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### Applied Organometallic WILEY Chemistry

# Green synthesis of 3,4-disubstituted isoxazol-5(4H)-ones using ZnO@Fe<sub>3</sub>O<sub>4</sub> core-shell nanocatalyst in water

M. Shanshak<sup>1</sup> | Srinivasa Budagumpi<sup>1</sup> | Jan Grzegorz Małecki<sup>2</sup> | Rangappa S. Keri<sup>1</sup>

<sup>1</sup>Centre for Nano and Material Sciences, Jain University, Jain Global Campus, Kanakapura, Ramanagaram, Bangalore, 562112. India

<sup>2</sup>Department of Crystallography, Institute of Chemistry, University of Silesia, 9th Szkolna St., 40-006, Katowice, Poland

#### Correspondence

Rangappa S. Keri, Organic and Medicinal Chemistry Laboratory, Centre for Nano and Material Sciences, Jain University, Jain Global Campus, Jakkasandra post, Kanakapura Road, Ramanagara District, Karnataka 562112, India. E-mail. Email: keriphd@gmail.com; sk. rangappa@jainuniversity.ac.in

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## Abstract

An effective and environmentally benign methodology for the synthesis of isoxazol-5(4H)-one derivatives has been developed using a ZnO@Fe<sub>3</sub>O<sub>4</sub> core-shell nanocatalytic system. The one-pot, multicomponent reaction of an aromatic/heterocyclic aldehyde, hydroxylamine hydrochloride and ethyl acetoacetate under aqueous conditions at slightly elevated temperature resulted in the formation of title compounds in extremely good yields. The present new protocol is environmentally friendly as it offers heterocyclization with some interesting promising features such as safety, atom efficiency, low cost, mild conditions, minimal waste, catalyst recyclability, water as a solvent, easy workup and possession of excellent functional group tolerance for the synthesisis of structurally diverse isoxazole derivatives. All products were characterized by spectral and analytical methods. A representative title derivative was studied for its structure by single crystal X-ray diffraction method.

### **KEYWORDS**

Fe<sub>3</sub>O<sub>4</sub>, green synthesis, isoxazoles, multicomponent reaction, nanocatalyst

#### 1 INTRODUCTION 1

Functionalized heterocyclic small molecules are important in the discovery of new drug molecules owing to their selective binding ability to the biological targets.<sup>[1]</sup> Development of organic transformations for the construction of bioactive heterocyclic molecules that can serve as effective drug molecules in a reduced number of synthetic steps with high molecular complexity is a key aspect of green chemistry. In the past decade, the synthesis of heterocyclic molecules through one-pot multicomponent reactions has gained considerable attention as they avoid multistep synthesis and consequently reduce costs. Therefore, these reactions can efficiently assist as synthetic tools for the formation of structurally combined molecular frameworks that suitable for diverse biological applications.<sup>[2]</sup> are

Multicomponent reactions, where three or more accessible reactants react together in one step to form a single product without isolating the intermediates, have been found to be effective from an industry perspective as they reduce the required labor and energy, simplify workup and improve cost-effectiveness, among other advantages.<sup>[3]</sup> Multicomponent reactions offer many benefits such as shorter reaction times, high yields, reduced waste generation, minimized reagent comsumption and purification stages, and many other significant advantages over conventional multistep synthesis. Meanwhile, the pharmaceutical industry supports the use of water rather than toxic organic solvents for the synthesis of drug entities. As a result, much effort has been directed towards using water as a solvent for organic reactions in recent years.<sup>[4]</sup>

Nitrogen-containing heterocycles are core structures of numerous bioactive natural and synthetic compounds. A recent analysis showed that nearly 60% of small-molecule-based drugs approved by the US Food and Drug Administration contain at least one N-heterocyclic moiety.<sup>[5]</sup> Among these, isoxazole and its derivatives are an important class of nitrogen- and oxygen-containing heterocyclic compounds with a variety of applications in the pharmaceutical industry, medicinal chemistry and organic synthesis, as well as optoelectronic and lightconversion molecular devices.<sup>[6]</sup> Among isoxazoles, 3,4-disubstituted isoxazol-5(4H)-ones are attractive targets in both medicinal chemistry and organic synthesis.<sup>[7,8]</sup> These heterocyclic systems play an important role in the field of chemotherapy and agrochemicals owing to their properties, such as antitumor,<sup>[9]</sup> anti-HIV,<sup>[10]</sup> fungicidal,<sup>[11]</sup> antiobesity,<sup>[12]</sup> selective inhibition of protein kinase C<sup>[13]</sup> and enzyme inhibition.<sup>[14]</sup> Owing to the broad biological and material importance of this heterocycle, researchers have reported various methods to construct different motifs depending on the target applications.

