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# Facile Knoevenagel condensation Using Sulfonic Acid Functionalized Nanoporous silica (SBA-Pr-$SO_3H$)

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**ABSTRACT**

Knoevenagel condensation between barbituric acid and aldehyde was investigated in the presence of sulfonic acid functionalized nanoporous silica (SBA-Pr-$SO_3H$) and resulted in the formation of arylidene and bis-arylidene barbiturates. Excellent yields and short reaction times are related to the high efficiency of SBA-Pr-$SO_3H$ that the reactions take place easily in its nano-pores. SBA-Pr-$SO_3H$ as an efficient heterogeneous nanoporous solid acid catalyst which was prepared by silica functionalization with (3-mercaptopropyl) trimethoxysilane followed by oxidation with $H_2O_2$, can be easily removed from the reaction mixture by simple filtration, and also recovered and reused without noticeable loss of reactivity.

**Keywords:** Arylidene barbiturates; Barbituric acid; Functionalized SBA-15; Heterogeneous acid catalyst; Knoevenagel condensation

## 1. INTRODUCTION

Barbituric acid is a strong organic acid, having a $pK_a$ =4.01 in water. It has got an "active" methylene group and can be involved in condensation reactions with aldehydes or ketones that do not contain an α-hydrogen [1]. The general type of this reaction is called the Knoevenagel condensation. Knoevenagel condensation is a facile and versatile method for the formation of carbon-carbon double bond like arylidene barbiturates [2]. Generally, the reaction is catalyzed by bases [3], ionic liquids [4], amino acids [5], basic MCM-41 silica [6], Na-SBA-1 [7], Ni-$SiO_2$ [8], and some acidic condition such as sulfuric acid [9] and PEG-$OSO_3H$ [10].

The derivatives of barbituric acid that are known as barbiturates have special places in pharmaceutical chemistry because of their biological activities in hypnotic, sedative, and anaesthetic drugs [11] and antitumor [12] and anticancer treatments [13]. Arylidene barbiturates have been reported to have various biological activities such as antimicrobial, antiurease, and antioxidant activities [14]. They may be synthesized by Knoevenagel condensation reaction of barbituric/thiobarbituric acid with various aldehydes. In this study,

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in continuation of our studies towards using nanoporous solid catalysts in organic reactions [15-18], we used a kind of solid acid catalyst, SBA-Pr-$SO_3H$, as a heterogeneous Bronsted acid with efficient and important advantages such as high surface area, great wall thickness, controllable and narrowly distributed pore size, and high thermal stability [19]. It was observed that SBA-Pr-$SO_3H$ improved the reaction condition to access arylidene barbiturates via Knoevenagel and bis Knoevenagel condensation reactions.

## 2. MATERIALS AND METHODS

The chemicals employed in this work were obtained from Merck Company (Germany) and used without further purifications. IR spectra were recorded from KBr disk using an FT-IR Bruker Tensor 27 instrument. Melting points were measured using the capillary tube method with an Electrothermal 9200 apparatus. GC-Mass analysis (Gas chromatography–mass spectrometry) was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 Agilent. SEM analysis was performed on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV, while TEM was carried out on a Tecnai $G_2$ F30 at 300 kV.

### *2.1. Preparation of catalyst*

According to our previous report [20], the nanoporous compound SBA-15 was synthesized and functionalized and the modified SBA-Pr-$SO_3H$ was used as a nanoporous solid acid catalyst in the following reaction.

### *2.2. General procedure for the preparation of bisarylidene barbiturate 4a-c*

A mixture of barbituric acid (2 mmol, 0.26 g), terephthalaldehyde (1 mmol, 0.13 g) and SBA-Pr-$SO_3H$ (0.02 g) was refluxed in water (4 mL) for the appropriated length of time, as mentioned in Table 2. After completion of the reaction, as indicated by TLC, the generated solid product was dissolved in hot dimethylformamide (DMF), filtered for removing the 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 reused several times without significant loss of activity.

