FULL PAPER



Preparation of choline chloride–urea deep eutectic solventmodified magnetic nanoparticles for synthesis of various 2-amino-4*H*-pyran derivatives in water solution

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A novel hybrid magnetic nanocatalyst was synthesized by covalent coating of Fe_3O_4 magnetic nanoparticles with choline chloride–urea deep eutectic solvent using 3iodopropyltrimethoxysilane as a linker. The structure of this new catalyst was fully characterized via elemental analysis, transmission and scanning electron microscopies, X-ray diffraction and Fourier transform infrared spectroscopy. It was employed in the synthesis of various 2-amino-4*H*-pyran derivatives in water solution via an easy and green procedure. The desired products were obtained in high yields via a three-component reaction between aromatic aldehyde, enolizable carbonyl and malononitrile at room temperature. The employed nanocatalyst was easily recovered using a magnetic field and reused four times (in subsequent runs) with less than 8% decrease in its catalytic activity.

KEYWORDS

eutectic, green, magnetic, nanocatalyst, pyran

1 | **INTRODUCTION**

Organic reactions in water without use of harmful organic solvents have attracted much attention, because water is cheap and safe, and it is regarded as one of the most suitable solvents from an environmental point of view due to a lack of inflammable, explosive and mutagenic properties; so, it is very suitable for use as a solvent in organic synthesis.^[1]

Magnetite nanoparticles have been employed as an important type of support for various catalysts because of their high surface area, superparamagnetic properties, low toxicity, ease of preparation, high potency for surface functionalization and facile recovery using an external magnetic field.^[2] Moreover, they have high Lewis acidity for catalysing various organic syntheses that mean they have a wide range of catalytic applications.^[3] Their surface functionalization potency provides a wide range of coating possibilities that prevent their aggregation and loss of catalytic activities. In this regard, various coating systems have been used for magnetic nanoparticles. However, coating them with deep eutectic solvents (DESs) has not been reported, which seems a useful way to create a new class of catalysts.

DESs have been considered as green solvents with catalytic activity composed of quaternary ammonium salts and a catalyst (hydrogen donor or acceptor). DESs have significant advantages, such as easy and cheap preparation, mostly biodegradable, chemical stability, non-flammability, low toxicity and low cost.^[4-9] DESs have been of great interest for their high solvent abilities and are known to dissolve diverse compounds such as carbohydrates, enzymes, synthetic polymers and metals.^[10–16] This means that when they are used as both solvent and catalyst in organic synthesis, they could be considered as homogeneous catalysts. It seems interesting to examine them as a coating of heterogeneous catalysts to prepare supported DES on heterogeneous catalysts for modification purposes. In recent years, DESs have been used as modifying agents in several studies. Abbott et al. first applied a DES of chlorocholine chloride (ChCl)-urea to modify cellulose.^[4] Later, Wibowo and Lee employed ChCl-urea to modify cotton fibres, and to adsorb hyaluronic acid.^[17] In 2013, Park *et al.* applied 3,3',4,4'-benzophenone tetracarboxylicdianhydride with ChCl-urea DES to produce antibacterial cotton fibres.^[18] In 2014, Tang *et al.* used DES for successful modification of silica. The prepared modified silica is a Lewis acid–base or a Lewis adduct and can exchange ions with organic acids.^[19]

In the study presented here, the integration of an organosilicon structure with magnetic nanoparticles to form porous magnetic nanocomposites and functionalization of the product with ChCl-urea DES were investigated in order to produce an active hybrid nanocatalyst with Lewis adduct associated with the DES. To determine the catalytic activity of the prepared catalyst, it was employed in the synthesis of the well-known 2-amino-4H-pyran family. 2-Amino-4Hpyrans are exciting heterocyclic compounds with several evident biological and pharmacological activities including antitubercular.^[20] antibacterial.^[21] antimicrobial,^[22,23] antifungal,^[24] anticancer,^[25,26] neuroprotective^[27] and photoactive properties,^[28] cosmetic and pigment abilities,^[29] agrochemical biodegradation potencies^[30] and HIV inhibitory activity.^[31] Although various methods have been reported for the synthesis of 2-amino-4H-pyrans, some of these methods have a series of drawbacks, such as hazardous reaction conditions, the use of expensive catalysts and solvents, long reaction times, complex work-up, high temperatures and poor yield.^[32–35] To overcome these problems, we have attempted to employ a new, effective, clean and recoverable catalyst in the synthesis of 2-amino-4H-pyran derivatives. Therefore, in the course of our previous efforts in new methodologies in organic syntheses,^[36-39] we have developed a green, practical and efficient method for the synthesis of 2-amino-4H-pyran derivatives via three-component reaction of malononitrile, aromatic aldehydes and carbonyl derivatives in the presence of DES-magnetic nanoparticles in water solution at room temperature.^[40-42] The details of methods employed and related results are discussed in the following.

