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1. Introduction

The development of more efficient and stable catalysts has been an increasingly important goal for chemists in organic synthesis due to environmental and economic factors.1 Recently, the immobilization of ionic liquids has proven to be an effective approach to improve their catalytic efficiency by facile catalyst recycling and reuse, and polymers, such as polystyrene, as well as inorganic materials, such as silica and magnetic nanoparticles, have been employed as the solid supports for these heterogeneous systems.^{2,3} Moreover, more attention has been paid to magnetic nanoparticles (MNPs) as excellent supports for ionic liquids because of their good stability, easy synthesis and functionalization, high surface area and facile separation under a magnetic field, as well as low toxicity and price.⁴ These attractive features have made MNPs a promising alternative to catalyst supports. On the other hand, supported ILs containing different metal particles or ions have been used as catalysts in different reactions such as the Heck reaction,5,6 the Suzuki reaction,⁷ and hydrogenation reactions.⁸ Sasaki et al. prepared a Ni ion-containing ionic liquid salt and a Ni ion-containing immobilized ionic liquid on silica for the Suzuki reaction.7 Han et al. synthesized a Ni²⁺-containing ionic liquid (IL) immobilized on silica to catalyze styrene oxidation with H2O2 to produce benzaldehyde.º Sasaki et al. prepared immobilized

A magnetic nanoparticle supported Ni²⁺-containing ionic liquid as an efficient nanocatalyst for the synthesis of Hantzsch 1,4-dihydropyridines in a solvent-free dry-system

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The highly efficient synthesis of 1,4-dihydropyridines (1,4-DHPs) is reported *via* the condensation reaction of aldehydes, ethyl acetoacetate and ammonium acetate, using an environmentally benign Ni²⁺-containing 1-methyl-3-(3-trimethoxysilylpropyl) imidazolium chloride ionic liquid on magnetic Fe_3O_4 nanoparticles (IL–Ni(II)–MNPs) as a new catalyst under solvent-free conditions at 70 °C. The method presented here applies the tenets of green chemistry to generate biologically interesting products in solvent-free media. The key features of this protocol from the green chemistry point of view are the use of a heterogeneous and reusable catalyst, high yields of products, and short reaction times. The catalyst can be easily recovered from the reaction mixture using an external magnet, and reused several times without significant loss in performance.

 ${\rm Cu}^{2+}\text{-}{\rm containing}$ ionic liquid catalysts for the Kharasch reaction between styrene and ${\rm CCl}_4.{}^{10}$

1,4-Dihydropyridin compounds are a common feature of various bioactive compounds such as vasodilator, geroprotective, bronchodilator, antitumor, antiatherosclerotic, hepatoprotective, and antidiabetic agents.¹¹ More than twelve commercial, clinically important drugs such as amlodipine, nifedipin, nimodipin, felodipine, isradipine, and nicardipine containing the 1,4-dihydropyridine parent nucleus have been manufactured and used worldwide.¹² Despite their importance from a pharmacological, industrial, and synthetic point of view, comparatively few protocols for their preparation have been reported.¹³

Preparation of 1,4-DHP was first reported by Hantzsch in 1882 *via* the reaction of aldehydes with ethyl acetoacetate and ammonia in acetic acid or by refluxing in alcohols.¹⁴ This method, however, involves long reaction times, harsh reaction conditions, and generally gives low yields of products. Up until now, numerous literature citations exist relating to various attempts to improve the Hantzsch reaction using alternative catalysts and greener methods.¹⁵ Therefore, the search continues for a better catalyst for the synthesis of 1,4-DHP in terms of operational simplicity, reusability, economic viability, and greater selectivity.

Herein, we would like to report Hantzsch 1,4-dihydropyridin derivative synthesis catalyzed by Ni²⁺-containing 1-methyl-3-(3-trimethoxysilylpropyl) imidazolium chloride ionic liquid on magnetic Fe₃O₄ nanoparticles under solvent-free conditions, using an aromatic aldehyde, ethylacetoacetate and ammonium acetate at 70 °C (Scheme 1). This method not only preserves the

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simplicity of the reaction, but also consistently gives the corresponding products in good to excellent yields. The heterogeneous catalyst could be recovered easily and reused many times without significant loss of its catalytic activity.

2. Results and discussion

We have reported here the possibility of applying nanotechnology to the design of a novel, active, recyclable, and magnetically recoverable IL–Ni(π)–MNPs as a new catalyst for the synthesis of 1,4-dihydropyridine compounds under mild reaction conditions for the first time.

