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FULL PAPER

Environmentally friendly and highly efficient synthesis of benzoxazepine and malonamide derivatives using HPA/TPI-Fe_3O_4 nanoparticles as recoverable catalyst in aqueous media

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A magnetic inorganic–organic nanohybrid material (HPA/TPI-Fe_3O_4 NPs) was produced as an efficient, highly recyclable and eco-friendly catalyst for the one-pot multi-component synthesis of malonamide and 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine derivatives with high yields in short reaction times (25–35 min) in aqueous media at room temperature. The nanohybrid catalyst was prepared by the chemical anchoring of $H_6P_2W_{18}O_{62}$ onto the surface of modified Fe_3O_4 nanoparticles (NPs) with *N*-[3-(triethoxysilyl)propyl]isonicotinamide (TPI) linker. The magnetic recoverable catalyst was easily recycled at least ten times without any loss of catalytic activity.

KEYWORDS

2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine, green chemistry, HPA/TPI-Fe_3O_4 NPs, malonamide

1 | INTRODUCTION

Today, most emphasis of chemical synthesis is on the development of green synthetic routes with heterogeneous catalysts and aqueous media.[1] Multi-component reactions (MCRs) are chemical transformations in which three or more different starting materials react to generate a final complex product in a one-pot reaction.[2]

Heteropolyacids (HPAs) are water-soluble complex metal-oxo structures which have been extensively exploited as catalysts in various homogeneous and heterogeneous organic transformations in applications ranging from fine chemical industries to pharmaceuticals and food industries.[3] The advantages afforded by applying Keggin-type HPA reactions include strong acidities, lower proportion of side reactions and production of non-toxic wastes. The use of HPAs, as catalysts for fine organic synthetic processes, is to develop and synthesize antioxidants, medicinal preparations, vitamins and biologically active substances as reported previously.[4]

Recently, science and technology are shifting emphasis to environmentally friendly and sustainable resources and processes. For these reasons several heterogeneous materials with supported dodecatungstophosphoric acid (HPW), such as HPW/C,[5] HPW/CNTs,[6] HPW/TiO_2,[7] HPW/SnO_2,[8] HPW/C-Al_2O_3,[9] HPW/Nb_2O_5,[10] HPW/ZrO_2,[11] HPW/hydrous zirconia[12] and HPW/SiO_2,[13] have been studied.

Paramagnetic Fe_3O_4 nanoparticles (NPs) have attracted worldwide attention and have been studied extensively due to their technological and biological applications such as in drug delivery, bioseparation, biomolecular sensors and magnetic resonance imaging.[14,15]

Benzoxazepine derivatives are important scaffolds in medicinal chemistry with various biological activities,[16] and attractive compounds of growing pharmaceutical interest as documented by many publications. Among compounds containing this fragment are a non-nucleoside histamine receptor agonist,[17] HIV-1 reverse transcriptase inhibitor[18] and calcium antagonists,[19] as well as analgesics[20] and antidepressants.[21] The benzo[*b*][1,4]oxazepine derivatives demonstrate various forms of bioactivity such as antidepressant and anxiolytic activity,[22] they are used for treating bronchial asthma and allergic bronchitis[23] and they show antiserotoninergic and antihistaminic effects,[24] and tetrahydrobenzo[*b*][1,4]oxazepines are progesterone receptor

agonists[25] and show anticancer activity against breast cancer cells.[26]

Malonamide derivatives are some of the most important targets in synthetic chemistry because they display a number of interesting properties in various fields.[27] In medicinal and pharmaceutical chemistry, their derivatives are identified as selective γ-opioid receptor agonists,[28] as a γ-secretase inhibitor in treatment of Alzheimer's disease[29] and as a potent c-Met/VEGFR2 multi-targeted kinase inhibitor for cancer therapy.[30] Recent studies have also shown that some malonamides can act as gelators where their gelling properties strongly depend on their stereochemistry.[31,32] Because of the broad range of applications that these compounds have, new and simple synthetic methods for their preparation are warranted, and recently MCRs have provided practical synthetic routes.[33]