2 | EXPERIMENTAL

All chemical compounds were purchased from Merck Chemical Co. (Germany) and Daejung Co. (South Korea) in high purities (>99%) and used without any further purification. Melting points were measured in capillary tubes using a Gallen Kamp melting point instrument. Fourier transform infrared (FT-IR) spectra were recorded with KBr pellets using a JASCO FT-IR spectrometer. ¹H NME and ¹³C NMR spectra were recorded with a Bruker Ultrashield 400 MHz spectrometer in CDCl₃ solution (University of Isfahan, Isfahan, Iran). CHN analyses were recorded with a LECO CHNS-932 elementary chemical analyser (model 601–800-500). X-ray diffraction (XRD) patterns were collected using a Philips X'pert MPD diffractometer with a copper target at a tube voltage of 40 kV. Transmission electron microscopy (TEM) images were obtained using an S360 Mv2300 with an accelerating voltage of 100 kV. The microstructure of nanoparticles was examined using field emission scanning electron microscopy (SEM) analyses (S-4160, Hitachi, Japan).

2.1 | Synthesis of 3-Iodopropyltrimethoxysilane (IPS)

First, 3-chloropropyltrimethoxysilane was converted to the more reactive IPS. For this purpose, NaI (0.0686 g, 3.5 mmol) was dissolved in acetone (15 ml) in a dry 50 ml round-bot-tomed flask equipped with a reflux condenser and chloropropyltrimethoxysilane (0.75 g, 3.5 mmol) was added. The mixture was refluxed overnight under argon flow. After centrifugation to remove NaCl, the acetone was removed by evaporation, and the residue was dissolved in CH_2Cl_2 to precipitate the remaining inorganic salts. Finally, the solvent was removed using a rotary evaporator to afford the pure product.

2.2 | Coating of Fe₃O₄ with IPS

First, naked magnetic Fe_3O_4 (MAG) nanoparticles were prepared through a chemical co-precipitation method (as described previously^[43,44]) and subsequently were coated with IPS to achieve IPS-functionalized magnetic nanoparticles (MAG/IPS), as mentioned in the previous literature.^[45,46] For this purpose, Fe_3O_4 nanoparticles (1 g) were suspended in ethanol (10 ml) and then IPS (4 ml) was added. The suspension was stirred at 60 °C for 8 h. The particles were separated using an external magnet and, after cooling to room temperature, washed three times with water and acetone and dried to afford MAG/IPS.

2.3 | Synthesis of DES

The employed DES (ChCl-2urea) was synthesized according to a reported method.^[41] This involved reaction of ChCl (1 mol) with urea (2 mol) at 80 °C and stirring to afford a clear solution that was used without further purification.

2.4 | Synthesis of ChCl-urea immobilized on MAG/IPS (MAG/IPS/DES)

The prepared MAG/IPS (0.1 g) and ChCl-2urea DES (2 g) were added to a 50 ml round-bottomed flask, and the suspension was stirred at 90 °C for 18 h. The reaction mixture was then cooled to room temperature. The particles were separated using an external magnet, washed three times with

water and acetone and dried to afford the final catalyst (MAG/IPS/DES).

