

# Covalently anchored sulfonic acid onto silica as an efficient and recoverable interphase catalyst for the synthesis of 3,4-dihydropyrimidinones/thiones

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Received 9 September 2006; received in revised form 18 October 2006; accepted 18 October 2006

Available online 24 October 2006

## Abstract

A novel covalently anchored sulfonic acid onto the surface of silica was prepared and investigated for the Biginelli reaction. The catalyst is highly stable, completely heterogeneous and recyclable for several times. The work-up procedure is very simple and Biginelli compounds were obtained in good to excellent yields.

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**Keywords:** Sulfonic acid functionalized silica; Biginelli reaction; Re-usable heterogeneous catalyst; Green procedure; Solid–liquid phase catalysis

## 1. Introduction

In recent years, there has been an increasing interest in developing greener processes [1]. In this context, heterogeneous catalysis [2] is emerging as an alternative to homogeneous processes since catalysts can be recovered after the reaction and re-used several times to achieve very high turn-over numbers. One strategy to transform a homogeneous into heterogeneous process is to anchor the active site onto a large surface solid carrier provided that the anchoring methodology maintains the intrinsic activity and selectivity of the catalytic center [3]. Among various solid supports, silica is usually preferred since it displays many advantageous properties—excellent stability (chemical and thermal), high surface area, good accessibility, and organic groups can be robustly anchored to the surface, to provide catalytic centers [3,4].

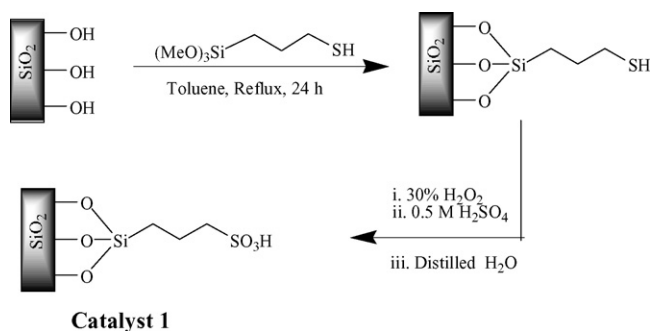
In recent years, attention has turned towards solid acid catalysts for catalyzing organic reactions [2c,5]. Recently, silica functionalized sulfonic acid as heterogeneous solid acid catalyst has been used to carry out variety of reactions [6].

Nowadays, there has been renewed interest in the three-component cyclocondensation of ethyl acetoacetate with

aromatic aldehydes and urea (or thiourea) discovered by Biginelli in 1893 [7]. 3,4-Dihydropyrimidinones and their sulfur analogs have been reported to possess diverse pharmacological properties such as antiviral, antibacterial, and antihypertensive, as well as efficacy as calcium channel modulators, and  $\alpha$ -1a-antagonists [8]. The batzelladine alkaloids containing the dihydropyrimidine unit are particularly notable, as they recently were found to be potent HIV gp-120-CD<sub>4</sub> inhibitors [9]. Therefore, the preparation of this heterocyclic core unit is under active investigation [10]. However, many of these reported methods suffer from drawbacks such as low yield of products, harsh reaction conditions, cumbersome experimental procedures, and use of moisture sensitive, toxic and costly catalysts. Therefore, there is a need to develop new catalysts which are easily available or prepared, cost-effective, recoverable and hence re-usable and environment-friendly. Moreover, the work-up procedure should be simpler.

Keeping in view the importance of Biginelli compounds and heterogeneous catalysis, we wish to report a mild and efficient method for the one-pot synthesis of 3,4-dihydropyrimidinones/thiones in the presence of catalytic amount of covalently anchored sulfonic acid onto silica gel under heterogeneous conditions. The preparation procedure for catalyst **1** is outlined in Scheme 1 with slight modification than the already reported method [6a].

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Scheme 1.

## 2. Experimental

### 2.1. General remarks

Silica gel (K100, 0.063–0.200 mm) was purchased from Merck (Germany) and 3-mercaptopropyltrimethoxy silane from Aldrich Chemical Company. All melting points were determined on a Perfit melting point apparatus and are uncorrected.  $^1\text{H}$  NMR spectra were registered on a Bruker DPX-200 NMR spectrometer (200 MHz) in  $\text{CDCl}_3 + \text{DMSO-}d_6/\text{DMSO-}d_6$  using tetramethylsilane as an internal standard and IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer using KBr discs. Mass spectral data was recorded on Jeol JMS D-300 mass spectrometer at 70 eV. Thermal analysis was carried out on DTG-60 Shimadzu make thermal analyzer. All yields refer to the isolated yields.