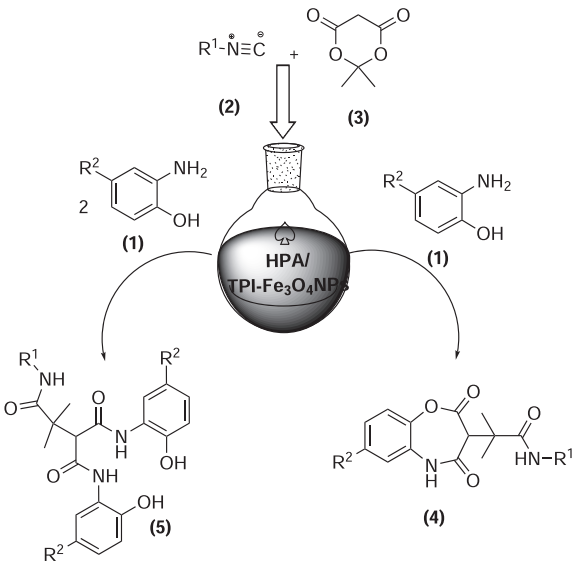
Shaabani *et al.* have reported novel routes for the synthesis of benzoxazepines and malonamide derivatives in the absence of catalyst in CH_2Cl_2 solvent and with long reaction times using isocyanide-based MCRs.[33]

In view of our current studies on MCRs,[34] and considering our previous results, herein we report a highly versatile, eco-friendly and efficient one-pot three-component heterogeneous protocol for the synthesis of benzoxazepines and malonamide derivatives in the presence of a catalytic amount of $H_6P_2W_{18}O_{62}$/pyridino-Fe_3O_4 NPs in water as a solvent at room temperature (Scheme 1).

2 | EXPERIMENTAL

2.1 | General considerations

All reagents and solvents were obtained from Merck (Germany) and used without further purification. Melting points were measured with an Electrothermal 9100 apparatus.



SCHEME 1 Synthesis of malonamide and 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine derivatives.

2.2 | General procedure for preparation of malonamide (4a–h) and 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine (5a–h) derivatives

A solution of 2-amino-4-methylphenol (1.00 or 2.00 mmol), isocyanide derivatives (1.00 mmol) and Meldrum's acid (1.00 mmol) was stirred in the presence of HPA/TPI-Fe_3O_4 NPs (0.02 g) in 3 ml of water as solvent at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate–*n*-hexane, 1:1), ethanol (3 ml) was added and the resulting mixture was heated at 60°C. The catalyst was recovered using an external magnet. Then, the solution crystallized to give products **4a**–**h** and **5a**–**h**.

2.3 | Preparation of $H_6P_2W_{18}O_{62}\cdot24H_2O$

$H_6P_2W_{18}O_{62}\cdot24H_2O$ was prepared from an α/β-$K_6P_2W_{18}O_{62}\cdot10H_2O$ isomer mixture.[35–37] Concentrated phosphoric acid in a 4:1 acid-to-salt ratio was added to a boiling aqueous solution of $Na_2WO_4\cdot2H_2O$ and the mixture was kept boiling in a reflux system for 12 h. The salt was precipitated by adding KCl, then purified by recrystallization and cooled overnight to 5°C. The product consisting of a mixture of the α- and β-isomers, was filtered, washed and then vacuum-dried for 10 h. The acid was obtained from an aqueous solution of α/β-$K_6P_2W_{18}O_{62}\cdot10H_2O$ salt, which was treated with ether and concentrated HCl (37%) solution. The acid so released formed an addition compound with ether, which allowed it to be separated from the solution. Then, the ether was eliminated by dry air and the remaining solution was crystallized in a vacuum desiccator.

2.4 | Synthesis of *N*-[3-(Triethoxysilyl)propyl] isonicotinamide (TPI)-functionalized Fe_3O_4

Fe_3O_4 NPs were synthesized according to previously reported methods.[38,39] $FeCl_3\cdot6H_2O$ (5.2 g) and $FeCl_2\cdot4H_2O$ (2.0 g) were added to a three-necked flask containing deionized water (50 ml) and heated at 80°C under nitrogen gas blowing. Then, NH_3 aqueous solution (8 ml, 32%) was added dropwise to the reaction mixture. After 15 min, the obtained NPs were separated using an external magnet and washed three times with brine solution. The pyridine-functionalized Fe_3O_4 NPs were obtained using a dispersion of Fe_3O_4 NPs (0.5 g) in dry toluene (50 ml), the mixture being stirred for 1 h. Then, TPI (1 ml) was added and the mixture and refluxed for 24 h. The TPI-Fe_3O_4 NPs were collected using a strong magnet, washed with toluene and ethanol and then dried at ambient temperature.