2.5 | General procedure for preparation of 2-Amino-4,6-diphenyl-4*H*-pyran-3-carbonitrile derivatives

Aldehyde (1 mmol) and malononirile (1 mmol) were added to a 25 ml round-bottomed flask containing MAG/IPS/DES (0.1 g) and water (2 ml). The mixture was stirred for 30 min and ketone (1 mmol) was added. The resulting mixture was stirred at room temperature. After completion of the reaction (as monitored by TLC), the catalyst was removed using a magnet, and then water (10 ml) was added. The water layer was extracted with CH_2Cl_2 (3 × 30 ml), dried (MgSO₄) and concentrated. The product was purified by recrystallization or TLC on 20×20 cm glass plate with hexane-EtOAc (1:1 ratio) as solvent, or both. All products were known compounds and their physical and spectroscopic data (m.p., FT-IR, ¹H NMR, ¹³C NMR and elemental analysis) were compared with those of authentic samples in the literature.^[39-42] The physical and spectroscopic data for selected compounds are detailed below. Moreover, the images of all analyses related to this products were shown in the supporting informations.

2.5.1 | **2-Amino-4-(4-bromophenyl)-6-***p***-tolyl-4***H***-pyran-3-carbonitrile** (4c)

White solid; yield 94%; m.p. 175–177 °C. FT-IR (KBr, cm ⁻¹): 810, 1073, 1504, 1674, 2350, 2922, 3436. ¹H NMR (400 MHz, CDCl₃, δ , ppm): 2.35 (s, 1H), 3.82–3.87 (m, 1H), 4.56 (d, J = 6.4 Hz, 1H), 7.18–7.27 (m, 5H), 7.48 (d, J = 8 Hz, 1H), 7.77 (d, J = 9.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃, δ , ppm):21.78, 28.59, 40.8, 111.49, 111.70, 123.40, 124.42, 128.23, 128.38, 129.04, 129.65, 129.72, 130.44, 131.91, 132.19, 132.52, 133.19, 135.51, 145.45.

2.5.2 | Ethyl 6-amino-4-(4-chlorophenyl)-5cyano-2-methyl-4*H*-pyran-3-carboxylate (4j)

Pale yellow solid; yield 94%; m.p. 169–170 °C. FT-IR (KBr, cm⁻¹): 837, 1059, 1173, 1267, 1409, 1608, 1648, 1696, 2193, 2981, 3332, 3409. ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.14 (t, J = 7 Hz, 3H), 2.40 (s, 3H), 4.06 (m, 2H), 4.46 (s, 1H), 4.49 (s, 2H), 7.16 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃, δ , ppm): 13.9, 18.5, 38.3, 60.8, 107.6, 118.6, 128.8, 128.9, 133.0, 142.3, 152.8, 157.1, 157.4, 165.6. Anal. Calcd for C₁₆H₁₅N₂O₃Cl (%): C, 60.29; H, 4.71; N, 8.79. Found (%): C, 60.30; H, 4.75; N, 8.81.

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2.5.3 | Ethyl 6-amino-4-(4-bromophenyl)-5cyano-2-methyl-4H-pyran-3-carboxylate (4 k)

Pale yellow solid; yield 92%; m.p. 174–175 °C. FT-IR (KBr, cm⁻¹): 835, 1068, 1264, 1370, 1485, 1608, 1691, 2194, 2980, 3329, 3409. ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.14 (t, J = 7 Hz, 3H), 2.40 (s, 3H), 4.06 (m, 2H), 4.44 (s, 1H), 4.52 (s, 2H), 7.11 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃, δ , ppm): 13.9, 18.4, 38.4, 60.8, 105.6, 115.9, 118.5, 129.3, 131.7, 144.5, 157.5, 159.9, 160.2, 165.8. Anal. Calcd for C₁₆H₁₅N₂O₃Br (%): C, 52.89; H, 4.13; N, 7.71. Found (%): C, 52.82; H, 4.19; N, 7.66.

2.5.4 | Ethyl 6-amino-4-(4-nitrophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (4 1)

Pale yellow solid; yield 75%; m.p. 172–173 °C. FT-IR (KBr, cm⁻¹): 850, 1059, 1173, 1270, 1345, 1519, 1608,1691, 2199, 2982, 3332, 3403. ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.13 (t, *J* = 7 Hz, 3H), 2.45 (s, 3H), 4.07 (q, *J* = 7 Hz, 2H), 4.57 (s, 2H), 4.59 (s, 1H), 7.40 (d, *J* = 8 Hz, 2H), 8.21 (d, *J* = 8 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃, δ , ppm): 14.0, 18.7, 38.8, 61.0, 106.8, 118.2, 124.1, 128.4, 151.0, 152.1, 153.1, 157.6, 158.1, 165.3. Anal. Calcd for C₁₆H₁₅N₃O₅ (%): C, 58.36; H, 4.56; N, 12.76. Found (%): C, 57.54; H, 3.00; N, 12.80.

