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Facile and rapid synthesis of some novel polysubstituted imidazoles by employing magnetic Fe_3O_4 nanoparticles as a high efficient catalyst

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Multicomponent, one-pot, highly efficient, and environmentally adapted synthesis of some novel polysubstituted imidazoles by the use of various aldehydes, benzil, aliphatic, and aromatic primary amines and ammonium acetate in the presence of Fe_3O_4 nanoparticles as catalyst under solvent-free condition is explained. A highly efficient role of Fe_3O_4 nanoparticles as catalyst in this synthesis was shown. By this advantage, several polysubstituted imidazoles as pharmaceutical important molecules can be prepared in high yield and high purity. This method is very easy and rapid for the synthesis of imidazole derivatives. All products were deduced from their IR and NMR spectroscopic data. The Fe_3O_4 nanoparticles were characterized by powdered X-ray diffraction (XRD), transmission electron microscopy (TEM), and FT-IR spectroscopy.

Key Words: Benzil, polysubstituted imidazoles, aldehydes, amines, heterogeneous catalyst

Introduction

Multicomponent reactions (MCRs) are a special type of organic reaction that afford complex products from reaction of 3 or more simple starting materials in 1 pot. Because of the atom-economy, convergent character, operational simplicity, structural diversity, and complexity of the molecules in these reactions, they have attracted much attention.[1,2] The imidazoles and their derivatives are very important molecules because of their

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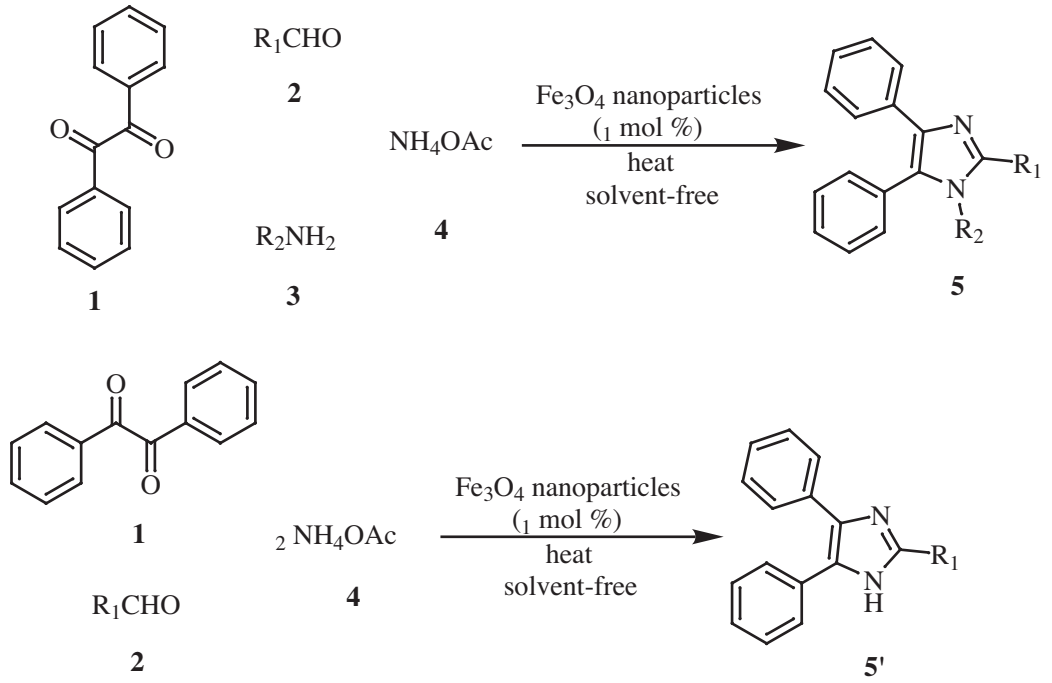
many applications in chemical processes, especially in pharmaceuticals.[3,4] Various substituted imidazoles act as inhibitors of p38 MAP kinase,[5] B-Raf kinase,[6] glucagon receptors,[7] plant growth regulators,[8] antitumorals,[9] and pesticides.[10]

There are many methods for the synthesis of polysubstituted imidazoles such as condensation of diones, aldehydes, primary amines, and ammonia in the presence of various acid catalysts;[11–13] N-alkylation of trisubstituted imidazoles;[14] and condensation of benzil or benzoin acetate with aldehydes, primary amines, and ammonia in the presence of copper acetate.[15,16] The first mentioned method is the most well-known and classical method. However, some of these methods involve long reaction times and unsatisfactory yields. Therefore, improvements in these syntheses have been sought continuously.

In recent years, magnetic nanoparticles (MNPs) of Fe_3O_4 have been attracting increasing interest in many different fields due to their intrinsic properties such as high surface area, low toxicity, superparamagnetic behavior, and easy separation and recovery from the reaction medium by magnetic decantation.[17]

In this work, the preparation, high activation, and regeneration of Fe_3O_4 nanoparticles as a high efficient catalyst in organic synthesis are shown. Using magnetic Fe_3O_4 nanoparticles not only gives high yield, purity, and short reaction time but also is a cheap, speedy, facile, and eco-friendly method throughout the course of the reaction.

