FULL PAPER

Superparamagnetic core-shell metal–organic framework Fe₃O₄@Ni-MOF as efficient catalyst for oxidation of 1,4-dihydropyridines using hydrogen peroxide

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Abstract

A facile and efficient method was described for oxidation of some 3,5-diacyl or 3,5-diester 1,4-dihydropyridines using H_2O_2 in the presence of superparamagnetic core-shell metal-organic framework Fe₃O₄@Ni-MOF. The Fe₃O₄@Ni-MOF has been obtained by Step-by-Step method in which magnetic Fe₃O₄ magnetic nanoparticles were coated with Ni-MOF using a mercaptoacetic acid linker. The synthesized catalyst was characterized using thermogravimetric analysis, FT-IR spectroscopy, powder X-ray diffraction, field emission scanning electron microscopy and energy-dispersive X-ray analysis. The novel superparamagnetic core-shell metal-organic framework Fe₃O₄@Ni-MOF revealed high efficiency for oxidation of various 1,4-dihydropyridines using hydrogen peroxide. The Box-Behnken design matrix and the response surface method were applied to investigate the optimization of the reaction conditions. The conditions for optimal reaction yield and time were: amount of catalyst ≈ 17 mmol, temperature $\approx 78^{\circ}$ C and amount of hydrogen peroxide ≈ 1 ml. A variety of 3,5-diacyl or 3,5-diester 1,4-dihydropyridines with different substituted functional groups have been converted to corresponding pyridines with good to excellent isolated yields using H₂O₂ and Fe₃O₄@Ni-MOF. The catalyst was reused up to five times for the oxidation of 1,4-dihydropyridines without a significant loss in catalytic activity. The short reaction times, simplicity of method, good to excellent yields and reusability of catalyst were some advantages of the proposed procedure.

K E Y W O R D S

1–4-dihydropyridine, hydrogen peroxide, magnetic nanoparticles, metal organic framework, oxidation

1 | INTRODUCTION

1,4-Dihydropyridines (DHPs) have played a dominant role in biological activities and have been employed as potential drugs due to their calcium antagonistic, antianginal, antitumor, anti-inflammatory, antitubercular, analgesic, and antithrombotic effects.^[1,2] It was found that 1,4-dihydropyridines are analogues of nicotinamide adenosine dinucleotide hydride (NADH) coenzyme that undergo oxidative aromatization to the corresponding pyridine due to the catalysis of cytochrome P-450 in biological systems.^[3] Recently, the synthesis of

pyridines has attracted considerable attention due to their use as natural products, pharmaceuticals, building blocks, dyes, reagents, and ligands in organic chemistry.^[4] Oxidation of 1,4 dihydropyridines is one of the main methods for the preparation of 4-substuted pyridine derivatives which are hard to access via the friedel crafts alkylation. Several reagents and chemicals have been used for the oxidation of DHPs such as NaBrO₃,^[5] NaClO₂,^[6] V₂O₅/SiO₂ nanoparticles,^[7] Bi₂O₃ nanorods,^[8] Na₂S₂O₄/TBHP (tert-butylhydroperoxide),^[9] and SiO₂-CAN (ceric ammonium nitrate).^[10] In this study, H₂O₂ and Fe₃O₄@Ni-MOF were selected as the oxidant and catalyst, respectively, for oxidation of 1,4-dihydropyridines. Hydrogen peroxide is a cheap and green oxidant for oxidation of a large number of substrates.^[11] Literature survey shows that oxidation of 1,4-dihydropyridine derivatives using H_2O_2 in the presence of urea,^[12,13] acetic acid,^[14] $AlCl_{3}$,^[15] NaI,^[16] SiO_{2} -VO (OH)₂,^[17] MOO_{3} ,^[18] KBr/HOAc^[19] as a catalyst, has been reported. In addition, metal-organic frameworks (MOFs) as heterogeneous catalysts have been successfully applied as catalysts in oxidation and hvdrogenation reactions.^[20] MOFs, also called Porous Coordination Polymers, (PCPs) are novel three dimensional organic-inorganic hybrids self-assembled by metal ions and organic ligands. The large density of active sites in MOFs, with respect to other porous materials, enhances their catalytic application efficiency.^[21] A Ni-MOF nanosheet with catalytic activities was used as a peroxidase mimetic and could catalyze the oxidation of 3,3,5,5-tetramethylbenzidine (TMB) using hydrogen peroxide (H_2O_2) .^[22]

