J. Chem. Sci. Vol. 125, No. 6, November 2013, pp. 1359–1364.

Mesostructured SBA-15-Pr-SO_3H: An efficient solid acid catalyst for one-pot and solvent-free synthesis of 3,4-dihydro-2-pyridone derivatives

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MS received 10 January 2013; revised 22 July 2013; accepted 12 August 2013

Abstract. 3,4-Dihydro-2-pyridone derivatives have been prepared efficiently via a one-pot four-component reaction of benzaldehyde derivatives, Meldrum's acid, methyl acetoacetate and ammonium acetate in the presence of sulphonic acid-functionalized ordered nanoporous SBA-15 as a nano heterogeneous catalyst under solvent-free conditions. This process is a simple, environmentally friendly, rapid and high yielding reaction.

Keywords. Functionalized SBA-15; pyridone; Meldrum's acid; multicomponent reaction; solvent-free.

1. Introduction

Development of new methods for the synthesis of heterocyclic compounds will always be important, not just because of their remarkable structural diversity, but also their importance in a broad range of therapeutic areas.[1,2] 1,4-Dihydropyridine (1,4-DHP) derivatives are a class of heterocyclic compounds well-known as Ca^{+2} channel blockers.[3,4] These heterocyclic rings are also a common feature found in a variety of bioactive compounds such as vasodilator,[5] anti-atherosclerotic,[6] anti-diabetic,[7] and bioprotector agents.[8] Generally, the basic skeleton of DHP was first discovered by Hantzsch in 1882.[9] In a typical Hantzsch procedure, an aldehyde, ammonia, and a β-keto ester are enclosed to give a dihydropyridine, which is subsequently oxidized to pyridine.

2-Pyridones are structurally very similar to 1,4-dihydropyridines. Many naturally occurring and synthetic compounds containing the 2(1*H*)-pyridone ring, possess important pharmacological activities and useful biological properties.[10–12]

Multicomponent reactions (MCRs) have been emerged as rapid and selective synthetic routes towards molecular complexity and diversity.[13] Such protocols have proved to be a valuable asset in medicinal chemistry, drug design and drug discovery because of their simplicity, efficiency and high selectivity.[14,15] Therefore, the growth of combinatorial chemistry in the drug discovery process is considerably dependent on further advances in heterocyclic MCR methodology and according to the current synthetic requirements, environmentally benign multi-component procedures are particularly welcome.

Propylsulphonic-modified SBA-15 has been proved to be an efficient heterogeneous nanoporous solid acid catalyst in the green one-pot synthesis of a variety of heterocyclic compounds.[16–19] As part of our continuing interest in the synthesis of heterocyclic compounds of biological importance,[20–23] we decided to utilize this catalyst in the synthesis of 2(1*H*)-pyridone derivatives.

2. Experimental

2.1 *General remarks*

All commercially available chemicals were purchased from Merck Company and used without further purification. IR spectra were recorded from KBr disk using a Fourier Transform InfraRed (FT-IR) Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ^{1}H NMR (250 MHz) was run on a Bruker DPX at 250 MHz in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 Agilent.

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Surface areas were calculated by the Brunauer–Emmett–Teller (BET) method, and pore sizes were calculated by the Barrett–Joyner–Halenda (BJH) method. Scanning Electron Microscopy (SEM) analysis was performed on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV while Transmission Electron Microscopy (TEM) was carried out on a Tecnai G^2 F30 at 300 kV.

2.2 *Synthesis and functionalization of SBA-15*

Nanoporous compound SBA-15 was synthesized and functionalized according to our previous report[20] and the modified SBA-15-Pr-SO_3H was used as nanoporous solid acid catalyst in the following reactions.