Essentially, these heterocyclic compounds have been synthesized via a multicomponent condensation reaction of various aldehydes,  $\beta$ -keto esters and hydroxylamine hydrochloride in the presence of a catalyst. A number of catalysts have been used in one-pot multicomponent reactions for the synthesis of isoxazol-5(4H)-one scaffolds including boric acid,<sup>[15]</sup> citric acid,<sup>[16]</sup> molecular iodine, KI, Ag/SiO<sub>2</sub>, 4-(*N*,*N*-dimethylamino) pyridinium acetate, tetrabutylammonium perchlorate/glycine/sodium oxalate, amine-modified montmorillonite nanoclay, antimony trichloride, mesolite, DABCO functionalized dicationic ionic liquid, nano-MgO, sodium silicate pentahydrate, citrus fruit juice, pyridinium p-toluenesulfonate, cerium chloride heptahydrate, pyridine, nickel (II) acetate and many more.<sup>[17]</sup> Also, advanced techniques such as microwave heating,<sup>[18]</sup> grinding,<sup>[19]</sup> ultrasonic irradiation<sup>[20]</sup> and visible light in the presence of sodium acetate in aqueous EtOH<sup>[21]</sup> have also been reported for the preparation of isoxazol-5(4H)-ones, Although many of these protocols suffer from drawbacks and limitations such as low yields/long reaction times, strongly acidic or basic conditions and the use of toxic reagents, stringent reaction conditions, the use of expensive catalyst, multistep synthetic sequence and difficult work up procedures that restrict their scope in practical applications. Considering the above points, we report an efficient and green method for the synthesis of a wide variety of isoxazol-5(4H)-one derivatives via the one-pot, three-component process catalyzed by ZnO@Fe<sub>3</sub>O<sub>4</sub> core-shell nanoparticles under aqueous conditions (Scheme 1).



**SCHEME 1** Synthesis of 3,4-disubstituted isoxazole-5(4H)ones catalyzed by ZnO@Fe<sub>3</sub>O<sub>4</sub>

#### 2 | RESULTS AND DISCUSSION

The heterogeneous catalyst was prepared in two steps following literature procedures with slight modification.<sup>[22]</sup> First, Fe<sub>3</sub>O<sub>4</sub> (magnetite nanoparticles) was prepared by the reaction of ferric and ferrous chlorides in water at 80°C for 30 min after which ammonium hydroxide was added and stirred for a further 30 min under the same conditions. Next the obtained precipitate was repeatedly washed with plenty of water and methanol, and dried under vacuum to obtain a black powder of Fe<sub>3</sub>O<sub>4</sub>. Secondly, the ZnO@Fe<sub>3</sub>O<sub>4</sub> core-shell nanoparticles were achieved by subsequent deposition of a layer of ZnO on the surface of magnetite nanoparticles through thermal decomposition of zinc precursor in the presence of magnetite seeds (Scheme SI1). The fourier-transform infrared spectroscopy (FTIR) spectrum of the nanocatalyst showed a strong band at 445  $\text{cm}^{-1}$  as indicated by the vibration of the Zn-O bonding. Other two characteristic peaks near to each other at 536 and 620 cm<sup>-1</sup> were attributed to the vibrations of the Fe-O bonding (Figure SI1). In the UVvis spectrum of the catalyst two absorption maxima at 315 and 371 nm were observed, which were unlike the maxima observed for individual metal oxides (Figure 1a). In the X-ray powder diffraction(p-XRD) pattern of the catalyst, characteristic peaks for Fe<sub>3</sub>O<sub>4</sub> nanoparticles  $(2\theta = 30.16, 35.48, 43.13, 53.49, 56.91 \text{ and } 62.71^{\circ})$  marked by their indices (220, 311, 400, 422, 511 and 440, respectively), were recognized. These peaks are well matched with the magnetite characteristic peaks (ICDD card no. 19-0629). The characteristic peaks for ZnO complex  $(2\theta = 31.84, 34.52, 36.33, 47.63, 56.71, 62.96, 68.13$  and  $69.18^{\circ}$ ) confirm that Fe<sub>3</sub>O<sub>4</sub> nanoparticles are coated with ZnO (Figure 1b). Further, from field emission scanning electron microscope (FESEM) analysis using a 20.0 kV acceleration voltage, uniform-sized magnetic nanoparticles with fairly flake-like morphology were observed for Fe<sub>3</sub>O<sub>4</sub> nanoparticles (Figure 1c) with a marked tendency to form large clusters. Furthermore, the image (Figure 1d) of core-shell nanocatalyst indicates the coating of ZnO over Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles, which was further complemented by energy-dispersive X-ray spectroscopy (EDX) studies (Figure SI2).

