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Nano-Fe_3O_4/O_2: Green, Magnetic and Reusable Catalytic System for the Synthesis of Benzimidazoles

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ABSTRACT

Magnetic nano-Fe_3O_4 was applied in the presence of atmospheric air as a green, efficient, heterogeneous and reusable catalytic system for the synthesis of benzimidazoles via the reactions of *o*-phenylenediamine (1 eq) with aryl aldehydes (1 eq) in excellent yields (85–97 %) and short reaction times (30–100 min) with a proposed mechanism.

KEYWORDS

Benzimidazole, benzene-1,2-diamine, aldehyde, nano-Fe_3O_4, heterogeneous catalyst, magnetite, O_2.

1. Introduction

Benzo-fused heterocyclic systems such as benzimidazole derivatives have g)ained special attention in the last few years because of their ever-increasing and undeniable roles in medicinal and organic fields of chemistry.[1] The benzimidazole unit is regarded as an important pharmacophore in modern drug discovery.[2] Benzimidazole derivatives exhibit significant activity against several viruses such as HIV,[3] herpes (HSV-1),[4] RNA[5] and influenza.[6,7] Based on a recent report, benzimidazole Plk1 inhibitor (R)-**1** has been shown to have excellent activity against Nek2 (Fig. 1).[8]

The classical method for the benzimidazole synthesis is the condensation of *o*-arylenediamines with carboxylic acids or their derivatives, which suffer from strongly acidic conditions and high temperatures (more than 200 °C).[9] The other approach is the oxidation of benzimidazoline intermediates that are generated from the condensation of *o*-arylenediamines and aldehydes.[10] This method produces benzimidazoles at relatively low temperatures (approximately 100 °C), but requires unstable aldehydes as reactants and stoichiometric or excess amounts of strong oxidants such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), 1,4-benzoquinone,[11] $PhI(OAc)_2$,[12] oxone[13] and H_2O_2/HCl.[14] Recent advances in this method have allowed the use of molecular oxygen as an oxidant,[15] but these processes require homogeneous catalysts, such as metal triflates, and a free radical.

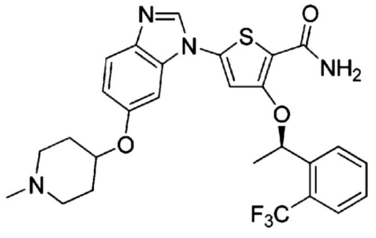
Transition-metal catalyzed organic reactions are often considered to follow the principles of 'Green Chemistry', i.e. these catalyzed reactions consume a minimum of energy and reagents or auxiliaries and minimize waste. Nanocatalysts are considered to be a bridge between homogeneous and heterogeneous catalysis.[16] The nanomaterials present high specific surface area of the active component, thereby enhance the contact between reactants and catalyst support.[17] Also a higher surface area gives nanomaterials with more active surface and they are easy to agglomerate and hard to be isolated. Therefore, it is important to design a recoverable and well-dispersed catalysts. Having mentioned the above facts, magnetite nanoparticles (MNPs) as catalyst supports are very promising due to their large specific surface area and magnetic properties.[18,19] It can be collected easily using a magnet for reuse to prevent loss of the catalyst. Recently, the chemists have focused on the surface modification with appropriate capping agents on to the MNP surface to anchor the catalytically active complexes.[20–23] One of the outstanding highlights of our presented work is the use of various oxidation states of iron which are present in one nano-structure (nano-Fe_3O_4) and acts as a versatile catalytic system.

Herein, we were intrigued by the possibility of applying nanotechnology to design a novel, active, recyclable, and magnetically recoverable 'Cfree' nano-Fe_3O_4 as a versatile system (Fe(III) as a Lewis acid/Fe(II) as an oxidant-acceptor in the structure of nano-Fe_3O_4). It is utilized for the first time for the synthesis of arylbenzimidazole derivatives under mild reaction conditions. This report will assist in the more efficient preparation of similar products.

2. Experimental

2.1. General

All chemicals were purchased from Merck, Fluka or Acros Chemical Companies and used without any further purification. Fe_3O_4 magnetite nanoparticles were prepared using a partial reduction co-precipitation method according to a known procedure in the literature.[24] The crystal structure of synthesized Fe_3O_4 (magnetite) was determined by an X-ray diffractometer



(*R*)-**1**

Figure 1 The structure of Plk1 inhibitor (R)-**1.**

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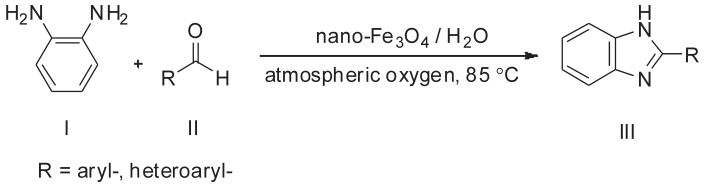


Scheme 1
The reaction of *o*-phenylenediamine with aryl aldehydes catalyzed by the nano-Fe_3O_4.

