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ARTICLE

Novel Approach to Benzimidazoles Using Fe_3O_4 Nanoparticles as a Magnetically Recoverable Catalyst

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Abstract: Magnetically recoverable Fe_3O_4 nanoparticles have been synthesized as a catalyst for the cyclocondensation of 1,2-phenylenediamines with orthoesters under solvent-free conditions. Catalyst loadings can be as low as 1 mol% to give high yields of the corresponding benzimidazole derivative at 80 °C. This green method offers significant advantages in terms of its simplicity, low catalyst loadings, high product yields, and non-toxic nature. The Fe_3O_4 nanoparticles were characterized by X-ray diffraction, transmission electron microscopy, and Fourier transform infrared spectroscopy.

Key words: ferroferric oxide nanoparticle; 1,2-phenylenediamine; orthoester; benzimidazole

The challenge in chemistry is to develop practical methods with convenient conditions and reagents, and the concept of “green chemistry” is becoming ever important in the scientific community. Green chemistry is emerging as a high-priority guiding principle for organic synthesis. Recently, the preparation and application of nanoparticles (NPs) in organic synthesis has been the subject of intense interest [1–4]. Using NPs offers advantages for “clean” chemistry, since, in addition to being readily recovered, they are non-toxic and widely accessible. The NP surface can also be functionalized to append catalytically active groups [5,6].

In this work, we describe a new and green strategy for the preparation of novel and known benzimidazoles using Fe_3O_4 nanoparticles. These have proved as powerful, safe, and recyclable catalysts under solvent-free conditions. In a previous study, Goosen and co-workers [7] reported the catalytic decarboxylative cross-ketonisation of aryl- and alkylcarboxylic acids using Fe_3O_4 nanoparticles.

In recent years, the development of improved synthetic routes to heterocyclic compounds has attracted special attention [8–10]. Among the wide variety of nitrogen heterocycles that have been explored as pharmaceutically important compounds, benzimidazoles exhibit relatively high biological activities. They have exhibited activity against cancer [11], HIV [12,13], herpes (HSV-1) [14], influenza [15], certain fungi [16], and raf kinase [17]. The most prominent benzimidazole compound in nature is *N*-ribosyldimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12} [18].

Until now, several methods for the synthesis of benzimidazoles and derivatives thereof have been reported. The most common method is the condensation of an arylenediamine with a carbonyl equivalent [19,20]. Esters, lactones, and anhydrides can also produce benzimidazoles through the cyclization of amide [21]. However, some of these reported methods suffer from drawbacks, such as the requirement for toxic and expensive catalysts and solvents, long reaction times, low yields, and difficult work-up procedures.

1 Experimental

1.1 Preparation of Fe_3O_4 nanoparticles

$FeCl_3$ (5.2 g) and $FeCl_2$ (2.0 g) were successively dissolved in 25 ml distilled water with 0.85 ml 12.1 mol/L HCl. The resulting solution was added dropwise to a 250 ml 1.5 mol/L NaOH solution with vigorous stirring. The last step generates an instant black precipitate. The precipitate was isolated in a magnetic field, and the supernatant was removed from the precipitate through decantation [22].

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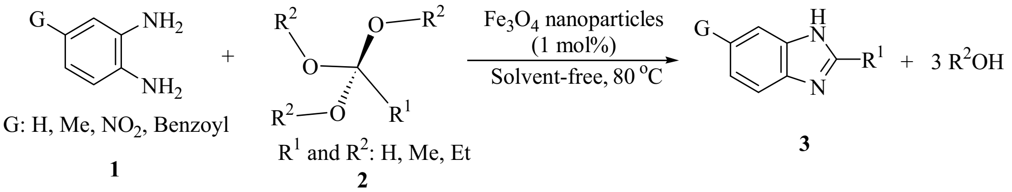


Scheme 1. Synthesis of benzimidazole derivatives using Fe_3O_4 nanoparticles.

1.2 Characterization of Fe_3O_4 nanoparticles

Transmission electron microscopy (TEM) studies were carried out with a JEOL JEM 3010 instrument, operating at an accelerating voltage of 300 kV. X-ray diffraction (XRD, D8, Advance, Bruker, axs) patterns were obtained for the characterization of the heterogeneous catalysts. Fourier transform infrared (FT-IR) spectra were recorded on a Shimadzu-470 spectrometer using KBr pellets.

1.3 Synthesis of benzimidazole derivatives

A mixture of 1,2-phenylenediamine **1** (1 mmol), orthoester **2** (1 mmol), and Fe_3O_4 nanoparticles (2.32 mg, 1 mol%) was stirred and heated at 80 °C for the appropriate time. Upon completion (as adjudged by TLC, silica-gel 60 F_{254}, *n*-hexane:ethyl acetate), hot $EtOH/H_2O$ (50/50, 10 ml) was added to the reaction mixture and the catalyst was separated through magnetic absorption using a magnet. After separating the catalyst, the solution was heated and filtered to afford the pure product **3** in the crystal form. At the end of the reaction, the separated catalyst was washed with diethyl ether, dried at 130 °C for 1 h, and reused in another cycle. The general procedure is shown in Scheme 1.

