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A green and simple approach to α-acyloxycarboxamides

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Abstract. In this study, a mild and sustainable three-component passerini reaction in biodegradable deep eutectic solvent based choline chloride:urea (1:2) is described. The reaction proceeds at room temperature involving substituted benzaldehyde, benzoic acid, and cyclohexyl isocyanide with a short reaction time and good to excellent yields (65-90%) without tedious workup.

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1. Introduction

Since a long time ago, development of eco-friendly synthetic methods has been a great challenge for the scientific community. Some chemical pollution in organic synthesis is inevitable. The major chemical pollution in organic synthesis is based on harmful organic solvents. Thus, designing eco-friendly approaches to reduce drawbacks of the common synthetic methods such as hazardous solvent and catalyst is one of the major concerns.

In recent years, the Ionic Liquids (ILs) have received great attention due to their unique properties such as low vapor pressure, recyclability, and non-flammability [1]. Cheap and green alternatives to ILs are Deep Eutectic Solvents (DESs) or low melting mixtures. Comparing DES with traditional IL endorses many advantages of DES such as low cost, chemical inertness with water, simple preparation, easy storage, purification needlessness, and often being composed of environmentally green components [2], which leads to their biodegradable [3], biocompatible [4], and non-toxic properties [5]. Although there are limited reports on toxicity and biodegradability of DES [6], to the best of our knowledge, there is no evidence to approve any environmentally destructive influence for DES. Thus DES based on choline chloride has been called a "biocompatible" or "biorenewable" solvent. Despite all great differences of DES with IL, the physico-chemical properties such as density, viscosity, conductivity, reffractive index, surface tension, and chemical inertness in it are very close to the traditional IL. DESs are typically formed by two- or three-component mixtures of quaternary ammonium salt with a Hydrogen Bond Donor (HBD) such as carboxylic acid, an amide, sugar, or a Lewis acid. Studies have shown that the chemical nature of HBD and acidic or basicity of DES have a significant relationship [2]. All valuable properties of DESs have made them a suitable choice in academic and industrial researches as a green reaction media in recent years [7-10].

Multi Component Reactions (MCRs), especially isocyanide-based MCRs, are noteworthy for scientific community in preparation of compound libraries of low molecular drugs, like compounds. Large libraries are accessible within a short reaction time with small sets of starting materials [11]. One of the most widely known and important isocyanide-based multicomponent reactions (IMCRs) is the Passerini three-component reaction, known as a well suited domino reaction for combinational chemistry and potential drug candidate libraries [12,13]. The classical reaction

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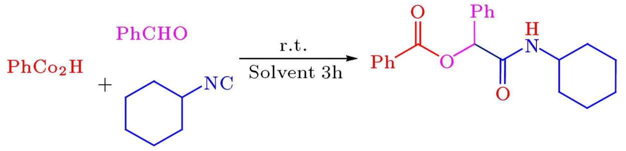
is performed often in conventional organic solvents such as CH_2Cl_2 and methanol [11,12,14] with long reaction time. In the last decade, some optimizations have been made to modify the ecological impact, yield, and reaction time. To reach this goal, the reaction has been performed in a solvent-free condition with microwave irradiation [15] even at room temperature [16], or heated [17] in an aqueous solution [18] and ionic liquid [19,20]. Despite all reported advantages for these methods, some shortcomings such as difficult isolations, high cost, etc. are still remaining. To the best of our knowledge, there is no report on the use of DESs for the α-acyloxycarboxamides synthesis. Herein, an efficient and green one – pot approach for α-acyloxycarboxamides synthesis via three-component passerini reaction in a choline chloride based DES – is developed. Its potential for application in green and fast multi component reactions as a solvent and catalyst is the most appealing.

2. Results and discussion

Due to our interest in developing new green media for organic syntheses [21-25], herein we describe a one-pot, three-component passerini reaction in DES as a green solvent and catalyst for α-acyloxycarboxamides synthesis. Furthermore, the isolation and purification steps of this DES are very simple and easy. The three-component passerini reaction of benzaldehyde, benzoic acid, and cyclohexyl isocyanide was performed in six different conditions, containing two different organic solvents and water (for investigation of DES efficiency), and also three choline chloride based DESs. Comparing the results (Table 1), Urea:ChCl showed the best yield and the shortest reaction time, while all the other traditional solvents needed more time for reaction completion. By comparing the DESs, the best yield was obtained from urea:ChCl. In PTSA:ChCl, the desired α-acyloxycarboxamide was not produced which is probably related to isocyanide and PTSA reaction [26]. Thus, reaction of benzaldehyde, benzoic acid, and cyclohexyl isocyanide in urea:ChCl was adopted as a model reaction to evaluate the reaction condition. The reaction was stirred for 3 h at room temperature; the reaction mixture was solidified and the reaction completion was monitored by TLC; then, 5 mL of water was added to the reaction mixture. The components of the DES dissolved in water and the products precipitated. The solid was isolated by filtration and pure product was obtained by washing with 3 mL of diethyl ether. The DES was dried under vacuum and obtained without any significant changes in physical and chemical properties. FTIR spectra of the reused DES did not show any significant change, which proved its stability under the reaction conditions. The reaction was performed in some conventional organic solvents such as CH_2Cl_2, MeOH, CH_3CN, and three various DESs (Table 1).

Table 1. Comparing different media on reaction efficiency.



