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Synthesis of dihydropyrido[2,3-*d*]pyrimidine derivatives in the presence of sulfonic acid functionalized SBA-15 and the study of their antimicrobial activities

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6-amino-1,3-dimethyl uracil; pyrido[2,3-d]pyrimidine; 1,3-dicarbonyl compounds; SBA-Pr-SO_3H; Multicomponent reaction.

Abstract. SBA-Pr-SO_3H was used as a green and recyclable catalyst for the synthesis of dihydropyrdo[2,3-*d*]pyrimidine derivatives by a three component one-pot reaction between 6-amino-1,3-dimethyl uracil, aromatic aldehydes and 1,3-dicarbonyl compounds under reflux conditions. Some of the synthesized dihydropyrido[2,3-*d*]pyrimidines showed antimicrobial activity against some fungi and gram positive and negative bacteria.

1. Introduction

Uracil derivatives have been reported to contain a variety of biological and clinical features [1]. Furthermore, pyrido[2,3-*d*]pyrimidines have received great interest over the past years because of their diverse range of pharmacological activities, including antitumor [2], antibacterial [3], antihypertension [4], antimicrobial [5], analgesic [6], as an adenosine kinase inhibitor [7], AbI kinase inhibitor [8], tyrosine kinas inhibitor [9] and calcium channel antagonist [10].

Multicomponent reactions are attractive for several reasons, including atom economy, direct reaction design, reduced amount of work up, and minimized waste generation [11].

A number of methods have been reported for the synthesis of dihydropyrido[2,3-*d*]pyrimidine derivatives from aldehydes, 1,3-dicarbonyl compounds and 1,3-dimethyl uracil condensation. These are microwave irradiation [12], reflux conditions [13], thiourea dioxide (TUD) [14] and nano magnetic catalyst (Fe_3O_4@SiO_2-SO_3H) [15]. Most of the reported methods require prolonged reaction times, toxic solvents, reagents in stoichiometric amounts, and generate low yields of the product.

In recent years, mesoporous materials, especially mesoporous silica, such as SBA-15, have attracted considerable attention [16,17]. SBA-15 is a unique inorganic solid support with high surface area, large pore size and high thermal stability [18]. Grafting various organic compounds onto the surface of SBA-15 can improve the catalytic activity of the silica surface [19-23]. Sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) was proved to be an efficient heterogenous nanoporous

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solid acid catalyst that can be used in the synthesis of various heterocyclic compounds [24,25]. In continuation of our previous studies on the development of heterogeneous solid acid catalysts in heterocyclic synthesis [26-30], we used SBA-Pr-SO_3H nanoporous silica as a highly efficient heterogeneous acid catalyst for the synthesis of dihydropyrido[2,3-*d*]pyrimidine derivatives via a three-component condensation.

2. Results and discussion

2.1. Synthesis of dihydropyrido[2,3-d]pyrimidine derivatives

In this article, dihydropyrido[2,3-*d*]pyrimidine derivatives **4** were synthesized by condensation of aromatic aldehydes **1**, 1,3-dicarbonyl compounds **2** and 6-amino-1,3-dimethyl uracil, in the presence of SBA-Pr-SO_3H as a green, reusable and eco-friendly catalyst in refluxing CH_3CN (Scheme 1).

In our initial investigations, as shown in Table 1, evaluations of different solvents were performed for the synthesis of ethyl 5-(4-hydroxyphenyl)-1,3,7-trime- thyl-2,4-dioxo-1,2,3,4,5,8-he xahydropyrido[2, 3-*d*]pyrimidine-6-carboxylate **4a** by the condensation of 4-hydroxy benzaldehyde **1a**, ethyl acetoacetate **2** and 6-amino-1,3-dimethyl uracil **3**, in the presence of SBA-Pr-SO_3H in different solvents, such as H_2O, EtOH, CH_3CN and solvent free 120°C. The best result was obtained after 40 min in CH_3CN under reflux conditions in good yield.

