Research Article

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Magnetic nanoparticle-supported sulfonic acid as a green catalyst for the one-pot synthesis of 2,4,5-trisubstituted imidazoles and 1,2,4,5-tetrasubstituted imidazoles under solvent-free conditions

<https://doi.org/10.1515/hc-2020-0125>

received December 17, 2020; accepted July 23, 2021

Abstract: In this work, magnetic nanoparticle-supported sulfonic acid ($\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$) is used as an efficient catalyst in the synthesis of 2,4,5-trisubstituted imidazoles and 1,2,4,5-tetrasubstituted imidazoles in a short time (40–70 min for trisubstituted imidazoles and 30–40 min for tetrasubstituted imidazoles) and high-purity products were obtained (92–98% for trisubstituted imidazoles and 94–98% for tetrasubstituted imidazoles) in simple multicomponent reactions. The structure of these products was confirmed via FT-IR and NMR. Green and recyclable catalysts, eco-friendly and solvent-free conditions, high catalytic activity, shorter reaction time, easy recovery by an external magnet, high purity, and excellent yields are some features of these reactions.

Keywords: green chemistry, multicomponent reactions, $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$, 2,4,5-trisubstituted imidazoles, 1,2,4,5-tetrasubstituted imidazoles, solvent-free conditions, recyclable catalysts

1 Introduction

Due to the effects of the chemical industry on the environment since the 1940s, fundamental changes have been

carried out to increase the adoption of green chemistry principles [1,2]. Therefore, due to the significance of green chemistry goals, the use of green catalysts, especially nanocatalysts, has strongly attracted scientific interest. Owing to the properties of magnetic nanocatalysts such as large special surface area and simple separation with external magnets, [3–7] they play a crucial role in the removal of hazardous and toxic compounds from the environment.

Multicomponent reactions (MCRs) have applications in organic and medicinal chemistry that produce complex products from simple substances in one-pot processes. These reactions, which follow green chemistry concepts, are recognised as one of the most effective and economical methods for synthesising complex molecules in recent decades [8]. Imidazoles, one of the important heterocycles [9], can be synthesised by this method. Imidazoles have pharmaceutical and medicinal properties and are used in pesticides, dyeing, agent for resins, polymers, anion sensors, and ionic liquids [10,11]. Moreover, imidazole derivatives have been found to be anti-fungal, anti-bacterial, anti-malarial, anti-nociceptive, anti-inflammatory, anti-hypertensive, hypoxic cell therapy, imaging agents, anti-cancer, and anti-plasmodium [10–12]. In addition, imidazoles are an important component of natural compounds such as vitamin B12, histamine, histidine, and biotin [11].

According to the importance of green chemistry goals, in this project, we use magnetic particle-supported sulfonic acid ($\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$) [13] as a recyclable catalyst in the synthesis of 2,4,5-trisubstituted imidazoles and 1,2,4,5-tetrasubstituted imidazoles, which are valuable biologically active compounds [14], in a simple one-pot procedure from which substituted imidazoles were obtained with high efficiency and purity.

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2 Results and discussion

2.1 Optimisation of reaction conditions for the preparation of substituted imidazoles

Firstly, to optimise the reaction conditions for the preparation of 2,4,5-trisubstituted imidazoles, condensation of benzil (1 mmol), ammonium acetate (5 mmol) and benzaldehyde (1 mmol) in the presence of the γ -Fe₂O₃-SO₃H catalyst (10 mol%) under solvent-free conditions was selected as a model reaction (Scheme 1). Then, different amounts of the catalyst were studied. As shown in Table 1 entry 2a, the use of 10 mol% of the γ -Fe₂O₃-SO₃H catalyst afforded the best efficiency (94% for trisubstituted imidazoles). Further increasing the amount of catalyst did not improve the efficiency (Table 1, entry 3a).

Secondly, we examined the effect of different temperatures on the yield, under solvent-free conditions. The highest efficiency was achieved at 100°C (94%) for the synthesis of 2,4,5-trisubstituted imidazoles (Table 2, entry 3a). As indicated in Table 2, increasing the reaction temperature from 80 to 100°C resulted in an improvement in yield from 85 to 94% (Table 2, entries 1a and 3a), but upon increasing the temperature to 120°C the reaction yield decreased to 88% due to the formation of by-products (Table 2, entry 4a). All of the reactions were monitored by TLC. Further reactions were performed at 100°C.

