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Graphic Abstract



Magnetic $Cu^0@HAP@\gamma-Fe_2O_3$ nanoparticles: an efficient catalysts for one-pot three-component reactions for the synthesis of imidazo[1,2-a]pyridines

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Abstract

Cu(0) incorporated magnetic hydroxyapatite nanoparticles (Cu⁰@HAP@γ-Fe₂O₃ NPs) was conveniently synthesized *via* the ion exchange reaction, oxidation, and reduction steps. The structure and composition of the nanohybrid were confirmed by FT-IR, SEM, EDS, TEM, XPS, and TGA. The magnetic Cu⁰@HAP@γ-Fe₂O₃ hybrid can efficiently catalyzed a one-pot multicomponent synthesis of imidazo[1,2-a]pyridine derivatives from 2-aminopyridine, aldehyde or glyoxylic acid, and phenylacetylene or alkynyl carboxylic acids in excellent yields. The magnetic nanocatalyst was easily separated from reaction mixture using an external magnet and was successfully examined for three runs with a slight loss of catalytic activity.

Keywords: imidazo[1,2-a]pyridine, multicomponent reaction, hydroxyapatite, copper, magnetic nanocatalyst

1. Introduction

Among the various categories of nitrogen-containing heterocyclic compounds endowed with numerous biological activities, imidazo[1,2-a]pyridine as an indispensable core of the emerging drugs (Fig. 1) have attracted considerable

attention due to their ring system exists in wide range of bioactive molecules and also known for their antiviral [1], analgesic [2], antipyretic [2], anti-inflammatory [2,3], antiulcer [4], antibacterial [5], and anticonvulsant [6]. Commercial drugs such as zolpidem [7-9], alpidem [7,10,11], olprinone [7,12-14], and minodronic acid [15] containning imidazo[1,2-a]pyridine framework have already been on the market.



Fig. 1. Examples of imidazo[1,2-a]pyridine-based drug molecules.

In view of their extreme significance, for the synthesis of imidazo[1,2-a]pyridine scaffold, numerous synthetic methods have been recently documented in the literature [16,17]. The common methods include: (1) the heterocyclization of 2-aminopyridines with α -halocarbonyl compounds (Scheme 1, Path a)[18,19]; (2) one-pot multicomponent reaction of 2-aminopyridine, aldehyde, and isonitrile (Scheme 1, Path b).[20-23] Despite that, it is still a huge demand to synthesize the

significant imidazopyridines from readily available and easily extensible raw materials using a simple procedure. Efficiently straightforward protocol for the synthesis of imidazo[1,2-a]pyridines from conveniently available 2-aminopyridines, aldehydes, and terminal alkynes has been first developed in 2010 by Gevorgyan *et al* using CuCl/Cu(OTf)₂ co-catalyst and Lin *et al* using CuSO₄/TsOH catalytic system (Scheme 1, Path c) [24,25].



Scheme 1. Syntheses of imidazo[1,2-*a*]pyridine from 2-aminopyridine.

Subsequently, various catalysts employed for the synthesis of imidazo[1,2-a]pyridines from 2-aminopyridines, aldehydes, and terminal alkynes include InBr₃ [26], CuI-NaHSO₄·SiO₂ [27], CuSO₄/glucose [28], Cu-MOFs [28], magnetic *nano*-Fe₃O₄-KHSO₄·SiO₂ [29], Cu-Mn spinel oxide [30], iodine [31], Fe₃O₄@SiO₂[32], CuO-CuAl₂O₄-D-glucose [33], CuO NPs [34], ZnAlO₄ NPs [35] and so on. In spite of their advantages, most of these catalytic systems suffer from certain

limitations such as use of homogeneous catalysts, requirements of an inert atmosphere condition, and need of additives such as glucose, and bisulfate. Hence, the development of an efficient, high-yielding, and environmentally benign procedure for the one-pot synthesis of imidazo[1,2-a]pyridine derivatives with diverse bioactivity is of great interest.

