Periodic Mesoporous Organosilica Functionalized Sulfonic Acids (PMO-ICS-SO_3H) as an Efficient and Recyclable NanoCatalyst for the Unsymmetric Hantzsch reaction

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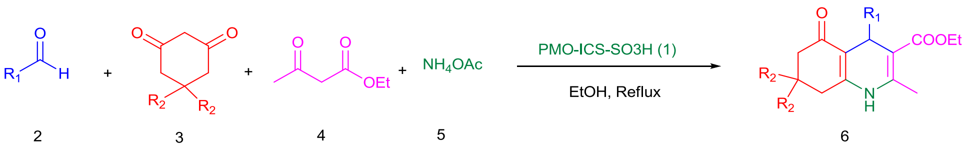
Abstract: Isocyanurate bridging periodic mesoporous organosilica functionalized sulfonic acids (PMO-ICS-SO_3H) was shown to be a highly active and efficient recyclable catalyst for the synthesis of polyhydroquinolines derivatives from dimedone, different aldehydes, ethyl acetoacetate and NH_4OAc under mild reaction conditions in short reaction times and good to excellent yields in EtOH. The PMO-ICS-SO_3H catalyst was characterizred by Fourier transformer infrared (FTIR) spectroscopy, thermogravimetry analysis (TGA) and nitrogen adsorption–desorption isotherms (NADI) techniques as well as field emission scanning electron microscopy (FESEM). Compared to the classical methodologies, this method illustrated significant advantages including low loading of the catalyst, avoiding the use of toxic transition metals, short reaction times, high to excellent yields, easy separation and purification of the products, and reusability of the catalyst

Keywords: Multicomponent reactions, Polyhydroquinolines, Periodic Mesoporous Organosilica, Nanocatalyst

Introduction

Polyhydroquinolines, as a family of 1,4-dihydropyridine (1,4-DHP) derivatives, are one of the most significant groups of nitrogen heterocycles that have attracted extensive attention due to their promising pharmacological and therapeutic activities such as, antiatherosclerotic, antitumor, calcium channel blockers, vasodilating, bronchodilating, geroprotective, hepatoprotective, and antidiabetic. Furthermore, some 1,4-dihydropyridines display other medicinal applications which include platelet antiaggregatory activity, neuroprotectant, cerebral antischemic activity in the treatment of Alzheimer's disease, and chemosensitizer acting in tumour therapy. As an example, quinolines having a 1,4-dihydropyridine nucleus are being used as antiinflammatory, antiasthamatic, antibacterial, and tyrosine kinase inhibiting agents [1]. On the other hand, multicomponent reactions (MCRs) offer high atom economy and bond-forming efficiency for the synthesis of diverse and complex molecules especially heterocyclic compounds in a fast and often experimentally simple procedure. Considering that most of the atoms of the starting materials (three or more components) are incorporated into the final product, and that water is the byproduct for some MCRs, these reactions became synthetic tools found in a prominent position. MCRs have the advantage of conserving most of the atoms from the building blocks that are present in the product to generate libraries of compounds in an efficient manner [2-4].

In this context, many catalytic methodologies have been tested to improve MCR adduct formation, to reduce reaction times, to improve yields, selectivities and for more amenable reaction conditions, as noted in many recent reviews. However, many of the reported synthetic protocols for the synthesis of Polyhydroquinolines have limitations in terms of the use of excess amounts of expensive or toxic catalysts, formation of byproducts and unsatisfactory yields, lengthy reaction times, difficult work-up, unavoidable metal pollution, significant amounts of waste materials, and low selectivity. Therefore, development of new methodologies and introducing green catalysts to overcome aforementioned disadvantages is still desirable. We herein wish to report the catalytic application of an isocyanurate-based periodic mesoporous organosilica functionalized sulfonic acids (PMO-ICS-SO_3H, **1**) nanomaterial with active Bronsted or Lewis acid centres, as an efficient and recoverable catalyst, for the synthesis of polyhydroquinolines derivatives.



Scheme 1 The one-pot four-component synthesis of polyhydroquinolines derivatives

Results and discussion

PMO-ICS-SO_3H (**1**) was prepared through a known procedure described by Kim and his co-workers [5]. The catalyst was then characterized using techniques including Fourier transform infrared (FTIR) spectroscopy, field emission scanning electron microscopy (FESEM), and thermal gravimetric analysis (TGA). The IR spectrum of PMO-ICS-SO_3H (**1**) shows the presence of organic functional groups in the material framework. Indeed, the bands observed at 2935 and 2850 cm^{-1} are assigned to C–H stretching of aliphatic moieties. Moreover, the signals appeared at 1689 and 1471cm^{-1} are attributed to the stretching vibrations of the isocyanurate ring. On the other hand, PMO-ICS-SO_3H (**1**) showed bands at 1120, 1070 and 935 cm^{-1} corresponding to asymmetric and symmetric vibrations of Si–O–Si (siloxane) bonds, respectively. The strong and broad signal appeared about 3334 cm^{-1} is attributed to O–H bonds of silanol groups.

