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Mesoporous SBA-15 Silica Phenylsulfonic Acid (SBA-15-Ph-SO_3H) as Efficient Nanocatalyst for One-pot Three-component Synthesis of 3-Methyl-4-aryl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-ones

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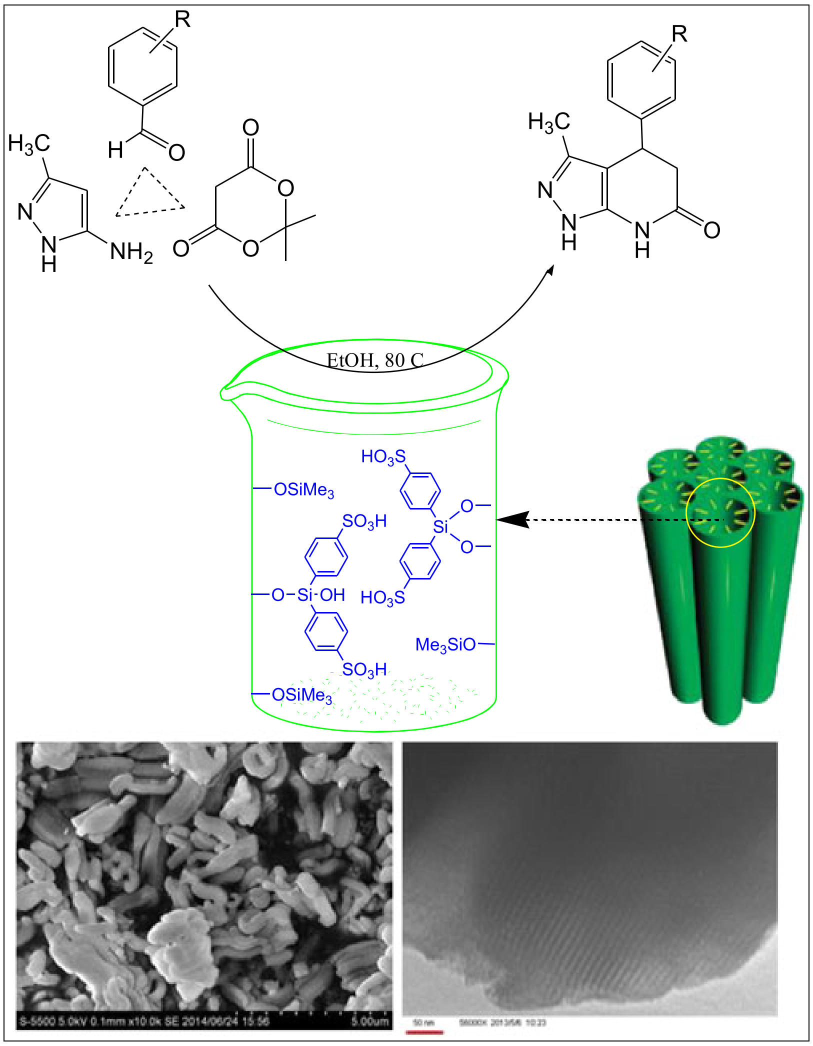


A simple, economical, and efficient approach to the one-pot synthesis of 3-methyl-4-aryl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-ones by multicomponent assembling of 5-methylpyrazol-3-amine, aldehydes, and Meldrum's acid using mesoporous silica phenylsulfonic acid (SBA-15-Ph-SO_3H) as recyclable and heterogonous solid acid nanocatalyst has been described. This protocol has the advantages of high yields, wide application scope, and an environmental benign procedure.

