Biginelli Multicomponent Condensation Reaction Promoted by 4,4ʹ-Bipyridinium Dichloride Ordered Mesoporous Silica Nanocomposite under Solvent Free Conditions

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In this paper, 4,4ʹ-bipyridinium dichloride supported SBA-15 (SBA@BiPy₂⁺₂Cl⁻) was used for the synthesis of dihydropyrimidinones. The synthesized catalyst was characterized by FT-IR spectroscopy, scanning electron microscopy (SEM), Transmission electron microscopy (TEM) and Thermogravimetric analysis (TGA). This nanocomposite was shown to be an efficient heterogeneous catalyst for the synthesis of dihydropyrimidinones derivatives via one-pot multicomponent method under solvent-free conditions. In addition, the catalyst can be recycled several times with no significant loss of catalytic activity.

Keywords: Organic-inorganic hybrid nanocomposite, Dicationic 4,4ʹ-bipyridine silica hybrid nanocomposite, Mesoporous silica, Dihydropyrimidinones

INTRODUCTION

Mesoporous silicate materials have gained an increased attention in the past decades owing to their interesting properties that include tunable pore sizes, stabilities and shape selectivity [1]. These materials have been extensively employed in a range of applications including adsorption, catalysis, support and advanced materials [2].

Among these materials, ordered mesoporous silicas such as SBA-15 and its functionalized family have received considerable interest due to their potential applications such as adsorbents and host-guest chemical supports for large organic molecules [2]. However, the nature of the neutral framework of SBA-15 with few lacuna, poor ion-exchange ability and lack of active sites, limits its applications in catalysis [3]. In this context, very recently, organized hybrid xerogel mesoporous materials, where the organic component is bonded to a polymeric silica framework, have attracted significant attention due to their outstanding properties [4,5].

Green chemistry has attracted considerable attention to overcome the problem pertaining to the environmental pollution being encountered by the global population. In this context, Multi-component reactions (MCRs) under solvent free conditions are gaining more and more attention from organic, medicinal and synthetic chemists especially in the total synthesis of natural products, and medicinal heterocyclic compounds [6].

The Biginelli reaction is one of the fundamental one-pot three-component cyclocondensation strategies for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones(-thiones) (DHPMs). In the past decade, dihydropyrimidinones (DHPMs) and their derivatives attracted considerable interest due to their wide spectra of biological activities [7-10]. Different catalysts have been proposed to catalyze this reaction including: HCl/MeOH [11], [BMim][PF₆] [12], HBF₄ [13], Nafion-H resin/EtOH [14], SmCl₃.6H₂O/Montmorillonite clay [15], CdCl₂/MeCN [16], SbCl₅/MeCN...
[17]. Most of these methods have drawbacks such as long reaction times, harsh reaction conditions and unsatisfactory yields. Thus, novel methodologies which could overcome these disadvantages are still needed.

We report herein the preparation and characterization of dicationic 4,4′-bipyridinium dichloride ordered mesoporous silica nanocomposite as a new organic-inorganic hybrid catalyst. The catalytic activity of this new heterogeneous catalyst was tested by the synthesis of dihydropyrimidinones under solvent-free conditions (Scheme 1).

**EXPERIMENTAL**

**General**

All commercially available chemicals were purchased from Fluka and Merck companies and used without further purification. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ on a Bruker Advanced DPX 400 MHz spectrometer using TMS as internal standard. Reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. The SEM analyses were carried out using a LEO 1455VP Scanning Electron Microscope, operating at 1-30 KV.

**Preparation of Bis(n-propyltriethoxysilane) Bipyridinium Chloride, BPTBC**

In a 25 ml three-neck round-bottom flask, bipyridine (8 mmol, 1.25 g) was added to DMF (5 ml), and stirred to make a clear solution. To this solution, (3-chloropropyl)triethoxy silane (16 mmol, 3.18 g) was added dropwise; and the mixture was stirred at 90 °C for 72 h under argon atmosphere. Afterwards, the white solid, BPTBC, was filtered and washed with methanol. This solid was dried for 2 h in an oven at 90 °C.

