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Nano-$NiFe_2O_4$ catalyzed microwave assisted one-pot regioselective synthesis of novel 2-alkoxyimidazo[1,2-*a*] pyridines under aerobic conditions**

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Here, we have demonstrated an efficient and regioselective protocol for the synthesis of novel 2-alkoxy-3-arylimidazo[1,2-a]pyridines *via* microwave (MW) assisted one-pot reactions of 2-aminopyridine, β–nitrostyrenes and alcohols using nano-$NiFe_2O_4$ as reusable catalyst under aerobic conditions. This is the first method to produce alkoxy functionalized imidazopyridine moieties and furnished *via* sequential one-pot three component reactions. The MW irradiation expedited the reaction rate and increased the yields of products.

Functionalized imidazo[1,2-*a*]pyridine derivatives are well established as "privileged medicinal scaffolds" and these moieties have shown interesting biological activities such as antiviral, antitumor, antiparasitic, antimicrobial, fungicidal, anti-inflammatory, hypnotic and many more.[1] These derivatives are also act as GABA and benzodiazepine receptor agonists, β-amyloid formation inhibitors, and cardiotonic agents.[2] Moreover, the imidazo[1,2-*a*]pyridine constitute as core entities in many commercially available drugs which includes alpidem, olprinone, minodronic acid (to treat anxiety, heart failure, and osteoporosis), zolimidine (peptic ulcer), necopidem, and saripidem (Figure 1).[3] Furthermore, a few of them exhibit excited-state intramolecular proton transfer.[4]

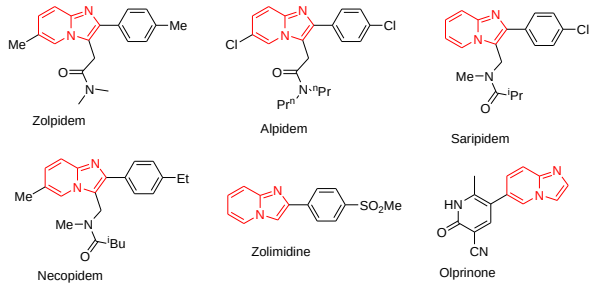

Figure 1 Few imidazo[1,2-a]pyridine based marketed drugs.

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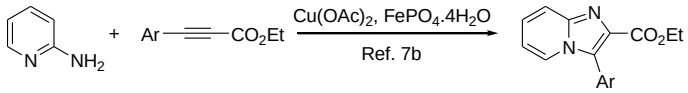
‡Electronic Supplementary Information (ESI) available: [Detailed experimental procedure and characterization of catalyst and 2-alkoxyimidazopyridines; copies of ^1H and ^{13}C NMR of all products listed in Table 2, reusability of $NiFe_2O_4$]. See DOI: 10.1039/x0xx00000x

Previous Work:



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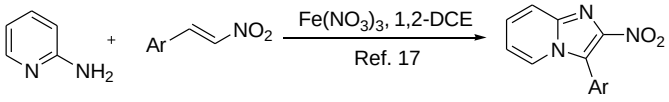

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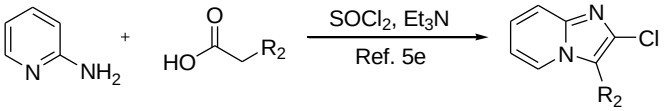

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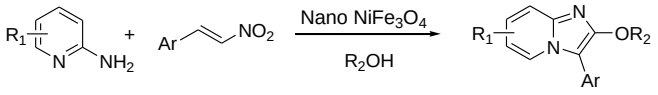


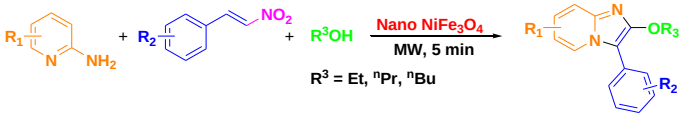
Scheme 1 Synthesis of 2-functionalized imidazopyridine derivatives.

