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Superparamagnetic Fe_3O_4 Nanoparticles in Deep Eutectic Solvent: an Efficient and Recyclable Catalytic System for the Synthesis of Primary Carbamates and Mono-Substituted Urea

Iman Dindarloo Inaloo,*[a] Sahar Majnooni[b] and Mohsen Esmaeilpour[a]

Dedication ((optional))

Abstract: Superparamagnetic Fe_3O_4 nanoparticles were prepared and tested for the synthesis of various primary carbamates and mono- or *N,N*-disubstituted ureas using urea as the eco-friendly carbonyl source in the presence of a biocompatible deep eutectic solvent (DES). This efficient and phosgene-free process provided an inexpensive and attractive route to synthesize the products in moderate to excellent yields. The employed DES plays both catalytic roles and green reaction medium for this reaction. Moreover, the magnetic catalyst and DES have been reused several times in this procedure without significant loss of activity.

Introduction

In the current century, the development of simple, efficient, green and low-cost methodologies for the synthesis of organic compounds has been attracted scientists' attentions and industrial interests. Although traditional methods focused mainly on high-yield procedures in the shortest time, modern methods are keen to improve reusability, prevent waste production, and reduce toxicity. Obviously, hazardous reagents should be replaced by safe resources and more green and eco-friendly methodologies to minimize the amount of toxic byproducts.[1]

The concept of "Green Chemistry" refers to actions aimed to improve the reaction efficiency using natural resources, comprising the design and implementation of new chemical processes and transformations that operate in a more efficient, safe, and environmentally way.[1] Thanks to the framework of green chemistry, solvents occupy a strategic place. To be qualified as a green medium, the components of this solvent must possess different criteria such as availability, non-toxicity, recyclability, thermal stability, non-flammability, renewability, low vapor pressure, cheap and also biodegradability.[2] Deep eutectic solvents (DESs) are particularly attractive in organic synthesis owing to their ability to dissolve both polar and non-polar reactants and their facile recovery.[3-6] For the first time, DESs were reported at the beginning of the 21st century by Abbot and co-workers in which the combination of quaternary ammonium or phosphonium salts with an organic molecule is typically occurred by hydrogen bond donor units.[4] Up to now, different kinds of DESs have been synthesized that present notable advantages in organic syntheses.[3,4] Recently, an efficient and novel DES has been formed from the reaction of choline chloride and zinc chloride, which can be used as stable Lewis acid and green solvent for organic syntheses.[5,6] Compared with other DESs, the advantages of this DES are having an easy synthetic process, low melting point, high purity, non-toxicity, biodegradability and lower price.[6]

Transition-metal catalyzed organic reactions are often considered to follow the principles of green chemistry because of using minimum energy and more clean reagents or auxiliaries as well as the minimization of wastes.[7] Nanocatalysts are considered to be a bridge between heterogeneous and homogeneous catalysts.[8] One of the attractive properties of nanomaterials is that the active component has a high specific surface area leading to an increase of the contact with the reactants.[8] Also, a higher surface area gives nanomaterials more active surface; they are hardly separable. Therefore, it is important to design a recoverable and well-dispersed catalyst. Magnetite nanoparticles (MNPs) are very promising catalytic structures due to their large specific surface area and magnetic properties.[9] They can be collected very easily by using a magnet to prevent any loss of catalyst amount.[9] Recently, the chemists have focused on the catalytic aspects of magnetite nanoparticles of Fe_3O_4 (MNP-Fe_3O_4) to improve the protocols of catalytic activity.[10]

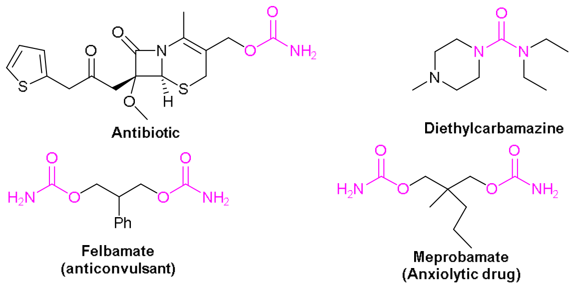

Figure 1. Some biologically active carbamates and ureas.

Carbamates (carbamic esters) and ureas are important industrial intermediates for agrochemicals (i.e., herbicides, pesticides, bactericides and antiviral agents),[11] pharmaceuticals (i.e., carisoprodol, methocarbamol, felbamate, zafirlukast, retigabine, diethylcarbamazine and meprobamate),[12] organic syntheses (i.e., synthesis of heterocyclic compounds and protection of amino group in peptide chemistry)[13] and polymer syntheses (i.e.,

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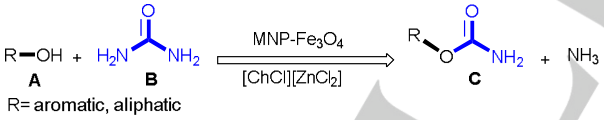
polyurethanes and peptides).[14] Some important carbamate and urea derivatives with biological activities are depicted in Figure 1.[11-14]