3 | **RESULTS AND DISCUSSION**

First, the desired catalyst was prepared according to the details presented in Section 1. The employed methodology for this synthesis is shown in Scheme 1. After loading of IPS on the surface of MAG via Fe–O–Si bonds, the



SCHEME 1 Preparation of MAG/IPS/DES

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hydroxyl groups of DES attack the C—I bonds and iodide leaves the compound, the covalent bonding between DES and IPS leading to the final catalyst.

The structure and properties of the catalyst were confirmed with FT-IR spectroscopy, elemental analysis, SEM, TEM and XRD experiments, the details of are presented here.

The FT-IR spectra of magnetite, MAG/IPS and MAG/ IPS/DES are depicted in Figure 1. The FT-IR spectrum of magnetite nanoparticles (Figure 1a) shows the stretching vibrations at 584 and 3200–3500 cm⁻¹, respectively corresponding to Fe—O and water (free or adsorbed water that still remained in the sample) stretching vibrations. FT-IR spectra of both MAG/IPS (Figure 1b) and MAG/IPS/DES (Figure 1 c) also show the same peaks for Fe—O vibrations. The coating of IPS on the surface of MAG can be confirmed by the bands at 1080 cm⁻¹ assigned to the Si—O stretching vibrations in Figure 1(b,c).

In addition, the broad band at 3392 cm^{-1} is assigned to the O–H stretching vibrations and the presence of the anchored propyl group is confirmed by C–H stretching vibrations that appear at 2880 and 3000 cm⁻¹ (Figure 1b,c). The characteristic peaks of the final catalyst (MAG/IPS/ DES) are seen at 1657 cm⁻¹, was attributed to C=O symmetric stretching vibration of amidic carbonyl of urea, and peaks around 1268 and 1040 cm⁻¹, respectively corresponding to the stretching vibrations of C–N and C–O groups. These results indicate that magnetite nanoparticles were successfully coated with the IPS and then the ChCl-2urea DES.

To confirm the loading of IPS and DES on the surface of magnetite nanoparticles, elemental analysis was used to



FIGURE 1 Comparison of FT-IR spectra of (a) MAG, (b) MAG/IPS and (c) MAG/IPS/DES

determine the atomic structure of the final catalyst. According to this analysis, the amounts of nitrogen, carbon and hydrogen are respectively 0.385, 2.746 and 0.424 wt%. The presence of nitrogen and carbon confirms the loading of DES (consisting of urea) and the presence of carbon and



FIGURE 2 XRD patterns of (a) Fe₃O₄ and (b) MAG/IPS/DES



FIGURE 3 SEM images of MAG/IPS/DES

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hydrogen confirms the loading of IPS on the surface of the magnetic core.

To examine the crystalline structure of the catalyst, XRD patterns of MAG and MAG/IPS/DES were obtained. The results are shown in Figure 2. The positions and relative intensities of all peaks in the XRD pattern of MAG/IPS/DES are consistent with the XRD pattern of Fe₃O₄, which confirm that the grafting process does not induce any phase change of Fe₃O₄.

To investigate the shape and size of the prepared nanocatalyst, SEM images were recorded for the final catalyst and the results are shown in Figure 3. The SEM images for the employed catalyst are shown at 500 and 750 nm scales. These images show slight aggregation which might be because the layer of DES surrounding may interact with each other. However, the SEM images confirm the nanosized structure of the MAG/IPS/DES nanocatalyst. For more clarification and to obtain more detailed images of the catalyst, TEM images were recorded as shown in Figure 4. These images were obtained at 20, 46, 60 and 100 nm sizes to better present the structure of the catalyst. In addition, particle size analysis was used to define the sizes of particles. These images indicate that the prepared catalyst has particles of nearly spherical shape with an average diameter of the core of around 13 nm.