It has been found that the magnetic MOFs have obvious advantages in catalytic activity, stability, biological activity, convenient separation and recovery.^[23-27] Recently, nanomaterials have been used as catalyst or very effective supports for immobilization of many catalysts due to their very large surface areas and ease of functionalization.^[28-33] Among a variety of promising supports, magnetic iron (III) oxide nanoparticles (Fe_3O_4) MNPs) has attracted great attention due to its preparation simplicity, biological compatibility and recyclability with an external magnetic field.^[34,35] Herein, we hope to report a facile and impressive approach to prepare the new magnetic MOF composite (Fe₃O₄@Ni-MOF) and its catalytic activity for oxidation study of 1,4-dihydropyrines using hydrogen peroxide. A threelevel Box-Behnken design (BBD) was applied in this research to identify optimal conditions and estimate the effects of temperature, the amounts of catalyst and hydrogen peroxide on yield and reaction time. The design of experiments (DOE) using the Box-Behnken design has recently received significant attention.[36-38]

2 | RESULTS AND DISCUSSION

Recently, we have been using Nickel (II) MOF (Ni-MOF) as a new and effective catalyst for the preparation of 2-aryl benzimidazole and benzothiazole derivatives.^[39] In continuation of our research to develop efficient and green methods for the synthesis of heterocyclic compounds,^[40–42] here, we describe a facile and convenient procedure for the oxidation of 3,5-diacyl or 3,5-diester 1,4-dihydropyridines using H_2O_2 in the presence of Fe₃O₄@Ni-MOF as a catalyst (Scheme 1).

The superparamagnetic core-shell MOF Fe₃O₄@Ni-MOF was prepared by Step-by-Step method.^[43] At first, Fe₃O₄ magnetic nanoparticles were functionalized by mercaptoacetic acid (MAA). Next, functional MNPs were covered with MOF (Ni-MOF) after repeated cycles (Scheme 2). The growth of Ni-MOF shell on the MAA-functionalized Fe₃O₄ core can be started by the metal ions binding to the MAA on the Fe₃O₄ surface and then attaching the ligands from the solution.^[43] The structural properties of synthesized Fe₃O₄@Ni-MOF were identified by FT-IR, thermogravimetric analysis (TGA), X-ray diffraction, TEM, and FESEM spectroscopy.

The powder XRD patterns of Fe₃O₄, Ni-MOF and Fe₃O₄@Ni-MOF in the range 10–80° are shown in Figure 1. The diffraction peaks for the samples confirm the crystal structures of them. The XRD pattern of Fe₃O₄@Ni-MOF indicate that peaks observed at 30.1, 35.5°, 43.1°, 53.4°, 57.0°, and 62.6° corresponded to the crystalline state of cubic Fe₃O₄ magnetic nanoparticles and their crystal structure is well retained. Furthermore, additional peaks agree with the XRD pattern of Ni-MOF.^[39]

Figure 2 shows the FT-IR spectra of Fe₃O₄, Ni-MOF and Fe₃O₄@Ni-MOF. The relatively strong adsorption peak at 560 cm⁻¹ could be attributed to the Fe-O stretching vibration of Fe₃O₄, indicating the existence of Fe₃O₄ in the catalyst.^[44] The other bands, 1142 and 1298 (stretching vibration of SO₂), 1498 and 1623 (aromatic C=C), 1594 (bending vibration of N-H) confirmed the presence Ni-MOF.^[39]

In order to study thermal stability of the synthesized Fe_3O_4 @Ni-MOF, TGA of Fe_3O_4 @Ni-MOF under a nitrogen atmosphere from room temperature to 800°C is given





SCHEME 2 Preparation of Fe₃O₄@Ni-MOF





in Figure 3. The initial weight loss of 2.71% from 30.66° C to 108.16° C was observed resulting from the loss of adsorbed water. The second step shows a weight loss of 10.19% from 108.16 to 797.88° C which can be attributed to the decomposition of organic moiety and the breakdown of the MOF. However, the results of TGA showed that the catalyst is stable below 300° C.