Generally, the synthesis of substituted carbamates involves the reaction of suitable amines and alcohols with phosgene ($COCl_2$) as a carbonyl source,[15] though, such well-established protocols present some drawbacks such as insufficiency for *N*-unsubstituted (primary) carbamates, using highly toxic and corrosive reagents, the production of massive toxic-wastes, longer reaction time, and low efficiency and yields.[15, 16]

During past few years, great efforts have been done to explore the environmentally benign routes that employ other carbonyl sources including 1,1,1-trichloromethyl formate (diphosgene),[17] trichloroacetylchloride,[18] 1,1-carbonyldiimidazole (CDI),[19] carbonate esters,[20] *N*-acylbenzotriazoles,[21] isocyanates or cyanate salts,[22] isocyanides,[23] dialkylazodicarboxylate,[24] azides,[25] amides,[26] CO_2 [27] and CO [28] instead of $COCl_2$ for carbamate production. Despite the development of new carbonyl sources, these processes utilize strong bases and/or toxic metal-based catalysts, expensive ligands, multi-step procedures and harsh reaction conditions.

Pursuing our interest in the development of eco-friendly approaches to find carbamate derivatives bearing remarkable applications in pharmaceuticals and agrochemistry, the use of urea and polyurea as safe and green carbonyl sources is being considered.[29]

As part of our interest in the development of simple, efficient and eco-friendly protocols for the synthesis of useful organic compounds, we recently reported the synthesis of primary carbamates under solvent-free conditions.[30] In continues, we report an experimentally and environmentally convenient one-pot process for the synthesis of primary carbamates by using urea as a safe carbonyl source via MNP-Fe_3O_4 and choline chloride:Zinc (II) chloride [ChCl][$ZnCl_2$] as recoverable catalyst and solvent, respectively (Scheme 1).

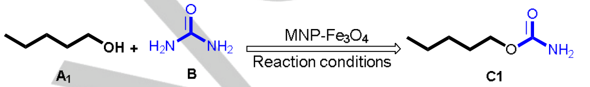


Scheme 1. Primary carbamates synthesis **(C)** via urea.

Results and Discussion

In an initial endeavor to determine the best conditions, the reaction of 1-pentanol (**A**1) and urea (**B**) was chosen as a model reaction in the presence of MNP-Fe_3O_4. Firstly, a series of common solvents and choline chloride-based DESs including [ChCl][$MCl]_2$ (M = Fe, Zn, Sn, Al, Ni, Cu, Co, La, Cr, Mn and Ca) were selected to study their performance on the synthesis of 1-pentyl carbamate (**C**1). The activity of these solvents was evaluated using the calculated yield of synthesized 1-pentyl carbamate (**C**1) and obtained results were summarized in Table 1. As shown in which, DES originated from choline chloride and Zinc (II) chloride [ChCl][$ZnCl_2$] had the highest activity for the preparation of the desired product. The effect of molar ratio of urea to 1-pentanol on this reaction was also investigated. The best yield of 1-pentyl carbamate (**C**1) was observed when the molar ratio of urea:1-pentanol be 2:1 (Table 1, entry 10). For the further corroborate of the effect of MNP-Fe_3O_4 as a catalyst, the reactions were performed by some different amount of catalyst. The desired product did not proceed with excellent yield without using MNP-Fe_3O_4 (Table 1, entry 24). To obtain the best amount of the catalyst, these conditions were studied using different amounts of MNP-Fe_3O_4 (5, 10, 15 and 20 mol %). These experiments showed that the reduction of the catalyst amount from 10 to 5 mol% extensively made a decrement in the reaction yield (Table 1, entry 25).

Table 1. Optimization of reaction parameters for the synthesis of 1-pentyl carbamate (**C**1).



Entry	Molar ratio Phenol:Urea	Solvent	Cat (mol %)	Temp [°C]	Yield (%)[a]
1	1:2	None	10	130	23
2	1:2	$ClCH_2CH_2Cl$	10	130	43
3	1:2	CH_3CN	10	130	44
4	1:2	Toluene	10	130	41
5	1:2	DMF	10	130	46
6	1:2	DMSO	10	130	40
7	1:2	PEG 400	10	130	38
8	1:2	ChCl:urea (1:2)	10	130	42
9	1:2	ChCl:$FeCl_3$ (1:1)	10	130	78
10	1:2	ChCl:$ZnCl_2$ (1:1)	10	130	93
11	1:2	ChCl:$SnCl_2$ (1:1)	10	130	81
12	1:2	ChCl:$AlCl_3$ (1:1)	10	130	61
13	1:2	ChCl:$NiCl_2$ (1:1)	10	130	65
14	1:2	ChCl:$CuCl_2$ (1:1)	10	130	57
15	1:2	ChCl:$CoCl_2$ (1:1)	10	130	62
16	1:2	ChCl:$LaCl_3$ (1:1)	10	130	73
17	1:2	ChCl:$CrCl_3$ (1:1)	10	130	81
18	1:2	ChCl:$MnCl_2$(1:1)	10	130	72
19	1:2	ChCl:$CaCl_2$ (1:1)	10	130	69
20	1:1	ChCl:$ZnCl_2$ (1:1)	10	130	72
21	1:1.5	ChCl:$ZnCl_2$ (1:1)	10	130	81
22	1:2.5	ChCl:$ZnCl_2$ (1:1)	10	130	91
23	1:3	ChCl:$ZnCl_2$ (1:1)	10	130	92
24	1:2	ChCl:$ZnCl_2$ (1:1)	None	130	15
25	1:2	ChCl:$ZnCl_2$ (1:1)	5	130	63
26	1:2	ChCl:$ZnCl_2$ (1:1)	15	130	91
27	1:2	ChCl:$ZnCl_2$ (1:1)	20	130	89
28	1:2	ChCl:$ZnCl_2$ (1:1)	10	110	71
29	1:2	ChCl:$ZnCl_2$ (1:1)	10	150	92

