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A short and highly efficient synthesis of cyanohydrins in recyclable and biodegradable magnetic deep eutectic solvent is described.



Journal Name

ARTICLE

A magnetic nanoparticle catalyzed eco-friendly synthesis of cyanohydrins in deep eutectic solvent

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Magnetic Fe₃O₄ nanoparticles in deep eutectic solvents (DESs) have been regarded as excellent catalysts for a highly efficient cyanosilylation of various aldehydes and epoxides using trimethylsilyl cyanide TMSCN in high yields with excellent selectivity. Fe₃O₄ nanoparticles were synthesized and applied as catalyst for the preparation of a wide variety of cyanohydrins (α -hydroxy nitriles and β -hydroxy nitriles) in readily available urea–choline chloride deep eutectic solvent DES as the most promising environmentally benign and cost-effective green solvents. Magnetic DES operates at very mild reaction conditions and can be easily recycled without significant loss of its catalytic activity.

Introduction

Among the several principles of green chemistry, the reduction of volatile organic solvents and catalysts has attracted a significant attention worldwide. Environmental pollution due to the use of a huge amount of volatile organic solvents in the chemical industry and laboratory may cause environmental problems and creates adverse effects on organisms and human health.¹ The search for a safer solvents and catalysts instead of currently used harmful solvents is thus holding a key role in the green chemistry. Among the various environmentally benign alternative solvents that have been explored in recent years, imidazolium based ionic liquids has attracted significant interest as potentially benign media for a wide range of applications.² Ionic liquid is often the solvent of choice not only for their thermal stability in a wide temperature range and a negligible vapour pressure but also for reusability and nonflammability. However, the main disadvantages of imidazolium based ionic liquids, such as toxicity, non-renewable resources, high cost and difficulty of preparation deceive chemists to discover appropriate alternative solvent. Related to ionic liquids with similar properties with additional advantages are low melting mixtures or deep eutectic solvents (DESs).³ In fact, eutectic mixtures have been known for a long time,⁴ however, a great potential of this entirely composed biomaterials inspired researchers to exploit the unusual properties of this system in the extraction of natural products, metal deposition, catalysis, and green reaction medium in recent years.⁵ Furthermore,

because of this relative novelty, an interesting area of research is the preparation several types of DESs and investigation of their physicochemical properties.⁶

Magnetic heterogeneous catalysis, in which a solid catalyst with large surface area promotes the transformation of an organic compound, is one of the most challenging.⁷ Particularly, when a homogenous catalysis are recoverable by magnetic separation over filtration or centrifugation. In this context, Fe₃O₄ and surface modified Fe₃O₄ nanoparticles are extensively studied as cheap and magnetically recoverable catalysts in various organic transformations in recent years.⁸ However, it is well known that Fe₃O₄ nanoparticles tend to aggregate or deformate to form the bulk metal or react with covering shells to form the mixed oxides with silica. Therefore, the development of a new reaction conditions that combine high activity, selectivity, stability and recyclability is a challenging task in magnetic heterogeneous catalysis research. The main two principles of green chemistry are the use of safer solvents and the other one is to prevent the generation of the waste in the chemical processes.¹ Thus, the possibility of developing an ideal catalytic process, with the combining the advantages of DES as green and reusable solvent, and the stabilizer with magnetic nanocatalyst, by taking into consideration their merits.

Cyanohydrin derivatives are important synthetic intermediates and chiral building blocks in organic synthesis.⁹ They are also key intermediates in various biological systems, and are responsible for numerous pharmacological and biological activities. The common methods for the preparation of α -hydroxy nitriles (cyanohydrins) and β -hydroxy nitriles, are the addition of cyanide source to carbonyl compounds and epoxides respectively. The rates as well as yields of reaction were increased in the presence of Lewis acids, Lewis bases, organocatalyst and ionic liquids.¹⁰ Furthermore, it is

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noteworthy to mention that the cyanide compounds are extremely toxic and TMSCN and acetone cyanohydrin are the most effective and comparatively safer sources of cyanide for this transformation. However, to the best of our knowledge, no magnetic catalyst in DES has been used in the organic synthesis.

Currently, DES has become an attractive medium for metal catalyzed transformations, due to the good solubility of metal oxides in their systems. In these processes, DES can play multiple roles such structure directing agent, stabilizer, solubilizing and ionic solvent.⁴ Our continued interest in the synthesis and application of DES in organic synthesis.¹¹

Herein, we explore the catalytic activity of magnetic Fe₃O₄ nanoparticle for synthesis of cyanohydrin using deep eutectic solvent of choline chloride and urea.