### 2.2. Synthesis of 3-mercaptopropylsilica (MPS)

Silica (K100, 0.063–0.200 mm) was activated by refluxing in a mixture of conc. HCl and distilled water (1:1) for 24 h and then washed thoroughly with distilled water and dried at  $110^\circ\text{C}$  for 12 h. The activated silica (10 g) was added to a solution of 3-mercaptopropyl(trimethoxy)silane (10 mmol) in dry toluene and refluxed for 24 h. The 3-mercaptopropyl silica (MPS) was filtered off, washed with hot toluene and dried at  $110^\circ\text{C}$  for 5 h to give the surface bound thiol (MPS) groups.

### 2.3. Synthesis of covalently anchored sulfonic acid onto silica gel (catalyst 1)

The mixture of 3-mercaptopropyl silica (MPS, 5 g), 30%  $\text{H}_2\text{O}_2$  solution (50 mL) and conc.  $\text{H}_2\text{SO}_4$  (0.078 g, 0.8 mmol) was stirred at room temperature for 20 h. The solid was filtered off at pump and washed with excess distilled water till the washing were neutral. In order to confirm that all the sulfonic acid groups are protonated, the solid material was further suspended in 0.05 M  $\text{H}_2\text{SO}_4$  (30 mL) for 5 h. The solid was then filtered off and washed with excess distilled water till washings were neutral. Finally it was dried in air at  $110^\circ\text{C}$  for 5 h.

### 2.4. General procedure for the synthesis of 3,4-dihydropyrimidinones/thiones

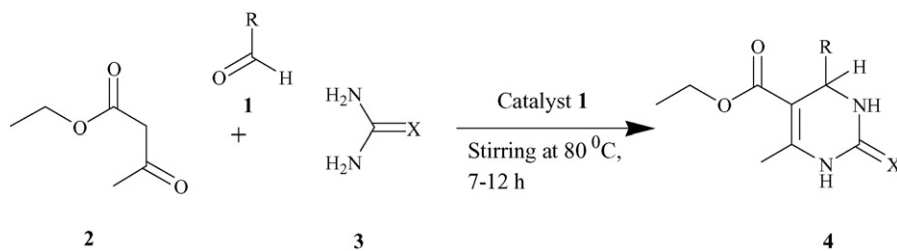
To a mixture of aldehyde **1** (2.5 mmol), ethyl acetoacetate **2** (2.5 mmol) and urea or thiourea **3** (2.5 mmol) in a round-

Table 1  
Covalently anchored sulfonic acid onto silica gel catalyzed synthesis of Biginelli compounds under heterogeneous conditions

Compound <sup>a</sup>	R	X	Time (h)	Yield (%) <sup>b</sup>
4a	$\text{C}_6\text{H}_5$	O	8	90
4b	4-MeOC <sub>6</sub> H <sub>4</sub>	O	7	92
4c	4-ClC <sub>6</sub> H <sub>4</sub>	O	7	93
4d	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	O	7	93
4e	4-(OH)-3-MeOC <sub>6</sub> H <sub>3</sub>	O	9.5	90
4f	2-Furfuryl	O	7.5	89
4g	Ph-CH=CH	O	9.5	87
4h		O	10	75
4i		O	12	62
4j	$\text{C}_6\text{H}_5$	S	7.5	88
4k	4-MeOC <sub>6</sub> H <sub>4</sub>	S	8	91
4l	4-ClC <sub>6</sub> H <sub>4</sub>	S	8	95
4m	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	S	8.5	92
4n	4-(OH)-3-MeOC <sub>6</sub> H <sub>4</sub>	S	10	88
4o	2-Furfuryl	S	8.5	90
4p	Ph-CH=CH-	S	9	92
4q		S	10.5	77
4r		S	12	65

<sup>a</sup> Structures of the products were confirmed by  $^1\text{H}$  NMR, IR, mass spectral data and comparison with authentic samples prepared according to the known procedures.

<sup>b</sup> Isolated yield from three experimental runs.



Scheme 2.