After the characterization of the prepared catalyst, to explore its catalytic activity, it was employed in a one-pot, three-component synthesis of 2-amino-4H-pyran derivatives using mild conditions. The general reaction for this synthesis is shown in Scheme 2. First, to obtain the optimum

conditions for this reaction, model substrates 4bromobenzaldehyde, malononitrile and acetophenone were selected and various parameters such as the amount of catalyst (0.01, 0.05 and 0.1 g), solvent (water, ethanol, acetonitrile and toluene), reaction temperature (25, 75 and 100 °C) and reaction time (55 and 120 min) were examined. The results of all optimization experiments for the model reaction are listed in Table 1.

In the absence of catalyst, only a trace amount of product was obtained (Table 1, entry 1) and in the presence of DES alone (entry 10) the yield was only 35%. These two experiment show that the reaction needs an effective catalyst. Next, the catalytic activity of MAG/IPS was compared with that of MAG/IPS/DES. For this purpose, the reactions were carried out separately at room temperature in water with both the catalysts for the appropriate time (Table 1). In the presence of MAG/IPS (entry 12), the yield was only 74%. This shows the enhancing effect of DES. Therefore, this result indicated that the catalytic efficiency of DES was increased by immobilization onto MAG/IPS.

Obviously, increasing the amount of catalyst from 0.01 to 0.1 g increases the yield of product from 52 to 93% in water at room temperature (Table 1, entries 2–4). Therefore, 0.1 g was selected as optimum amount of catalyst. Then, the effect of solvent was considered using various polar and nonpolar solvents (water, toluene, acetonitrile and ethanol). The best results were obtained when 0.1 g of MAG/IPS/DES was used in water at room temperature. Moreover, the reaction was performed in the absence of any solvent (in the presence of catalyst) and only a small amount of product was observed



FIGURE 4 TEM images (left) and particle size analysis (right) for MAG/IPS/DES



SCHEME 2 General procedure for synthesis of 2-amino-4*H*-pyrans

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TABLE 1 Optimization of three-component reaction of 4-methylacetophenone, 4-bromobenzaldehyde and malonitrile under various conditions^a

Entry	Catalyst	Catalyst amount (g)	Solvent	Temp. (°C)	Time (min)	Yield (%) ^b
1	_	_	_	100	120	<5
2	Mag/IPS/des	0.01	Water	25	55	52
3	Mag/IPS/des	0.05	Water	25	55	75
4	Mag/IPS/des	0.1	Water	25	55	94
5	Mag/IPS/des	0.1	Water	70	55	95
6	Mag/IPS/des	0.1	Water	25	35	60
7	Mag/IPS/des	0.1	Ethanol	25	55	94
8	Mag/IPS/des	0.1	CH ₃ CN	25	55	81
9	Mag/IPS/des	0.1	Toluene	25	55	55
10	ChCl-2urea	0.1	Water	25	120	35
11	Mag/IPS/des	0.1	_	25	120	<20
12	Mag/IPS	0.1	Water	25	55	75

^aReaction conditions: 4-bromobenzaldehyde (1 mmol), 4-methylacetophenone (1 mmol), malononitrile (1 mmol), water (2 ml), and the required amount of catalyst at 95 °C.

^bIsolated yield.

 TABLE 2
 Details for syntheses of 2-amino-4H-pyran derivatives in presence MAG/IPS/DES

NSubstrate	R1	R2	R3	Product ^b	M.p. (°C)	Time (min)	Yield ^c (%)	Ref.
4a	Ph	Η	Η	NC O	Oil	90	62	[47]
4b	Ph	Н	2-Naphthyl	NC Ph	Oil	90	63	[47]
4c	4-me-Ph	Н	4-BrPh	NC NH ₂ O Br Me	175–177	55	94	[48]
4d	Ph	Ph	4-MePh	NC O Me Ph D	204–207	65	85	[48]
4e	Ph	Ph	4-OMePh	NC O Ph	186–189	150	45	[48]
4f	Ph	Ph	Ph	NC O Ph	225–228	75	64	[48]

(Continues)

TABLE 2 (Continued)

