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### HPA decorated Halloysite Nanoclay: An efficient catalyst for the green synthesis of Spirooxindole derivatives

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Majid Heravi, Department of Chemistry, School of Science, Alzahra University, PO Box 1993891176, Vanak, Tehran, Iran. Email: mmh1331@yahoo.com; mheravi@alzahra.ac.ir A novel heterogeneous catalyst, HPA@HNTs-IMI-SO<sub>3</sub>H, was designed and synthesized based on functionalization of halloysite nanotubes with ionic liquid and subsequent incorporation of heteropolyacid. The structure of the catalyst was studied and confirmed by using SEM/EDX, FTIR, XRD, ICP-AES, TGA, DTGA and BET. Moreover, the catalytic activity of HPA@HNTs-IMI-SO<sub>3</sub>H was investigated for promoting ultrasonic-assisted three-component reaction of isatines, malononitrile or cyanoacetic esters and 1,3-dicarbonyl compounds to afford corresponding spirooxindole in high yields and short reaction time. The reusability of the catalyst was also studied. Notably, the catalyst could be recovered and reused for three reaction runs. However, reusing for fourth reaction runs led to the decrease of the catalytic activity. Considering leaching test results, that observation was attributed to the leaching of heteropolyacids, which can be induced by ultrasonic irradiation.

#### **KEYWORDS**

halloysite, hybrid, ionic liquid, nanocatalyst, spirooxindole

#### **1** | INTRODUCTION

Spirooxindole derivatives such as are biologicallyattractive heterocycles which can be found in alkaloids and pharmaceuticals. The synthesis of these compounds is an appealing target in the organic synthesis due to their diverse biological activities including fungicidal, anticonvulsant, herbicidal and anti-cancer properties.<sup>[1,2]</sup> Spirooxindoles can also be used as a key intermediate for the synthesis of clinical pharmaceuticals.<sup>[3]</sup> To date many attempts have been devoted to disclose efficient protocols for the synthesis of spirooxindoles. In this line, the utilities of many catalysts such as triethylamine, piperidine, ethylenediamine diacetic acid, L-Proline,<sup>[4]</sup> chiral phoshoic acid<sup>[5]</sup> and potassium tetrachloroaurate trihydrate have been proved.<sup>[1]</sup>

Heteropolyacids, HPAs, belong to a class of inorganic compounds that are composed of cations and polyanion

clusters. The unique feature of HPAs and their salts is that they can exert both acidic (Bronsted acidity(and redox activity.<sup>[6]</sup> This outstanding property renders these catalysts bi-functional and broadens their applications as efficient catalysts in catalytic processes.<sup>[7-10]</sup> Considering the non-toxic and non-corrosive entity of HPA, they can be very promising for developing green protocols for the synthesis of various chemicals. However, HPAs are highly soluble in water and most organic solvents which is a drawback from the green chemistry and industrialization point of views. To circumvent this issue, immobilization of HPA on heterogeneous supports such as zeolites and clays has been suggested.<sup>[11,12]</sup>

Halloysite nanotubes, HNTs, are naturally occurring clays with the general formula of  $(Al_2(OH)_4Si_2O_5.2H_2O)$ .<sup>[13,14]</sup> The HNTs tubes are relatively long (~ 100 nm to 4000 nm).<sup>[15]</sup> Moreover, the external diameters of HNTs range from 30 to 190 nm while their internal diameters vary between 10–100 nm.<sup>[16]</sup> This structure of HNTs as well as their biocompatibility, abundance, high mechanical and thermal stability and surface area makes them promising candidates for using as drug delivery system<sup>[17]</sup> and loading catalytic active species.<sup>[17,18]</sup> Notably, the applications of HNTs are not limited to the abovementioned fields. They also proved to be efficient for optical, magnetic and electrical applications,<sup>[17]</sup> water treatment,<sup>[19]</sup> and membrane for gas separation.<sup>[20]</sup> Recently, the functionalization of HNTs surface has gained growing interest.<sup>[21]</sup> The functionalized HNTs can be considered as an efficient hybrid system for accommodating diverse range of active species such as catalytic species.<sup>[22,23]</sup>

In the following of our research<sup>[18,24–28]</sup> on the synthesis of novel heterogeneous catalysts and disclosing mild and environmentally benign methodologies for organic transformations, herein, we wish to present a novel hybrid catalytic system, HPA@HNTs-IMI-SO<sub>3</sub>H, consists of heteropolyacids, ionic liquids and halloysite nanoclay as an efficient and heterogeneous catalyst for promoting the synthesis of spirooxindole from reaction of isatines, malononitrile or cyanoacetic esters and 1,3-dicarbonyl compounds (Scheme 1). The reaction proceeded rapidly in the mixture of ethanol and water under ultrasonic irradiation as a green and environmentally benign protocol to afford the desired products in excellent yields. The reusability of the catalyst as well as the HPA leaching is also studied to disclose the nature of the catalysis and stability of the catalyst.