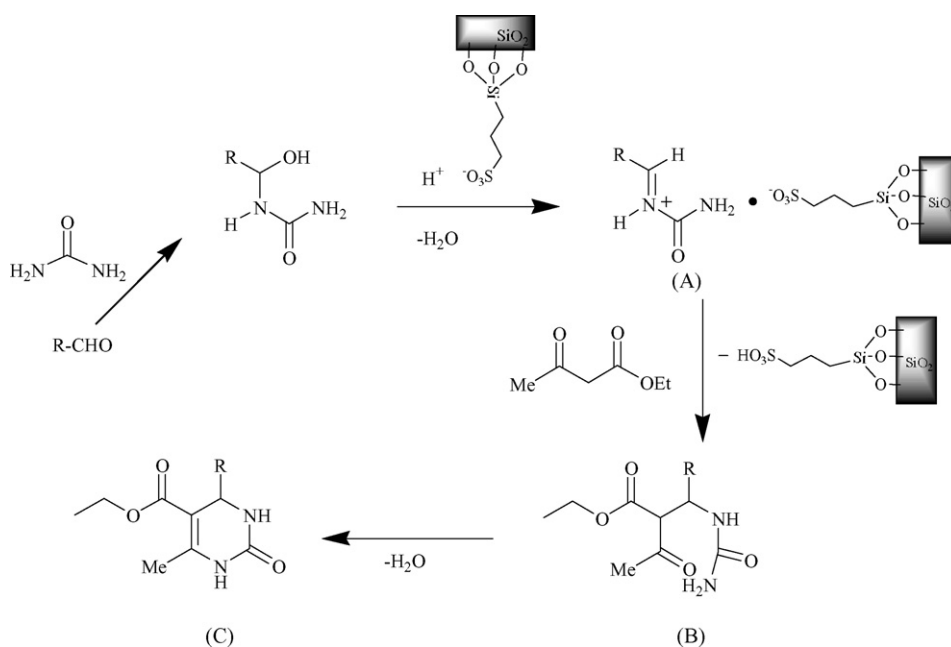
bottomed flask (100 mL), acetonitrile (15 mL) was added. The reaction mixture was stirred at RT for 5 min and then catalyst **1** (0.2 g, 2.4 mol% of  $\text{SO}_3\text{H}$ ) was added and the stirring was continued at  $80^\circ\text{C}$  in an oil-bath for an appropriate time (Table 1). After completion of the reaction (monitored by TLC), the reaction mixture was filtered off. The product was obtained after removal of the solvent under reduced pressure followed by treatment with water and finally crystallization from EtOH or EtOAc:pet. ether. The residue was washed with acetonitrile and distilled water, dried at  $110^\circ\text{C}$  for 3 h and re-used for eight times without loss of significant activity.

### 3. Results and discussion

The presence of covalently anchored organic functionality onto the surface of silica gel was determined by thermogravimetric analysis (TGA). The TGA curve shows the initial weight loss below  $100^\circ\text{C}$ , which was attributed to residual solvent or water molecules trapped into the silica gel framework, then the subsequent weight loss occurs between 240 and  $550^\circ\text{C}$ , which was because of the loss of organic functionalities covalently anchored onto the surface of silica gel. Typically, a loading of 0.3 mmol/g was obtained, which is based on the determination of sulfur content by the elemental analysis and acid–base titrations.

In order to achieve the optimum conditions, the reaction of *p*-anisaldehyde, ethyl acetoacetate and urea was selected as the model to examine the effects of catalyst **1** (1–5 mol%), different solvents (methylene chloride, toluene and acetonitrile) and reagents at different temperatures (RT: 60, 80 and  $100^\circ\text{C}$ ). The results were evaluated qualitatively through TLC. The best conditions employ 0.024:1:1 mole ratios of catalyst (2.4 mol% of  $\text{SO}_3\text{H}$ , 0.2 g of the catalyst), *p*-anisaldehyde, ethylacetoacetate and urea at  $80^\circ\text{C}$  for 7 h using acetonitrile as solvent.

