Conference paper

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Green multicomponent synthesis of four different classes of six-membered N-containing and O-containing heterocycles catalyzed by an efficient chitosan-based magnetic bionanocomposite

Abstract: In this work, an efficient chitosan-based magnetic bionanocomposite was synthesized via a two-step method and characterized by Fourier-transform infrared (FT-IR) spectroscopy, thermo gravimetric analysis (TGA), energy-dispersive X-ray (EDX) analysis and scanning electron microscopy (SEM) images. Then, it was used as a heterogeneous catalyst for the one-pot multicomponent syntheses of a variety of heterocyclic compounds including 2-amino-4H-pyran, 2-amino-4H-chromen and polyhydroquinoline derivatives in ethanol at room temperature. The catalyst was simply separated from the reaction mixture by an external magnet and reused several times. The products were isolated from the reaction mixtures, without any need of column chromatography, in high-to-excellent yields. A reusable and easily recoverable catalyst, use of a green solvent, room temperature and mild reaction conditions are some advantages of the present work.

Keywords: bionanocomposite; chitosan; copper ferrite; heterocycles; ICGC-6; magnetic.

Introduction

Catalysts have an important role in chemical reactions, and sometimes they become a necessity. Recently, nanomaterials have been applied as efficient nanocatalysts in chemical fields such as multicomponent reactions (MCRs) [1]. Nanocatalysts have numerous merits in comparison to bulk materials. However, they have disadvantages too. For example, separation of the nanoscale particles from reaction mixtures using conventional methods, such as filtration, can be complicated. To overcome this issue, researchers have applied magnetic-nanocatalysts in reactions, separating these from the reaction mixture, by using an external magnet simply [2, 3]. Coating or supporting magnetic nanocatalyst can improve their catalytic activity and enhance their physical properties and ranges of different materials have been used as coating, or supporting agents. Biomaterials, particularly nontoxic and eco-friendly biopolymers can be useful in this regard, yielding magnetic bionanocatalysts that can efficiently applied in reactions. Copper ferrite magnetic nanocatalyst has been applied in many organic reactions and transformations [4–6] and chitosan is a natural aminopoly saccharide [7], popular as a coating or supporting agent for nanoparticles [8, 9]. Supporting copper ferrite on chitosan can improve its activity and leads to another efficient catalyst to be applied in organic reactions.

Multicomponent reactions (MCRs) are one pot reactions involving more than two reactant that produce a single product, ideally containing most reactant atoms or vital parts of the starting materials [10]. This type
of reaction is advantageous as a method for synthesizing heterocycles using fewer steps, compared to classical synthesis routes [11], and allow for production of complex molecules via simple one-pot reactions [12]. Heterocycles containing oxygen, nitrogen, or sulfur are important classes of molecules in organic chemistry. 4H-Pyran and 4H-chromen derivatives, both containing a six-membered ring with an oxygen atom in their structures, possess biological and pharmaceutical activities and this moiety can be found in some natural product structures. These compounds exhibit biological activity such as: antiallergic, antiviral, spasmolytic, anticoagulant, anti-anaphylactic and cytotoxicity [13–17].

Polyhydroquinolines are another important class of heterocycles that have a nitrogen atom in their six-membered ring core. In addition, they are biologically active molecules [18], with some exhibiting cytotoxicity [19], anti-inflammatory [20] or antibacterial [21] properties while others are calcium channel modulators [22].

In continuation of our research to find sustainable and green routes for synthesis of chemically and biologically-important molecules and application of efficient and green catalysts in various organic reactions [9, 23–28], and due to the disadvantages of previously reported methods for synthesis of many class of heterocycles despite their valuable properties, we present a green and efficient synthesis method for synthesis of some nitrogen and oxygen containing heterocycles using a magnetic bionanocomposite, CuFe2O4/chitosan, as a recyclable and green catalyst. To the best of our knowledge, this is the first time that CuFe2O4/chitosan has been applied as catalyst for synthesis of these classes of heterocycles.