2.3 *Typical procedure for the preparation of pyridone derivatives (**5a–h**)*

The SBA-Pr-SO_3H (0.02 g) was activated in vacuum at 100°C and then after cooling to room temperature, Meldrum's acid **1** (0.43 g, 3 mmol), methyl acetoacetate **2** (0.32 mL, 3 mmol), aromatic aldehyde **3** (3 mmol), and ammonium acetate **4** (0.38 g, 5 mmol) were added to it. The mixture was heated at 140°C under solvent-free condition for an appropriate time and the completion of reaction was indicated by Thin layer chromatography (TLC). The resulting solid product was dissolved in hot ethanol, filtered for removing the unsolvable catalyst and then the filtrate was cooled to afford the pure product. The catalyst was washed subsequently with diluted acid solution, distilled water and then acetone, dried under vacuum and re-used several times without loss of significant activity.

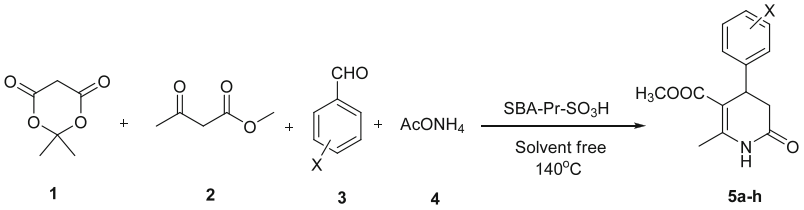
2.4 *Selected spectral data*

2.4a *4-(3-Nitrophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**5c**)*: Mp 194–196°C; IR (KBr): 3351, 1704, 1648, 1528, 1348 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 2.45 (3H, s, CH_3), 2.66 (1H, dd, J = 16.4 Hz, J = 1.5 Hz), 3.01 (1H, dd, J = 16.4 Hz, J = 8.0 Hz), 3.66 (3H, s, OCH_3), 4.34 (1H, dd, J = 8.0 Hz, J = 1.5 Hz), 7.24–7.73 (2H, m, ArH), 8.03–8.35 (3H, m, ArH, NH) ppm; MS (EI, m/z): 290 (M^+), 273 (100), 257, 245, 231.

2.4b *4-(2,4-Dichlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**5d**)*: Mp 204–206°C; IR (KBr): 3229, 1705, 1642, 1591, 800 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 2.45 (3H, s, CH_3), 2.78 (1H, dd, J = 16.5 Hz, J = 1.9 Hz), 2.94 (1H, dd, J = 16.5 Hz, J = 8.3 Hz), 3.60 (3H, s, OCH_3), 4.64 (1H, dd, J = 8.3 Hz, J = 1.9 Hz), 6.96 (1H, d, J = 8.25 Hz, ArH), 7.14 (1H, d, J = 7.5 Hz, ArH), 7.40 (1H, s, ArH), 8.79 (1H, br s, NH) ppm; MS (EI, m/z): 313 (M^+, 100), 281, 246, 226, 199.

2.4c *4-(2,4-Dimethoxyphenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**5f**)*: Mp 136–139°C; IR (KBr): 3225, 1694, 1611, 1260, 1036 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.50 (3H, s, CH_3), 2.42 (1H, dd, J = 16.5 Hz, J = 1.9 Hz), 2.80 (1H, dd, J = 16.5 Hz, J = 8.3 Hz), 3.46 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.63 (1H, dd, J = 8.3 Hz, J = 1.9 Hz), 6.86 (1H, d, J = 5.25 Hz, ArH), 7.04 (1H, d, J = 9.25 Hz, ArH), 7.26 (1H, s, ArH), 8.20 (1H, br s, NH) ppm; MS (EI, m/z): 305 (M^+), 273, 246 (100), 230.

2.4d *4-(2-Methoxyphenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**5h**)*: Mp 206–208°C; IR (KBr): 3240, 1699, 1634, 1245, 1051 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 2.42 (3H, s, CH_3), 2.77 (1H, dd, J = 16.5 Hz, J = 1.9 Hz), 2.87 (1H, dd, J = 16.5 Hz, J = 8.3 Hz), 3.60 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.57 (1H, dd, J = 8.3 Hz, J = 1.9 Hz), 6.79–6.96 (2H, m, ArH), 7.19 (1H, d, J = 7.75 Hz, ArH), 7.26 (1H, d, J = 10 Hz, ArH), 8.15 (1H, br s, NH) ppm; MS (EI, m/z): 275 (M^+), 260, 243, 216 (100).