2.5 | Immobilization of $H_6P_2W_{18}O_{62}{\cdot}24H_2O$ on TPI-Fe_3O_4 NPs

HPA/TPI-Fe_3O_4 NPs was synthesized according to a previously reported procedure.[40] The immobilization of $H_6P_2W_{18}O_{62}{\cdot}24H_2O$ onto the TPI-Fe_3O_4 NPs was done in methanol solution (100 ml) containing 0.6 g of $H_6P_2W_{18}O_{62}{\cdot}24H_2O$ and TPI-Fe_3O_4 NPs (1.2 g), and the mixture was refluxed for 3 h. Then, the heterogeneous catalyst was collected and extracted in a Soxhlet extractor using methanol for 12 h and thereafter was dried at 105°C at reduced pressure.

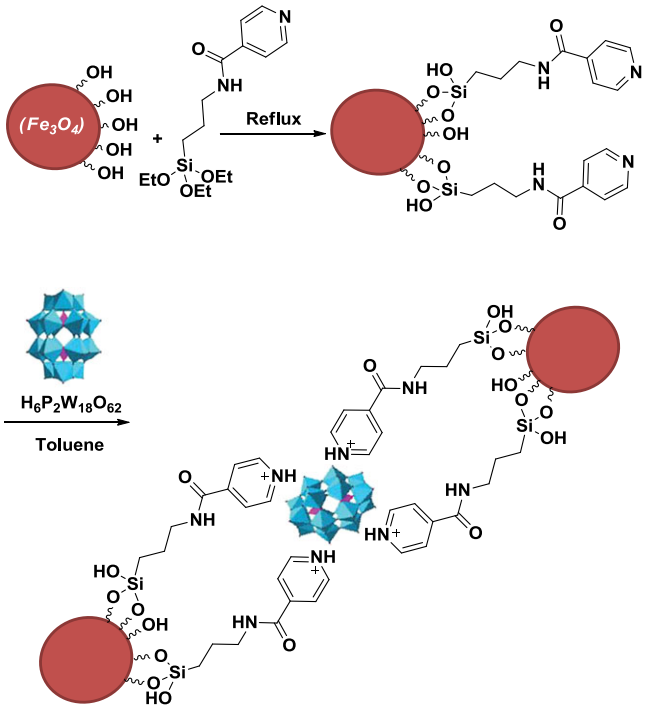
A schematic for the preparation of HPA/TPI-Fe_3O_4 NPs is shown in Scheme 2. All of the synthesized nanoparticles were characterized using Fourier transform infrared (FT-IR) spectroscopy, X-ray diffraction (XRD), thermal analysis (DTA/TGA), transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

3 | RESULTS AND DISCUSSION

3.1 | Structural characterization of HPA/TPI-Fe_3O_4 NPs

3.1.1 | FT-IR spectroscopy

FT-IR spectroscopy was used to characterize the HPA/TPI-Fe_3O_4 NPs. The FT-IR spectrum of $H_6P_2W_{18}O_{62}$/TPI-Fe_3O_4 NPs has a distinct band with shoulders at about 1035 cm^{-1}, confirming a strong interaction of the pyridine-modified Fe_3O_4 NPs with $H_6P_2W_{18}O_{62}$. In addition, observation of the fingerprinting FT-IR bands of the Wells–Dawson structure in the 750–1010 cm^{-1} region confirms the loading of $H_6P_2W_{18}O_{62}$ onto the surface of TPI-Fe_3O_4 NPs (Figure 1).[40]



SCHEME 2 Preparation of HPA/TPI-Fe_3O_4 NPs.