2.1. Characterization of the catalysts

Scheme 2 shows the sequence of events in the functionalization of Fe₃O₄ MNPs with IL–Ni²⁺.¹⁶ The magnetite nanoparticles of 18–20 nm were prepared using the method described by Massart.¹⁷ Then, 1-methyl-3-(3-trimethoxysilylpropyl) imidazo-lium chloride (IL) was prepared from the reaction of *N*-methyl imidazole with (3-chloropropyl)trimethoxysilane at 80 °C. Then IL was added to an acetonitrile solution of NiCl₂ in a 250 ml round bottom flask and refluxed for 24 h and IL–Ni(π) was obtained. In the second step, the external surface of Fe₃O₄ nanoparticles was coated with IL–Ni(π) to obtain IL–Ni(π)–MNPs (Scheme 2).

Fig. 1 shows the FTIR spectra of both the Fe_3O_4 -MNPs and IL-Ni(II)-MNPs. The Fe-O stretching vibration near 580 cm⁻¹, O-H stretching vibration near 3432 cm⁻¹ and O-H deformed vibration near 1625 cm⁻¹ were observed both in Fig. 1(a) and (b). The significant features observed for Fig. 1(b) are the appearance of the peaks at 1007 cm⁻¹ (Si-O stretching), at 1612 cm⁻¹ (C=N stretching) and at 2800 cm⁻¹ (-CH₂ stretching). A peak at about 3390 cm⁻¹ can be observed in Fig. 1(b), this indicates the presence of hydrogen bonding (C-H···Cl interactions), which has been observed in analogous compounds containing the 1-methyl-3-methylimidazolium cation [MmIM]⁺ and NiCl₄²⁻ ([MmIM]₂[NiCl₄]) on Fe₃O₄ nanoparticles.¹⁸ These results provided the evidence that IL-Ni²⁺ was successfully attached to the surface of the Fe₃O₄ nanoparticles.¹⁶

The TEM and SEM images in Fig. 2(a) and (b) show that the Fe_3O_4 nanoparticles have a mean diameter of about 18–20 nm and a nearly spherical shape. The SEM in Fig. 2(c) and the TEM micrographs show that IL–Ni(μ)–MNPs have a larger particle size and a smoother surface, and that silica is uniformly coated on the Fe_3O_4 particles to form a silica shell.

Fig. 3 presents the XRD-diffraction patterns of the prepared MNPs and IL–Ni(π)–MNPs. The position and relative intensities of all peaks in the XRD pattern of IL–Ni(π)–MNPs (JCPDS card no. 01-1143) agree well with the standard XRD pattern of Fe₃O₄ (JCPDS card no. 79-0417), indicating retention of the crystalline cubic spinel structure during the immobilization process of Ni²⁺. It is implied that the resultant nanoparticles are pure Fe₃O₄ with a spinel structure and that the grafting process did not induce any phase change of the Fe₃O₄ nanoparticles.¹⁶

The components of the Fe_3O_4 nanoparticles and IL-Ni(π)–MNPs were analyzed using energy dispersive spectroscopy (EDS) in Fig. 4(a) and (b), respectively. The EDS spectrum shows the elemental composition (Ni, Cl, Si, and Fe) of the IL-Ni(π)–MNPs.¹⁶

The magnetization curves for the Fe₃O₄-MNPs and IL-Ni(II)-MNPs are shown in Fig. 5. Room temperature specific magnetization (*M*) versus applied magnetic field (*H*) curve measurements of the sample indicate a saturation magnetization value (M_s) of 14.26 emu g⁻¹, lower than that of the bare magnetic nanoparticles (62.40 emu g⁻¹) due to the coated shell.

2.2. Evaluation of the catalytic activity of IL-Ni (π) -MNPs in the Hantzsch reaction

For the initial optimization of the reaction conditions and the identification of the best catalyst, temperature, and amount of the catalyst; ethyl acetoacetate **1**, benzaldehyde **2**, and ammonium acetate **3** were chosen as model substrates (Scheme 1).

This reaction occurs more efficiently in solvent-free conditions than it does in solution since the catalyst and reagents are in greater proximity to each other when solvent is not used. Therefore, without solvent, reactions usually need shorter reaction times, simple and efficient workup procedures, simpler reactors, and are often more environmentally friendly. To determine the appropriate amount of catalyst, we investigated the model reaction described above under different concentrations of IL–Ni(II)–MNPs, namely 0.008, 0.01, 0.012, 0.013, and 0.014 g at 50 °C. We found that the product is obtained in 45%, 65%, 75%, 75%, and 74% yields, respectively (Table 1, entries 1–5). This indicates that 0.012 g of catalyst produces the best results with respect to product yield.