In the scope of our previous works for the synthesis of heterocyclic compounds by inorganic solid acids and heterogeneous catalyst,[18] herein we report a new, simple, rapid, and one-pot procedure for the synthesis of tri- and tetrasubstituted imidazoles by using magnetic Fe_3O_4 nanoparticles with short reaction times, and high yields and purities (Scheme 1).



Scheme 1. Synthesis of polysubstituted imidazoles in the presence of magnetic nanoparticles Fe_3O_4 as catalyst.

Using benzil **1**, aromatic aldehydes **2**, aromatic and aliphatic amine **3**, ammonium acetate **4**, and magnetic Fe_3O_4 nanoparticles as catalyst under solvent-free conditions led to tetrasubstituted imidazoles **5**; in the absence of aromatic and aliphatic amine **3**, trisubstituted imidazoles **5'** were obtained.

Experimental

Transmission electron microscopy (TEM) studies of the nanostructures were carried out with a JEOL JEM 3010 instrument operating at an accelerating voltage of 300 kV. X-ray diffraction (XRD, D8, Avance, Bruker, axs) patterns were obtained for characterization of the heterogeneous catalyst. Melting points were measured on an electrothermal KSB1N apparatus. IR spectra were recorded in the matrix of KBr with a JASCO FT-IR-680 plus spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 and 100.62 MHz in $CDCl_3$ as solvent in the presence of tetramethylsilane as internal standard. TLC was performed on TLC-grade silica gel-G/UV 254 nm plates. The products were isolated and characterized by physical and spectral data and they were compared with authentic samples (Table 1).[13,19–29]

Table 1. Synthesis of polysubstituted imidazoles catalyzed by magnetic Fe_3O_4 nanoparticles.

Product	R^1	R^2NH_2	Time (min)	Yield[a] (%)	Mp (°C)/(lit.)
5a	C_6H_5	$C_6H_5CH_2NH_2$	20	96	170-172[18]
5b	4-Br-C_6H_4	$C_6H_5CH_2NH_2$	25	90	169-170[13]
5c	4-CH_3-C_6H_4	$C_6H_5CH_2NH_2$	45	98	163-166[19]
5d	4-Cl-C_6H_4	$C_6H_5CH_2NH_2$	30	85	160-162[19]
5e	2-Cl-C_6H_4	$C_6H_5CH_2NH_2$	25	85	193-195[20]
5f	3-NO_2-C_6H_4	$C_6H_5CH_2NH_2$	20	80	150-152[b]
5g	4-CH_3-C_6H_4	CyclohexylNH_2	40	75	160-161[21,22]
5h	4-OCH_3-C_6H_4	$C_6H_5CH_2NH_2$	20	90	148-151[23]
5i	2-OH-5-Br-C_6H_3	4-Cl-$C_6H_4NH_2$	25	98	156-158[b]
5j	4-Benzyloxy-C_6H_4	$C_6H_5CH_2NH_2$	25	96	138-139[b]
5k	2,4-di-Cl-C_6H_3	$C_6H_5CH_2NH_2$	25	95	216-219[b]
5l	4-CH_3-C_6H_4	$C_6H_5NH_2$	50	93	182-184[22]
5'a	C_6H_5	—	30	90	272-273[18]
5'b	3-Br-C_6H_4	—	35	89	120-122[24]
5'c	2-OH-C_6H_4	—	45	90	209-211[25]
5'd	2-OCH_3-C_6H_4	—	30	92	204-206[23]
5'e	4-OCH_3-C_6H_4	—	35	70	227-230[18]
5'f	4-Benzyloxy-C_6H_4	—	25	68	235-236[26]
5'g	2-Fluorenyle	—	55	97	283-286[b]
5'h	3-Indolyl	—	40	83	311-313[b]
5'i	4-Cl-C_6H_4	—	25	90	257-259[27]
5'j	3-NO_2-C_6H_4	—	10	91	308-309[28]

[a]Refers to isolated yields, [b]Novel compound

General procedure for preparation of Fe_3O_4 nanoparticles

To prepare Fe_3O_4 nanoparticles, 5.2 g of $FeCl_3$ and 2.0 g of $FeCl_2$ were successively dissolved in 25 mL of distilled water containing 0.85 mL of 12.1 N HCl. The resulting solution was 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.[30]

General procedure for the facile and rapid synthesis of 1,2,4,5-tetrasubstituted imidazoles by Fe_3O_4 nanoparticles

A mixture of aromatic aldehyde (1 mmol), benzil (1 mmol), primary amine (1 mmol), ammonium acetate (1 mmol), and magnetic Fe_3O_4 nanoparticles (1 mol%) was stirred at 80 °C in solvent-free conditions. The progress of reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and was solved in 50 mL of acetone and then was filtered. The obtained products were purified by crystallization from acetone-water (10:1). The products were characterized by IR, NMR, and through comparison of their physical properties with those reported in the literature.[13,19–29]

Hence, the general procedure for the synthesis of 2,4,5-trisubstituted imidazoles is the same as that for 1,2,4,5-tetrasubstituted imidazoles, but it needs 2 mmol of ammonium acetate instead of 1 mmol in the absence of primary amine.