Scheme 1. Synthesis of 5-acetyl-4-aryl-3,4-dihydro-6-methyl-2(1*H*) pyridone derivatives in the presence of SBA-Pr-SO_3H.

Table 1. Optimization of reaction conditions for the synthesis of compound **5d**.

Entry	Solvent	Time (h)	Yield[a] (%)
1	H_2O	5	80
2	EtOH	5	81
3	EtOH/H_2O (1:1)	5	64
4	CH_3CN	3	80
5	Neat (140°C)	30 min	95

[a]Isolated yields

Table 3. Reuse of SBA-Pr-SO_3H for synthesis of **5a**.

Entry	Time (min)	Yield (%)
1	40	90
2	40	84
3	40	80
4	40	72

3. Results and discussion

Although several approaches for the synthesis of these skeletons have been reported,[24–28] development of simple and convenient synthetic procedures for the synthesis of such nitrogen-containing heterocycles represents an attractive area of research in synthetic organic chemistry. In this article, we wish to report our results on the synthesis of pyridone derivatives by the reaction of Meldrum's acid **1**, methyl acetoacetate **2**, benzaldehyde derivatives **3**, and ammonium acetate **4** using SBA-Pr-SO_3H as the nano catalyst (scheme 1). To study the effect of solvent on this four-component reaction, the reaction of 2,4-dichlorobenzaldehyde, Meldrum's acid, methyl acetoacetate, and ammonium acetate was chosen as a model reaction (table 1). The results clearly show that among the different tested solvents such as H_2O, EtOH, MeCN, and solvent-free system, the best result was obtained after 30 min in solvent-free medium in excellent yield. Then, different substituted aldehydes were used to undergo the Hantzsch reaction in the presence of catalytic amount of SBA-Pr-SO_3H under solvent-free condition at 140°C and all pyridines were obtained in high to excellent yields (table 2). After completion of the reaction (monitored by Thin layer chromatography (TLC)), the crude product was dissolved in hot ethanol and separation of the heterogeneous solid catalyst from the reaction medium was easily carried out by simple filtration. The acid catalyst can be reactivated by simple washing subsequently with diluted acid solution, water and acetone, and then reused without noticeable loss of reactivity. Reusability of the catalyst was investigated under optimized conditions for the synthesis of the model compound **5a**. As shown in table 3, the process of recycling was completed four times and no significant decrease in activity was observed. The yields for the four runs were found to be 90 %, 84 %, 80 % and 72 %, respectively.

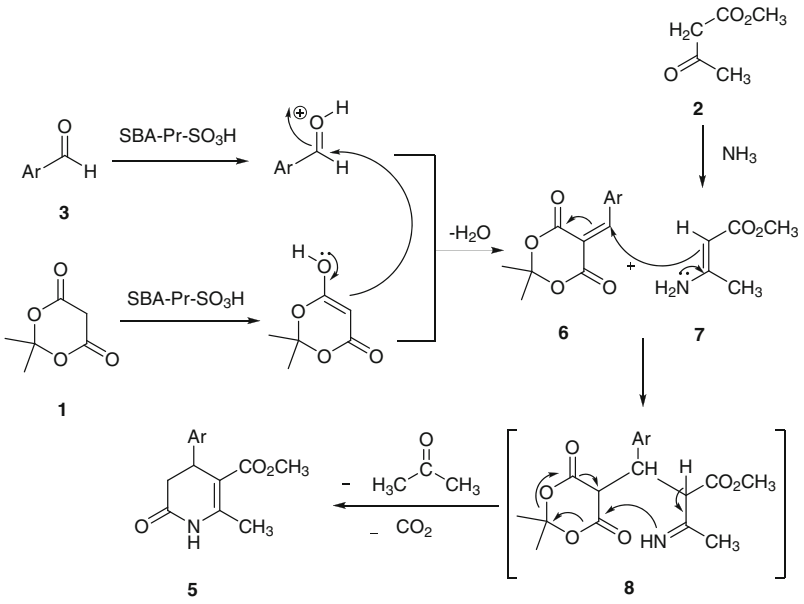
Due to the greater acidity of Meldrum's acid (pK_a = 9.97) in comparison with methyl acetoacetate (pK_a = 11.0), we do not obtain 1,4-dihydropyridines.[32] This reaction may occur via a condensation, addition, cyclization and elimination mechanism (scheme 2). The acid catalyst (SBA-Pr-SO_3H) acts as a source of H^+, which can protonate carbonyl group to create a more reactive species. The reaction occurs via a Knoevenagel condensation reaction between Meldrum's acid and aldehyde to provide intermediate **6** which undergoes a Michael-type addition with enamino compound **7** (resulting from the reaction between ammonium acetate and methyl acetoacetate). Intramolecular cyclodehydration in intermediate **8** results in the formation of desired product **5**.