### *2.3. General procedure for the preparation of arylidene barbiturate 5a-d*

A mixture of barbituric acid (1 mmol, 0.13 g), aldehyde (1 mmol) and SBA-Pr-$SO_3H$ (0.02 g) was refluxed in water (4 mL) for the appropriated length of time, as mentioned in Table 2. After completion of the reaction, as indicated by TLC, the generated solid product was dissolved in hot ethanol, filtered for removing the catalyst and then the filtrate was cooled to afford the pure product.

### *2.4. Spectral data of products*

5,5'-(1,4-Phenylenebis(methanylylidene))bis-(pyrimidin-2,4,6(1*H*,3*H*,5*H*)-trione) (**4a**)
IR (KBr, $cm^{-1}$): $\upsilon_{max}$= 3205, 3093, 1746, 1678, 1575, 1440, 1408, 1210, 815. MS (m/z (%)): 354 ($M^+$, 1.8), 319 (20), 312 (11), 55 (100).

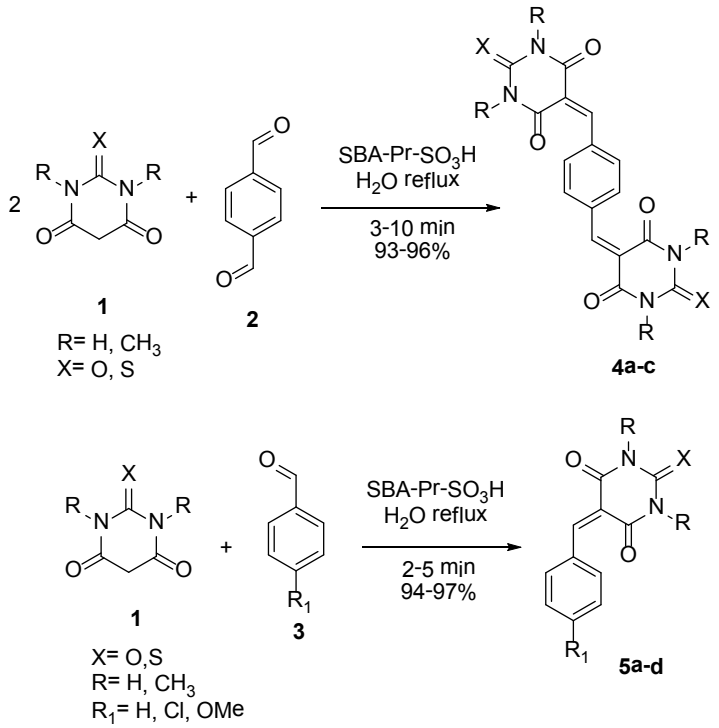
5,5'-(1,4-Phenylenebis(methanylylidene))bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (**4b**)
IR (KBr, $cm^{-1}$): $\upsilon_{max}$= 2960, 1675, 1538, 1457, 1424, 1378, 1087, 752.

5,5'-(1,4-Phenylenebis(methanylylidene))bis(2-thioxodihydropyrmidine-4,6(1*H*,5*H*)-dione) (**4c**)
IR (KBr, $cm^{-1}$): $\upsilon_{max}$= 3138, 2920, 1662, 1565, 1527, 1421, 1380, 1155, 521.

5-(4-Methoxyphenyl)methylenebarbituric acid (**5a**)
IR (KBr, $cm^{-1}$): $\upsilon_{max}$= 3208, 3069, 2922, 1729, 1674, 1601, 1548, 1508, 1460, 1435, 1400, 1346, 1306, 1269, 1211, 1179, 1080, 1048, 1013, 749, 518.

5-Phenylmethylene-1,3-dimethylbarbituric acid (**5b**)
IR (KBr, $cm^{-1}$): $\upsilon_{max}$= 3116, 3030, 2922, 2852, 1671, 1580, 1562, 1447, 1419, 1378, 1358, 1299, 1267, 1212, 1182, 1148, 1069, 831, 794, 771, 502.