#### 2 | EXPERIMENTAL

#### 2.1 | Material and instrument

All chemicals and reagents used for the synthesis of the catalyst including halloysite clay, (3-chloropropyl) trimethoxysilan, imidazole, 1,2-oxathiane 2,2-dioxide, phosphotungstic acid, EtOH, toluene, water and acetonitrile were analytical grade reagents, purchased from Sigma-Aldrich, and used as received. The organic compounds employed for the synthesis of spirooxindoles included isatines, malononitrile, cyanoacetic esters, 1,3dicarbonyl compounds and were provided from Merck. The progress of the organic processes was monitored by TLC on commercial aluminium-backed plates of silica gel 60 F254, visualized, using ultraviolet light. Melting points were determined in open capillaries using an Electrothermal 9100 without further corrections.

HPA@HNTs-IMI-SO<sub>3</sub>H was fully characterized by using various analytical techniques including BET, FTIR, SEM/EDX, Thermogravimetric analysis (TGA), DTGA, XRD, and ICP-AES. TGA was carried out on a METTLER TOLEDO thermogravimetric analysis apparatus with a heating rate of 10 °C min<sup>-1</sup> from 50 to 600 °C under N<sub>2</sub> atmosphere. FTIR spectra of the fresh and reused catalyst were recorded by using PERKIN-ELMER- Spectrum 65 instrument. Room temperature powder X-ray diffraction patterns were obtained by using a Siemens, D5000. CuKa radiation from a sealed tube. SEM/EDX images were obtained by a Tescan instrument, using Au-coated samples and acceleration voltage of 20 kV. The BET analyses of the catalyst and pure HNTs were carried out by employing BELSORP Mini II instrument. Prior to BET analyses, the catalyst or pure HNTs were degassed at 423 K for 3 h. The ultrasonic apparatus applied for performing the organic reactions was Bandelin HD 3200 with output power of 150 W and tip TT13.

#### 2.2 | Synthesis of HNTs/cl

HNTs (1.2 g) was added into a mixture of 4 ml (3-chloropropyl)trimethoxysilan in 50 ml dry toluene. Then, to obtain a homogenized mixture, the suspension was subjected to ultrasonic irradiation for half an hour. Subsequently the mixture was refluxed for 24 h at 110 °C. Upon completion of the reaction, the reaction mixture was cooled to ambient temperature and the precipitate was filtered off, washed with dry toluene repeatedly and dried at 80 °C overnight.

#### 2.3 | Synthesis of HNTs/1-(3-(trimethoxysilyl)propyl)-1H-imidazole (HNTs-IMI)

In this step, a mixture of imidazole (1.361 g, 22 mmol) and HNTs/Cl (1.5 g) in 50 ml dry toluene were refluxed at 80 °C for 48 h in the absence of any catalyst. After the end of the reaction, the obtained product was washed with diethyl ether (3\*10 ml) and dried at 80 °C in oven for 12 h, to yield a cream powder.



**SCHEME 1** Three-component reaction catalyzed by HPA@HNTs-IMI-SO<sub>3</sub>H under ultrasonic irradiation

#### 2.4 | Synthesis of HNTs/4-(1-(3-(trimethoxysilyl)propyl)-1H-imidazol-3ium-3-yl)butane-1-sulfonate (HNTs-IMI-SO<sub>3</sub>H)

To a suspension of HNTs-IMI (1 g) in dried toluene, 1,2oxathiane 2,2-dioxide (5.8 mmol, 0.75 g) was added. The as-made mixture was then stirred overnight. At the end of the reaction, the cream powder was filtered, washed with dry toluene and dried at 80  $^{\circ}$ C in oven for 12 h.

## 2.5 | Immobilization of HPA on HNTs-IMI-SO<sub>3</sub>H: Synthesis of HPA@HNTs-IMI-SO<sub>3</sub>H

Wetness impregnation method was used to immobilize phosphotungstic acid on HNTs-IMI-SO<sub>3</sub>H. To this purpose, a mixture of HNTs-IMI-SO<sub>3</sub>H (1 g) in acetonitrile (25 ml) were prepared and stirred vigorously. Then, a solution of  $H_3PW_{12}O_{40}$  (0.2 g) in acetonitrile (5 ml) was dropwise added to the suspension. The resulting mixture was subsequently stirred vigorously at ambient temperature overnight. Upon completion of the reaction, the solid was filtered, washed with acetonitrile and dried in oven at 90 °C overnight. The schematic synthesis of the catalyst is described in Figure 1.