Experimental

Materials and methods

All starting materials, reagents and solvents are commercially available and were purchased and used without further purification. All products were confirmed by melting point or boiling point, FT-IR spectroscopy, ¹H NMR spectroscopy and mass spectrometry. Water and other solvents were distilled before used. All the reactions are monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel with UV light as detecting agents. Melting points and boiling points were recorded in Buchi 535 melting point apparatus and are uncorrected. FT-IR spectra were determined on a BrukerVector-22 infrared spectrometer using KBr disks.¹ ¹H NMR spectra were recorded at r.t. on a FT-NMR Bruker Ultra ShieldTM (500 MHz) instrument as CDCl₃ as a solvent, chemical shifts have been expressed in (ppm) downfield from TMS. Flash column chromatography was performed with silica gel eluting with ethyl acetate-petroleum ether.

2.2. Deep eutectic solvent preparation

Choline chloride-urea based deep eutectic solvent was prepared according to the literature.¹¹ The obtained deep eutectic solvent was used without any further purification.

2.3. Preparation of catalyst

The magnetic Fe₃O₄ nanoparticles were synthesized through modified co-precipitation reaction according to the previously reported method.¹² FeCl₂·7H₂O (5 mmol) and FeCl₃·6H₂O (10 mmol) were dissolved in deionized water (50 mL) and stirred mechanically at 80 °C for 15 min under a nitrogen atmosphere. This was followed by drop wise addition (about 10 min) of NaOH (40 mmol) solution to the reaction mixture and was stirred for 2 h. Then the precipitate was collected by a strong permanent magnet and washed with deionized water to pH 7. The collected precipitate was washed twice with ethanol and dried under vacuum at 60 °C overnight to obtain the Fe₃O₄ nanoparticles.

2.4. General procedure

A dried test tube, equipped with a magnetic stir bar, was charged with DES (0.5 mL), carbonyl compounds or epoxides (1.0 mmol), TMSCN (1.2 mmol), and Fe₃O₄ (10 mg), and the mixture was heated at 60 °C until the reaction was complete. After this time, ethyl acetate was added, to extract the product from DES phase. After evaporation of ethyl acetate, the resulting solid or viscous liquid was treated with acidic water and was purified by flash column chromatography or recrystallization with ethanol or diethyl ether to give pure products.

Results and discussion

Monodisperse Fe₃O₄ nanoparticles were synthesized according to reporting procedures, and were characterized by different techniques, including X-ray diffraction (XRD), scanning electron microscopy (SEM), vibrating-sample magnetometer (VSM) and fourier transforms infrared (FT-IR) spectra. The wide angle XRD patterns of the Fe₃O₄ nanoparticles showed a strong peak at 2θ = 35.1° along with a several peaks around 30°, 46°, 58°, 62° were related to the characteristic peak of crystallized Fe₃O₄ and were found to be similar to the reported values in the literature (Fig. 1). The average nanocrystalline size at 2θ = 36° was calculated by means of the Debye-Scherrer equation about 20-35 nm, which showed that the synthesized particles are nanometer sized.

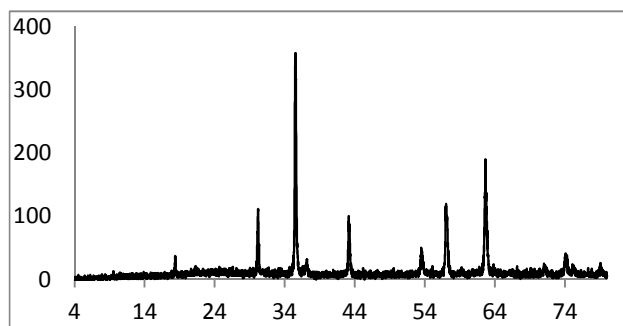


Fig. 1: XRD patterns of the Fe₃O₄ nanoparticles

Fourier transforms infrared (FT-IR) spectra (Fig. 2) shows the characteristic vibration bands 576 cm⁻¹ due to the Fe-O bonds and the bands at around 3423 and 1629 cm⁻¹ for water molecules.