5-(4-Chlorophenyl)methylenethiobarbituric acid (**5c**)
IR (KBr, $cm^{-1}$): $\upsilon_{max}$= 3108, 2921, 1626, 1564, 1491, 1442, 1383, 1330, 1286, 1206, 1140, 1092, 1012, 870, 831, 793, 529.




***Scheme 1:*** *Synthesis of arylidene and bis-arylidene barbiturates.*

5-(4-Methoxyphenyl)methylenethiobarbituric acid (**5d**)

IR (KBr, $cm^{-1}$): $\upsilon_{max}$= 3057, 2921, 1696, 1651, 1600, 1562, 1507, 1431, 1391, 1343, 1310, 1268, 1210, 1177, 1150, 1002, 871, 570.

## 3. RESULTS AND DISCUSSION

In this investigation, the synthesis of arylidene 5 and bis-arylidene barbiturates **4** from the condensation of barbituric acid derivatives **1** and aldehydes **2-3** in the presence of SBA-Pr-$SO_3H$ as a heterogeneous nano-catalyst under reflux condition was studied (Scheme 1).

In order to achieve optimum conditions, we initially investigated the reaction of barbituric acid **1** and terephthalaldehyde **2** as a model reaction under reflux conditions in acetic acid and $H_2O$ and solvent-free conditions. The best result was obtained under reflux conditions in water after **4** minutes with high yield (95%) in the presence of the optimum quantity of SBA-Pr-$SO_3H$ (0.02 g). As shown results in Table 1, the presence of the catalyst was found to give higher yield in shorter reaction time. This reaction condition was developed with three types of barbituric acids and four types of substituted aldehydes in a molar ratio of (2:1) and (1:1). Corresponding arylidene and bis-arylidene barbiturates were successfully prepared in 92-97%. It was observed that the nature of substituent

***Table 1:*** *The optimization of reaction condition in the synthesis of bis-arylidene barbiturate 4a[a].*

| Entry | Solvent | Temperature (°C) | Time (min) | Yield[b] (%) |
|---|---|---|---|---|
| 1[c] | $CH_3CO_2H$ | Reflux | 30 | 65 |
| 2 | $H_2O$ | Reflux | 4 | 95 |
| 3 | Neat | 70 °C | 90 | 85 |

*[a]Reaction conditions: barbituric acid (2 mmol), terephthalaldehyde (1 mmol), SBA-Pr-$SO_3H$ (0.02 g); [b]Isolated yield; [c]Catalyst free*

