

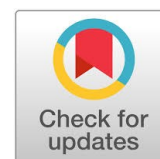


Original Research Article

Efficient and green synthesis of trisubstituted imidazoles by magnetically nanocatalyst and microwave assisted

Hamid Reza Mardani*, Mehdi Forouzani, Rasoul Emami

Department of Chemistry, Payame Noor University (PNU), PO BOX 19395-3697 Tehran, Iran



ARTICLE INFORMATION

Received: 25 October 2018
Received in revised: 9 November 2018
Accepted: 10 November 2018
Available online: 4 February 2019

DOI: [10.33945/SAMI/AJGC/2019.4.9](https://doi.org/10.33945/SAMI/AJGC/2019.4.9)

KEYWORDS

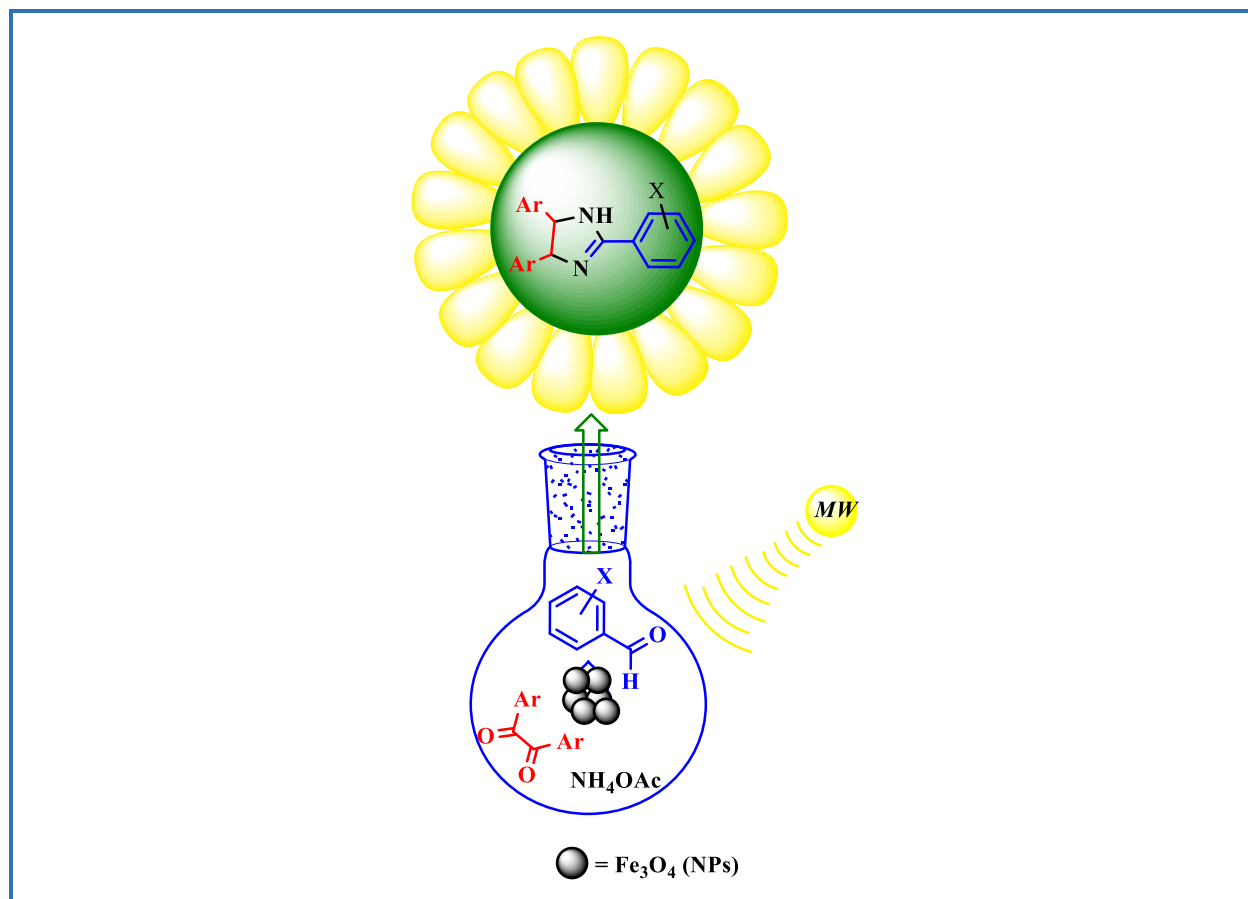
Imidazole
Benzil
Microwave irradiation
Green synthesis
Magnetic nanoparticles