[a] Isolated yield.

However, using larger values (15 and 20 mol %) exhibited no significant enhancement in the reaction yield (Table 1, entries 26 and 27). The yield of 1-pentyl carbamate (**C**1) was also checked

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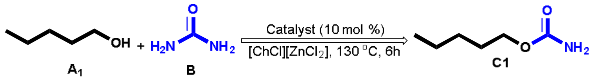
out by temperature. These results showed that the better yield of the desired product was obtained when the reaction temperature and the reaction time were 130 °C and 6 h, respectively.

As a part of our interests to find the best and the greenest conditions for the synthesis of primary carbamates, the effect of Lewis acids such as MNP-MFe_2O_4 (M = Ni, Co, Mn, Cu, Zn and Sn), bulk Fe_3O_4, Fe_2O_3, $FeCl_3$, $FeBr_2$, $Fe(OAc)_2$, $Cu(OAc)_2$, $AlCl_3$, $CoCl_2$, $ZnCl_2$, $SnCl_2$, $NiCl_2$ and TiO_2 was explored instead of MNP-Fe_3O_4 on the model reaction. On the basis of results exhibited in Table 2, the reaction was led to the desired product in the presence of all checked catalysts but lower yields were received after 6 h at 130 °C.

Table 2. Results of 1-pentyl carbamate (**C1**) from 1-pentanol (**A1**) and urea (**B**) over different catalysts.[a]



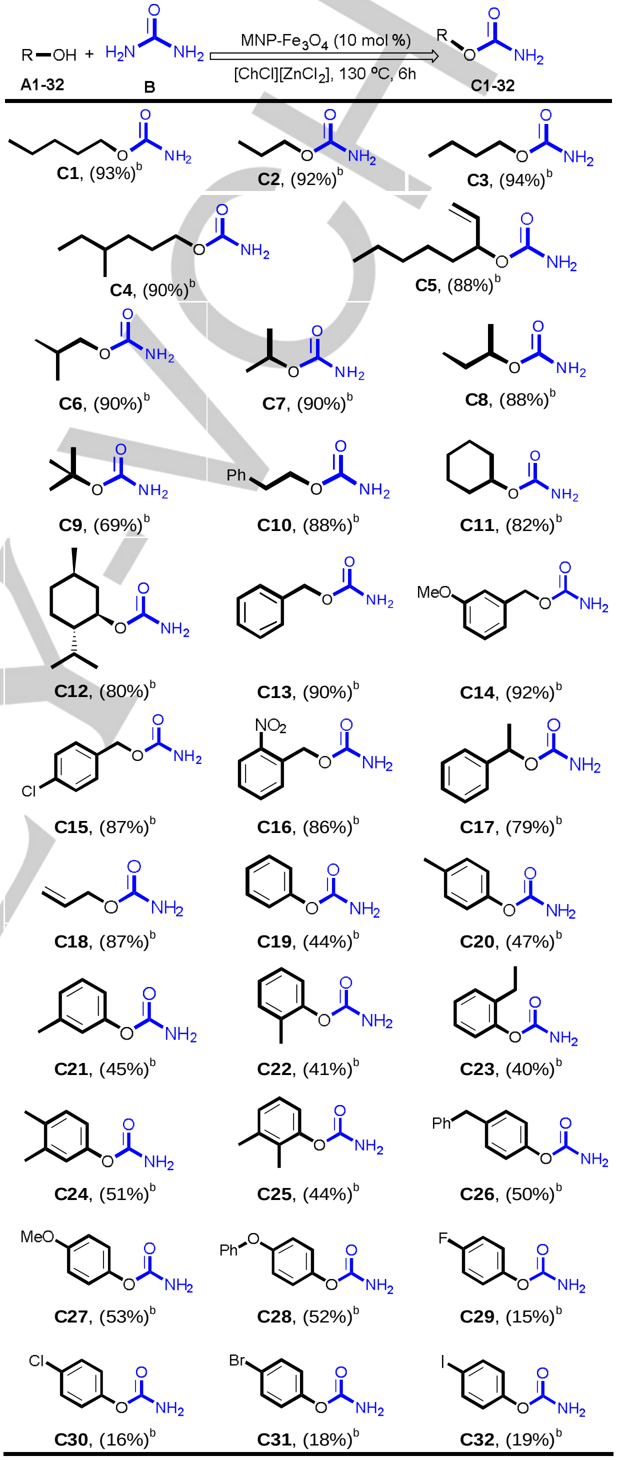
Entry	Catalyst	Yield (%)[b]
1	MNP-Fe_3O_4	93
2	Bulk-Fe_3O_4	81
3	MNP-$NiFe_2O_4$	81
4	MNP-$CoFe_2O_4$	86
5	MNP-$MnFe_2O_4$	82
6	MNP-$CuFe_2O_4$	87
7	MNP-$ZnFe_2O_4$	89
8	MNP-$SnFe_2O_4$	88
9	Fe_2O_3	79
10	$FeCl_3$	83
11	$FeBr_2$	82
12	$Fe(OAc)_2$	86
13	$Cu(OAc)_2$	74
14	$AlCl_3$	71
15	$CoCl_2$	79
16	$ZnCl_2$	69
17	$SnCl_2$	81
18	$NiCl_2$	70
19	TiO_2	73

