Sulphamic acid-functionalized magnetic Fe₃O₄ nanoparticles as recyclable catalyst for synthesis of imidazoles under microwave irradiation

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Abstract. Trisubstituted imidazoles have been synthesized in high yield in the presence of sulphamic acid-functionalized magnetic Fe₃O₄ nanoparticles (SA-MNPs) as a novel solid acid catalyst under solvent-free classical heating conditions or using microwave irradiation. The heterogeneous catalyst could be recovered easily and reused many times without significant loss of catalytic activity.

Keywords. Magnetic nanoparticles; sulphamic acid; imidazole; solid acid catalyst; microwave irradiation.

1. Introduction

In recent years, advances in nanoscience and nanotechnology have led to a new research interest in employing nanometer-sized particles to construct a magnetically recyclable nanocatalyst system in heterogeneous catalysis.¹

Among heterogeneous catalysts, magnetic catalysts are widely used in organic reactions. Due to their large surface area, which can carry a high payload of catalytically active species, nanoparticles exhibit very high catalytic activity and chemical selectivity under mild conditions. At the end of the reaction, these catalysts, can be isolated efficiently from the product solution through a simple magnetic separation process. It is an attractive candidate in the development of a cost-effective catalysis process.^{2,3} On the other hand, solid acid catalysts such as clays, zeolites, sulphated metal oxides or carbons and heteropolyacids have already attracted extensive research interests.^{4–7} Among these solid acid catalysts, magnetically recyclable nanocatalyst systems, are unique due to simple work-up procedure, ease of separation, and higher catalytic activity, etc.^{1,8}

Multi-substituted imidazoles, an important class of pharmaceutical compounds, display a wide spectrum of biological activity.^{9,10} Several methods are used for

synthesis of multi-substituted imidazoles.^{11–22} Recently, one-pot condensations of an aldehyde and ammonium acetate with an α -hydroxy ketone, an α -keto oxime, or a 1, 2-diketone have been achieved by using a variety of acid catalysts, for example silica sulphuric acid (SSA),^{23,24} boric acid,²⁵ phosphomolybdic acid,²⁶ H₂SO₄,²⁷ H₃PO₄,²⁸ oxalic acid²⁹ and *p*-toluenesulphonic acid.³⁰

Despite their potential utility, some of these methods are not environment-friendly and suffer from one or more disadvantages, for example, hazardous reaction conditions, complex work-up and purification, strongly acidic conditions, high temperature, poor yield, occurrence of side reactions and long reaction time. Therefore, the development of a mild general method to overcome these shortcomings remains a challenge for organic chemists in the synthesis of highly substituted imidazoles.¹⁰ Microwave-assisted reactions are extremely attractive to synthetic organic chemists due to their ability to shorten reaction times and in some cases improve regio- and/or chemoselectivity.³¹ Reactions that previously required hours to run to completion can now be finished within minutes.³² Employing microwave irradiation and the use of solid acid catalyst will lead to minimal pollution and waste material and application of such catalysts in fine chemical manufacturing is likely to be especially important in future.⁸

In this study, we report immobilization of sulphamic acid groups on synthesized magnetic Fe₃O₄ nanoparticles, as a new heterogeneous catalyst for the synthesis

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Figure 1. One-pot synthesis of 2, 4, 5-trisubstituted imidazoles catalysed by SA-MNPs conventional heating conditions or using microwave irradiation.

of trisubstituted imidazoles via one-pot condensation of 1, 2-diketone **1** with aldehyde **2** and NH_4OAc in the presence of sulphamic acid-functionalized magnetic Fe_3O_4 nanoparticles as an inexpensive solid acid catalyst under solvent-free classical heating conditions or using microwave irradiation (figure 1).

2. Experimental

2.1 Characterization methods

Chemical reagents of high purity were purchased from Merck Chemical Company. All materials were of commercial reagent grade. Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus and are uncorrected. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX-400 Avance spectrometer. Tetramethyl silane (TMS) was used as an internal reference. IR spectra were obtained on a Magna-550 Nicolet instrument. Vibrational transition frequencies were reported as wave numbers (cm^{-1}), and band intensities designated as weak (w), medium (m) and strong (s). A mass spectrum was recorded by a QP-1100EX Shimadzu spectrometer. The element analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyser carried out on Perkin-Elmer 240c analyser. The UV-vis measurements were obtained with a GBC cintra 6 UV-vis spectrophotometer. Nanostructures were characterized using a Holland Philips Xpert X-ray powder diffraction (XRD) diffractometer (CuK α radiation, $\lambda = 0.154056\text{ nm}$), at a scanning speed of $2^\circ/\text{min}$ from 10° to 100° (2θ). Particle size and morphology were investigated by a JEOL JEM-2010 transmission electron microscope (TEM) on an accelerating voltage of 200 kV. Microwave synthesis was carried out on a Sanle SPII-2 singlemode microwave reactor (Made in Nanjing, China) with infrared temperature probe and successively adjustable 0–700 W output power.