ABSTRACT

Fe₃O₄ magnetic nanoparticles (Fe₃O₄ MNPs) were prepared and used as an eco-friendly, reusable, low-cost and efficient catalyst for the synthesis of 2,4,5-trisubstituted imidazoles *via* three-component reaction of aromatic aldehydes with benzil and ammonium acetate under low power microwave irradiation and solvent-free condition. This one-pot procedure was very simple with good to excellent yields. Easy separation of Fe₃O₄ MNPs from the reaction mixture by an external magnet and the reusability of the catalyst were the considerable points of the reaction.

© 2019 by SPC (Sami Publishing Company), Asian Journal of Green Chemistry, Reproduction is permitted for noncommercial purposes.

Graphical Abstract



Introduction

Multi-substituted imidazoles are an important class of heterocyclic compounds with wide biological and pharmaceutical applications [1–3]. The substituted imidazoles are well known as inhibitors of P38 MAP kinase [4] and therapeutic agents [5]. Imidazoles chemistry, because of its use in ionic liquids [6] and in *N*-heterocyclic carbenes (NHCs) [7], gave a new dimension in the area of organometallics and “green chemistry”. Other important features of these compounds are including, anti-inflammatory [8], anti-parasitic [9], antifungal [10], antidepressant [11], anti tubercular [12], anticancer [13] and antiviral activities [14], and anti leishmanial activity against the leishmania donovani [15].

There are many methods available in the literature which describe reliable synthesis of 2,4,5-trisubstituted imidazoles *via* three-component condensation of aldehydes, benzyl and ammonium acetate at the presence of various catalytic species, such as acetic acid [16], silica sulfuric acid [17], I₂ [18], (Zr(acac)₄) [19], *L*-proline [20], montmorillonite K10 [21], Cu(NO₃)₂-zeolite [22], ionic liquids [23–25], DABCO [26], urea-functionalized Fe₃O₄/SiO₂ [27] and Fe₃O₄@SiO₂.HM.SO₃H under

microwave irradiation at 450 W [28]. Despite the efficiency of the reported protocols, some of them suffer from some drawbacks such as long reaction time, harsh reaction conditions, corrosiveness, toxicity, cost, and reusability of catalyst.

In recent years, Fe_3O_4 MNPs have attracted a great attention in many different fields due to their intrinsic properties including, high surface area, low toxicity, super-paramagnetic behavior, and easy separation and recovery from the reaction medium by magnetic decantation [27–29]. In other words, the use of microwave for the synthesis of organic compounds under solvent-free condition has proved to be efficient, safe and environmentally benign technique, with shorter reaction time, high yields, and easier work-up [23, 30–32]. However, incorporation of the cyclo condensation pathway with MW irradiation and property of Fe_3O_4 MNPs causes imidazoles be achieved in higher yields and shorter time. Therefore, in this research study, we introduced the Fe_3O_4 MNPs as a green heterogeneous catalyst for the synthesis of 2,4,5-trisubstituted imidazoles *via* the three-component reaction of various aromatic aldehydes with ammonium acetate and benzil under solvent-free condition and low power microwave irradiation (Scheme 1).

Experimental

Materials and Methods

Chemical materials were purchased from Merck and aldrich chemical companies in high purity. Microwave irradiation was carried out by a kenwood microwave oven with power output of 1000 W. The progress of the reactions and purity of the products were monitored by TLC (thin layer chromatography). The melting points were determined using the electro-thermal-IA9200 melting point apparatus. Fourier transform infrared spectroscopy (FT-IR) was recorded on a PERKIN-ELMER RXI spectrometer using KBr pressed powder discs. The NMR spectra were measured in pure deuteriated dimethyl sulfoxide (DMSO-d_6) as solvent on a Bruker avance 400 MHz instrument (^1H NMR 400 MHz) with tetramethylsilane (TMS) as the internal reference. The XRD data of the synthesized nanoparticle was obtained with a Bruker x-ray diffractometer (Advanced-D8) using $\text{Cu-K}\alpha$ radiation.