[a] Reaction conditions: 1-pentanol (1 mmol), urea (2 mmol), [ChCl][$ZnCl_2$] (3 mL), catalyst (10 mol %), 130 °C, 6 h. [b] Isolated yield.

Under these optimized conditions, the scope and generality of this protocol were pursued using various alkyl and aryl alcohols and the results are summarized in Table 3.

The reaction of alkyl alcohols with urea gave the corresponding primary carbamates in good to excellent yields (Table 3, entries **C1-12**). Interestingly, alkyl alcohol like *tert*-butyl alcohol with steric hindrance was also reactive in this method and procreated a product in 69% yield (Table 3, entry **C9**). As expected, allyl alcohol and benzyl alcohol derivatives presented the desired products in excellent yields even in the presence of electron-withdrawing groups in which no reduction in the efficiency was observed (Table 3, entries **C13-19**). However, lower yield was beholden for 1-phenylethanol, which suffers from steric hindrance (Table 3, entry **C18**). Moreover, the same results were apperceived for different phenols that are substituted by nucleophiles. The use of phenols and their derivatives bearing electron-rich substitutions afforded the desired products in moderate yields (Table 3, entries **C20-28**). Unfortunately, using phenols with halogen substitutions as nucleophile led to a drastic decrease in reaction conversion and the reaction will be quenched in low yields (<20%) (Table 3, entries **C29-32**).

Table 3. Substrate scopes.[a]



C1, (93%)[b]
C2, (92%)[b]
C3, (94%)[b]
C4, (90%)[b]
C5, (88%)[b]
C6, (90%)[b]
C7, (90%)[b]
C8, (88%)[b]
C9, (69%)[b]
C10, (88%)[b]
C11, (82%)[b]
C12, (80%)[b]
C13, (90%)[b]
C14, (92%)[b]
C15, (87%)[b]
C16, (86%)[b]
C17, (79%)[b]
C18, (87%)[b]
C19, (44%)[b]
C20, (47%)[b]
C21, (45%)[b]
C22, (41%)[b]
C23, (40%)[b]
C24, (51%)[b]
C25, (44%)[b]
C26, (50%)[b]
C27, (53%)[b]
C28, (52%)[b]
C29, (15%)[b]
C30, (16%)[b]
C31, (18%)[b]
C32, (19%)[b]

[a] Reaction conditions: Phenol or alcohol (1 mmol), urea (2 mmol), [ChCl][$ZnCl_2$] (3 mL), MNP-Fe_3O_4(10 mol %), 130 °C, 6 h. [b] Isolated yield.

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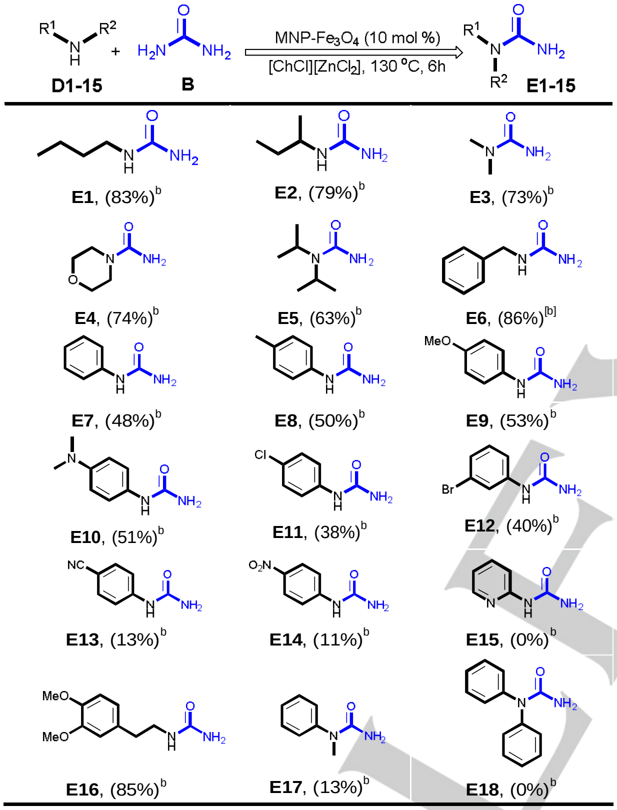
Apparently, phenol derivatives do not have enough nucleophilic properties to provide the primary *O*-aryl carbamates with excellent efficiency. It should be noted that in the case of L-(-)-menthol, the reaction can produce the corresponding L-(-)-menthyl carbamate without any epimerization (Table 3, entry **C12**).