Thirdly, the reaction was examined in various solvents. As shown in Table 3, solvent-free conditions resulted in higher yields than those obtained in any of the solvents investigated (Table 3, entry 6a).

For 1,2,4,5-tetrasubstituted imidazoles, a mixture of benzil (1 mmol), ammonium acetate (2 mmol), benzaldehyde (1 mmol), and aniline (2 mmol) in the presence of the γ -Fe₂O₃-SO₃H catalyst (10 mol%) under solvent-free

Table 1: Optimisation of catalyst amount for model reactions (a: trisubstituted imidazole, b: tetrasubstituted imidazole)

Entry	Catalyst amount (mol%)	Time (min) 1a	Yield (%)* 1a	Time (min) 1b	Yield (%)* 1b
1	5	50	90	40	92
2	10	50	94	40	97
3	20	50	92	40	94

*Yields refer to isolated products.

Table 2: Optimisation of temperature for model reactions (a: trisubstituted imidazole, b: tetrasubstituted imidazole)

Entry	Temperature (°C)	Time (min) 1a	Yield (%)* 1a	Time (min) 1b	Yield (%)* 1b
1	80	50	85	40	85
2	90	50	90	40	87
3	100	50	94	40	97
4	120	50	88	40	91

*Yields refer to isolated products.

conditions was selected as the model reaction (Scheme 1). The catalyst loading, temperature and solvent condition optimisation steps were repeated. The best yield (97%) was obtained in the presence of 10 mol% catalyst (Table 1, entry 2b) at 100°C (Table 2, entry 3b) under solvent-free conditions (Table 3, entry 6b).

Inspired by previous reports [15–17], a possible mechanism for the synthesis of 2,4,5-trisubstituted imidazoles using a γ -Fe₂O₃-SO₃H catalyst is illustrated in Scheme 2. In the process, γ -Fe₂O₃-SO₃H as an acidic catalyst can activate the aldehyde and the 1,2-diketone, which react with ammonium acetate to form imine intermediates. Then, the imine nitrogen

Scheme 1: One-pot synthesis of polysubstituted imidazoles in the presence of the γ -Fe₂O₃-SO₃H catalyst (a: trisubstituted imidazole, b: tetrasubstituted imidazole).

Table 3: Solvent effect on the model reactions (a: trisubstituted imidazole, b: tetrasubstituted imidazole)

Entry	Solvent	Condition 1a	Yield (%) [*] 1a	Condition 1b	Yield (%) [*] 1b
1	EtOH	10 mL/50 min/60°C	85	10 mL/40 min/50°C	80
2	MeOH	10 mL/50 min/60°C	74	10 mL/40 min/40°C	68
3	THF	10 mL/50 min/60°C	40	10 mL/40 min/60°C	55
4	DMSO	10 mL/50 min/100°C	30	10 mL/40 min/100°C	45
5	CH ₃ CN	10 mL/50 min/60°C	50	10 mL/40 min/60°C	50
6	Solvent-free	50 min/100°C	94	40 min/100°C	97

^{*}Yields refer to isolated products.

Scheme 2: Mechanism for the synthesis of trisubstituted imidazoles.

of imine intermediate (1) reacts with the positive carbonyl carbon of 1,2-diketone imine intermediate (2) to form carbocation (3). Finally, dehydration and the sigmatropic shift results in the 2,4,5-trisubstituted imidazole. In addition, a similar mechanism is suggested for the synthesis of 1,2,4,5-

tetrasubstituted imidazoles, except that at the beginning of the reaction amine derivatives participate instead of ammonium acetate [18].

An investigation was also performed to optimise the amount of ammonium acetate used in this reaction under solvent-free conditions, and the best result was achieved with 5 mmol ammonium acetate (Table 4, entry 3).

