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Original article

The SBA-15/SO_3H nanoreactor as a highly efficient and reusable catalyst for diketene-based, four-component synthesis of polyhydroquinolines and dihydropyridines under neat conditions

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ABSTRACT

An efficient diketene ring-opening synthesis of polyhydroquinoline derivatives using SBA-15 sulfonic acid modified mesoporous substrates a green and reusable catalyst in a single-pot four-component coupling reaction of diketene, alcohol, enamine, and aldehydes is reported. Dihydropyridine derivatives based on neat adduct of diketene, alcohols and aldehydes using SBA-15/SO_3H nanoreactor as catalyst *via* a four-component reactions are also synthesized. The advantages of the present method include the use of a small amount catalyst, simple procedure with an easy filterable work-up, waste-free, green and direct synthetic method with an excellent yield of products with efficient use of catalyst and a short reaction time.

1. Introduction

The functionalized SBA-15 silica family of mesoporous materials with nano-channels have shown excellent catalytic performance because of their high surface area, high thermal and mechanical stability as a result of small nanoparticle pore sizes [1]. Hydrothermally stable, the sulfonic acid modified SBA-15 nanoreactor (SBA-15/PrSO_3H or SBA-15/SO_3H) with organic–inorganic mesochannels as catalyst provides a synergistic means to acidic sites, and suitable mesochannels to drive out the products for further recycles [1]. Additionally, based on green chemistry desires, the development of new strategies for recycling of the catalyst, which minimizes the consumption of auxiliary substances, energy and time required in achieving separations, can result in significant economic and environmental benefits [1].

Polyhydroquinolines, as interesting and versatile *N*-heterocycles, have attracted much attention due to their pharmacological properties, such as antitumor, bronchodilator, antidiabetic, anti-inflammatory, antibacterial, and antimalarial agents [2]. Consequently, many different synthetic methods for producing polyhydroquinolines derivatives have been reported using ionic liquids, molecular iodine, $HClO_4$–SiO_2, HY-zeolites, CAN, heteropolyacid, and polymers [3]. With regard to most of these methods, however, there exist significant drawbacks, such as high temperature, long reaction time, low product yields and requirements for high amounts of organic solvents and catalysts. In addition, the use of soluble metal catalysts in organic reactions requires several catalyst separation steps. As a result, the challenge in this field becomes that of developing waste-free and effective green approaches with high yields.

Very recently, we discovered a new multi-component method [4] for the ring-opening of diketenes to achieve some interesting heterocycles based on Biginelli condensation [5]. In this work, our aim has been to investigate fabrication of the mesoporous sulfonic acid catalyst to accomplish the desired polyhydroquinolines with a minimum of by-products, based on ring-opening of the diketene under clean, neat conditions.

2. Experimental

In this work SBA-15 nanoreactor was synthesized by the procedure reported by Zhao *et al.* [6a] and then modified with mercaptopropyltrimethoxysilane (MPTMS) and oxidized to the sulfonic acid [6b] nanoparticle using hydrogen peroxide (Fig. 1). A mixture of diketene (3 mmol), aldehyde (1 mmol), enamine (1 mmol) and alcohol (4 mL) and SBA-15/SO_3H (0.07 g, ~4 mol%) was reacted under neat conditions for appropriate time (TLC). After that, 20 mL hot EtOH was added to the reaction vessel and, with simple centrifuging, the catalyst was removed as filtrate, washed and then the product recrystallized from hot ethanol. All of the products are synthesized by four-component