Representative spectral data

1-Benzyl-2,4,5-triphenyl-1*H*-imidazole (compound **5a**): mp 162-164 °C; IR (KBr) (ν_{max}, cm^{-1}): 3061, 3026, 2308, 1601, 1521, 1497, 1350, 761, 696. ^{1}H-NMR (250 MHz, DMSO-d6): δ (ppm) 5.13(s, 2H), 7.18-8.41 (m, 20H). ^{13}C-NMR (62.69 MHz, DMSO-d_6)δ (ppm): 48.29, 126.00, 126.38, 126.81, 128.11, 129.08, 129.58, 129.90, 130.09, 130.98, 131.09, 135.09, 137.57, 148.09.

1-Benzyl-2-(4-bromophenyl)-4,5-diphenyl-1*H*-imidazole (compound **5b**): mp 169-170 °C; IR (KBr) (ν_{max}, cm^{-1}): 3059, 3027, 2938, 1599, 1479, 1358, 1070, 835, 758, 694. ^{1}H-NMR (400.13 MHz, DMSO-d6): δ (ppm) 4.86 (s, 2H), 6.61-7.46 (m, 19H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 49.41, 125.86, 126.51, 126.78, 127.53, 128.14, 128.25, 128.74, 128.87, 130.48, 130.79, 131.03, 131.79, 137.33.

1-Benzyl-4,5-diphenyl-2-*p*-tolyl-1*H*-imidazole (compound **5c**): mp 156-158 °C; IR (KBr) (ν_{max}, cm^{-1}): 3060, 3027, 2926, 1600, 1496, 1349, 826, 767, 694. ^{1}H-NMR (400.13 MHz, DMSO-d_6)δ (ppm): 2.08 (s, 3H), 4.91 (s, 2H), 6.61-7.40 (m, 19H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 22.52, 49.41, 127.15, 127.47, 127.94, 128.46, 129.22, 129.72, 129.92, 130.10, 130.45, 131.03, 132.23, 138.80, 140.01, 146.34.

1-Benzyl-2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (compound **5d**): mp 160-162 °C; IR (KBr) (ν_{max}, cm^{-1}): 3059, 3029, 2936, 1600, 1480, 1357, 1089, 835, 758, 693. ^{1}H-NMR (400.13 MHz, DMSO-d_6)δ (ppm): 4.9 (s, 2H), 6.60-7.50 (m, 19H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 48.31, 125.88, 126.55, 127.54, 129.13, 129.31, 130.28, 130.43, 130.74, 131.04, 134.18, 135.04, 136.81, 137.30, 138.22.

1-Benzyl-2-(2-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (compound **5e**): mp 139-140 °C; IR (KBr) (ν_{max},

cm^{-1}): 3062, 3026, 2930, 1602, 1485, 1349, 1079, 758, 690. ^{1}H-NMR (400.13 MHz, DMSO-d_6)δ (ppm): 4.74 (s, 2H), 6.42-7.42 (m, 19H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 43.17, 126.00, 126.50, 126.68, 127.48, 128.44, 128.69, 128.99, 129.15, 129.36, 129.74, 129.81, 130.33, 130.61, 130.89, 131.08, 131.15, 132.92, 133.80, 134.24, 134.95, 136.80, 137.65, 145.13.

1-Benzyl-2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (compound **5f**): mp 150-152 °C; IR (KBr) (ν_{max}, cm^{-1}): 3061, 3026, 2308, 1601, 1521, 1497, 1350, 810, 730, 696. ^{1}H-NMR (400.13 MHz, DMSO-d6): δ (ppm) 5.19 (s, 2H), 6.89 (d, J = 6.15 Hz, 2H), 7.21-7.63 (m, 14H), 8.04 (d, J = 7.8 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.57 (s, 1H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 47.42, 122.30, 122.59, 124.71, 125.67, 125.73, 126.71, 127.15, 127.84, 127.97, 128.56, 129.36, 129.93, 130.24, 131.57, 132.98, 133.51, 135.78, 144.23, 147.20. Anal. Calcd for $C_{28}H_{21}N_3O_2$ (431.49): C, 77.94; H, 4.91; N, 9.74. Found: C, 77.87; H, 4.83; N, 9.62.

1-Cyclohexyl-4,5-diphenyl-2-*p*-tolyl-1*H*-imidazole (compound **5g**): mp 160-161 °C; IR (KBr) (ν_{max}, cm^{-1}): 3058, 3020, 2930, 1600, 1495, 1349, 825, 766, 695. ^{1}H-NMR (400.13 MHz, $CDCl_3$)δ (ppm): 0.95 (m, 2H), 1.35-1.55 (m, 6H), 1.75 (m, 2H), 2.35 (s, 3H), 3.80-3.97 (m, 1H), 6.70-7.45 (m, 14H). ^{13}C-NMR (100.62 MHz, $CDCl_3$)δ (ppm): 21.45, 25.12, 26.21, 33.59, 58.31, 125.94, 126.01, 126.68, 127.60, 127.89, 127.97, 128.18, 128.65, 128.76, 128.89, 129.01, 129.04, 129.15, 129.50, 129.87, 132.25, 132.81, 134.77, 137.68, 138.74, 147.84.