In the synthesis of trisubstituted imidazoles, several aromatic aldehydes with electron-withdrawing or electron-donating substituent groups were evaluated. High efficiency was achieved for substituent groups in *ortho*, *meta* or *para* positions of the aromatic ring (Table 5). Similar results were obtained for the synthesis of tetrasubstituted imidazoles from combinations of differently substituted aromatic aldehydes and amine derivatives (Table 6). The structure of polysubstituted imidazoles was characterized by IR and NMR.

Table 7 compares the performance of $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ with several other reported catalysts for the synthesis of substituted imidazoles. As one can see, high efficiency and a short time for the reaction are the features of this catalyst.

After the reaction completion, the $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ catalyst used can be easily separated from the products by an external magnet and reused. Therefore, the catalyst was recycled and reused several times in subsequent reactions. At the end of these reactions, the products were still obtained with satisfactory yields (Figure 1).

Table 4: Optimisation of the ammonium acetate amount for model reactions (a: trisubstituted imidazole, b: tetrasubstituted imidazole)

Entry	NH ₄ OAc amount (mmol)	Condition 1a	Yield (%) [*] 1a	Condition 1b	Yield (%) [*] 1b
1	1.5	50 min/100°C	70	40 min/100°C	72
2	3	50 min/100°C	79	40 min/100°C	83
3	5	50 min/100°C	94	40 min/100°C	97

^{*}Yields refer to isolated products.

Table 5: One-pot synthesis of trisubstituted imidazoles catalysed by γ -Fe₂O₃-SO₃H

Compound	R ¹	Time (min)	Yield (%) [*]	M.p. (°C)
1a	C ₆ H ₅	50	94	277–279 [19]
2a	4-ClC ₆ H ₄	55	97	266–268 [20]
3a	2-ClC ₆ H ₄	40	98	194–196 [19]
4a	4-MeOC ₆ H ₄	50	98	231–233 [9]
5a	2-MeOC ₆ H ₄	40	95	208–210 [20]
6a	4-FC ₆ H ₄	40	95	253–255 [21]
7a	4-BrC ₆ H ₄	50	96	260–262 [9]
8a	2-HOC ₆ H ₄	55	90	212–214 [9]
9a	3-O ₂ NC ₆ H ₄	60	93	321–323 [22]
10a	4-O ₂ NC ₆ H ₄	60	92	241–243 [9]
11a	4-MeC ₆ H ₄	70	93	232–235 [20]
12a	2,4-Cl ₂ C ₆ H ₃	65	97	173–175 [9]
13a	3-HOC ₆ H ₄	50	94	261–263 [23]
14a	3-BrC ₆ H ₄	50	95	303–305 [23]
15a	3,4-(MeO) ₂ C ₆ H ₃	40	96	220–222 [9]
16a	4-(Me) ₂ NC ₆ H ₄	60	92	256–258 [20]

^{*}Yields refer to isolated products.

Table 6: One-pot synthesis of tetrasubstituted imidazoles catalysed by γ -Fe₂O₃-SO₃H

Compound	R ¹	R ²	Time (min)	Yield (%) [*]	M.p. (°C)
1b	C ₆ H ₅	C ₆ H ₅	40	97	219–221 [9]
2b	2-HOC ₆ H ₄	C ₆ H ₅	30	98	252–254 [24]
3b	4-ClC ₆ H ₄	C ₆ H ₅	35	98	171–173 [9]
4b	4-MeOC ₆ H ₄	C ₆ H ₅	40	97	180–182 [25]
5b	4-MeC ₆ H ₄	C ₆ H ₅	35	96	185–187 [26]
6b	4-Br C ₆ H ₄	C ₆ H ₅	30	95	193–195 [27]
7b	3-HOC ₆ H ₄	C ₆ H ₅	25	96	186–188 [27]
8b	3-O ₂ NC ₆ H ₄	C ₆ H ₅	35	95	242–245 [28]
9b	4-O ₂ NC ₆ H ₄	C ₆ H ₅	40	96	196–198 [28]
10b	4-HOC ₆ H ₄	C ₆ H ₅	20	97	285–287 [9]
11b	3-BrC ₆ H ₄	C ₆ H ₅	35	95	148–150 [29]
12b	2-HOC ₆ H ₄	4-MeC ₆ H ₄	40	97	222–225 [9]
13b	4-MeC ₆ H ₄	4-MeC ₆ H ₄	40	96	196–198 [9]
14b	3-O ₂ NC ₆ H ₄	4-MeC ₆ H ₄	25	97	155–157 [9]
15b	4-O ₂ NC ₆ H ₄	4-MeC ₆ H ₄	30	94	220–222 [9]
16b	3-HOC ₆ H ₄	4-MeC ₆ H ₄	35	94	229–231 [9]
17b	4-ClC ₆ H ₄	4-ClC ₆ H ₄	35	95	182–185 [26]
18b	4-MeC ₆ H ₄	4-ClC ₆ H ₄	30	97	169–170 [26]