**Preparation of the Organic-inorganic Hybrid Nanocomposite, SBA@BiPy$^{2+}$2Cl$^-$.**

In a 110 ml round-bottom flask, Pluronic 123 (2.0 g, 0.344 mmol, $M_n = 5800$) was dissolved in HCl 2 M (62.5 ml) at room temperature. To the solution, tetraethyl orthosilicate (TEOS) (4.2 g, 20 mmol) and BPTBC (0.65 g, 1.0 mmol) was added and the mixture stirred at 40 °C for 20 h. The mixture was left to stand unstirred at 95 °C for 24 h. The resulting solid was filtered and washed with excess water and left on the filter paper overnight to dry. The dried solid was then soxhlet extracted with ethanol (400 ml per 1.5 g) for 48 h, to remove Pluronic 123. The obtained solid was repeatedly washed with ethanol and water and dried at 50 °C for 24 h.

![Scheme 1. One-pot preparation of dihydropyrimidinones derivatives](image_url)
Typical Procedure for the Preparation of 4-Dihydropyrimidin-2(1H)-ones(-thiones)

A mixture of ethyl acetoacetate/acetyl acetone (2.3 mmol), urea/thiourea (3-5 mmol), aromatic aldehyde (1 mmol), and SBA@BiPy2+ 2Cl− (0.005 g) was heated at 110 °C. Completion of the reaction was indicated by TLC [TLC acetone/n-hexane (3:10)]. After completion of the reaction the insoluble crude product was dissolved in hot ethanol and the catalyst filtered. The crude product was purified by recrystallization in ethanol to afford the pure product.

Selected Spectra of some Representative Compounds

5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one, White solid, m.p.: 207-209 °C; IR (KBr): ν [cm⁻¹] 3230, 3120, 1730, 1710, 1650; ¹H NMR (DMSO-d₆) δ (ppm): 1.11 (t, J = 7.5 Hz, 3H), 2.29 (s, 3H), 4.00 (q, J = 7.5 Hz, 2H), 5.29 (d, J = 3.0 Hz, 1H), 7.51 (d, J = 10 Hz, 2H), 7.91 (br s, 1H), 8.23 (d, J = 8.7 Hz, 2H, arom CH), 9.37 (s, 1H, NH).

5-Ethoxycarbonyl-6-methyl-(4-p-tolyl)-3,4-dihydropyrimidin-2(1H)-one, White solid, m.p.: 233-236 °C; IR (KBr): ν [cm⁻¹] 3329, 3152, 1691, 1562, 1232, 1051, 783; ¹H NMR (DMSO-d₆) δ (ppm): 1.12 (t, J = 7.5 Hz, 3H), 2.28, 2.30 (s, 3H), 4.00 (q, J = 7.5 Hz, 2H), 5.11 (d, J = 3.0 Hz, 1H), 7.25 (m, 4H), 7.70 (br s, 1H, NH), 9.19 (br s, 1H, NH).

5-Ethoxycarbonyl-6-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-on, White solid, m.p.: 215-218 °C; IR (KBr): ν [cm⁻¹] 3220, 3100, 1720, 1700; ¹H NMR (DMSO-d₆) δ (ppm): 1.10 (t, J = 7.2, 3H), 22 (s, 3H), 3.96 (q, J = 7.2, 2H), 5.02 (s, J = 3.2, 1H), 6.64 (d, J = 8.4, 2H), 7.02 (d, J = 8.4, 2H), 7.57 (s, 1H), 9.07 (s, 1H).