Accordingly different strategies have been reported to synthesize imidazo[1,2-*a*]pyridine scaffolds which include condensation reactions[5], oxidative coupling reactions[6-9] and three-component coupling,[5,10-12] intramolecular amino oxygenation[13]/C–H amination[14] and coupling between 2-aminopyridine and nitroalkenes.[15-17] However, looking inside the synthetic strategies, it was observed that most of the methods have used binucleophilic 2-aminopyridine as starting material and the initial nucleophilic addition mostly proceeds by exocyclic amino group resulting 3-nitro/carboxylic ester/keto/amino/sulfenyl[18] functionalized imidazopyridine moieties. In contrast, nucleophilic addition by endocyclic pyridinium nitrogen resulting 2-functionalized imidazopyridines have rarely been observed and only 2-

CO_2R[7b]/nitro[17]/chloro[5e] substituted imidazopyridines were reported (Scheme 1).

Moreover, hydroxyl derivatives (-OH, -OR, OCOR etc.) are frequently observed in many important natural products such as Betaxolol Betablokker, Morfin, Petidine, Dextropropoxyphen, Angiotensin II antagonists, Tubocurarin, Aspirin, Pethidine, Reserpine, Protoaescigenin, Valtrate, Methysticin, Vinblastine, Bruceantin, Michellamine B, Prostratin, warfarin, fenclofenac[19] and presence of these groups on any heterocycles could impart marked biological properties.[19] It is obvious that introduction of alkoxy group is challenging due to the poor nucleophilicity of alcohols and as a matter of fact there is no such method available to produce alkoxy functionalized imidazopyridine moieties. Thus, invention of an efficient catalytic system to activate the poor nucleophile alcohol leading to one-pot synthesis of new class of alkoxyimidazopyridine derivatives is long-awaited.

As a part of our interest in nanocatalysis,[20] here, we have observed a unique and unprecedented catalytic activity of nano-$NiFe_2O_4$ and demonstrated an efficient microwave assisted one-pot protocol for the synthesis of novel 2-alkoxy-3-arylimidazo[1,2-*a*]pyridine derivatives. The reactions proceed rare regioselectively *via* sequential aza-Michael addition, C-H imination and nucleophilic ligand transfer reaction under ambient air (Scheme 2).



Scheme 2 One-pot synthesis of 2-alkoxy-3-arylimidazo-[1,2-*a*]pyridines using nano-$NiFe_2O_4$ as catalyst.

This is the first method to produce alkoxy functionalized imidazo[1,2-*a*]pyridine moieties. Initially, we have synthesized nano sized $NiFe_2O_4$ *via* sol-gel method following a previously reported protocol[21] (See ESI-1 for detailed procedure) and formation of nanoparticles was confirmed by powder X-ray diffraction (XRD), high resolution transmission electron microscopic (HRTEM), and field emission scanning electron microscopic (FESEM) studies.

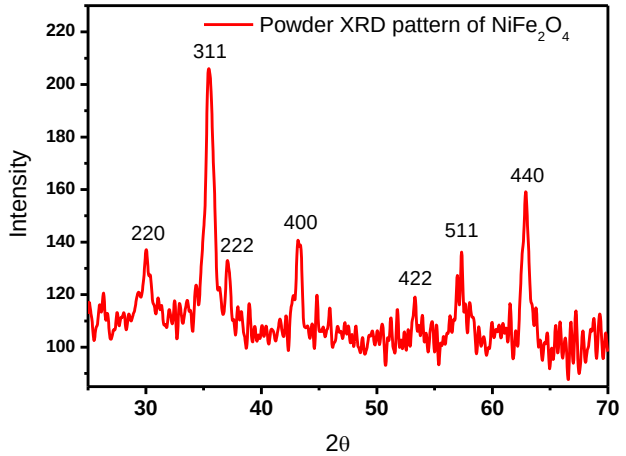


Fig. 2 The powder XRD pattern of nano-$NiFe_2O_4$.

