A Green Multicomponent One-pot Synthesis of 9, 10-Diaryl-7H-benzo[d,e]imidazo[2,1-a]isoquinolin-7-one Derivatives using Nanoporous Base Silica (SBA-Pr-NH2) as Catalyst

Ghodsi Mohammadi Ziarani1,*, Alireza Badiei2, Parvin Hajiabbas Tabar Amiri1, Negar Lashgari2

1Department of Chemistry, Alzahra University, Vanak Square, Tehran, Iran
2School of Chemistry, College of Science, University of Tehran, Tehran, Iran

ARTICLE INFO

Article History:
Received 07 October 2018
Accepted 20 December 2018
Published 01 January 2019

Keywords:
Amino-Functionalized Silica
Functionalized SBA-15
Fused Imidazoles
Green Synthesis
Heterogeneous Catalyst

ABSTRACT

Organic-inorganic hybrid mesoporous materials such as amino functionalized silica (SBA-Pr-NH2) have received considerable attention due to their basic catalytic applications and adsorption functions. In this work, we investigated the efficient role of SBA-Pr-NH2 as a heterogeneous nano catalyst in the synthesis of 9,10-diaryl-7H-benzo[d,e]imidazo[2,1-a] isoquinolin-7-one derivatives. Application of SBA-Pr-NH2 as an eco-friendly and reusable catalyst resulted in reducing reaction time and temperature in this method. The preparation method was developed using a green one-pot three-component reaction of acenaphthoquinone, benzils and ammonium acetate under solvent-free condition. Besides, the synthesis of benzil derivatives as starting material was carried out. The new compounds were characterized by IR, mass, and NMR spectroscopy. The significant merits of this protocol are its simplicity, short reaction times, low reaction temperature, catalyst reusability, and non-chromatographic purification of products. Also, imidazole and benzimidazole moieties represent significant substructures of a wide variety of bioactive compounds and also significant structural motifs in biological systems, natural products, and drugs.

INTRODUCTION

The SBA-15 (SBA = Santa Barbara Amorphous) mesoporous silica with high specific surface area, great pore wall thickness, large pore size, and high thermal stability is a unique inorganic solid support [1]. Surface modification of mesoporous materials has a significant role in the employment of these materials in many interesting applications [2, 3]. Recently, organic-inorganic hybrid mesoporous materials such as amino functionalized nanoporous silica (SBA-Pr-NH2) have received considerable attention with regard to applications as excellent adsorbents and heterogeneous catalysts [4-6]. Moreover, amino-functionalized mesoporous silica SBA-15 materials were found to be beneficial as support for drug delivery systems [7] and enzyme immobilization [8], absorbent for removal of heavy metals [9] and finally spacer for further chemical modifications [10].

Imidazole and benzimidazole derivatives are an important class of N-containing heterocyclic organic compounds that found to possess various biological and pharmacological properties [11] such as antibacterial [12], anti-inflammatory [13], antimalarial [14], and cyclin-dependent kinase inhibitors [15]. They are also common structural motifs in marine natural products that represent key moieties responsible for observed biological activities [16, 17]. Despite their importance from...
pharmacological point of view, with a broad range of applications in many different fields, imidazoles have drawn a great deal of interest. They are used in photography as photosensitive compounds [18] and as fluorescent emitting materials for organic light-emitting diodes (OLEDs) [19, 20].

As part of our program for applying heterogeneous solid catalysts to multicomponent reactions [21-26], in this work, we investigate the effective role of SBA-Pr-NH₂ as a nano base catalyst in the synthesis of fused imidazoles, 9,10-diaryl-7H-benzo[d,e]imidazo[2,1-a]isoquinolin-7-one derivatives from the three-component reaction of acenaphthoquinone, benzils, and ammonium acetate (Fig. 1). To the best of our knowledge, there is only one report for the synthesis of these compounds through the heating a mixture of acenaphthoquinone, a benzil, and ammonium acetate under solvent-free conditions which resulted in the formation of 7H-benzo[d,e]imidazo[2,1-a]isoquinolin-7-ones in 3 h and at 200 °C and the products were purified by column chromatography [27]. Herein, application of SBA-Pr-NH₂ as an eco-friendly and reusable catalyst resulted in reducing reaction time and temperature in this method.