1-benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (compound **5h**): mp 163-166 °C; IR (KBr) (ν_{max}, cm^{-1}): 3063, 3019, 2295, 1609, 1519, 1493, 1354, 696. ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ (ppm) 3.81(s, 3H), 5.08 (s, 2H), 6.82-7.56 (m, 15H), 7.58 (d, J = 2.3 Hz, 4H). ^{13}C-NMR (100.62 MHz, $CDCl_3$)δ (ppm): 47.16, 54.26, 112.95, 122.40, 124.94, 125.21, 125.71, 126.26, 127.00, 127.49, 127.52, 127.71, 128.02, 128.70, 129.37, 130.03, 130.12, 133.53, 136.64, 136.78, 146.94, 159.04.

1-(4-Chlorophenyl)-2-(2-hydroxy-5-bromophenyl)-4,5-diphenyl-1*H*-imidazole (compound **5i**): mp 156-158 °C; IR (KBr) (ν_{max}, cm^{-1}): 3458, 3063, 1659, 1593, 1578, 1211, 1174, 1096. ^{1}H-NMR (400.13 MHz, DMSO-d_6)δ (ppm): 6.92-8.53 (m, 17H), 13.06 (s, 1H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 115.17, 123.92, 125.53, 127.64, 134.31, 137.31, 139.26, 140.54, 151.31, 164.74, 166.94. Anal. Calcd for $C_{27}H_{18}BrClN_2O$ (501.80): C, 64.62; H, 3.62; N, 5.58. Found: C, 64.51; H, 3.53; N, 5.49.

1-Benzyl-2-(4-(benzyloxy)phenyl)-4,5-diphenyl-1*H*-imidazole (compound **5j**): mp 138-139 °C; IR (KBr) (ν_{max}, cm^{-1}): 2857, 1601, 1575, 1526, 1289, 1247, 1177. ^{1}H-NMR (400.13 MHz, DMSO-d_6) δ (ppm): 2.18 (s, 2H), 5.06 (s, 2H), 6.83-7.82 (m, 24H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 48.29, 70.03, 115.05, 123.79, 126.06, 126.38, 126.85, 127.41, 127.53, 128.11, 128.16, 128.68, 128.86, 129.89, 130.50, 131.14, 131.23, 134.70, 136.76, 137.75, 137.94, 148.02, 159.33. Anal. Calcd for $C_{35}H_{28}N_2O$ (492.61): C, 85.34; H, 5.73; N, 5.69. Found: C, 85.18; H, 5.61; N, 5.54.

1-Benzyl-2-(2,4-dichlorophenyl)-4,5-diphenyl-1*H*-imidazole (compound **5k**): mp 216-219 °C; IR (KBr) (ν_{max}, cm^{-1}): 3069, 2924, 1557, 1523, 1459, 1092. ^{1}H-NMR (400.13 MHz, DMSO-d_6)δ (ppm): 2.18 (s, 2H), 7.45-8.41 (m, 13H), 8.64 (d, J = 7.6 Hz, 1H), 8.77 (t, J = 8.4 Hz, 2H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 120.88, 121.13, 122.98, 123.47, 123.76, 125.00, 126.03, 126.82, 127.20, 127.39, 127.43, 127.56, 129.00, 129.58, 131.28, 132.31, 133.77, 135.20, 136.93, 145.22. Anal. Calcd for $C_{28}H_{20}Cl_2N_2$ (455.38): C, 73.85; H, 4.43; N, 6.15. Found: C, 73.71; H, 4.36; N, 6.09.

1,4,5-Triphenyl-2-*p*-tolyl-1*H*-imidazole (compound **5l**): mp 182-184 °C; IR (KBr) (ν_{max}, cm^{-1}): 3055, 3022, 2930, 1600, 1495, 1349, 826, 767, 694. ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 7.07-7.36

(m, 17H), 7.64 (d, J = 7.1 Hz, 2H). ^{13}C-NMR (100.62 MHz, $CDCl_3$)δ (ppm): 20.23, 124.24, 125.49, 126.39, 126.67, 126.85, 127.09, 127.12, 127.27, 127.45, 127.77, 127.79, 127.98, 128.46, 129.74, 130.11, 136.23, 137.10, 146.06.

2-(3-Bromophenyl)-4,5-diphenyl-1H-imidazole (compound **5'b**): mp 120-122 °C; IR (KBr) (ν_{max}, cm^{-1}): 3387, 3062, 1584, 1529, 1480, 1241, 1100. ^{1}H-NMR (400.13 MHz, $CDCl_3$) δ (ppm): 7.26-7.78 (m, 14H), 9.40 (s, 1H). ^{13}C-NMR (100.62 MHz, $CDCl_3$)δ (ppm): 121.86, 125.62, 126.02, 126.75, 127.41, 127.70, 127.76, 128.11, 131.05.

2-(2-Hydroxyphenyl)-4,5-diphenyl-1H-imidazole (compound **5'c**): mp 209-211 °C; IR (KBr) (ν_{max}, cm^{-1}): 3450, 3385, 1584, 1529, 1480, 1240, 1098. ^{1}H-NMR (400.13 MHz, $CDCl_3$) δ (ppm): 6.92 (d, J = 7.28 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.26-7.62 (m, 12H), 9.36 (s, 1H), 12.83 (s, 1H). ^{13}C-NMR (100.62 MHz, $CDCl_3$)δ (ppm): 111.39, 116.80, 117.92, 122.00, 126.32, 127.14, 127.38, 128.07, 129.54, 144.67, 156.45.