Preparation of nano catalyst

Synthesis of the Fe_3O_4 nanoparticles was carried out using a modified procedure [33]. A typical procedure, 5.2 g of FeCl_3 and 2.0 g of FeCl_2 were successively dissolved in 25 mL of double-distilled water containing 0.85 mL of 12.1 N HCl. The resulting solution was then added dropwise into 250 mL of 1.5 M NaOH solution under vigorous stirring. The last step generated an instant black precipitate.

The precipitate was isolated in the magnetic field, and the supernatant was removed from the precipitate by decantation.

General procedure for synthesis of 2,4,5-trisubstitutedimidazoles

The aromatic aldehyde (1 mmol), benzils (1 mmol), NH_4OAc (5 mmol, 0.385 g) and catalyst (Fe_3O_4 , 0.05 gr) were mixed thoroughly in a glass vessel. The reaction mixture was irradiated in a domestic microwave oven at 200 W for appropriate time. After completion of the reaction, as monitored with TLC, the reaction mixture was cooled at room temperature. Then, 10 mL acetone was added into crude reaction mixture and the catalyst was separated using an external magnet. The products were obtained by the addition of 10 mL cold water to the acetone solution. Further purification by column chromatography and recrystallization gave the desired products. The products were characterized on the basis of their melting point, IR, ^1H , and ^{13}C NMR spectra. It was found that the recovered catalyst could be used directly for five cycles without noticeable drop in the catalytic activity.

2,4,5-Triphenyl-1H-imidazole

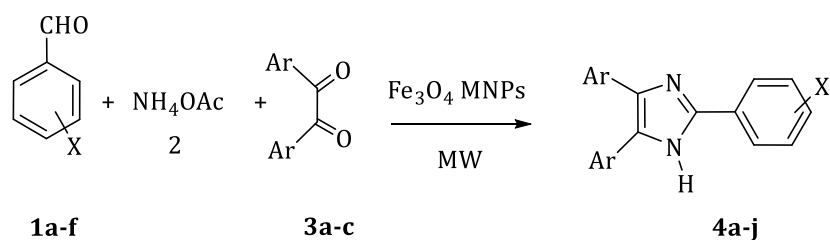
mp 273–275 °C, IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3434, 2993, 2470, 1638, and 1216. ^1H NMR ($\text{CDCl}_3/\text{DMSO-d}_6$): δ 12.61 (1H, brs), 7.42–8.12 (15H, m). ^{13}C NMR ($\text{CDCl}_3/\text{DMSO-d}_6$): δ 136.5, 129.1, 128.5, 127.2, 122.1. Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_2$: C, 85.11; H, 5.44; N, 9.45; Found: C, 85.02; H, 5.1; N, 9.12.

2-(4-Methoxy-phenyl)-4,5-diphenyl-1H-imidazole

mp 227–229 °C, IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3428, 2893, 2465, 1636, and 1216. ^1H NMR ($\text{CDCl}_3/\text{DMSO-d}_6$): δ 3.85 (s, 3H), 12.52 (1H, brs), 8.02–8.05 (2H, d), 7.25–7.59 (10H, m), 6.93–6.96 (2H, d), 3.85 (3H, s). ^{13}C NMR ($\text{CDCl}_3/\text{DMSO-d}_6$): δ 159.1, 145.7, 132.8, 127.6, 126.5, 126.3, 122.7, 113.2, 54.6. Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$: C, 80.96; H, 5.56; N, 8.58; Found: C, 80.68; H, 5.23; N, 8.42.

2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole

mp 259–262 °C, IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 3447, 1620, and 1519. ^1H NMR ($\text{CDCl}_3/\text{DMSO-d}_6$): δ 12.71 (br, s, 1H), 7.76–7.89 (d, 2H), 7.44–7.51 (d, 2H), 7.10–7.41 (m, 10H). ^{13}C NMR ($\text{CDCl}_3/\text{DMSO-d}_6$): δ 124.9,



Scheme 1. Synthesis of trisubstitutedimidazoles using Fe_3O_4 MNPs under solvent-free and microwave irradiation conditions.