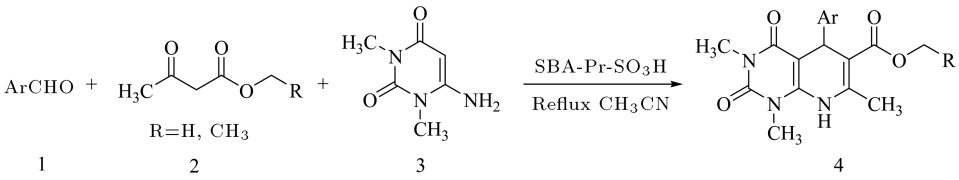
Table 1. The optimization of reaction conditions for the synthesis of **4a**.

Entry	Solvent	Condition	Time (h)	Yield* (%)
1	—	120°C	2	Trace
2	H_2O	Reflux	2	69
3	EtOH	Reflux	2	75
4	CH_3CN	Reflux	40 (min)	92

*: Isolated yield.

Based on the observed results, various aromatic aldehydes (electron rich and electron deficient) and 1,3-dicarbonyl compounds were used in the presence of SBA-Pr-SO_3H (0.02 g). The results are summarized in Table 2. The experimental procedure is very simple, convenient and has the ability to tolerate a variety of other functional groups, such as hydrogen, methoxy, nitro and halides, under the reaction conditions. It was indicated that both electron rich and electron deficient aldehydes worked well, mostly leading to high yields of product. As shown in Table 2, 3-nitobenzaldehyde and 2,4-dichlorobenzaldehyde have very short reaction times, which can be attributed to the presence of electron deficient groups on these aldehydes. For all substrates, the reaction could be completed in 5-45 min with high yields. Upon completion of the reaction, monitored by TLC, the generated solid product was dissolved in hot ethanol, filtered to remove the catalyst and then the filtrate was cooled to afford the pure product (**4a-h**). The advantages of this procedure are short reaction time, a benign and green catalyst and easy work-up.

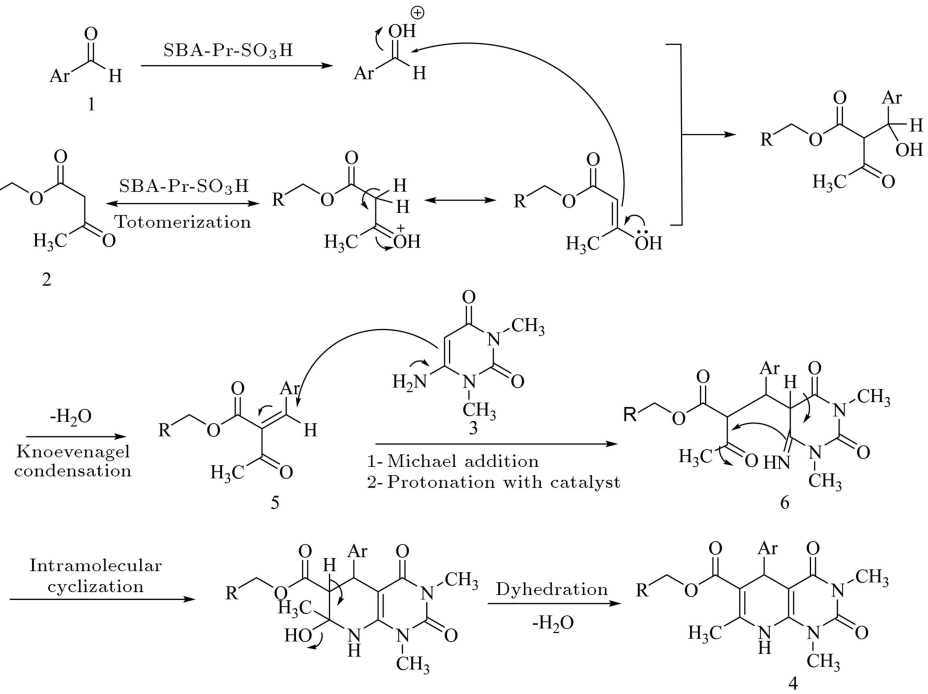
The acid catalyst can be reactivated by simple washing subsequently with a diluted acid solution, water and acetone, and then reused without noticeable loss of reactivity. As shown in Table 3, the recovered SBA-Pr-SO_3H could be recycled four times without any significant loss of yield.