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# 2.6 | Synthesis of spirooxindole in the presence of HPA@HNTs-IMI-SO<sub>3</sub>H as catalyst

A tube was charged with a mixture of isatines (1 mmol), malononitrile or cyanoacetic esters (1 mmol), 1,3dicarbonyl compounds (1 mmol), and HPA@HNTs-IMI-SO<sub>3</sub>H as a catalyst (0.025 g) in H<sub>2</sub>O/EtOH (8:2, 10 ml). The reaction mixture was then sonicated at 80 W at room temperature for proper reaction time (Table 2). After complete conversion (monitored by TLC), 10 ml of hot EtOH was added into the reaction mixture to dissolve the resulting products. Then, the catalyst was filtered, washed with EtOH and dried at 90 °C overnight for reusing in consecutive reaction runs. The filtrate on the other hand, was cooled to room temperature to let the dissolved products crystalize. Then, the product was filtrated. Finally, the pure product was achieved by recrystallization from hot EtOH.

#### 3 | RESULT AND DISCUSSION

#### 3.1 | Characterization of HPA@HNTs-IMI-SO<sub>3</sub>H as catalyst

The FTIR spectra of HPA@HNTs-IMI-SO $_{3}$ H and pure HNTs are depicted in Figure 2. As shown, the FTIR



FIGURE 1 Synthesis of HPA@HNTs-IMI-SO<sub>3</sub>H as catalyst



spectrum of the catalyst clearly exhibited the characteristic bands of HNTs, i.e. the bands at 669  $\text{cm}^{-1}$  and 1660 cm<sup>-1</sup>which are indicative of Al-O-Si vibration and the interlayer water as well as the bands at  $3702 \text{ cm}^{-1}$ and  $3693 \text{ cm}^{-1}$  which can be assigned to internal and external hydroxyl groups of HNTs structure. The comparison of FTIR spectra of HPA@HNTs-IMI-SO3H and pure HNTs established that the two FTIR spectra are distinguished to some extent and the FTIR spectrum of the catalyst exhibited some additional bands and broadening of some bands. More precisely, an additional band can be observed at 2954 cm<sup>-1</sup> which can be assigned to  $-CH_2$ stretching, confirming the conjugation of (3-chloropropyl) trimethoxysilan. Moreover, the broad band, broaden in the range of 1042–1154 cm<sup>-1</sup>can be assigned to the Si–O stretching as well as the sulfur trioxide ion. This observation along with the increase in the intensity of the band at 1660 cm<sup>-1</sup>, which can also be assigned to the C = Nstretching, can confirm the presence of ionic liquid in the structure of the catalyst. Finally, The sharp bands at 808 and 783  $\text{cm}^{-1}$  can be assigned to symmetric stretching of W-Oc-W, W-Oe-W respectively and proved the presence of heteropolyacid.<sup>[29]</sup> It is worth noting that due to the overlap of some characteristic bands, FTIR spectroscopy cannot individually prove the formation of the catalyst. Hence, other analyses were performed to establish the structure of the catalyst.

The SEM images of HPA@HNTs-IMI-SO<sub>3</sub>H are illustrated in Figure 3. As shown, the catalyst exhibited the rod like morphology which packed together to form aggregates. This morphology is very similar to that of pure HNTs, Figure 3, indicating that functionalization and HPA incorporation did not destruct the morphology of the HNTs.

The EDX image of HPA@HNTs-IMI-SO<sub>3</sub>H is depicted in Figure 3. As shown, Si, Al and O atoms are present in the EDX image which can be representative of the HNTs

**FIGURE 2** FTIR spectra of pure HNTs (a) and HPA@HNTs-IMI-SO<sub>3</sub>H (b)

structure. Moreover, the observation of C, N and S atoms in EDX is indicative of incorporation of IMI-SO<sub>3</sub>H in the catalyst structure. The immobilization of HPA can be confirmed by the presence of the W and P atoms in EDX image.