***Table 2:*** *SBA-Pr-$SO_3H$ catalyzed the synthesis of arylidene and bis-arylidene barbiturates.*

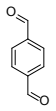
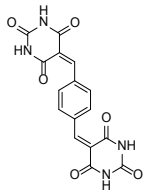
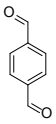
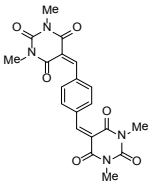
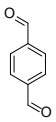
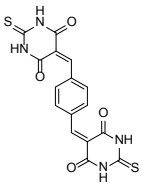
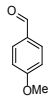
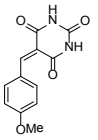
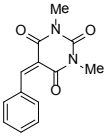
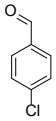
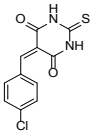
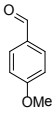
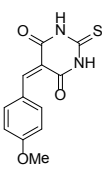
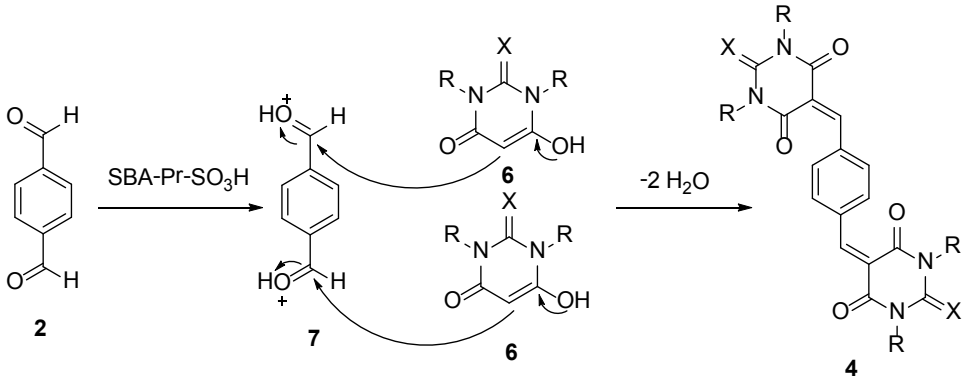
| Entry | X | R | Aldehyde | Product | Time (min) | Yield (%) | MP (°C) | MP (Lit.) |
|---|---|---|---|---|---|---|---|---|
| 1 | O | H |  |  4a | 4 | 94 | >300 | >300 [10] |
| 2 | O | Me |  |  4b | 3 | 96 | >300 | >300 [10] |
| 3 | S | H |  |  4c | 10 | 92 | >300 | >300 [10] |
| 4 | O | H |  |  5a | 2 | 95 | 283-285 | 276 [21] |
| 5 | O | Me |  |  5b | 4 | 94 | 156-157 | 159-160 [22] |
| 6 | S | H |  |  5c | 5 | 96 | 288-290 | 291-292 [23] |
| 7 | S | H |  |  5d | 5 | 97 | >300 | >300 [23] |

***Table 3:*** *Comparison of different conditions in the synthesis of bis-arylidene barbiturate 4a.*

| Entry | Catalyst | Solvent | Condition | Time (min) | Yield (%) | Year |
|---|---|---|---|---|---|---|
| 1 | $H_2SO_4$ | $CH_3CO_2H$ | Reflux | 60 | 93 | 2003 [9] |
| 2 | PEG-$OSO_3H$ | Neat | Stir. (70°C) | 3 | 97 | 2013 [10] |
| 3 | Lipase | EtOH | Stir. (40-45°) | 300 | 90 | 2013 [24] |
| 4 | SBA-Pr-$SO_3H$ | $H_2O$ | Reflux | 4 | 94 | This work |




***Scheme 2:*** *Plausible mechanism for synthesis of bis-arylidene barbiturates in the presence of SBA-Pr-$SO_3H$.*

on the aromatic ring of aldehydes did not affect the yield of desired products. The results are summarized in Table 2.

The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature; the resulting solid product of bis-arylidene barbiturate derivatives were dissolved in hot dimethylformamide (DMF) and arylidene barbiturate derivatives were dissolved in hot ethanol. After filtration of catalyst and cooling of the filtrate, the pure crystals were obtained. The catalyst was subsequently washed with diluted acid solution, distilled water and then acetone, dried under vacuum and re-used for several times without significant loss of activity. Table 3 illustrates a comparison of the effectiveness of various catalysts used in the synthesis of bis-arylidene barbiturate **4a**. It is clear from Table 3 that SBA-Pr-$SO_3H$ is one of the most efficient and less time-consuming catalysts, when compared with other existing methods.