Scheme 1. Synthesis of dihydropyrido[2,3-*d*]pyrimidine derivatives **4**.

Table 2. Synthesis of dihydropyrido[2,3-*d*]pyrimidine derivatives **4** using SBA-Pr-SO_3H.

Entry	Ar	R	Product	Time (min)	Yield (%)	mp (°C)	mp (Lit.)
1	4-OHC_6H_4	CH_3	**4a**	40	92	242-244	240-242 [12]
2	C_6H_5	CH_3	**4b**	30	82	299-300	298-299 [15]
3	2,4-$Cl_2C_6H_3$	CH_3	**4c**	15	89	284-285	New
4	2,3-$Cl_2C_6H_3$	CH_3	**4d**	40	85	288-290	New
5	4-$OMeC_6H_4$	CH_3	**4e**	25	88	267-269	267-269 [15]
6	3-$NO_2C_6H_4$	CH_3	**4f**	5	80	253-255	256-258 [13]
7	4-FC_6H_4	CH_3	**4g**	45	93	240-241	240-241 [13]
8	3-$NO_2C_6H_4$	H	**4h**	15	89	272-273	273-274 [13]



Scheme 2. Possible mechanism for synthesis of dihydropyrido[2,3-*d*]pyrimidine derivatives using SBA-Pr-SO_3H.

Table 3. Synthesis of dihydropyrido[2,3-*d*]pyrimidine derivative **4a** with recycled SBA-Pr-SO_3H.

	1st run	2nd run	3rd run	4th run
Time (min)	40	40	45	45
Yield (%)	92	88	88	85

The suggested mechanism is shown in Scheme 2. At first, the acid catalyst protonates the carbonyl group of aldehyde **1**. Then, a Knoevenagel condensation of ethyl (or methyl)acetoacetate **2** with protonated carbonyl group generates 2-aryl ethyl(or methyl)acetoacetate **5**. Michael addition of 6-amino-1,3-dimethyl uracil **3** to intermediate **5** produces the intermediate **6**, which, after intramolecular cyclization and dehydration, results in the target product **4**.

Synthesis of dihydropyrido[2,3-*d*]pyrimidines has been reported under different conditions in the literature, as shown in Table 4. In contrast with other existing methods, short reaction time, a recyclable catalyst, simple procedure and easy work-up are the advantages of the current methodology.

2.2. Antimicrobial activities of dihydropyrido[2,3-d]pyrimidine derivatives

All synthesized compounds were screened for antimicrobial activity using a disc diffusion method (Table 5). In this project, five microorganisms were used, such as *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginusa* ATCC 85327 (gram negative bacteria), *Bacillus subtilis* ATCC 465 and *Staphylococcus aureus* ATCC 25923 (gram positive bacteria), *Candida albicans* ATCC 10231 (fungi). Dihydroyrido[2,3-*d*]pyrimidines were dissolved in DMSO (100 μg/mL), of which 25 μL were loaded to 6 mm paper discs. In this project, one hundred microliters of 10^9 cell/mL suspension of the microorganisms were spread on sterile Muller-Hinton Agar plates, and the discs were placed on the surface of culture plates. The inhibition zone of compounds around the disc are illustrated in Table 5,

Table 4. Comparison of different conditions in the synthesis of alkyl-5-(aryl)-1,3,7-trimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2, 3- *d*]pyrimidine-6-carboxylate.