The powder XRD pattern (Figure 2) reveals that the Bragg reflection peaks were indexed to face centered cubic $NiFe_2O_4$,[22] and Fd3m space group (JCPDS file No. 10-0325) and the diffraction peaks at 30.32°, 35.81°, 37.27°, 43.45°, 53.89°, 57.41° and 62.96° are attributed to the reflections of {220}, {311}, {222}, {400}, {422}, {511} and {440} planes of the $NiFe_2O_4$, respectively.High resolution TEM image indicates the formation of spherical nano-$NiFe_2O_4$ with average size of 15 nm (Figure 3). The selected area electron diffraction (SAED) pattern (in inset of Figure 3) also indicates the formation of face centered cubic spinel nano-$NiFe_2O_4$ and corresponding planes {440}, {400}, {220}, {311} can be well indexed by using the SAED pattern, which is consistent with the results of XRD.

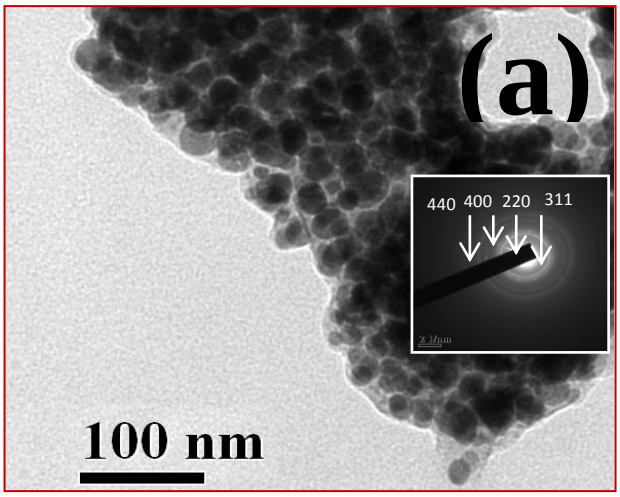


Fig. 3 HRTEM image of nano-$NiFe_2O_4$.

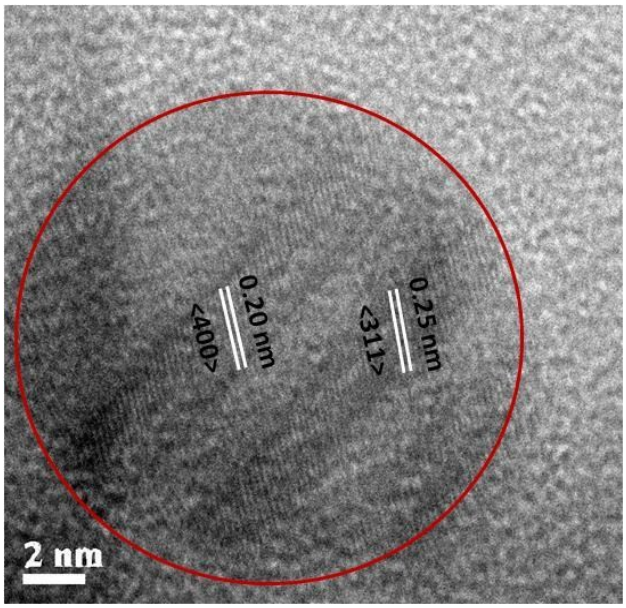
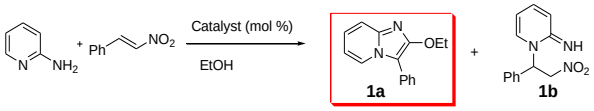


Fig. 4 Magnified HRTEM image of nano-$NiFe_2O_4$ showing lattice fringes.

Magnified HRTEM image (Figure 4) of $NiFe_2O_4$ nanoparticles indicate the lattice fringes with spacing of 0.20 and 0.25 nm correspond to the (400) and (311) planes of $NiFe_2O_4$, respectively. The EDAX study (Figure 1S, ESI 2.1) indicates that the material contains only Fe, Ni and O and no other element was observed. The FESEM image of $NiFe_2O_4$ also supported the formation of spherical particles (Figure 2S, ESI 2.2).