In the next step, to enhance the utility of this methodology and to extend the scope and the generality of which, we explored the reaction for the synthesis of mono-substituted ureas and 1,1-disubstituted ureas under similar reaction conditions were used for the synthesis of primary carbamates.

Table 4. Substrate scopes.[a]



E1, (83%)[b] **E2**, (79%)[b] **E3**, (73%)[b]
E4, (74%)[b] **E5**, (63%)[b] **E6**, (86%)[b]
E7, (48%)[b] **E8**, (50%)[b] **E9**, (53%)[b]
E10, (51%)[b] **E11**, (38%)[b] **E12**, (40%)[b]
E13, (13%)[b] **E14**, (11%)[b] **E15**, (0%)[b]
E16, (85%)[b] **E17**, (13%)[b] **E18**, (0%)[b]

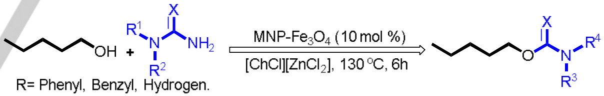
[a] Reaction condition: Aniline or amine (1 mmol), urea (2mmol), [ChCl][$ZnCl_2$] (3 mL), MNP-Fe_3O_4 (10 mol %), 130 °C, 6 h. [b] Isolated yield.

It has been observed that the reaction of primary alkyl amines with urea results higher yields for mono-substituted urea (Table 4, entries **E1-2** and **E16**). In the case of secondary alkyl amines, the desired products were formed with lower yields, which probably were related to steric effects (Table 4, entries **E3-5**). Also, benzylamine showed a reactivity as same as the aliphatic amine (compare entries **E1-2** with entry **E6**). Aromatic amines have less reactivity than aliphatic amines and this difference in reactivity can be attributed to low nucleophilicity of aromatic amines. Therefore, aniline and the electron-rich arylamines such as 4-methylaniline, 4-methoxyaniline and 4-(dimethylamino) aniline gave moderate yields (Table 4, entries **E7-10**), but very low yields were obtained from the reactions of anilines with bearing halogen substitutions like 4-chloroaniline and 3-bromoaniline (Table 4, entries **E11-12**). Unfortunately, anilines with strong electron-withdrawing (CN and NO_2) and heteroaromatic amine such as pyridin-2-amine failed to carry out the reaction under optimized experimental conditions (Table 4, entries **E13-15**). Most likely these functional groups decrease the nucleophilicity of the aryl amin nitrogen atom for effective attack. On the other hand, when *N*-methylaniline was used as a nucleophile, the desired product was formed in low yield (Table 4, entry **E17**). However, no products were formed in the case of diphenylamine, which was probably due to steric effects and low nucleophilicity of diphenylamine compared with other amines (Table 4, entry **E18**). An increasing in reaction time and temperature did not improve the efficiency of these reactions.

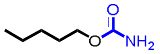
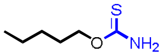
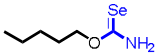
Encouraged by this success, the preparation of primary *S*-thiocarbamates from alkyl or aryl mercaptans and urea has been examined under the same conditions. Unfortunately, the desired products were not produced in all cases. An increasing in the reaction temperature up to 200 °C did not show any positive effect on the formation of *S*-thiocarbamate derivatives.

To show the versatility of this protocol, we tested different electrophiles in the reaction conditions with 1-pentanol. Initially, we chose mono-substituted and 1,1- disubstituted ureas to study the potential formation of primary 1-pentyl carbamate. Unfortunately, the reaction of 1-pentanol (1 mmol) with phenyl urea (2 mmol) in the presence of the MNP-Fe_3O_4 catalyst (10 mol %) and [ChCl][$ZnCl_2$] (3 mL) at 130 °C created the corresponding product in 65% yield after 6 h (Table 5, entry 1). However, when benzyl urea and 1,1-dibenzyl urea were used as the electrophile, the desired primary carbamate was obtained in 88% and 89% yields (Table 5, entries 2 and 3).

Table 5. Investigation of the reaction between 1-pentanol and various substituted of ureas, thioureas and selenoureas.[a]



R= Phenyl, Benzyl, Hydrogen.
X= O, S, Se.

Entry	Electrophile structure	R		Product structure	Yield (%)[b]
		R_1	R_2		
1		Ph	H		65
2		Bn	H		88
3		Bn	Bn		89
4		H	H		n.d.
5		Bn	H		n.d.
6		Bn	Bn		n.d.
7		H	H		n.d.
8		Bn	H		n.d.
9		Bn	Bn		n.d.