Nowadays the developments of metal nanocatalyst with tunable catalytic performance in organic synthesis have much significance in academia and industry [36]. The transition metal-based nanocatalysts are more promising, efficient, and practical compared to buck catalysts due to their high surface-to-volume ratios and the high activity of surface atoms. Unfortunately, metal NPs are unstable and easily aggregate and precipitate to bulk metal, and therefore, decrease their catalytic activity. Furthermore, the recycling of these nanoctalysts is often tedious because the recovery of these very tiny particles requires the use of an expensive ultra-centrifugation technique that has limited their application. This limitation can be overcome by using magnetic NPs (MPs), which can be simply recovered from the reaction mixture by magnetic separation. MNPs have recently emerged as an attractive alternative to immobilize catalytic species for various synthetic transformations because of their easy recyclability, reusability, high surface area, low toxicity, and excellent activity [37]. However ultrafine bare MPs always tend to undergo agglomeration due to the high ratio of surface area-to-volume and the dipole-dipole attractions between MNPs. To further address the issue of agglomeration of MNPs, a passive coating of inert inorganic and/or organic materials

such as carbons, silicas, and polymers on the surfaces of MNPs could be feasible to prevent their aggregation and improve their stability [38,39]. However, the surface-coating techniques has some disadvantage of multistep synthetic process, using expensive reagents and hazardous solvents, harsh condition, and tedious operation. In order to overcome these defects, hybridization of magnetic MNPs may be a practical choice. Hydroxyapatite (HAP), *i.e.* Ca₁₀(PO₄)₆(OH)₂, as the main inorganic constituent of bone and tooth has unique properties like ion exchange ability, adsorption capacity, acid-base properties, and high surface area, and good stability [40]. In the light of the characteristic of ion exchange of Ca^{2+} with either bivalent or trivalent cations, we speculative that HAP can be served as an efficient template for the preparation of HAP-encapsulated Fe_2O_3 magnetic hybrid material (HAP@ γ -Fe₂O₃) in which HAP not only is served as coating material to trap Fe₂O₃ NPs but also acted as a support to anchor Cu(II) ions *via* metathesis (Cu^{II}@HAP@y-Fe₂O₃). Further, the Cu(II) ions immobilized on HAP can be readily reduced to Cu(0) species to produce encapsulated the magnetic HAP Fe₂O₃-supported Cu(0)hybrid $(Cu^0@HAP@\gamma-Fe_2O_3)$

In this paper, we reported a facile and novel methodology for the synthesis of magnetic $Cu^0@HAP@\gamma$ -Fe₂O₃ hybrid catalyst and successfully demonstrated its high catalytic activity and reusability in the synthesis of imidazo[1,2-a]pyridines under mild condition (Scheme 2). Our careful literature survey at this stage revealed that there is no report of employing this strategy for the preparation of catalyst for the synthesis of these target compounds.



Scheme 2. Synthesis of imidazo[1,2-a]pyridines using magnetic $Cu^0@HAP@Fe_2O_3$ hybrid catalyst.

2. Results and discussion

Considering the characteristic of ion exchange of Ca^{2+} of HAP with metal cations, the HAP can be used as an efficient template for the preparation of both HAP-encapsulated Fe₃O₄ magnetic hybrid (HAP@ γ -Fe₂O₃) [42] and $Cu^0@HAP@Fe_2O_3$ magnetic hybrid. The schematic route for the self-assembly of $Cu^0@HAP@Fe_2O_3$ NPs is outlined in Scheme 3.