Four specific N- and O-heterocycles including 2-amino-4H-pyrans, 2-amino-4H-chromens and two types of polyhydroquinolines were studied. For the synthesis of 2-amino-4H-pyrans 6, a one-pot three-component reaction of an aldehyde 1, malononitrile 2, ethylacetoacetate 3, in the presence of CuFe2O4/chitosan as an efficient and reusable catalyst under mild reaction conditions were run and high to excellent yields were obtained. Another one-pot three-component reaction between an aldehyde 1, malononitrile 2 and dinedone 4 by using CuFe2O4/chitosan in ethanol were run to obtain 2-amino-4H-chromen derivatives 7 under mild conditions.

In order to synthesise polyhydroquinoline derivatives, we use the unsymmetrical Hantzsch condensation of an aldehyde 1, malononitrile 2 or ethylacetoacetate 3, cyclohexane-1,3-dione or dinedone 4 and ammonium acetate 5 using CuFe2O4/chitosan as the catalyst in ethanol, at room temperature, to obtain a range of polyhydroquinoline derivatives 8, 9 (Scheme 1).

**Experimental**

**Materials and methods**

All the solvents, chemicals and reagents were purchased from Merck, Fluka and Aldrich. Thin layer chromatography (TLC) was performed using Silica gel 60 F254 (Merck) plates. Compounds were visualized with

UV light (254 nm). Melting points were measured on an electrothermal 9100 apparatus and are uncorrected. FT-IR spectra were recorded on a Shimadzu FT-IR 8400 instrument with samples prepared as KBr disks. 1H NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 500 MHz in DMSO-<i>d</i><sub>6</sub> as the solvent. SEM micrographs and energy-dispersive X-ray (EDX) spectra were taken using a Tescan-Vega II microscope. Thermal analysis was conducted on a Bahr-STA 504 instrument under argon atmosphere. VSM was measured on a Magnetic Daghigh Daneshpajouh Co., Iran, vibrating sample magnetometer.

**Preparation of CuFe<sub>2</sub>O<sub>4</sub>/chitosan magnetic bionanocomposite**

The CuFe<sub>2</sub>O<sub>4</sub>/chitosan nanocomposite was prepared by a two-step process. First, CuFe<sub>2</sub>O<sub>4</sub> magnetic nanoparticles were synthesized via a previously reported method [29]. Briefly, CuFe<sub>2</sub>O<sub>4</sub> nanoparticles were prepared by thermal decomposition of Cu(NO<sub>3</sub>)<sub>2</sub> and Fe(NO<sub>3</sub>)<sub>3</sub> in water in the presence of sodium hydroxide. Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (3.34 g, 8.2 mmol) and Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (1 g, 4.1 mmol) were dissolved in 75 mL of distilled water. Then, 3 g (75 mmol) of NaOH dissolved in 15 mL of water was added over a 10 min period resulting in a formation of a reddish-black precipitate. The reaction mixture was warmed to 90 °C, stirred under ultrasonic irradiation for 2 h and then cooled to room temperature. Magnetic particles so formed were separated using an external magnet, washed with distilled water (3 × 30 mL) dried in air oven overnight at 80 °C, grounded in a mortar and pestle, heated in a furnace at 700 °C for 5 h (step up temperature 2 °C/min) and finally cooled to room temperature. The synthesized ferrite nanopowder (20 wt%) was added gradually to a chitosan polymer solution (1.5 % chitosan in 1 % aqueous acetic acid) and stirred at room temperature for 6 h. Ammonia solution was added dropwise to neutralize the solution and the resultant gel separated from the reaction mixture using a permanent magnet, washed several times with distilled water, and vacuum dried at 50 °C for 12 h to obtain the chitosan-supported magnetic nanoparticles.

