

Novel magnetic nanoparticle acid catalyst for synthesis of a facile, efficient and one-pot tri substituted imidazoles

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Abstract

Modified nanomagnetic acid catalyst $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$ was synthesized in simple method and used for synthesizing 2,4,5-tri substituted imidazole by combining three components such as benzil, aldehydes and ammonium acetate of which the last component was as an ammonia source. High yield of tri-substituted imidazole without significant loss of efficiency and easy recovery by an external magnetic field and several times of reusability with less deterioration are advantages of $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$ catalyst. A large amount of acid existing on the surface of the magnetic layer leads to more activities of the catalyst and as a result, the yielding of tri-substituted imidazole increases. The acidic functioned nanomagnetic core-shell catalyst was approved as per Fourier transfer infrared (FT-IR), X-ray diffraction powder (XRD), Energy dispersive X-Ray spectroscopy (EDS), Thermal gravimetric analysis (TGA), Vibrating sample magnetometer (VSM) and transmission electron microscopy (TEM).

Keywords: Nanomagnetic, Acid catalyst, Core-shell, Imidazole, Heterogenous.

1. Introduction

The imidazole ring system is used in pharmaceutical leading material. Amino acid histidine is hypnotic agent etomidate [1], The anti ulcerative agent cimetidine [2] fungicide ketoconazole [3] as examples. Compounds with an imidazole moiety have biological and pharmaceutical importance [4, 5] Highly substituted imidazoles like lepidilines [6] exhibit micro molar cytotoxicity against several human cancer cell lines.

Trifenagrel [7] is a potent 2,4,5-triarylimidazole that reduces platelet aggregation in several animal species and humans. In recent years, substituted imidazoles are substantially used in ionic liquids [8, 9] that have been given a new approach to 'Green Chemistry'. The imidazole compounds are also used in photography as photosensitive compound [10].

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hydrogen bond donor-acceptor ability as well as its high affinity for metals. Many of the substituted The potential and wide range of application of the imidazole pharmacophore may be attributed to its imidazoles are known as fungicides, herbicides, plant growth regulators, antibacterial, antitumor, pesticides and therapeutic agents [11-17]. There are several methods reported in literature for the synthesis of imidazoles, mainly using nitriles and esters [18, 19] as the starting substrates. Japp and et al proposed the first synthesis of the imidazole core in 1882, starting from 1,2-dicarbonyl compounds, aldehydes, and ammonia, to obtain 2,4,5-triphenylimidazoles [20, 21]. Several methods are reported in the literature for the synthesis of 2,4,5-triaryl-1H-imidazoles by condensation of benzil/benzoin with a wide variety of aldehydes, aromatic primary amines and ammonium acetate using different catalysts such as N-methyl-2-pyrrolidonium hydrogen sulphate [22] nano-TiCl₄-SiO₂ [23], zeolite HY/silica gel [24], cellulose supported sulphuric acid [24], NiCl₂.6H₂O [25] ultrasonic irradiation [26], cyclic phosphoric acid [27], potassium dihydrogen phosphate [28], Amberlyst A-15 [29], L-proline [30] and PEG-400 [31]. Given these proven applications in the field of medical, biological and synthetic organic chemistry, there has been tremendous interest in developing an efficient method for the synthesis of imidazoles. Recently, some methods for the synthesis of substituted imidazoles have been reported [32-34]. However, some of these methods suffer from one or more drawbacks like high temperature requirement, highly acidic conditions, and the use of metal cyanides for preparation of the nitrile compounds that limit their use [35, 36]. Some of the methods have resorted to harsh conditions (e. g., the formamide synthesis, which requires excess reagents, H₂SO₄ as a condensing agent, 150–200 C, 4–6h resulting in yields of 40–90%)[37-40]. Therefore, the development of a mild, efficient, and versatile method is still strongly desirable. Reusable heterogeneous catalysts have attracted a great deal of interest in recent years. Since most of the catalysts are expensive and contaminate the

environment, the development of efficient methods for recovery and reuse of the catalysts is a very important aspect in this chemistry. Herein we wish to report a simple, economic and efficient one-pot method for the synthesis of 2,4,5-trisubstituted imidazoles from benzil, ammonium acetate, aromatic aldehyde by a heterogeneous nanomagnetic acid catalyst which is inexpensive. It can also be prepared by existing instruments in any laboratory and easily separated from the reaction by an external magnetic field and reusable frequently.