126.3, 126.8, 128.1, 129.2, 129.9, 132.3, 143.9. Anal. Calcd. for $C_{21}H_{16}N_2$: C, 76.25; 76.14; H, 4.53; 4.55; N, 8.47; Found: C, 76.14; H, 4.55; N, 8.37.

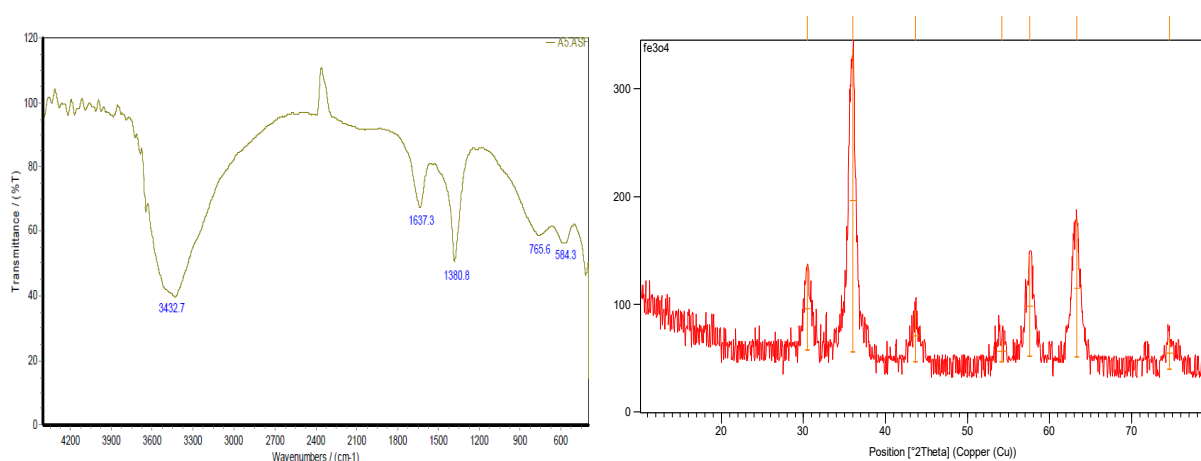
2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole

mp 263–265 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3450, 3070, 1615, and 1320. ^1H NMR (400 MHz, DMSO- d_6): δ 12.68 (s, 1H), 8.15 (d, 2H), 7.50–7.13 (m, 12H). ^{13}C NMR (400 MHz, DMSO- d_6): 146.1, 130.5, 129.6, 129.1, 128.4, 127.2, 127.0, 126.6, 125.5, 125.1, 123.0, 116.2. Anal. Calcd. for $C_{21}H_{15}\text{BrN}_2$: C, 67.21; H, 4.03; N, 7.47; Found: C, 67.06; H, 3.71; N, 7.21.

Results and Discussion

Fe_3O_4 MNPs were synthesized according to the reported procedures in the literature [28]. The nano catalyst structure was characterized using FT-IR, SEM, and EDX [36]. For Fe_3O_4 nanoparticles, the broad peak observed at 584 cm^{-1} and 765 cm^{-1} should be attributed to the Fe–O stretching absorption, the peaks at 1637 and 3432 cm^{-1} are attributed to the O–H of H_2O , similar to the literature. The XRD pattern of the prepared Fe_3O_4 nanomaterial was similar to the references information of library data. It has got 9 line, the position and relative intensities of the peaks are compatible with the cubic crystals. The average crystallite sizes of Fe_3O_4 was found to be 18.5 nm. The EDX spectrum is demonstrated Fe and O elements in sample. The FESEM image showed a tiny spherical mushroom morphology for Fe_3O_4 (Figure 1).

In the next step, to assess the catalytic activity of Fe_3O_4 MNPs in the synthesis of 2,4,5-trisubstituted imidazoles, the three component condensation of *P*-hydroxybenzaldehyde **1b** (1 mmol) with NH_4OAc **2** (5 mmol) and benzil **3a** (1 mmol) was investigated as a model reaction under different conditions, and the results are summarized in Table 1. It was observed that, when the model reaction was carried out in the absence of any catalyst under solvent-free condition and microwave irradiation at 200 W, no desired product was formed after 10 min (Table 1, entry 1).