3.1.2 | XRD analysis

The crystallinity of $H_6P_2W_{18}O_{62}$/TPI-Fe_3O_4 NPs was investigated by XRD method.[40] The positions and relative intensities of all diffraction peaks match well with those from the JCPDS card (75–1610). The XRD pattern of Fe_3O_4 (Figure 2) exhibited (220), (311), (400), (422), (511) and (440) reflections.[38] The spinel structure of Fe_3O_4 is retained after functionalization with TPI and immobilization of $H_6P_2W_{18}O_{62}$ onto TPI-Fe_3O_4 NPs. Moreover, the sample is crystalline and Fe_3O_4 NPs with a spinel structure is the only obtained phase together with some additional peaks, indicated by star marks in Figure 2, associated with the Wells–Dawson-structured $H_6P_2W_{18}O_{62}$.[39]

3.1.3 | TEM and SEM analyses

The size and morphology of the HPA/TPI-Fe_3O_4 NPs were investigated using TEM. The micrographs (Figure 3) illustrate that the Fe_3O_4 NP core is coated with a TPI shell uniformly, and particles have semi-spherical morphology with

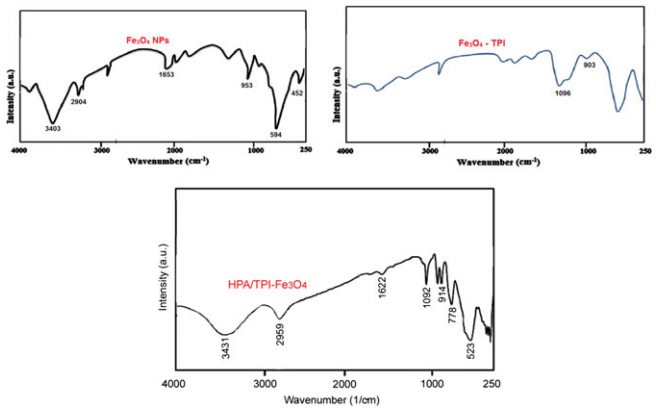


FIGURE 1 FT-IR spectra of Fe_3O_4, TPI-Fe_3O_4 and $H_6P_2W_{18}O_{62}$/TPI-Fe_3O_4 NPs.

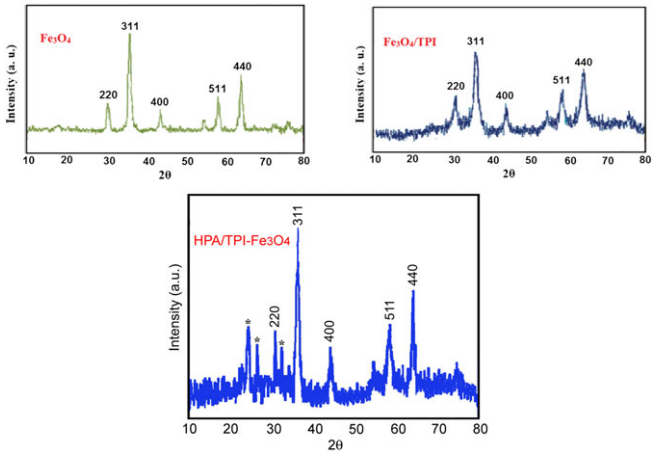


FIGURE 2 XRD patterns of Fe_3O_4, TPI-Fe_3O_4 and $H_6P_2W_{18}O_{62}$/TPI-Fe_3O_4 NPs.

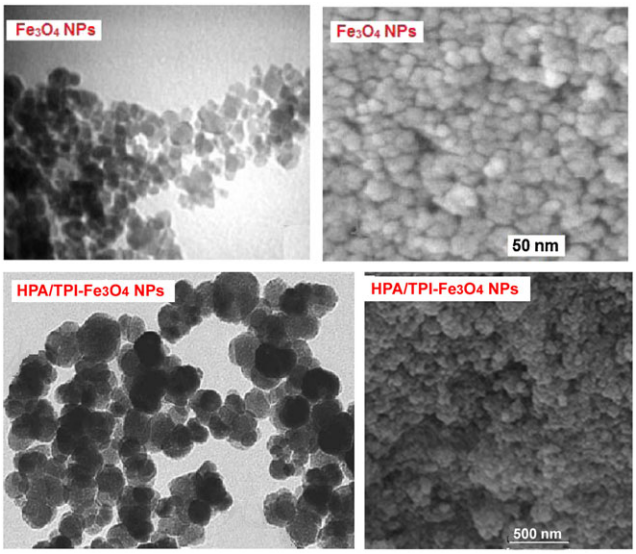


FIGURE 3 TEM and SEM images of Fe_3O_4 and $H_6P_2W_{18}O_{62}$/TPI-Fe_3O_4 NPs.

narrow size distributions and an average diameter of approximately 40 nm. According to the SEM images (Figure 3), the morphology of HPA/TPI-Fe_3O_4 NP surface clearly indicates the homogeneity of the material and also shows that $H_5PW_{10}V_2O_{40}$ is well dispersed in TPI-Fe_3O_4 NPs.