The structure of HPA@HNTs-IMI-SO<sub>3</sub>H was also analyzed by XRD analysis. In Figure 4 the XRD patterns of HPA@HNTs-IMI-SO<sub>3</sub>H and pure HNTs are illustrated. The comparison of the XRD patterns indicated that both patterns exhibits peaks at 8°, 13°, 23°, 28°, 31°, 58° and 67° which are representative of HNTs structure (JCPDS No. 29–1487).<sup>[16,30]</sup> This observation demonstrated that the HNTs functionalization with IMI-SO<sub>3</sub>H and incorporation of HPA did not collapse of HNTs framework. Noteworthy, the unchanged interlayer distances of HPA@HNTs-IMI-SO<sub>3</sub>H established that the functionality and HPA did not located within the interlayer of HNTs, but on the surface and the edges of the HNTs tubes. This is in good agreement with previous reports.<sup>[16]</sup>

The thermal stability HPA@HNTs-IMI-SO<sub>3</sub>H was studied by using of TGA and DTGA analyses. In Figure 5 the thermogram of HPA@HNTs-IMI-SO<sub>3</sub>H is illustrated. Compared to pure HNTs which showed one degradation step due to loss of water<sup>[31,32]</sup> over the range of 35–550 °C, the TGA thermogram of HPA@HNTs-IMI-SO<sub>3</sub>H possessed two degradation stages. The initial degradation stage is due to the loss of adsorbed H<sub>2</sub>O molecules in the catalyst. The next one, however, can be assigned to the thermal decomposition of organic component.

Using TGA analysis the weight percentage of organic motif in HPA@HNTs-IMI-SO<sub>3</sub>H was calculated to be about 18 w/w%.

To study the textural properties of HPA@HNTs-IMI-SO<sub>3</sub>H and elucidate whether the incorporation of HPA and IMI-SO<sub>3</sub>H can affect these properties, Nitrogen adsorption–desorption isotherms of HPA@HNTs-IMI-SO<sub>3</sub>H and pure HNTs were obtained and compared,



FIGURE 3 a) the SEM-EDX picture of HPA@HNTs-IMI-SO<sub>3</sub>H, b) SEM image of HNTs

Figure 6. As shown, both isotherms exhibited the shape which is in good agreement with the type II nitrogen adsorption–desorption isotherms with H3 hysteresis loops.<sup>[16]</sup> This observation clearly established that both HPA@HNTs-IMI-SO<sub>3</sub>H and pure HNTs possess porous structure. Moreover, it can be concluded that upon

functionalization of HNTs and incorporation of HPA, the porous structure of HNTs was preserved. It was also found that upon functionalization and HPA incorporation, the specific surface area of pure HNTs (~ 51 m<sup>2</sup> g<sup>-1</sup>) increased and reached to ~99 m<sup>2</sup> g<sup>-1</sup>. Moreover, compared to HNTs, the average pore diameter and total pore volume increased



FIGURE 4 XRD pattern of HPA@HNTs-IMI-SO<sub>3</sub>H

**FIGURE 5** TGA and DTGA analysis of HPA@HNTs-IMI-SO<sub>3</sub>H

in HPA@HNTs-IMI-SO<sub>3</sub>H (Table 1). These observations are in good agreement with the previous reports in which the increase in specific surface area was attributed to the presence of catalytic species on HNTs surface.<sup>[33]</sup> According to the previous reports,<sup>[34]</sup> the increase of average pore diameter and total pore volume could be attributed to the presence of more interparticle pores of the composites.

To calculate the amount of heteropolyacid in HPA@HNTs-IMI-SO<sub>3</sub>H, a known amount of HPA@HNTs-IMI-SO<sub>3</sub>H was digested in concentrated HCl and HNO<sub>3</sub> solution. Then, the extract was subjected to ICP-AES analysis. Through this procedure, the content of heteropolyacid was estimated to be about 4 wt%.

#### 3.2 | Catalytic activity

In the next step, we move on to study the catalytic activity of the HPA@HNTs-IMI-SO<sub>3</sub>H for promoting chemical transformations. In this line, we selected synthesis of biologically active spirooxindole from three component reaction of isatines, malononitrile or cyanoacetic esters and 1,3-dicarbonyl compounds. In this context, the reaction of malononitrile, isatines and dimedone was selected as the model reaction. Notably, the ultrasonic irradiation was used to promote an efficient, green and rapid route for the synthesis of spirooxindole. Initially, the model reaction was performed in the absence of the catalyst (Table 2). It was found that the reaction proceed very slowly (2 h) in the absence of the catalyst and only a trace amount of the desired product was obtained. Hence, the necessity of the use of the catalyst was confirmed. Next, the reaction variables including, the catalyst amount, solvent and power of ultrasonic irradiation were optimized. As development of a green methodology was targeted, water was first selected as the reaction solvent. Comparison of the yield of the desired product in water as solvent with those of some organic solvents such as toluene or acetonitrile confirmed the superior efficiency of the water as a solvent. However, the yield of the model