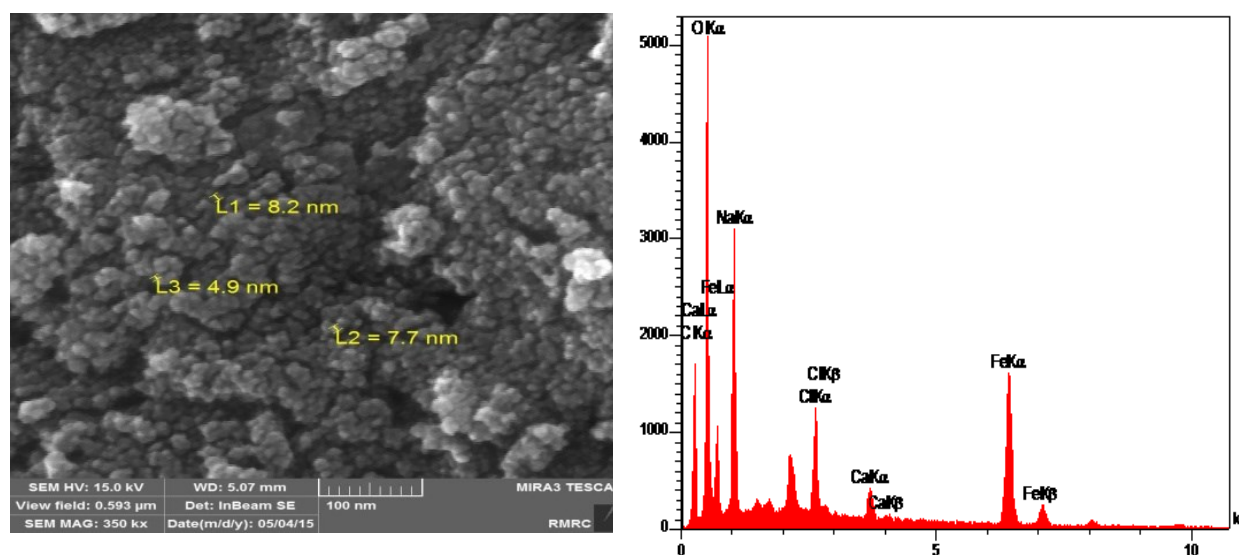


Figure 1. The FT-IR spectrum, XRD pattern, EDX and FESEM image of the Fe_3O_4

Table 1. Optimization of reaction conditions for the synthesis of 2-(*P*-hydroxyphenyl)-4,5-diphenyl imidazole **4b**

Entry	Catalyst (g)	Solvent	Power(w)	Time (min)	Yield (%) ^a
1	-	-	200	10	-
2	SiO_2 (0.2)	-	400	10	trace
3	BaCl_2 (0.2)	-	400	10	60
4	Na_2SO_4 (0.1)	-	400	10	22
5	Fe_3O_4 (0.05)	-	200	10	95
6	Fe_3O_4 (0.01)	-	200	10	20
7	Fe_3O_4 (0.1)	-	200	10	97
8	Fe_3O_4 (0.05)	-	100	10	75
9	Fe_3O_4 (0.05)	-	400	10	95
10	Fe_3O_4 (0.05)	H_2O	200	10	50
11	Fe_3O_4 (0.05)	$\text{CH}_3\text{CO}_2\text{H}$	200	10	60
12	Fe_3O_4 (0.05)	EtOH	200	10	50
13	Fe_3O_4 (0.05)	THF	200	10	70
14	Fe_3O_4 (0.05)	CH_2Cl_2	200	10	50
15	Fe_3O_4 (0.05)	Et_2O	200	10	50

^a Yields refer to isolated products

Table 2. Fe₃O₄ MNPs catalyzed synthesis of 2,4,5-trisubstituted imidazoles under solvent-free and microwave irradiation conditions^a