2. Experimental procedure

All reagents have been purchased at Aldrich, Fluka and Merck companies marked with 'Synthesis Degree' and used without any purification. The products were characterized by spectroscopy data FT-IR, and melting points.

We should point out that we have achieved the accuracy of our experiments by using the following machines and tools in detailed explanations:

FT-IR SHIMADZU 8400 spectrometer was used to record IR spectra using KBr pellets. Melting points were determined by an open capillary method using a THERMO SCIENTEFIC 9100 melting point apparatus without further corrections.

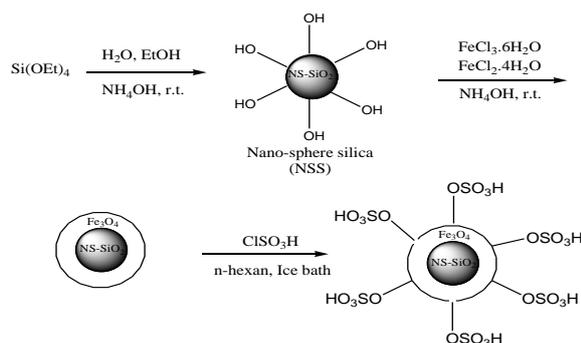
Some purchased aluminum-backed plates of silica gel 60 F254 of Thin Layer Chromatography or TLC for short were applied to monitor the progress of reactions. The sizes of magnetic nanoparticles (MNPs) were assessed by a Transmission Electron Microscope (TEM, 100 kV, Philips-CM 10).

The XRD D8 Advanced Bruker patterns were obtained to prove the catalyst contents.

The TG50 instrument of Thermo Gravimetric Analysis or TGA for short was applied to confirm core shell structure of catalyst.

A Philips 515 Scanning Electron Microscope equipped with an EDS Phoenix micro analyzer was applied to locate the elements of the catalyst.

VSM spectrum performed in room temperature by VSM Lake Shore, Model 7410 showed the magnetic properties of catalyst.



Scheme 1. . Synthesis of acid nanomagnetic catalyst by sphere silica core

2. 1. Catalyst production steps

a) Synthesis of sphere silica nanoparticles (SiO₂)

Different silica nanoparticles were produced by adjusting the concentrations of ethanol, water, TEOS (tetraethyl orthosilicate) and ammonium hydroxide. The above-mentioned ethanol, water, TEOS, and ammonium hydroxide were mixed in molar ratio 75:31:1:4 respectively. In other words 54 ml of ethanol and 5 ml of water stirred together in a beaker. Then 2.6 ml tetra ethyl ortho silicate was added to the mixture by drop wise manner in half an hour. At last 5 ml ammonium hydroxide was added to the beaker. The suspension was further stirred for another 3 hours till the solution turned into milky color in time. The sphere silica nanoparticles were separated by centrifugation and washed with 15 ml distilled water three times totally [41].

b) Synthesis of nanomagnetic on sphere silica core (SiO₂/Fe₃O₄)

A mixture of 6 g FeCl₃·6H₂O (0.022 mol), 2.2 g FeCl₂·4H₂O (0.011 mol) in water was added to 0.66 g (0.011 mol) well dispersed sphere silica which was in 10% ammonia solution. We let an ultrasonic bath agitate the mixture for 15 minutes continually. The reaction terminated after an hour. The produced SiO₂/Fe₃O₄ was separated from the mixture. It was then washed with ethanol and distilled water separately three times. Each time we used 5 ml of ethanol and water respectively. The yielded nanomagnetic on sphere silica core was dried at 100 °C in an oven for an hour afterwards [42].

c) Coating the nanomagnetic on sphere silica core with an acidic layer (SiO₂/Fe₃O₄/SO₃H)

Chlorosulfonic acid (0.5 g, 4.5 mmol) was added in a drop-wise manner during two hours to a n-hexane (5 ml) solution containing one gram of the SiO₂/Fe₃O₄. The whole process was conducted in a balloon surrounded with ice cubes floating in water (ice-bath). We should notice that the ice-bath was placed in a laboratory hood during the process. Upon completing the adding of the Chlorosulfonic acid, we continued stirring the mixture more three hours in order to completing the separation of Hydrochloric (HCl) which was an unwanted byproduct from the beginning of the reaction. However we let it remain in the mixture. The produced nanomagnetic on sphere silica core with an acidic layer was separated by using an external magnet. The final product (SiO₂/Fe₃O₄/SO₃H) was washed with methanol before being dried over one night in an oven at 60 °C prior to finishing.

