) XRD pattern of Ag NP-CS composite

cagon receptor antagonism [26]. These heterocyclic compounds are also the key intermediates in the preparation of several therapeutic agents. Losartan, Eprosartan, and Trifenagrel are some of the leading drugs in the market containing imidazole scaffolds [27]. In addition, pyrazine scaffolds are important compounds that are observed as cores of the many drugs and biologically active molecules. Also, these remarkable heterocyclic scaffolds have found many uses as including antidiabetic and anti-

ral effects, in particular, against retroviruses such as HIV [28,29]. Pyrazines possess biological activity, namely, as inhibitors of cholesteryl ester transfer proteins [30]. Due to the many biological and medicinal properties associated with these heterocyclic rings, the development of new synthetic methods for the synthesis of nitrogen-containing heterocycles under efficient and green reaction conditions is in the spotlight [31,32].



Scheme 2. Structure and isolated yields of imidazole derivatives

## 2. Materials and Methods

Shells of marine shrimp (*Penaeus merguensis*) were provided from the south coast of the Iran (Persian Gulf). AgNO<sub>3</sub> (99.98%) was used as the silver precursor, and was obtained from Merck. Meanwhile, NaBH<sub>4</sub>, the reducing agent, was obtained from Sigma-Aldrich. All the other reagents were of analytical grade and used without further purification. All the aqueous solutions were prepared with double-distilled water.

The X-ray Diffraction (XRD) pattern of the catalyst was recorded on a diffractometer (STOE & CIE STADI P). Transmission Electron Microscopy (TEM) was performed using a transmission microscope (Philips CM30) with an accelerating voltage of 150 kV. Infrared (IR) spectra were recorded on a spectrometer (Shimadzu IR470). Scanning Electron Microscopy (SEM) observations were carried out using an environmental scanning electron microscope (Philips XL30 ESEM). Melting points (mp) were measured on a melting point instrument (Electrothermal IA9100) and are uncorrected. The elemental analyses were performed with an Elementar Analysensysteme GmbH Vario EL. Proton (<sup>1</sup>H) Nuclear Magnetic Resonance spectroscopy (NMR) spectra were recorded on a spectrometer (Bruker Avance DRX300) at 300.13 and 75.47 MHz. The NMR spectra were obtained in deuterated DMSO.

### 2.1 Extraction of Chitin from Shrimp Shells

The shrimps were kept on ice for 2 or 3 days before being peeled; the shells were scraped

free of loose tissue then separated from cephalothoraxes, washed individually in lightly salted water and dried in the oven at 60 °C for 3 h. Then the shells were powdered by grinding for better production of chitin and chitosan.

In the next step, 10.0 g of shrimp shells was stirred in NaOH solution (10 %wt) for 1 h, filtered and washed with appropriate amount of water. For elimination of CaCO<sub>3</sub>, the sample was hydrolyzed with HCl (10 %v) for 3 h at 70 °C. The samples were then filtered and washed. For removal of lipid, the sample was heated with NaOH (10 %wt) for 3 h at 70 °C, following by washing and drying under vacuum to obtained 6 g chitin powder with 58% purity.

### 2.2 Chitosan Preparation from Chitin Powder

In a typical procedure, 1.5 g of obtained powder were heated with NaOH (50 %v) for 3 h at 100 °C. After filtration with buchner funnel and washing with water, the sample was dried in oven for 3 h until complete removal of water. The observed yield for chitosan in this procedure was 70-80 %.

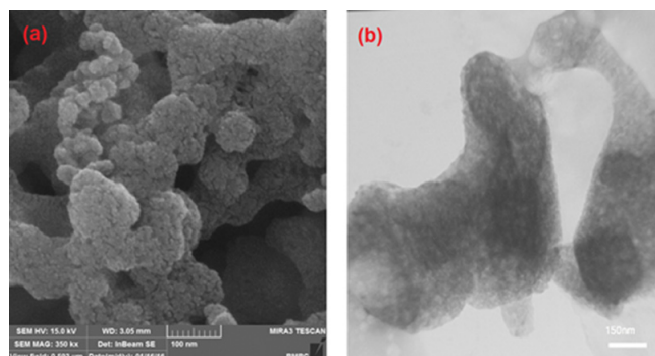
### 2.3 Synthesis of Ag NPs on the Surface of the Chitosan

The chitosan suspension was prepared by solubilizing chitosan (1.0 g) in acetic acid (50 mL, 1.0 %wt) solution. Then, AgNO<sub>3</sub> (50 mL, 0.01 M) was added immediately into the suspension under constant stirring for 2 h for the preparation of the AgNO<sub>3</sub> in chitosan suspension. NaBH<sub>4</sub> (20 mL, 0.04 M) was added to the suspension of AgNO<sub>3</sub>/Cs and an immediate color change from pale yellow to brown indicating the formation of Ag NPs was noted. This suspension was stirred for 1 h more, then the final synthesized Ag NPs-Cs composite were obtained.

