**Friedländer Synthesis of Substituted Quinolines Using an Efficient and Reusable Brønsted Acid Ionic Liquid Supported on Fe₃O₄@SiO₂ Nanoparticles under Solvent-free Conditions**

M. Fallah-Mehrjadi⁶,⁎ and S. Kalantari⁴

⁶Department of Chemistry, Payame Noor University (PNU), P. O. Box: 19395-3697, Tehran, Iran

⁷Research Center of Environmental Chemistry, Payame Noor University, Anak, Yazd, Iran

(Received 18 September 2019, Accepted 1 January 2020)

In this study, a highly efficient and recyclable Brønsted acid ionic liquid, 1-methyl-3-(3-triethoxysilylpropyl)-1H-imidazol-3-ium hydrogensulfate, immobilized on the surface of Fe₃O₄@SiO₂ (MNP-IL-HSO₄) was prepared and characterized. Then, the catalytic activity of this nanomagnetic catalyst was investigated in the Friedländer synthesis of substituted quinolines through the cyclocondensation reaction of α-aminoaryl ketones with α-methylene carbonyl compounds under the solvent-free conditions. The present protocol has several advantages, including short reaction times, high yield of products, simplicity in operation, simple work-up and reusability of the catalyst.

**Keywords:** Magnetic nanoparticles, Supported ionic liquids, Quinolines, Friedländer synthesis, Solvent-free conditions

**INTRODUCTION**

Ionic liquids (ILs) have attracted much attention from many areas of chemistry. These liquids have several properties, such as low melting point, insignificant vapor pressure, low coordinating ability, and excellent thermal and chemical stability, which make them attractive alternatives to usual organic solvents in a wide range of chemical processes [1]. One of the most commonly used ionic liquid cations is based on imidazolium species that have shown a great catalytic activity and received a remarkable interest as eco-friendly catalyst in organic reactions [2]. However, they suffer from high viscosity causing that only a minor part of ILs takes part in the catalyzed reaction, and also because of their homogeneous nature, the recoverability of ILs from the final reaction product is not considerable [3]. The immobilization of ILs into solid supports is one of the main solutions for these disadvantages [4-8]. Some drawbacks of homogeneous ILs such as high cost, low hydrothermal stability, and undesirable catalyst recyclability have hindered their catalytic applications. So, it is very desirable to develop a new support to immobilize ionic liquids.

Nowadays, magnetic nanoparticles (MNPs) due to their large ratio of surface to volume, low cost, facile synthesis, easy fictionalization, and simple separation have been developed as a prominent catalyst support [9]. Because of their advantages, in recent years, magnetic nanoparticles, especially ferrite nanoparticles, have been utilized to immobilize homogeneous ionic liquids. The nanomagnetic supported ILs combines the benefits of ILs and heterogeneous catalysis, such as the design ability, good solubility of the catalytically active species, ease of handling, separation, and recycling [10].

Quinoline and its derivatives are an important class of nitrogen-containing heterocyclic compounds exhibiting potential biological and pharmaceutical activities [11]. These compounds act as an antibacterial [12], antiparasitic [13], anti-asthmatic [14], anticancer [15], antifilarial [16], anti-inflammatory [17], anti-hypertensive [18], anti-platelet [19], antitubercular [20], and antifungal [21]. Among the various procedures reported for the synthesis of quinolines [22-27], the Friedländer heteroannulation is still the simplest and most common method for the synthesis of poly-substituted quinolines [27]. The Friedländer synthesis
involves a condensation reaction between an $\alpha$-aminoaryl ketone and a carbonyl compound containing $\alpha$-methylene group followed by a cyclodehydration reaction. This procedure has been catalyzed by several catalysts such as bases, Brønsted and Lewis acids, nanomaterials, ionic liquids, etc. [28].

Herein, we report a versatile procedure for the synthesis of substituted quinolines through the cyclocondensation of $\alpha$-aminoaryl ketones with $\alpha$-methylene carbonyl compounds catalyzed by 1-methyl-3-(3-triethoxysilylpropyl)-1H-imidazol-3-ium hydrogensulfate immobilized on the surface of Fe$_3$O$_4$@SiO$_2$ (MNP-IL-HSO$_4$) as an efficient and magnetically recyclable Brønsted acid ionic liquid under solvent-free conditions (Scheme 1).

**EXPERIMENTAL**

**General**

All of the commercially available chemicals were purchased from Merck, Fluka and Aldrich and used without further purification. Fe$_3$O$_4$, Fe$_3$O$_4$@SiO$_2$ and MNP-IL-HSO$_4$ were prepared according to the reported procedures [29-31]. All of the products were characterized for their physical properties and by comparison with authentic samples. The reactions were monitored by TLC on silica gel polygram SILG/UV 254 plates. Melting points were obtained in open capillary tubes and were measured with an electrothermal 9200 apparatus. The infrared (IR) spectra were recorded on KBr Pellets on a Shimadzu IRPrestiging-21 spectrophotometer in the range of 4000-400 cm$^{-1}$. The NMR spectra were recorded in DMSO-$d_6$ on a Bruker Advanced DPX 400 MHz spectrometer using TMS as an internal reference.

**General Procedure for the Preparation of Catalyst**

First, a mixture of 1-methylimidazole (0.82 g, 10 mmol) and 3-chloropropyltriethoxysilane (2.41 g, 10 mmol) was stirred at 80 °C for 72 h under N$_2$ atmosphere. The resulting viscous yellowish liquid was washed with diethyl ether (3 × 5 ml) to remove any unreacted material. The resulting product was dried under high vacuum. Next, the suspension of Fe$_3$O$_4$@SiO$_2$ nanoparticles (1 g) in CHCl$_3$ (30 ml) was dispersed under ultrasonic irradiation for 1 h, and 1-methyl-3-(3-triethoxysilylpropyl)-1H-imidazol-3-ium chloride (0.28 g, 1 mmol) was then added and the reaction was stirred under nitrogen and refluxed conditions for 48 h. The product was collected magnetically, washed three times with CHCl$_3$ and dried at 60 °C in a vacuum oven. Finally, for exchanging the Cl$^-$ anion, MNP-IL-Cl (1 g) was suspended in dry CH$_2$Cl$_2$ (20 ml). During vigorous stirring, concentrated H$_2$SO$_4$ (0.07 ml, 1.3 mmol) was introduced drop by drop at 0 °C. Then, the mixture was warmed up to the room temperature and refluxed for 48 h. The mixture was cooled, filtered, and dried to give supported hydrogensulfate ionic liquid on Fe$_3$O$_4$@SiO$_2$ nanoparticles.

**General Procedure for the Synthesis of Quinolines**

A mixture of 2-aminobenzophenone or 2-amino-5-chlorobenzophenone (1 mmol), $\alpha$-methylene carbonyl compounds (1.2 mmol) and MNP-IL-HSO$_4$ (0.025 g) was heated in an oil bath at 110 °C under solvent-free conditions for the times shown in Table 2. After the reaction completion, as indicated by TLC ($n$-hexane:EtOAc, 3:1) and cooling, hot ethanol (3 ml) was added to the mixture and stirred for 5 min. The catalyst was removed in the presence of a magnet and the desired product was isolated and purified by recrystallization from EtOH. All products are
and spectroscopic data (IR, NMR) with those of the authentic samples [32-40].

Selected Spectroscopic Data

Ethyl 2-methyl-4-phenylquinoline-3-carboxylate (3a). M. p.: 93-95 °C; IR (KBr): $\tilde{\nu}$ (cm$^{-1}$) = 3059, 2978, 1724, 1611, 1566, 1485, 1230, 1064, 702 (Fig. S1); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm) 1.03 (t, 3H, $J = 6.3$ Hz), 2.79 (s, 3H), 4.23-4.31 (q, 2H, $J = 6.3$ Hz), 7.40-7.45 (m, 2H), 7.48-7.51 (m, 1H), 7.55-7.59 (m, 3H), 7.65 (m, 1H), 7.82-7.87 (m, 1H), 8.27 (m, 1H) (Fig. S2); 13C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 14.5, 148.1, 153.7, 154.8, 167.2 (Fig. S3).

7-Chloro-3,3-dimethyl-9-phenyl-3,4-dihydro-2H-acridin-1-one (3h). M. p.: 209-212 °C; IR (KBr): $\tilde{\nu}$ (cm$^{-1}$) = 3075, 2954, 2870, 1693, 1600, 1554, 1481, 1215, 987, 698 (Fig. S4); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm) 1.12 (s, 6H), 2.58 (s, 2H), 3.22 (s, 2H), 7.14-7.17 (m, 2H), 7.44 (m, 1H), 7.50-7.52 (m, 3H), 7.66-7.68 (m, 1H), 7.99-8.02 (m, 1H) (Fig. S5); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 28.3, 32.3, 48.3, 54.2, 123.3, 126.7, 127.9, 128.1, 128.4, 130.5, 132.3, 132.7, 136.7, 147.9, 150.1, 154.3, 161.5, 197.9 (Fig. S6).
RESULTS AND DISCUSSION

The Brønsted acid ionic liquid supported on magnetic nanoparticles (MNP-IL-HSO₄) was prepared as shown in Scheme 2. The Fe₃O₄ nanoparticles were easily prepared by the co-precipitation method of FeCl₂ and FeCl₃ in ammonia solution. The MNPs surface was successfully coated with silica by the ammonia-catalyzed hydrolysis of tetraethylorthosilicate (TEOS) to produce Fe₃O₄@SiO₂ core-shell nanoparticles. The reaction between 1-methylimidazole and 3-chloropropyltriethoxysilane at 80 °C resulted in the production of ionic liquid, 1-methyl-3-(3-triethoxysilylpropyl)-1H-imidazol-3-iium chloride. The ionic liquid was supported on the surface of Fe₃O₄@SiO₂ nanoparticles via the treatment of hydroxyl groups on the surface of MNPs and organosilane group of ionic liquid. Ultimately, ion exchange of chloride anions with HSO₄⁻ was performed by adding H₂SO₄.

The catalyst was characterized by FT-IR, SEM, EDAX, VSM, XRD and TGA. The FT-IR spectra of Fe₃O₄, Fe₃O₄@SiO₂ and MNP-IL-HSO₄ are shown in Fig. 1. The FT-IR spectrum of Fe₃O₄ (Fig. 1a) displays a strong absorption band at low wave numbers (578 cm⁻¹) due to Fe-O vibration and a broad band at 3200-3600 cm⁻¹ which is attributed to the surface -OH groups. The FT-IR spectrum of Fe₃O₄@SiO₂ (Fig. 1b) shows three additional absorption bands around 460 cm⁻¹, 980 cm⁻¹ and 1080 cm⁻¹ which are related to Si-O-Si bending, symmetric stretching and
asymmetric stretching vibrations, respectively. These peaks confirm the existence of a silica coating around the Fe₃O₄ magnetic nanoparticles. The introduction of linker to the surface of Fe₃O₄@SiO₂ was confirmed by the C-H bending and stretching bands at 1400-1500 cm⁻¹ and 2850-2950 cm⁻¹, respectively. In addition, the band around 1600 cm⁻¹ was assigned to the imidazole C=N bending and imidazole ring stretching vibrations (Fig. 1c).

The morphological characterization of MNP-IL-HSO₄ and particle size distribution were evaluated by measuring SEM using a Philips XL30 scanning electron microscope. As shown in Fig. 2, MNP-IL-HSO₄ has spherical shape with nano dimension ranging 20-30 nm.

The data from EDAX analysis are consistent with our expectations and confirm the presence of carbon, nitrogen, oxygen, iron, silica and sulfur in MNP-IL-HSO₄ (Fig. 3).

The magnetic property of the catalyst was studied by vibrating sample magnetometer (VSM) as shown in Fig. 4. As can be seen from the diagrams, the saturation magnetization value decreases from 42 emu g⁻¹ in Fe₃O₄@SiO₂ to about 27 emu g⁻¹ in the case of MNP-IL-HSO₄. This decrease is due to the coating of nonmagnetic ionic liquid over magnetic nanoparticles.

The crystalline structure of MNP-IL-HSO₄ nanoparticles was studied in the 2θ region of 0-80°, exhibiting peaks at 30.26° (30.31°), 35.63° (35.69°), 43.39° (43.32°), 53.72° (53.81°), 57.33° (57.26°) and 62.85° (62.92°), which closely matches with the corresponding Fe₃O₄ pattern (shown in
The thermogravimetric analysis (TGA) of MNP-IL-\(\text{HSO}_4\) was investigated by raising its temperature at the rate of 10 °C min\(^{-1}\) in air up to 600 °C to analyze its thermal decomposition behavior (Fig. 6). Three main stages of weight loss are observed. The first small weight loss at below 130 °C (~2%) are assigned to removal of physically adsorbed water as well as dehydration of the surface OH groups. The major weight losses in the region of 130-250 °C (~8%) and 250-430 °C (~7%) are probably due to decomposition of organic groups. The curve shows a weight loss about 17% from 130 to 430 °C, resulting from the decomposition of organic spacer grafting to the magnetite surface.

After preparation and characterization of the MNP-IL-\(\text{HSO}_4\) nanoparticles, their catalytic activity was explored in the cyclocondensation reaction of \(o\)-aminobenzophenone with ethyl acetoacetate under various reaction conditions (Table 1). The results revealed that the reaction did not proceed in various polar and non-polar solvents under reflux conditions and gave the best results under solvent-free conditions at 110 °C. Also, the results showed that the reaction did not proceed in the absence of the catalyst and the best results were obtained in the presence of 0.025 g of catalyst. Using a higher amount of catalyst did not have a discernible impact on the yield or the rate of the reaction.

The generality of this procedure for the synthesis of various substituted quinolines was demonstrated through the condensation reaction of various 1,3-dicarbonyl compounds with \(o\)-aminoaryl ketones in the presence of MNP-IL-\(\text{HSO}_4\) under the optimal conditions (Table 2). As shown in Table 2, various 1,3-dicarbonyl compounds including ethyl acetoacetate and acetylacetone, cyclic \(\beta\)-diketones such as 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) reacted with 2-aminobenzophenone and 2-amino-5-chlorobenzophenone to give the corresponding
substituted quinolines without any side products (Table 2, Entries 1-8). Interestingly, cyclic ketones such as cyclohexanone and cycloheptanone also reacted with 2-aminoaryl ketones to afford the respective tricyclic quinolines in good yields (Table 2, Entries 9-11).

The recyclability and reusability of the MNP-IL-HSO₄ nanocatalyst were tested in the cyclocondensation of o-aminobenzophenone with dimeredone under solvent-free conditions at 110 °C. After the reaction completion (20 min.), hot ethanol was added and MNP-IL-HSO₄ nanocatalyst was separated magnetically using external magnet from the reaction mixture and washed thoroughly with ethanol and acetone followed by drying in vacuum oven at 60 °C and then reused in another catalytic cycle. We found that the catalyst is magnetically recoverable and reused without any appreciable loss in catalytic activity for at least five consecutive catalytic cycles (Fig. 7).

Comparison of the catalytic efficiency of MNP-IL-HSO₄ in the condensation reaction between 2-aminobenzophenone and dimeredone with some of methods reported in the

![VSM magnetization curves of Fe₃O₄@SiO₂ (Left) and MNP-IL-HSO₄ (Right).](image-url)
Fig. 5. XRD patterns of Fe$_3$O$_4$ (a) and MNP-IL-HSO$_4$ (b).

Fig. 6. TGA curve of MNP-IL-HSO$_4$. 
Table 1. Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ethyl acetoacetate (mmol)</th>
<th>Catalyst (g)</th>
<th>Solvent/conditions</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>0.05</td>
<td>EtOH, reflux</td>
<td>3</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>0.05</td>
<td>Et₂O, reflux</td>
<td>3</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>0.05</td>
<td>EtOAc, reflux</td>
<td>3</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>0.05</td>
<td>CH₂Cl₂, reflux</td>
<td>3</td>
<td>Trace</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>0.05</td>
<td>MeCN, reflux</td>
<td>3</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>-</td>
<td>Neat, 110 °C</td>
<td>3</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>0.05</td>
<td>Neat, 110 °C</td>
<td>1.5</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>0.025</td>
<td>Neat, 110 °C</td>
<td>1.5</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>0.025</td>
<td>Neat, 110 °C</td>
<td>1.5</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>1.2</td>
<td>0.025</td>
<td>Neat, 110 °C</td>
<td>1.5</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>1.2</td>
<td>0.025</td>
<td>Neat, 100 °C</td>
<td>3</td>
<td>77</td>
</tr>
</tbody>
</table>

*Reaction conditions: α-aminobenzophenone (1.0 mmol) and ethyl acetoacetate (1.0-1.5 mmol) were heated with varying amounts of catalyst (MNP-IL-HSO₄), either in solvent or under solvent-free conditions.

CONCLUSIONS

In conclusion, the present study described the synthesis of substituted quinolines. The optimization of reaction conditions is presented in Table 3. The results showed that MNP-IL-HSO₄ is a better catalyst with respect to reaction times and yields of the products.
Table 2. Synthesis of Substituted Quinolines Using MNP-IL-HSO₄ under Solvent-free Conditions at 110 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound 1</th>
<th>Compound 2</th>
<th>Product (^a)</th>
<th>Time (min)</th>
<th>Yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>3a</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2a</td>
<td>3b</td>
<td>25</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2b</td>
<td>3c</td>
<td>50</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>2b</td>
<td>3d</td>
<td>35</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2c</td>
<td>3e</td>
<td>25</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>2c</td>
<td>3f</td>
<td>10</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2d</td>
<td>3g</td>
<td>20</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>2d</td>
<td>3h</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>2e</td>
<td>3i</td>
<td>75</td>
<td>82</td>
</tr>
</tbody>
</table>

\(^a\)All products were characterized by IR, \(^1\)H and \(^13\)C NMR, and their spectra were compared with those of the authentic samples. \(^b\)Isolated yield.
of polysubstituted quinolines using an efficient and magnetically recyclable Brønsted acid ionic liquid, MNP-IL-\(\text{HSO}_4\). This catalytic method offers several advantages including environmental friendliness, high yield, short reaction time, simple work-up procedure, ease of separation, and recyclability of the catalyst. So, we think that this procedure could be considered as a new and suitable addition to the present methodologies in this area.

**ACKNOWLEDGMENTS**

We are grateful to the Research Council of Payame Noor University for financial support.

**REFERENCES**


Friedländer Synthesis of Substituted Quinolines