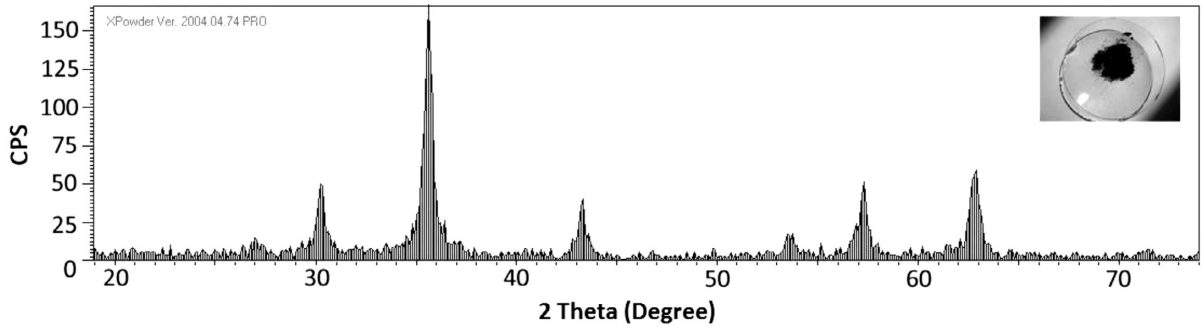


Figure 2 The XRD pattern of the nano-Fe_3O_4.

(Italstructure ADP2000 XRD diffractometer) at ambient temperature. The magnetic measurement was carried out in a vibrating sample magnetometer (VSM-4 inch, Daghigh Meghnatis Kashan Co., Kashan, Iran) at room temperature. Transmission electron microscopy (TEM) analyses were performed on a Philips model CM 10 instrument. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel SIL G/UV 254 plates. The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.9 MHz) were run on a Bruker Avance DPX, FT-NMR spectrometers. Mass spectra were obtained with Shimadzu GC-MS-QP 1100 EX instrument at 70 or 20 eV. Infrared spectrum of compounds was recorded by Perkin Elmer PE-1600-FTIR.

2.2. General Procedure for the Synthesis of Benzimidazoles Derivatives (Scheme 1)

For each reaction, *o*-phenylenediamine (1 mmol), aryl aldehyde (1 mmol) and 5 mL of H_2O as solvent were stirred in a 10 mL round-bottomed flask in the present of nano-Fe_3O_4 (5 mol%) at 85 °C. After completion of the reaction (monitored by TLC), the catalyst was simply collected by a magnet within 20–30 seconds for reuse to the next cycles (up to six runs) (Table 1) and the solvent was evaporated to give the crude product which was purified by silica gel column chromatography employing n-hexane/ethyl acetate (8:1) as the eluent.

3. Results and Discussion

3.1. Studies to Confirm the Structure of Nano-Fe_3O_4

Typical synthesis of nano-Fe_3O_4 (magnetite) was carried out in a partial reduction, co-precipitation method. The synthesized powders of magnetite were investigated by Fourier transform infrared spectroscopy (FT-IR), X-ray diffractometer (XRD), transmission electron microscopy (TEM) and vibrating sample magnetometer (VSM). As shown in Fig. 2, the XRD patterns of magnetite Fe_3O_4 nanoparticles reveal at $2\theta \approx 30.241°$, 35.621°, 43.334°, 53.634°, 57.290° and 62.806°, respectively, which matched well with the reported value (JCPDS 01-1111). The average size of the nanocrystals is approximately 9 nm, which is in good agreement with the following TEM observation (~10 nm) (Fig. 3).

Magnetic property of the catalyst was also studied by a VSM at 298 K. The magnetization curves showed that the magnetization saturated up to 60 emu g^{-1} at an applied field of 7000 Oe and reveals the superparamagnetic behaviours at room temperature. (Fig. 4)

Table 1 Recovery and reuse of the nano-Fe_3O_4 as the catalyst in the reaction of *o*-phenylenediamine with benzaldehyde in water.

Run	1	2	3	4	5	6
Yield [a]/%	95	95	94	95	94	93

[a] Yield of purified product.