RESULTS AND DISCUSSION

Following our interest to introduce organic units into the framework of the ordered mesoporous silica [18-19], very recently we reported, preparation of SBA@BiPy2+ 2Cl− and investigate its application as heterogeneous catalyst for the preparation of 1H-Pyrazolo[1,2-b]phthalazine-5,10-dione derivatives [20]. At first, (N-N’-bis(triethoxysilylpropyl)-4,4’-bipyridinium dichloride precursor (BPTBC) was synthesized by the reaction of 3-chloropropyltriethoxysilane with 4,4’-bipyridine. The organic-inorganic hybrid nanocomposite, SBA@BiPy2+ 2Cl−, was then synthesized by hydrolysis and polycondensation of the precursor and tetraethylothsilicate under mild acidic conditions in the presence of poly(ethyleneoxide)-b-poly(propyleneoxide)-b-poly(ethylene-oxide), Pluronic P123, (Scheme 2). The processes are the self-assembly of the amphiphilic surfactant P123 serving as template, the interaction at the interface between P123 and mixture of TEOS and (TEOS); BiPy2+ 2Cl−, and the sol-gel process that introduce 4,4’-bipyridine into the framework of the ordered mesoporous silica.

The SBA@BiPy2+ 2Cl− catalyst was characterized by various techniques. In order to confirm the incorporation of bipyridinium moiety into the framework of the ordered mesoporous silica, FT-IR spectroscopy was utilized. As it is apparent from Fig. 1, in the FT-IR spectrum of SBA@BiPy2+ 2Cl− two bands at 807 and 1100 cm⁻¹ are observed which are ascribed to the asymmetrical and symmetrical vibrations of the Si-O-Si bonds and the band at about 960 cm⁻¹ is assigned to the Si-OH bond. Meanwhile a broad peak is obvious at 3417 cm⁻¹ which is relevant to stretching vibration of hydroxyl groups on the silica surface.

Thermal stability of the catalyst has a great effect on its catalytic activity and recyclability. The TGA of SBA@BiPy2+ 2Cl− was recorded by heating the sample at the rate of 10 °C min⁻¹ under nitrogen atmosphere (Fig. 2). The TGA curve shows that the first weight loss occurs before 100 °C, which was assigned to the release of adsorbed water; representing approximately 0.18 g g⁻¹ of the sample. The second weight loss is concentrated in the range of 300-700 °C, resulting from the decomposition of the organic parts of framework during hydrothermal treatment. The weight losses of the organic parts are 0.19 g g⁻¹ of the sample. Therefore, the nanocatalyst is completely stable below 300 °C and can be applied without degradation.

The morphology of SBA-15 and SBA@BiPy2+ 2Cl− were studied by SEM and TEM. The SEM images (Fig. 3) shows...
a dominant lengthy rod-like morphology for SBA@BiPy\textsuperscript{2+} 2Cl\textsuperscript{-}, in a bundle arrangement with a diameter of approximately 0.6 µm (Fig. 3b). The same morphology is observed for SBA-15 (Fig. 3a). The TEM image of SBA@BiPy\textsuperscript{2+} 2Cl\textsuperscript{-} are presented in Fig. 4, indicating that the mesoporous structure of SBA-15 has not been destroyed while introducing of organic part into the framework of SBA. It should be also mentioned that, the characteristic XRD pattern of SBA@BiPy\textsuperscript{2+} 2Cl\textsuperscript{-} was observed (Fig. 5). In addition, the presence of organic parts in framework was also confirmed by CHN analysis (14.51, 3.23, 3.62 for C, H, N, respectively).

After qualification of the catalyst, it was decided to evaluate the catalytic activity of SBA@BiPy\textsuperscript{2+} 2Cl\textsuperscript{-} in preparation of 3,4-dihydropyrimidin-2(1\textit{H})-ones(-thiones), so-called Biginelli reaction. A model of three-component coupling reaction of ethyl acetoacetate, urea and benzaldehyde under solvent-free conditions at 110 °C in the absence and presence of SBA@BiPy\textsuperscript{2+} 2Cl\textsuperscript{-} (0.005-0.03) was examined (Table 2).

![Scheme 2. Preparation of SBA@BiPy\textsuperscript{2+} 2Cl\textsuperscript{-}](image_url)
Fig. 1. The FT-IR spectrum of the synthesized mesoporous SBA@BiPy\textsuperscript{2+} 2Cl\textsuperscript{-}.