**Table 1.** Optimization of the reaction conditions for the synthesis of compound 3a<sup>a</sup>

Entry	Solvent	Catalyst (g)	T (°C)	Yields (%) <sup>b</sup>
1	CH <sub>2</sub> Cl <sub>2</sub>	0.04	40	Trace
2	CHCl <sub>3</sub>	0.04	60	15
4	EtOH	0.04	76	68
5	H <sub>2</sub> O	0.04	100	Trace
7	Solvent Free	0.04	80	55
8	Solvent Free	0.04	100	88
9	Solvent Free	0.04	110	88
10	Solvent Free	0.05	100	90
11	Solvent Free	0.03	100	83

<sup>a</sup> Reaction conditions: benzaldehyde (0.10 g, 1.00 mmol), benzyl (0.21g, 1.00 mmol), and ammonium acetate (0.19 g, 2.50 mmol) in 70 min. <sup>b</sup> isolated yields



**Figure 2.** SEM image (a) and TEM image (b) of Ag NPs-Cs composite

#### 2.4 General Procedure for the Synthesis of Imidazoles

To a test tube equipped with a stir bar, a mixture of aromatic aldehyde (1.0 mmol), benzil (1.0 mmol), ammonium acetate (2.5 mmol), and Ag NPs-Cs composites (0.04 g) was added. The mixture was stirred under solvent free condition at 100 °C for 70-100 minutes. The progress of the reaction was monitored using TLC. After completion of the reaction, ethanol was then added to the mixture, which was subsequently filtered to remove the catalyst. After evaporation of the solvent, the residue was crystallized from ethanol:water (8:2).

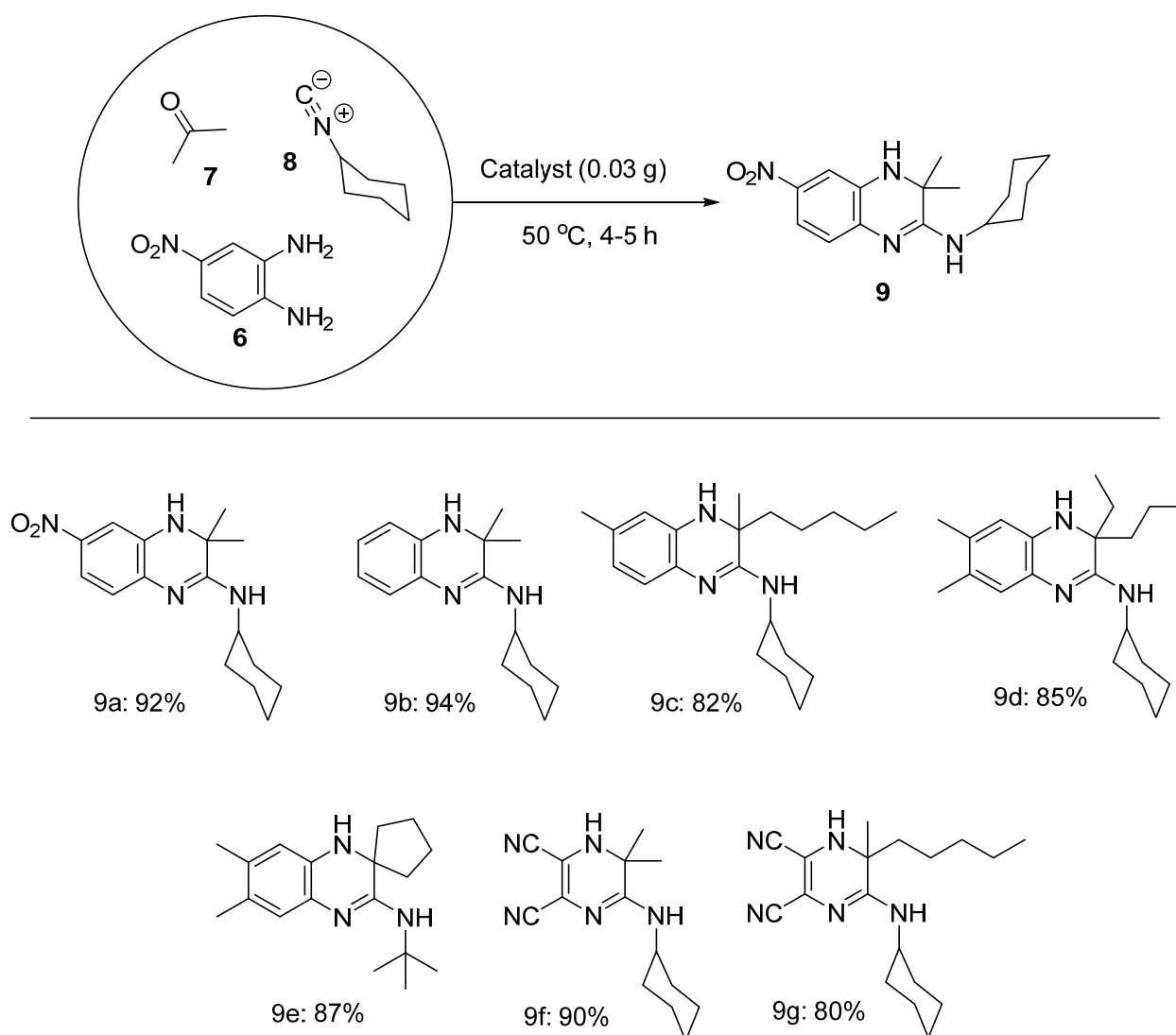
#### 2.5 General Procedure for Synthesis of Dihydropyrazine Derivatives