**FIGURE 6** The N<sub>2</sub> adsorption– desorption isotherm of HPA@HNTs-IMI-SO<sub>3</sub>H

product in water was not comparative to some of the previous reports. To increase the yield of the product, ethanol was used as a co-solvent. Gratifyingly, use of scant amount of ethanol enhanced the yield of the desired product remarkably. In the next step, the catalyst amount was optimized by using various amount of the catalyst (0.01-0.05 g). It turned out that the higher the amount of the catalyst, the higher the yield of the product. However, this was not a sustainable trend and increase of the catalyst amount further than the optimum value (0.025 g) had no effect on the yield of the product. Hence, 0.025 g was selected as the best catalyst amount. Finally, the effect of ultrasonic irradiation on the yield of the product was studied. It was found that the yield of the product was markedly dependent on the power of ultrasonic irradiation. Upon using low power (30 W), the reaction did not

**TABLE 1**Textural properties of the HPA@HNTs-IMI-SO3H andpure HNTs

Sample	$S_{BET}$ (m <sup>2</sup> g <sup>-1</sup> )	Average pore diameter (nm)	Total pore volume (cm <sup>3</sup> g <sup>-1</sup> )
HPA@HNTs- IMI-SO <sub>3</sub> H	99	36	0.8
HNTs	51	15	0.2

proceed efficiently and low yield of the product was obtained. Increase of the power of ultrasonic irradiation to 80 W dramatically enhanced the yield of the product. However, further increase to 100 W had a detrimental effect and the yield of the desired product decreased. This observation was attributed to the side-reactions; induce by high ultrasonic power that led to the formation of by-products. The results established that using 0.025 g of the catalyst, the mixture of water: ethanol and ultrasonic power of 100 W were the optimum reaction variables.

Having the optimum reaction conditions in hand, we investigated the generality of the protocol by using various isatines, cyanoacetic esters or malononitrile and 1,3-dicarbonyl compounds (Table 3).

The results established that using various isatines, cyanoacetic esters or malononitrile and 1,3-dicarbonyl compounds led to the corresponding products in high yields. However, the use of isatin with electron withdrawing group led to the desired product in shorter reaction time. Moreover, compared to 4-hydroxycoumarin, use of dimedone resulted in shorter reaction times. These results showed that the electron density of the substrate can affect the yield of the product.

In the next step, the efficiency of the present protocol, i.e. using HPA@HNTs-IMI-SO<sub>3</sub>H catalyst and ultrasonic irradiation, for promoting of the reaction of 4-

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TABLE 2 Effects of loading of catalyst, duration of reaction and solvent on the yield of model product via model reaction<sup>a</sup>

Entry	Catalyst (g)	Condition Solvent/ temperature (°C)/ power (W)	Time (min)	Yield (%) <sup>b</sup>
1	6	H <sub>2</sub> O/EtOH: 8/2 / r.t./ 80	120	Trace
2	0.01	H <sub>2</sub> O/EtOH: 8/2 / r.t./ 80	15	55
3	0.025	H <sub>2</sub> O/EtOH: 8/2 / r.t./ 80	15	95
4	0.05	H <sub>2</sub> O/EtOH: 8/2 / r.t./ 80	15	95
5	0.025	H <sub>2</sub> O/EtOH: 8/2 / r.t./ 30	15	30
6	0.025	H <sub>2</sub> O/EtOH: 8/2 / r.t./ 100	15	80
7	0.025	H <sub>2</sub> O/EtOH: 8/2 / 50/ 80	15	85
8	0.025	Water/ r.t. / 80	15	75
9	0.025	EtOH/ r.t./ 80	15	60
10	0.025	CH <sub>3</sub> CN/ r.t./ 80	15	50
11	0.025	Toluene/ r.t./ 80	15	40
12	0.025	H <sub>2</sub> O/EtOH: 5/5 / r.t./ 80	15	80

<sup>a</sup>Reaction condition: a mixture of isatine 1a (1 mmol), dimedone 2a (1 mmol), malononitrile 3a (1 mmol) and HPA@HNTs-IMI-SO<sub>3</sub>H was reacted by ultrasonic irradiation.

<sup>b</sup>Isolated yield.