Literature survey reveals that SBA-Pr-SO_3H is the only catalyst that has been used for the synthesis of

Table 2. SBA-Pr-SO_3H catalysed the synthesis of 3,4-dihydro-2-pyridones **5a–h** under solvent-free condition.

Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	M.p. (°C)	M.p. (Lit)
1	Ph	**5a**	40	90	190–193	197–198[29]
2	4-ClC_6H_4	**5b**	35	89	189–191	198–200[30]
3	3-$NO_2C_6H_4$	**5c**	30	92	194–196	205–206[31]
4	2,4-$Cl_2C_6H_3$	**5d**	30	95	204–206	–
5	4-$NO_2C_6H_4$	**5e**	30	87	210–213	210–211[30]
6	2,4-$(OCH_3)_2C_6H_3$	**5f**	30	89	136–139	–
7	4-$OCH_3C_6H_4$	**5g**	40	88	177–179	187–188[29]
8	2-$OCH_3C_6H_4$	**5h**	35	92	206–208	–

[a]Isolated yields



Scheme 2. Proposed mechanism.

Table 4. Comparison of different conditions in the synthesis of compound **5a**.

Entry	Catalyst	Solvent	Condition	Time (min)	Yield (%)	Year
1	-	AcOH	Reflux	10 h	65	1996[33]
2	-	-	Microwave	15	86	2003[31]
3	-	-	Ultrasound	12	85	2011[30]
4	SBA-Pr-SO_3H	-	Heating (140°C)	40	90	This study

pyridone derivatives though the four-component reaction and in other reported methods, microwave irradiation and ultrasound conditions were used to result in lower yields (table 4).

Stucky and coworkers introduced hexagonal SBA-15 having high surface area, long range order and thick walls (typically between 3 and 9 nm), which make them thermally and hydrothermally stable materials.[34] Organic functionalities such as R-SO_3H can be incorporated into mesoporous materials, either by post-grafting or direct synthesis methods.[35,36] Integration of acidic functional groups (e.g., $-SO_3H$) into SBA-15 has been explored to produce promising solid acids.

A schematic illustration for the preparation of SBA-Pr-SO_3H is shown in figure 1. First, the calcined SBA-15 silica was functionalized with (3-mercaptopropyl) trimethoxysilane (MPTS) and then, the thiol groups could be completely oxidized into sulphonic acid groups by hydrogen peroxide.

The texture properties of SBA-15 and SBA-Pr-SO_3H are given in table 5. The surface area, average pore diameter calculated by BET method and pore volume

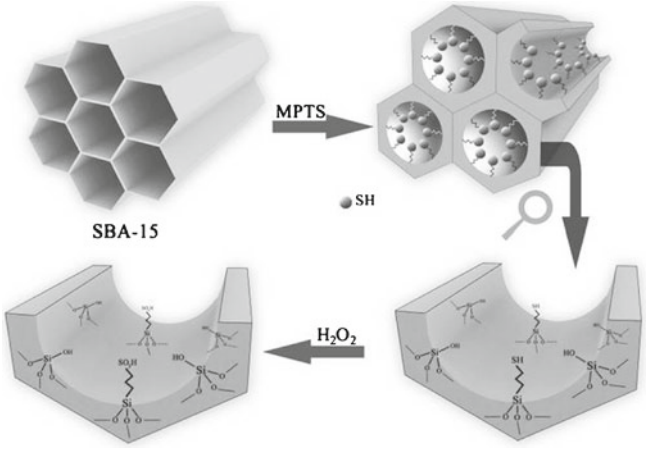


Figure 1. Schematic representation of SBA-Pr-SO_3H.