^{*}Yields refer to isolated products.

3 Conclusion

Here, we introduce a simple method for producing 2,4,5-trisubstituted imidazoles and 1,2,4,5-tetrasubstituted imidazoles, valuable heterocyclic compounds with pharmaceutical properties and medical applications, in a simple

one-pot procedure with a recyclable catalyst in a green process. This project has various advantages such as a recyclable catalyst, high catalytic activity, eco-friendly solvent-free conditions, short reaction time, easy separation of catalyst by an external magnet, high-purity products, and excellent yields.

Table 7: Comparison of the γ -Fe₂O₃-SO₃H catalyst with several catalysts for the synthesis of imidazoles

Entry	Catalyst	Condition for trisubstituted imidazoles	Yield (%)	Condition for tetrasubstituted imidazoles	Yield (%)
1	[(CH ₂) ₄ SO ₃ HMIM] [HSO ₄] [30]	—	—	SF/140°C/150 min	88
2	SASPSPE [29]	—	—	SF/140°C/70 min	89
3	PTSA [31]	Ethanol/80°C/60 min	90	Ethanol/80°C/60 min	84
4	Y(NO ₃) ₃ ·6H ₂ O [32]	SF/140°C/50 min	90	—	—
5	ZnO nanorods [20]	H ₂ O/reflux/150 min	80	—	—
6	I ₂ [12]	DMSO/130°C, EtOH/100°C/ 1440-120	86	—	—
7	This work	SF/100°C/50 min	94	SF/100°C/40 min	97

Figure 1: The reusability of the catalyst for model reactions (a: Trisubstituted imidazole and b: tetrasubstituted imidazole).

4 Experimental section

4.1 General

All chemicals used in this study were commercially available, synthesis-grade compounds, purchased from Merck or Fluka and used without any further purification. The products were identified by comparison of their melting points and spectral data with those reported in the literature. Melting points were recorded on the Electrothermal 9100 apparatus and are uncorrected. The reaction progress was monitored by TLC on commercial aluminum-backed plates of silica gel 60 F₂₅₄, using ultraviolet light. FT-IR spectra were obtained with a Shimadzu 8400 spectrometer in the range 400–4000 cm⁻¹ and the ¹H NMR (500 or 300 MHz) and ¹³C NMR (125 or 75 MHz) spectra were recorded on a Bruker Avance 300 spectrometer in

pure deuterated chloroform, with tetramethylsilane (TMS) as the internal standard.

4.2 General procedure for the synthesis of the γ -Fe₂O₃-SO₃H catalyst

According to the reported method [13,33–35] for the synthesis of the desired γ -Fe₂O₃-SO₃H catalyst, 3 g of γ -Fe₂O₃ nanoparticles and chlorosulfonic acid (1.163 g, 9.98 mmol) was added over a period of 30 min (Scheme 3). For comparison with the reported literature [13], the γ -Fe₂O₃-SO₃H catalyst particles were characterized via FT-IR, XRD, TGA, XPS, TEM, titration, VSM, and DLS.

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

A mixture of benzil 1 (1 mmol), ammonium acetate (5 mmol), aromatic aldehyde (1 mmol), and the γ -Fe₂O₃-SO₃H catalyst (10 mol%) was stirred at 100°C under solvent-free conditions for an appropriate time. The progression of the reaction was monitored by TLC. After completion of the reaction, acetone was added to the contents of the reaction vessel, the product was completely dissolved in acetone, and the catalyst was separated by an external magnet. For further purification, the solid product was recrystallised from acetone/water 9:1 (v/v) to obtain the pure product.