The surface morphology of synthesized Fe_3O_4 @Ni-MOF was characterized by FESEM. As shown in Figure 4, the FESEM image exhibited a uniform morphology for the catalyst. In addition, the presence of C₄ N^{\cdot} S^{\cdot} Ni, Fe, and O atoms was demonstrated using EDX analysis confirming that Fe₃O₄ was coated with Ni-MOF (Figure 5).

The TEM image of Fe_3O_4 @Ni-MOF was showed in Figure 6. TEM image demonstrated that synthesized Fe_3O_4 @Ni-MOF were composed of a Fe_3O_4 core and a Ni-MOF shell.

In the next step, catalytic activity of synthesized Fe_3O_4 @Ni-MOF was investigated for the oxidation of 1,4-dihydropyridin derivatives. For the optimization of the reaction conditions, oxidation of diethyl 2,6-dimethyl-

%Transmittance



FIGURE 3 Thermogravimetric analysis (TGA) plot for the synthesized Fe₃O₄@Ni-MOF

4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (0.5 mmol) using hydrogen peroxide (30%, 1 ml) in the presence of 15 mg of catalyst in 3 ml of a different solvent was selected as a model reaction (Table 1).

The results in Table 1 indicate that the presence of catalyst and solvent was necessary for the reaction (entries 1 and 2). In addition, it was found that Fe_3O_4 @Ni-MOF is more appropriate than the others. In this work, Ni-MOF acted the key role as a catalyst in Fe_3O_4 @Ni-MOF and was supported on Fe_3O_4 MNPs,

which can easily be recovered by applying an external magnetic field.

The results in Table 1 led us to investigate the effect of various reaction parameters such as temperature, the amounts of catalyst and hydrogen peroxide on the oxidation of 1,4-dihydropyridines with a three-level 15-run Box–Behnken design (BBD) method which was used by utilizing Design-Expert 7.0.0 Trial software (Stat-Ease Inc., Minneapolis). Table 2 shows the level of parameters, experimental design matrix and results. The input parameters in the reaction process optimization include (A) temperature (i.e., 30° C, 55° C, and 80° C), (B) the amount of catalyst (i.e., 10, 15, and 20 mg), and (C) the amount of hydrogen peroxide (i.e., 0.2, 0.6, and 1 ml). The response function (Y) had a shorter reaction time and a greater yield for oxidation of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1b**).



FIGURE 4 FESEM image of Fe₃O₄@Ni-MOF

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Response surface methodology and the BBD were used to study the interaction of three factors on the yield and reaction times, and to determine optimal conditions for the reaction (Tables 3 and 4). The analysis of variance (ANOVA) test at 95% confidence level was used and the smaller *p* values (*p* value < 0.05) indicate a greater significance. The results revealed that A, B, C, AB, A², B², and C² were statistically significant.

The Equations 1 and 2 show second-order polynomial models for time and yield based on significant levels and actual values.



FIGURE 6 Thermogravimetric analysis (TEM) image of Fe₃O₄@Ni-MOF



FIGURE 5 EDX analysis of Fe₃O₄@Ni-MOF

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Entry	Catalyst	condition	Time (h)	Yield (%)
1	—	EtOH/reflux	5	—
2	Fe ₃ O ₄ @Ni-MOF	Solvent free/80°C	4	30
3	Fe ₃ O ₄ @Ni-MOF	EtOAc/reflux	5	63
4	Fe ₃ O ₄ @Ni-MOF	CH ₃ CN/reflux	6	70
5	Fe ₃ O ₄ @Ni-MOF	H ₂ O/reflux	5	_
6	Fe ₃ O ₄ @Ni-MOF	EtOH/reflux	4	97
7	Fe ₃ O ₄ @Ni-MOF	EtOH/r.t.	8	25
8	Ni-MOF	EtOH/reflux	6	93
9	Fe_3O_4	EtOH/reflux	5	92

TABLE 1 Optimization of reaction conditions

TABLE 2 The experimental factors, levels and results for the BBD

			Levels		
Factors	Unit	Symbol	High (+1)	Central (0)	Low (–1)
Temperature	°C	А	30	55	80
Catalyst amount	mg	В	10	15	20
H_2O_2	ml	С	0.2	0.6	1