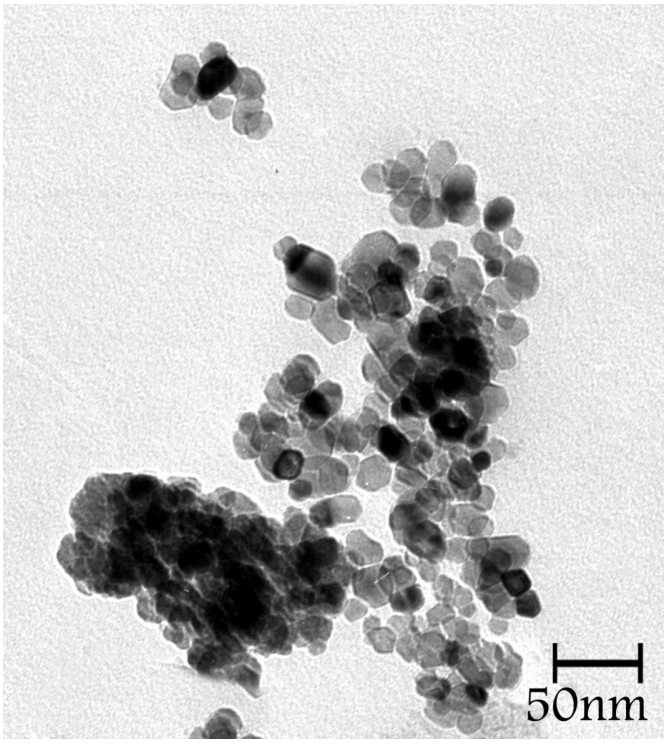


Figure 3 Transmission electron microscopy (TEM) of the nano-Fe_3O_4.

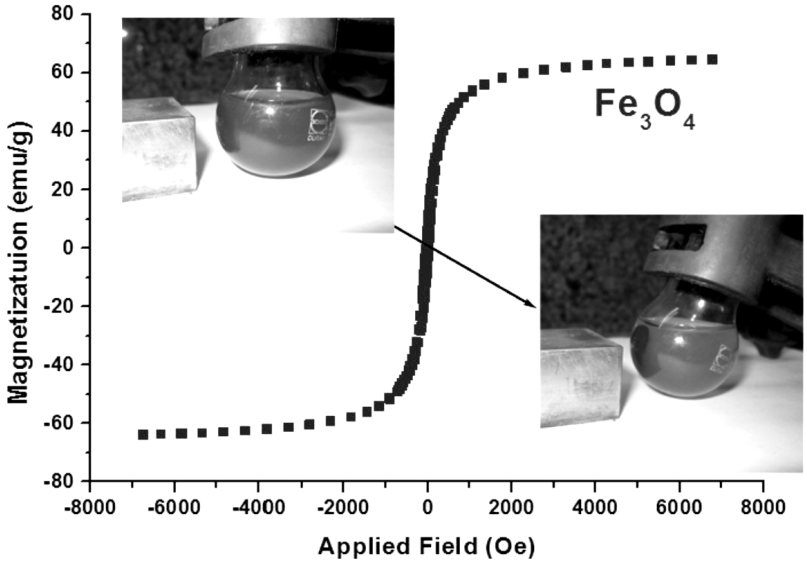


Figure 4 The vibrating sample magnetometer (VSM) of the nano-Fe_30_4.

To further study the composition of the catalyst, an FT-IR spectrum of Fe_3O_4 was examined as shown in Fig. 5, the peak at 582 cm^{-1} is the stretching vibration related to the interactions of Fe-O-Fe bonds in Fe_3O_4 (Fig. 5).

3.2. Study of the Efficiency of Nano Magnetite Catalyst in the Synthesis of Benzimidazoles

Having characterized the nano-Fe_3O_4, we set out to study its efficiency for the synthesis of benzimidazole derivatives via the reaction of benzene-1,2-diamine with aldehydes. To optimize the reaction conditions, the reaction of benzene-1,2-diamine (1 mmol) with benzaldehyde (1 mmol) was selected as a model reaction. Initially, various amount of nano-Fe_3O_4 was examined in the model reaction in H_2O as a green solvent at 85 °C under atmospheric air used as a 'green' oxidant. 0.011 g of nano-Fe_3O_4 was found to be the most effective catalyst loading in terms of reaction rate and yield of the purified product (Table 2, entry 1).

The mentioned reaction was also examined in the absence of the catalyst. Interestingly, the reaction did not have any noticeable progress after 120 min. In the next step, the effect of different solvents was investigated and it was found that the best solvent in the model reaction is water (Table 3, entry 1). The use of different solvents such as: EtOAc, CH_3CN, Dioxane, Ethanol, Diethyl ether, Xylene, THF, DMSO and DMF were not found suitable in this reaction (Table 3, entries 2–10).