MATERIALS AND METHODS

All chemicals were obtained commercially and used without further purification. IR spectra were established from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured using the capillary tube method with an Electrothermal 9200 apparatus. The 1H NMR and 13C NMR (300 MHZ and 100 MHz) were run on a Bruker DPX using TMS as an internal standard (CDCl₃ solution). Gas chromatography-mass spectrometry (GC-MS) analysis was performed on an Agilent 6890-5973 GC/MS detector.

Nitrogen adsorption-desorption isotherms were recorded at -196 °C using a BELSORP-mini II. All samples were degassed at 100 °C for 3 h under vacuum and argon gas flow before analysis. The specific surface area (S_{BET}) was evaluated using the Brunauer-Emmett-Teller (BET) equation, and the pore size distribution (D_{BJH}) was measured from the desorption branches by means of the Barret-Joyner-Halenda (BJH) model, with the pore volume being taken at P/P₀ = 0.995. Transmission electron microscopy (TEM) analysis was obtained on a Tecnai G₂ F30 at 300 kV.

SBA-15 nanoporous silica: Synthesis and functionalization

The nanoporous compound SBA-15 was synthesized and functionalized according to our previous report [28].

General procedure for the preparation of benzil compounds (2c-2e) [29]

In the first step, benzadehyde (47.5 mL, 0.47 mol) and a solution of 5 g sodium cyanide (96%) were refluxed in water (50 mL) for 4 h. The reaction mixture was cooled in iced water, and then the crude benzoin was obtained after filtering and washing with cold water. In the second step, 20 g benzoin was heated with concentrated nitric acid (100 mL) on the water-bath until the evolution of nitrogen oxides from the stirring mixture was ceased. After pouring the reaction mixture into the cold water benzil crystals (2c-e) were obtained and recrystallized in ethanol.

General procedure for the preparation of products (4a-h)

The SBA-Pr-NH₂ (0.02 g) was activated in vacuum at 100 °C to remove any surface humidity and then

![Fig. 1. Synthesis of 9,10-diaryl-7H-benzo[d,e]imidazo[2,1-a]isoquinolin-7-ones in the presence of SBA-Pr-NH₂ as a nano-reactor.](image-url)
was cooled to room temperature. A mixture of acenaphthoquinone (1 mmol), benzils (1 mmol), and ammonium acetate (2 mmol) was added to the catalyst under solvent-free condition, and the resulting mixture was stirred at 100 °C for 15-40 min. Upon completion of the reaction (monitored by TLC), the resulting solid product was dissolved in dimethyl formamide (DMF), and was filtered for removing the unsolvable catalyst and then the filtrate was cooled and crystallized. In addition, the recovered catalyst could be washed sequentially with diluted aqueous Et3N solution, water, and acetone to reuse without any noticeable loss in reactivity.

**Selected spectral data**

**9,10-Bis(2,6-dimethoxyphenyl)-7H-benzo[d,e]imidazo[2,1-a]isoquinolin-7-one (4f)**

Yellow crystals (yield 66%); mp: 253-254 °C. IR (KBr, ν_{max} (cm⁻¹)): 3061, 2925, 2855, 1719 (C=O), 1595, 1305, 1013, 830, 776. ^1H NMR (300 MHz, CDCl₃): δ 3.83 (s, 3H, OMe), 3.84 (s, 3H, OMe), 7.81-7.83 (m, 5H, Ar-H), 8.03 (d, J = 7.0, 3H, Ar-H), 8.24-8.27 (4H, Ar-H), 8.54 (d, J = 7.3, 2H, Ar-H). ^13C NMR (100 MHz, CDCl₃): δ 59.8 (OMe), 60.6 (OMe), 120.0, 123.8, 124.1, 125.3, 125.8, 126.1, 128.3, 129.0, 129.4, 129.6, 130.9, 131.1, 132.5, 132.9, 142.8, 143.3, 143.5, 151.9, 152.6, 160.8 (C=O). Ei-MS: 432 (M⁺), 344, 198, 182, 154, 126, 74, 63, 50.