2.2. Measuring the coated acid layer of the catalyst

To determine the acid layer of catalyst, a 0.1 mol/L aqueous solution of KOH (2 ml) was added to the SiO₂/Fe₃O₄/SO₃H (0.01 g) in an Erlenmeyer flask. Then the mixture was stirred for 15 minutes. The catalyst was then removed from the Erlenmeyer flask by exposing it to an external magnetic field. We keep the resulted clear solution for further analysis. Two drops of phenolphthalein indicator was added to the clear solution. The mixture was titrated to a neutrality point by using a 0.1 mol/L aqueous HCl solution to determine the acid layer of the SiO₂/Fe₃O₄/SO₃H nanocatalyst. The H⁺ loading of the nano-catalyst determined in this way was found to be 7 mmol/g.

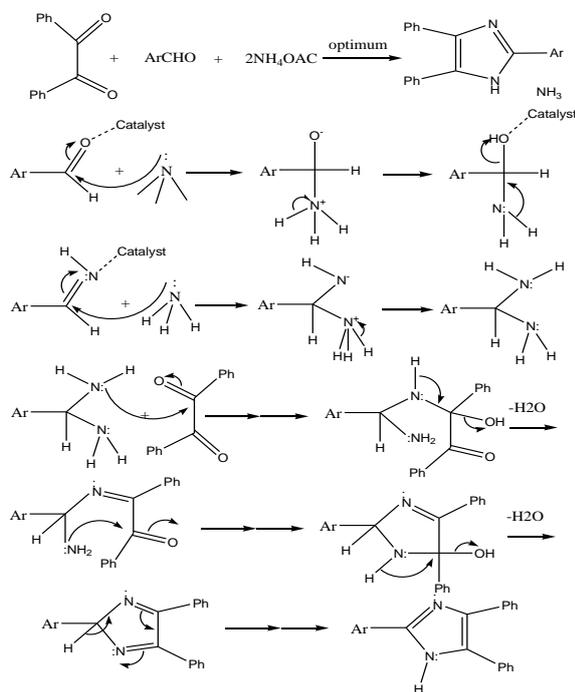
2.3. Typical procedure for the synthesis of 2,4,5-triphenyl-1H-imidazole

A mixture of 0.01 g SiO₂/Fe₃O₄/SO₃H (10% mol), benzil (0.21 g, 1 mmol), benzaldehyde (0.154 g, 1.1 mmol) and NH₄OAc (0.154 g, 2 mmol) was poured into a balloon, and then stirred to reaching an appropriate time, temperature, etc under optimum conditions (Tables 1 to 7). We monitored the reaction by using a thin layer of chromatography (TLC). We should point out that the abovementioned SiO₂/Fe₃O₄/SO₃H acted as

a catalyst during the reaction. The catalyst was separated by exposing it to an external magnetic field. The remaining solid was filtered from the solution and recrystallized with ethanol or 2-propanol to obtain the pure product. The reaction yield was 95% (0.281 g) and also the melting point was 267–269 °C [43]. Melting points recorded following the final product were compared with the corresponding literature. The yielded melting point matched completely.



Scheme 2. Nanomagnetic acid catalyst: a) disperse b) separated by an external magnet



Scheme 3. The scheme shows a plausible mechanism related to the formation of Trisubstituted Imidazoles.