Next, using well-characterized nano-$NiFe_2O_4$ (10 mol %), we have performed the synthesis of imidazopyridines by the reaction of 2-aminopyridine (1 mmol) and (*E*)-1-(2-nitrovinyl)benzene (1 mmol) in ethanol. Interestingly, 2-ethoxy-3-phenylimidazo[1,2-*a*]pyridine (**1a**) was obtained (65%) after 4 h under refluxing conditions (entry 1, Table 1) *via* unprecedented participation of ethanol in the reaction. Inspired by the result, different reaction parameters have been examined to improve the yield and optimized the reaction conditions. The results were summarized in Table 1.

Table 1 Optimization of reaction conditions

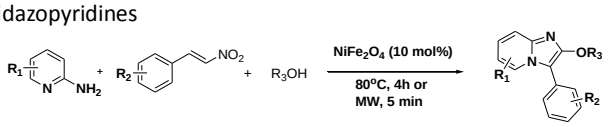


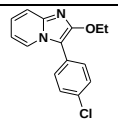
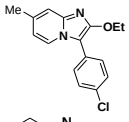
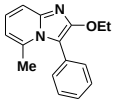
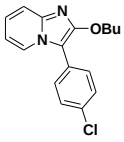
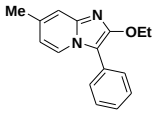
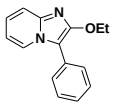
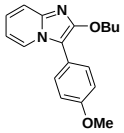
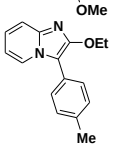
Sl. No.	Catalyst	Time	Products	Yield[a] (%)
1	$NiFe_2O_4$ NPs	4 h	1a	59[b]
2	$NiFe_2O_4$ NPs	4 h	1a	72
3	$NiFe_2O_4$ NPs	4 h	1a	78[c]
4	$NiFe_2O_4$ NPs	4 h	-	-[d]
5	$CuFe_2O_4$ NPs	4 h	1a	21
6	$CoFe_2O_4$ NPs	4 h	1a	22
7	$MnFe_2O_4$ NPs	4 h	1a	27
8	Fe_3O_4 NPs	4 h	1a	44
9	NiO NPs (10)	4 h	1b	90
10	$NiFe_2O_4$ NPs	15 h	1b	85[e]
11	No Catalyst	15 h	1b	50
12	$NiFe_2O_4$ NPs	5 min.	1a	85[f]

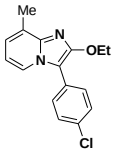
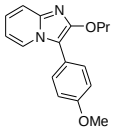
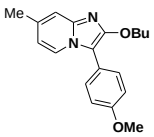
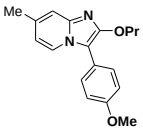
Reaction conditions: 2-aminopyridine (1.3 mmol), (*E*)-1-(2-nitrovinyl)benzene (1 mmol), ethanol (2 ml) and 10 mol% of catalyst under reflux unless otherwise stated; [a]Isolated yields; [b]2-aminopyridine (1.0 equivalent); [c]20 mol% of $NiFe_2O_4$ is used; [d]In DCM 2-nitro-3-phenyl-imidazopyridines was obtained; [e]Room temperature reactions; [f]Reaction was conducted using MW irradiation (70W).