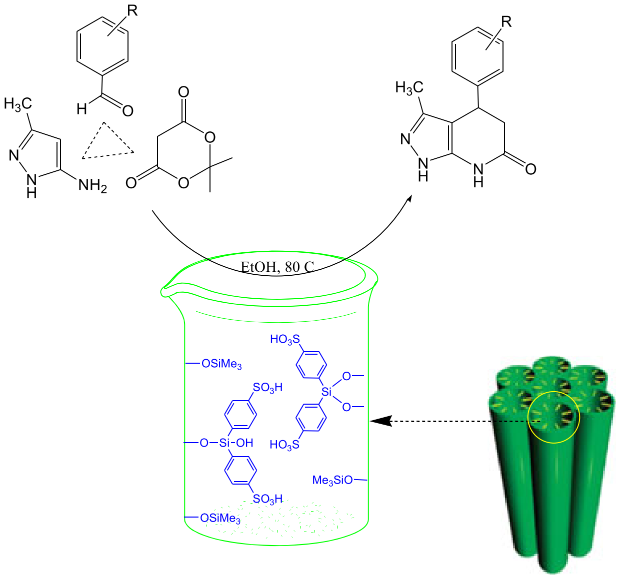
INTRODUCTION

Pyrazolo[3,4-*b*]pyridines are gaining importance in medicinal and organic chemistry. They have displayed broad spectrum of pharmacological and biological activities such as antibacterial [1], antimicrobial [2], antiviral [3], oncogenic Ras-inhibiting [4], and cyclooxygenase-inhibiting activities [5]. The synthesis of pyrazolopyridone derivatives has been extensively explored in recent years [6–14]. However, some of the reported methodologies for the synthesis of these products are associated with several drawbacks such as prolonged reaction time, low yields, harsh reaction conditions, use of expensive reagents and catalysts, and tedious workup. Therefore, any new facile and highly efficient synthetic approach to corresponding pyrazolopyridones is highly desirable.

There has been considerable interest in the development of heterogeneous solid acid catalysts to avoid the use of traditional homogeneous acid catalytic systems (H_2SO_4, HF, $AlCl_3$, BF_3,…) that present serious drawbacks including hazards in handling, corrosiveness, production of toxic waste, and difficulties in separation. In this context, organically functionalized ordered mesoporous silicas [15–18] with a tunable pore structure, high surface area, and tailored composition have received great attention with broad applications. The catalytic activity of the sulfonic acid-functionalized mesoporous silica materials is controlled by location and distribution of the acidic sites and solvent interactions [19]. While several types of solid sulfonic acids, based on ordered mesoporous silicas, have been created in recent years [20].

In our continued interest in the development of a highly expedient methodology [21] for the synthesis of fine chemicals and heterocyclic compounds of biological importance, we report here a simple and efficient method for the one-pot synthesis of 3-methyl-4-aryl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-ones by multicomponent assembling of 5-methylpyrazol-3-amine, aldehydes, and Meldrum's acid using mesoporous silica phenylsulfonic acid (SBA-15-Ph-SO_3H) as recyclable and heterogonous solid acid nanocatalyst to promote the reactions (Scheme 1).

Scheme 1. Synthesis of 3-methyl-4-aryl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-ones using SBA-15-Ph-SO_3H. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



EXPERIMENTAL

Synthesis and functionalization of SBA-15. According to our previous report,^{20h} the nanoporous compound SBA-15 was synthesized and functionalized (Fig. 1). Figure 1 also illustrated the scanning electron microscopy and transmission electron microscopy images of SBA-15-Ph-SO_3H. As can be seen in Figure 1 (left), functionalized SBA-15 has uniform particles about 1 lm in scanning electron microscopy image that is same as observed morphology for SBA-15. This indicates that during the surface modifications, morphology of solid was saved without significant change. Also the transmission electron microscopy image of SBA-15-Ph-SO_3H in Figure 1 (right) shows the parallel channels, which is similar to the pore configuration of SBA-15. It means that during tree step reactions, the pore of SBA-15-Ph-SO_3H was not collapsed.

General procedure for synthesis of pyrano[2,3-d] pyrimidine-2,4,7-trione derivatives in the presence of SBA-15-Ph-SO_3H. A mixture of aldehydes (1 mmol), Meldrum's acid (1 mmol), and 5-methylpyrazol-3-amine (1 mmol) were taken in a mixture of SBA-15-Ph-SO_3H (10 mol%) and ethanol (5 mL) in a round bottomed flask. The resulting mixture was vigorously stirred at reflux temperature until completion of the reaction as monitored by thin-layer chromatography (*n*-hexane/acetone, 4:1). After complication of reaction, the insoluble solid catalyst was removed by filtration. The crude products were obtained after cooling of the filtrates and purified by recrystallization from ethanol afforded pure products. All the products were characterized by spectroscopy and from physical data.