**General procedure for the synthesis of 5-ethoxycarbonyl-2-amino-4-aryl-3-cyano-6-methyl-4H-pyran (6a–k) and 2-amino-7,7-dimethyl-5-oxo-4-aryl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (7a–j)**

A solution of an arylaldehyde (1 mmol), malononitrile (1 mmol), ethylacetacetate (1 mmol) for (6a–k) and dimedone (1 mmol) for (7a–j), containing CuFeO<sub>4</sub>/chitosan (0.01 g) was stirred in 5 mL ethanol at room temperature until the completion of the reaction [monitored by TLC using mobile phase ethylacetate/n-hexane; 1:3 for (6a–k) and ethylacetate/n-hexane; 1:4 for (7a–j)]. After completion of the reaction, the catalyst was simply removed from reaction mixture with an external magnet without any need for filtration or other typical separation procedures. Products solidified at room temperature in ethanol. The solid product was recovered by filtration and recrystallized from ethanol. The reaction mixture has been left for a while (container openings was covered to prevent solvent vaporization). After some hours/days crystals or precipitates appeared. All the products were known compounds that were identified by comparison of their physical data (melting points) with data reported for authentic samples. Furthermore, some selected spectral data of the products was provided in the supplementary information file.

**General procedure for the synthesis of 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolines (8a–j) and ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(aryl)-5(6H)-oxoquinolin-3-carboxylate (9a–l)**

A mixture of aryl aldehyde (1 mmol), malononitrile (1 mmol) for (8a–j) and ethyl acetoacetate (1 mmol) for (9a–l), dimedone (1 mmol) for (8a–j) and dimedone/cyclohexane-1,3-dione (1 mmol) for (9a–l), ammonium acetate (1.5 mmol) containing CuFeO<sub>4</sub>/chitosan (0.01 g) was stirred in 5 mL ethanol at room temperature until the completion of the reaction (monitored by TLC). After completion of the reaction, the catalyst was simply...
removed from reaction mixture with an external magnet. Then, the reaction mixture was further purified by recrystallization in hot ethanol. All the products were known compounds that were identified by comparison of their physical data (melting points) with data reported for authentic samples. Furthermore, some selected spectral data of the products was provided in the supplementary information file.

Results and discussion

Characterization of the nanocatalyst

The FT-IR spectrum of the synthesized magnetic bionanocomposite is shown in Fig. S1. In the FT-IR spectrum of CuFe$_2$O$_4$/chitosan, absorption band at 3431 cm$^{-1}$ referred to stretching band of OH and NH groups of chitosan that bind to the copper ferrite nanoparticles and shift to lower frequency. It is also referred to O–H of nanoparticles. The absorption bands around 1059 cm$^{-1}$ showed the stretch vibration of C–O bond and the 598 cm$^{-1}$ band represented the Fe–O group of CuFe$_2$O$_4$. EDX analysis was performed for determination of the elements constitutes catalyst (Fig. S2). It showed that there was mainly C, Fe, Cu and O atoms in the bionanocomposite structure. Field-emission scanning electron microscopy (FE-SEM) images are used to investigate the surface structure of the nanocomposite. As it is seen in Fig. 1, distribution of the nanoparticles on the chitosan surface is obvious. Furthermore, FE-SEM image of CuFe$_2$O$_4$ confirmed its accordance with nanoparticles incorporated in the catalyst nanostructure (Fig. S3). TG curve of CuFe$_2$O$_4$/chitosan shows first weight loss at about 100 °C due to evaporation of adsorbed water in the sample (Fig. S4). TG curve shows no weight loss up to about 300 °C. The nanocomposite is stable to above temperature and is suitable for organic reactions.

Fig. 1: FE-SEM image of CuFe$_2$O$_4$/chitosan nanocomposite.
Application of the catalyst in the synthesis of $N$- and $O$-heterocycles

The first catalytic application of this magnetic bionanocomposite has been reported by our research group recently [23]. To optimize the reaction conditions for the synthesis of 2-amino-$4H$-pyrans (6) and 2-amino-$4H$-chromens (7), the three-component reactions of 4-chlorobenzaldehyde, malononitrile and ethylacetoacetate or dimedone in the presence of CuFe$_2$O$_4$/chitosan was selected as test reactions under various conditions at room temperature, to give the products 6j and 7i. Only ethanol, water or solvent-free conditions were tested and ethanol found to be the best choice for the reactions (Table 1).