As a test experiment, the model reaction was run under nitrogen atmosphere and only a trace amount of product was isolated (Scheme 2). This result shows that atmospheric oxygen acts as an oxidant in this reaction. Having optimized the reaction conditions, the generality of the procedure was studied using a number of substituted aromatic aldehydes and benzene-1,2-diamine (Table 4). The effect of electron-releasing and electron-withdrawing substituents on the aromatic ring of aldehydes upon the reaction was investigated. As Table 4 indicates, electron-releasing substituents slightly decreased the yields and

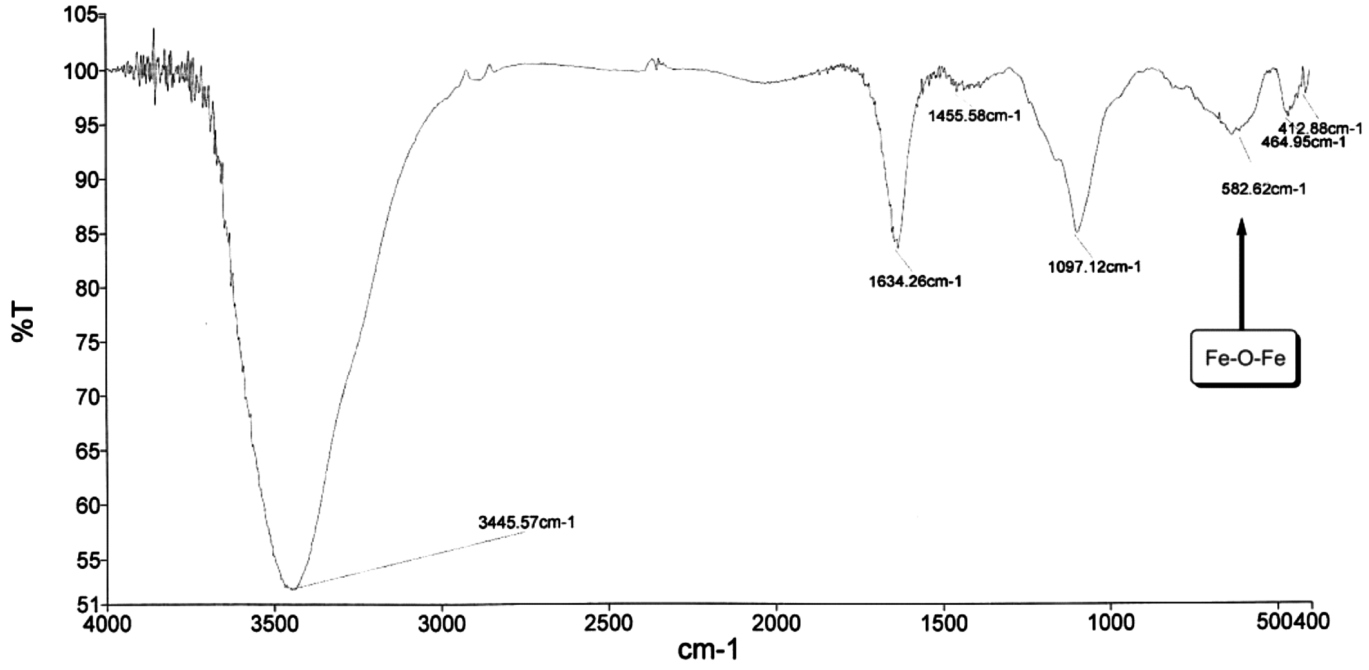
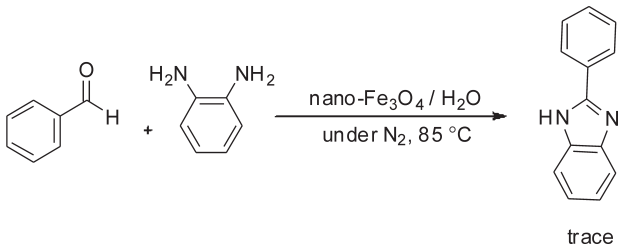


Figure 5 FTIR spectrum of the nano-Fe_3O_4

Table 2 Effect of catalyst loading (nano-Fe_3O_4) on the reaction of *o*-phenylenediamine with benzaldehyde in water as the model reaction.

Entry	Amount of catalyst/g	Yield [a]/%	Time/min
1	0.011	95	45
2	0.005	55	85
3	0.022	96	45
4	0.033	96	45

[a] Yield of purified product.