Entry	R	X	Yield (%) ^b	Time(min)	MP (°C)/observe	MP (°C)/report
1	H	H	85	20	273-275	272-273 [18]
2	H	<i>p</i> -OH	95	10	265-266	268-270 [34]
3	H	<i>p</i> -Cl	87	25	259-261	262-264 [18]
4	H	<i>p</i> -OCH ₃	85	30	227-229	230-232
5	H	<i>p</i> -Br	80	15	263-265	261-263
6	H	<i>m</i> -NO ₂	90	10	313-315	308-309 [17]
7	F	<i>p</i> -OH	90	35	264-267	-
8	OMe	H	80	50	198-202	-
9	OMe	<i>p</i> -OH	95	60	217-219	-
10	H	<i>o</i> -Cl	87	25	195-196	195-196

^a The reaction condition: benzil (1 mmol), aldehyde (1 mmol), ammonium acetate salt (5 mmol), solvent-free, microwave irradiated at 200 W

^b Yields of the isolated product

To explore the suitable reaction conditions, the above model reaction was performed at the presence of various catalysts such as nano SiO₂, BaCl₂, Na₂SO₄ and Fe₃O₄ MNPs under solvent-free and microwave irradiation conditions (Table 1, entries 2-5). The Fe₃O₄ MNPs demonstrated superior catalytic activity among those examined (Table 1, entry 5). To investigate the effect of solvent, the condensation reaction of the model substrates was carried out in different solvents including CH₂Cl₂, Et₂O, THF, EtOH and H₂O using 0.05 g Fe₃O₄ MNPs under the microwave irradiation conditions (Table 1, entries 10-15). Screening the solvent in this reaction revealed that the under solvent-free conditions, highest yield of the desired product is obtained as compared to the tested solvents (Table 1, entry 5).

We also evaluated the amount of catalyst required for this transformation. The amount of Fe₃O₄ MNPs, which afforded the best yields, was 0.05 g. Increasing the amount of catalyst did not change the yield dramatically (Table 1, entry 7), whereas reduction of it significantly decreased the product

yield (Table 1, entry 6). Then the reaction was studied at the presence of different molar ratios of NH_4OAc (1-8 mmol) as an ammonia source, and the best result was obtained with 5 mmol of NH_4OAc . Power of the microwave instrument was also optimized and the best operating power was found to be 200 W.

To explore the generality and applicability of this catalyst a variety of aromatic aldehydes reacted with benzils and ammonium acetate under the optimal reaction conditions and the results are presented in Table 2. Aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and in all cases the desired product was synthesized in high yield. As seen in Table 2, when 4,4'-dimethoxybenzil **3c** was used instead of benzyl **3a**, the reaction time was increased (Table 2, entries 8 and 9). The structure of products **4a-j** was characterized on the basis of their ^1H and ^{13}C NMR, IR and mass spectroscopic data.

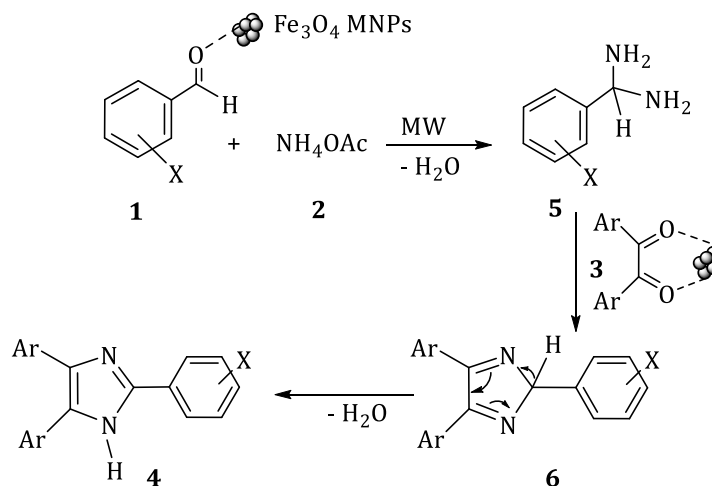
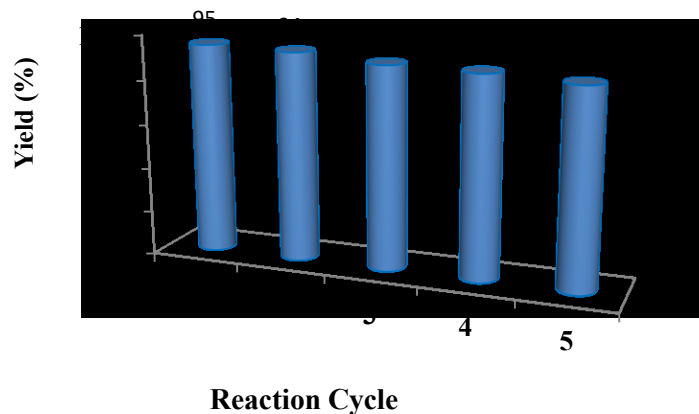
To evaluate the recyclability and stability of the catalyst, we designed a set of experiments by conducting successive condensation of model substrates using the recovered Fe_3O_4 MNPs under by applying the optimized conditions. After the completion of the first reaction run, acetone was added to the reaction mixture and catalyst was easily removed by an external magnet and recovered simply by washing with EtOH, and vacuum drying, and then reused for at least 4 times without observation noticeable drop in activity (Figure 2).