2-(2-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (compound **5'd**): mp 204-206 °C; IR (KBr) (ν_{max}, cm^{-1}): 3388, 3062, 2933, 1584, 1530, 1481, 1240, 1099. ^{1}H-NMR (400.13 MHz, DMSO-d_6)δ (ppm): 4.05 (s, 3H), 7.03-7.69 (m, 13H), 8.50 (d, J = 8 Hz, 1H), 10.51 (s, 1H). ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ (ppm): 126.45, 126.83, 127.33, 128.22, 128.59, 129.07, 129.67, 129.91, 130.26, 131.02, 132.98, 133.97.

2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (compound **5'e**): mp 227-230 °C; IR (KBr) (ν_{max}, cm^{-1}): 3433, 3027, 1613, 1578, 1542, 1248, 1176. ^{1}H-NMR (400.13 MHz, DMSO-d_6) δ (ppm): 3.87 (s, 3H), 6.98-7.86 (m, 10H), 7.55 (s, 2H), 7.85 (d, J = 8.4 Hz, 2H), 9.23 (s, 1H). ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ (ppm): 55.36, 114.27, 122.78, 126.78, 127.30, 127.80, 128.55, 146.14, 160.16.

2-(4-Benzyloxyphenyl)-4,5-diphenyl-1H-imidazole (compound **5'f**): mp 235-236 °C; IR (KBr) (ν_{max}, cm^{-1}): 3054, 3018, 2930, 1608, 1578, 1541, 1230, 1181. ^{1}H-NMR (400.13 MHZ, DMSO-d_6)δ (ppm) 5.16 (s, 2H), 7.11-7.54 (m, 17H), 8.01 (d, J = 8.8 Hz, 2H), 12.51 (s, 1H). ^{13}C-NMR (100.62 MHz, DMSO-d_6) δ (ppm): 69.78, 115.42, 123.82, 126.09, 127.18, 127.52, 128.26, 128.36, 128.63, 128.82, 128.93, 129.10, 135.79, 137.41, 146.06, 158.99.

2-Fluorenyl-4,5-diphenyl-1H-imidazole (compound **5'g**): mp 283-286 °C; IR (KBr) (ν_{max}, cm^{-1}): 3350, 3054, 2950, 1601, 1532, 1500. ^{1}H-NMR (400.13 MHz, DMSO-d_6)δ (ppm): 4.01 (s, 2H), 7.33-8.00 (m, 15H), 8.130 (d, J = 7.6 Hz, 1H), 8.32 (s, 1H), 12.733 (s, 1H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 39.92, 120.36, 120.68, 122.37, 124.57, 125.64, 126.73, 127.42, 128.28, 128.90, 129.36, 141.23, 141.63, 143.88, 143.95, 146.42. Anal. Calcd for $C_{28}H_{20}N_2$ (384.47): C, 87.47; H, 5.24; N, 7.29. Found: C, 87.41; H, 5.29; N, 7.22.

3-Indolyl-4,5-diphenyl-1H-imidazole (compound **5'h**): mp 311-313 °C; IR (KBr) (ν_{max}, cm^{-1}): 3413, 3055, 1598, 1490, 1451. ^{1}H-NMR (400.13 MHZ, DMSO-d_6)δ (ppm): 7.128-7.587 (m, 13H), 8.006 (d, J = 2.4 Hz, 1H), 8.462 (d, J = 7.2 Hz, 1H), 11.404 (s, 1H), 12.4 (s, 1H). ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 106.95, 112.13, 120.24, 121.92, 122.40, 124.53, 125.51, 127.36, 128.05, 128.92, 136.75, 144.11. Anal. Calcd for $C_{23}H_{17}N_3$ (335.40): C, 82.36; H, 5.11; N, 12.53. Found: C, 82.29; H, 5.21; N, 12.40.

2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (compound **5'i**): mp 257-259 °C; IR (KBr) (ν_{max}, cm^{-1}): 3386, 3062, 1584, 1529, 1481, 1240, 1099. ^{1}H-NMR (400.13 MHZ, $CDCl_3$)δ (ppm): 6.99-7.36 (m, 12H), 7.86 (d, J = 7 Hz, 2H), 12.09 (s, 1H). ^{13}C-NMR (100.62 MHz, $CDCl_3$)δ (ppm): 125.94, 126.72, 127.39, 127.68, 128.24, 132.70, 144.31.

2-(3-Nitrophenyl)-4,5-diphenyl-1H-imidazole (compound **5'j**): mp 308-309 °C; IR (KBr) (ν_{max}, cm^{-1}):

3380, 3065, 1580, 1527, 1479, 1239, 1099, 810, 758. ^{1}H-NMR (400.13 MHZ, DMSO-d_6) δ (ppm): 7.30-7.53 (m, 10H), 7.78 (t, J = 8 Hz, 1H), 8.51 (d, J = 8 Hz, 1H), 8.95 (t, J = 1.8 Hz, 1H), 9.41 (d, J = 8 Hz, 1H), 13.10 (s, 1H), ^{13}C-NMR (100.62 MHz, DMSO-d_6)δ (ppm): 119.40, 122.61, 127.13, 128.44, 128.68, 130.44, 131.17, 131.82, 143.38, 148.37.