**9,10-Bis(2,6-dimethoxyphenyl)-7H-benzo[d,e]imidazo[2,1-a]isoquinolin-7-one (4g)**

Yellow crystals (yield 76%); mp: 300 °C. IR (KBr, ν_{max} (cm⁻¹)): 3053, 2924, 2854, 1723 (C=O), 1586, 1305, 1124, 1012, 776. ^1H NMR (300 MHz, CDCl₃): δ 7.83-7.91 (m, 4H, Ar-H), 8.14 (d, J = 7.0, 2H, Ar-H), 8.30-8.36 (m, 4H, Ar-H), 8.65 (d, J = 7.3, 2H, Ar-H). ^13C NMR (100 MHz, CDCl₃): δ 120.2, 120.5, 123.5, 124.3, 126.1, 126.4, 128.2, 129.1, 129.6, 129.9, 130.8, 131.1, 132.0, 142.1, 142.6, 142.9, 150.2, 151.4, 160.3 (C=O). Ei-MS: 508 (M⁺), 344, 198, 182, 154, 126, 98, 74, 50.

**9,10-Bis(2,6-dichlorophenyl)-7H-benzo[d,e]imidazo[2,1-a]isoquinolin-7-one (4h)**

Yellow crystals (yield 81%); mp: 255-256 °C. IR (KBr, ν_{max} (cm⁻¹)): 3051, 2923, 1718 (C=O), 1598, 1304, 1013, 830, 756. ^1H NMR (300 MHz, CDCl₃): δ 7.82-7.90 (m, 4H, Ar-H), 8.12 (d, J = 7.0, 3H, Ar-H), 7.29-8.36 (m, 4H, Ar-H), 8.36 (d, J = 7.3, 1H, Ar-H). ^13C NMR (100 MHz, CDCl₃): δ 122.8, 123.6, 124.5, 126.6, 126.8, 126.9, 128.3, 129.2, 129.5, 129.9, 130.6, 131.0, 132.2, 132.5, 142.2, 142.4, 142.8, 150.8, 151.0, 160.6 (C=O). Ei-MS: 508 (M⁺), 475, 391, 369, 344, 293, 216, 154, 126, 105, 77, 57.

**Fig. 2. Synthesis of 9,10-diaryl-7H-benzo[d,e]imidazo[2,1-a]isoquinolin-7-one derivatives 4a-h in the presence of SBA-Pr-NH₂.**
125.5, 126.1, 128.0, 129.2, 129.3, 129.5, 131.0, 131.4, 131.9, 132.4, 132.6, 141.3, 141.6, 146.3, 146.9, 150.4, 160.5 (C=O). EI-MS: 462 (M⁺), 340, 293, 218, 172, 154, 126, 105, 77, 57.

RESULTS AND DISCUSSION

A green one-pot synthesis of 9,10-diaryl-7H-benzo[de]imidazo[2,1-a]isoquinolin-7-one derivatives 4 was performed by the reaction of acenaphthoquinone 1, various benzils 2, and ammonium acetate 3 in the presence of SBA-Pr-NH₂ as a heterogeneous base catalyst (Fig. 2). The goals of this study were: (1) using a suitable heterogeneous base catalyst in a multicomponent reaction, (2) illustration of this heterogeneous catalyst efficiency, and (3) applying the present catalytic system in the synthesis of a variety of fused imidazoles.