The proposed mechanism for the synthesis of trisubstituted imidazoles **4** can be described as shown in Scheme 2 [20–35]. Fe_3O_4 MNPs act as Lewis acid and play a significant role in increasing the electrophilic character of the aldehyde. Subsequently, the reaction of the activated aldehyde with two molecules of ammonia to afford diamine intermediate **5**, which condenses with the carbonyl carbons of the benzyl at the presence of Fe_3O_4 MNPs followed by dehydration to form the imino intermediate **6**, which rearranged to the desired trisubstituted imidazole **4**.

Conclusion

In this study, we have confirmed a simple method for the synthesis of 2,4,5-trisubstituted imidazoles using Fe_3O_4 MNPs as an eco-friendly, reusable, low-cost, and efficient catalyst under low power microwave irradiation and solvent-free condition. Environmental acceptability, high yield of product, simple workup, easy removal, and recyclability of the catalyst are the most important features of this atom economical protocol.

Figure 2. Reusability of Fe_3O_4 NPs for the synthesis of **4b**, [Reaction conditions: benzil (1 mmol), *P*-hydroxybenzaldehyde (1 mmol) and NH_4OAc (1 mmol), solvent-free, microwave irradiated at 200 W; reaction time (10 min)]



Scheme 2. Proposed mechanism for the synthesis of trisubstituted imidazoles.

Acknowledgements

The authors are grateful for the financial support of the Payame Noor University (PNU) of Iran.

Disclosure Statement

No potential conflict of interest was reported by the authors.

References

- [1]. Lombardino J.G., Wiseman E.H. *J. Med. Chem.*, 1974, **17**:1182
- [2]. Lindberg P., Nordberg P., Alming T., Brandstorm A., Wallmark B. *J. Med. Chem.*, 1986, **29**:1327
- [3]. Pagano M.A., Andrzejewska M., Ruzzene M. *J. Med. Chem.*, 2004, **47**:6239