	Independent variables		Dependent varia	able (Time/min)	Dependent var	Dependent variable (Yield/%)	
Run	Α	В	С	Experimental	Predicted	Experimental	Predicted
1	80.00	15.00	1.00	230	228.00	97	99.25
2	55.00	10.00	1.00	360	360.25	56	55.38
3	55.00	10.00	0.20	420	418.75	34	34.13
4	55.00	15.00	0.60	297	299.00	65	66.00
5	55.00	20.00	1.00	300	301.25	68	67.88
6	80.00	10.00	0.60	320	321.75	86	84.38
7	55.00	15.00	0.60	298	299.00	65	66.00
8	55.00	15.00	0.60	300	299.00	65	66.00
9	30.00	10.00	0.60	420	419.25	8	10.13
10	55.00	15.00	0.60	300	299.00	67	66.00
11	30.00	20.00	0.60	400	398.25	19	19.00
12	80.00	20.00	0.60	220	220.75	85	85.00
13	30.00	15.00	1.00	440	440.50	30	28.50
14	55.00	15.00	0.60	300	299.00	68	66.00
15	30.00	15.00	0.20	420	422.00	5	4.00
16	55.00	20.00	0.20	356	355.75	30	30.63

$$Y (Time) = +299 - 68.75A - 30.5B - 28.25C - 20AB - 37.5 AC + BC + 22.25A2 + 18.75B2 + 41.25 R2 = 0.9959 Adjusted R2 = 0.9930 (1)$$

$$Y (Yied\%) = +66 + 34.13A + 2.25B + 14.63C - 3AB + 1.25 AC + 4 BC - 7.13A2 - 9.37B2 - 9.63C2 R2 = 0.9968 Adjusted R2 = 0.9991 (2)$$



TABLE 3 ANOVA for Box-Behnken quadratic model for reaction time of oxidation of 1b

Source	Sum of squares	Df	Mean square	F value	p value	Remark
Model	70652.53	9	7850.28	2035.26	< 0.0001	significant
A—Temperature	37812.5	1	37812.5	9803.24	< 0.0001	
B—Catalyst amount	7442	1	7,442	1929.41	< 0.0001	
C—H ₂ O ₂	6384.5	1	6384.5	1655.24	< 0.0001	
AB	1600	1	1,600	414.81	< 0.0001	
AC	5625	1	5,625	1458.33	< 0.0001	
BC	4	1	4	1.04	0.3424	
A^2	2084.47	1	2084.47	540.42	< 0.0001	
B ²	1480.26	1	1480.26	383.77	< 0.0001	
C^2	7164.47	1	7164.47	1857.46	< 0.0001	
Residual	27	7	3.86			
Lack of Fit	19	3	6.33	3.17	0.1473	not significant
Pure Error	8	4	2			
Cor Total	70679.53	16				

TABLE 4 ANOVA for Box-Behnken quadratic model for yield of oxidation of 1b

Source	Sum of squares	Df	Mean square	F value	p Value	Remark
Model	12259.78	9	1362.2	252.59	< 0.0001	significant
A—Temperature	9316.13	1	9316.13	1727.49	< 0.0001	
B—Catalyst amount	40.5	1	40.5	7.51	0.0289	
$C-H_2O_2$	1711.13	1	1711.13	317.29	< 0.0001	
AB	36	1	36	6.68	0.0363	
AC	6.25	1	6.25	1.16	0.3174	
BC	64	1	64	11.87	0.0108	
A^2	213.75	1	213.75	39.64	0.0004	
B ²	370.07	1	370.07	68.62	< 0.0001	
C^2	390.07	1	390.07	72.33	< 0.0001	
Residual	37.75	7	5.39			
Lack of Fit	29.75	3	9.92	4.96	0.078	not significant
Pure Error	8	4	2			
Cor Total	12297.53	16				

where Y is the predicted response as yield and reaction time; A, B, and C are temperature, amount of catalyst, and the amount of hydrogen peroxide, respectively; and AB, AC, and BC are the interaction coefficients of these factors.