Results and discussion

Based on the importance of heterogeneous catalyst in the synthesis of organic compounds,[31] herein we found a new application of Fe_3O_4 nanoparticles as a highly efficient catalyst for the synthesis of novel and known polysubstituted imidazoles with high yields. After the preparation of Fe_3O_4 nanoparticles, firstly this catalyst was characterized. Figure 1a shows the XRD patterns of the Fe_3O_4 nanoparticles. A number of prominent Bragg reflections by their indices ((220), (311), (400), (422), (511), and (440)) reveal that the resultant nanoparticles were Fe_3O_4 with a spinel structure.[32] The size of the Fe_3O_4 nanoparticles was also determined from X-ray line broadening using the Debye–Scherrer formula given as $D = 0.9\ \lambda/\beta\ \cos\theta$, where D is the average crystalline size, λ the X-ray wavelength used, β the angular line width at half maximum intensity, and θ the Bragg's angle. For (311) reflection, the average size of the Fe_3O_4 nanoparticles is estimated to be around 13 nm. In Figure 1b transmission electron microscopy (TEM) analyses were used for characterization. The TEM image reveals the spherical Fe_3O_4 nanoparticles with average size $\sim$10 nm. The FT-IR spectra of Fe_3O_4 nanoparticles are shown in Figure 2. The absorbance bands at 584.3 cm^{-1} are ascribed to Fe^{+2} O^{-2}, which are consistent with the reported IR spectra for spinel Fe_3O_4.[33,34]

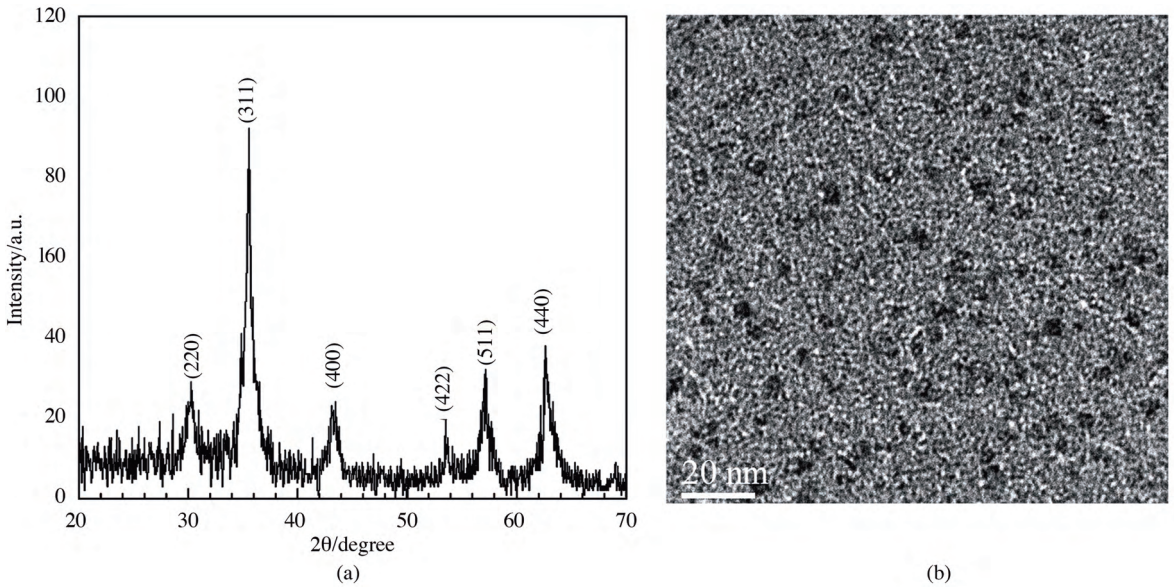


Figure 1. (a) The powder X-ray diffraction pattern of the Fe_3O_4 nanoparticles; (b) TEM image shows spherical Fe_3O_4 nanoparticles with approximately $\sim$10 nm.

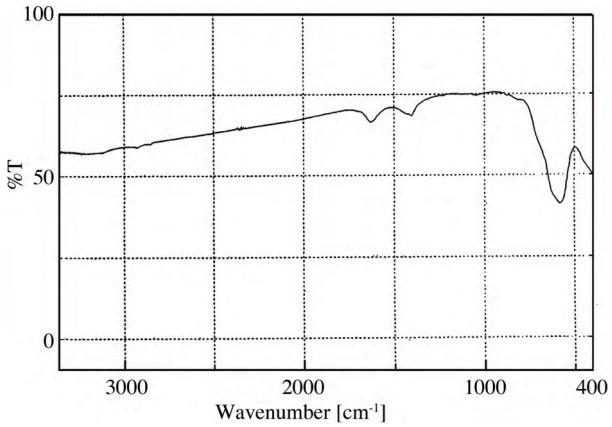


Figure 2. FT-IR spectra of Fe_3O_4 nanoparticles.

Firstly, synthesis of 1-benzyl 2,4,5-triphenyl imidazoles was chosen as a model reaction (compound **5a**) in the synthesis of polysubstituted imidazoles to determine the optimum condition for this synthesis. The model reaction, in the presence of an optimized molar ratio of magnetic Fe_3O_4 nanoparticles (1 mol%), benzaldehyde (1 mmol), ammonium acetate (1 mmol), and benzylamine (1 mmol), was carried out in different solvents such as water, ethanol, methanol, chloroform, and acetonitrile under refluxing and solvent-free conditions at 80 °C. From these experiments, it was clearly demonstrated that the solvent-free condition is the best for accomplishing this synthesis (Table 2).