Next, we studied the effect of temperature for the model Hantzsch reaction. The reaction was studied at various



Scheme 1 Solvent-free synthesis of 1,4 dihydropyridines catalyzed by IL-Ni(II)-MNPs at 70 °C.

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Scheme 2 Preparation steps for fabricating IL–Ni(II)-functionalized magnetic Fe₃O₄ nanoparticles.



temperatures, including room temperature, 40, 50, 60, 70 and 80 °C. The yield of the product increased up to 70 °C. Therefore, our optimized conditions are 0.012 g of IL–Ni(π)– MNPs under solvent-free conditions at 70 °C (Table 1, entry 8). The uncatalyzed reaction run in parallel under otherwise identical conditions gave a poor yield (only 32%) of the corresponding product within the time required for completion of the other catalyzed transformations (Table 1, entry 12).

Using the optimized conditions, we continued to study the reaction using various aldehydes. The results summarized in Table 2 indicate that both aromatic and heterocyclic aldehydes underwent smooth reactions with ethyl acetoacetate and ammonium acetate to give reasonable to high yields of the corresponding products. The catalytic system worked

Fig. 2 Images of the samples: (a) SEM of MNPs; (b) TEM of MNPs; (c) SEM of IL–Ni(n)–MNPs and (d) TEM of IL–Ni(n)–MNPs.

well. Clearly, the nature of the substituents on the aromatic ring showed no obvious effect on this conversion, because products were obtained in high yields in relatively short reaction times.

The proposed mechanism for the formation of the 1,4dihydropyridines is shown in Scheme 3. In this Hantzsch reaction, Ni^{2+} is supposed to facilitate the condensation between ethyl acetoacetate 1 and the aldehyde 2 to form the corresponding Knoevenagel product 5a, as well as the Michael addition between this intermediate and the enamine 6a obtained from the reaction of ethyl acetoacetate 1a and ammonium acetate 3, to form the open chain intermediate 7a



Fig. 3 XRD patterns of (a) MNPs and (b) IL-Ni(II)-MNPs.

which undergoes cyclohydration to furnish the desired DHP product 4.¹⁸

The structure of compounds **4a–n** was deduced from their high-field ¹HNMR, ¹³CNMR, IR, and UV spectral data. Also, their melting points were compared with literature reports. The ¹H NMR spectrum for compound **4l** is given in Fig. 6. In the ¹H NMR spectrum, the two signals around $\delta = 1.2$ and $\delta =$ 2.3 ppm correspond to the two methyl groups at C-2 (C-6) and the ethoxy groups, respectively, in 2,6-dimethyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-diethylcarboxylate. The tow signals around $\delta = 4.1$ and $\delta = 5.3$ ppm are related to OCH₂ and CH protons, respectively. In this figure, the signals of the aromatic protons can be seen at $\delta = 6.8$ –7.0 ppm and the signal at 5.98 ppm is related to the NH protons. The presence of this signal confirmed the formation of the desired product in the reaction. In the interests of green chemistry and developing an environmentally benign process, the reusability of the catalyst was explored using the model reaction system under the optimized conditions. After completion of the reaction, the mixture was triturated with EtOH. In the presence of a magnetic stirrer bar, IL–Ni(π)–MNPs moved onto the stirrer bar steadily and the reaction mixture turned clear within 15 s. The magnetic catalyst can be isolated by simple decantation. After being washed with acetone, ethyl acetate, ethanol and dried in air, the catalyst can be directly reused without any deactivation, even after five rounds of synthesis of product **4a** (Fig. 7).

3. Conclusions

In conclusion, supported IL–Ni (π) –MNPs have been shown to be a highly active catalyst for preparing a variety of 4-substituted-



Fig. 4 The EDS spectra of (a) MNPs and (b) IL-Ni(II)-MNPs.





Fig. 5 Magnetization curves for the prepared MNPs and IL–Ni(μ)–MNPs at room temperature.

 Table 1
 Optimization one-pot synthesis of for the Hantzsch synthesis of 1,4-dihydropyridine 4a

Entry	Catalyst (g)	Time (min)	Temperature (°C)	Yield (%)
1	0.000 (II N;($_{\rm N}$) MNDc)	40	50	45
1	0.008 (IL-MINPS)	40	50	45
2	0.01 (IL-Ni(II)-MNPs)	35	50	65
3	0.012 (IL-Ni(II)-MNPs)	35	50	75
4	0.013 (IL-Ni(II)-MNPs)	35	50	75
5	0.014 (IL-Ni(II)-MNPs)	35	50	74
6	0.012 (IL-Ni(II)-MNPs)	40	40	53
7	0.012 (IL-Ni(II)-MNPs)	25	60	85
8	0.012 (IL-Ni(II)-MNPs)	25	70	98
9	0.012 (IL-Ni(II)-MNPs)	25	80	97
10	0.012 (MNPs)	25	70	65
11	0.012 (IL-MNPs)	25	70	80
12	0.0	720	70	32

1,4-dihydropyridines from the one-pot three-component condensation reaction. The catalytic research on novel approaches toward nanomaterials should be furthered to enhance organic reactions. Magnetic catalysts provide a new method for repeatable processes, because of their simple recyclability. From a scientific standpoint, our results expand the application of magnetic nanoparticle supported ILs containing Ni²⁺ ions. They should be helpful in understanding the advantageous combination of the properties of homogeneous and heterogeneous catalysis and the development of new catalytic systems.

4. Experimental

4.1. Chemicals and apparatus

Chemical reagents in high purity were purchased from the Merck and Sigma Chemical Company. All materials were of commercial reagent grade. ¹H NMR and ¹³C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. FT-IR spectra were obtained with potassium bromide pellets in the range of 400-4000 cm^{-1} with a Perkin-Elmer 550 spectrometer. The element analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on a Perkin-Elmer 240c analyzer. Nanostructures were characterized using a Holland Philips X'Pert X-ray powder diffraction (XRD) diffractometer (CuKa, radiation, $\lambda = 0.154056$ nm), at a scanning speed of 2° min⁻¹ from 10° to 100° (2 θ). Scanning electron microscopy (SEM) was performed on a FEI Quanta 200 scanning electron microscope operated at a 20 kV accelerating voltage. The samples for SEM were prepared by spreading a small drop containing the nanoparticles onto a silicon wafer and left in air at room temperature for 2 h until almost completely dry, after which they were transferred onto SEM conductive tape. The transferred sample was coated with a thin layer of gold before measurement.

4.2. Preparation of the magnetic Fe_3O_4 nanoparticles (MNPs)

 Fe_3O_4 -MNPs were prepared using chemical coprecipitation as described in the literature.²² In short, 20 mmol of $FeCl_3 \cdot 6H_2O$

Table 2	IL–Ni(II)–MNPs ca	atalyzed Hantzsch	synthesis of 1	,4-dihydropyridines
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Entry	R	Product	Time (min)	Yield of Present Work (%)	Yield in the literature (%)	Mp (°C)	
						Found	Lit.
1	Ph	4a	25	98	96	155-157	155 (ref. 19)
2	p-MeC ₆ H ₄	4b	30	96	88	143-144	142-145 (ref. 21)
3	$p-ClC_6H_4$	4c	15	98	90	144-146	14-146 (ref. 20)
4	<i>p</i> -OMeC ₆ H ₄	4 d	35	95	95	155-156	156 (ref. 19)
5	$p-(CH_3)_2NC_6H_4$	4e	45	93	90	202-203	201 (ref. 19)
6	m-NO ₂ C ₆ H ₄	4f	20	98	96	165-167	165-167 (ref. 21)
7	m-ClC ₆ H ₄	4g	20	98	92	141-142	141 (ref. 19)
8	m-OHC ₆ H ₄	4h	30	90	87	173-175	172-175 (ref. 21)
9	o-NO ₂ C ₆ H ₄	4 i	35	90	91	170-171	170 (ref. 19)
10	$m_{1}p_{1}(CH_{3}O)_{2}C_{6}H_{3}$	4j	40	93	90	163-164	161 (ref. 19)
11	C ₆ H ₅ -CH=CH	4k	15	99	86	143-145	146-148 (ref. 20)
12	2-Thienyl	41	20	99	90	172-174	170-172 (ref. 20)
13	2-Furyl	4m	20	98	50	160-161	159-162 (ref. 20)
14	3-Pyridyl	4 n	20	98	90	189-190	188-190 (ref. 21)



and 10 mmol of FeCl₂·4H₂O were dissolved in 75 ml of distilled water in a three-necked round bottom flask (250 ml) under a N₂ atmosphere for 1 h. Thereafter, under rapid mechanical stirring, 10 ml of NaOH (10 M) was added into the solution within 30 min with vigorous mechanical stirring and ultrasound treatment under a continuous N₂ atmosphere. After being rapidly stirred for 1 h, the resultant black dispersion was heated to 80 °C for 1 h. The black precipitate formed was isolated by magnetic decantation, extensively washed with double-distilled water until neutral, and further washed twice with ethanol and dried at 60 °C under vacuum.