Scheme 2
Reaction scheme in absence of oxygen.

increased the reaction times (Table 4, entries 5, 6, and 8–10), and electron-withdrawing substituents had no significant effects on the yields of products, but slightly decreased the reaction times (Table 4, entries 2–4, 7, 11–13). In fact, electron-releasing substituents deactivate aldehyde for nucleophilic attack of benzene-1,2-diamine, but electron-withdrawing groups activate the aldehyde. These are in accordance with the proposed mechanism.

To recognize the applicability of our method in larger scale, we examined several reactions in scale of 10 mmol (more than 1 g). For this purpose, benzaldehyde or its derivative (10 mmol) was reacted with 1,2-diaminobenzene (10 mmol) in the presence of nano-Fe_3O_4 (1.5 mmol, 0.347 g) at 85 °C. The respective results are summarized in Scheme 3. As shown in Scheme 3, the reactions were successfully performed at the larger scale without significant loss of the yields.

To compare the applicability and the efficiency of our catalysts with the reported catalysts for the synthesis of benzimidazoles, we have tabulated the results of these catalysts in Table 5. As shown in Table 5, nano-Fe_3O_4 remarkably has improved the synthesis of benzimidazoles in different terms e.g. reaction time, yield and turn-over frequency (TOF) of the reaction. The reaction times were shorter, and the yields and TOFs were higher when our catalyst was utilized.

Table 3 Effect of solvent in the reaction of *o*-phenylenediamine with benzaldehyde as the model reaction.

Entry	Solvent	Yield [a]/%	Time/min
1	Water	95	45
2 [b]	Ethyl acetate	80	70
3 [b]	Acetonitrile	30	60
4	Dioxane	35	70
5 [b]	Diethyl ether	25	80
6	Xylene	50	100
7 [b]	THF	50	85
8	DMSO	60	120
9	DMF	55	120

[a] Yield of purified product.
[b] The reaction was carried out under reflux conditions.

3.3. Proposed Mechanism

As it is shown in Scheme 4, the plausible mechanism, which is consistent with the literature,[10a] has been given in two steps: preparation of intermediate III followed by its oxidation. At first, the aromatic aldehyde is activated by Fe(III) in the structure of nano-Fe_3O_4, and then, benzene-1,2-diamine attacks the carbonyl g)roup of the activated aldehyde and produces I and also the intermediate II. The latter is generated *via* the elimination of H_2O. In the next step, intermediate II is activated again by Fe(III) to g)ive III. Afterwards, molecular oxygen is bound to Fe(II) within the structure of nano-Fe_3O_4 resulting in oxidation of Fe(II) to Fe(IV), then Fe(IV) oxidizes III to IV, respectively, in two steps, and regenerate Fe(II) (initial state of the catalyst). Finally, atmospheric O_2, oxidizes Fe(II) to high-valent oxidoiron(IV), and this cycle continues until completion of the reaction.

4. Spectral Data of Benzimidazoles

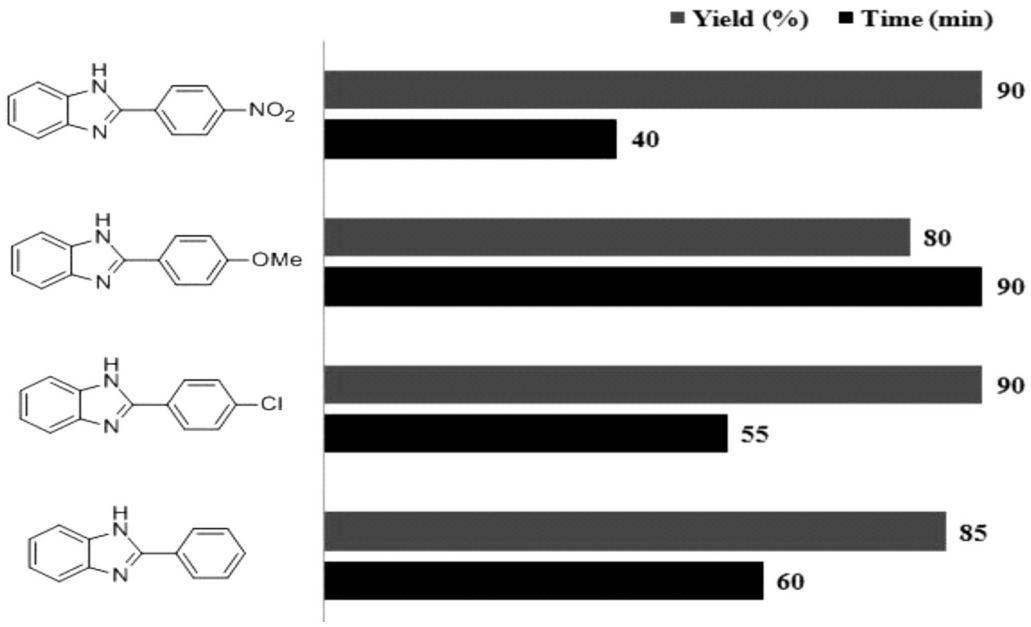
2-Phenyl-1H-benzimidazole (**3a**)