2.2 Catalyst preparation

Fe_3O_4 -MNPs were prepared using simple chemical coprecipitation described in literature³³ and subsequently coated with 3-aminopropyltriethoxysilane (APTES) to achieve aminofunctionalized magnetic nanoparticles APTES-MNPs.³⁴ Sulphamic acid-functionalized magnetic Fe_3O_4 nanoparticles were prepared by means of a procedure reported elsewhere with little modification.⁸ In short, the APTES-MNPs (500 mg) were dispersed in dry CH_3CN (5 ml) by ultrasonic bath for 20 min. Subsequently, chlorosulphuric acid (1 ml) was added drop-wise over a period of 30 min at room temperature under ultrasonic irradiation. Hydrogen chloride gas evolved from the reaction vessel immediately. Then, the as-prepared functionalized MNPs nanoparticles were separated by magnetic decantation and washed thrice with dry EtOH to remove unattached substrates.

2.3 General procedure for synthesis of 2,4,5-trisubstituted imidazoles

A mixture of benzil or benzoin (1 mmol), ammonium acetate (4 mmol), aldehyde (1 mmol), and 0.01 g (equal to 0.012 mmol H^+) sulphamic acid-functionalized magnetic Fe_3O_4 nanoparticles (SA-MNPs) was stirred at 100°C for 15–35 min or irradiated in a microwave oven for 10 min adding a few drops (1 mL) dry petroleum ether 80°C for a homogeneous reaction environment. The progress of the reaction was monitored by TLC (petroleum ether–ethyl acetate 9:1). After the reaction was completed, the reaction mixture was dissolved in acetone and the catalyst was separated by an external magnet and the reaction mixture was filtrated. The filtrate was concentrated on a rotary evaporator under reduced pressure and the solid product obtained was washed with water and recrystallized from acetone–water 9:1 (v/v). Pure products were obtained in excellent yields, as summarized in table 1. Most of the products are known and were identified by comparison of their physical and spectral data with those of authentic samples.

3. Results and discussion

3.1 Characterization of the prepared SA-MNPs

Magnetite nanoparticles of 18–20 nm were prepared by coprecipitation of iron(II) and iron(III) ions in basic solution at 85°C using the method described by Massart.³⁵ For surface modification, the magnetic nanoparticles were coated with APTES to achieve

Table 1. One-pot synthesis of trisubstituted imidazoles in the presence of SA-MNPs as a solid acid catalyst under solvent-free classical heating conditions or using microwave irradiation.

Entry	Aldehyde	Ar	Product	Yield (%) ^a Time (min)		M.p. (°C)	
				Δ^b	MW ^c	Found	Reported
1	3a	C ₆ H ₆	4a	85 (30)	96 (10)	272–273	270–272 ^d
2	3b	<i>p</i> -MeOC ₆ H ₄	4b	87 (25)	99 (10)	229–230	230–232 ^e
3	3c	<i>m</i> -MeOC ₆ H ₄	4c	76 (20)	95 (10)	258–261	259–262 ^d
4	3d	<i>p</i> -MeC ₆ H ₄	4d	82 (25)	98 (10)	231–233	230–233 ^d
5	3d	<i>p</i> -ClC ₆ H ₄	4e	78 (20)	95 (10)	260–261	262–264 ^e
6	3e	<i>m</i> -ClC ₆ H ₄	4f	80 (20)	95 (10)	282–283	285–287 ^e
7	3f	<i>p</i> -BrC ₆ H ₄	4g	83 (20)	93 (10)	262–264	261–263 ^f
8	3g	<i>m</i> -BrC ₆ H ₄	4h	88 (20)	95 (10)	302–303	301–303 ^f
9	3h	2-Naphthyl	4i	78 (20)	94 (10)	272–274	273–276 ^d
10	3i	2,4-Cl ₂ C ₆ H ₃	4j	77 (35)	94 (10)	171–173	174–176 ^f
11	3j	2-Thienyl	4k	79 (20)	95 (10)	261–263	262–266 ^f
12	3k	<i>m</i> -O ₂ NC ₆ H ₄	4l	75 (15)	93 (10)	267–270	265–267 ^f
13	3l	<i>p</i> -(Me) ₂ NC ₆ H ₄	4m	85 (25)	96 (10)	256–258	255–257 ^d
14	3m	<i>o</i> -HOC ₆ H ₄	4n	77 (30)	93 (10)	198–202	198–201 ^d
15	3n	<i>m</i> -OH C ₆ H ₄	4o	85 (20)	93 (10)	260–262	259 ^f

^aIsolated yield based on aldehyde, ^bunder classical heating conditions at 100°C, ^cusing microwave irradiation, ^dref. 40, ^eref. 41, ^fref. 42

aminofunctionalized magnetic nanoparticles. Ultimately, the reaction of amino groups with chlorosulphuric acid led to sulphamic acid-functionalized magnetic Fe₃O₄ nanoparticles (SA-MNPs) (figure 2).