Initially, a model reaction was conducted comprising three components, benzaldehyde (1a), hydroxylamine hydrochloride (2) and ethyl acetoacetate (3), with varying FIGURE 1 (a) Stacked UV-vis spectra of bare metal oxides and the core-shell nanocatalyst; (b) p-XRD of core-shell nanocatalyst; (c) FESEM image of Fe<sub>3</sub>O<sub>4</sub> nanoparticles; (d) FESEM image of Fe<sub>3</sub>O<sub>4</sub> nanoparticles decorated with ZnO: (e) molecular structure of isoxazole derivative 4b; hydrogen atoms are excluded due to clarity; (f) Recyclability profile of the nanocatalyst in obtaining 4a under optimized reaction conditions



nanocatalyst loading, temperature and solvent, as these are the important parameters which affect the yield of desired product 4a to a great extent. The effects of the reaction temperature and amounts of catalyst were investigated and the experimental results are summarized in Table 1. First, the reaction was carried out without any catalyst with varying temperature (70, 100 and 120 °C; entries 1, 2 and 3), and a trace amount of product formed. Further, the multicomponent catalytic reaction was carried out with 5 mg of nanocatalyst at room temperature for 40 h in water, which resulted in the formation of trace amount of product (entries 4 and 5). Therefore, the reaction temperature was increased and time decreased to obtain an optimized temperature of 70°C that resulted in the yield of 93% in 30 min. However, further increase in the temperature affected the yield owing to rapid deactivation of the active species. Furthermore, catalyst loading was decreased to 1, 2 and 3 mg (entries 12, 13 and 14), with the corresponding yield of oxazole 47, 63 and 79%, respectively, while loading of 10 mg (entry 16) resulted in the formation of 92% yield. Therefore, a nanocatalyst loading of 5 mg at 70°C for 30 min was considered as optimum reaction conditions for this multicomponent

catalytic heterocyclization reaction. Conversely, the reaction was carried out without catalyst at 70°C, which did not yield any product even after 40 h (entry 1), indicating the significance of the core-shell nanocatalyst.

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With the parameters optimized as water as a solvent and 5 mg of nanocatalyst at 70°C, the universality of the catalytic system was explored. A series of structurally and electronically diverse aldehydes were treated with ethyl acetoacetate and hydroxylamine hydrochloride to access diverse isoxazole derivatives (Scheme 2). All of the substrate variants reacted with 2 and 3 under the optimized reaction conditions to afford corresponding 3,4-disubstituted isoxazol-5(4H)-one products in high yields (57-93%). Aromatic aldehydes bearing electrondonating or electron-withdrawing groups at different positions on the aromatic ring system reacted efficiently and smoothly under the optimized conditions. It was found that substituted benzaldehydes containing electron-donating groups on the phenyl ring at the para and meta positions afforded corresponding heterocyclic products, 4b-4i, in high isolated yields in the range 67-91%. The para nitro and fluoro substituted benzaldehydes resulted in the formation of products with the

	н 1а	2 3 H <sub>2</sub> O	4a 0/2 0	
Entry	Catalyst (mg)	Temperature (°C)	Time (min)	Yield (%) (isolated)
1		70	2400	
2		100	2400	Trace
3		120	2400	Trace
4	5	r.t	2400	Trace
5	5	40	600	Trace
6	5	50	120	45
7	5	60	60	81
8	5	70	30	93
9	5	80	30	92
10	5	90	30	83
11	5	100	30	74
12	1	70	200	47
13	2	70	90	63
14	3	70	90	79
15	5	70	30	93
16	10	70	30	92

TABLE 1 Optimization of the reaction conditions for a multicomponent heterocyclization using ZnO@Fe<sub>3</sub>O<sub>4</sub> core-shell catalyst

lowest and highest percentage yields, respectively. The interesting fact of this protocol is that the ortho-hydroxy benzaldehyde can also undergo cyclocondensation, providing a corresponding product in 57% yield, which is not reported in some of the reported methods. Further, this methodology has also been extended to  $\alpha$ . $\beta$ -unsaturated and heteroaromatic aldehydes, which also reacted very well and afforded good to high yields - 84, 75 and 82% of the corresponding isoxazole-5(4*H*)-ones (4k, 4l and 4m), respectively. This protocol was also applicable to aliphatic and alicyclic aldehydes, which is still under investigation. The model reaction (Scheme 2, Figure SI3) was scalable up to 10 g with mechanical overhead stirring resulting in the formation of the desired product.

