



Full paper/Mémoire

A sustainable approach to the Ugi reaction in deep eutectic solvent

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ABSTRACT

The Ugi reaction goes fast with high yields in a recyclable and biodegradable low-melting mixture of choline chloride and urea (DES) as a novel and efficient reaction medium. The DES is applicable to a wide range of aldehydes, amines, isocyanides, and acids in good to excellent isolated yields (60–92%) and short reaction times (2–5 h) and can be reused four times without any loss of activity.

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1. Introduction

In the context of green chemistry, room-temperature ionic liquids (RTILs), also called molten salts, are green alternatives to organic solvents, because of their unique properties, such as negligible vapor pressure, large liquid range, high thermal stability, more solvation capacity, and non-flammability. Expected cheaper and greener alternatives to RTILs are room-temperature deep eutectic solvents (DESS). DESSs are obtained by complexation of quaternary ammonium salts with hydrogen bond donors, such as urea, carboxylic acid, sugar and amide or Lewis acids. DESSs have many characteristics of conventional ILs (e.g., high thermal stability, excellent solubility of organic and inorganic substances, low toxicity and non-volatility), while they offer certain advantages. For instance, the preparation of DES in a pure state is easy and economically viable as it shows 100% atom economy, with no need for the post-synthesis purification that was used for the ILs. Furthermore, choline chloride (ChCl) and urea are both

naturally occurring biocompatible compounds that are not hazardous if they are released back into nature separately. Although there are only a limited amount of research in the field of toxicity and biodegradability of DESSs, to the best of our knowledge, there is no reversal report so far. Besides, they are cheap and the processes that use these deep eutectic solvents are economically viable and green [1–12].

A major challenge of modern chemistry is the design of new artificial chemical reaction sequences that provide novel compounds in high yields and short reaction times. Undoubtedly, one-pot multicomponent reactions (MCRs) from low-cost materials are convergent reactions with high atom efficiency, and higher yields in comparison to a similar multistep reaction. They are faster and cheaper than classical reactions, since they are done by just mixing compounds together in one vessel, without isolating any intermediate. The additional benefits of this resource-effective and ecologically benign process are readily available starting materials, operational simplicity, easy automation, atom economy, with minimization of reaction time, labor, cost, and waste production [13–19].

A large and important class of MCRs is constituted by the isocyanide-based Passerini and Ugi four-component reactions [20–24]. These reactions have become one of the

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most investigated transformations during the past decade, in conjunction with the enabling technologies, such as high-throughput screening, combinatorial and assembling complex pharmacologically important structures. The classical Ugi reaction is carried out in solvents, such as methanol and dichloromethane under stirring at room temperature overnight [25–30]. In order to further comply with the green chemistry, alternative green solvents, such as water and trifluoroethanol or ionic liquids, were used in an isocyanide-based multicomponent reaction [31–34].

2. Results and discussion

Throughout our investigations to develop green chemistry by using water and deep eutectic solvent as reaction medium [35–39], in the present work, we report the first example of an efficient and green procedure for a one-pot multicomponent Ugi reaction in DES based on choline chloride and urea as a novel and green catalyst and reaction medium.

The experimental procedure is very simple and easy. The deep eutectic solvent DES was prepared by simply mixing choline chloride (100 mmol) with urea (200 mmol), and heated to ca. 80 °C in air with stirring till a clear solution was obtained, which was used without any purification. Since this method forms eutectic mixture with no by-product formation, it provides 100% atom economy.

In a typical experiment, benzaldehyde (0.5 mmol), aniline (0.5 mmol), benzoic acid (0.5 mmol), cyclohexylisocyanide (0.5 mmol) and deep eutectic solvent (1 mL) were stirred at room temperature. After completion (180 min), the reaction mixture was diluted with water, and the white solid mass was separated by simple filtration. The corresponding Ugi product **5** was formed as the only detectable product and isolated in 90% yield after washing with water and ethanol (Table 1).