Table 2. Solvent effect in the synthesis of 1-benzyl 2,4,5-triphenyl imidazole as a model reaction (compound **5a**).

Entry	Solvent	Time (min)	Yield (%)
1	Water	90	46
2	Ethanol	35	75
3	Methanol	40	78
4	Chloroform	120	49
5	Acetonitrile	80	73
6	Solvent-free	20	96

Moreover, the reaction in the presence of small amount of acetic acid was tested both in the presence and absence of magnetic Fe_3O_4 nanoparticles at different temperatures. The results showed that the catalyst and temperature are 2 key factors for the progress of the reaction and the best temperature for catalytic activity of magnetic Fe_3O_4 nanoparticles is 80 °C (Table 3).

We carried out the model reaction in the absence of catalyst in solvent-free conditions and at room temperature for 24 h, which led to very poor yield (12%) of 1-benzyl 2,4,5-triphenyl imidazoles as 1,2,4,5-tetrasubstituted imidazoles. In the absence of catalyst for enhancing the yield of the desired product, the temperature of the reaction was increased to 200 °C, but no appreciable increment in the product yield was observed. Therefore, we found that presence of a catalytic amount of magnetic Fe_3O_4 nanoparticles and solvent-free conditions are the best conditions for this synthesis.

Table 3. Effects of catalyst and temperature in the synthesis of imidazole derivatives (model reaction).

Entry	Temp. (°C)	In the absence of catalyst		In the presence of catalyst[a]	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1	r.t.	300	Trace	120	72
2	30	240	Trace	100	72
3	40	240	20	80	78
4	50	240	35	60	80
5	60	180	45	25	85
6	70	180	50	25	90
7	80	180	60	20	96
8	90	180	65	25	92

[a] Optimized molar ratio of catalyst (1 mol%)

We also evaluated the quantity of required catalyst in this synthesis for the model reaction. It was found that maximum yield (96%) obtained when the reaction was loaded with 1 mol% of magnetic Fe_3O_4 nanoparticles (Table 4).

Table 4. Optimization of molar ratio of the catalyst for model reaction (compound **5a**).

Entry	Fe_3O_4 nanoparticles (mol%)	Time (min)	Yield (%)
1	0.1	60	90
2	1	20	96
3	2	30	96
4	5	30	95
5	10	45	95
6	20	50	95

In the following study of the model reaction, we examined the reaction at various temperatures to find out its effect on the progress of the reaction (Table 5). The maximum rate of reaction was obtained at 80 °C as the optimum temperature.

Table 5. Optimization of temperature for model reaction (compound **5a**).

Entry	Temp. (°C)	Time (min)	Yield (%)
1	r.t.	120	70
2	60	25	85
3	80	20	96
4	100	30	96
5	120	30	90

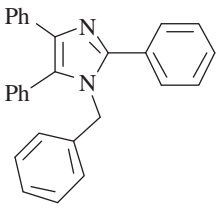
As can be seen from Table 5, at room temperature the reaction was completed slowly. With increasing temperature to 80 °C, the reaction yield was increased and time of the reaction decreased; when the reaction was heated above 80 °C there was no further improvement in yield or decrease in the time of the reaction.

According to the optimal conditions, we conducted the synthesis of polysubstituted imidazoles in the presence of magnetic Fe_3O_4 nanoparticles as catalyst in solvent-free conditions at 80 °C.

Reusability of the catalyst

At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 130 °C for 1 h, and reused in another reaction. We found that the magnetic Fe_3O_4 nanoparticles showed high catalytic activity with a very short reaction time. Moreover, it can be recovered and reused several times without significant loss of activity. The results of these observations for the model reaction are shown in Table 6 and Figure 3.

Table 6. Reusability results of Fe_3O_4 nanoparticles on the reaction process for the model reaction (compound **5a**).

product	Total reusability	Yield (%)	Time (min)
	1	96	20
	2	95	20
	3	95	25
	4	97	40
	5	97	45