Using optimized conditions, the reaction of various aromatic/heterocyclic aldehydes, ethyl acetoacetate and urea or thiourea were investigated (Scheme 2). It was found that all the reactions proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones in high yields (Table 1). Cinnamaldehyde, which showed poor yield in the absence of catalyst and 81% yield in the presence of very expensive lanthanide triflate [11], gave the corresponding pyrimidinones/thiones **4g** and **4p** in 87 and 92% yields, respectively. Both aromatic aldehydes bearing electron-donating groups such as 4-OMe (**4b**, 92%) and electron-withdrawing groups such as 4- $\text{NO}_2$  (**4d**, 93%) gave excellent yields. More importantly, 2-furfuraldehyde, which normally give low yield of products [12,13] afforded the desired products in 89 (**4f**) and 90% (**4o**) yields, respectively, in 7.5 and 8.5 h. 2-Chloro-3-formylquinoline also gave good yield



Scheme 3.

of products (**4i**, 62% and **4r**, 65%). The mildness of the procedure makes this procedure very selective as chlorine atoms in **4h**, **i**, **q** and **r** remain unaffected under the reaction conditions. The results are summarized in Table 1, which clearly indicates the generality and scope of the reaction with respect to various aromatic, heterocyclic and unsaturated aldehydes.

With catalyst **1**, the proposed mechanism for the Biginelli reaction involves the acid catalyzed formation of an *N*-acyliminium ion intermediate of the type **A** from aldehyde and urea component. Interception of the iminium ion **A** by ethyl acetoacetate produces an open chain ureide **B**, which subsequently cyclizes to dihydropyrimidinone **C** (Scheme 3).

When using a supported metal catalyst, two important issues need to be addressed to qualify this to be purely heterogeneous catalyst. One is the possibility that some active species migrates from the solid to the liquid phase and that this leached species would become responsible for a significant part of the catalytic activity. To rule out the contribution of the homogeneous catalysis in the results shown in Table 1, the reaction of *p*-anisaldehyde, ethyl acetoacetate and urea was carried out in the presence of catalyst **1** until the conversion was 40% (after 1 h) and at that point, the solid was filtered off at the reaction temperature. The liquid was then transferred to another flask and the reaction was continued for rest of the time, but no further significant formation of product was observed (Fig. 1). This indicates that no active species was present in the supernatant and that the observed catalysis is purely heterogeneous. The second important point concerning heterogeneous catalysis is the deactivation and re-usability of the catalyst. To test this, a series of eight consecutive runs of the reaction of *p*-anisaldehyde, ethyl acetoacetate and urea with catalyst **1** were carried out (Fig. 2). These results demonstrate that there is almost no significant change in the activity of the catalyst, so it can be used for eight times successfully leading to high turn-over numbers (TONs).

In order to verify that whether the reaction was catalyzed by catalyst **1** or with silica gel used for preparing the catalyst or no

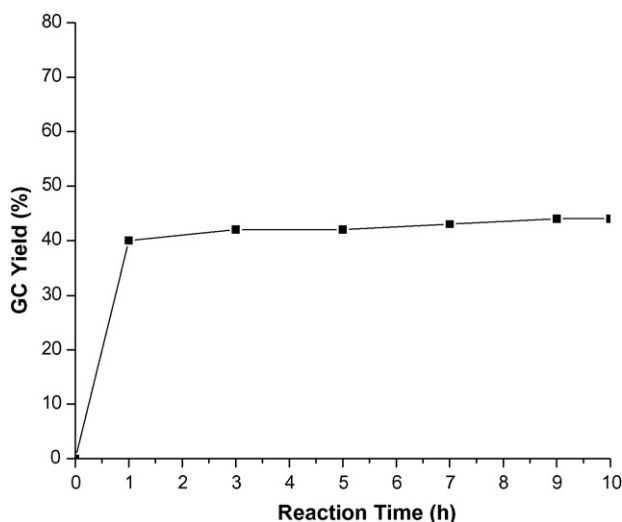


Fig. 1. Hot filtration test for catalyst **1** for the synthesis of **4b** from 4-methoxy benzaldehyde, ethyl acetoacetate and urea at 80 °C using acetonitrile as solvent.

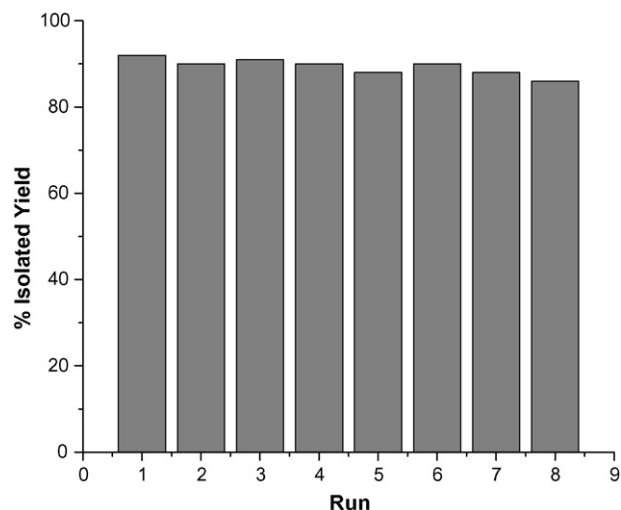


Fig. 2. Recyclability of catalyst **1** for the one-pot synthesis of **4b** from 4-methoxybenzaldehyde, ethyl acetoacetate and urea at 80 °C using acetonitrile as solvent.