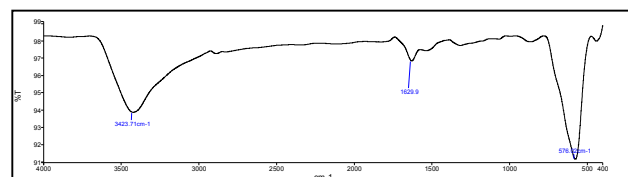


Fig. 2: Fourier transforms infrared (FT-IR) spectra of the Fe₃O₄ nanoparticles

SEM results showed that Fe₃O₄ nanoparticles have good dispersion tunable and uniform size (Fig. 3).

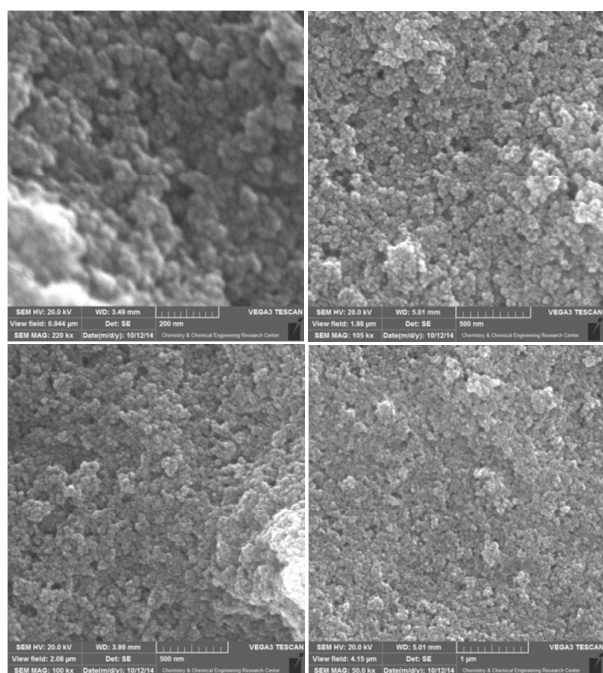


Fig. 3: SEM of the Fe₃O₄ nanoparticles

The relation between the applied magnetic field (H) (Oe) and the magnetization (M) (emu/g) of Fe₃O₄ nanoparticles shows the saturation magnetization of Fe₃O₄ is 50.15 emu g⁻¹ (Fig. 4).

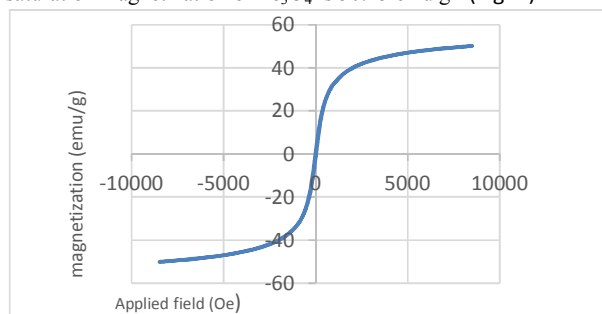


Fig. 4: Magnetization curve of the Fe₃O₄ nanoparticles

To evaluate so prepared magnetic nanoparticles in the synthesis of cyanohydrin, benzaldehyde (1 mmol) and TMSCN (1.2 mmol) was selected as model substrates in urea-choline chloride based deep eutectic solvent (0.5 mL). After stirring the reaction mixture for 6 h at room temperature, a yield of 20% cyanohydrin was obtained. The reaction was best performed by heating the reaction mixture in 60 °C in DES containing Fe₃O₄ (10 mg), the corresponding product **2a** was obtained in very good isolated yield in just 1 h. A control reaction was carried out in the absence of Fe₃O₄ under otherwise identical conditions gave low yields of products (10%) within a prolonged reaction time (5 h). Overall, employing Fe₃O₄ nanoparticles (10 mg) in DES was identified as the optimum conditions, giving the desired cyanohydrin in 92 % isolated yield. Having established optimal reaction conditions, we further studied the generality and the substrate scope for the condensation reaction of various aldehydes with TMSCN in DES. The results are summarized in Table 1. Various

aromatic aldehydes bearing either electron-withdrawing or electron-donating groups such as -Br, -Cl, -NO₂, -Me, -OMe, CO₂Me at different positions in the aromatic ring, provided the corresponding cyanohydrins **2a-p** in good yields. It is interesting to note that, both electron-withdrawing and electron-donating groups participate well in this reaction without the nature of substitutes in the aldehydes. Notably, even sterically hindered aldehydes, aliphatic aldehydes and heterocyclic aldehydes proved to be effective to afford the respective cyanohydrins. To verify the generality and further scope of this procedure, similar reactions were executed with various ketones under identical reaction conditions. The products (**2q-r**) were obtained in good yields with some extended reaction times, which are represented in Table 1 (entries 16, 17).