RESULTS AND DISCUSSION

Initially, to evaluate the synthetic potential of the procedure proposed, the one-pot multicomponent condensation of benzaldehyde, Meldrums acid, and 5-methylpyrazol-3-amine into 3-methyl-4-phenyl-2,4,5,7-tetrahydropyrazolo [3,4-b]pyridine-6-one in the presence of SBA-15-Ph-

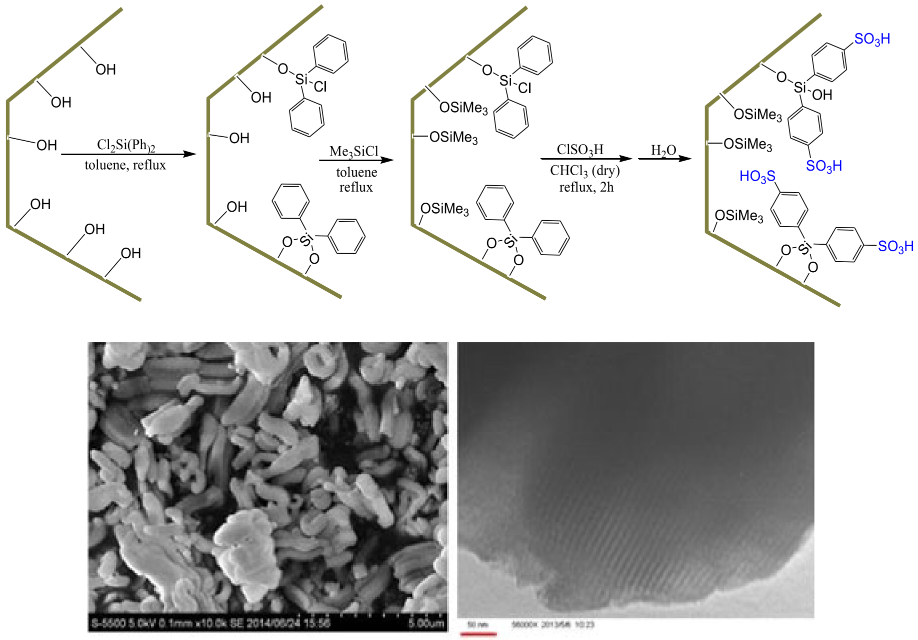
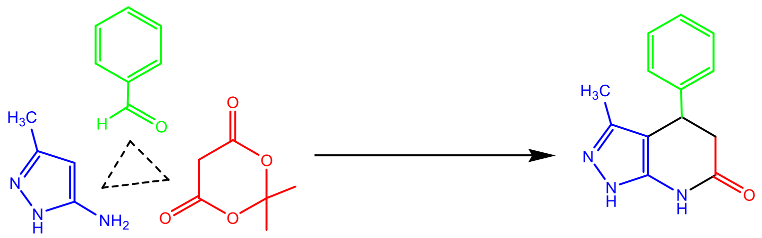


Figure 1. Preparation of SBA-15-Ph-SO_3H and its scanning electron microscopy and transmission electron microscopy images. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Effect of the solvent, temperature, reaction time, amount of catalyst on the synthesis of 3-methyl-4-phenyl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-one.[a]



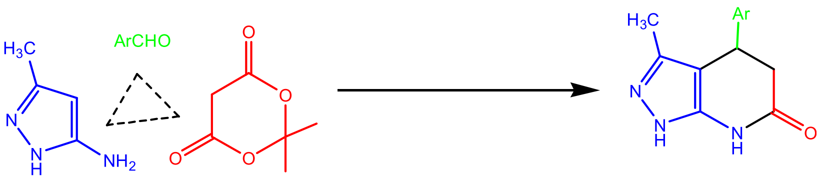
Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)
1	MeOH	10[a]	65	240	70
2	H_2O	10	78	240	60
3	CH_3Cl	10	60	240	65
4	CH_2Cl_2	10	40	240	50
5	Toluene	10	110	240	55
6	CH_3CN	10	82	240	70
7	EtOH	10	80	120	96
8	EtOH	20	80	120	96
9	EtOH	5	80	120	80
10	EtOH	10	25	240	45
11	EtOH	0	80	240	Trace

[a] 5-methylpyrazol-3-amine (1 mmol), aldehydes (1 mmol), Meldrum's acid (1 mmol), and solvent (5 mL).