The determination coefficients of the two equations $(R^2 = 0.9959 \text{ and } 0.9968 \text{ for time and yield respectively})$ indicate a good correlation between the observed and predicted results. The contour plots and 3D response surfaces can be applied for investigation of the interaction

between the reaction parameters on the response reaction yield and time. The optimal experimental conditions for obtaining the minimum time and maximum yield are presented in Figures S1 and S2 represented by dark blue and dark red areas respectively. The results of DOE indicated that the optimal conditions for oxidation of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-

3,5-dicarboxylate (**1b**) for the minimum reaction time of 214 min (3.57 h) and maximum yield of 97% are temperature = 77.97° C (reflux condition), amount

TABLE 5 Oxidation of 1b under optimized conditions

	Factors			Dependent variabl min)	e (Time/	Dependent variable (Yield/%)	
Approach	Temperature (°C)	Amount of catalyst (mg)	H ₂ O ₂ (ml)	Experimental (Mean <u>+</u> SD)	Predicted	Experimental (Mean <u>+</u> SD)	Predicted
BBD	77.97	17.07	0.93	215 ± 2.49	214.357	96.66 ± 1.24	97.370

TABLE 6 Oxidation of some 1,4-dihydropyridines using hydrogen peroxide in the presence of Fe₃O₄@Ni-MOF

Entry	R ₁	R ₂	Product	Time (h)	Yield (%)	Melting pointd ^O C [Found.]	Melting pointd ^O C ^[Ref.]
1	Н	OC_2H_5	2a	0.5	90	68–69	69–71 ^[46]
2	C_6H_5	$\mathrm{OC}_{2}\mathrm{H}_{5}$	2b	3.5	97	64–66	63-65 ^[47]
3	$4\text{-BrC}_6\text{H}_4$	OC_2H_5	2c	6.5	86	oil	Oil ^[47]
4	$3-NO_2C_6H_4$	$\mathrm{OC}_{2}\mathrm{H}_{5}$	2d	7	88	61–63	62–64 ^[41]
5	$4\text{-}\mathrm{ClC}_6\mathrm{H}_4$	OC_2H_5	2e	4	98	64–65	64-65 ^[48]
6	$4-\mathrm{NO}_2\mathrm{C}_6\mathrm{H}_4$	$\mathrm{OC}_{2}\mathrm{H}_{5}$	2 f	7	83	112–114	113–114 ^[48]
7	2-furyl	OC_2H_5	2 g	2.5	92	oil	Oil ^[48]
8	$4\text{-}\mathrm{CH}_3\mathrm{OC}_6\mathrm{H}_4$	OC_2H_5	2 h	3.5	92	48-50	49–52 ^[49]
9	$2\text{-}CH_3OC_6H_4$	OC_2H_5	2i	3	84	57-60	58-60 ^[49]
10	Н	CH_3	2j	2	85	64–65	65–67 ^[46]
11	C_6H_5	CH_3	2 k	5.5	95	184–186	186–188 ^[41]
12	$3-NO_2C_6H_4$	CH_3	2 L	7.5	84	123–125	124–126 ^[41]
13	$4\text{-}ClC_6H_4$	CH_3	2 m	5.5	88	174–176	172–174 ^[41]
14	$4\text{-}CH_3OC_6H_4$	CH_3	2n	4	93	165–167	165–166 ^[41]
15	$2\text{-}CH_3OC_6H_4$	CH_3	20	5	90	140–142	142–143 ^[50]

of catalyst = 17.07 mg and amount of hydrogen peroxide = 0.93 ml (Figure S3).

In order to investigate the validity of the model, fourtime reactions were done using these optimal experimental conditions, so that predicted values were in a good agreement with experimental values (Table 5).

Following the optimization of the reaction conditions, a variety of 1,4-dihydropyridine derivatives were oxidized using H_2O_2 in the presence of Fe₃O₄@Ni-MOF to study the generality of this method (Table 6).