Colourless solid; 97 % yield (0.188 g)); R_f (MeOH/DCM: 1/19) = 0.46; IR (KBr): 1620 (C=N), 3444 cm^{-1} (NH). ^1H NMR (DMSO-d_6,

Table 4 The preparation of benzimidazole derivatives from *o*-phenylenediamine and aromatic aldehydes using nano-Fe_3O_4 under atmospheric oxygen in water.

Entry	Aldehydes	Compound **3**	Yield [a]/%	Time/min	M.P./°C
1	Benzaldehyde	3a	95	45	291–292 [10a]
2	2-chlorobenzaldehyde	3b	91	55	232–233 [10a]
3	3-chlorobenzaldehyde	3c	93	43	231–233 [10a]
4	4-chlorobenzaldehyde	3d	96	40	290–292 [10a]
5	4-methylbenzaldehyde	3e	90	55	270–271 [10a]
6	4-methoxybenzaldehyde	3f	94	70	226–227 [10a]
7	4-cyanobenzaldehyde	3g	93	60	262–263 [10a]
8	2-hydroxybenzaldehyde	3h	90	95	241–242 [10a]
9	3-hydroxybenzaldehyde	3i	94	75	183–184 [10a]
10	4-hydroxybenzaldehyde	3j	85	85	254–255 [10a]
11	2,6-dichlorobenzaldehyde	3k	93	100	279–280 [10a]
12	3-nitrobenzaldehyde	3l	95	35	205–207 [10a]
13	4-nitrobenzaldehyde	3m	97	30	315–316 [10a]
14	2-naphthaldehyde	3n	95	65	217–218 [10a]
15	2-thiophenecarbaldehyde	3o	89	90	329–330 [10a]
16	2-pyridinecarbaldehyde	3p	92	45	218–219 [10a]

[a] Yield of purified product.



Scheme 3
The large-scale preparation of several benzimidazole derivatives using nano-Fe_3O_4.

250 MHz): δ 7.14–7.25 (m, 2H), 7.44–7.61 (m, 5H), 8.20 (d, J = 7.2 Hz, 2H), 12.94 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 122.1, 126.4, 128.4, 128.9, 129.2, 129.8, 130.1, 151,2; Mass *m/z* (%): 194 (M^+, 97.4), 149 (45.6), 115 (20.2), 97 (27.2), 73 (46.5), 57 (100.0); Anal. Calcd. for C_{13} H_{10} N_2 (194.235): C, 80.39; H, 5.19; N, 14.42. Found: C, 80.30; H, 5.25; N, 14.39.

2-(3-Chlorophenyl)-1H-benzimidazole (**3c**)

Colourless solid; 95 % yield (0.217 g)); R_f (MeOH/DCM: 1/19) = 0.54; IR (KBr): 1623 (C=N), 3445 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 7.21 (m, 2H), 7.49–7.64 (m, 4H), 8.13 (dd, J_1 = 6.6 Hz, J_2 = 1.8 Hz, 1H), 8.21 (s, 1H), 13.04 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 111.5, 119.0, 122.0, 122.9, 125, 126, 129.5, 130.9, 132.1, 133.7, 143.5, 149.7; Mass *m/z* (%): 230 (M^++2, 16.1), 229 (M^++1, 25.0), 228 (M^+, 38.6), 167 (20.5), 149 (62.8), 111 (19.6), 94 (99.8), 71 (37.3), 55 (100.0); Anal. Calcd. for C_{13} H_9 Cl N_2 (228.681): C, 68.28; H, 3.97; N, 12.25. Found: C, 68.21; H, 4.09; N, 12.18.