3. Results and discussion

Formation of nanomagnetic acid catalyst ($\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$) which has been shown in scheme 1 was fully described in the previous section. The schematic of catalyst separating by an external magnet

shown in scheme 2 illustrates the magnetic properties of catalyst. The factors which outstands our innovation relating to magnetic separation of catalyst from the final product is its separation simplicity. The trisubstituted imidazoles synthesizing plausible mechanism illustrated in Scheme 3 will be summarized as following:

The catalyst activated the aldehyde by withdrawing its electrons. Then the free electron pair of an ammonia attacked the activated carbon of aldehyde.

Then the activated carbon of aldehyde was attacked again by free electron pair of another ammonia. The reaction between the produced diamine and diketone led to synthesizing one of the imidazole derivatives [44]. To obtain $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$, the nano Fe_3O_4 particles were accumulated on nano SiO_2 particles, then the SO_3H group coated the nano Fe_3O_4 particles.

When $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$ nanomagnetic particles obtained, we used it as a catalyst for synthesizing of imidazole derivatives.

The FT-IR spectra of the $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$ recorded by FT-IR spectrophotometer in the range of 400–4000 cm^{-1} has been shown in figure 1. The **blue** spectrum is related to SiO_2 : the band at 467 cm^{-1} belongs to bending vibration of Si-O-Si, the band at 815 cm^{-1} has been assigned to Si-O-Si symmetric stretching vibrations. The very strong and broad band at 1130 cm^{-1} with a shoulder at 1211 cm^{-1} has been assigned to the Si-O-Si asymmetric stretching vibrations. The weak band at 958 cm^{-1} relates to the non bridging oxygen stretching vibration of silanol Si-O groups. The band at 3200–3400 cm^{-1} relates to the stretching vibration of H_2O molecules, correspondingly, the band at 1632 cm^{-1} relates to the bending vibration of H_2O molecules. The **red** spectrum in figure 1 related to $\text{SiO}_2/\text{Fe}_3\text{O}_4$: the broad band at 636 cm^{-1} belongs to stretching vibration of Fe-O, the band at 955 belongs to bending vibration of Fe-OH, the bands at 1280 cm^{-1} has been assigned to Fe-O-Si asymmetric stretching, the broad band at 1133 cm^{-1} and 1215 cm^{-1} belongs to the Si-O-Si asymmetric stretching vibrations. The band at 3200–3400 cm^{-1} and 1650 cm^{-1} relates to H_2O stretching and bending

vibration respectively. The **green** spectrum in figure 1 relates to $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$: the band at 467 cm^{-1} belongs to bending vibration of Si-O-Si, the band at 660 cm^{-1} belongs to S-O stretching.

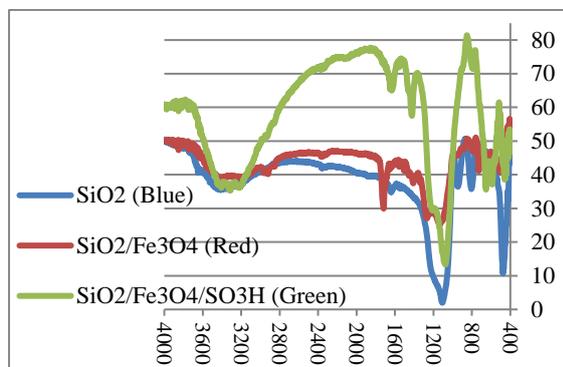
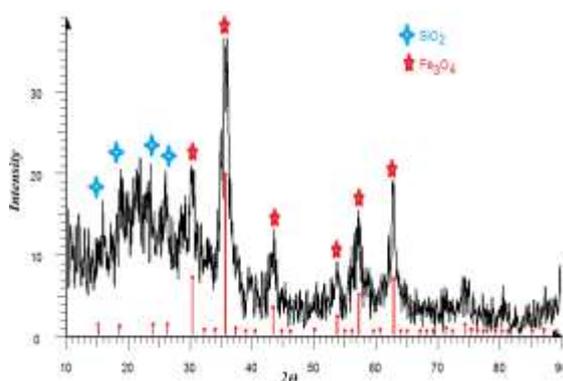


