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Synthesis of benzimidazole derivatives using Ni^{2+} supported on hydroxyapatite-core@shell γ-Fe_2O_3 nanoparticles both under solvent and solvent-free conditions

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ABSTRACT

Ni^{2+} supported on hydroxyapatite-core@shell γ-Fe_2O_3 nanoparticles (γ-Fe_2O_3@HAp-Ni^{2+}) was found to be a useful catalyst for the synthesis of benzimidazole derivatives from *o*-phenylenediamine and aldehydes under solvent and solvent-free conditions at 80°C. This reaction affords the corresponding benzimidazole derivatives compared with the classical reactions this method consistently gives a high yield, easy magnetic separation, a short reaction time, simple workup and recyclable property of the catalyst. In this way, the catalyst was readily recovered using an external magnet and could be reused in five consecutive runs without significant loss of reactivity. The mean size and the surface morphology of the nanocatalyst were characterized by TEM, SEM, VSM, XRD and FTIR techniques.

Keywords: *Benzimidazole, Ni^{2+} supported, γ-Fe_2O_3 nanoparticles, o-Phenylenediamine.*

1. Introduction

Benzimidazoles [1] contain a bicyclic system in which benzene has been fused to the 4 and 5 position of the hetero cycle (imidazole). Benzimidazoles are very useful compounds for the expansion of pharmaceutical molecules or biological interest [2]. They exhibit noteworthy activity against several viruses including HIV [3], herpes (HSV-1) [4], RNA [5], influenza [6], and human cytomegalovirus (HCMV) [3]. also looks that some benzimidazole derivatives are used to act as topoisomerase deterrent [7], selective neuropeptide YY1 receiver antagonists [8], angiotensin II inhibitors [9], potential antitumor agents [10] and smooth torus cell reproduction deterrent [11]. A number of methods have been designed for the synthesis of benzimidazole derivatives, which include conversion of esters using an aluminum reagent [12], the reaction between N-ethoxycarbonylthioamides with 1,2-diamines [13], the reaction of an appropriate 1,2-phenylenediamine with carboxylic acid and its derivative [14], nitriles [15], or orthoesters [16] in the presence of a strong acid at elevated temperature. In recent years, many methods have been designed, where aldehydes [17], acid chloride [18], o-dinitrobenzene [19], Gold's reagent [20], and 2-nitroanilines [21] are used as precursors for this synthesis. In recent years, solvent-free synthesis of benzimidazoles under microwave irradiation using $Yb(OTf)_3$ [22], KSF clay [23], PPA [24], Na_2SO_4 [25], K-10clay [26], metal halide supported alumina [27] and solid support [28] have been reported. Although these methods are convenient for certain synthetic conditions, sometimes, there are some drawbacks such as long reaction time, high temperature, low yields of products in some cases, use of an additional microwave oven, corrosive reagents and large amounts of solid supports which would eventually result in the generation of a large amount of toxic waste. Hence, a requirement for developing the synthesis of benzimidazole derivatives is in high demand. In this work, we describe an efficient protocol for the synthesis of benzimidazole derivatives using γ-Fe_2O_3@HAp-Ni^{2+}. This method has some advantages including the use of an inexpensive and reusable catalyst, easy handling, short reaction times, high yield, and simplicity of the product isolation.

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2. Experimental

2.1. General

Aromatic aldehydes and other chemical materials were purchased from Fluka and Merck and were used without further purification. All Products were characterized by comparison of their physical data, IR and ^{1}HNMR and ^{13}CNMR spectra and physical, properties with those reported in the literature. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates. IR spectra of the compounds were obtained on a PerkinElmer spectrometer version 10.03.06 using a KBr disk.

2.2. Synthesis of γ-Fe_2O_3@HAp-Ni^{2+}

γ-Fe_2O_3@HAp-Ni^{2+} was prepared as reported in the literature [29]. The Iron oxide magnetic particles (IOMP) were synthesized by co-precipitation method in the basic condition. IOMP/HAp was prepared by the impregnation method according to known procedures with some modifications [30]. Then hydroxyapatite-encapsulated γ-Fe_2O_3 (0.6 g) was introduced into 100 mL of distilled water containing 6.4 mmol of $NiCl_2.6H_2O$. The mixture was stirred (500 rpm) for 48 h, filtered, and washed several times with ethanol. The recovered solid was dried at 50°C overnight (Scheme 1). The mean size and the surface morphology of the γ-Fe_2O_3@HAp-Ni^{2+} were characterized by TEM, SEM, VSM, XRD and FTIR techniques.

2.3. Typical Procedure for the Synthesis of Benzimidazoles

A mixture of *o*-phenylenediamine (1 mmol) and aromatic aldehyde (1.1 mmol) was well stirred with the catalyst (20 mg) in 10 mL of water was stirred in a round bottomed flask, or under solvent-free conditions at 80°C (Scheme 2). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was added drop wise with vigorous stirring into a H_2O (15 mL). In cases where the product was extracted into EtOAc, the organic phase was washed with H_2O and dried. Since the catalyst can be separated from the aqueous layer using an external magnetic field, it was recovered with a simple magnet after the dilution of the reaction mixture with water.