3.1.4 | Thermal analyses

The thermal stability of HPA/TPI-Fe_3O_4 NPs was investigated by carrying out TGA/DTA analysis (Figure 4). The DTA profile exhibits a wide endothermic peak from 25 to 200°C which is attributed to the elimination of adsorbed water molecules. A weight loss occurs between 200 and 500°C which is accompanied by a broad exothermic peak between 350 and 450°C in the DTA curve, corresponding to the oxidative decomposition of the organic part (TPI). As can be seen in TGA curve, the 3% decrease of mass of the catalyst from 200 to 500°C is related to the modification by TPI on the sorbent. Also, the prepared HPA/TPI-Fe_3O_4 NPs are stable up to 200°C.[40]

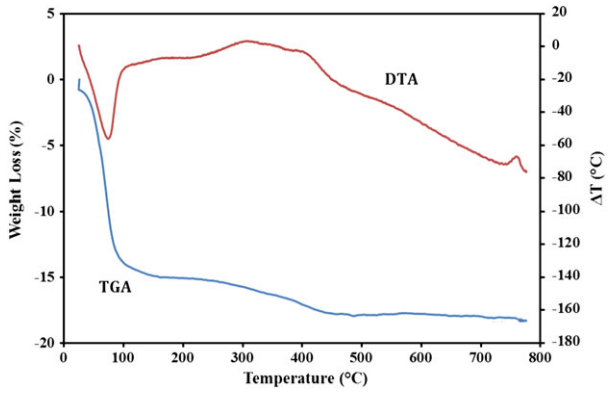
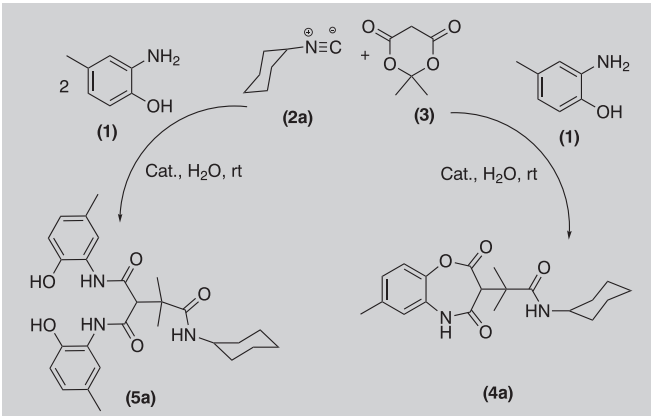


FIGURE 4 TGA and DTA curves of HPA/TPI-Fe_3O_4 NPs.

3.2 | Catalytic study

The catalytic efficiency of the HPA/TPI-Fe_3O_4 NPs heterogeneous catalytic system was studied for the preparation of malonamide and 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine derivatives (Scheme 1). To illustrate the need for a catalyst for these reactions, in a typical experiment, one or two equivalents of 2-amino-4-methylphenol (**1**) with cyclohexylisocyanide (**2a**) and Meldrum's acid (**3**) as a model system were stirred in water at room temperature in the absence of catalyst. The yield in this case was a trace amount after 12 h showing that catalyst is an important part of the reaction.

TABLE 1 Optimization of catalyst for synthesis of 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine and malonamide[a]



Catalyst	Time (min)	Yield (%)[b]	Yield (%)[c]
HPA	25	64	69
Fe_3O_4 NPs	25	33	36
TPI-Fe_3O_4 NPs	25	52	57
HPA/TPI-Fe_3O_4 NPs	25	90	95

[a]Reaction conditions: **1** (1.00 or 2.00 mmol), **2a** (1.00 mmol), **3** (1.00 mmol) and catalyst (0.02 g) in H_2O as solvent at room temperature.

