NANO-Fe₃O₄–SUPPORTED, HYDROGENSULFATE IONIC LIQUID–CATALYZED, ONE-POT SYNTHESIS OF POLYSUBSTITUTED PYRIDINES

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GRAPHICAL ABSTRACT

Abstract Anchoring 1-methyl-3-(triethoxysilylpropyl) imidazolium chloride onto silica-coated magnetic Fe₃O₄ particles afforded the corresponding supported ionic liquid. Exchanging the Cl⁻ anion by treating with H₂SO₄ gave Brønsted ionic liquid 1-methyl-3-(triethoxysilylpropyl) imidazolium hydrogensulfate. The synthesized catalyst was characterized by various techniques such as infrared, x-ray diffraction, scanning electron microscopy, thermogravimetric analysis, and elemental analyses. The results indicated that the prepared catalyst had a nanostructure. The catalytic activity of the supported ionic liquid was examined in the synthesis of the polysubstituted pyridines by reaction of aromatic aldehydes with acetophenones and ammonium acetate in moderate to good yields under solvent-free conditions. The catalyst can be easily recovered by applying an external magnetic field and reused for at least seven runs without deterioration in catalytic activity.

Keywords Magnetic nanoparticle; nano-Fe₃O₄; polysubstituted pyridines; solvent-free condition; supported ionic liquids
INTRODUCTION

Multicomponent reactions (MCRs) via one-pot reaction have received a great deal of interest because of their atom economy and straightforward reaction design, which substantially minimizes waste, labor, time, and cost.[1–3]

Nowadays, exploration of solvent-free conditions in reactions, a central tenet of green chemistry, has gained importance because of several advantages, including experimental simplicity, less energy requirement, and almost quantitative reactivity of the substrates.[4,5]

Room-temperature ionic liquids (RTILs) as homogeneous catalysts[6] have received increasing interest in the area of green chemistry because of their particular properties, such as undetectable vapor pressure and the ability to dissolve many organic and inorganic substances.[7] The acidic nature of these ionic liquids leads to applications in reactions as catalysts or dual catalyst-solvents.[8] Although these compounds possess such promising advantages, their widespread practical application is still hampered by some drawbacks that lead to economic and environmental problems. High viscosity, which not only limits their mass transfer during catalytic reactions but also makes their handling difficult, the high cost for the use of relatively large amounts of ionic liquids, and their homogeneity cause toxicological concerns and environmental problems. These problems and also desire by the chemical industry to use heterogeneous catalysts can be resolved by immobilization of ILs onto solid supports.[9–11] Among different reported methods for the preparation of supported ionic liquids, in the recent years, magnetic nanoparticles (MNPs) have recently appeared as a new type of catalyst supports because of their good stability and facile separation.[12,13] In this regard, nano-Fe3O4 has attracted much attention because of its unique physical properties such as high surface area, excellent thermal and chemical stability, low toxicity, and many potential applications. Magnetic catalysts can be recycled by an external magnetic field and reused in subsequent reactions. Owing to these properties and attractive features, Fe3O4 has been used as a promising support for ILs.[13–17]

Pyridine ring systems, particularly 2,4,6-triarylpyridines, have potential pharmaceutical activities and could be used as antimalarials, vasodilators, anesthetics, anticonvulsants, antiepileptics, antitumor drugs, and agrochemicals (e.g., fungicides, pesticides, and herbicides).[18–20] Because of their π-stacking ability, they are prominent synthons in supramolecular chemistry.[21–23] Their excellent thermal stabilities have led to their use as monomeric building blocks in thin films and organometallic polymers.[24,25] Pyridines (Kröhnke pyridines) have been synthesized using various methods and procedures. Traditionally, these compounds have been synthesized through the reaction of N-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of NH4OAc.[26,27] Recently, several new improved methods have been developed for the synthesis of 2,4,6-triaryl pyridines. Among all these methods, the one-pot synthesis of polysubstituted pyridines from acetophenones, aryl aldehydes, and NH4OAc is the well-established protocol. These protocols include using NaOH in polyethylene glycol (PEG),[28–30] catalytic amounts of HOAc,[31] HClO4–SiO2,[32] Preyssler-type heteropolyacid H14[NaP5W30O110],[33] wet 2,4,6-trichloro-1,3,5-triazine (TCT),[34] and Brønsted acidic ionic liquids.[35]
In this study, we synthesized IL of 1-methyl-3-(trimethoxysilylpropyl) imidazolium hydrogensulfate supported on nano-Fe₃O₄ (MNP-[pmim]HSO₄) (Fig. 1) and used it as a recyclable catalyst for the synthesis of polysubstituted pyridines (Fig. 2).