[a] Reaction conditions: 1-pentanol (1 mmol), ureas or thioureas or selenoureas (2 mmol), [ChCl][$ZnCl_2$] (3 mL), MNP-Fe_3O_4 (10 mol %), 130 °C, 6 h. [b] Isolated yield.

n.d.: not detected.

Furthermore, we investigated the synthesis of primary *O*-alkyl thiocarbamates and primary *O*-alkyl selenocarbamates, but the reaction of 1-pentanol with thiourea and selenourea showed no

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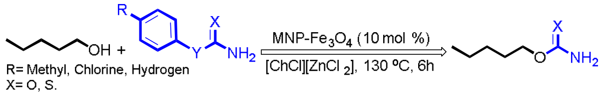
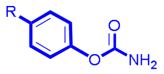
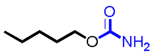
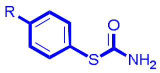
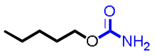
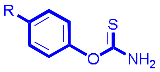
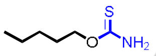
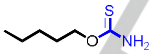
conversion (Table 5, entries 4 and 7). Also, the used of 1-benzyl or 1,1-dibenzyl thiourea and selenoureas as the electrophile showed no benign products (Table 5, entries 5, 6, 8 and 9). Apparently, in these cases, the reaction conditions can't activate the electrophile by coordination to the sulfur and selenium atoms. In addition, different substituted primary *O*-aryl carbamates, *S*-aryl thiocarbamates, *O*-aryl thiocarbamates and *S*-aryl dithiocarbamates were employed in the model reaction to confirm more versatility of which. As shown in Table 5, these reaction conditions are unable to activate sulfur atom.

Table 6. Investigation of the reaction between 1-pentanol with varies substituted primary aryl carbamates, aryl thiocarbamates and aryl dithiocarbamates.[a]



Entry	Electrophile structure	R	Product structure	Yield (%)[b]
1		H		88
2		CH_3		82
3		Cl		90
4		H		91
5		CH_3		86
6		Cl		95
7		H		n.d.
8		CH_3		n.d.
9		Cl		n.d.
10		H		n.d.
11		CH_3		n.d.
12		Cl		n.d.

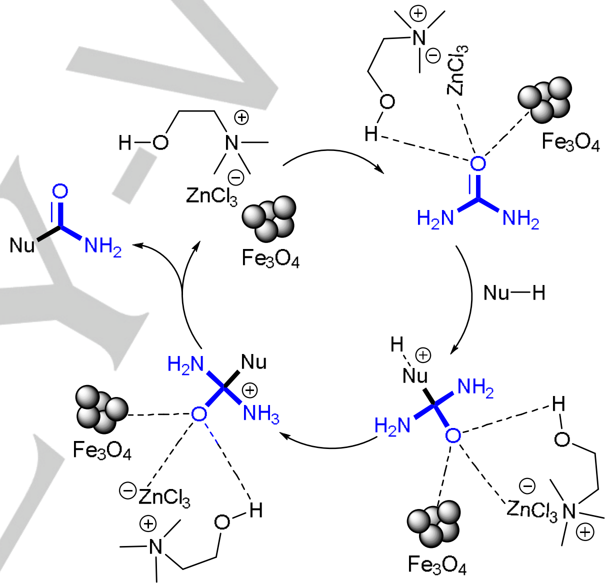
[a] Reaction condition: 1-pentanol (1 mmol), ureas or thioureas or selenoureas (2 mmol), [ChCl][ZnCl$_2$] (3 mL), MNP-Fe$_3$O$_4$ (10 mol %), 130 °C, 6 h. [b] Isolated yield.

n.d.: not detected.

Therefore, using *O*-aryl thiocarbamates and *S*-aryl dithiocarbamates as electrophile did not lead to the production of the desired product (Table 6, entries 7-12). Fortunately, the Fe$_3$O$_4$-catalyzed transcarbamoylation reaction using different substituted primary *O*-aryl carbamates and *S*-aryl thiocarbamates works well (Table 6, entries 1-6). However, this method did not work for the synthesis of primary *O*-aryl carbamates or primary *N*-aryl urea as efficient as *O*-alkyl carbamates and primary *N*-alkyl ureas. Obviously, primary *O*-aryl carbamates and *S*-aryl thiocarbamates showed great efficiency as electrophoresis in the synthesis of primary *O*-alkyl carbamates. In this case, a competitive substitution reaction between alcohol as the precursor and the leaving group can occur, but 1-pentanol was shown to be more reactive in all examples.

The electronic effect of the leaving group in *O*-aryl carbamates and *S*-aryl thiocarbamates showed an interesting influence on the reaction. Electron-deficient aryl alcohols and thiols such as 4-chlorophenol and 4-chlorothiophenol as leaving group gave excellent yields (Table 6, entries 3 and 6), but good yields were obtained from the reactions in which leaving groups are electron-rich aryl alcohols and thiols including 4-methylphenol and 4-methylthiophenol (Table 6, entries 2 and 5). As expected, *S*-aryl thiocarbamates showed better performance than primary *O*-aryl carbamates (compare entries 1-3 with entries 4-6).