The DES was recovered easily from the filtrate by evaporating water under vacuum and reused for three successions of the reaction without much loss in the product yields. Furthermore, it was possible to monitor the reaction visually. A white suspension solution was obtained after addition of all the components to the deep eutectic solvent, and the reaction mixture became an orange viscous liquid or solid after the reaction is

complete. To consider the efficiency of DES relative to conventional organic solvents, some protic and aprotic solvents were performed with the optimized conditions of DES; the results are summarized in Table 1. The results confirmed that DES is the best solvent and catalyst for the one-pot multicomponent Ugi reaction.

Under these reaction conditions, the evaluation of DESs as solvents was tested for a wide range of carbonyl compounds. A variety of structurally diverse aldehydes and ketones, including saturated, unsaturated, aromatic and heteroaryl aldehydes underwent green reaction smoothly, without using any catalyst to afford the corresponding Ugi products in good to excellent yields. The results are summarized in Table 2. Aryl aldehydes substituted with various electron-withdrawing and electron-donating groups, as well as heteroaryl aldehydes, aliphatic aldehydes and simple ketones did not seem to influence the reaction time and yields, as revealed by the similarity of the results, and all the carbonyl groups readily converted into their corresponding Ugi products in the presence of a variety of functional groups.

Encouraged by this success, the reaction is also studied for various aromatic amines, isocyanides, and carboxylic acid. Benzaldehyde was reacted with aromatic amines, such as 4-methylaniline, 4-methoxyaniline, 2-methylaniline, 4-chloroaniline, and 4-bromoaniline in DES at room temperature, giving good to excellent yields. To further increase the diversity at this point, we next tested other benzoic acid derivatives, which also produced the desired α -aminoacyl amide derivatives in good yields. The scope of the isocyanide component was then examined. The reaction of benzaldehyde, aniline, benzoic acid and *t*-butyl isocyanide, tosylmethyl isocyanide (TOSMIC) also gave the desired products in moderate to good yields in this type of process (Fig. 1).

The experimental procedure is easy and the reactions went to completion at room temperature, within 2–5 h, depending on the reactivity of the aldehydes and carboxylic acids. The products were easily separated by easy extraction of the deep eutectic solvent with water, and were usually obtained in high purity.

In general, the reactions are very mild and clean, and no side-products were obtained between the starting materials of the Ugi reaction with DES in any run. Furthermore, in the separated model reaction, aniline as well as benzoic

Table 1
Comparison of conventional organic solvents with DES.

Entry	Solvent (1 mL)	Yields (%)
1	Urea–choline chloride	90
2	Neat (solvent free condition)	60
3	CH ₃ OH	40
4	H ₂ O	45
5	CH ₂ Cl ₂	30
6	CH ₃ CN	45

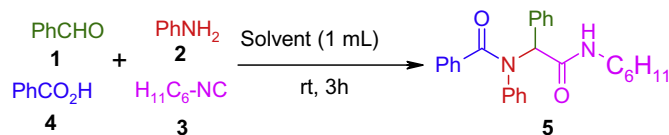


Table 2
Green Ugi reaction in deep eutectic solvent.

1	2	3	4	68-95%		5	
Entry	R ₁ CHO (1)	R ₂ NH ₂ (2)	Yields (%) ^a	Entry	R ₁ CHO (1)	R ₂ NH ₂ (2)	Yields (%) ^a
5a			90	5j			72
5b			85	5k			70
5c			92	5l			72
5d			88	5m			88
5e			84	5n			90
5f			85	5o			92
5g			82	5p			86
5h			75	5q			80
5i			60	5r			76

^a NMR yields

acid was stirred in DES for 5 h, and only aniline and benzoic acid were recovered without any reaction with DES; so, these results will completely contradict any possibility of DES' participation in the reaction.

Finally, the recycling of DES was examined using the Ugi reaction under optimized conditions. The recovered DES was then reused for three runs without obvious loss of activity. After completion, water (3 mL) was added to the reaction mixture, which was shaken vigorously, and a solid or viscous liquid was separated by filtration. The deep eutectic solvent was recovered from the filtrate by evaporating the water phase at 80 °C under vacuum and reused for the next batch and recycled again (Table 3).