To obtain the solid-state bonding and special connectivity information for these isoxazol-5(4H)-ones, a representative derivative, 4d (Figure 1e), was analyzed by single-crystal X-ray diffraction technique (Table SI1). Suitable X-ray quality crystals were obtained through the diffusion of diethyl ether into ethanol solution of isoxazole over a period of 7 days at room temperature. Compound 4d crystalized in a monoclinic system with a C2/c space group having one molecule in an asymmetric unit. Both isoxazole and phenyl ring systems are coplanar,

separated by an angle 133.23(12)° (for C2-C5-C6). Internal bond angles at heteroatoms 109.75(10) (for C1-O1-N1) and 107.33(10)° (for O1-N1-C3) (Table SI2), are in line with the reported isoxazole analogs. Compound 4d possessed weak  $\pi - \pi$  stacking interactions between isoxazole and phenyl rings of adjacent molecules with a centroid-to-centroid distance of 3.444 Å, along with The O3-H3 ... hydrogen bonding interactions.  $N1[-\frac{1}{2} + x, -\frac{1}{2} + y, z]$  hydrogen bond between creates the infinite chain of  $C_1^1(10)$  type along the *a* axis (Table SI3).

Recyclability of the catalyst is an important attribute for industrial suitability. Therefore, the reusability of the nanocatalyst in the model reaction under optimized reaction conditions was evaluated. After completion of the reaction, the catalyst was recovered with an external magnet and was washed with ethanol and dried at 120-150 °C under reduced pressure for 2 h. The recycled nanocatalyst was found to be reusable without significant loss of catalytic activity for six consecutive runs. Figure 1f depicts the yields of 4a in the second and third runs, which are almost identical to that in the first run. In the fourth and sixth runs 90 and 88% yields of 4a were obtained, respectively.

**TABLE 2** Scope of aldehydes for ZnO@Fe<sub>3</sub>O<sub>4</sub>-catalyzed heterocyclization to obtain 3,4–disubstituted isoxazol-5(4*H*)-one derivatives (isolated yields). Reaction conditions: aldehyde (1 equiv.), ethyl acetoacetate (2 equiv.) and hydroxylamine hydrochloride (1 equiv.) in the presence of ZnO@Fe<sub>3</sub>O<sub>4</sub> (5 mg) catalyst at 70°C for 30 min in 10 ml water



A plausible mechanism (Figure 2) for the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-one is suggested over  $ZnO@Fe_3O_4$  core-shell nanocatalyst on the basis of the Knoevenagel condensation reaction. In this catalysis,

initially the core-shell nanocatalyst is coordinated with oxygen of the carbonyl group of ethylacetoacetate (A) then the lone pair of nitrogen attacks to the carbonyl carbon and water is eliminated to form (B). Then, *keto*-

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**FIGURE 2** A plausible mechanism for the synthesis of 3,4–disubstituted isoxazol–5(4H)– ones catalyzed by ZnO@Fe<sub>3</sub>O<sub>4</sub>

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*enol* tautomerism results to form the intermediate (C), after which nucleophilic addition of aldehyde is coordinated with nanocatalyst to form intermediate (D). Further removal of water molecules leads to the formation of an intermediate (E), which eventually undergoes cyclization to form the intermediate (F) that removes the ethanol molecule to obtain the target molecule.

# 3 | CONCLUSIONS

In summary, we prepared ZnO-decorated Fe<sub>3</sub>O<sub>4</sub> magnetic core-shell nanoparticles and characterized them by FTIR, UV-vis, FESEM, EDX and p-XRD techniques. Further, this nanocatalyst was used for the highly efficient, green and one-pot, three-component reaction for the synthesis of structurally electronically varied 3.4-disubstituted isoxazol-5(4H)-ones, which are considered as biologically and pharmacologically active compounds. The present procedure was accomplished by the use of nanocatalyst in water, which in turn helps to reduce cost-effectiveness and energy. The significant merits of the nanocatalyst were ascribed to its high selectivity, promising catalytic activity, easy separation and recyclability. The process does not require the use of any volatile organic solvent, harmful metal catalysts and high temperatures. Moreover, this method also has the ability to tolerate a wide variety of substituents with varied steric and electronic parameters. The versatility of this methodology is suitable for library synthesis in drug discovery efforts. We believe that the present improved modification is a convenient and efficient alternative to the existing methods for the multicomponent synthesis of isoxazol-5(4H)-one derivatives.

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#### ORCID

*Rangappa S. Keri* https://orcid.org/0000-0001-6262-8379

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