Fig. 2. The TGA curve of SBA@BiPy\textsuperscript{2+} 2Cl\textsuperscript{-}.
Fig. 3. SEM images of (a) SBA and (b) SBA@BiPy$^{2+}$ 2Cl$^-$.  

Fig. 4. TEM image of SBA@BiPy$^{2+}$ 2Cl$^-$. 
Fig. 5. XRD pattern of SBA@BiPy\(^{2+}\)2Cl\(^-\).

Table 1. Specific Surface Area (S\(\text{BET}\)), Diameter Pore and Total Pore Volume

<table>
<thead>
<tr>
<th>Sample</th>
<th>BET surface area (m(^2) g(^{-1}))</th>
<th>Diameter (nm)</th>
<th>Pore volume (cm(^3) g(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBA@BiPy(^{2+})2Cl(^-)</td>
<td>339</td>
<td>6.18</td>
<td>0.3</td>
</tr>
</tbody>
</table>
It was found out that 0.005 g of the catalyst shows maximum yield in minimum time. Next, the effect of temperature was evaluated. It was observed that the reaction did not proceed at low temperatures. We were fortunate to find that the reaction proceeded effectively, and almost complete conversion of product was observed at 110 °C, affording 3,4-dihydropyrimidin-2(1H)-ones in 90% yield within shorter time (Table 2, Entry 7).

Subsequently, with optimal conditions in hand, 1:1:3 molar ratios of aromatic aldehyde, ethyl acetoacetate and urea and 0.005 g of SBA@BiPy$^{2+}$2Cl at 110 °C under solvent-free conditions, the synthetic scope of this procedure was demonstrated by synthesizing a series of 3,4-dihydropyrimidin-2(1H)-ones (Table 3). Gratifyingly, a wide range of aromatic aldehydes were well tolerated under the optimized reaction conditions. We were greatly surprised to obtain the same results with the substitution of urea with thiourea due to their therapeutic potential. The time taken for complete conversion (monitored by TLC) and the isolated yields are recorded in Table 3. All the compounds were characterized by comparison of their physical and spectral data with those of the authentic ones. In the same way, it was decided to substitute ethyl acetoacetate with acetyl acetone, under the same optimal conditions at 110 °C under solvent-free conditions (Table 4).

To demonstrate the superiority of SBA@BiPy$^{2+}$2Cl over the reported catalysts, the reaction of benaldehyde, acetyl

<p>| Table 2. Optimum Conditions for the Three-Component Condensation Reaction of Bezaldehyde (1 mmol), Ethyl Acetoacetate, Urea under Thermal Solvent-Free Conditions |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Entry</th>
<th>Ethyl acetoacetate (mmol)</th>
<th>Urea (mmol)</th>
<th>Catalyst (g)</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>1.0</td>
<td>0.03</td>
<td>100</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>2.0</td>
<td>0.03</td>
<td>100</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>2.3</td>
<td>3.0</td>
<td>0.005</td>
<td>60</td>
<td>180</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>2.3</td>
<td>3.0</td>
<td>0.005</td>
<td>90</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>2.3</td>
<td>1.0</td>
<td>0.005</td>
<td>110</td>
<td>90</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>2.3</td>
<td>1.5</td>
<td>0.005</td>
<td>110</td>
<td>34</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>3.0</td>
<td>0.005</td>
<td>110</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>2.3</td>
<td>5.0</td>
<td>-</td>
<td>110</td>
<td>45</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>2.3</td>
<td>5.0</td>
<td>0.01</td>
<td>110</td>
<td>23</td>
<td>91</td>
</tr>
</tbody>
</table>
acetone or ethyl acetoacetate with urea was considered as a representative example (Table 3/Table 4). While in some of these cases comparative yields of the desired product were obtained following the SBA@BiPy$^{2+}$ 2Cl$^{-}$-catalyzed procedure (except entry 3, 4, 5), all of the reported procedures required long reaction time (except for entry 1, 2), or high catalyst loading (entry 3, 4). These results clearly demonstrate that SBA@BiPy$^{2+}$ 2Cl$^{-}$ is an equally or more efficient catalyst for this reaction.