SO_3H was chosen as model. In order to establish the optimum conditions for this reaction, initially, the influence of the reaction temperature, the amounts of catalyst, and the reaction time were tested and optimized. The results are summarized in Table 1. As it is indicated in Table 1 (entry 7), the optimal catalyst loading (10 mol%) and the temperature at 80 °C in EtOH were found to be the optimum one for the synthetic process and afforded the highest yield of

Table 2

Synthesis of 3-methyl-4-aryl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-ones.



Entry	Aldehyde	Yield (%)[b]	Mp (°C)[a]	Mp (°C)[ref]
1	C_6H_5CHO	96	303–305	304–306 [12]
2	4-Me-C_6H_4CHO	96	>300	>300 [11]
3	4-MeO-C_6H_4CHO	95	>300	308–310 [12]
4	3-NO_2-C_6H_4CHO	92	266–268	264–266 [14]
5	4-Cl-C_6H_4CHO	92	>300	>300 [14]
6	2-Me-C_6H_4CHO	92	>300	>300 [11]
7	4-N(Me)$_2$-C_6H_4CHO	96	>300	>300 [14]
8	2-Cl-C_6H_4CHO	92	>300	>300 [16]
9	3,4,5-(MeO)$_3$-C_6H_2CHO	96	>300	>300 [16]
10	2,4-Cl_2-C_6H_3CHO	90	>300	>300 [14]
11	4-OH-C_6H_4CHO	88	274–276	274–276 [14]
12	2-MeO-C_6H_4CHO	96	278–280	279–280 [14]
13	2-thienylaldehyde	90	300–302	303–305 [12]
14	Butanal	80	258–260	259–260 [11]
15	2-Propanal	75	290–292	290–292 [14]

[a] General procedure, 5-methylpyrazol-3-amine (1 mmol), aldehydes (1 mmol), Meldrum's acid (1 mmol), SBA-15-Ph-SO_3H (10 mol%), EtOH (5 mL), 120 min at 80 °C.
[b] Yield of isolated product.

product (96%). It should be noted that the optimal catalyst loading in the synthesis of 3,3-dimethyl-13-(4-chlorophenyl)-3,4-dihydro-1H-indazolo[1,2-b] phthalazine-1,6,11(2H,13H)-trione product peaked at a concentration of 10 mol%. When the amount of catalyst was lower, the yield of the product decreased (Table 1, entry 9), whereas raising the catalyst concentration did not lead to a pronounced increase to the product yield (Table 1, entry 8). In the absence of catalyst, low product's yield was observed, even after prolonged reaction time (Table 1, entry 11).

Under the optimal conditions, the scope and generality of the reaction was explored. A variety of aryl aldehydes were investigated to react with Meldrum's acid and 5-methylpyrazol-3-amine over a 120 min reaction period, and the results are summarized in Table 2. Aldehydes containing various electron-donating and electron-withdrawing substituents were reacted under the experimental conditions, and the corresponding products were obtained in good yields. Therefore, no remarkable electronic effects were observed in the reaction. Good yield was also obtained when the alkyl aldehydes was reacted (Table 2, entries 14 and 15).

The structures of all compounds were established by spectroscopic (FTIR, [1]H-NMR, [13]C-NMR, Mass) and elemental analyses and those of known products by comparison of their spectral data and melting points with literature reports.

With the previous results taken into consideration and the mechanistic data on the catalytically induced Henry and aldol reactions and also tandem Knoevenagel–Michael reactions, the following mechanism for the preparation of the related products is depicted in Scheme 2 [13]. The first step involves the Knoevenagel reaction of Meldrum's acid with aldehyde to form an intermediate **A**. The next step is

Scheme 2. Proposed mechanism for the preparation of 3-methyl-4-aryl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-ones.