The role of MNP-Fe$_3$O$_4$ and [ChCl][ZnCl$_2$] are shown in the proposed mechanism in Scheme 2. The results implied that the MNP-Fe$_3$O$_4$ and [ChCl][ZnCl$_2$] act as Lewis acid and activate the urea to improve the nucleophilic addition. On the other hand, [ChCl][ZnCl$_2$] has multiple roles in this reaction: solvent, hydrogen bond catalyst and stabilizer for the stabilization of MNP-Fe$_3$O$_4$. However, more researches will be required to postulate the exact reaction mechanism.



Scheme 2. Proposed mechanism for the synthesis of primary carbamates and mono-substituted ureas catalyzed by MNP-Fe$_3$O$_4$ and [ChCl] [ZnCl$_2$].

The recovery and reusability of catalyst and DES are necessary for economic and environmental aspects. Therefore, at the final step of this study, the operational stability (recycle-ability) of the MNP-Fe$_3$O$_4$ and [ChCl][ZnCl$_2$] has been explored in the model reaction. After the completion of the model reaction, diethyl ether (20 mL) was added to the reaction mixture for extraction the 1-pentyl carbamate as desired product. Then water (5 mL) was added to the magnetic DES and MNP-Fe$_3$O$_4$ was extracted with the external magnet. DES was recovered with evaporation process of the aqueous layer. The recycled catalysts (MNP-Fe$_3$O$_4$ and DES) used for six consecutive runs. The data presented in figure 2a show that the yield of the product decreased slightly after each run. Therefore, these results are useful for future industrial applications and environmental protection.

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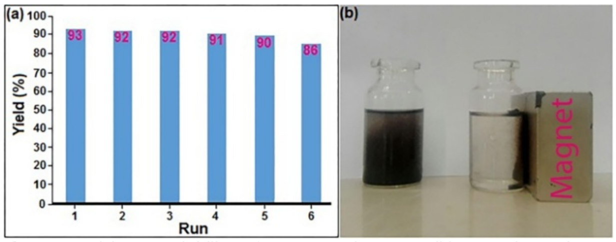

Figure 2. (a) Recyclability of a magnetic DES; (b) Reaction mixture containing MNP-Fe_3O_4 and magnetic separation after the reaction.

Along with high catalytic capacity and stability, a noticeable feature of catalyst is that it can be easily removed by magnetic separation after reaction. As shown in Figure 2b, MNP-Fe_3O_4 was concentrated in 10 s by applying an external magnet to the side wall of sealed vessel.

In order to further affirmation of the catalyst structure, the FT-IR spectrum was recorded at room temperature, which is illustrated in Fig. 3a. The FTIR spectrum of the MNP-Fe_3O_4 catalyst demonstrated that no obvious changes occur after recovery on the magnetite nanoparticles.

The XRD technique is an effective tool to determine the phase and purity of prepared samples under various conditions. The representative XRD patterns of fresh and recovered nanoparticles perfectly matches with the expected cubic spinel structure of MNP-Fe_3O_4 (Fig .3b).The position and relative intensities match well with those from JCPDS card (19-0629) for Fe_3O_4.Thus, the magnetite nanocatalyst is stable during the synthesis of carbamates in eutectic solvent.

Furthermore, to investigate the MNP-Fe_3O_4 better, TEM images of the fresh and reused catalyst (after the sixth recycling) have been represented in Fig. 3c and d. As shown in Fig. 3, there was no significant change in the morphology and dispersion of the particles. Also, TEM images indicated that the magnetite NPs were present as uniform nanospheres and the size of the nanospheres was about 15 nm. Moreover, as shown in Fig. 3e, a narrow size distribution of MNP-Fe_3O_4 after the six recycle was obtained with a mean size of around 15 nm, which is in accordance with the XRD and TEM results.

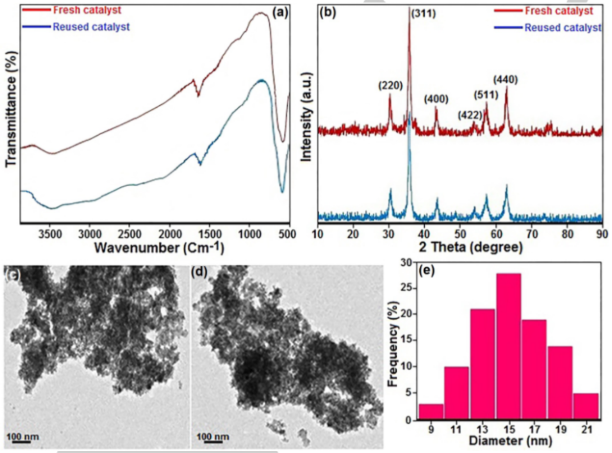

Figure 3. (a) FT-IR spectra of fresh and recovered Fe_3O_4; (b) XRD patterns of fresh and recovered MNP-Fe_3O_4 after six recoveries; (c) and (d) TEM images of the MNP-Fe_3O_4 before reaction and after six cycles of reactions; (e) DLS image of MNP-Fe_3O_4 after six reaction cycles.