Scheme 3. Schematic routes for self-organized fabrication of magnetic $Cu^0@HAP@Fe_2O_3 NPs.$

As shown in Scheme 3, the hybrid was prepared with a multistep process. First,

HAP encapsulated Fe₃O₄ NPs was easily prepared using the cation-exchange method, hydrolysis, and oxidation reaction. Subsequent, the resultant HAP@Fe₃O₄ was calcined at 130 °C to directly form the desirable reddish-brown powder HAp@ γ -Fe₂O₃. Next, metathesis of a HAp@ γ -Fe₂O₃ with an aqueous CuSO₄ solution at room temperature yielded the Cu^{II}@HAP@ γ -Fe₂O₃. Last, reduction of Cu^{II}@HAP@ γ -Fe₂O₃ with an aqueous solution of hydrazine yielded the embedding of the Cu(0) NPs onto the magnetic nanohybrid (Cu⁰@HAP@ γ -Fe₂O₃).

To gain insight into the structures of $Cu^0@HAP@\gamma-Fe_2O_3$, characterization by ICP-AES, FT-IR, XRD, FE-SEM, EDS, FE-TEM, and TGA techniques was employed.

Fig. 2 shows the FT-IR spectra of HAP (a), HAP@ γ -Fe₂O₃ (b), and Cu⁰@HAP@ γ -Fe₂O₃ (c) in the range of 400–4000 cm⁻¹. The peak at 464 cm⁻¹ can be assigned to the Fe-O band absoption (curve b and c). The adsorption peak at 1036 cm⁻¹ was attributed to the stretching band of O–P–O. The adsorption peaks at 3412 cm⁻¹ was ascribed to water molecule absorbed on catalysts. The absorption peak at 3566 cm⁻¹ was due to the O–H bond of HAP.



Fig. 2. FT-IR spectra of HAP (a), HAP@ γ -Fe₂O₃ (b), and Cu⁰@HAP@ γ -Fe₂O₃ (c).

The XRD of the HAP (a), HAP@ γ -Fe₂O₃ (b), and Cu⁰@HAP@ γ -Fe₂O₃ (c) which shown in Fig. 3 depicted the diffraction peaks at $2\theta = 25.9^{\circ}$, 31.8°, 32.2°, 32.9°, 34.0°, 39.8°, 46.7°, 49.5°, 50.5°, 53.1° are related to HAP (JCPDF cards, 24-0033) (Fig. 3a). The peaks at 30.2°, 35.6°, 57.3° and 62.9° correspond to the diffraction of (220), (311), (511) and (440) of γ -Fe₂O₃ (curve b) (JCPDF card 39-1346). The peaks at 43.3°, 50.4°, 74.1° corresponding to the (111), (200) and (220) planes of cubic Cu(0) NPs are consistent with the standard reflection peaks (Fig. 3c) (JCPDF card 04-0836). This observation identifies the presence of Cu(0) NPs onto the surface of hybrid. The characteristic diffraction peaks of HAP have not any change after encapsulated Fe₂O₃ and even the immobilization of Cu(0) species (curve a, b, and c), indicating retention of the crystalline structure of HAP.



Fig. 3. XRD patterns of (a)HAP, (b)HAP@ γ -Fe₂O₃, and (c)Cu⁰@HAP@ γ -Fe₂O₃.

The SEM image of freshly prepared $Cu^0@HAP@\gamma-Fe_2O_3$ shows that the hybrid NPs have morphology with irregular sheet shapes and different sizes (Fig. 4).



Fig. 4. SEM image of $Cu^0@HAP@\gamma$ -Fe₂O₃ (bar of left image at 5 µm, bar of right

image at 10 μ m)

The existence of metalic element was investigated by EDS along with the SEM. The EDS spectrum exhibits peaks for Fe, Cu, Ca, P and O in $Cu^0@HAP@\gamma$ -Fe₂O₃ (Fig. 5).



Fig. 5. EDS analysis of Cu⁰@HAP@γ-Fe₂O₃

The corresponding elemental maps based on the SEM images of the catalysts confirmed the presence of Fe, Cu, P, Ca, and O, indicating these elements were in a homogenously distribution in the hybrid catalyst. The images show in Fig. 6.