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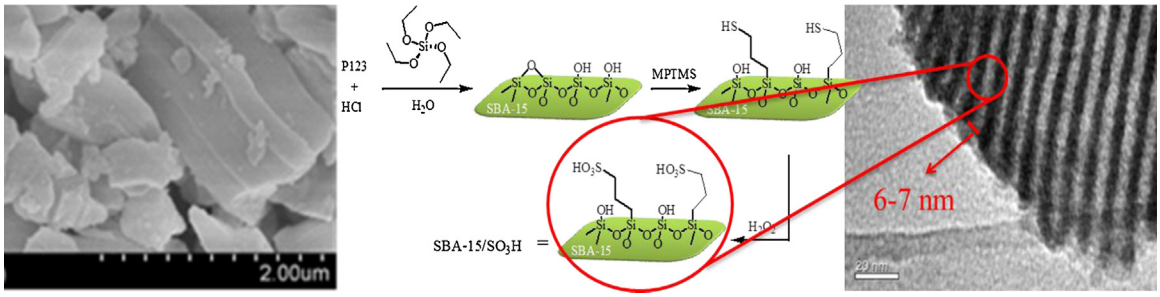
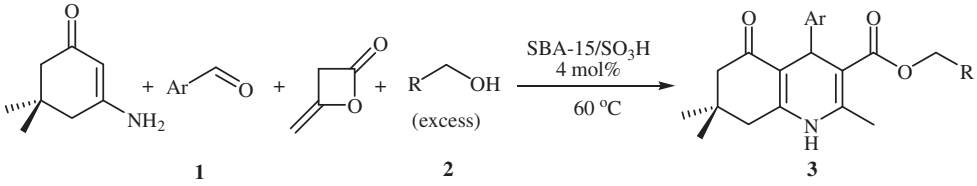


Fig. 1. SEM and TEM images of SBA-15/SO_3H nanoreactor.

method and were identified by their physical and spectral data (mp, IR, ^{1}H NMR and ^{13}C NMR). Methyl 4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro-3-quinolinecarboxylate (**3d**, Table 1). IR (KBr, cm^{-1}): ν_{max} 3289, 2951, 1707, 1654, 1608, 1490, 1222, 1080, 1034, 827, 773, 540. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.07 (s, 3 H), 2.04–2.36 (m, 7 H), 3.57 (s, 3 H), 5.38 (s, 1 H), 6.81 (s, 1 H), 7.00–7.34 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.19, 27.15, 29.37, 32.54, 35.61, 40.96, 50.62, 50.83, 105.17, 111.37, 126.42, 127.26, 129.61, 131.64, 131.64, 133.10, 143.87, 144.33, 148.92, 167.91, 195.51. Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Table 2, entry 4). IR (KBr, cm^{-1}): ν_{max} 3346, 1703, 1657, 1473, 1198. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, 6 H, J = 7.0 Hz, 2× OCH_2CH_3), 2.31 (s, 6H, 2× CH_3), 4.09 (q, 4 H, J = 7.0 Hz, 2× OCH_2CH_3), 5.01 (s, 1 H, CH), 6.20 (s, 1 H, NH), 7.10–7.39 (m, 5H, C_6H_5).

Table 1
SBA-15/SO_3H catalyzed the neat four-component synthesis of polyhydroquinolines derivatives of **3**.



1 2 3

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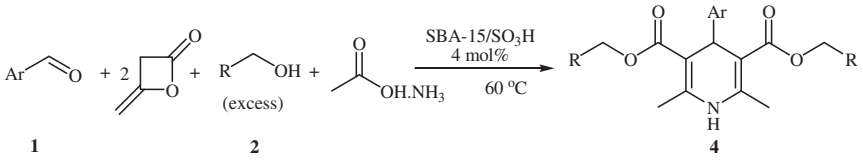
Entry	Ar	R	Time (min)	mp (°C)		Yield (%)
				Found	Reported [3]	
3a	C_6H_5	H	25	257–259	258–260	90
3b	4-Cl-C_6H_4	H	25	220–222	221–222	90
3c	2-Me-C_6H_4	H	25	260–264	–	85
3d	2-Cl-C_6H_4	H	25	235–238	–	85
3e	4-OMe-C_6H_4	H	30	247–250	–	90
3f	2-Cl-C_6H_4	Me	30	217–223	208–210	85
3g	4-NO_2-C_6H_4	Me	25	244–246	242–244	95
3h	4-OMe-C_6H_4	Me	20	234–243	257–259	90
3i	4-Cl-C_6H_4	Me	25	238–240	245–246	90
3j	2-Me-C_6H_4	Me	35	201–205	–	85

Table 2
The neat four-component synthesis of dihydropyridines derivatives of **4**.