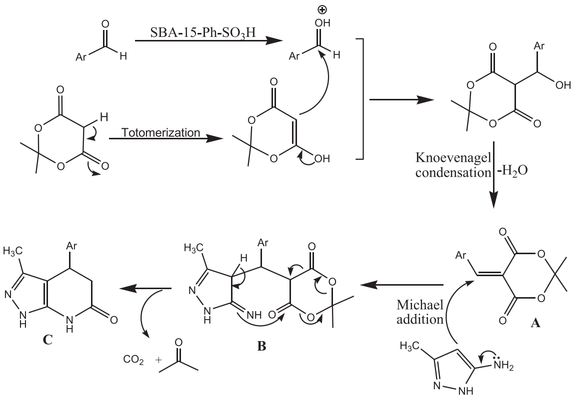


Table 3

Comparison of the activity of different catalysts in the synthesis of pyrazolo[3,4-b]pyridine-6-ones.

Aldehyde	Catalyst	Reaction conditions	Yield (%)	Ref.
4-$MeOC_6H_4CHO$	SBA-15-Ph-SO_3H	EtOH, 80 °C, 120 min.	96	This study
	Ultrasound	EtOH, 60 °C, 3 min.	87	12
	Microwave Irradiation	100 °C, 8 min.	92	13
	Fe^{+3}@K10	H_2O 100 °C, 12 min.	90	14
	(PEG)-400	90 °C, 15 min.	89	11
C_6H_5CHO	SBA-15-Ph-SO_3H	EtOH, 80 °C, 120 min.	96	This study
	Fe^{+3}@K10	90 °C, 10 min.	90	14
	Microwave Irradiation	100 °C, 9 min.	90	13
	Ultrasound	EtOH, 60 °C, 3 min.	95	12

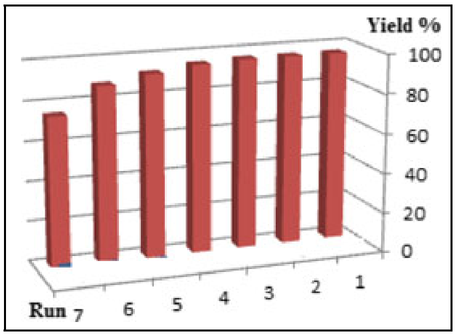


Figure 2. The reusability of SBA-15-Ph-SO_3H. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the Michael addition of 5-methylpyrazol-3-amine to the electron-deficient Knoevenagel adduct **A**. Cyclization of **B** via a translactonization reaction leads to liberation of an acetone molecule and a molecule CO_2 and also produced the final product **C**.

Finally, to assess the present protocol with respect to other reported methods for the preparation of 3-methyl-4-aryl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-ones, the presented procedure was compared with some of the reported catalysts. From Table 3, it can be seen that present system exhibited higher conversions and yields compared with the other reported system.

The reusability of the catalyst in the reaction of benzaldehyde, Meldrums acid and 5-methylpyrazol-3-amine in ethanol at 80°C was studied. In this procedure, after completion of each reaction, hot ethanol was added to the reaction mixture and was shaken for a few minutes to dissolve the product. The catalyst (insoluble in solvent) was filtered and washed with hot ethanol and dried. The recovered catalyst was reused seven times, and smooth loss of catalytic activity was observed from the seventh time of reuse (Fig. 2).

CONCLUSIONS

In conclusion, we have described a novel, efficient, and green procedure using SBA-15-Ph-SO_3H as an acidic nanocatalyst (10 mol%) for the facile synthesis of 3-methyl-4-aryl-2,4,5,7-tetrahydropyrazolo[3,4-b]pyridine-6-ones via one-pot, three component condensation of aldehyde, Meldrum's acid, and 5-methylpyrazol-3-amine. The advantages of the method include (i) reusability of the catalyst, (ii) high yields, (iii) easy workup, (iv) short reaction times, and furthermore, this procedure is cheap, safe, and environmentally benign. Moreover, the catalyst has suitable hydrophobicity to drive out the water that is formed during the reaction from mesochannels.

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