Fig. 6. SEM images and the corresponding elemental mapping images of

Cu^0 @HAP@ γ -Fe₂O₃.

TEM of $Cu^0@HAP@\gamma-Fe_2O_3$ (Fig. 7a) revealed that the Cu(0) NPs and $\gamma-Fe_2O_3$ had been incorporated in the HAP successfully. Some dark spots in the TEM images of $Cu^0@HAP@\gamma-Fe_2O_3$ can be attributed to the presence of Cu(0) NPs and $\gamma-Fe_2O_3$ NPs in catalyst. The average particle size of the catalyst was measured using image analysis, and the frequency histogram shows a size of around 40 nm (Fig. 7b).





Fig. 7. TEM images of Cu⁰@HAP@γ-Fe₂O₃ (scale of left image in 200 nm, scale of right image in 500 nm) (a), nanoparticles diameter histogram (b).

XPS was used to investigate the valence state of the elements in catalyst. As shown in Fig. 8, the binding energies of O_{1s} 531.30 eV indicates the existence of P-O

bonds in hydroxyapatite [43]. Two intense doublets peaks corresponding to Cu $2p_{1/2}$ and Cu $2p_{3/2}$ at 932.3 and 952.2eV is typically attributed to Cu⁰ [44]. These results indicated that the oxidation state of copper in the catalyst was is zero valence, which is in good agreement with XRD analysis of pure crystal of Cu NPs (Fig. 3c)



Fig. 8. XPS for Cu⁰@HAP@γ-Fe₂O₃ catalyst

The stability of the catalyst was examined by TGA. As shown in Fig. 9, no significant weight loss was observed in the range of 25 to 800°C, which fully demonstrated that the catalyst shows good thermal stability in high temperature.



ΓΙΥ. 3. Ι GA CUIVE OI OU WΠΑΡ WΥ-FE2O3.

In order to achieve the optimal conditions, the three-component reaction of 2-aminopyridine, 4-chlorobenzaldehyde, and phenylacetylene was selected as a model. Typical reaction parameters including several catalysts and its loading, various solvents, and temperature are screened. The results were shown in Table 1.

Table 1

Optimization of the reaction conditions^a

N NH2 +	сіСно +	−==−R ₃ Cu ⁰ @HAP@γ-Fe ₂ O ₃ Solvent	
		Convent	

Entry	Catalyst (mol %)	Solvent	Temp (°C) ^b	Yield (%) ^c
1	HAP@ γ -Fe ₂ O ₃ (10)	<i>i</i> -PrOH	80	N.R. ^d
2	Cu ^{ll} @HAP@γ-Fe ₂ O ₃ (10)	<i>i</i> -PrOH	80	25
3	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	EtOH	80	69
4	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	DMSO	100	22
5	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	DMF	100	36
6	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	Dioxane	100	53
7	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	H ₂ O	100	18
8	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	MeCN	80	31
9	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	Toluene	100	23
10	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	<i>t</i> -BuOH	80	67
11	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	neat	80	60
12	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (5)	<i>i</i> -PrOH	100	71
13	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (10)	<i>i</i> -PrOH	100	82
14	Cu ⁰ @HAP@γ-Fe ₂ O ₃ (15)	<i>i</i> -PrOH	100	82

^aConditions: 2-aminopyridine (1 mmol), 4-chlorobenzaldehyde (1.2 mmol), phenylacetylene (1.5 mmol), Cu⁰@HAP@γ-Fe₂O₃ (10 mol %), solvent (1 mL), reaction time 12 h. ^bSilicon oil bath temperature. ^cIsolated yields. ^dNo reaction.