All synthesized compounds (**3a–3i**) were characterized via analytical and spectroscopic methods. Melting points were determined on a KRUSS model instrument. ^1H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer at 400 MHz, in which $CDCl_3$ was used as solvent and TMS as the internal standard. All products (except for novel compounds) were characterized through comparison with the reported in the literatures [23–27].

2 Results and discussion

Figure 1 shows the XRD pattern for the Fe_3O_4 nanoparticles. A number of prominent Bragg reflections, as assigned from their indices ((220), (311), (400), (422), (511), and (440)), reveal that the resultant nanoparticles are Fe_3O_4 with a spinel structure [28]. The size of the Fe_3O_4 nanoparticles was also determined from X-ray line broadening, using the Debye-Scherrer formula, which is given as $D = 0.9\lambda/\beta\cos\theta$, where D is the average crystalline size, λ is the applied X-ray wavelength, β is the angular line width at half maximum intensity, and θ is the Bragg's angle. For the (311) reflection, the average size of the Fe_3O_4 nanoparticles was estimated to be around 13 nm.

Figure 2 shows the TEM image of the Fe_3O_4 nanoparticles. The TEM image reveals spherical Fe_3O_4 nanoparticles with an average size of 10 nm.

The FT-IR spectrum for the Fe_3O_4 nanoparticles is shown in Fig. 3. The absorbance bands at 584.3 cm^{-1} are ascribed to Fe^{2+}–O^{2-}, and are consistent with those reported for spinel Fe_3O_4 [29,30].

In the past few years, we have been involved in a program directed towards developing simple, novel, and facile methods for the preparation of organic compounds using a range of catalysts and readily available starting materials [23–27]. In this study, we present a simple route towards novel and known benzimidazoles **3** through the reaction of 1,2-phenylenediamines **1** with orthoesters **2** using Fe_3O_4 nanoparticles as a

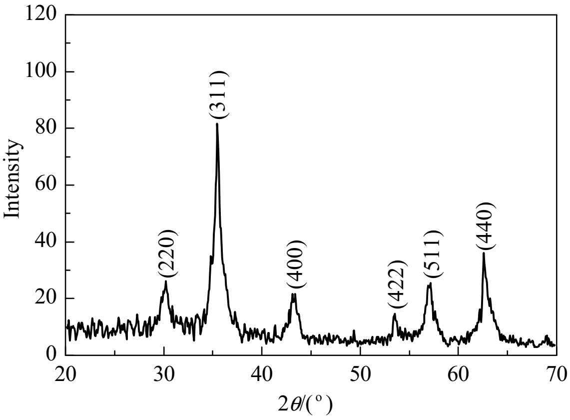


Fig. 1. XRD pattern for the Fe_3O_4 nanoparticles.

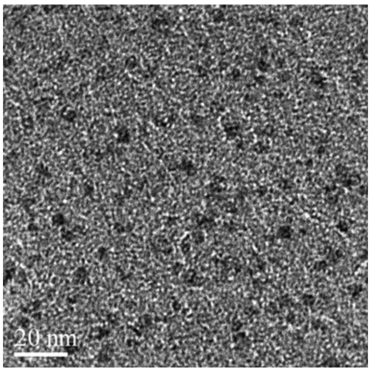


Fig. 2. TEM image for the Fe_3O_4 nanoparticles.

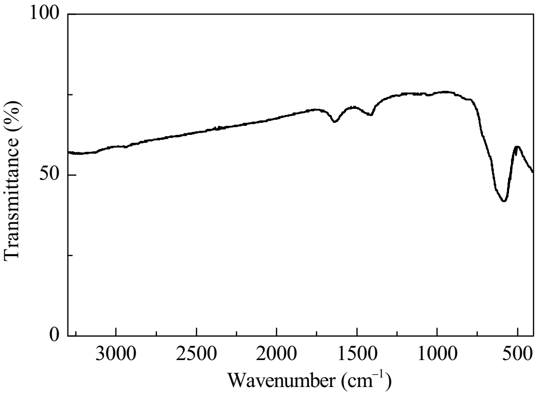


Fig. 3. FT-IR spectrum for the Fe_3O_4 nanoparticles.

magnetically recoverable catalyst (Scheme 1).

To identify the suitable reaction conditions for the synthesis of benzimidazole derivatives **3** using these Fe_3O_4 nanoparticles, triethyl orthoformate and *o*-phenylene diamine were selected as the model reaction. As can be seen in Table 1, we found that in the absence of the catalyst, the reaction did not proceed, even at a high temperature. Through screening, we found that this reaction proceeded smoothly with 1 mol% catalyst at 80 °C under solvent-free conditions in only 12 min. Higher loadings of catalyst did not affect a marked influence on the product yield. This may be due to the coordination of excessive catalyst to the diamine.

To prove the general applicability of this method, after optimizing the reaction conditions, different orthoesters and *o*-phenylenediamines were examined. The results are summarized in Table 2.