By increasing the amount of $NiFe_2O_4$ (20 mol%), no significant improvement of yield was observed (entry 3, Table 1). However, better yield (72%) was obtained using of 1.3 equivalent 2-aminopyridine (entry 2, table 1) instead of 1 equivalent (entry 1, table 1). When, ethanol is replaced by DCM, 2-nitroimidazopyridine was obtained (entry 4, table 1). $NiFe_2O_4$ NPs has showed superiority over Cu-/Mn-/Co-ferrites for the synthesis of 2-ethoxyimidazopyridines. Nano-Fe_3O_4 catalyst yielded 44% of product (1a), whereas only NiO NPs were inefficient in producing the desired product (1a) and reaction stopped after Michael addition of endocyclic nitrogen to (*E*)-1-(2-nitrovinyl)benzene (1b) (entry 9, Table 1). The Michael adduct (1b) also obtained using standard conditions at room temperature (entry 10, Table 1) under catalyst-free reaction conditions. Possibly, basic Ni-sites in $NiFe_2O_4$ NPsaccelerate the initial Michael addition and Fe-site promoted subsequent oxidative C-H imination and nucleophilic substitution which provides a synergistic effect for the production of unprecedented 2-ethoxy-3-phenyl-imidazopyridine (1a). Here, nano-$NiFe_2O_4$ acts as both catalyst and oxidant. In addition, use of magnetic $NiFe_2O_4$ as catalyst, added additional advantages of easy recovery by an external magnet.[21] Further, $NiFe_2O_4$ nanoparticles may have exhibited extraordinary activities due to its larger and reactive surface. To improve the yield up to satisfactory level, we have conducted the reaction under microwave (MW) conditions.

Table 2 Nano-$NiFe_2O_4$ catalyzed synthesis of 2-alkoxy imidazopyridines



Sl. No.	Product	Yield (%)[a]	
		MW/70W[b]	Heat/80°C
1		85	72
2		80	72
3		85	73
4		84	74
5		85	78
6		85	72
7		84	70
8		86	72

9		81	69
10		80	67
11		86	70
12		82	65

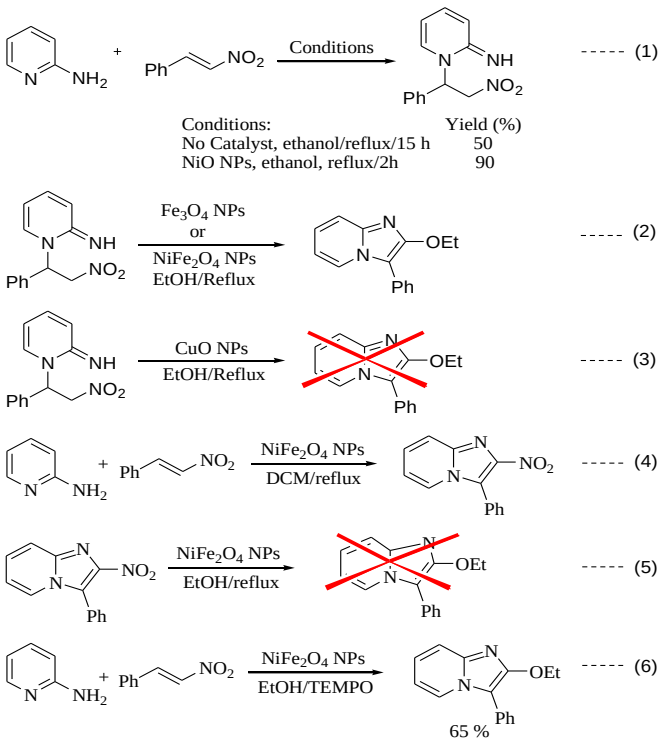
Reaction conditions: 2-aminopyridine (1.3 mmol), (*E*)-1-(2-nitrovinyl)benzene (1 mmol), ethanol (2 ml) and 10 mol% of $NiFe_2O_4$ NPs catalyst; [a]Isolated yield; [b]Reaction was conducted using MW irradiation (70W).

It is well-known that, MW technology shortens the reaction time and improves the purity, yield and selectivity of product.[23] As expected, when the same reaction was performed under MW conditions (70 W) for 5 minutes, significant improvement of yield (85%) was observed (entry 12, Table 1). Thus, the optimized yield (85%) was obtained using 1.3 equivalent of 2-aminopyridine in presence of 10 mol% $NiFe_2O_4$ NPs under MW (70W) irradiation.