[b]Isolated yields from **4a**.

[c]Isolated yields from **5a**.

TABLE 2 Optimization of solvent for synthesis of 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine and malonamide[a]

Entry	Solvent	Time (min)	Yield (%)[b]	Yield (%)[c]
1	H_2O	25	90	95
2	EtOH	25	91	96
3	CH_3CN	25	91	92
4	C_7H_8	25	45	48
5	CH_2Cl_2	25	89	94
6	$CHCl_3$	25	89	91
7	Tetrahydrofuran	25	84	85

[a]Reaction conditions: **1** (1.00 mmol or 2.00 mmol), **2a** (1.00 mmol), **3** (1.00 mmol) and HPA/TPI-Fe_3O_4 NPs (0.02 g), solvent (3.00 ml), at room temperature.

[b]Isolated yields from **4a**.

[c]Isolated yields from **5a**.

TABLE 3 Effect of catalyst amount on reaction of 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine and malonamide[a]

Entry	Catalyst (g)	Time (min)	Yield (%)[b]	Yield (%)[c]
HPA	0.02	25	64	69
HPA	0.01	25	44	49
Fe_3O_4 NPs	0.04	25	38	43
Fe_3O_4 NPs	0.02	25	32	37
Fe_3O_4 NPs	0.01	25	24	29
TPI-Fe_3O_4 NPs	0.02	25	52	57
TPI-Fe_3O_4 NPs	0.01	25	39	44
HPA/TPI-Fe_3O_4 NPs	0.02	25	90	95
HPA/TPI-Fe_3O_4 NPs	0.01	25	78	83

[a]Reaction conditions: **1** (1.00 or 2.00 mmol), **2a** (1.00 mmol), **3** (1.00 mmol) and catalyst in H_2O as solvent at room temperature.

[b]Isolated yields from **4a**.

[c]Isolated yields from **5a**.

In a pilot experiment, one or two equivalents of **1** with **2a** and **3** were stirred in water at room temperature using each of HPA, Fe_3O_4 NPs, TPI-Fe_3O_4 NPs and HPA/TPI-Fe_3O_4 NPs as catalyst. Table 1 summarizes the catalytic performance for the synthesis of compounds **4a** and **5a**. The catalytic activity decreased in the order: HPA/TPI-Fe_3O_4 NPs > HPA > TPI-Fe_3O_4 NPs > Fe_3O_4 NPs.

In order to obtain the best synthesis conditions, one or two equivalents of **1** with **2a** and **3** in the presence of HPA/TPI-Fe_3O_4 NPs in various protic and aprotic solvents were allowed to react at room temperature (Table 2). It is important to note that organic solvents such as ethanol and acetonitrile give similar yields. Furthermore, water was selected as the solvent due to its accordance with green chemistry principles.

The catalytic efficiency can be influenced by the amount of catalyst. Therefore, a set of experiments using various amounts of catalyst was conducted using the reaction of one or two equivalents of **1** with **2a** and **3** in water at room temperature (Table 3). The optimum catalyst amount is 0.02 g f HPA/TPI-Fe_3O_4 NPs leading to 90 and 95% yields of compounds **4a** and **5a**, respectively. Lower amounts of catalyst result in a decrease in the efficiency of the reaction, while higher amounts lead to complete conversion in a short reaction time.

The generality of the process was studied using a range of isocyanides and 2-aminophenol derivatives for the synthesis of **4a–h** and **5a–h** in the presence of HPA/TPI-Fe_3O_4 NPs as catalyst (Table 4).

The catalyst is very active, stable, non-toxic and inexpensive. To explore the reusability of the HPA/TPI-Fe_3O_4 NPs catalyst, it was easily separated from the reaction medium using an external magnet and washed thoroughly with CH_2Cl_2. The catalyst was then dried in air and activated in a vacuum oven at 70°C for 4 h. Finally, the recycled catalyst was reused for another condensation reaction. The results indicate the same catalytic activity as the fresh catalyst, without any loss of its activity. In addition, to ensure reproducibility of the transformation, repeated typical experiments were carried out under identical reaction conditions (Table 5).