At the beginning, the model reaction was investigated in the presence of various catalysts such as HAP@y-Fe₂O₃, Cu^{II}@HAP@y-Fe₂O₃, and Cu⁰@HAP@y-Fe₂O₃ separately in refluxing *i*-PrOH. Among them, Cu⁰@HAP@y-Fe₂O₃ showed the higher catalytic performance with 69% yield of product (Table 1, entry 3), and Cu^{II} @HAP@ γ -Fe₂O₃ showed low activity (Table 1, entry 2), while HAP@ γ -Fe₂O₃ afford no desired product (Table 1, entry 1). These findings revealed the Cu(0) plays crucial role in the reaction. Subsequently, we investigated the Cu loading ranging from 5 to 15 mol % in catalyst. Lowering the amount of the Cu to 5 mol% still allowed the reaction to proceed smoothly, decreasing the desired product in 71% yield respectively (Table 1, entry 12). However, a further increase of the catalyst to 15 mol% resulted in no apparently improvement in yield at all (Table 1, entry 14). Next, our attempts are focused on the screens of the efficiency of various solvents. Moderate yields are observed when the reaction proceeded in EtOH, dioxane, t-BuOH, and solvent-free condition (Table 1, entries 3, 6, 10, and 11). DMSO, DMF, H₂O, and toluene provide lower yields (Table 1, entries 4, 5, 7, and 9). Last, the temperature on reaction was explored. Remarkably, the temperature had an influence on the reaction. The highest yield of the product was obtained when the reaction was carried out in *i*-PrOH at 100°C (Table 1, entry 13), and the yield of the product decreased from 82 to 69% as the temperature was decreased from 100 to 80 °C (Table 2, entries 13, and 3).

With the optimized reaction conditions in hand, the three-component reactions of 2-aminopridine, a variety of aryl aldehydes, and phenylacetylenes or phenylpropiolic acid were performed to explore the general effectiveness of the Cu⁰@HAP@y-Fe₂O₃ catalyst. As shown in Table 2, in all cases, the nature of functional groups on the aryl ring of aldehyde exerted a slight influence on the reaction. All aryl aldehydes containing electron-donating or electron-withdrawing group proceeded efficiently. In addition, the heteroaromatic aldehydes are also viable substrates for this type transformation (Table 2, entries 7, and 8). These successful results clearly indicated that the present catalytic approach is extendable to a wide scope of substrates. Then we turned our attention toward phenylpropiolic acid which is a valuable surrogate to phenylacetylene. The substrate of phenylpropiolic acid reacted well via decarboxylative coupling under the optimal condition to give the corresponding imidazo[1,2-a]pyridines in excellent yields (Table 2, entries 18-21). Encouraged by these results of the decarboxylative coupling, we attempt to use phenylglyoxylic acid as the substrates instead aldehydes to achieve the desired product. Fortunately, the target compound was also obtained in good yield (Table 2, entries 22, and 23). To achieve a more universal approach, we further expanded the substrates to a phenylglyoxylic acid as an aldehyde source and an alkynyl carboxylic acid as a phenylacetylene source. Surprisingly, the double decarboxylative coupling reaction afforded the corresponding imidazo[1,2-a]pyridines in good yields (Table 2, entries 24, and 25).

Table 2

Scope of reaction of various substrates using $Cu^0@HAP@\gamma$ -Fe₂O₃ catalytic system^a



10	CI N NH ₂	NCСНО	— н	85	4j
11	CI N NH ₂	Ме-СНО	⟨ун	83	4k
12	Me N N NH ₂	Ме-СНО	————————————————————————————————————	83	41
13	Me N N NH ₂	МеО-СНО	<_>−=−н	81	4m
14	Me N NH ₂	СІ—	H	84	4n
15	NNH2	Ме-СНО	Дун	75	40
16	N NH ₂	МеО-СНО	Кн	70	4p
17	N NH ₂	СІ—СНО	⟨ун	76	4q
18	N NH ₂	СІ-СНО	СО ₂ Н	82	4a
19	N NH ₂	Ме-СНО	СО₂Н	84	4c
20	N NH ₂	МеО-СНО	<−СО₂Н	80	4d
21	N NH ₂	СНО	<−СО₂Н	80	4f
22 ^c	N NH ₂	ОН	<hr/>	63	4f



^aConditions: 2-aminopyridine (1 mmol), aldehyde/phenylglyoxylic acid (1.2 mmol), phenylacetylene/alkynyl carboxylic acids (1.5 mmol), Cu⁰@HAP@γ-Fe₂O₃ (10 mol%), solvent (isopropanol, 1mL), temperature 100 °C, reaction time 12h. ^bIsolated yields.