Table 1 Synthesis of benzimidazole (**3a**) catalyzed with various loadings of Fe_3O_4 nanoparticles at 80 °C under solvent-free conditions

Catalyst amount (mol%)	Time (min)	Yield[a] (%)
—	540	50[b]
1	12	91
3	12	90
5	15	90

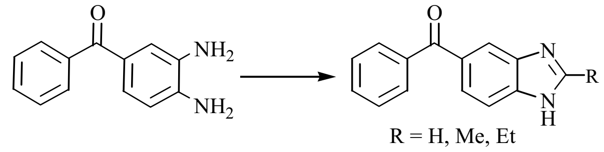
[a]Isolated yields. [b]Not completed.

Table 2 Synthesis of benzimidazole derivatives using 1 mol% Fe_3O_4 nanoparticles at 80 °C under solvent-free conditions

Product[a]	G	R^1	R^2	Time (min)	Yield[b] (%)	Melting point (°C)	
						Found	Ref. [31]
3a	H	H	Et	12	91	172–174	170–172
3b	H	Me	Me	15	88	176–178	172–174
3c	H	Et	Et	17	93	166–168	163–165
3d	Me	H	Et	36	77	108–110	112–114
3e	Me	Me	Me	22	84	198–200	198–200
3f	Me	Et	Et	25	80	165–167	160–163
3g	NO_2	H	Et	7	91	208–210	206–208
3h	NO_2	Me	Me	10	82	225–227	225–227
3i	NO_2	Et	Et	8	82	178–180	177–179

[a]Identified by comparison with authentic samples. [b]Isolated yields.

Table 3 Synthesis of new benzimidazole derivatives using 1 mol% Fe_3O_4 nanoparticles at 80 °C under solvent-free conditions



3j–**3k**

Product	Orthoester	R	Time (min)	Yield[a] (%)	Melting point (°C)
3j	$HC(OEt)_3$	H	17	85	136–138
3j	$HC(OMe)_3$	H	14	82	136–138
3k	$MeC(OMe)_3$	Me	10	88	168–170
3l	$EtC(OEt)_3$	Et	12	90	140–142

[a]Isolated yields.

Encouraged by the above results, we then focused our attention on 4-benzoyl-1,2-phenylenediamine, to prepare new benzimidazoles **3j**, **3k**, and **3l**. The results obtained are summarized in Table 3.

The ^1H NMR spectrum for **3l** gave a triplet for the protons of the methyl group (δ = 1.47), a quartet for the protons of the methylene group (δ = 3.00) and a set of multiplet signals (δ = 7.82–7.45, 7.23–7.27) that correspond to the aromatic protons. The resonance for the NH proton appeared as a broad signal at δ = 10.80–10.40. The carbonyl groups in the ^{13}C NMR spectrum of **3l** appeared at δ = 197.62.

To compare the catalytic activity of Fe_3O_4 powder with that of the Fe_3O_4 nanoparticles, two parallel reactions were performed. As shown in Table 4, the product yields were moderate (55%–75%) after 50–70 min with the Fe_3O_4 powder, whilst the

Table 4 Comparing the catalytic activities of Fe_3O_4 powder and Fe_3O_4 nanoparticles in the synthesis of benzimidazoles.

Product	Fe_3O_4 powder		Fe_3O_4 NPs	
	Yield[a] (%)	Time (min)	Yield[a] (%)	Time (min)
3a	75	50	91	12
3g	60	56	91	7
3i	55	70	82	8

[a]Isolated yields.

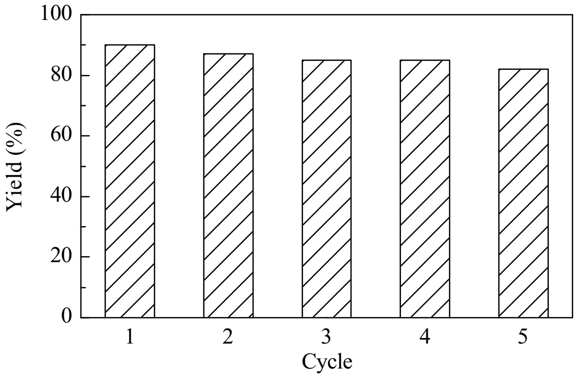


Fig. 4. Recyclability of the Fe_3O_4 nanoparticle catalyst in the synthesis of **3a** at 80 °C under solvent-free conditions (reaction time = 12–15 min).

Fe_3O_4 nanoparticles provided excellent yields (82%–91%) after 8–12 min under solvent-free conditions.

The design and synthesis of recoverable catalysts is a highly challenging interdisciplinary field, which combines chemistry, materials science, and engineering from economic and environmental perspective. The main disadvantage for many of the reported methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or re-used. In this process, as outlined in Fig. 4, the recycled catalyst can be used in up to five cycles, during which there are negligible losses in the catalytic activity.

3 Conclusions

A green methodology for the preparation of novel and known benzimidazole derivatives, using magnetically recoverable Fe_3O_4 nanoparticles under solvent-free conditions has been presented. This method not only provides high yields and purities, but it is also cheap, convenient, quick, and economically friendly.

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