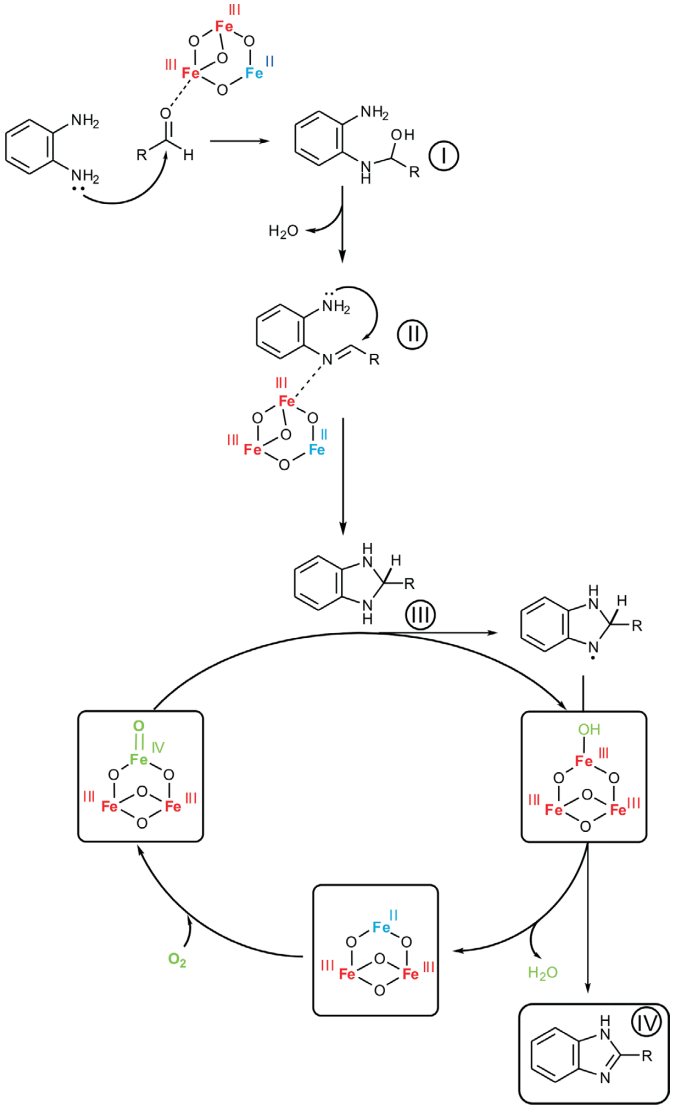
2-(4-Methylphenyl)-1H-benzimidazole (**3e**)

Colourless solid; 95 % yield (0.197 g)); R_f (MeOH/DCM: 1/19) = 0.52; IR (KBr):1620 (C=N), 3649 cm^{-1} (NH); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.35 (s, 3H), 7.15–7.20 (m, 2H), 7.33(d, J = 8.1 Hz, 2H), 7.46–7.56 (m, 2H), 8.07 (d, J = 8.1 Hz, 2H), 12.84 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 20.9, 121.9, 126.3, 127.4, 128.9, 129.4, 139.5, 151.3; Mass *m/z* (%): 208 (M^+, 66.5), 149 (49.1), 111 (18.0), 83

Table 5 Comparison of the results for the reaction of *o*-phenylenediamine with benzaldehyde by our new catalytic system with those obtained by the recently reported catalysts.

Entry	Reagent	Time/min	Yield [a]/%	Ref.
1 [b]	Nano-Fe_3O_4	45	95	–
2	Zn^{2+}-K10-clay (clayzic)	1440	94	25a
3	Pyridine/$SOCl_2$	1080	92	25b
4	Air in capped tube	960	85	25c
5	PEG 400 (at 110 °C)	360	90	25d
6	Zeolite	180	81	25e
7	Polyaniline-sulfate salt	120	92	25f
8	$MnZrO_3$-450 (at 80 °C)	60	95	25g

[a] Yield of purified product.
[b] Our method.



Scheme 4
The proposed mechanism for the synthesis of benzimidazoles.

(44.9), 57 (100.0); Anal. Calcd. for $C_{14}H_{12}N_2$ (208.262): C, 80.74; H, 5.81; N, 13.45. Found: C, 80.69; H, 5.90; N, 13.38

4-(1H-benzimidazol-2-yl)benzonitrile (**3g**)

Colourless solid; 94 % yield (0.206 g)); R_f (MeOH/DCM: 1/19) = 0.32; IR (KBr): 1612 (C=N), 2230 cm^{-1} (CN); ^1H NMR (DMSO-d_6, 250 MHz): δ 7.22–7.24 (m, 2H), 7.50–7.70 (m, 2H) 7.97 (d, J = 8.3 Hz, 2H), 8.31(d, J = 8.3 Hz, 2H), 13.17 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 111.8, 118.5, 119.3, 122.2, 123.2, 126.4, 126.9, 132.9, 134.2, 149.3; Mass m/z (%): 220 (M^++1, 9.7), 219 (M^+, 14.1), 149 (18.6), 97 (19.6), 69 (100.0), 57 (82.1); Anal. Calcd. for $C_{14}H_9N_3$ (219.245): C, 76.70; H, 4.14; N, 19.17. Found: C, 76.63; H, 4.21; N, 19.11.