In order to optimize the reaction condition, various solvents such as CH₃CN, H₂O, EtOH, DMF, and also solvent-free system were studied for the synthesis of 9,10-diaryl-7H-benzo[de]imidazo[2,1-a]isoquinolin-7-ones (Table 1). It was found that solvent-free condition is the most effective system for the reaction of acenaphthoquinone 1, benzil 2 and ammonium acetate 3 which affords the desired product 4a in higher yield (87%) within 15 min at 100 °C in the presence of SBA-Pr-NH₂ (Table 1, entry 7).

After completion of the reaction (monitored by TLC), the crude product was dissolved in hot DMF, the heterogeneous solid catalyst was simply

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Catalyst</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>Reflux</td>
<td>SBA-Pr-NH₂</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>Reflux</td>
<td>SBA-Pr-NH₂</td>
<td>2 h</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>Reflux</td>
<td>SBA-Pr-NH₂</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>rt.</td>
<td>SBA-Pr-NH₂</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>Reflux</td>
<td>SBA-Pr-NH₂</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>rt.</td>
<td>SBA-Pr-NH₂</td>
<td>2 h</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>Solvent free</td>
<td>100</td>
<td>SBA-Pr-NH₂</td>
<td>15</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>Solvent free</td>
<td>200</td>
<td>-</td>
<td>3 h</td>
<td>92 [27]</td>
</tr>
</tbody>
</table>

Table 2. Synthesis of 9,10-diaryl-7H-benzo[de]imidazo[2,1-a]isoquinolin-7-one derivatives in the presence of SBA-Pr-NH₂.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>mp [Lit]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>4a</td>
<td>15</td>
<td>87</td>
<td>&gt;300</td>
<td>&gt;300 [27]</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl</td>
<td>4b</td>
<td>25</td>
<td>85</td>
<td>&gt;300</td>
<td>&gt;300 [27]</td>
</tr>
<tr>
<td>3</td>
<td>4-OMe</td>
<td>4c</td>
<td>30</td>
<td>66</td>
<td>253-254</td>
<td>Not reported</td>
</tr>
<tr>
<td>4</td>
<td>4-Me</td>
<td>4d</td>
<td>25</td>
<td>65</td>
<td>&gt;300</td>
<td>&gt;300 [27]</td>
</tr>
<tr>
<td>5</td>
<td>3-OMe</td>
<td>4e</td>
<td>25</td>
<td>68</td>
<td>248-250</td>
<td>Not reported</td>
</tr>
<tr>
<td>6</td>
<td>2,3-Cl₂</td>
<td>4f</td>
<td>35</td>
<td>76</td>
<td>&gt;300</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>2,6-Cl₂</td>
<td>4g</td>
<td>35</td>
<td>81</td>
<td>255-256</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>3-NO₂</td>
<td>4h</td>
<td>40</td>
<td>79</td>
<td>&gt;300</td>
<td>-</td>
</tr>
</tbody>
</table>

Fig. 3. The proposed mechanism.
removed by filtration, and after cooling of the filtrate during the time, the pure yellow crystals were obtained. The catalyst can be reactivated, and then reused without considerable loss of reactivity. The new compounds were characterized by IR, mass, and NMR spectroscopy. The desired products were illustrated in Table 2.

The proposed mechanism for the synthesis of the fused imidazoles 4a-h starts by crucial role of SBA-Pr-NH₂ in activating ammonium acetate as the source of ammonia. The condensation of benzil 2 and ammonium acetate 3 is occurred by releasing two water molecules to form imine intermediate 6, which subsequently is condensed with carbonyl group of acenaphthoquinone 1 to form the intermediate 7. Finally, a ring opening-ring closure occurs to form target compounds 4a-h, as illustrated in Fig. 3.

Synthesis of benzil derivatives was performed at the first step by condensation of aromatic aldehydes treated with an alkali sodium cyanide in aqueous solution to prepare α-hydroxy ketone or benzoin 9. In the second step, oxidation of benzoin was performed in the presence of nitric acid to afford benzil derivatives 2c-2e (Fig. 4). The results are summarized in Table 3.