Table 5. Porosimetery values for SBA-15 and functionalized SBA-15.

	Surface area, cm^2g^{-1}	Pore volume, cm^3g^{-1}	Pore diameter, nm
SBA-15	649	0.806	6.2
SBA-Pr-SO_3H	440	0.660	6.0

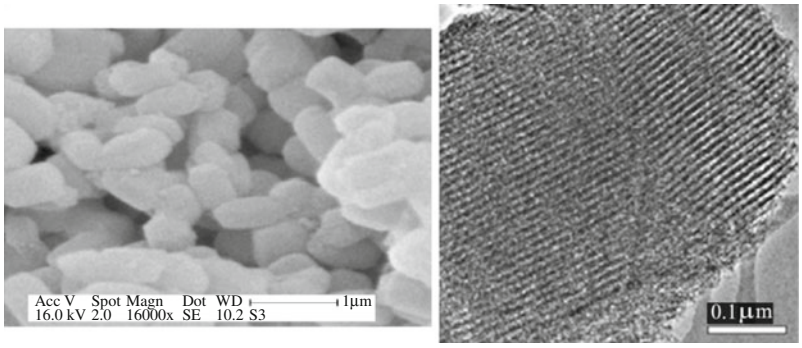


Figure 2. SEM and TEM image of SBA-Pr-SO_3H.

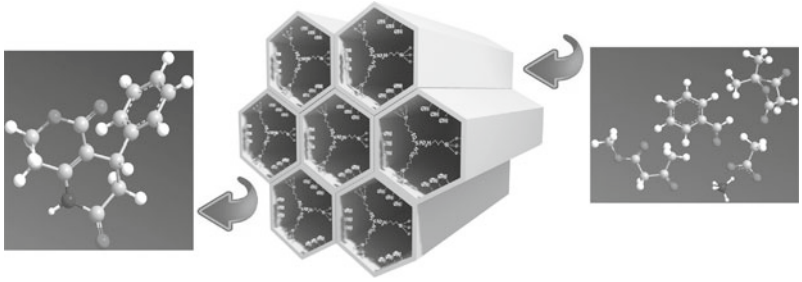


Figure 3. SBA-Pr-SO_3H acts as nano-reactor.

of SBA-Pr-SO_3H are 440 m^2g^{-1}, 6.0 nm and 0.660 cm^3 g^{-1}, respectively, which are smaller than those of SBA-15 due to immobilization of sulphonosilane groups into the pores.

Figure 2 illustrates the Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) images of SBA-Pr-SO_3H. Scanning Electron Microscopy (SEM) image (figure 2, left) shows uniform particles of about 1 μm. The same morphology was observed for SBA-15. It can be concluded that morphology of solid was saved without change during surface modifications. On the other hand, the Transmission Electron Microscopy (TEM) image (figure 2, right) reveals parallel channels, which resemble the pores configuration of SBA-15. This indicates that the pore of SBA-Pr-SO_3H did not collapse during two-step reactions. This catalyst acts as a nano-reactor in this reaction (figure 3).

4. Conclusion

In conclusion, we have successfully developed one-pot facile methodology for synthesis of a series of 5-acetyl-4-aryl-3,4-dihydro-6-methyl-2(1*H*) pyridone derivatives **5a–h** in the presence of catalytic amount of SBA-Pr-SO_3H under solvent-free conditions. High yields, simple work-up procedure, no side reactions and simplicity in process are the advantages of this method.

Supplementary information

The electronic supporting information can be seen in www.ias.ac.in/chemsci.

Acknowledgement

We thank the Research Council of Alzahra University and the University of Tehran for financial support.

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