Among the cyanohydrine derivatives (α -hydroxy nitriles and β -hydroxy nitriles) the chemistry of the β -hydroxy nitriles, which are important structural units in many natural products, medicinal and coordination chemistry has been much less explored. Further application of this procedure was extended in a cyanosilylation of various epoxides using TMSCN.

The reactions proceeded smoothly under above optimized reaction condition to give the desired β -hydroxy nitriles in good to excellent yields (Table 2, entries 1–7). The scope and generality are demonstrated for various epoxides such as phenyl 2,3-epoxypropyl ether, isopropyl 2,3-epoxypropyl ether and styrene oxide to give the corresponding β -hydroxy nitriles in good to excellent yield. The reaction with unsymmetrical epoxides in most cases was regioselective, since the major products isolated were those arriving from the attack of the nucleophile to the less hindered position of the epoxide. Cyanolysis of a variety of substituted styrene oxides by TMSCN were fast and complete conversion was reached with the mixture of products.

A plausible mechanism for the regioselective ring-opening reaction was shown in Fig. 5. The chelation control with high surface area Fe₃O₄ which could bring the epoxide and TMSCN into close proximity, is an important tool to guide product regioselectivity. The dual role of Fe₃O₄ to coordinate to the epoxy oxygen atom and TMSCN, and the hydrogen bonding of DES might be among the most significant factors for this transformation. Furthermore, steric hindrance of epoxide and trimethylsilyl group in the TMSCN was responsible to attack from the less sterically hindered side of epoxide.

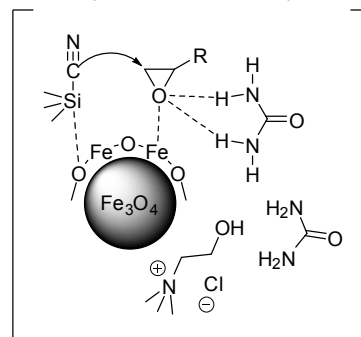


Fig. 5 Proposed model for epoxide ring-opening in DES

Based on the product distribution a plausible mechanism for green synthesis of cyanohydrin via cyanation reaction using TMSCN in the magnetic DES is illustrated in Figure 6. This reaction presumably occurs via activation of the carbonyl group of aldehyde with hydrogen bonding ability of deep eutectic solvent. Magnetic Fe_3O_4 nanoparticles may serve the dual role in this system, as a Lewis acidic surface and so can activate the carbonyl group of aldehydes by coordination of the Fe in the Fe_3O_4 . Furthermore, Fe_3O_4 assist in improving reactivity of TMSCN through weak interaction between oxygen of Fe_3O_4 with the silicon atom of TMSCN, leading to the formation of intermediate. The nucleophilic attack of TMSCN on thus activated carbonyl to form the corresponding α -hydroxy nitriles products.

The recyclability of magnetic DES in was important which helps address both economical and environmental view points in industrial scale. The magnetic DES easily be recovered, regenerated by heating to 80 °C in vacuum and reused with minimal loss of activity. Two procedures were tested in the recycling of DES for the formation of **2a**. First, after completion of the reaction, water (2 mL) was added and Fe_3O_4 was extracted with external magnet and DES was recovered with evaporating of the aqueous layer. In the second method, that was more efficient and practical, ethyl acetate (5 mL) was added to remove the product and reused the magnetic DES in subsequent reactions after washing with ethyl acetate (Table 3).

To further understand the stability and efficiency of the Fe_3O_4 nanocatalyst during the reaction and the recycling process, the amount of Fe leaching was determined by a flame atomic absorption spectroscopy (FAAS). The amount of Fe in anhydrous ethyl acetate after four cycles was 0.6 ppm that confirmed the catalytic activity and the stability of Fe_3O_4 during the course of reaction and work-up process. However, there was significant loss of the catalytic activity for the recycled Fe_3O_4 in DES in a minimum of water in the commercial ethyl acetate.