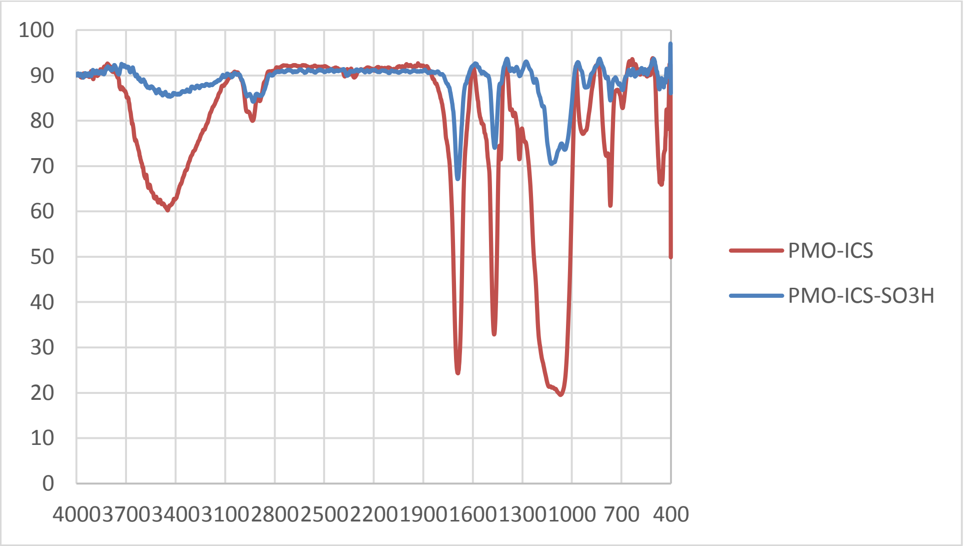


Figure 1. FT-IR of PMO-ICS and PMO-ICS-SO_3H

To show the efficiency of the catalyst for the synthesis of polyhydroquinolines derivatives (**6**), the reaction of 4-chlorobenzaldehyde (**2a**, 1 mmol), dimedone (**3**, 1 mmol), ethyl acetoacetate (**4**, 1 mmol) and NH_4OAc (**5**, 1 mmol) was investigated as the model reaction. The reaction conditions were optimized with regard to the best catalyst loading, different solvents and temperature for the synthesis of polyhydroquinolines derivatives. The results have been summarized in Table **1**. It was observed that only 30% of the desired product (**6a**) was obtained in the absence of the catalyst (**1**) under reflux conditions after 2h in EtOH (Table **1**, entry 1). Interestingly, after addition of 10 mg of PMO-ICS-SO_3H (**1**) as the catalyst, the yield of the desired product **6a** was increased significantly under similar reaction conditions in refluxing EtOH compared to catalyst-free conditions (Table **1**, entry 2). Furthermore, 20 mg loading of PMO-ICS-SO_3H (**1**) afforded higher yield of the desired product **6a** in shorter reaction time in refluxing EtOH (Table **1**, entry 3). In the next step, the effect of other solvents such as H_2O, CH_2Cl_2 and CH_3CN on the model reaction was investigated. These solvents afforded lower yield of the desired product **6a** (Table **1**, entries 4-6). Furthermore, increasing of amount of the catalyst to 30 mg loading had no significant effect on the yield of the desired product **6a** under similar reaction conditions in refluxing EtOH. (Table **1**, entry 7). Finally, the desired product **6a** was obtained in lower yield and longer reaction time at 80 ˚C under solvent-free conditions compared to reflux conditions in EtOH (Table **1**, entry 8). In order to demonstrate the scope of this protocol, the optimized reaction conditions were developed to other aromatic, heterocyclic aldehydes **2a-e**. The results are summarized in Table **2**. After completion of the reaction (monitored by TLC), EtOH was added to the mixture and the catalyst was easily isolated from the reaction mixture by simple filtration during recrystallization of the products. As it can be seen, high to excellent yields were obtained under the optimized conditions in short reaction times for the desired products **6a-e.**

Table 1 Optimization of conditions in the reaction of 4-chlorobenzaldehyde (**2a**), dimedone (**3**), ethyl acetoacetate (**4**) and NH_4OAc under different conditions^a**.**

Entry	Amount of Catalysts **(1)**/mg	Solvent	Temp.(˚C)	Time (min)	Yeild^b (%)
1	-	EtOH	Reflux	120	30
2	10	EtOH	Reflux	60	80
3	20	EtOH	Reflux	20	96
4	20	CH_2Cl_2	Reflux	70	40
5	20	CH_3CN	Reflux	80	45
6	20	H_2O	Reflux	60	60
7	30	EtOH	Reflux	20	96
8	20	Solvent-free	80 °C	30	89

^{a} Reaction conditions: 4-chlorobenzaldehyde (**2a**, 1 mmol), dimedone (**3**, 1 mmol) and ethyl acetoacetate (**4**, 1 mmol), NH_4OAc in the presence of the catalyst (**1**). ^{b} Isolated Yields.