Scheme 3: Synthesis of the γ -Fe₂O₃-SO₃H catalyst.

4.3.1 2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (2a)

M.p.: 266–268°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 690, 750, 830, 1,475, 1,600, 3,100, 3,400. ^1H NMR (500.13 MHz, DMSO- d_6), δ/ppm : 7.25–7.82 (m, 14H, H-Ar), 12.60 (s, 1H, –NH).

4.3.2 2-(2-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (5a)

M.p.: 208–210°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 690, 750, 900, 1,475, 1,600, 1,650, 3,100, 3,300. ^1H NMR (500.13 MHz, DMSO- d_6), δ/ppm : 3.882 (s, 3H, OCH₃), 6.862–8.025 (m, 14H, H-Ar), 11.855 (s, 1H, NH).

4.3.3 2-(2,4-Dichlorophenyl)-4,5-diphenyl-1H-imidazole (12a)

M.p.: 173–175°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 690, 900, 1,475, 1,560, 1,600, 3,100, 3,300. ^1H NMR (500.13 MHz, DMSO- d_6), δ/ppm : 7.175–7.808 (m, 13H, H-Ar), 12.658 (s, 1H, NH).

4.3.4 2-(3-Bromophenyl)-4,5-diphenyl-1H-imidazole (14a)

M.p.: 303–305°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 690, 900, 1,075, 1,475, 1,600, 1,650, 3,100, 3,300. ^1H NMR (500.13 MHz, DMSO- d_6), δ/ppm : 7.234–8.314 (m, 14H, H-Ar), 12.99 (s, 1H, NH).

4.3.5 2-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1H-imidazole (15a)

M.p.: 220–222°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1475, 1,600, 1,650, 3,100, 3,400. ^1H NMR (500.13 MHz, DMSO- d_6), δ/ppm : 3.137 (s, 3H, OCH₃), 3.814 (s, 3H, OCH₃), 7.014–7.636 (m, 13H, H-Ar), 12.477 (s, 1H, NH).

4.4 General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles

A mixture of benzil (1 mmol), ammonium acetate (2 mmol), aromatic aldehyde (1 mmol), amine derivative (2 mmol), and the $\gamma\text{-Fe}_2\text{O}_3\text{-SO}_3\text{H}$ catalyst (10 mol%) was stirred at 100°C under solvent-free conditions for an appropriate time. The progression of the reaction was monitored by

TLC. After the completion of the reaction, acetone was added to the reaction vessel, the product was completely dissolved in the acetone, and the catalyst was separated by an external magnet. For further purification, the solid product was recrystallised from acetone/water 9:1 (v/v) to obtain the pure product.

4.4.1 1,2,4,5-Tetraphenyl-1H-imidazole (1b)

M.p.: 219–221°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 690, 900, 1,475, 1,520, 1,600, 3,100. ^1H NMR (500.13 MHz, DMSO- d_6), δ/ppm : 7.23–7.61 (m, 20H, H-Ar). ^{13}C NMR (125.76 MHz, DMSO- d_6), δ (ppm): 127.136, 129.95, 132.17, 135.87, 138.26.

4.4.2 2-(4-Methylphenyl)-1,4,5-triphenyl-1H-imidazole (5b)

M.p.: 185–187°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 690, 770, 820, 1,475, 1,500, 1,600, 2,920, 3,100. ^1H NMR (500.13 MHz, DMSO- d_6), δ/ppm : 2.28 (s, 3H, CH₃), 7.23–7.61 (m, 19H, H-Ar). ^{13}C NMR (125.76 MHz, DMSO- d_6), δ (ppm): 21.22, 138.26, 138.36, 138.75, 147.29.

4.4.3 3-(1,4,5-Triphenyl-1H-imidazol-2-yl)phenol (7b)

M.p.: 186–188°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 694, 1,274, 1,494, 1,606, 3,060, 3,466. ^1H NMR (500.13 MHz, DMSO- d_6), δ/ppm : 4.675 (s, 1H, OH), 6.475–7.556 (m, 19H, H-Ar).

Acknowledgements: The authors gratefully acknowledge the Semnan University Research Council for supporting this work.

Funding information: The authors state no funding involved.

Conflict of interest: The authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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