As shown in Table 6, this procedure is effective for oxidation of 3,5-diacetyl and 3,5-diester 1,4-dihydro pyridine derivatives to afford corresponding pyridines with retention of the substituent in position 4 in good to excellent yields. Furthermore, 3,5-diester 1,4-dihydro pyridines converted to the corresponding pyridine more readily than 3,5-diacetyl 1,4-dihydropyridines under identical conditions. However, compounds **1a** and **1j**, with no substituent in position 4 of the dihydropyridine ring, were oxidized in a shorter time than other 1,4-dihydropyridines. We do not find a clear correlation between substituent in position 4 of dihydropyridine ring and reaction times. Nevertheless some electron releasing groups, such as methoxy, facilitate the reaction, and some electron *withdrawing* groups, such as nitro, increase the reaction times. When synthesized Fe_3O_4 @Ni-MOF was used for oxidation of some 1,4-dihydropyridines under identical conditions after several months, the reaction was performed without reducing initial catalyst activity.

It has been found that some MOFs were applied as peroxidase mimetic with catalytic activities and nonenzymatic electrochemical hydrogen peroxide sensors.^[22,45] Thus, in this work, it is proposed that H_2O_2 was adsorbed in the pores of Ni-MOF and absorbed hydrogen peroxide was reduced into H_2O along with the oxidation of 1,4-dihydropyrines to corresponding pyridines (Scheme 3).

The reaction mechanism probably consists of two steps. First, hydrogen peroxide was adsorbed in the pores

of Ni-MOF onto the surface of Fe_3O_4 @Ni-MOF, and the O–O bond was broken into *hydroxyl radical*.^[22] Then, abstraction of a hydrogen of dihydropyridine ring by hydroxyl radical yielding.monohydropyridyl radical which reduces the hydroxyl radical to produce corresponding pyridine (Scheme 4).^[51]

Moreover, reusability of Fe_3O_4 @Ni-MOF was studied in the oxidation of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1b**) under optimized conditions. After completion of the reaction, the mixture was cooled to room temperature and the catalyst was easily separated using a strong external permanent magnet. The separated Fe_3O_4 @Ni-MOF was washed four times with methanol (5 ml) and then dried. The recovered catalyst was reused five times for the oxidation of 1a without a significant loss in catalytic activity (Figure 7). The stability of the recovered



SCHEME 3 Schematic illustration of the reduction of H_2O_2 and oxidation of DHPs by Fe_3O_4 @Ni-MOF

 Fe_3O_4 @Ni-MOF was investigated using EDX analysis (Figure 8). The comparison of the results showed that the main composition of the fresh catalyst and the recycled catalyst were the same.

Finally, the performance of this procedure was compared with various procedures for the oxidation of 1,4-dihydropyridines (Table 7). Most of these methods are applied only for oxidation of 3,5-diester 1,4-dihydropyridines. The results indicate that core-shell MOF Fe_3O_4 @Ni-MOF is an efficient catalyst for oxidation of 3,5-diacyl or 3,5-diester 1,4-dihydropyridines using hydrogen peroxide and this procedure is comparable with some other reported methods in terms of reaction times and yield.

3 | EXPERIMENTAL

3.1 | General

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All chemicals and reagents were purchased from Sigma-Aldrich and were used without further purification. All Hantzsch 1,4-dihydropyridines were prepared similar to the reported methods,^[49,52] Their physical and spectroscopic data were in agreement with those of authentic samples. All yields are from the isolated products after purification. Melting points were

1)
$$H_2O_2 \xrightarrow{\text{Fe}_3O_4(\underline{W}|\text{NI-MOF})} 2 \text{ OH}$$

2) $\dot{O}H + H_2Py \longrightarrow H_2O + HPy \xrightarrow{OH} Py + H_2O$



SCHEME 4 A plausible mechanism for oxidation of DHPs by Fe_3O_4 @Ni-MOF

FIGURE 7 Recyclability of Fe₃O₄@Ni-MOF as a catalyst for the oxidation of **1b** as a model reaction



TABLE 7 Comparison of the efficiency of some method used in the oxidation of 1,4-dihydropyridines