Using optimized reaction conditions *i.e.* 1.3 equivalents 2-aminopyridine, 10 mol% of $NiFe_2O_4$ NPs and microwave (MW, 70 W) irradiation (entry 12, Table 1), we have explored the scope of the methodology for the synthesis of library of novel 2-alkoxy-3-arylimidazopyridines. It was observed that 2-aminopyridine and β-nitrostyrene with different substituent participated in this domino reaction with primary aliphatic alcohol without any problem resulting the desired 2-alkoxy-3-arylmidazo[1,2-*a*]pyridine derivatives under MW irradiation. The experimental procedure is simple. Briefly, a mixture of β-nitrostyrene (1 mmol), 2-aminopyridine (1.3 mmol), ethanol (2 ml) and $NiFe_2O_4$ (10 mol %) was taken in a sealed MW tube and was irradiated MW irradiation at 70 W up to 5 minutes. After that, the mixture was cooled to room temperature and the catalyst separated by a strong external magnet and finally, product was extracted with ethyl acetate, washed with water with Brine solution. The organic phase was dried over anhydrous Na_2SO_4. The crude product was obtained by evaporation of solvent in vacuum which was purified by column chromatography over silica gel (60–120 mesh) using mixture of petroleum ether and ethyl acetate (9:1) as an eluting solvent to afford the pure product. The similar protocol was used for the entire product listed in Table 2.

The results of MW assisted synthesis of 2-alkoxyimidazopyridines were also compared with conventional heating conditions (see Table 2). Different, aliphatic alcohols *e.g.* ethanol, n-propanol and n-butanol were participated smoothly, however, tertiary butyl alcohol and phenols were found to inactive in this reaction. This could be due to the steric hindrance at C-2 and/or poor nucleophilic nature of such substrates. Interestingly, dehydrogenation of secondary alcohol (e.g. isopropanol) took place under the similar reaction conditions and results 100% hydrogenation of β–nitrostyrene. All the imidazopyridines were properly characterized by spectroscopic (FT-IR, ^{1}H NMR, ^{13}C NMR etc.) studies and elemental analysis (ESI 7). This method enables to furnish alkoxy substituted imidazopyridines. Here nano-$NiFe_2O_4$ performed showed unique action by accelerating selective aza-Michael addition and promoting oxidative imination, followed by displacing nitro group by alkoxy group resulting products. Finally, magnetic nano-$NiFe_2O_4$ has been recycled and reused for eight times without significant loss of activities (See ESI 9).

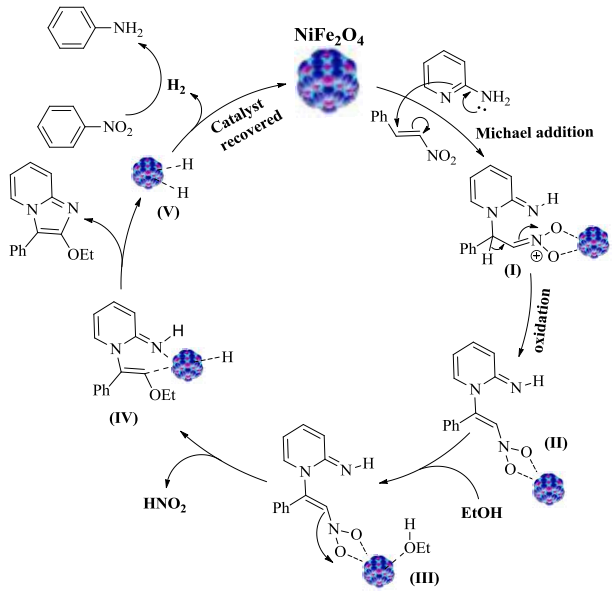
To understand the reaction mechanism, we performed few control experiments (Scheme 3). The reaction of 2-aminopyridine and (*E*)-1-(2-nitrovinyl)benzene in absence of catalyst produced aza-Michael addition product (50%) under optimized reaction conditions after 15 h (Eq. 1, Scheme 3).



Scheme 3 Control experiments.

The same reaction using NiO NPs also stopped after aza-Michael addition (90%) without further oxidative imination (Eq. 1, Scheme 3). The Michael adduct underwent oxidative imination followed by nucleophilic substitution reaction in presence of $NiFe_2O_4$ NPs or Fe_3O_4 NPs to provide the desired product (Eq. 2, Scheme 3).