^cConducted in solvent (*i*-PrOH/*t*-BuOH = 1:1, v/v, 1 mL) at 110 °C for 12h.

Aiming for the practical application, the reusability of catalyst was an indispensable factor. In order to clarify the recycling abilities of $Cu^0 @HAP @\gamma-Fe_2O_3$, the model reactions of 2-aminopyridine, 4-chlorobenzylaldehyde, and phenylacetylene were chosen under the optimal conditions. After completion of reaction, the catalyst was recollected using an external magnet from the reaction mixture, washed, dried, and reused for next cycle. It was found that the catalyst can be reused at least three consecutive runs with a slight decreasing its activity in the yield of 81%, 79%, and 76% respectively.

3. Conclusion

In this study, we fabricated a novel nanocatalyst architecture of Cu⁰ NPs loaded onto the magnetic hydroxyapatite-encapsulated γ -Fe₂O₃ (Cu⁰@HAp@ γ -Fe₂O₃) hybrid for the synthesis of imidazo[1,2-a]pyridines in excellent yields. The as-prepared

magnetic nanocatalyst is well characterized by ICP, FTIR, SEM, EDS, TEM, XPS, and TGA analyses. The experimental results showed that $Cu^0@HAp@\gamma$ -Fe₂O₃ not only enhances the activity of MCR of 2-aminopyridine, aryl aldehyde, and phenylacetylene but also leads to the decarboxylative couplings of alkynyl carboxylic acid and/or glyoxylic acid for the synthesis of imidazo[1,2-a]pyridines. The alkynyl carboxylic acid of this coupling reaction shows similar reactivity to that of a terminal alkyne, and the reactivity of the glyoxylic acid is almost identical to that of an aldehyde. We also found that both alkynyl carboxylic acids and glyoxylic acids proceed well through a double decarboxylative coupling with a 2-aminopyridine under the optimal condition. Moreover, the catalyst can be easily recovered from the reaction mixture by using an external magnet and reused at least three consecutive runs with a slight loss of catalytic activity. From a synthetic point of view, the magnetic nanocatalyst owns salient features of simple isolation, low cost, high catalytic activity, shorter reaction times, and tolerance of wide scope of substrates which make the process efficient and practical.

4. Experimental section

4.1. Chemical and characterizations.

All solvents and reagents were purchased from commercial sources and were used without prior purification. Calcium hydroxyapatite $[Ca_{10}(PO_{4)6}(OH)_2]$ was synthesized according to the literature procedure [41].

Melting pointing was measured by an Electrothermal X6 microscopic digital melting pointing apparatus. Fourier transform infrared (FT-IR) spectra were recorded

from KBr pellets on a Bruker Equinox-55 spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a 300MHz Bruker-300 Advance spectrometer at 25°C with CDCl₃ as solvent and TMS as internal standard. Scanning electron microscopy (SEM) and energy disperse spectroscopy (EDS) were conducted with a Philips XL 30ESEM instrument. Transmission electron microscopy (TEM) was obtained with Philips Tecnai instrument. The curves obtained from thermo gravimetric analysis (TGA) were recorded in nitrogen atmosphere using Netzsch STA449F3 in the range of 25-850°C. High resolution mass spectrometry (HRMS) data were recorded on a MAT 95XP (Termol) (LCMS-IT-TOF). Qualitative analysis of Cu⁰@HAP@γ-Fe₂O₃ MNPs was performed by using X-ray powder diffraction (XRD) on a MSALXRD2 diffractometer instrument using Cu Ka radiation in a range of Bragg's angles (10-80°). X-ray photoelectron spectroscopy (XPS) analysis was measured by Thermo SCIENTIFIC ESCALAB 250Xi using a monochromatized AI Ka excitation, pass energy is 1487ev. The element of copper content of the catalyst was detected by inductively coupled plasma atomic emission spectrometry (ICP-AES) using PerkinElmer Optima 2000 DV. 4.2. Preparation of magnetic HAP encapsulated Fe₂O₃-supported Cu(0) hybrid catalyst (Cu⁰@HAP@γ-Fe₂O₃).