catalyst was required, we have carried out the reaction (in case of product **4b**) without using any catalyst as well as using activated silica gel (0.2 g) under similar conditions as with catalyst **1**. It was found that **4b** was formed in traces when no catalyst was used (as observed on TLC) and 23% yield (based on <sup>1</sup>H NMR) when silica gel (0.2 g) was used as catalyst in 7 h.

### 3.1. Spectral data of ethyl 6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one-5-carboxylate (**4b**)

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.01–1.20 (t, 3H, *J* = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.30 (s, 3H, CH<sub>3</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 3.90–4.20 (q, 2H, *J* = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>), 5.60 (s, 1H, C4-H), 6.80–6.90 (d, 2H, *J* = 7.2 Hz, ArH), 7.15–7.25 (d, 2H, *J* = 7.2 Hz, ArH), 7.65 (bs, 1H, NH), 9.17 (bs, 1H, NH).

IR (KBr,  $\nu_{\max}$  in cm<sup>-1</sup>): 3390, 3243, 3106, 2958, 1706, 1651, 1278, 1088. *m/z* (%) = 290 (M<sup>+</sup>).

### 3.2. Spectral data of ethyl 6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one-5-carboxylate (**4d**)

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.05–1.20 (t, 3H, *J* = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.35 (s, 3H, CH<sub>3</sub>), 4.00–4.20 (q, 2H, *J* = 7 Hz, CH<sub>2</sub>CH<sub>3</sub>), 5.45 (s, 1H, C4-H), 7.40–7.60 (d, 2H, *J* = 7.2 Hz, ArH), 8.10–8.25 (d, 2H, *J* = 7.2 Hz, ArH), 7.69 (bs, 1H, NH), 9.27 (bs, 1H, NH).

IR (KBr,  $\nu_{\max}$  in cm<sup>-1</sup>): 3449, 3258, 3184, 3015, 1686, 1648, 1582. *m/z* (%) = 305 (M<sup>+</sup>).

### 3.3. Spectral data of ethyl 4-(2-chloro-3-quinolinyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one-5-carboxylate (**4i**)

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.95–1.15 (t, 3H, *J* = 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 3.95–4.15 (q, 2H, *J* = 7.1 Hz,

CH<sub>2</sub>CH<sub>3</sub>), 5.70 (s, 1H, C4-H), 7.60–7.90 (m, 3H, ArH), 8.04 (s, 1H, ArH), 8.30 (bs, 1H, NH), 9.35 (bs, 1H, NH).

IR (KBr,  $\nu_{\max}$  in cm<sup>-1</sup>): 3438, 3312, 3227, 2973, 1704, 1648, 1562, 1446. *m/z* (%) = 344 (M<sup>+</sup>).

### 3.4. Spectral data of ethyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxylate (4j)

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.02–1.18 (t, 3H, *J* = 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 4.02–4.21 (q, 2H, *J* = 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 5.50 (s, 1H, C4-H), 7.15–7.35 (m, 5H, ArH), 8.90 (bs, 1H, NH), 9.95 (bs, 1H, NH).

IR (KBr,  $\nu_{\max}$  in cm<sup>-1</sup>): 3412, 3312, 3174, 3096, 2967, 1667, 1610, 1575. *m/z* (%) = 276 (M<sup>+</sup>).

## 4. Conclusion

In conclusion, we have developed a mild, simple, cost-effective and green procedure for the synthesis of 3,4-dihydropyrimidinones/thiones using re-usable covalently anchored sulfonic acid onto the surface of silica gel solid acid catalyst under heterogeneous catalysis conditions. Moreover, the mild reaction conditions, high yield of products, ease of work-up, compatibility with various functional groups, and the ecologically clean procedure, will make the present method a useful and important addition to the present methodologies for the Biginelli synthesis.

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