The characterization of the nanocatalyst by different techniques such as N₂ adsorption-desorption isotherm, XRD, FT-IR spectra, and TEM image was discussed in our previous reports [28, 32]. For example, three textural parameters of SBA-15 and SBA-Pr-NH₂, including specific surface area (BET method), total pore volume, and pore diameter (BJH method) are provided in Table 4. A decrease in pore size and BET surface area, as well as pore volume are apparently indicative of the successful attachment of organic moieties within the mesopores of SBA-15.

Fig. 5 displays the low-angle XRD patterns of SBA-15 and SBA-Pr-NH₂. There were three well-resolved reflections for SBA-Pr-NH₂ similar to that for SBA-15 which demonstrates that functionalized samples possess mesoordered two-dimensional hexagonal structures.

The TGA analysis of SBA-Pr-NH₂ (Fig. 6) confirmed the amount of grafted organic groups

**Fig. 4. Synthesis of benzil derivatives.**

![Fig. 4. Synthesis of benzil derivatives.](image)

**Table 3. Preparation of various synthetic benzil compounds (2c-e).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Product</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-OMe</td>
<td>2c</td>
<td>81</td>
<td>131-133 [30]</td>
</tr>
<tr>
<td>2</td>
<td>4-Me</td>
<td>2d</td>
<td>80</td>
<td>100-102 [30]</td>
</tr>
<tr>
<td>3</td>
<td>3-OMe</td>
<td>2e</td>
<td>85</td>
<td>81-82 [31]</td>
</tr>
</tbody>
</table>

**Fig. 5. Low-angle XRD patterns of SBA-15 and SBA-Pr-NH₂.**

![Fig. 5. Low-angle XRD patterns of SBA-15 and SBA-Pr-NH₂.](image)

**Fig. 6. Thermogravimetric analysis (TGA) of SBA-Pr-NH₂.**

![Fig. 6. Thermogravimetric analysis (TGA) of SBA-Pr-NH₂.](image)
Table 4. Characteristics of the synthesized materials derived from nitrogen adsorption-desorption.

<table>
<thead>
<tr>
<th>Sample</th>
<th>( S_{BET}(\text{m}^2/\text{g}) )</th>
<th>( V_{total}(\text{cm}^3/\text{g}) )</th>
<th>( D_{BJH}(\text{nm}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBA-15</td>
<td>481</td>
<td>1.3</td>
<td>5.9</td>
</tr>
<tr>
<td>SBA-Pr-NH₂</td>
<td>356</td>
<td>1.0</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Fig. 7. TEM image of SBA-Pr-NH₂.

The TEM image was employed to directly visualize the pore geometry of SBA-Pr-NH₂ (Fig. 7). The TEM image reveals parallel channels resembling the configuration of the pores of SBA-15. This indicates that the pores of SBA-Pr-NH₂ have not been collapsed during the functionalization reaction.

Finally, the recovered catalyst could be washed sequentially with diluted aqueous Et₃N solution, water, and acetone to reuse without any noticeable loss in reactivity. Reusability of the catalyst was evaluated under optimized conditions for the preparation of the model compound 4a. As illustrated in Fig. 8, the process of recycling was completed four times with no significant decrease in the activity of the catalyst. The yields for the four runs were established to be 87, 81, 77, and 72%, respectively.

CONCLUSIONS

In summary, we have successfully synthesized 9,10-diaryl-7H-benzo[\(d,e\)]imidazo[2,1-\(a\)]isoquinolin-7-one derivatives in the presence of amino functionalized nanoporous silica (SBA-Pr-NH₂) as an efficient catalyst under solvent-free conditions. The attractive features of this protocol are simple method, short reaction times, low reaction temperature, simple workup, and non-chromatographic purification of products. Catalyst reusability and ease of recovery makes this method a benign, economic and waste-free chemical procedure.

ACKNOWLEDGEMENTS

We gratefully acknowledge the financial support from the Research Council of Alzahra University and University of Tehran.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES