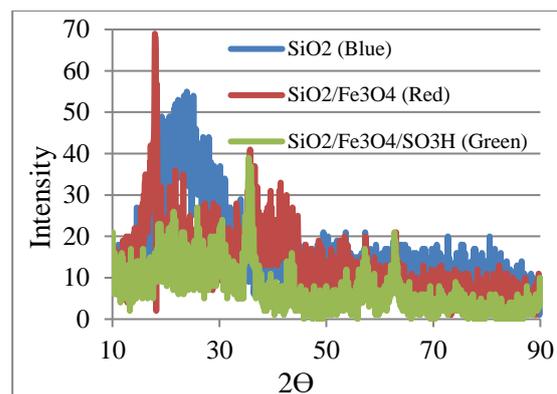
Fig. 1. FT-IR spectra of $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$ nanomagnetic particles

the band at 1228 cm^{-1} and 1431 cm^{-1} relate to symmetric and asymmetric stretching of S=O respectively (The band at 1228 cm^{-1} overlaps with Si-O-Si asymmetric stretching band between 1130 to 1200 cm^{-1} .), the band at 3200 - 3400 cm^{-1} has been assigned to the stretching vibration of H_2O molecules, correspondingly, the band at 1635 cm^{-1} relates to the bending vibration of H_2O molecules.

The XRD peaks has been shown in figure 2. The SiO_2 peak appears at 2θ of 15 to 30 in figures 2a and 2b blue of which intensity was decreased due to it is covered with Fe_3O_4 which has been shown in figure 2b red. As figure 2b green illustrates, the SO_3H has completed the cover. The pattern at 2θ of 30, 36, 43, 54, 57 and 63 belong to the spinel reflection inverse of Fe_3O_4 nanoparticles which has been illustrated in figure 2a.



a



b

Fig. 2. XRD pattern of:

- a) $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$.
b) SiO_2 (blue) and $\text{SiO}_2/\text{Fe}_3\text{O}_4$ (red) and $\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$ (green)

In this step, nano-sized and spherical structure of catalyst is going to be confirmed with transmission electron microscopy (TEM) which has been shown in figure 3. According to a calculation performed with a software called Image Program, figure 3 indicates that the catalyst has been composed of 98-nm sphere SiO_2 and 9-nm Fe_3O_4 . The SO_3H at the surface of the catalyst was detected with the acid layer test. The amount mentioned earlier shows that such amount is among the highest acid layers on the surface of the catalyst [45-48].

As shown in figure 4, TGA analysis of the catalyst has been performed in the temperature conditions from 25 to $800\text{ }^\circ\text{C}$ at a heating rate of $10\text{ }^\circ\text{C min}^{-1}$. The TGA curve analysis shows that the catalyst has lost its mass slightly prior to reaching $140\text{ }^\circ\text{C}$ because of losing its water and solvent, between 140 to $500\text{ }^\circ\text{C}$ because of losing the SO_3H group, and finally the catalyst has decomposed completely over $500\text{ }^\circ\text{C}$.

The EDS spectrum in figure 5 which shows energy versus intensity (count) proves that the catalyst contains S, Fe and Si elements.

Figure 6 shows a VSM spectrum performed at room temperature. The spectrum inferred that the saturation magnetization is equal to 47.6 (emu/g) . The result proves the high ability of nanocatalyst in response to the external magnetic field as we claimed before.

After confirming nanomagnetic acid catalyst ($\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$), we used it to synthesis the imidazole derivatives. Unlike some of the previous methods which were hard and time consuming and expensive, ours is time and energy saving, and low cost. Furthermore, we have simplified the production method by using ordinary existing laboratory instruments.

Explanations relating to the following tables:

By referring to Item number 5 in Table 1, we infer that our produced catalyst ($\text{SiO}_2/\text{Fe}_3\text{O}_4/\text{SO}_3\text{H}$) has the highest yield among other kinds of catalysts.

Table 2 shows condition optimization of the catalyst mass. The table infers that adding mass to the reaction affects only up to 0.01 gram.

Table 3 shows that adding any kinds of solvent to the reaction decreases the yield.

Table 4 infers that increasing temperature of the reaction affects only up to 110 degrees of Centigrade.

Table 5 shows that needed time to complete the reaction is just up to forty-five minutes. In other words, spending more than the mentioned time is wasting time and energy.