Entry	Catalyst	Solvent	Condition	Time	Yield (%)	Year
1	———	*i*-PrOH	Reflux	8 h	75-88	1990 [15]
2	Wang & Merrifield resins	CH_3COOH	Microwave irradiation	Step 1: 60 × 15 s Step 2: 60 × 4 s	82-92	2005 [12]
3	Thiourea dioxide	H_2O	50°C	10 h	90-95	2012 [14]
4	SBA-Pr-SO_3H	CH_3CN	Reflux	5-45 min	80-93	This work

Table 5. Inhibition zone (mm) of synthesized pyrido[2,3-*d*]pyrimidines against fungi and gram positive and negative bacteria by disc diffusion method.

Compound	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginos*	*C. albicans*
4a	0	0	0	0	0
4b	0	0	0	0	0
4c	0	0	0	0	0
4d	0	0	0	0	0
4e	0	0	0	0	0
4f	15	26	0	0	0
4g	0	0	0	0	0
Chloramphenicol	26	22	24	8	—
Gentamicin	28	20	20	18	—
Nystatin	—	—	—	—	18

Table 6. Minimum inhibitory concentration (μg/mL) of synthesized pyrido[2,3-*d*]pyrimidines against fungi and gram positive and negative bacteria.

Compound	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginos*	*C. albicans*
4a	—	—	—	—	—
4b	—	—	—	—	—
4c	—	—	—	—	—
4d	—	—	—	—	—
4e	—	—	—	—	—
4f	128	6	—	—	—
4g	—	—	—	—	—
Chloramphenicol	4	8	4	256	—
Gentamicin	0.125	0.5	0.5	1	—
Nystatin	—	—	—	—	8

and are compared with three commercial antibiotics, such as chloramphenicol, gentamicin and nystatin. Among them, only compound **4f** shows activity against *B. subtilis* and *S. aureus*.

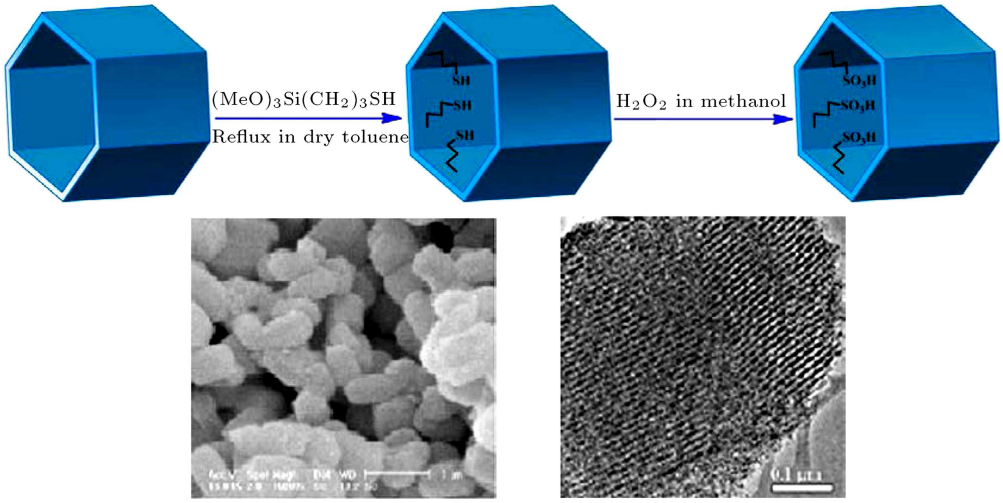
Table 6 illustrates the Minimum Inhibitory Concentration (MIC) of compounds that displays antibiotic activity in disc diffusion tests, which were also determined by the microdilution method [9] in compare with three commercial antibiotics: Chloramphenicol, Gentamicin and Nystatin.