3. Experimental

¹H NMR spectra were recorded with a 500 MHz NMR spectrometer using CDCl₃ or DMSO as a solvent; chemical shifts have been expressed in (ppm) downfield from TMS.

Table 3
Recycling of deep eutectic solvent.

Entry	Cycle	Yields (%)
1	Fresh	90
2	First recycle	90
3	Second recycle	88
4	Third recycle	80

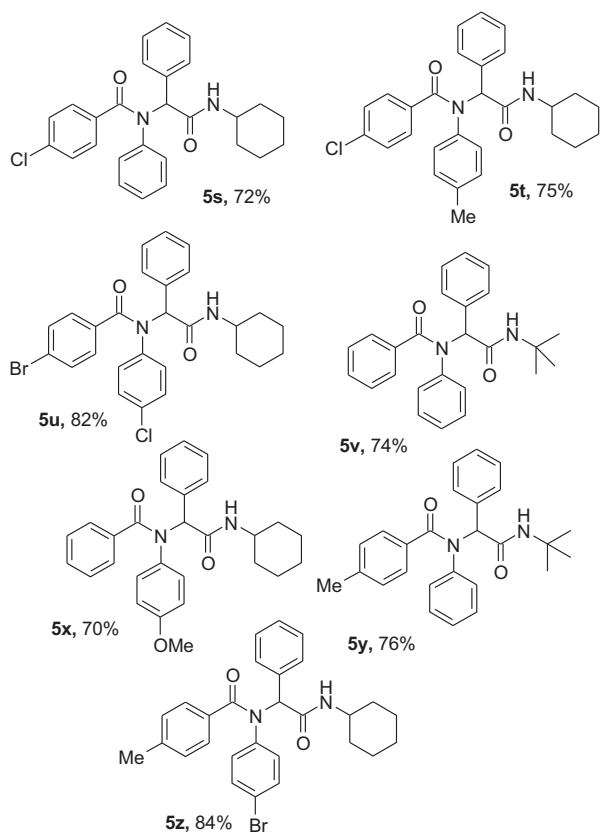


Fig. 1. Green synthesis of Ugi products in urea–choline chloride.

All the amines, aldehydes, isocyanides and acids are commercially available. Water and ethanol were distilled before use. All the reactions are monitored by thin layer chromatography (TLC), carried out on 0.25 mm silica gel with UV light as the detecting agent. The melting points were recorded with a Buchi 535 melting point apparatus and are uncorrected.

3.1. Deep eutectic solvent preparation

The choline chloride–urea ionic liquid was prepared according to the literature [2]. For DES preparation, urea (200 mmol) and choline chloride (100 mmol) were mixed, stirred and heated until a clear liquid appeared. The

obtained ion liquid was used without any further purification (Fig. 2).

3.2. General procedure for the Ugi reaction

The aldehyde (0.50 mmol), the carboxylic acid (0.50 mmol), the amine (0.50 mmol) and the cyclohexyl isocyanide (0.50 mmol) were dissolved in a choline chloride–urea-based deep eutectic solvent (1 mL), and were mixed and vigorously stirred at room temperature. After completion of reaction, water was added. The DES is soluble in water and comes into the water layer. The white solid was separated by filtration and was purified with water then with ethanol to give the pure compounds.

3.3. Selected data

3.3.1. N-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-N-phenylbenzamide (5a)

Mp = 163–169 °C, $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 1.12–1.22 (m, 3H), 1.38–1.43 (m, 3H), 1.95–2.03 (m, 3H), 2.23 (s, 2H), 3.90 (m, 1H), 5.84 (d, J = 5 Hz, 1H), 6.20 (s, 1H), 7.05 (s, 5H), 7.15 (t, J = 10 Hz, 2H), 7.21 (t, J = 10, 5 Hz, 1H), 7.29 (s, 3H), 7.30–7.31 (m, 1H), 7.35 (d, J = 5 Hz, 2H).

3.3.2. 2-(4-Chlorophenyl)-N-cyclohexyl-4-oxo-3,4 diphenylbutanamide (5c)

Mp = 107 °C, $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 1.12–1.30 (m, 3H), 1.36–1.46 (m, 2H), 1.62–1.76 (m, 4H), 1.94–2.03 (m, 2H), 3.89–3.94 (m, 1H), 5.94 (d, J = 5 Hz, 1H), 6.17 (s, 1H), 7.02–7.03 (m, 1H), 7.08–7.10 (m, 3H), 7.16 (t, J = 5 Hz, 2H), 7.22–7.30 (m, 5H), 7.33 (d, J = 5 Hz, 2H).

3.3.3. N-(2-(cyclohexylamino)-1-(2,4-dichlorophenyl)-2-oxoethyl)-N-phenylbenzamide (5f)

Mp = 292 °C, $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 1.17–1.29 (m, 3H), 1.38–1.43 (m, 2H), 1.63–1.69 (m, 1H), 1.72–1.79 (m, 2H), 1.90 (d, J = 5 Hz, 1H), 2.03 (d, J = 10 Hz, 2H), 3.83–3.90 (m, 1H), 6.11 (d, J = 10 Hz, 1H), 6.57 (s, 1H), 7.33 (q, 1H), 7.41 (q, 2H), 7.48 (d, J = 2 Hz, 1H), 7.48–7.52 (m, 4H), 7.60 (d, J = 10 Hz, 1H), 7.64 (t, J = 5, 10 Hz, 1H), 7.91 (d, J = 5 Hz, 1H), 8.11 (d, J = 10 Hz, 1H).

3.3.4. N-cyclohexyl-2-(4-nitrophenyl)-4-oxo-3,4-diphenylbutanamide (5g)

Mp = 213 °C, $^1\text{H NMR}$ (500 MHz, CDCl_3): δ = 1.18–1.26 (m, 3H), 1.41–1.46 (m, 2H), 1.63–1.66 (m, 2H), 1.71–1.78

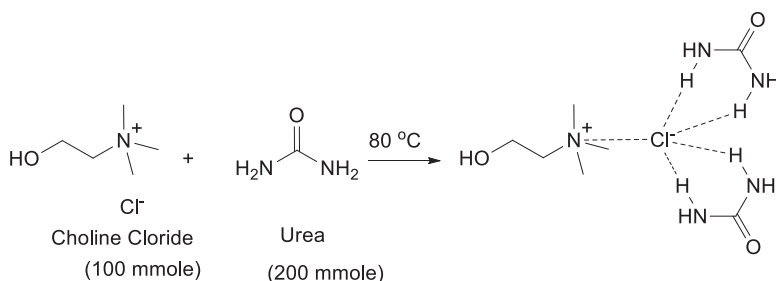


Fig. 2. Deep eutectic solvent preparation.

(m, 2H), 1.95–2.05 (m, 2H), 3.91–3.97 (m, 1H), 6.28 (s, 2H), 7.03–7.05 (m, 1H), 7.11–7.12 (m, 3H), 7.18 (t, $J = 10$, 5 Hz, 2H), 7.23–7.30 (m, 1H), 7.34 (d, $J = 5$ Hz, 1H), 7.56 (d, $J = 5$ Hz, 2H), 8.13 (d, $J = 10$ Hz, 2H).

3.3.5. 3-Cyclohexyl-1-(1-(4-methoxyphenyl)-2-oxo-2-phenylethyl)-1-phenylurea (5l)

Mp = 182–184 °C, $^1\text{H NMR}$ (500 MHz, CDCl_3): $\delta = 1.11$ – 1.17 (3H, m), 1.38 (2H, m), 1.62–1.69 (3H, m), 1.94–1.99 (2H, m), 3.78 (3H, s), 5.80 (1H, s), 6.16 (1H, s), 6.77 (2H, d, $J = 7.19$ Hz), 7.03 (5H, s), 7.14 (2H, d, $J = 6.4$ Hz), 7.20 (3H, d, $J = 7$ Hz), 7.29–7.33 (3H, m).

4. Conclusion

In summary, we have developed an environmentally benign and green Ugi reaction using bio-based and biodegradable deep eutectic solvents based on a choline chloride–urea mixture as a novel and efficient reaction medium. Further studies in our laboratory are under way to develop isocyanide-based multicomponent reactions in this green reaction media.

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