NSubstrate	R1	R2	R3	Product ^b	M.p. (°C)	Time (min)	Yield ^c (%)	Ref.
4 g	Ph	Ph	4-BrPh	NC O Br Ph	195–197	55	93	[48]
4 h	Ph	Ph	4-NO ₂ Ph	NC O O ₂ N Ph	130–133	55	94	[48]
4i	Ph	Ph	4-ClPh		200–203	55	92	[20]
4j	Me	CO ₂ Et	4-ClPh		169–170	65	94	[49]
4 k	Me	CO ₂ Et	4-BrPh	NC O Br O OEt	174–175	65	92	[49]
41	Me	CO ₂ Et	4-NO ₂ Ph	NC O O ₂ N O OEt	172–173	65	75	[49]

^aReaction conditions: aldehyde (1 mmol), malononirile (1 mmol), ketone (1 mmol), water (2 ml, r.t.), catalyst (0.1 g).

^bAll compounds are known and their structures were established from their spectral data and melting points as compared with literature values.

^cYields refer to isolated products.

(Table 1, entry 11). In these experiments, the most encouraging result was obtained when water was employed as the solvent, and so it was selected as the solvent of choice for the reaction. Next, two different temperatures (25 and 70 °C) were employed for the reaction, the best result being obtained at 25 °C. On increasing the temperature from 25 to 70 °C, no significant increase in the yield was observed. In other experiments, various reaction times were employed, and 55 min was determined as the optimum time for this reaction (Table 1, entries 4–6).

Table 2 presents the variation of time for other derivatives, when MAG/IPS/DES was employed as catalyst. These optimized values were employed in reactions for the synthesis of other 2-amino-4*H*-pyran derivatives, and the obtained results are summarized in Table 2. According to these results, the reaction yields for different derivatives were between 45 and 95%. In addition, using benzaldehydes with electron-withdrawing groups (at C4), the product was obtained in higher yields. This is because, in the two steps of the reaction mechanism, electron-withdrawing groups

facilitate nucleophilic addition to benzylic position of the aromatic aldehyde. Evidently, electron-releasing groups at C4 decrease the yield of the final product. Therefore, among all substrates, the reaction of 4-methoxybenzaldehyde gave the least yield (Table 2, 4e).

A plausible mechanism for this reaction is proposed, as illustrated in Scheme 3. According to this mechanism, hydrogen bonding of the catalyst and Brønsted basicity of urea are the main factors that influence the catalytic ability of MAG/ IPS/DES and carrying the reaction process. The reversible hydrogen bonding between urea and carbonyl could activate aldehyde or malononitrile for addition of the nucleophile. Moreover, the catalyst facilitates the keto–enol tautomerism of enolizable aldehyde to make it suitable for nucleophilic addition to the intermediate.

Finally, the recyclability of the catalyst was examined under the optimized conditions. The results are shown in Figure 5, involving consecutive experiments for the model reaction (between 4-bromobenzaldehyde, 4methylacetophenone and malononitrile under the optimum



FIGURE 5 Recyclability of MAG/IPS/DES in the model reaction

conditions) and obtaining the reaction yield. As shown in Figure 5, the catalyst was recycled five times with only 8% loss in the reaction yield. It is important to highlight that in each process, the catalyst was easily recovered using an external magnet, washed with acetone and ethanol and reused in the next run after being dried. These experiments show that further reactions (up to five consecutive runs) using the recycled magnetic catalyst can be performed effectively.

4 | CONCLUSIONS

In summary, a new catalyst was prepared and employed in the synthesis of 4H-pyran derivatives at room temperature via a one-pot, multicomponent reaction between aromatic aldehyde derivatives, malononitrile and acetophenone derivatives or ethyl acetoacetate in water solution. The prepared catalyst is a magnetic, nano-sized and hybrid catalyst because of



covalent bonding between magnetic core and DES. Therefore, this catalyst could exhibit the properties of both magnetic catalysts and DESs. The presented method offers several advantages including use of a magnetically recoverable nanocatalyst, high yields, simple work-up procedure, using water as green solvent and mild conditions (room temperature). Various 4H-pyrans with different structural parts have been synthesized by this method in a short time and at room temperature.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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