**RESULTS AND DISCUSSION**

**Characterization of the Catalyst**

The external surface of magnetite nanoparticles was coated with silica (Fe₃O₄@SiO₂) to improve the chemical stability and prevent further aggregation of MNPs. 1-Methyl-3-(trimethoxysilylpropyl) imidazolium chloride was anchored onto solid support via treatment with silanol groups of Fe₃O₄@SiO₂. Ion exchange of Cl⁻/C₀ anions with H₂SO₄ afforded MNP-[pmim]HSO₄. Fourier transform–infrared (FT-IR) spectroscopy was used to provide evidence for immobilization of IL onto solid support. The FT-IR spectra of MNPs (a), MNP@SiO₂ (b), [pmim]Cl (c), MNP [pmim]Cl (d), and MNP [pmim]HSO₄ (e) are shown in Fig. 3. In the FT-IR spectrum of MNP-[pmim]Cl [Fig. 3(d)] characteristic peaks corresponding to Fe-O stretching, stretching vibration of framework and Si-O-Si groups, and stretching vibrations of C=N and C-N are observed that confirm the structure of the catalyst, which is in good agreement with the reported FT-IR data. For MNP-[pmim]HSO₄ (e), the appearance of the O=S=O asymmetric and symmetric stretching modes lie in 1133 and 1076 cm⁻¹ respectively together with the broad OH stretching absorption around 2800 to 3380 cm⁻¹, confirming the exchange of Cl⁻ ions with HSO₄⁻ ions.

Crystalline structure of MNP-[pmim]HSO₄ was characterized by X-ray diffraction (XRD) in Fig. 2. The characteristic peaks in the diffraction pattern can be assigned to crystal planes in Fe₃O₄ cubic lattice (JCPDS 19-0629). Moreover, in MNP-[pmim]HSO₄ [Fig. 4(b)] relative to pure MNP [Fig. 4(a)], the peaks of amorphous silica in 2θ = 20 to 30 confirmed the successful coating of MNPs with SiO₂.
Thermogravimetric (TGA) analyses for MNP@SiO₂ (a) and MNP-[pmim]HSO₄ (b) are shown in Fig. 5. For MNP-[pmim]HSO₄, weight loss within 0–160°C (2.75%) is due to physically adsorbed moisture whereas the major weight losses occur at 160–340 °C (10.03%) and 360–650 °C (11.83%) relating to the decomposition of 1-methyl-3-propylimidazolium groups grafted on the MNP@SiO₂ surface.

The particle sizes of MNP-[pmim]HSO₄ and MNP@SiO₂ were evaluated using scanning electron microscopy (SEM). The SEM images (Fig. 6) showed flocules without having a regular structure. On the other hand, the shape of these particles was mostly spherical and the surface of them was not smooth, which resulted in an increase in the surface areas of these particles. In these cases, average diameter of MNP@SiO₂ and MNP-[pmim]HSO₄ were 20–30 nm.

Loading amount of IL ([pmim]HSO₄) grafted on MNP was also quantified via contents of C, H, and N determined by elemental analysis (C, 8.36%; H, 1.32%; N, 2.67%; and S, 3.19%). The content ratio of C/N (3.13) is very near to the theoretical calculation (3.00). The content of sulfur further confirmed the amount of loading.
Figure 4. XRD pattern of MNP (a) and MNP-[pmim]HSO₄ (b).

Figure 5. TGA thermogram of MNP@SiO₂ (a) and MNP-[pmim]HSO₄ (b).

Figure 6. SEM images of MNP@SiO₂ (left) and MNP-[pmim]HSO₄ (right).
The loading level of IL (0.99 mmol/g) was determined based on the chloride content in MNP-[pmim]Cl by titration method. The evaluated loading by titration method was in good agreement with the results obtained from TGA and conventional elemental analysis.

After characterization of the catalyst (MNP-[pmim]HSO₄), the catalytic activity of the catalyst was investigated in the one-pot synthesis of 2,4,6-triarylpyridines.

**Synthesis of Triaryl Pyridines Catalyzed by MNP-[pmim]HSO₄**

The three-component process of benzaldehyde (1 mmol), acetophenone (2 mmol), and NH₄OAc (1.3 mmol) was chosen as a model reaction to optimize the reaction conditions such as molar ratio of the catalyst, temperature, and solvent (Table 1). Three separated reactions were examined in the absence of any catalyst and in the presence of MNP and MNP-[pmim]Cl. The results of these studies showed that trace amount of the desired product was formed (Table 1, entries 12–14). A similar reaction in the presence of imidazolium hydrogen sulfate ([Hmim]HSO₄) and methyl imidazolium hydrochloride ([Hmim]Cl) as two nonsupported ILs gave the desired product in 80% and 60% yields respectively (Table 1, entries 15 and 16).

When the model reaction was carried out in the presence of 1.2 mol% of MNP-[pmim]HSO₄ in protic solvents such as H₂O, MeOH, and EtOH, a poor yield of the product was obtained (Table 1, entries 1–3). This could be due to insolubility of the reactants in H₂O and low boiling points of MeOH and EtOH. However, this reaction in aprotic solvents such as CH₂Cl₂, ethyl acetate, and acetonitrile did not give a reasonable yield of the expected product (Table 2, entries 4–6). The model reaction under solvent-free conditions gives suitable yield of the product (Table 1, entries 8–11).

**Table 1.** Optimization of reaction conditions for synthesis of triaryl pyridines

| Entry | Catalyst (mol%) | Solvent | Conditions | Time (h:min) | Yield (%) |
|-------|-----------------|---------|------------|--------------|-----------|
| 1     | MNP-[pmim]HSO₄ (1.2) | H₂O     | Reflux     | 4            | 50        |
| 2     | MNP-[pmim]HSO₄ (1.2) | EtOH    | Reflux     | 4            | 40        |
| 3     | MNP-[pmim]HSO₄ (1.2) | MeOH    | Reflux     | 4            | 25        |
| 4     | MNP-[pmim]HSO₄ (1.2) | CH₂CN   | Reflux     | 4            | 45        |
| 5     | MNP-[pmim]HSO₄ (1.2) | EtOAC   | Reflux     | 4            | 40        |
| 6     | MNP-[pmim]HSO₄ (1.2) | CH₂Cl₂  | Reflux     | 4            | 55        |
| 7     | MNP-[pmim]HSO₄ (1.2) | Toluene | Reflux     | 4            | 60        |
| 8     | MNP-[pmim]HSO₄ (1.4) | Solvent free | 100°C | 0:50       | 90        |
| 9     | MNP-[pmim]HSO₄ (1.2) | Solvent free | 100°C | 0:50       | 90        |
| 10    | MNP-[pmim]HSO₄ (1) | Solvent free | 100°C | 1:30       | 85        |
| 11    | MNP-[pmim]HSO₄ (0.8) | Solvent free | 100°C | 3          | 80        |
| 12    | MNP-[pmim]Cl (1.2) | Solvent free | 100°C | 4          | Trace     |
| 13    | MNP@[SiO₂] | Solvent free | 100°C | 4          | Trace     |
| 14    | [Hmim]HSO₄ (1.2) | Solvent free | 100°C | 1:10       | 80        |
| 15    | [Hmim]Cl (1.2)  | Solvent free | 100°C | 1:30       | 60        |

*aConditions: benzaldehyde, acetophenone, and NH₄OAc 1:2:1.3.

*bIsolated yields.
8–11). It was found that the best yield of product was obtained at 100 °C under solvent-free conditions in the presence of 1.2 mol\% of MNP-[pmim]HSO$_4$ (Table 1, entry 9). Increasing the amount of catalyst does not improve the yield of the product any further but decreasing the amount of catalyst leads to decrease in the product yield. Because the best solvent from green chemistry point of view is no solvent, combination of solvent-free conditions with a multicomponent reaction has been shown to be a powerful strategy for making complex molecular structures, and we chose it as optimal reaction condition (entry 9).

To establish the generality of this method, synthesis of various triarylpyridines was studied using different aldehydes and acetophenones under optimized reaction conditions (Table 2).

As is clear from Table 2, aromatic and heteroaromatic aldehydes were tolerated well in this reaction and varieties of aldehydes with electron-donating or electron-withdrawing groups on the aromatic ring had little effect on the reaction rate. Desired products were formed in good yields (Table 2, entries 1–8 and 13–16). Heteroaromatic aldehydes also tolerate the condensation reaction to afford the corresponding pyridines in good yields (Table 2, entries 10–12).

A plausible mechanism for the formation of 2,4,6-triphenylpyridines catalyzed by MNP-[pmim]HSO$_4$ is shown in Fig. 7. The first step of the process involves Knoevenagel condensation of aldehyde with acetophenone to form the corresponding chalcone (A). The reaction proceeds through Michael addition of second molecule of acetophenone to (A) followed by nucleophilic attack of ammonium acetate to the carbonyl group of adduct (B) and intramolecular cyclization by loss of water molecular to produce dihydropyridines (C). Aromatization and oxidation of dihydropyridines (C) by air under the reaction conditions give pyridines as final products.
Recovery and reuse of a catalyst is highly preferable for a catalytic process. In this regard the recyclability of MNP-[[pmim]HSO₄ was investigated in the model reaction of benzaldehyde, acetophenone, and ammonium acetate under optimized reaction conditions. After completion of the reaction, EtOAc was added and the whole amount of MNP-[[pmim]HSO₄ was simply separated from the product by an external magnet. The recovered catalyst was washed with ethyl acetate, dried at room temperature, and reused for the next reaction. The magnetic property of MNP-[[pmim]HSO₄ facilitates the efficient recovery of the catalyst from the reaction mixture during workup procedure, and the catalyst was recycled and reused for seven consecutive trials without significant loss of its catalytic activity (Fig. 8).

The recyclability test was stopped after seven runs. Comparison of the scanning electron microscopy (SEM) image and FT-IR spectra of used catalyst (Fig. 9) with those of the fresh catalyst [Figs. 6 and (3d)] showed that the size and structure of MNP-[[pmim]HSO₄ remained intact after seven recoveries.
EXPERIMENTAL

Materials were purchased from Merck and Aldrich Chemical Companies and used without further purification. All the solvents were distilled, dried, and purified by standard procedures. The samples were analyzed using a FT-IR vector 22 spectrometer (Bruker Vector in KBr matrix). NMR spectra were recorded on a Bruker DRX-400 Avance instrument (400.1 MHz for \(^1\)H, 100.6 MHz for \(^{13}\)C) with dimethylsulfoxide (DMSO) as the solvent. Chemical shifts (\(\delta\)) are given in parts per million (ppm) relative to tetramethylsilane (TMS), and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHNS/O-Rapid analyzer. Thermogravimetric analysis (TGA) was recorded on a Stanton Redcraft STA-780 (London, UK). X-ray diffraction (XRD) was carried out on a Philips Xpert Pro diffractometer using Cu K\(\alpha\) source (\(\lambda = 1.5418 \text{ Å}\)). FESEM images were obtained on a Hitachi S-1460 field-emission scanning electron microscope using an AC voltage of 15 kV. Melting points were measured on an Electrothermal 9100 apparatus.

General Procedure for the Synthesis of Catalyst

Silica-coated magnetite nanoparticles (Fe\(_3\)O\(_4@\)SiO\(_2\)) were prepared according to the reported method.\(^{[38,41]}\) Then ionic liquid of 1-methy-3-(trimethoxysilylpropyl)imidazolium chloride ([pmim]Cl) was synthesized according to the reported method.\(^{[42]}\) In the next step for anchoring of [pmim]Cl on the silica-coated magnetite nanoparticles, [pmim]Cl (0.5 gr, 1.3 mmol) was dissolved in 25 ml of dry toluene and treated with 1 g of previously prepared Fe\(_3\)O\(_4@\)SiO\(_2\). After heating the slurry at 90 °C for 16 h, the resulting solid was then separated by an external magnet and washed with 100 ml of dichloromethane. Afterward, the unreacted ionic liquid was removed by extraction for 24 h with boiling dichloromethane (soxhlet extraction) and the material (MNP-[pmim]Cl) was dried under high vacuum. At the end for exchanging the Cl\(^-\) anion, MNP[pmim]Cl (1 g) was suspended in 20 ml of dry CH\(_2\)Cl\(_2\). During vigorous stirring, concentrated H\(_2\)SO\(_4\) (1.3 mmol 98%) 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 of MNP-
[pmim]HSO4.

**General Procedure for the Synthesis of Triarylpyridines**

MNP-([pmim]HSO4) (0.012 gr, 1.2 mol%) was added to a mixture of aldehyde
(1.0 mmol), acetophenone (2.0 mmol), and ammonium acetate (1.3 mmol) and the
resulting mixture was stirred at 100°C for the specific period of time. The progress
of the reaction was monitored by thin-layer chromatography (TLC). After com-
pletion of the reaction, EtOAc (10 ml) was added to the cooled reaction mixture.
The catalyst was separated by an external magnet, washed with EtOAC, dried,
and reused for a consecutive run under the same reaction conditions. Evaporation
of the organic solvent under reduced pressure gave the crude products. Pure products
were obtained by recrystallization by aqueous EtOH. The products were character-
ized by IR, 1H NMR, and 13C NMR spectra.

To show the merit of the present protocol for the synthesis of the triarylpyri-
dines, we have compared our results with some of the reported in the literature
(Table 3). Although all the methods are effective, the present procedure compara-
tively affords good yield of the product with reusability for at least 7 consecutive
runs without loss of activity.

| Entry | Catalyst (amount) | Yield (%)/time (h) | Ref. |
|-------|------------------|--------------------|------|
| 1     | HClO4-SiO2 (0.1 g) | 80/4               | [32] |
| 2     | H2[NaP5w30O110] (0.1 g) | 98/3.5             | [33] |
| 3     | [HO3S(CH2)4 MIM][HSO4] (20 mol%) | 89/3              | [35] |
| 4     | Diphenylammonium triflate (2 mol%) | 96/4             | [44] |
| 5     | Pentafluorophenylammonium triflate (25 mol%) | 89/2         | [45] |
| 6     | Bi(OTf)3 (5 mol%) | 89/2 h            | [46] |
| 7     | MNP-[pmim]HSO4 (1 mol%) | 90/0.83          | This work |

*Note.* Conditions: benzaldehyde, acetophenone, and ammonium acetate.

**CONCLUSION**

In summary, we successfully synthesized a supported IL of 1-methyl-3-
(trimethoxysilylpropyl) imidazolium hydrogensulfate (MNP-[pmim]HSO4) from
readily available starting materials. It was applied as a magnetically recyclable het-
erogeneous catalyst for the one-pot, three-component synthesis of triarylpyridines.
This catalyst efficiently promoted the condensation of aromatic aldehydes and
acetophenone with ammonium acetate, leading to corresponding pyridines in
moderate to good yields under solvent-free conditions. Product separation and
catalyst recycling are easy and simple with the assistance of an external magnet.
The catalyst can be recovered and reused for seven cycles without significant
degradation in activity.
FUNDING

This research was supported by the Research Council of the University of Mazandaran, Iran.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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