4.3. Synthesis of 1-methyl-3-(3-trimethoxysilylpropyl)-1*H*-imidazol-3-ium chloride (IL)

(3-Chloropropyl) trimethoxysilane (31 ml, 0.17 mol) and 1methylimidazole (13.6 ml, 0.17 mol) were refluxed at 80 °C for three days in the absence of any catalyst and solvent under a N₂ atmosphere. The unreacted materials were washed with diethyl ether (3 × 8 ml). The diethyl ether was removed under reduced pressure at room temperature, followed by heating under high vacuum, to yield a yellowish viscous liquid. The isolated yield was 98%.²³



Fig. 6 ¹H NMR spectrum of 2,6-dimethyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-diethylcarboxylate (4I) in CDCl₃.



Fig. 7 Reuse of IL–Ni(η)–MNPs in the synthesis of 1,4-dihydropyridines in the model reaction.

FT-IR (KBr, cm⁻¹): 1656, 1612, 1584. ¹H NMR (400 MHz, CDCl₃): $\delta_{\rm H}$ (ppm): 10.22 (broad, 1H, Ar-H), 7.59 (1H, dd, J = 7.89 and 2.86 Hz, Ar-H), 7.26 (1H, dd, J = 7.89 and 2.79 Hz, Ar-H), 4.06 (2H, t, J = 7.25 Hz, -NCH₂), 3.86 (3H, s, -NCH₃), 3.30 (9H, s, OCH₃), 1.74 (2H, tt, J = 7.14 Hz, -CH₂), 0.37 (2H, t, J = 7.09 Hz, SiCH₂). ¹³C NMR (100 MHz, CDCl₃, TMS): $\delta_{\rm C}$ = 138.13, 123.34, 121.58, 58.53, 51.66, 36.51, 24.32, 18.2, 7.03. Anal. calcd: C, 48.45; H, 8.39; N, 8.69. Found: C, 48.35; H, 8.32; N, 8.79%.

4.4. Synthesis of IL-containing Ni²⁺

The IL-containing Ni²⁺ was synthesized according to a method reported by other authors.²⁴ In the experiment, anhydrous NiCl₂ (0.65 g, 0.05 mol), IL (3.23 g, 0.10 mol) and anhydrous acetonitrile (100 ml) were added into a 250 ml round bottom flask and the mixture was refluxed at 363 K for 24 h under a N₂ atmosphere until a transparent blue solution was obtained. After cooling, acetonitrile was evaporated under vacuum. A blue viscous liquid was obtained after washing with toluene, and was dried under vacuum for 24 h and the IL–Ni(II) was obtained.

4.5. Modification of magnetic nanoparticles with IL-Ni²⁺ (IL-Ni(π)-MNPs)

The detailed procedure for preparing the IL–Ni(II)–MNPs catalyst is described in the literature.¹⁶ In brief, freshly prepared Fe₃O₄ nanoparticles (2 g) were suspended in methanol (250 ml), and sonicated for 30 min. The resultant suspension was mechanically stirred, followed by the addition of a solution of methanol (100 ml) containing IL–Ni(II) (6 g) and concentrated ammonia (28%, 1 ml). Stirring under N₂ was continued for 36 h. The modified magnetite nanoparticles were magnetically separated and washed three times with ethanol (95%, 50 ml) and dried under a vacuum for 24 h.

4.6. Synthesis of 1,4-DHPs

To a mixture of the aromatic aldehyde (1 mmol), ethyl acetoacetate (2 mmol), and ammonium acetate (1.5 mmol) in a 10 ml round bottom flask, Fe_3O_4 –MNPs modified with IL–Ni²⁺ (the IL–Ni(II)–MNPs catalyst) (0.012 g) was added. The mixture was homogenized and stirred at 70 °C for the appropriate time until the reaction was complete. The progress of the reaction was monitored by TLC (petroleum ether–ethyl acetate 3 : 2). After completion, the reaction mixture was dissolved in hot ethanol (5 ml) and the catalyst was removed with an external magnet. The solvent was evaporated under reduced pressure to yield the crude product, which was then purified by recrystallization from hot ethanol and water to afford the pure 1,4-DHP.

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