Selected spectral data

*2-Phenyl-1H-benzimidazole (**Entry 1**)*:

Yellow solid. m.p.= 287-289°C (lit. 290-292°C [31]). IR (KBr): $\bar{\nu}$ = 3500, 1718, 1600, 948, 740 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 7.20 (m, 2H), 7.40–7.62 (m, 5H), 8.20 (d, *J*= 8.4 Hz, 2H), 12.92 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 115.03, 115.16, 139.17, 129.97, 129.06, 128.88, 126.50, 122.16 ppm.

*2-(4-Chlorophenyl)-1H-benzimidazole (**Entry 3**)*:

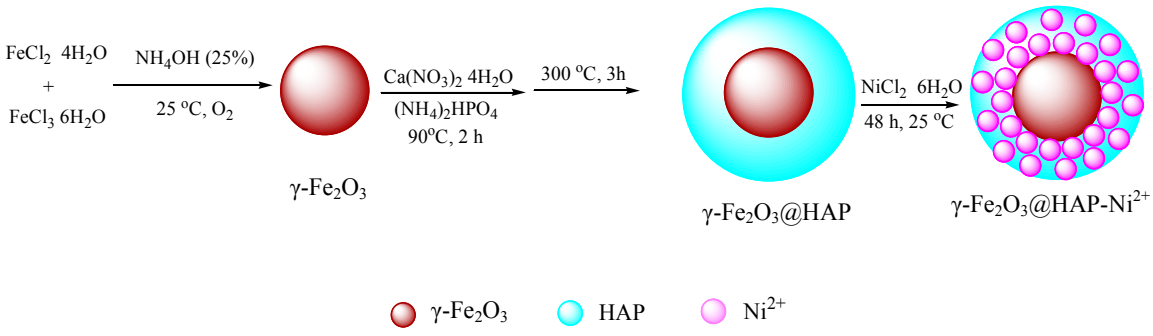
Pale brown solid. m.p.= 291-292°C (lit. 291-293°C [31]). IR (KBr): $\bar{\nu}$ = 3548, 1722, 1600, 1450, 1550, 748 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 7.21 (bs, 2H), 7.53 (d, *J*= 6.8 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J*= 6.8 Hz, 1H), 8.18 (d, *J*= 8.8 Hz, 2H), 12.94 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 111.31, 118.88, 121.73, 122.66, 128.06, 128.96, 129.00, 134.39, 134.95, 143.69, 150.08 ppm.

*2-(4-Nitrophenyl)-1H-benzimidazole (**Entry 8**)*:

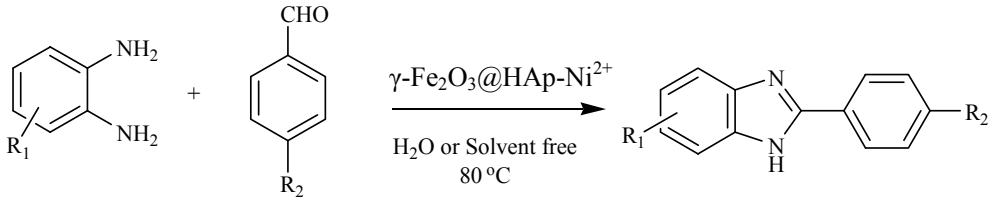
Brown solid. m.p.= 310-311°C (lit. 312-314°C [31]). IR (KBr): $\bar{\nu}$ = 3552, 1715, 1600, 1550, 1450, 848, 740 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 8.07 (d, *J*= 7.2 Hz, 2H), 8.31 (d, 7.2 Hz, 2H), 7.17 (m, 2H), 7.18 (m, 2H), 13.4 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 112.29, 119.92, 122.81, 124.02, 124.77, 127.85, 135.68, 136.50, 144.32, 148.25, 149.46 ppm.

*2-(4-Methoxyphenyl)-1H-benzimidazole (**Entry 10**)*:

Pale brown solid. m.p.= 221-223°C (lit. 225–226°C [31]). IR (KBr, cm^{-1}): $\bar{\nu}$ = 3544, 1724, 1610, 1450, 1100, 1200, 950. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 3.83 (s, 3H), 7.09 (d, *J*= 8.0 Hz, 2H), 7.15 (d, *J* =8 Hz, 2H), 8.10-8.12 (d, *J*= 8 Hz, 2H), 7.2–7.22 (m, 2H), 12.78 (s, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 55.12, 110.39, 114.28, 118.42, 121.35, 121.97, 122.67, 127.93, 134.92, 143.84, 151.28, 160.54 ppm.



Scheme 1. Preparation of γ-Fe_2O_3@HAp-Ni^{2+}.



Scheme 2. Synthesis of Benzimidazoles by using γ-Fe_2O_3@HAp-Ni^{2+}.

3. Results and Discussion

Magnetic nanoparticles (MNPs) have been considered as attractive and interesting materials because of their high surface area and unique magnetic properties.