2.3. Synthesis and functionalization of SBA-15

The synthesis and functionalization of SBA-15 were similar to our previous report, and the improved SBA-Pr-SO_3H was used as the nanoporous solid acid catalyst in the following reaction [31]. Triblock copolymer Pluronic P126 is used as directing agent in the preparation of SBA-15 as nanoporous silica [18]. Functionalization of SBA-15 is carried out with (3-mercaptopropyl) trimethoxysilane (MPTS), and thiol groups were oxidized to sulfonic acid by hydrogen peroxide (Scheme 3). Scheme 3 also illustrated the SEM and TEM images of SBA-Pr-SO_3H. The SEM image (Scheme 3 left) with uniform particles about 1 μm shows that during the surface modifications, the morphology of the solid was saved without change. Also, the TEM image (Scheme 3 right) with parallel pore channels demonstrates that the pore of SBA-Pr-SO_3H does not collapse during the two step reactions.

3. Experimental section

All chemicals employed in this work were purchased from the Merck Company and were used without any purification. IR spectra were recorded from a KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured using the capillary tube method with an electro thermal 9200 apparatus. Mass spectra data were obtained using the network mass selective detector (Agilent) 6890/5973 instrument. ^{1}H NMR spectra were run on a Bruker 400 MHz. SEM analysis was undertaken on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV, while TEM was performed on a Tecnai G2 F30 at 300 kV.



Scheme 3. Preparation of SBA-Pr-SO_3H and its SEM and TEM images.

3.1. General procedure for the synthesis of dihydropyrido[2,3-d]pyrimidine derivatives 4(a-h)

The SBA-Pr-SO_3H (0.02 g, 0.024 mmol H^+) was activated in a vacuum and then, after cooling to room temperature, a mixture of activated catalyst, 6-amino-1,3-dimethyl uracil (1 mmol), aromatic aldehydes (1 mmol), 1,3-dicarbonyl compounds (1 mmol) and CH_3CN (3 mL) was refluxed for an appropriate time. After completion of the reaction, which was monitored by TLC, the solid product was dissolved in hot ethanol. The catalyst is insoluble and could be removed by filtration. The pure products **4a-h** were obtained after cooling of the filtrates. The physical and spectral (IR, ^{1}H NMR and MS) data for new compounds are given below.

*Ethyl-5-(2,4-dichlorophenyl)-1,3,7-trimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (**4c**):*
Mp= 284-285°C. IR (ν_{max}, cm^{-1}) (KBr): 3351, 3216, 2954, 1702, 1675, 1594, 1554. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.05 (t, J = 6 Hz, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 4.33 (q, J = 6.1 Hz, 2H, CH_2), 5.56 (s, 1H, CH), 7.27 (dd, J = 2.4 Hz, J = 2.0 Hz, 1H, H arom), 7.34 (d, J = 8.4 Hz, 1H, H arom), 7.42 (d, J = 2.0 Hz, 1H, H arom), 7.49 (br. s, 1H, NH) ppm. Mass= 423 (M^+) (10), 412 (14), 368 (14), 312 (46), 276 (100), 219 (50), 155 (50), 57 (89).

*Ethyl-5-(2,3-dichlorophenyl)-1,3,7-trimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine-6-carboxylate (**4d**):*
Mp=288-290°C. IR (ν_{max}, cm^{-1}) (KBr): 3366, 3187, 2952, 1685, 1661, 1596, 1502. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.08 (t, J = 6.2 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 3.19 (s, 3H, CH_3),4.43 (q, J = 6.6 Hz, 2H, CH_2), 5.56 (s, 1H, CH), 7.23 (t, J = 8.0 Hz, 1H, H arom), 7.34 (d, J = 7.6 Hz, 1H, H arom), 7.43 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H, H arom), 7.48 (br. s, 1H, NH) ppm. Mass=423 (M^+) (10), 412 (17), 368 (25), 357 (25), 313 (32), 276 (100), 219 (42), 155 (42), 57 (92).

4. Conclusion

In conclusion, we have developed an efficient one-pot synthesis of dihydropyrido[2,3-*d*]pyrimidines derivatives using nano-SBA-Pr-SO_3H as a reusable and environmentally benign solid acid catalyst. Convenient work-up, reasonable reaction times, and good yield of product are the other features of this protocol. Compound **4f** displays antimicrobial activities against some fungi and gram positive and negative bacteria.

Acknowledgments

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