4.2.1. Preparation of HAP @ γ -Fe₂O₃ MNPs.

The HAP (1g) was added to a flask containing 100 mL of diluted water with vigorously stirring to obtain suspension. Afterwards, a solution containing 10 mmol of FeCl₂·4H₂O and 1 mmol of KNO₃ in 50 mL of water was added into the mixture solution with constantly stirring at r.t., then 10 mL of a 25wt % NH₄OH solution was

added and keeping the stirring rate for 30 mins. Finally, the suspension aged overnight. The resultant black solid was collected with an external magnet and washed by deionized water thoroughly until neutralized. The isolated solid was dried under vacuum at r.t, then calcined at 130 °C for 12h to provide the reddish-brown powder (HAP@ γ -Fe₂O₃).

4.2.2. Preparation of $Cu^0@HAP@\gamma$ -Fe₂O₃ MNPs.

The HAP@ γ -Fe₂O₃ (1g) are introduced into 100 mL aqueous solution of 10 wt% CuSO₄·5H₂O with constantly stirring at r.t. for 6 h. The resultant solid was separated from the solution by suction filtration and washed by deionized water thoroughly until neutralized, then dried at r.t. under vacuum. Next, the collected powder was suspended in ethanol and treated with 80% hydrazine hydrate until the suspension was turned to maroon. The resulting solid was separated by external magnet and dried under vacuum at r.t. giving the Cu⁰@HAP@ γ -Fe₂O₃ MNPs. The copper content was determined to be 2.60 mmol/g by ICP-AES.

4.3. General procedure for the synthesis of imidazo[1,2-a]pyridines catalyzed by Cu⁰@HAP@y-Fe₂O₃-catalyzed.

2-Aminopyridine (1.0 mmol), aldehyde or glyoxylic acid (1.2 mmol), phenylacetylene or phenylpropiolic acid (1.5 mmol), and catalytic amount of $Cu^0@HAP@\gamma-Fe_2O_3$ (10 mol%) were added to the sealed tube and stirred at specific temperature with 1 mL specific solvent (Table 2). The reaction process was monitored by TLC. Upon the completion of reaction, the catalyst was collected with an external magnet. The solution was extracted with ethyl acetate (15 mL×3), washed with brine

(15mL \times 3), and dried over anhydrous Na₂SO₄ to afford the crude product which was

further purified by preparative TLC or column chromatography on neutral alumina.

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Highlights

- 1. Employment of hydroxyapatite as a template to fabrication of magnetic $Cu^0@HAP@\gamma$ -Fe₂O₃ nanoparticles.
- Cu⁰@HAP@γ-Fe₂O₃ not only improve the activity of conventional couplings of 2aminopyridine, aryl aldehyde, and alkynes but also enhance the decarboxylative couplings of alkynyl carboxylic acid and/or glyoxylic acid for the synthesis of imidazo[1,2-a]pyridines.
- 3. Both alkynyl carboxylic acids and glyoxylic acids proceed well through a double decarboxylative coupling with a 2-aminopyridine.
- One-pot multicomponent reaction, broad substrate scope, good functional group toleration, mild reaction conditions, good to excellent yields, operational simplicity, high atom-economy.

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