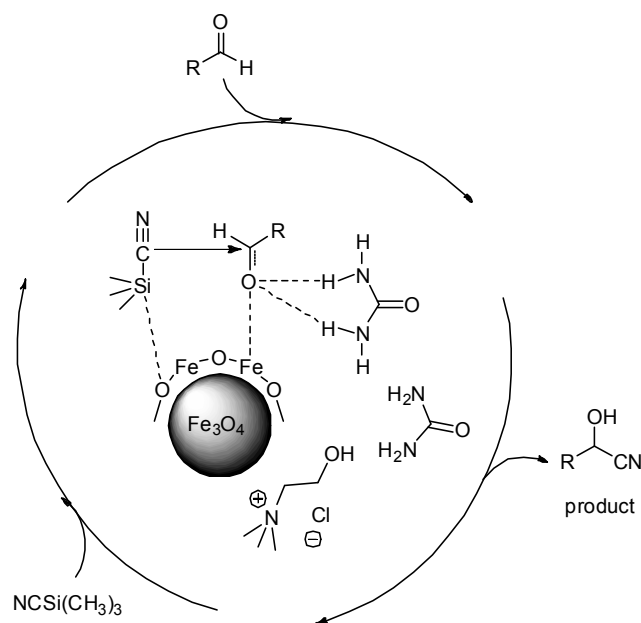


Fig. 6: Proposed mechanism for synthesis of cyanohydrines

Conclusions

A simple and efficient procedure using DES as a green solvent for the synthesis of cyanohydrin derivatives (α -hydroxy nitriles and β -hydroxy nitriles) by using a magnetic separable catalyst has been developed. A range of aromatic and aliphatic aldehydes with different functional groups as well as epoxides were successful substrates and proceeded in good to excellent yields (58–92%). The developed magnetic DES were notable features mild conditions, simple procedure, short reaction time, relatively broad substrate scope, especially environmental friendliness and good to excellent yields.

Acknowledgements

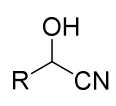
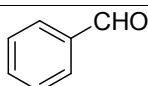
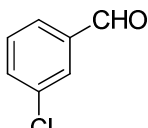
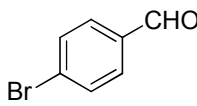
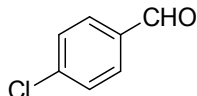
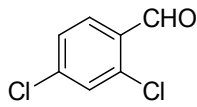
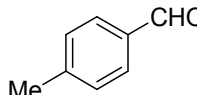
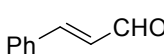
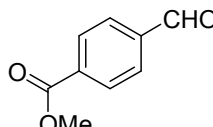
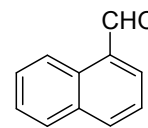
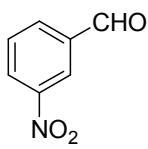
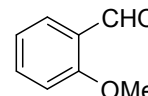
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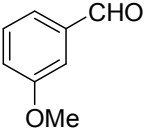
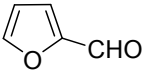
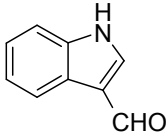
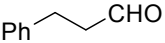
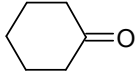
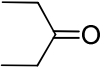
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Table 1. Synthesis of cyanohydrin in deep eutectic solvent

RCHO + TMSCN		$\xrightarrow[60\text{ }^\circ\text{C, 30-200 min}]{\text{Fe}_3\text{O}_4\text{ (10 mg) DES (0.5 mL)}}$		 2a-r
Entry	Aldehyde	Yield (%) ^a	Time (min)	Product
1		92	60	2a
2		82	60	2b
3		90	30	2c
4		75	100	2d
5		78	60	2e
6		80	40	2f
7		60	90	2g
8		68	120	2h
9		64	80	2i
10		78	74	2k
11		76	60	2l

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12		80	60	2m
13		68	120	2n
14		64	40	2o
15		58	100	2p
16		72	140	2q
17		64	200	2r

^a isolated yields.

Table 2. magnetic DES-catalyzed regioselective reaction of epoxides with TMSCN

Entry	Epoxide	Product	Yield (%) ^a	Ratio A:B
1			90	80:20
2			85	73:27
3			80	78:22
4			70	100:00
5			78	100:00
6			72	100:00
7			68	100:00

^a NMR Yields.

Table 3. Recyclability of a Magnetic DES

Entry	Run	Yields (%)
1	Fresh	92
2	First recycle	92
3	Second recycle	90
4	Third recycle	85