To optimize the synthesis of 2-amino-3-cyano-5-oxo-$1,4,5,6,7,8$-hexahydroquinoline 8 and $1,4,5,6,7,8$-hexahydroquinoline-3-carboxylate derivatives 9, four-component reaction of 4-chlorobenzaldehyde, malononitrile (8)/ethylacetoacetate (9), dimedone and ammonium acetate in the presence of CuFe$_2$O$_4$/chitosan was selected as test reaction under various conditions at room temperature, to give the product 8b and 9b. Only ethanol, water or solvent-free conditions were tested and ethanol found to be the best choice for all reactions (Table 2).

As indicated in the Tables 3 and 4, after optimization of the reactions conditions, various aldehydes were used in every method to get diversities of $O$- and $N$-heterocycles. High-to-excellent yields and relatively short reaction times were obtained for almost all of the starting materials including either electron-withdrawing or electron-releasing substituents. Melting points of the products could be found in Table S1.

**Table 1: Investigation of optimized conditions for synthesis of $O$-heterocycles.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst amount (g)</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6j</td>
<td>7i</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>–</td>
<td>EtOH</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>Water</td>
<td>120</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>–</td>
<td>12 h</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>CuFe$_2$O$_4$ $c$</td>
<td>–</td>
<td>EtOH 120</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>Chitosan $d$</td>
<td>–</td>
<td>EtOH 120</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
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<td>EtOH</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
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<td>EtOH</td>
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<td>47</td>
</tr>
<tr>
<td>8</td>
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<td>EtOH</td>
<td>60</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>0.02</td>
<td>EtOH</td>
<td>60</td>
<td>96</td>
</tr>
</tbody>
</table>

*aReaction were run between 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol) and ethylacetoacetate (1 mmol) (6j) or dimedone (1 mmol) (7i) in the presence of CuFe$_2$O$_4$/chitosan. *Isolated yields. *20 mol% of the catalyst. *0.01 g of the catalyst.

**Table 2: Investigation of optimized conditions for synthesis of $N$-heterocycles.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst amount (g)</th>
<th>Solvent</th>
<th>Yield (°)</th>
</tr>
</thead>
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<td>EtOH</td>
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<td>7</td>
<td>0.01</td>
<td>H$_2$O</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>0.01</td>
<td>H$_2$O/EtOH (50:50)</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>0.01</td>
<td>–</td>
<td>83</td>
</tr>
</tbody>
</table>

*aAll tests were run at 15 min, except entry 1 which was run in 1 h. Reaction between 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol) (8)/ethylacetoacetate (1 mmol) (9), dimedone (1 mmol) and ammonium acetate (1.5 mmol). *Isolated yields.
Catalyst recyclability

Catalyst recyclability was investigated in all four model-reactions (Fig. 2). After every run, catalyst was recovered using an external magnet, then washed with ethanol and dried. Magnetic bionanocomposite catalyst can be successfully reused in at least seven cycles with only small reduction in activity.

Conclusion

In summary, we have represented an efficient magnetic bionanocomposite CuFe$_2$O$_4$/chitosan as a green catalyst for the one-pot multicomponent synthesis of wide range of $N$- and $O$-heterocycles in ethanol, as a green solvent, at room temperature. All the reactions work easily for a wide variety of aromatic aldehydes, with both electron-donating and electron-withdrawing groups, to give corresponding $N$- and $O$-heterocycles in high-to-excellent yields. Fourier-transform infrared spectra showed that the copper ferrite nanoparticles were successfully coated by the chitosan matrix. The use of a green solvent, green and non-toxic catalyst,
easy separation of catalyst by using an external magnet, catalyst recyclability and reusability in several reaction runs, simple work-up procedure, high-to-excellent yields and mild reaction conditions are all notable advantages of this protocol.

Supporting information

Additional supporting information and spectroscopic characterization data are shown online in the supporting information tab for this article.

Acknowledgements: The authors gratefully acknowledge partial financial support from the Research Council of the Iran University of Science and Technology.

References


Supplemental Material: The online version of this article offers supplementary material (https://doi.org/10.1515/pac-2017-0702).