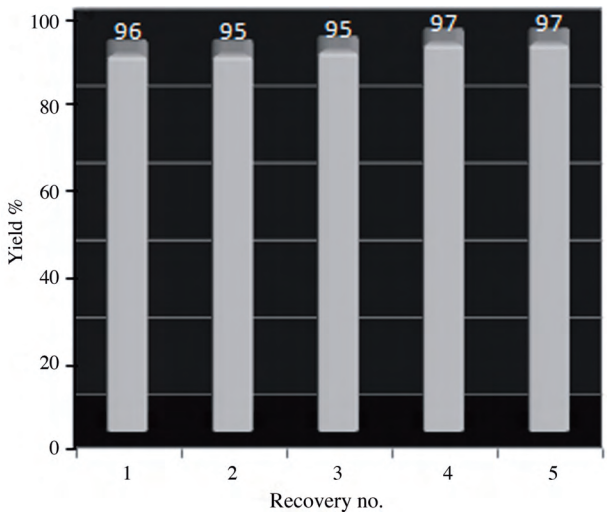
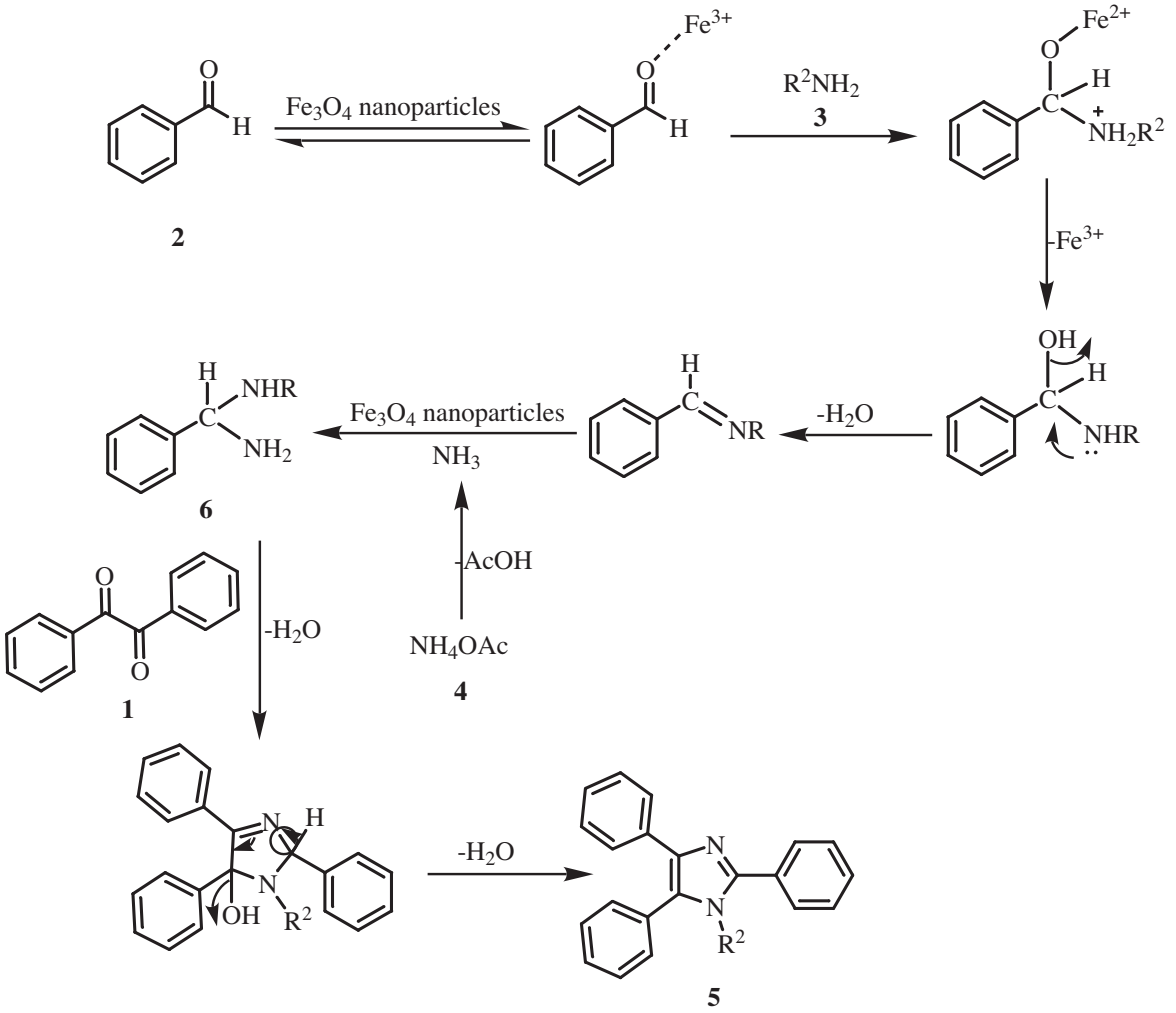


Figure 3. The reusability of the catalyst for model reaction.

A probable mechanism for the synthesis of tetrasubstituted imidazoles may be postulated as shown below (Scheme 2).



Scheme 2. The suggested mechanism for the synthesis of tetrasubstituted imidazoles.

As can be seen in Scheme 2, magnetic Fe_3O_4 nanoparticle is a Lewis acid and so it can active the carbonyl group of aldehydes **2** to decrease the energy of transition state. Then the nucleophilic attack of amine **3** on the activated carbonyl of aldehydes resulted in the formation of imine, and it was followed by nucleophilic attack of the in situ generated ammonia from **4** on the imine, giving the intermediate **6**. From condensation of intermediate **6** with benzil **1** and dehydration of it, corresponding imidazoles **5** were produced.

Moreover, the probable mechanism for synthesis of trisubstituted imidazoles is the same as that for tetrasubstituted imidazoles but in this case ammonium acetate was handled instead of primary amine.

Conclusions

In this work, we found a thermal exposure synthetic method for polysubstituted imidazoles that is simple, efficient, and green via a multicomponent one-pot reaction in the presence of magnetic Fe_3O_4 nanoparticles as an inexpensive and eco-friendly catalyst in solvent-free conditions. Furthermore, products were isolated

in excellent yields. Also the catalyst was efficiently recovered and reused, which is considered an economic advantage of this synthesis. It is thought that this procedure will find important applications in the synthesis of a wide range of polysubstituted imidazoles.

Acknowledgment

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