Table 6 shows the repeatability of the catalyst which means we can use the catalyst for several times. The more we use and reuse the catalyst, the more it loses its yield, but the loss can be ignored.

Table 7 compares the electron donating and electron withdrawing groups in which the methoxy group acts as an electron donator and nitrogen dioxide group acts as an electron withdrawing agent. By applying electron donating aldehyde, C=O bond loosens. As a result, it is absorbed with the catalyst more easily. The '97%' shown in the table 7 confirms our claim about palusible mechanism in scheme 3. On the other hand, the electron withdrawing group decreases the yield up to 85% [44].

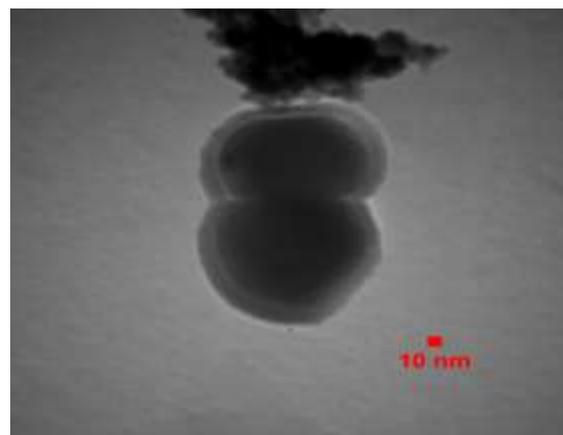


Fig. 3. TEM Image of nanomagnetic acid catalyst.

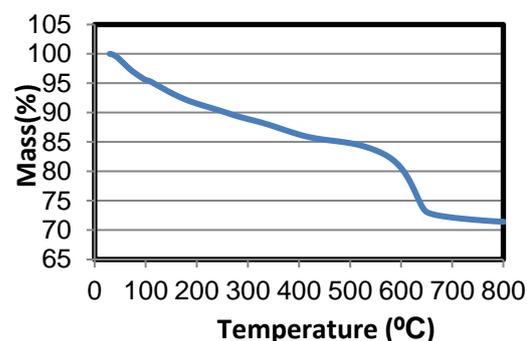


Fig. 4. TGA spectra of nanomagnetic acid catalyst.

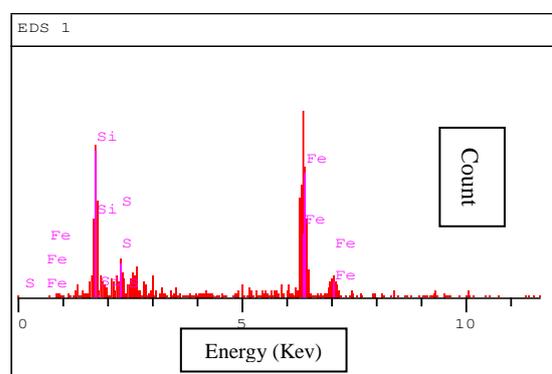


Fig. 5. EDS spectrum of nanomagnetic acid catalyst.

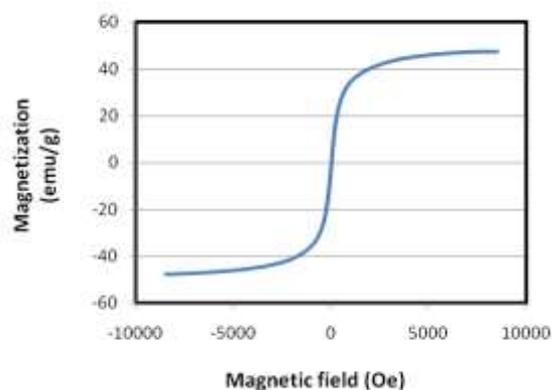


Fig. 6. VSM spectrum of nanomagnetic acid catalyst.

4. Conclusion

It was our group who proposed the new nanomagnetic acid catalyst (SiO₂/Fe₃O₄/SO₃H) for the first time. Some outstanding advantages of our produced catalyst are as following:

- 1) This heterogeneous catalyst has a high acid layer which can be used to synthesis heterocyclic compound such as imidazoles.
- 2) The catalyst has a vast surface because of its nano spherical structure.
- 3) Its removal from any reaction is done with an external magnet easily.
- 4) It can be reused several times without much deterioration.
- 5) Its synthesis is low-cost, time and energy saving, environmental friendly and user friendly.
- 6) Comparing to other catalysts mentioned in papers we have ever read and referring to Table 1 in the present work, our produced catalyst has the highest percentage of yield [49-51].