ΝίΚαΝίΚβ

FeKβ

5

100

0

Ó

Kβ

Entry	Reagent	Condition	Yield (%)	time [Ref.]
1	H ₂ O ₂ /Fe ₃ O ₄ @Ni-MOF	EtOH/Reflux	83-98	$0.57.5~h^{[\text{This work}]}$
2	H ₂ O ₂ /AlCl ₃ 6H ₂ O	H ₂ O/EtOH/Microwave	94–100	3–8 min ^[15]
3	NaIO ₄ /Mn (III)-BSMP	MeOH/r.t.	70–95	25–240 min ^[49]
4	Graphite Oxide	Toluene/100°C	90–96	3 h ^[53]
5	Guanidinium nitrate/Silica sulfuric acid	$CH_2Cl_2/r.t.$	92–99	15–560 min ^[54]
6	O ₂ /Transition metal chloride/Sodium nitrite/TEMPO	MeCN/AcOH/r.t.	90–98	30-60 min ^[48]
7	silica-supported/metal (Ni,Co,Fe,Cu)nitrates/	infra-red radiations	74–95	10–45 min ^[55]
8	H_2O_2/MoO_3	EtOH/Reflux	88-100	6 h ^[18]
9	Air/Na ₂ S ₂ O ₄ /TBHP	EtOAc/r.t.	73–96	2–6 h ^[9]
10	Bi ₂ O ₃	EtOH/Reflux	72–100	4–24 h ^[8]
11	H ₂ O ₂ /SiO ₂ -VO (OH) ₂	CH ₃ CN/r.t.	50-98	9–90 min ^[56]
12	DHPDMDO/NH ₄ Br/HOAc	H ₂ O/MeCN/r.t.	92–99	12–35 min ^[57]
13	NaClO ₂ /HCl	EtOH/H ₂ O/50°C	89–99	20 min ^[6]

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measured using a Barnstead Electrothermal apparatus. ¹H NMR spectra were recorded on a Brüker 300-MHz spectrometer in CDCl₃. elemental analysis was obtained using a Perkin–Elmer 2400 Series II CHNS/O analyzer. Surface morphology and elemental composition were obtained using a field emission SEM instrument (Tescan Mira III). TGA and DTA curves were measured using a TGA/DSC 1 (Mettler Toledo) at a heating rate of 10°C min⁻¹ from 25°C to 800°C under nitrogen atmosphere. The morphology of the catalyst was characterized by transmission electron microscopy (TEM, Zeiss—EM10C—100 KV). X-ray diffraction analysis was carried out using X'Pert Pro X-ray

diffractometer using a Cu tube over the 20 range from 10° to $80^\circ.$

3.2 | General procedure for the preparation of Fe₃O₄ nanoparticles

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Magnetic nanoparticles were synthesized by a modified chemical precipitation method.^[58] FeCl₂.4H₂O (2.0 g) and FeCl₃.6H₂O (5.4 g) were dispersed to double-distilled water (20 ml) and concentrated hydrochloric acid (2 ml). The solution was stirred vigorously under N₂ gas at 80° C. Ammonium hydroxide (2 M)

solution was added dropwise in to the solution under mechanical stirring to adjust the pH to 10 and cause precipitation. The precipitated particles were separated using a strong permanent magnet and were washed three times using double distilled water. After that the powder was dried to obtain nanomagnetic Fe_3O_4 .

3.3 | General procedure for the preparation of Fe₃O₄@Ni-MOF

Superparamagnetic core-shell MOF Fe₃O₄@Ni-MOF was synthesized according to a previous procedure of Oiu with minor modifications.^[59] In a typical procedure, 20 ml of ethanol solution of Fe_3O_4 MNPs (0.1 g) was added to 20 ml of ethanol solution of mercaptoacetic acid (0.58 mM) with shaking for 24 h. Mercaptoacetic acid (MAA)-functionalized Fe₂O₄ nanoparticles were collected by a strong magnet and washed two times with distilled ethanol and water. Subsequently, 0.1 g of modified Fe₃O₄ was dispersed in 2.5 ml of methanol solution of Nickel (II) nitrate hexahydrate (1 mmol) and shaken for 15 min at room temperature. Then 5 ml of methanol solution of 4,4'diaminodiphenyl sulfone (DDS) (1 mmol) was added to the mixture and stirred at room temperature for 30 min and again at 50°C for 30 min. After each step, the obtained powder was separated with a strong magnet and rinsed with ethanol. Finally, the magnetic core-shell MOF Fe₃O₄@Ni-MOF was obtained after 40 cycles. The synthesized catalyst was washed with ethanol, dried and identified by FT-IR, TGA, FE-SEM, TEM and XRD techniques.