Conclusions

In conclusion, we have demonstrated an efficient, green and simple method for the preparation of primary carbamates and *N*-mono substituted ureas with good to excellent yields. Compared with traditional methods, this new method has following advantages: (a) starting materials are green, inexpensive and commercially available; (b) the preparation of DES [ChCl][ZnCl]$_2$ is very easily operated, the cost is rather low and it can be reused directly with the initial activity; (c) the MNP-Fe_3O_4 catalyst was easily separated from the reaction mixture by an external magnet and reused, which made the protocol economic and sustainable; (d) the separation and purification process is very simple and convenient. All of these facts pointed out the possibility of carrying out this green protocol facilitates the access of these appropriate compounds for biological studies and designing new drugs.

Experimental Section

General experimental:

All chemicals were purchased from the Merck, Flucka and Aldrich Chemical Companies in high purity. The products were characterized by comparison of their spectral and physical data such as NMR, FT-IR, MS, CHNS and melting point with available literature data. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance DPX 250MHz instruments with Me_4Si or solvent resonance as the internal standard. Fourier transform infrared (FTIR) spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. Powder X-ray diffraction (XRD) patterns were recorded in a Bruker AXS D8-advance X-ray diffract to meter using Cu K α radiation (λ= 1.5418). Transmission electron microscopy (TEM) images were taken on a Philips EM208 microscope with an accelerating voltage of 100 kV. The hydrodynamic size of the particles was measured by dynamic light scattering (DLS) techniques, using a HORIBA-LB550 particle size analyzer. Palladium loading and leaching test were carried out with an inductively coupled plasma (ICP) analyzer (Varian, vista-pro). Determination of the purity of the substrate and monitoring of the reactions was accomplished by thin-layer chromatography (TLC) on a silica-gel polygram SILG/UV 254 plates.

Preparation of [ChCl][$ZnCl_2$] as deep eutectic solvent:[31]

For the preparation of this deep eutectic solvent, a mixture of choline chloride (10 mmol, 1.39 g) and zinc(II) chloride (10 mmol, 1.36 g) was heated to 100 ^oC until a clear colorless liquid appeared, then allowed to cool at room temperature and used without further purification.

General procedure for preparation of MNP-Fe_3O_4:

The Fe_3O_4 nanoparticles were prepared using a chemical co-precipitation method.[32] Firstly, 0.9 g of $FeCl_2.4H_2O$ (4.5 mmol),

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1.3 g of $FeCl_3.6H_2O$ (4.8 mmol) and 1 g of poly (vinyl alcohol) (PVA 15000) as a surfactant were added to 30 mL of water followed by ultrasonication for 5 min. The mixture solution was then heated to 80^{o}C for 30 min. The pH was adjusted to 10 by the dropwise addition of hexamethylenetetramine (1.0 mol l^{-1}) solution. The reaction mixture was then continually stirred for 2 h at 60 ^{o}C. The black precipitated nanoparticles were magnetically separated and washed several times with deionized water and ethanol until the pH reached 7, and then dried under vacuum at 80 ^{o}C for 10 h.

General procedure for preparation derivatives of primary carbamate (C1-33) and mono-substituted urea (E1-15):

A mixture of alcohol or amine (1 mmol), urea (2 mmol) and eutectic mixture stabilized ferrofluids (0.05 g of MNP-Fe_3O_4 in 3 mL of [ChCl][$ZnCl_2$] based eutectic mixture) was heated at 130 ℃ with stirring for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature. The reaction mixture was separated from MNP-Fe_3O_4 and [ChCl][$ZnCl_2$] by multiple dilutions with diethyl ether (10 × 5 mL). Then, all starting materials were washed with H_2O (2 × 15 mL).The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the final product. Finally, by recrystallization from the CH_2Cl_2 pure product was obtained.

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Keywords: Deep eutectic solvent (DES) • Fe_3O_4 • Nano catalyst • Primary carbamates • Urea

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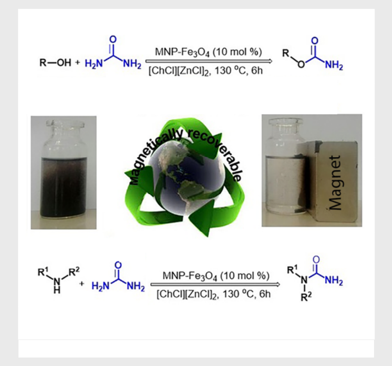
FULL PAPER

In this work, superparamagnetic Fe_3O_4 nanoparticles were prepared and tested for the synthesis of various primary carbamates and mono- or *N*,*N*-disubstituted ureas using urea as the eco-friendly carbonyl source in the presence of a biocompatible deep eutectic solvent (DES). This efficient and phosgene-free process provided an inexpensive and attractive route to synthesize the products in moderate to excellent yields.



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