We hope our catalyst will be used in drug delivery fields.

Table 1. Finding the *best catalyst* for synthesis of 2,4,5-triphenyl-1H-imidazole.

Item Number	Catalyst Type	Yield
1	-	Trace
2	SiO ₂	Trace
3	Nano Fe ₃ O ₄	48
4	SiO ₂ /Fe ₃ O ₄	46
5	SiO ₂ /Fe ₃ O ₄ /SO ₃ H	95
6	AlCl ₃	60 [49]
7	FeCl ₃	45 [49]
8	LaCl ₃	78 [49]
9	DABCO	92 [50]
10	InCl ₃ .3H ₂ O	82 [51]
11	SnCl ₂ .2H ₂ O	48 [51]
12	CoCl ₂ .2H ₂ O	39 [51]
13	NiCl ₂ .2H ₂ O	41 [51]
14	H ₃ BO ₃	34 [51]
15	Mg(OAc) ₂ .2H ₂ O	51 [51]

Table 2. Optimization of *catalyst mass* for synthesis of 2,4,5-triphenyl-1H-imidazole

Fix Parameter	Catalyst Mass(g)	Yield (%)
0.105g benzyl (0.5 mmol)	0	0
0.056ml benzaldehyde (0.5mmol)	0.005	70
0.154g ammonium acetate(2mmol)	0.01	89
1.5h	0.015	89
78 °C		
3ml ethanol		

Table 3. Effect of *solvent type* for synthesis of 2,4,5-triphenyl-1H-imidazole

Fix Parameter	Solvent Type	Yield (%)
0.105g benzyl (0.5 mmol)	Acetonitril	85
0.056ml benzaldehyde (0.5mmol)	Methanol	73
0.154g ammonium acetate(2mmol)	DMSO	60
1.5h	Ethanol	89
reflux		
0.01g catalyst	Solvent free	92

Table 4. Optimization of *temperature* for synthesis of 2,4,5-triphenyl-1H-imidazole

Fix Parameter	Temperature (°C)	Yield (%)
0.105g benzyl (0.5 mmol)	80	92
0.056ml benzaldehyde (0.5mmol)	100	93
0.154g ammonium acetate(2mmol)	110	95
1.5h		
0.01g catalyst	130	95
Solvent Free		

Table 5. Optimization of *time* for synthesis of 2,4,5-triphenyl-1H-imidazole

Fix Parameter	Time (min)	Yield (%)
0.105g benzyl (0.5 mmol)	30	94
0.056ml benzaldehyde (0.5mmol)	45	95
0.154g ammonium acetate(2mmol)		
0.01g catalyst	90	95
Solvent Free		
110 °C		

Table 6. *Repeatability* of catalyst for synthesis of 2,4,5-triphenyl-1H-imidazole

Fix Parameter	repeat	Yield (%)
0.105g benzyl (0.5 mmol)	1	95
0.056ml benzaldehyde (0.5mmol)	2	94
0.154g ammonium acetate(2mmol)		
0.01g catalyst	3	92
Solvent Free		
110 °C		
45 min		

Table 7. Synthesis of imidazoles derivatives, in optimum condition at the presence of different aldehydes^a

Entry	Aldehyde	Time (min)	Yield ^b (%)	Melting Point	
				Found	Reported
1	Ar-CHO	45	95	267-269	267-269 [43, 44]
2	2-OH-Ar-CHO	40	96	203-205	202-205 [44]
3	4-OMe-Ar-CHO	50	97	220-221	220-223 [44]
4	4-NO ₂ -Ar-CHO	100	85	237-238	235-238 [44]

^a Reaction condition: 0.5mmol Benzyl + 0.5mmol Aryl aldehyde + 2 mmol Ammonium acetate + 0.01g catalyst in 110 °C and Solvent free condition.

^b Isolated yield.

Acknowledgments

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