3-(1H-benzimidazol-2-yl)phenol (**3i**)

Colourless solid; 94 % yield (0.197 g)); R_f (MeOH/DCM: 1/19) = 0.36; IR (KBr): 1620 (C=N), 3261 cm^{-1} (OH, NH); ^1H NMR (DMSO-d_6, 250 MHz): δ 6.86–6.89 (m, 1H), 7.16–7.19 (m, 2H), 7.32 (t, J = 8.1 Hz, 1H), 7.55–7.58 (m, 4H), 9.81 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 112.6, 117.0, 117.2, 122.1, 129.6, 131.2, 151.4, 157.7; Mass m/z (%): 212 (M^++2, 1.5), 211 (M^++1, 8.2), 210 (M^+, 14.6), 150 (9.9), 137 (15.2), 111 (19.0), 97 (38.6), 83 (56.4), 70 (23.7), 55 (100.0); Anal. Calcd. for $C_{13}H_{10}N_2O$ (210.234): C, 74.27; H, 4.79; N, 13.33. Found: C, 74.19; H, 4.85; N, 13.32.

2-(2,6-Dichlorophenyl)-1H-1,3-benzimidazole (**3k**)

Colourless solid; 91 % yield (0.239 g)). R_f (MeOH/DCM: 1/19) = 0.22, IR (KBr): 1627 (C=N), 3447 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 250 MHz) δd (ppm): 7.11–7.30 (m, 7H), 7.54 (s, 1H). ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ (ppm): 115.4, 122.2, 128.3, 130.4, 132.4, 135.0, 137.0, 146.6; Mass m/z (%): 265 (M^++2, 7.0), 263 (M^+, 100.0), 228 (58.0), 193 (71.0). Anal. Calcd. for $C_{13}H_8Cl_2N_2$: C, 59.34; H, 3.06; N, 10.65. Found: C, 59.16; H, 3.15; N, 10.63.

2-(4-Nitrophenyl)-1H-benzimidazole (**3m**)

Yellow solid; 90 % yield (0.215 g)); R_f (MeOH/DCM: 1/19) = 0.44; IR (KBr): 1338, 1516 (NO_2), 1620 (C=N), 3421 cm^{-1} (NH); ^1H NMR (DMSO-d_6, 250 MHz): δ 7.22–7.26 (m, 2H), 7.62 (m, 2H), 8.38 (m, 4H), 13.27 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 111.7, 119.3, 122.3, 123.4, 124.1, 127.2, 135.9, 147.6, 148.9; Mass m/z (%): 240 (M^++1, 4.3), 210 (7.9), 181 (3.5), 150 (6.6), 123 (10.2), 97 (32.6), 57 (100.0); Anal. Calcd. for $C_{13}H_9N_3O_2$ (239.232): C, 65.27; H, 3.79; N, 17.56. Found: C, 65.19; H, 3.86; N, 17.52.

2-(2-Thienyl)-1H-benzimidazole (**3o**)

Yellow solid; 93 % yield (0.186 g)); R_f (MeOH/DCM: 1/19) = 0.49; IR (KBr): 1620 (C=N), 3447 cm^{-1} (NH); ^1H NMR (DMSO-d_6, 250 MHz): δ 7.16–7.22 (m, 3H), 7.48–7.58 (m, 2H), 7.73 (d, J = 3.1 Hz, 1H), 7.82 (d, J = 2.7 Hz, 1H), 12.96 (s, 1H); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 111.0, 118.4, 121.7, 122.6, 126.6, 128.2, 128.7, 133.6, 134.6, 147.0; Mass m/z (%): 201(M^++1, 2.4), 200 (M^+, 5.4), 167 (5.6), 149 (29.9), 123 (11.4), 94 (23.6), 73 (49.1), 57 (100.0); Anal. Calcd. for $C_{11}H_8N_2S$ (200.258): C, 65.98; H, 4.03; N, 13.99. Found: C, 65.95; H, 4.09; N, 13.92.

5. Conclusion

In summary, we have utilized nano-Fe_3O_4/O_2 as and efficient, green and heterogeneous catalytic system for the synthesis of benzimidazole derivatives in water for the first time. The promising points of this method are safety, low cost, ease of separation and reusability of the catalyst, minimization of chemical wastes, mild reaction conditions, high yields, simple experimental procedure, short reaction times and compliance with the green chemistry protocols.

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