To a mixture of diamine (1.0 mmol), ketone (1.0 mmol) and isocyanide (1.0 mmol) in 4 mL of water was added Ag NPs-Cs composites (0.03

g). The resulting mixture was stirred at 50 °C. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane 2/1), desired product was separated using ethyl acetate extraction and catalyst by centrifuge. The solid residues were purified by re-crystallization from ethanol.

### 3. Results and Discussion

Herein, we report an efficient procedure for the synthesis of silver nanoparticles on the surface of the chitosan support to obtain Ag NPs-Cs composites as a green and robust heterogeneous catalyst for organic reactions. The Ag NPs-Cs catalyst was prepared according to the previous reports [33], and fully characterized. The prepared catalyst exhibited high catalytic activity toward the multicomponent synthesis of imidazole and pyrazine scaffolds under green conditions, which caused to high yield



**Scheme 3.** Structure and isolated yields of pyrazine derivatives

with catalytic efficiency over several cycles (Scheme 1).

The Fourier transform infrared spectrum of Cs (Figure 1a-A) shows vibration bands at 3354 and 3294  $\text{cm}^{-1}$  due to overlapping of O–H and amine N–H stretching bands; a peak at 2876  $\text{cm}^{-1}$  indicated aliphatic C–H stretching; 1643 and 1584  $\text{cm}^{-1}$  for N–H bending; 1419, 1376, and 1318  $\text{cm}^{-1}$  for C–H bending; and 1061 and 1026  $\text{cm}^{-1}$  for C–O stretching. The spectrum of Ag NPs-Cs composite (Figure 1a-B) showed a blue shift of the Cs peaks at 1643 and 1584  $\text{cm}^{-1}$  to 1635 and 1544  $\text{cm}^{-1}$ , respectively, and also displayed a high intensity peak at 1544  $\text{cm}^{-1}$ .

The XRD pattern of synthesized catalyst confirmed the crystalline structures of Ag NPs and chitosan. The diffraction peak at  $2\theta = 21.8^\circ$  is attributed to the chitosan scaffold. Also, the peaks at  $2\theta = 37.97^\circ$ ,  $44.05^\circ$ ,  $64.21^\circ$  and  $77.25^\circ$  were associated with (111), (200), (220), and (311) corresponding to the crystallographic planes of the face-centered cubic Ag crystals, respectively (Figure 1b) [34].

Selected images obtained using SEM and TEM were used to study the morphology of synthesized catalyst and silver particle size were studied by SEM and TEM (Figure 2). The obtained SEM image clearly showed that Ag NPs were covered the surface of the chitosan bio-

polymer. The TEM image of Ag NP-Cs composite showed some aggregation of Ag NPs with the mean diameter of around 14 nm.

For investigation of the catalytic efficiency of the composite, the model reaction and optimization conditions were investigated. In order to optimize the reaction conditions, we investigated the various conditions such as solvent (water, ethanol, dichloromethane, chloroform), catalyst amount and temperature for the synthesis of 2,4,5-triphenylimidazole by utilization of benzil, benzaldehyde and ammonium acetate as a model reaction. As shown in Table 1, Ag NPs-Cs composite (0.04 g) under solvent-free condition at 100  $^\circ\text{C}$  provided the best results in terms of yields (Table 1, entries 8). From both scientific and environmental standpoints, organic reaction under solvent-free conditions has gained considerable attention in the recent years due to decreasing the pollutant production, reduced utilization of toxic and expensive organic solvent along with operational simplicity.