1 2 4

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Entry	Ar	R	mp (°C)		Yield (%)
			Found [4b]	Reported	
1	C_6H_5	Me	150–153	152–153	90
2	3-OMe-C_6H_4	H	168–169	171–172	84
3	4-NO_2-C_6H_4	H	163–165	161–165	80
4	2-OMe-C_6H_4	H	160–162	164–166	84
5	2-Cl-C_6H_4	Me	122–126	123–126	80
6	3-Cl-C_6H_4	Me	123–124	120–125	91
7	4-Cl-C_6H_4	Me	146–149	144–147	91
8	4-NO_2-C_6H_4	Me	125–129	124–126	93

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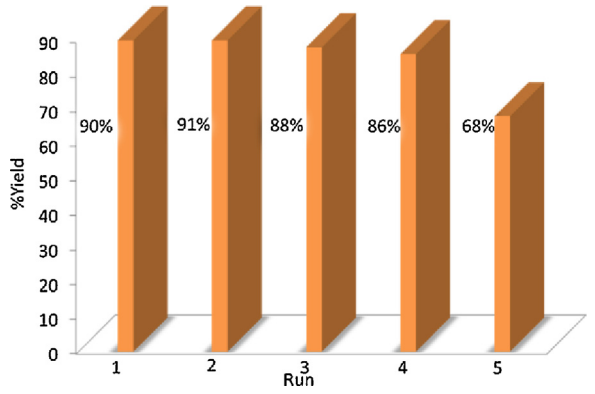

Fig. 2. Recycle of the SBA-15/SO_3H catalyst.

3. Results and discussion

In continuation of our investigations on the synthesis of heterocycles and the use of heterogeneous nanocatalysts for chemical preparation, we developed the applicability of reusable SBA-15/SO_3H as an efficient and convenient catalyst in synthesis of polyhydroquinolines by a one-pot, four-component reaction of diketene, alcohols, enamine, and aldehydes under neat conditions.

The SBA-15/SO_3H heterogeneous nanocatalyst was synthesized by grafting of –SO_3H onto the SBA-15 by refluxing a mixture of calcinated SBA-15 and MPTMS in dry toluene. Then the resulting solid product was oxidized with H_2O_2 (Fig. 1).

Then as a method reaction the mixture of enamine, aldehydes, diketene and methanol as reactant and solvent in the presence of SBA-15/SO_3H, after 16 min the reaction was completed with high yield of product **3**.

The activity and recyclability of the catalyst were studied (Fig. 2) using the reaction of a mixture of enamine, benzaldehyde, diketene and methanol in the presence of SBA-15/SO_3H, to achieve **3a**. After completion of the reaction, the catalyst was separated by simply centrifuging, and then washed with hot EtOH and water, supporting the use of the modified catalyst in the reaction method for at least 5 times.

The neat reaction of diketene, aldehydes **1**, alcohols **2**, with ammonium acetate in the presence of the SBA-15/SO_3H catalyst was found to generally afford the 1,4-dihydropyridines (DHPs) **4** in good yields (Table 2).

4. Conclusion

In conclusion, we demonstrated that covalently bonded sulfonic acid SBA-15 is an efficient solid catalyst for the synthesis of polyhydroquinoline and dihydropyridine derivatives based on the diketene ring-opening reaction under neat conditions and short reaction times. Simple separation, easy recovery and reusability of the catalyst make it a highly efficient and convenient catalyst.

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