TABLE 3 Synthesis of spirooxindole catalyzed by HPA@HNTs-IMI-SO<sub>3</sub>H<sup>a</sup>

Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3,</sub> <b>R</b> <sub>4</sub>		Time(min)	Yield(%) <sup>b</sup>
1	1a: H	2a: CN	3a: CH <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub> -C	H <sub>2</sub>	5	90
2	1a	2a	3b: CH <sub>3</sub>	$OC_2H_5$	30	90
3	1a	2b: CO <sub>2</sub> Et	3b	3b	55	90
4	1b: NO <sub>2</sub>	2a	3b	3b	10	90
5	1a	2a	4a		60	95
6	1a	2b	4a		30	85
7	1b	2a	3a		15	90
8	1b	2a	4a		30	98
9	1b	2b	4a		90	70
10	1b	2b	3a		25	85

<sup>a</sup>Reaction condition: a mixture of isatines (1 mmol), derivatives of malononitrile (1 mmol), 1,3-dicarbonyles (1 mmol) and HPA@HNTs-IMI-SO<sub>3</sub>H as a catalyst (0.025 g) in H<sub>2</sub>O/EtOH (8:2) subjected to ultrasonic irradiation at room temperature and 80 W. <sup>b</sup>isolated yields.

hydroxycumarine, malononitrile and 6-nitroindoline-2,3dione was compared with some of the previously reported methodologies, Table 4. As shown in Table 4, this reaction was performed previously under various conditions including ultrasonic irradiation, reflux and solvent-free condition. Compared to the tabulated reports, the present protocol led to the desired product in shorter reaction time. In the case of using piperidine under ultrasonic irradiation, the reaction time was comparative. However, the yield of the product was lower. Additionally, piperidine was a homogeneous and toxic catalyst. Hence, from the green chemistry point of view, the catalytic performance of HPA@HNTs-IMI-SO<sub>3</sub>H was superior to that of HPA@HNTs-IMI-SO<sub>3</sub>H. Use of *L*-proline, EDDA and PPL resulted in the desired product in comparative yield. However, all of these three catalysts were homogeneous and led to the product in longer reaction times. Other catalysts, exhibited inferior performance in terms of product yield and reaction time. Besides short reaction time, low catalyst amount and reusability of the catalyst are the advantageous of the present protocol.

#### 3.3 | Reaction mechanism

The plausible reaction mechanism is depicted in Scheme 2. It is postulated that the catalyst could promote

TABLE 4 Comparison of the result using our reaction system with results obtained by other published works for spirooxindole<sup>a</sup>

Entry	Catalyst (amount)	Reaction conditions	Yield (%)	Time (h:Min)	Ref
1	Carbon-SO <sub>3</sub> H (2.5 mol%)	EtOH/ reflux/S.F.	86	05:00	[1]
2	Piperidine (5 mol%)	EtOH/ US/ 50 C	84	00:07	[3]
	L-proline (10%)	H <sub>2</sub> O/ 80°C	94	00:20	[4]
	EDDA (10 mol%) <sup>b</sup>	H <sub>2</sub> O/ 60°C	95	01:00	[35]
	Nano-FGT (56 mg) <sup>c</sup>	H <sub>2</sub> O/ 80°C	91	00:15	[36]
	PPL (30 mg) <sup>d</sup>	EtOH:H <sub>2</sub> O/ 30°C	94	03:00	[37]
3	HPA@HNTs-IMI-SO <sub>3</sub> H (0.025 g)	H <sub>2</sub> O/EtOH: 8/2 / U.S/ 50°C	95	00:04	[this work]

<sup>a</sup>Reaction condition: a mixture of 4-hydroxycumarine (1 mmol), malononitrile (1 mmol.), 6-nitroindoline-2,3-dione (1 mmol) was reacted.

<sup>b</sup>Ethylenediamine diacetate.

<sup>c</sup>Glutathione grafted nano-organocatalyst

<sup>d</sup>Lipase from Porcine Pancreas (Anzyme)



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**SCHEME 2** The plausible mechanism of synthesis of spirooxindole in the presence of HPA@HNTs-IMI-SO<sub>3</sub>H

the Knoevenagle condenstion of isatin and malononitrile or cyanoacetic ester through activation of the carbonyl group of isatin. The resulting intermediate then reacted with 1,3-dicarbonyl compounds to furnish a new intermediate which subsequently tolerated.