- [4]. Lee J.C., Laydon J.T., McDonnell P.C., Gallagher T.F., Kumar S., Green D., McNulty D., Blumenthal M.J., Keys J.R., Landvatter S.W., Strickler J.E., McLaughlin M.M., Siemens I.R., Fisher S.M., Livi G.P., White J.R., Adams J.L., Young P.R. *Nature*, 1994, **372**:739
- [5]. Heeres J., Backx L.J.J., Mostmans J.H., Vancustem J. *J. Med. Chem.*, 1979, **22**:1003
- [6]. Wasserscheid P., Keim W. *Angew. Chem. Int. Ed. Eng.*, 2000, **39**:3772
- [7]. Bourissou D., Guerret O., Gabbai F.P., Bertrand G. *Chem. Rev.*, 2000, **100**:39
- [8]. Mukherjee A., Kumar S., Seth M., Bhaduri A.P. *Ind. J. Chem. B*, 1989, **28**:391
- [9]. Ayhan-Kilcigil G., Altanlar N. *Turk. J. Chem.*, 2006, **30**:223
- [10]. Hadizadeh F.H., Hosseinzadeh V., Shariaty M., Kazemi S.J. *Pharm. Res.*, 2008, **7**:29
- [11]. Shingalapuri R.V., Hosamani K.M., Keri R.S. *Eur. J. Med. Chem.*, 2009, **44**:4244
- [12]. Ozkay Y., Işıkdag I., Incesu Z., Akalin G. *Eur. J. Med. Chem.*, 2010, **45**:3320
- [13]. Tonelli M., Simone M., Tasso B., Novelli F., Bioso V. *Bioorg. Med. Chem.*, 2010, **18**:2937
- [14]. Bhandari K., Srinivas N., Marrapu V.K., Verma A., Srivastava S.N., Gupta S. *Bioorg. Med. Chem. Lett.*, 2010, **20**:291
- [15]. Srinivas N., Plane S., Gupta N.S., Bhandari K. *Bioorg. Med. Chem. Lett.*, 2009, **19**:324
- [16]. Wolkenberg S.E., Wisnoski D.D., Leister W.H., Wang Y., Zhao Z., Lindsley C.W. *Org. Lett.*, 2004, **6**:1453
- [17]. Shaabani A., Rahmati A. *J. Mol. Catal. A*, 2006, **249**:246
- [18]. Kidwai M., Mothsra P., Bansal V., Somvanshi R.K., Ethayathulla A.S., Dey S., Singh T.P. *J. Mol. Catal. A*, 2007, **265**:177
- [19]. Khosropour A.R. *Ultrason. Sonochem.*, 2008, **15**:659
- [20]. Samai S., Nandi G.C., Singh P., Singh M.S. *Tetrahedron*, 2009, **65**:10155
- [21]. Teimouri A., Najafi Chermahini A.R. *J. Mol. Catal. A*, 2011, **346**:39
- [22]. Sivakumar K., Kathirvel A., Lalitha A. *Tetrahedron Lett.*, 2010, **51**:3018
- [23]. Xia M., Lu Y.D. *J. Mol. Catal. A*, 2007, **265**:205
- [24]. Chary M.V., Keerthysri N.C., Vupallapati S.V.N., Srinivasu V.N., Lingaiah N., Kantevari S. *Catal. Commun.*, 2013, **2008**:9
- [25]. Zang H., Su Q., Mo Y., Cheng B.W., Jun S. *Ultrason. Sonochem.*, 2010, **17**:749
- [26]. Murthy S.N., Madhav B., Nageswar Y.V.D. *Tetrahedron Lett.*, 2010, **51**:5252
- [27]. Maleki, A., Alirezvani, J. *Chil. Chem. Soc.*, 2016, **61**, 3 N°
- [28]. H. Naeimi, D. Aghaseyedkarimi. *New J. Chem.*, 2015, **39**:9415
- [29]. Rezayati S., Torabi Jafroudi M., Rezaee Nezhad E., Hajinasiri R., Abbaspour S. *Research on Chemical Intermediates*, 2016, **42**:5887
- [30]. Caddick S. *Tetrahedron Lett.*, 1995, **51**:10403

- [31]. Taghavi Fardood S., Ramazani A., Ayubi M., Moradnia F., Abdpour Sh., Forootan R. *Chem. Methodol.*, 2019, **3**:519
- [32]. Kargar-Dolatabadi A., Zare A. *Chem. Methodol.*, 2019, **3**:655
- [33]. Karami M., Gholami B., Hekmat-Zadeh T., Zare A. *Chem. Methodol.*, 2019, **3**:509
- [34]. Sangshetti J.N., Kokare N.D., Kothakar S.A., Shinde D.B. *Mont. Fur. Chem.*, 2008, **139**:125
- [35]. Abd El Aleem M., El-Remaily A.A. *Tetrahedron*, 2014, **70**:2971
- [36]. Mardani H.R., Ziari M. *Res. Chem. Int.*, 2018, **44**:6605

How to cite this manuscript: Hamid Reza Mardani*, Mehdi Forouzani, Rasoul Emami. Efficient and green synthesis of trisubstituted imidazoles by magnetically nanocatalyst and microwave assisted. *Asian Journal of Green Chemistry*, 3(4) 2019, 525-535. DOI: [10.33945/SAMI/AJGC/2019.4.9](https://doi.org/10.33945/SAMI/AJGC/2019.4.9)