Table 2 PMO-ICS-SO_3H (**1**) catalyzed one-pot four-componet synthesis of polyhydroquinolines **6** from 4-chlorobenzaldehyde (**2a**), dimedone (**3**), ethyl acetoacetate (**4**) and NH_4OAc under the optimized conditions[a].

Entry	Aldehyde **2**	Product **6**	Time (min)	Yeild[b] (%)
1	4-Chlorobenzaldehyde (**2a**)	**6a**	20	96
2	4-Methoxybenzaldehyde (**2b**)	**6b**	20	93
3	2-Chlorobenzaldehyde (**2c**)	**6c**	20	95
4	4-Methylbenzaldehyde (**2d**)	**6d**	20	95
5	Thiophene-2-carbaldehyde (**2e**)	**6e**	20	94

[a] Reaction conditions: : 4-chlorobenzaldehyde (**2a**, 1 mmol), dimedone (**3**, 1 mmol) and ethyl acetoacetate (**4**, 1 mmol), NH_4OAc (**5**, 1 mmol) in the presence of 20 mg of the catalyst (**1**) under reflux conditions in EtOH. [b] Isolated Yields.

Experimental

General

All chemicals were purchased from Merck or Aldrich and used as received except for benzaldehyde which a fresh distilled sample was used. Field emission scanning electron microscopy (FESEM) images was obtained using Sigma instrument of Zeiss Company, Germany. The BET specific surface area of the catalyst was obtained using an equipment ASAP 2020™ micromeritics. Thermal gravimetric analysis (TGA) was performed by means of Bahr company STA 504 instrument.

General procedure for the synthesis of PMO-ICS-SO_3H (1)

In a typical one-step synthesis, 0.66 g of pluronic P123 was dissolved in 23.6 g of deionized water, 0.57 g of H_2O_2 (30 wt%), and 0.13 g of HCl (37 wt%). Then 0.47 g of tris [3-trimethoxysilyl) propyl] isocyanurate (ICS, Aldrich) and 0.0902 g (30 mol% in total silica precursors) of (3-mercaptopropyl) trimethoxysilane were added to the solution. The resulting mixture was agitated for 2 h at 40 °C and thereafter aged for 24 h at 100 °C. The resulting solid material was filtered and air-dried. To extract the residual block co-polymer, the solid material (0.5 g) was stirred in acetone (60 ml) for 10 h at 56 °C, followed by washing with deionized water. The final products were obtained after drying the samples in an oven for 1 day at 100 °C.

General procedure for the synthesis of polyhydroquinoline derivatives (6a-e)

In a 5 mL round-bottomed flask, 4-chlorobenzaldehyde (**2a**, 1 mmol), dimedone (**3**, 1 mmol), ethyl acetoacetate (**4**, 1 mmol) and NH_4OAc (**5**, 1 mmol) and 20 mg PMO-ICS-SO_3H (**1**) were added to EtOH 96% (2 mL). The obtained mixture was stirred at reflux conditions for times indicated in Table **2**. After completion of the reaction monitored by TLC (eluent: EtOAc: n-hexane), EtOH (3 mL) was added and the obtained mixture was heated and filtered off to separate the solid catalyst **1**. Water was added dropwise to the filtrate at 60 °C to give pure crystals of the desired products **6a-e** in 93–96% yields. The separated catalyst was suspended in EtOAc (1mL) for 30 min and the filtered. The obtained white powder was heated in an oven at 60 °C for 1 h and reused for successive runs.

Conclusions

We have introduced the catalytic application of PMO-ICS-SO_3H (1) in the synthesis of polyhydroquinoline derivatives. The reaction system was significantly affected by catalyst loading, temperature and solvent. The catalyst illustrated high efficiency and reactivity for the one-pot synthesis of polyhydroquinoline derivatives using different aldehydes, dimedone, ethyl acetoacetate and NH_4OAc under reflux conditions. In addition, the catalyst could be recovered and reused with no decrease in its activity. Therefore, the significant advantages of this procedure are low catalyst loading, short reaction times, high to excellent yields, simple workup, reusability of the catalyst and simple purification of the products.

Acknowledgment

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