#### 3.4 | Reusability of the catalyst

Ease of recovery of a heterogeneous catalyst and high reusability can render the catalyst green and cost-effective. Hence, the study of the reusability of the catalyst is imperative. In this context, the reusability of HPA@HNTs-IMI-SO<sub>3</sub>H for model reaction was investigated. To this purpose, the model reaction was carried out in the presence of fresh HPA@HNTs-IMI-SO<sub>3</sub>H. Upon the completion of the reaction, the catalyst was simply filtered off, washed and dried (Experimental section) and reused for consecutive reaction runs. The results, Figure 7, established that the catalyst could be

successfully recovered and reused for three successive reaction runs with only slight loss of the catalytic activity. Unfortunately, reusing the catalyst for fourth reaction run resulted in dramatic decrease in the catalytic performance and the model product was achieved only in 70% yield. To elucidate the reason of this observation, the FTIR spectrum of the reused catalyst for four times was obtained and compared with that of the fresh catalyst, Figure 8. Interestingly, the two spectra were distinguished and in the spectrum of the reused catalyst some extra bands could be observed. This observation can be attributed to the deposition of some organic species on the catalyst in the course of several reaction runs. Moreover, the intensities of the some characteristic bands were reduced. It is suggested that using ultrasonic irradiation for four reaction runs can induce the leaching of HPA and consequently the reduction of the catalytic activity. To confirm this postulation, the HPA leaching was examined after four reaction runs. It was found that upon reusing



**FIGURE 7** Reusability of the HPA@HNTs-IMI-SO<sub>3</sub>H catalyst for the three component reaction

**FIGURE 8** The comparison of FTIR analysis for fresh HPA@HNTs-IMI-SO<sub>3</sub>H (a) and after 4 runs (b)

the catalyst for four reaction runs the HPA leaching increased remarkably, justifying the observed lower catalytic activity.

To elucidate whether the loss of the catalytic activity is mostly induced by the ultrasonic irradiation or acidic and basic functionalities located on the reactants, we designed a control experiment in which the catalyst was suspended in the reaction solvent without any reagents and subjected to the ultrasonic irradiation. We postulated that if the ultrasonic irradiation could effectively promote the leaching of HPA, after several reaction runs the HPA leached in the filtrate could promote the organic transformation. Moreover, it is expected that if ultrasonic irradiation had a main role in HPA leaching, the catalyst reused from the reagent-less system after several times (forth run) must exhibit lower catalytic activity, similar to the one observed for the reused catalyst for four times in the presence of the reagents. Hence, the catalyst was suspended in the solvent in the absence of the reagent and subjected to the ultrasonic irradiation for 15 min, the time required for three reaction runs. Then, the catalyst was recovered and filtrate was kept for further test. The recovered catalyst was reused for fourth reaction run in the presence of the reagents. Moreover, the reagents were added to the filtrate to see whether the leached HPA are enough to promote the reaction. The results showed that the reaction could proceed in the filtrate and yield the desired product to 20% yield, indicating the significant amount of the leached HPA in the filtrate. The result of the reused catalyst also showed a decrease in the catalytic activity and the products were obtained in about 75% yield, implying the main role of ultrasonic irradiation on leaching of HPA.

For further study, the filtrate was subjected to the ICP test and the result established the leaching of HPA. Hence, it can be concluded that loss of the catalytic

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activity could stem from both ultrasonic irradiation and the effect of the reagents. However, the effect of the ultrasonic irradiation was predominant and more pronounced.

### 3.5 | Selected spectral data (Supporting data)

#### 3.5.1 | 2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'indoline]-3-carbonitrile (entry 1)

White powder, m.p: 250–252 °C. IR (KBr)  $\nu$  cm<sup>-1</sup>: 3296, 3196, 2968, 2205, 1712, 1673, 1471. <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  (ppm): 1.01 (s, 3H, CH<sub>3</sub>), 1.04 (s, 3H, CH<sub>3</sub>), 2.10 (d, J = 16.0 1H, CH<sub>2</sub>), 2.18 (d, J = 16.0 Hz, 1H, CH<sub>2</sub>), 2.54 (d, J = 18.0 Hz, 1H, CH<sub>2</sub>), 2.59 (d, J = 18.0 Hz, 1H, CH<sub>2</sub>), 6.79 (d, J = 7.6 Hz, 1H, ArH), 6.89 (t, J = 7.2 Hz, 1H, ArH), 6.98 (d, J = 7.2 Hz, 1H, ArH), 7.14 (t, J = 7.6 Hz, 1H, ArH), 7.24 (s, 2H, NH<sub>2</sub>), 10.40 (s, 1H, NH). <sup>13</sup>C NMR (DMSO- $d_6$ , 100 MHz)  $\delta$  (ppm): 27.1, 28.0, 32.3, 47.2, 50.4, 57.9, 109.7, 111.2, 117.7, 122.1, 123.4, 128.5, 134.8, 142.4, 152.4, 159.2, 166.5, 178.5, 195.4.