3.4 | General procedure for oxidation of 1,4-dyhdropyridine derivatives

А suspension of Hantzsch 1,4-dihydropyridines (0.5 mmol), Fe₃O₄@Ni-MOF (17 mg), and H₂O₂ (30%, 1 ml) in ethanol (3 ml) were stirred under reflux for a specific time. The reaction progress was followed by thin layer chromatography (ethyl acetate: petroleum ether 1:3). After completion of the reaction, the catalyst was easily separated using a strong external permanent magnet. The solvent was removed, and the crude product was purified by recrystallization from petroleum ether/ethyl acetate (4:1) to obtain a pure product. The structures of the products were characterized using IR and ¹H NMR spectroscopy which were in correlation with those reported before.

3.5 | Selected spectroscopic data

Diethyl-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (2b)

IR (KBr): $\nu^{-} = 1720 \text{ cm}^{-1}$ (C=O); ¹HNMR (300 MHz, CDCl₃, 25°C, TMS): $\delta = 0.86$ (t, J = 6.8 Hz, 6H, CO₂C-H₂CH₃), 2.58 (s, 6H, 2 and 6-CH₃), 3.97 (q, J = 6.8 Hz, 4H, CO₂CH₂CH₃), 7.28 ppm (m, 5H, C₆H₅); Anal. Calcd for C₁₉H₂₁NO₄: C 69.71; H 6.47; N, 4.28. Found: C, 69.60; H, 6.48; N, 4.32.

Diethyl-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2 h)

IR (KBr): $\nu^{\sim} = 1,697 \text{ cm}^{-1} (\text{C}=\text{O})$; ¹HNMR (300 MHz, CDCl₃, 25°C, TMS): $\delta = 0.97$ (t, J = 7.0 Hz, 6H, CO₂C-H₂CH₃), 2.60 (s, 6H, 2 and 6-CH₃), 3.90 (s, 3H, 40-OCH₃),4.00 (q, J = 7.0 Hz, 4H, CO₂CH₂CH₃), 7.28 ppm (m, 4H, C₆H₄OCH₃); Anal. Calcd for C₂₀H₂₃NO₅: C 67.21, H 6.49; N 3.92, Found: C 67.28; H 6.40; N 3.95.

3,5-Diacetyl-4-(4-chlorophenyl)-2,6-dimethylpyridine (2 m)

IR (KBr): $\nu^{-} = 1710 \text{ cm}^{-1}$ (C=O); ¹HNMR (300 MHz, CDCl₃, 25°C, TMS): $\delta = 1.80$ (s, 6H, 2-and 6-CH₃), 2.40 (s, 6H, 3-and 5-COCH₃), 7.20 ppm (m, 4H, C₆H₄Cl); Anal. Calcd for C₁₇H₁₆ClNO₂: C 67.66, H 5.34, N 4.64, Found: C 66.98, H 5.37, N 4.70.

4 | CONCLUSIONS

We described a facile and environmentally friendly method for oxidation of 1,4-dihydropyridines using H_2O_2 in the presence of Fe₃O₄@Ni-MOF. The core-shell MOF Fe₃O₄@Ni-MOF was successfully prepared using coating Ni-MOF on Fe₃O₄ magnetic nanoparticles with a mercaptoacetic acid linker utilizing the Step-by-Step method. The Fe₃O₄@Ni-MOF was applied as catalyst for oxidation of some 3,5-diacyl or 3,5-diester 1,4-dihydropyridines using H₂O₂. Following optimization of the reaction conditions with a three-level 15-run Box-Behnken design (BBD) method, several 3,5-diacyl or 3,5-diester 1,4-dihydropyridines were oxidized using H₂O₂ in the presence of Fe₃O₄@Ni-MOF with good to excellent isolated yields. The catalyst could be easily recovered with an external magnet and recycled with high activity. The simplicity of method, high yields of products, short reaction times, stability, reusability, and easy separation of the catalyst are the advantages of this methodology.

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AUTHOR CONTRIBUTIONS

Marzieh janani: Investigation. Masumeh Abdoli-Senejani: Investigation. Tahereh Momeni Isfahani: Investigation.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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