These reactions indicate that Ni-site in $NiFe_2O_4$ NPs accelerates the initial aza-Michael addition and Fe-sites in ferrite promoted the oxidative addition. The oxidative addition was unsuccessful in presences of Cu-catalyst (Eq. 3, Scheme 3).[17] Thus, Fe-sites play crucial role in the oxidative addition reaction. The reaction in DCM produced 2-nitroimidazopyridine (Eq. 4, Scheme 3) which under optimized reaction conditions does not produce 2-ethoxyimidazopyridine (Eq. 5, Scheme 3). These proved that once 2-position is occupied by a group, no substitution reaction takes place to yield desired 2-ethoxyimidazopyridine product. Thus, addition of ethoxy group and displacement of $–NO_2$ group takes place before formation of final product in an intermediate stage. A reaction was also carried out under optimized conditions in presence of 2.5 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical quencher and 65 % of the desired product was obtained which ruled out the possibility of radical pathway of this reaction. Based on the above control experiments and observations, we have proposed a plausible mechanism for the $NiFe_2O_4$ NPs catalyzed synthesis of 2-alkoy-3-aryimidazopyridine. A plausible mechanism has been outlined in Scheme 4 for 2-ethoxy-synthesis of 3-phenylimidazopyridine. The first step involves basic Ni-site of $NiFe_2O_4$ promoted aza-Michael addition of 2-aminopyridine to (*E*)-1-(2-nitrovinyl)benzene producing Michael adduct (I)in which the oxygen atoms of nitro group might be coordinating to Fe(III) of $NiFe_2O_4$similar to binding of dopamine with Fe_3O_4[22]



Scheme 4 Plausible mechanism for $NiFe_2O_4$ catalyzed synthesis of 2-ethoxy-3-phenylimidazo[1,2-*a*]pyridine

After that, the Michael adduct (I) undergoes oxidation followed by Fe-site promoted removal of nitro group as HNO_2.[12]The catalyst is regenerated after H_2 liberation. The elimination of H_2 was proved by the reduction of nitrobenzene to aniline.

In conclusion, we have demonstrated highly regioselective microwave assisted one-pot synthesis of 2-alkoxyimidazo[1,2-*a*]pyridine derivatives using magnetically separable nano-$NiFe_2O_4$ as reusable catalyst. The introduction of alkoxy group is challenging due to poor nucleophilicity of alcohols and has been achieved by this nano-$NiFe_2O_4$ catalyzed domino protocol. This is the first method to synthesize alkoxy functionalized imidazopyridine moieties. Interestingly, the alkoxy group entered in a rare pathway leading to C-2 alkoxyimidazopyridine derivatives. In addition, the microwave assisted protocol improved the yields (82%) and expedited the reaction rate. Here, Ni-site of nano-$NiFe_2O_4$ accelerated selective aza-Michael addition and Fe-site promoted oxidative imination, followed by displacement of nitro group by alkoxy group. Finally, use of magnetically separable nano-$NiFe_2O_4$ as catalyst, solvent-free reaction conditions made the method environment-friendly in nature. We believe that this novel 2-alkoxyimidazo[1,2-*a*]pyridine derivatives will attract much attention and will find many potential biological and pharmaceutical applications.

Notes and references

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Graphical Abstract

Nano-$NiFe_2O_4$ catalyzed microwave assisted one-pot regioselective synthesis of novel 2-alkoxyimidazo[1,2-*a*] pyridines under aerobic conditions**

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Here, we have demonstrated one-pot regioselective synthesis of novel 2-alkoxy-3-arylimidazo[1,2-a]pyridine derivatives using nano-$NiFe_2O_4$ as reusable catalyst under aerobic conditions. This is the first method to produce alkoxy-functionalized imidazopyridine scaffolds and furnished *via* microwave assisted sequential aza-Michael addition, Fe-promoted ligand transfer and C-H imination reactions.