The changes in the structure of the recovered HPA/TPI-Fe_3O_4 NPs were determined using FT-IR spectroscopy. As can be seen in Figure 5, the structure of the recycled catalyst

TABLE 4 Synthesis of 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine (**4a–h**) and malonamide (**5a–h**) derivatives in absence and presence of HPA/TPI-Fe_3O_4 NPs[a]

Product	R_1	R_2	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found[b]	Reported
4a	*c*-Hex	4-CH_3	25	90	250–252	249–251[34]
4b	*c*-Hex	4-Cl	30	88	229–231	228–230[33]
4c	*t*-Bu	H	35	87	151–153	151–153[33]
4d	*t*-Bu	4-CH_3	25	92	227–229	227–229[33]
4e	1,1,3,3-Tetramethylbutyl	H	30	89	212–214	214–216[33]
4f	*c*-Hex	H	35	93	171–173	169–171[33]
4 g	2,6-Dimethylphenyl	H	25	93	221–223	220–223[34]
4 h	2,6-Dimethylphenyl	4-CH_3	25	92	264–266	264–267[34]
5a	*c*-Hex	4-CH_3	25	95	221–223	220–222[33]
5b	1,1,3,3-Tetramethylbutyl	4-CH_3	25	92	228–230	227–229[33]
5c	2,6-Dimethylphenyl	H	35	91	244–246	242–244[33]
5d	2,6-Dimethylphenyl	4-CH_3	25	93	232–234	233–235[33]
5e	4-Methylphenylsulfonyl	H	30	91	172–174	172–174[33]
5f	4-Methylphenylsulfonyl	4-CH_3	30	92	151–153	151–153[33]
5 g	*c*-Hex	4-Cl	30	89	245–247	245–247[34]
5 h	*t*-Bu	4-CH_3	30	87	216–218	215–218[34]

[a]Reaction conditions: **1** (1.00 mmol or 2.00 mmol), **2** (1.00 mmol), **3** (1.00 mmol) and HPA/TPI-Fe_3O_4 NPs (0.02 g) in H_2O as solvent at room temperature.

[b]Isolated yields from **4a** and **5a**.

TABLE 5 Recycling of catalyst[a]

Cycle	Catalyst (g)	Yield (%)[b]	Yield (%)[c]
1	0.020	90	95
2	0.020	90	95
3	0.020	90	95
4	0.019	90	94
5	0.019	89	94
6	0.019	89	93
7	0.019	89	93
8	0.018	89	92
9	0.018	88	92
10	0.018	87	91

[a]Reaction conditions: **1** (1.00 mmol or 2.00 mmol), **2** (1.00 mmol), **3** (1.00 mmol) and HPA/TPI-Fe_3O_4 NPs in H_2O as solvent at room temperature.

[b]Isolated yields from **4a**.

[c]Isolated yields from **5a**.

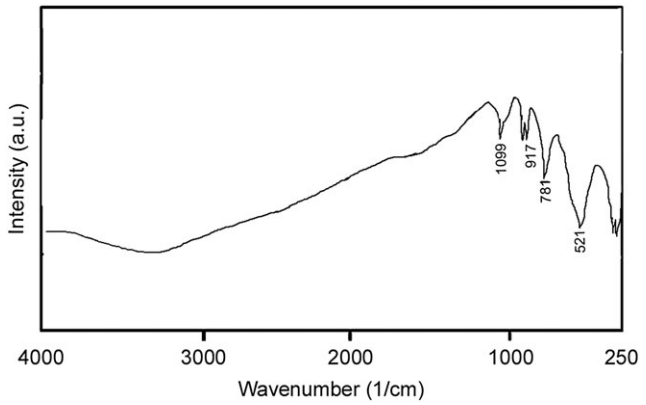


FIGURE 5 FT-IR spectrum of recovered HPA/TPI-Fe_3O_4 NPs.

does not change, and a very slight decrease in the reaction yield may be due to the covering of the surface of the catalyst by impurities.

4 | CONCLUSIONS

We report HPA/TPI-Fe_3O_4 NPs as a new and efficient solid acid catalyst for the synthesis of 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine and malonamide derivatives upon mixing readily available substrates in short reaction times at room temperature. Recyclability of the catalyst with no loss in its activity, mild reaction conditions and product isolation, use of non-toxic materials and excellent yields are important features of this new protocol for the preparation of 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine and malonamide derivatives.

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