**CONCLUSIONS**

In summary, we have described a simple and facile protocol for the synthesis of 3,4-dihydropyrimidin-2(1H)-

**Table 3. The One-Pot Three-Component Condensation Reaction of Aromatic Aldehydes (1 mmol), Ethyl Acetoacetate (2.3 mmol), and Urea (3 mmol)/Thiourea (5 mmol) Promoted by SBA@BiPy$^{2+}$ 2Cl$^{-}$ (0.005 g) under Solvent-Free Conditions at 110 °C**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituted benzaldehyde</th>
<th>Urea/thiourea</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Urea</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>4-NO$_2$</td>
<td>Urea</td>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>4-CH$_3$</td>
<td>Urea</td>
<td>37</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>4-OCH$_3$</td>
<td>Urea</td>
<td>37</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>4-Cl</td>
<td>Urea</td>
<td>25</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>3-OCH$_3$</td>
<td>Urea</td>
<td>35</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>Thiourea</td>
<td>45</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>4-CH$_3$</td>
<td>Thiourea</td>
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<td>87</td>
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<tr>
<td>9</td>
<td>4-NO$_2$</td>
<td>Thiourea</td>
<td>37</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>4-OCH$_3$</td>
<td>Thiourea</td>
<td>47</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>3-OCH$_3$</td>
<td>Thiourea</td>
<td>45</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>4-Cl</td>
<td>Thiourea</td>
<td>40</td>
<td>89</td>
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</table>
### Table 4. The One-Pot Three-Component Condensation Reaction of Aromatic Aldehydes (1 mmol), Acetyl Acetone (2.3 mmol), and Urea (3 mmol)/Thiourea (5 mmol) Promoted by SBA@BiPy$^{2+}$2Cl$^-$ (0.005 g) under Solvent-Free Conditions at 110 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituted Benzaldehyde</th>
<th>Urea/thiourea</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Urea</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>4-NO$_2$</td>
<td>Urea</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>4-CH$_3$</td>
<td>Urea</td>
<td>30</td>
<td>85</td>
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<tr>
<td>4</td>
<td>4-OCH$_3$</td>
<td>Urea</td>
<td>32</td>
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<td>4-Cl</td>
<td>Thiourea</td>
<td>35</td>
<td>87</td>
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### Table 5. Comparison of the Reaction of Benzaldehyde, Acetyl Acetone or Ethyl Acetoacetate with Urea

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>1</td>
<td>BMImBF$_4$/0.4 mol%</td>
<td>0.5</td>
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<td>[12]</td>
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<tr>
<td>2</td>
<td>HBF$_4$/10 mol%</td>
<td>0.58</td>
<td>95</td>
<td>[13]</td>
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<tr>
<td>3</td>
<td>Nafion-H/100 wt%</td>
<td>10</td>
<td>70</td>
<td>[14]</td>
</tr>
<tr>
<td>4</td>
<td>SbCl$_3$/20 mol%</td>
<td>20</td>
<td>77</td>
<td>[16]</td>
</tr>
<tr>
<td>5</td>
<td>H$_2$SO$_4$/0.5 ml</td>
<td>12</td>
<td>55</td>
<td>[17]</td>
</tr>
<tr>
<td>6</td>
<td>SBA@BiPy$^{2+}$2Cl$/0.005$ g</td>
<td>0.5</td>
<td>90</td>
<td>This work</td>
</tr>
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</table>
ones(-thiones) derivatives, using as a novel environmentally safe heterogeneous catalyst under solvent-free conditions. The method offers several advantages including high yields, application of an inexpensive catalyst, short reaction times, easy workup and performing multicomponent reaction under solvent-free conditions that is considered to be relatively environmentally benign.

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REFERENCES