#### 3.5.2 | Ethyl 2'-Amino-3'-cyano-6'-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (entry 2)

Cream powder, m.p. 260–262 °C, IR (KBr)  $\nu$  cm<sup>-1</sup>: 337, 3314, 3140, 2965, 2192, 1723, 1655, 1472. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  (ppm): 0.78 (t, *J* = 6.8 Hz, 3H, CH<sub>3</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 3.75–3.79 (m, 2H, CH<sub>2</sub>), 6.80 (d, *J* = 7.6 Hz, 1H, ArH), 6.93 (t, *J* = 7.2 Hz, 1H, ArH), 7.06 (d, *J* = 7.2 Hz, 1H, ArH), 7.15 (s, 2H, NH<sub>2</sub>), 7.18 (t, *J* = 7.6 Hz, 1H, ArH), 10.40 (s, 1H, NH). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 100 MHz)  $\delta$  (ppm): 13.6, 19.2, 49.6, 57.1, 60.9, 105.3, 110.0, 118.1, 122.5, 124.0, 129.2, 135.2, 142.8, 159.2, 159.6, 165.1, 179.2.

#### 3.5.3 | 2'-Amino-1,2-dihydro-2,5'dioxospiro[3*H*-indole-3,4'-[4*H*,5*H*] pyrano[3,2-c] [1] benzopyran]-3'carbonitrile (entry 5)

White solid, m.p. 273–274 °C, IR (KBr)  $\nu$  cm<sup>-1</sup>: 3378, 3300, 3199, 2905, 2203, 1673, 1606, 1474, 1417, 1359. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$  (ppm): 6.86 (d, *J* = 7.6 Hz, 1H, ArH), 6.94 (t, *J* = 7.6 Hz, 1H, ArH), 7.22 (t, *J* = 7.2 Hz, 2H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 7.54 (t, *J* = 8.0 Hz, 1H, ArH), 7.68 (s, 2H, NH<sub>2</sub>), 7.77 (t, *J* = 8.0 Hz, 1H, ArH), 7.95 (d, *J* = 7.6 Hz, 1H, ArH), 10.69 (s, 1H, NH).

#### 3.5.4 | 2'-Amino-5-nitro-1,2-dihydro-2,5'dioxospiro[3*H*-indole-3,4'-[4*H*,5*H*] pyrano[3,2-c] [1]benzopyr-an]-3'carbonitrile (entry 8)

White solid; m.p. 292–294 °C, IR (KBr)  $\nu$  cm<sup>-1</sup>: 3318, 3260, 3187, 2923, 2194, 1717, 1671, 1585, 1467, 1342. <sup>1</sup>H NMR (DMSO- $d_{6}$ , 400 MHz)  $\delta$  (ppm): 7.07 (d, J = 8 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 7.54 (t, J = 8 Hz, 1H), 7.66 (t, J = 8 Hz, 1H), 7.85 (s, NH<sub>2</sub>), 7.93 (d, J = 8 Hz, 1H), 8.19 (d, J = 8 Hz, 1H), 8.34 (s, 1H), 11.43 (s, 1H, NH), <sup>13</sup>C NMR (DMSO- $d_{6}$ , 100 MHz)  $\delta$  (ppm): 57.6, 70.5, 101.2, 109.9, 112.9, 117.2, 117.4, 122.5, 123.1, 124.8, 125.7, 129.3, 133.5, 134.1, 142.9, 152.4, 155.9, 155.9, 158.9, 177.6.

#### 4 | CONCLUSION

In summary, design and synthesis of the HPA@HNTs-IMI-SO<sub>3</sub>H through functionalization of halloysite nanotubes with ionic liquid and incorporation of heteropolyacid is disclosed. The hybrid system was successfully used for promoting ultrasonic-assisted three-component reaction of isatines, malononitrile or cyanoacetic esters and 1,3-dicarbonyl compounds to furnish the corresponding spirooxindole in short reaction time and high yields. The ICP-AES analysis and FTIR spectroscopy revealed that the catalyst preserved its catalytic activity for three reaction runs while exhibited lower catalytic activity upon reusing for fourth run. Leaching test using ICP-AES demonstrated that the lower catalytic activity stem from the HPA leaching which can be due to the ultrasonic irradiation for several reaction runs.

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#### SUPPORTING INFORMATION

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