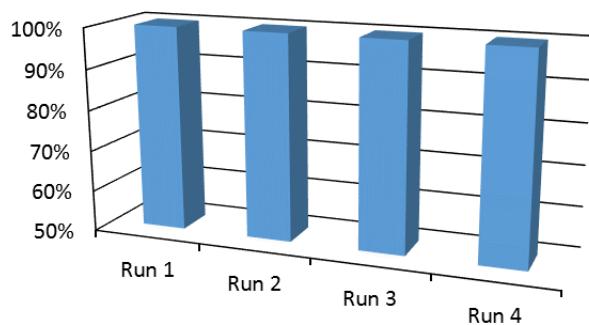
Previously, different metal catalysts have been reported for this reaction [35-37], but our literature scanning showed that there is no report available on the utilization of silver catalysts in this synthetic route. To explore the scope of this reaction, benzil derivatives and aromatic aldehydes containing both electron-

**Table 2.** Optimization of the reaction conditions for access to compound 9a<sup>a</sup>

Entry	Solvent	Catalyst (g)	T ( $^\circ\text{C}$ )	Yield <sup>b</sup> (%)	Time (h)
1	Solvent-free	-	r.t.	0	8
2	Solvent-free	-	50	0	8
3	Solvent-free	Ag NPs-Cs (0.03)	50	34	8
4	Ethanol	-	r.t.	0	8
5	Ethanol	Ag NPs-Cs (0.03)	r.t.	35	4
6	Ethanol	Ag NPs-Cs (0.03)	50	65	4
7	Methanol	Ag NPs-Cs (0.03)	50	56	4
8	$\text{CH}_3\text{CN}$	Ag NPs-Cs (0.03)	50	40	4
9	Water	-	r.t.	0	8
10	Water	Ag NPs-Cs (0.03)	r.t.	50	8
11	Water	Ag NPs-Cs (0.03)	50	92	4
12	Water	Ag NPs-Cs (0.03)	50	70	2
13	Water	Ag NPs-Cs (0.04)	50	92	4
14	Water	Ag NPs-Cs (0.02)	50	78	4

<sup>a</sup>Reaction conditions: 4-Nitrobenzene-1,2-diamine 1 (1 mmol), acetone 2 (1 mmol), and cyclohexyl isocyanide 3 (1 mmol)., <sup>b</sup> Isolated yields; r.t.: room temperature





**Figure 3.** Reusability of the catalyst

donating and -withdrawing groups on the phenyl ring and various amines as well as ammonium acetate were successfully applied and afforded the corresponding substituted imidazole compounds in good to excellent yields under solvent-free conditions (Scheme 2).

In recent years, only a few synthetic routes have been demonstrated for the synthesis of pyrazine rings [38,39]. Considering the high importance of pyrazine compounds, we also investigated the catalytic efficiency of Ag NPs-Cs composite in the synthesis of pyrazine scaffolds 9. Initially, we chose the reaction of 4-nitrobenzene-1,2-diamine 6, acetone 7, and cyclohexyl isocyanide 8 as a model reaction for the synthesis of compound 9a. In order to optimize the reaction conditions, we examined the model reaction under solvent-free conditions at different temperatures. The reaction was unsuccessful in the absence of Ag NPs-Cs at different temperatures and in presence of Ag NPs-Cs at room temperature. Additionally, this reaction was also carried out in organic solvents such as ethanol and methanol. Furthermore, the model reaction was successfully carried out in water as a solvent and in the presence of Ag NPs-Cs. But the desired product was obtained in low yields at room temperature that increased to 50 °C. Next, the amount of the Ag NPs-Cs was optimized in water and the results revealed that 0.03 grams of Ag NPs-Cs caused to the high yield of compound 9a (Table 2).

With the optimized conditions in hand, we initiated a study to explore the scope of the synthesis of dihydropyrazines 9a-g using different diamine compounds, such as: 2,3-diaminomaleonitrile and *ortho*-phenylenediamine derivatives, cyclohexyl or *tert*-butyl isocyanide with various ketones, such as: acetone, 2-heptanone 3-hexanone, cyclopentanone, cyclohexanone, acetophenone and 4-nitroacetophenone (Scheme 3).

The reusability of the catalyst, which is an important factor in green catalysis, was also in-

vestigated. The model reaction for the synthesis of 5a was studied under the optimized reaction condition. After carrying out the first reaction, the catalyst was centrifuged and washed with acetone (2×5 mL), dried at 60 °C and then reused. Only minor decreases in the reaction yield were observed after four repetitive cycles (Figure 3).

#### 4. Conclusion

We have introduced the design and synthesis of silver nanoparticles supported on chitosan as an environmentally benign and efficient heterogeneous catalyst that is applicable to the facile synthesis of biologically active molecules. Their reactions with simple and readily available reagents including benzoin or benzil, benzaldehyde, aniline and NH<sub>4</sub>OAc in the presence of catalytic amount of catalyst would provide an easy access to imidazole scaffolds. Also, the efficiency of the catalyst has been examined for the expeditious synthesis of pyrazine derivatives *via* a three-component reaction using different diamines, various ketones and isocyanides. This catalytic system showed unique properties including green condition, short reaction times, high product yield and the reusability of the catalyst.

#### Notes

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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