The suggested mechanism for the SBA-Pr-$SO_3H$ catalyzed formation of the product **4** is shown in

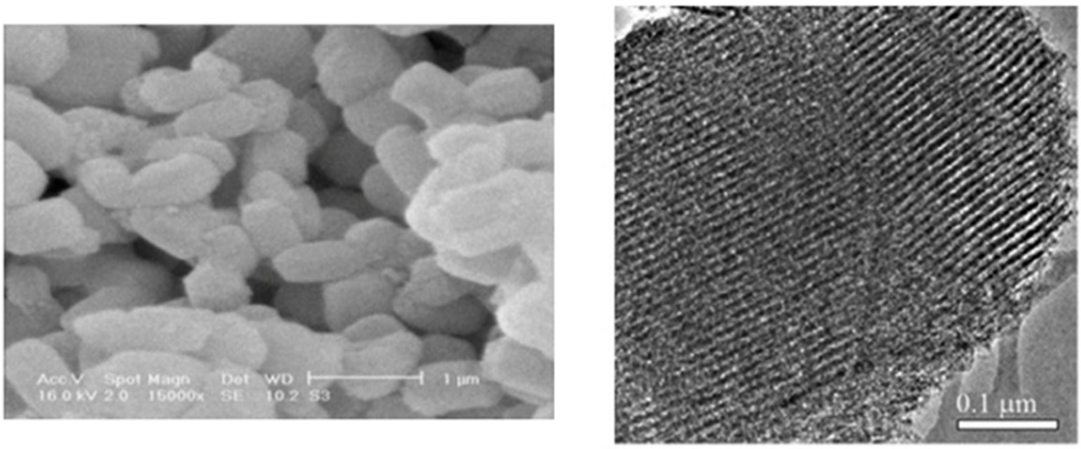



***Figure 1:*** *SEM image (left) and TEM image (right) of SBA-Pr-$SO_3H$.*

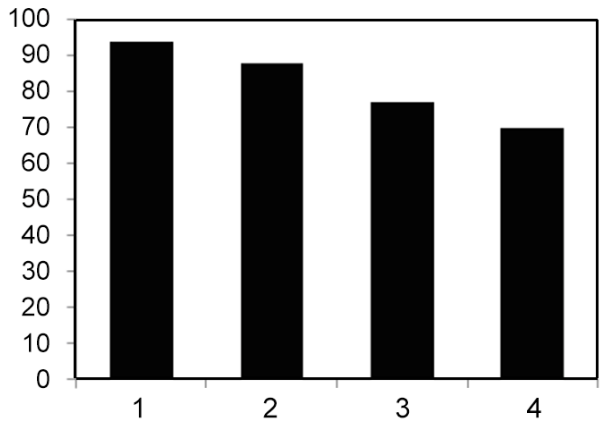



***Figure 2:*** *Reusability of SBA-Pr-$SO_3H$ in the synthesis of compound 4a.*

Scheme 2. Protonation of a carbonyl group of terephthalaldehyde **2** by the solid acid catalyst activates it toward nucleophilic attack of barbituric acid **6**. Subsequently elimination of water affords the corresponding bis-arylidene barbiturates **4** (Scheme 2). It is interesting that the reaction easily occurs in water although the mechanism involves a net dehydration. It was proposed that water helps the dissociation of thiobarbituric acid due to its high ε value, 78, which generates the nucleophilic species being able to attack the carbonium of the aldehyde [23].

Figure 1 shows the SEM and TEM images of SBA-Pr-$SO_3H$. SEM image (Figure 1, left) illustrates uniform particles about 1 μm which the same morphology was observed for SBA-15 and TEM image (Figure 1, right) demonstrated parallel channels, that resemble the pore configurations of SBA-15. The reusability of the catalyst was investigated under optimized conditions for the synthesis of the model compound **4a**. As it is shown in Figure 2, 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 94%, 88%, 77%, and 70%, respectively.

## 4. CONCLUSIONS

In summary, we have described a simple and efficient procedure for the synthesis of arylidene barbiturate derivatives using SBA-Pr-$SO_3H$ as a catalyst via Knoevenagel condensation reaction of barbituric acid and aldehydes in excellent yield. The advantages offered by using SBA-Pr-$SO_3H$ as a nano heterogeneous catalyst in this reaction are compatibility, reusability, high selectivity, and non-corrosiveness. This method provides desired products in short reaction times and high yields together with use of water as the solvent under green conditions.

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