The number on H⁺ sites on SA-MNPs was determined by pH–ISE conductivity titration (Denver Instrument Model 270) and found to be 1.25 H⁺ sites per 1 g of solid acid at 25°C (pH 2.30). Figure 3 presents the XRD-diffraction patterns of the prepared Fe₃O₄-MNPs, APTES-MNPs, and SA-MNPs. The position and relative intensities of all peaks confirm well with standard XRD pattern of Fe₃O₄ (JCPDS Card No. 79-0417) indicating retention of the crystalline cubic spinel structure during functionalization of MNPs. The XRD patterns of the particles show six characteristic peaks revealing

a cubic iron oxide phase ($2\theta = 30.35, 35.95, 43.45, 53.70, 57.25, 62.88, 71.37, 74.46$). These are related to their corresponding indices (2 2 0), (3 1 1), (4 0 0), (3 3 1), (4 2 2), (3 3 3), (4 4 0) and (5 3 1), respectively.³⁶ It is implied that the resultant nanoparticles are pure Fe₃O₄ with a spinel structure and that the grafting process did not induce any phase change of Fe₃O₄. A weak broad band ($2\theta = 18$ – 27°) appeared in the

Figure 2. Preparation steps for fabricating sulphamic acid-functionalized magnetic Fe₃O₄ nanoparticles. **Figure 3.** XRD patterns of (a) MNPs, (b) APTES-MNPs and (c) SA-MNPs.

SA-MNPs which could be assigned to the amorphous silane shell formed around the magnetic cores.³⁷

The crystal size of MNPs and SA-MNPs nanoparticles can be determined from the XRD pattern by using Debye–Scherrer's equation.

$$D(hkl) = \frac{0.94\lambda}{\beta \cos \theta},$$

where $D(hkl)$ is the average crystalline diameter, 0.94 is the Scherrer's constant, λ is the X-ray wavelength, β is the half-width of XRD diffraction lines and θ is the Bragg's angle in degree. Here, the (3 1 1) peak of the highest intensity was picked out to evaluate the particle diameter of the nanoparticles. MNPs and SA-MNPs were calculated to be 18 and 20 nm, respectively.

Figure 4 shows the Fourier transform infrared (FT-IR) spectra of both the unfunctionalized and functionalized magnetic nanoparticles. The Fe–O stretching vibration near 580 cm^{-1} , O–H stretching vibration near 3432 cm^{-1} and O–H deformed vibration near 1625 cm^{-1} were observed for both in figure 4(a) and (b). The significant features observed for figure 4(b) are the appearance of the peaks at 1002 cm^{-1} (Si–O stretching) and at 2800 cm^{-1} ($-\text{CH}_2$ stretching). The peak at 3423 cm^{-1} in figure 4(b) can be attributed to the free amino groups, which is overlapped by the O–H stretching vibration. These results provided the evidences that the amino groups were successfully attached to the surface of Fe_3O_4 nanoparticles.³⁸ Reaction of APTES–MNPs with chlorosulphuric acid produces SA-MNPs in which the presence of sulphonyl moiety is asserted with 1217 and 1124 cm^{-1} bands in FT-IR spectra.⁸

Figure 4. Comparative FT-IR spectra for (a) MNPs, (b) APTES–MNPs and (c) SAMNPs.

Figure 5. Magnetization curves for the prepared MNPs and SA-MNPs at room temperature.

The magnetization curve for Fe_3O_4 nanoparticles and SA-MNPs is shown in figure 5. Room temperature specific magnetization (M) versus applied magnetic field (H) curve measurements of the sample indicates a saturation magnetization value (M_s) of 52.3 emu g^{-1} , lower than that of bare magnetic nanoparticles (60.7 emu g^{-1}) due to the coated shell. In figure 5, we can also see that the two magnetization curves follow a Langevin behaviour over the applied magnetic field and the coercivity (H_c) could be ignored, which can be considered as superparamagnetism.³⁹

The sulphamic acid-functionalized magnetic Fe_3O_4 nanoparticles could be separated to the sidewall of the container after 30 s using a magnet of 2000 Gs, suggesting that the obtained magnetic microspheres had an excellent magnetic responsivity, which prevents composite microspheres from aggregating and enables them to redisperse rapidly when the magnetic field is removed. TEM micrographs provide more accurate information on the particle size and morphology of MNPs and SA-MNPs (figure 6). For both the pristine and SA-functionalized nanoparticles, the average diameter of the core is around 18 nm with an approximate spherical shape, which is in accordance with the XRD pattern. There is no detectable outer shell within the sensitivity limit of TEM (figure 6b). A reasonable explanation might be that silanization with APTES results in the formation of a monolayer Si–O network which is too thin to be recognized.⁸

3.2 Evaluation of catalytic activity of SA-MNPs through synthesis of 2,4,5-trisubstituted imidazoles

Efficiency of the reaction is mainly affected by the amount of catalyst and temperature. As indicated in table 2, the best results have been obtained at

Figure 6. TEM images of (a) MNPs and (b) SA-MNPs.