The catalyst concentration varied over a range of 5–25 mg γ-Fe_2O_3@HAp-Ni^{2+} on the basis of the total volume of the reaction mixture. As mentioned before, we have carried out the reaction of o-phenylenediamine and aromatic aldehyde. Different reaction conditions have been studied for optimization. Firstly, condensation of *o*-phenylenediamine and benzaldehyde was performed with different mg γ-Fe_2O_3@HAp-Ni^{2+} and temperatures to optimize the reaction conditions in water and solvent free condition (Table 1).

After obtaining the optimal conditions for *o*-phenylenediamine and aldehydes, we examined the generality of these conditions to other reactions of *o*-phenylenediamine and various aromatic aldehydes in the presence of optimized γ-Fe_2O_3@HAp-Ni^{2+} (Table 2). The conversion completed during 20–75 min. Most compounds used reacted under these conditions and this reaction provided good-to-excellent yields with all the substrates tested.

Table 1. Optimization of experimental conditions for synthesis of benzimidazole by using γ-Fe_2O_3@HAp-Ni^{2+}.

Entry	Fe_2O_3@HAp-Ni^{2+}(mg)	Temp. (°C)	In Water		Solvent-free	
			Time (min)	Yield (%)[a,b]	Time (min)	Yield (%)[a,b]
1	5	r.t.	75	38	75	32
2	5	60	40	52	40	45
3	10	60	30	63	30	58
4	20	80	20	95	20	92
5	25	80	20	93	20	86
6	20	60	25	90	25	81

[a]All products were characterized by spectroscopic data.
[b]Yield after purification.

Table 2. Synthesis of benzimidazoles catalyzed by γ-Fe_2O_3@HAp-Ni^{2+}.

Entry	R_1	R_2	In Water		Solvent-free	
			Time (min)	Yield (%)[a,b]	Time (min)	Yield (%)
1	H	*H*	20	95	20	92
2	4-Me	H	25	95	30	86
3	H	4-Cl	25	91	30	90
4	H	2-Cl	25	89	35	84
5	4-Me	4-Cl	20	91	30	93
6	H	2-NO_2	60	85	60	82
7	4-Me	2-NO_2	55	82	55	86
8	H	4-NO_2	60	83	75	88
9	4-Me	4-NO_2	50	87	60	85
10	H	4-OMe	20	92	20	90
11	4-Me	4-OH	20	93	20	91

[a]All products were characterized by spectroscopic data.
[b]Yield after Purification.

A wide variety of compounds were applied under optimal reaction conditions to prepare benzimidazoles. Aromatic aldehydes, with strong electronwithdrawing substituents, including the nitro group, required a relatively longer reaction time with lower yields (Table 2, entries 6-9), whereas aryl aldehydes, carrying electron donating groups, gave excellent yields of the products (Table 2, entries 10 and 11) in a shorter reaction time.

As it can be seen in Table 3, γ-Fe_2O_3@HAp-Ni^{2+} as a catalyst afforded good results in comparison to the other catalysts. In order to evaluate the efficiency of our introduced method, more recently developed methods were compared with our present method on the basis of the yields and reaction times parameters. The results were given in Table 3.

Catalyst reusability is of major importance in heterogeneous catalysis. The recovery and reusability of the catalyst was studied using *o*-phenylenediamine and benzaldehyde as model reaction. Since the catalyst can be separated from the reaction mixture using an external magnetic field, it was recovered with a simple magnet after the dilution of the reaction mixture with water. The catalyst was consecutively reused seven times without any noticeable loss of its catalytic activity (Table 4).

4. Conclusions

In this research, we have developed a simple and efficient method for the synthesis of benzimidazole derivatives using γ-Fe_2O_3@HAp-Ni^{2+} as catalyst under solvent-free conditions at 80 °C. Moreover, the advantages of this method are the experimental simplicity, inexpensive reagents, short reaction times and easy workup procedure. Moreover the catalyst can be easily recovered by simple magnetic decantation and reused several times with no loss of activity.

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Table 3. Comparison of catalytic ability of catalysts.

Entry	Catalyst/Solvent/Temp.	Time (min)	Yield %	Ref.
1	SBSA[a]/Water/r.t.	30	93	[32]
2	$Zn(OAc)_2$/Solvent Free/r.t.	10	92	[33]
3	$Yb(OPf)_3$/Toluene/90°C	6 h	98	[34]
4	$ZrCl_4$/EtOH/r.t.	60	93	[35]
5	γ-Fe_2O_3@HAp-Ni^{2+}/ Solvent Free /80°C	20	92	This work
6	γ-Fe_2O_3@HAp-Ni^{2+}/ Water /80°C	20	95	This work

[a]SBSA: Silica Boron Sulfonic Acid/

Table 4. The catalyst reusability of γ-Fe_2O_3@HAp-Ni^{2+}in 5 cycles.

Run	1	2	3	4	5
In Water Yield (%)	95	93	90	88	86
Solvent-free Yield (%)	92	91	87	86	85

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