100°C with an amount of 0.01 g SA-MNPs (equal to 0.012 mmol H^+); and the yield of reaction with increase in the amount of SA-MNPs or temperature does not considerably increase. It is important to note that in the absence of catalyst, the reaction yield is decreased to 35% even at 180°C after 1 h.

The successful results of SA-MNP-catalysed synthesis of trisubstituted imidazoles under solvent-free classical heating conditions or using microwave irradiation in absence of solvent are given in table 1. In a typical experiment, a mixture of aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (4 mmol) and SA-MNPs 0.01 g (equal to 0.012 mmol H^+) was stirred for 30–80 min in a tube under conventional heating conditions

at 100°C or using microwave irradiation for 5–10 min. After completion of the reaction, the reaction was cooled to room temperature and solid materials washed with acetone and after evaporating the solvent, the pure product was obtained.

Results from SA-MNPs-catalysed condensation reaction of benzil, with different aromatic aldehydes and ammonium acetate at 100°C under solvent-free conditions are given in table 1. As shown, these conditions proved to be general for the reacting aldehyde. Aldehydes bearing either electron-withdrawing or electron-donating groups perform equally well in the reaction and all imidazoles were obtained in high yields. Also, microwave irradiation has shown better yields and especially in the reaction times. For some of the aromatic aldehydes with high electron-withdrawing and steric effects such as $p-O_2NC_6H_5$ and 2,6- $Cl_2C_6H_4$, no reaction took place.

Table 2. Optimization of one-pot synthesis of 2,4,5-trisubstituted imidazoles under classical heating conditions.^a

Entry	Catalyst (mmol H^+)	Time (min)	Temperature (°C)	Yield (%)
1	0.0	60	60	10
2	0.009	35	60	35
3	0.012	35	60	45
4	0.025	35	60	45
5	0.0	45	80	15
6	0.009	30	80	52
7	0.012	30	80	67
8	0.025	30	80	67
9	0.0	30	100	25
10	0.009	25	100	60
11	0.012	25	100	80
12	0.025	25	100	80
13	0.0	25	130	30
14	0.009	20	130	63
15	0.012	20	130	80
16	0.025	20	130	80

^aBenzil **1** (1 mmol), benzaldehyde **3a** (1 mmol) and ammonium acetate (4 mmol)

Figure 7. Recyclability of SA-MNPs in the reaction of benzil (1 mmol), 4-methylbenzaldehyde (1 mmol), benzylamine (1 mmol) and ammonium acetate (4 mmol) under solvent-free conditions.

The possibility of recycling the catalyst was examined using the reaction of benzil, benzaldehyde, and ammonium acetate under optimized conditions. Upon completion, the catalyst was separated by an external magnet and was washed with acetone, and the recycled catalyst was saved for the next reaction. The recycled catalyst could be reused five times without any further treatment. Any appreciable loss in the catalytic activity of nanocatalyst was not observed (figure 7).

Most of the products are known and were identified by comparison of their physical and spectral data with those of authentic samples. All melting points compared satisfactorily with those reported in literature.

In summary, we have been able to introduce an efficient and environment-friendly approach for the synthesis of biologically active trisubstituted imidazoles via condensation of benzil with various aromatic aldehydes and ammonium acetate using SA-MNPs as a recyclable solid acid catalyst. Corrosiveness, safety, less waste, ease of separation and recovery, replacement of liquid acids with solid acid are all among desirable factors for the chemical industry which we have considered in our green chemistry approach. The approach has several benefits such as low waste, easy work-up, short reaction time and high yield.

4. Conclusion

In conclusion, an efficient and convenient procedure for the three-component one-step synthesis of 2,4,5-trisubstituted imidazoles has been developed by condensation reaction of 1, 2-diketones, aromatic aldehydes, and ammonium acetate using sulphamic acid-functionalized magnetic Fe_3O_4 nanoparticles as a novel and reusable catalyst under solvent-free conditions and microwave irradiation. This method offers several advantages including high yield, short reaction time, simple work-up procedure, ease of separation, and recyclability of the magnetic catalyst as well as the ability to tolerate a wide variety of substitutions in the reagents.

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