Entry	Solvent	Yield (%)
1	MeOH	trace
2	H_2O	38%
3	MeCN	15%
4	Urea:ChCl (2:1)	90%
5	PTSA: ChCl (2:1)	0%
6	Glycerin:ChCl (2:1)	62%

The substrate scope was explored under optimized condition and the representative results are summarized in Table 2. Different aromatic and aliphatic aldehydes were transformed into the corresponding α-acyloxycarboxamides in moderate to excellent yields ranging from 65% to 95%. Both electron-donating and electron-withdrawing groups on the aldehyde afforded the corresponding products in short reaction times. A number of functional groups such as NO_2, OMe, and halogens were tolerated.

Figure 1 presents the suggested mechanism for the Passerini reaction in DES.

3. Conclusion

In summary, a novel use of DES for three-component Passerini reaction of aldehydes, benzoic acid, and isocyanide is reported. The notable features of this approach are high yields, operational simplification, reaction rate enhancement, cleaner reaction media, and easy product separation which make this procedure more convenient and environmentally benign for α-acyloxycarboxamides synthesis. In addition, using DES as a green solvent and also catalyst makes this method eco-friendly and green.

4. Experimental

4.1. Materials and instruments

Starting material and DES components were purchased from Merck and were used without purification. NMR spectra were recorded on Brucker 500 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. All the reactions were monitored with Thin Layer Chromatography (TLC) carried out on 0.25 mm silica gel and UV light as the detecting agent.

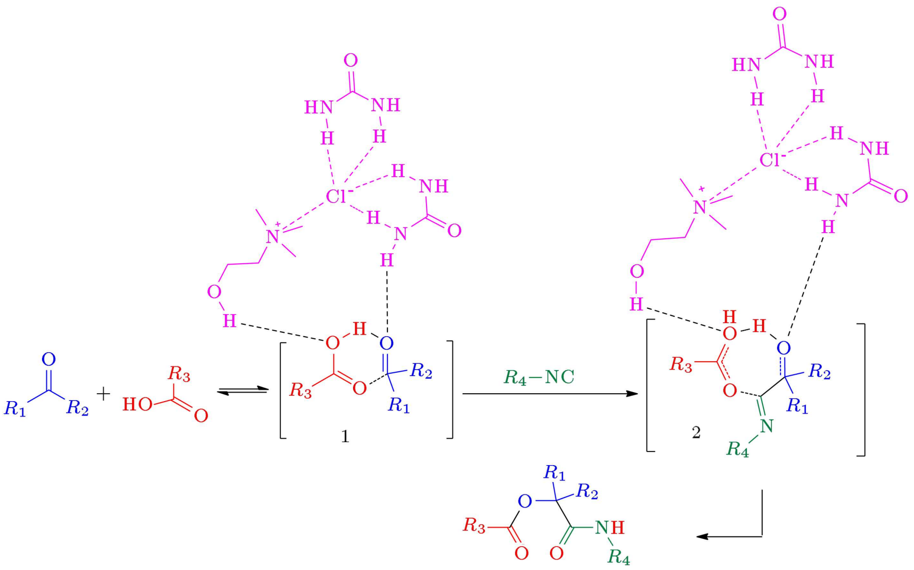


Figure 1. Proposed mechanism for three component Passerini reaction in DES as catalyst and solvent.

4.2. Deep eutectic solvent preparation

DESs based on choline chloride were prepared according to the literature [27-30]. For DES preparation, choline chloride (100 mmol) and the second component were mixed, stirred, and heated with reported fractions (mentioned in Table 1) until a clear liquid appeared. The obtained DES was used without any further purification. As the eutectic mixture forms with no by-product formation, it provides 100% atom economy.

4.3. General procedure for synthesis of α-acyloxycarboxamides

A mixture of benzaldehyde (0.5 mmol), benzoic acid (0.5 mmol), and cyclohexyl isocyanide (0.5 mmol) in presence of 0.5 mL urea-choline chloride (2:1) was stirred for 3 hr at room temperature. Water (5 mL) was added to the reaction mixture and the product appeared as a white solid in the test tube at the end of the reaction. The precipitate was filtered and washed with 2 mL diethyl ether. In cases that product appeared as a viscous liquid such as 2-furaldehyde, 3 mL ethyl acetate was added to extract the product. The organic layer was dried over sodium sulfate, filtered and evaporated. The crude product was washed with 2 mL diethyl ether for further purification. Products were characterized by melting point and NMR spectroscopy and compared with literature [17,20].

Selected spectral data:

2-(cyclohexylamino)-2-oxo-1-phenylethyl benzoate (4a): ^{1}H NMR, (500 MHz, $CDCl_3$): δ H (ppm) 1.66-1.24 (m, 4H), 1.38-1.41 (m, 2H), 1.63-1.65 (m, 1H), 1.69-1.72 (m, 2H), 1.95-1.99 (m, 2H), 3.84-3.90 (m, 1H), 6.09 (s, 1H), 6.35 (s, 1H), 7.48 (m, 3H), 7.52 (t, $J = 15$ Hz, 2H), 7.60 (d, $J = 10.4$ Hz, 2H), 7.67 (t, $J = 7$ Hz, 1H), 8.14 (d, $J = 7.3$ Hz, 2H).

2-(cyclohexylamino)-1-(3-methoxyphenyl)-2-oxoethyl benzoate (4e): ^{1}H NMR, (500 MHz, $CDCl_3$): δ H (ppm) 1.13-1.29 (m, 3H), 1.35-1.40 (m, 2H), 1.62-1.64 (m, 1H), 1.68-1.73 (m, 2H), 1.91-1.98 (m, 2H), 6.04 (bd, $J = 10$ Hz, 1H), 6.30 (s, 1H), 6.92 (d, $J = 10$ Hz, 1H), 7.11 (s, 1H), 7.15 (d, $J = 10$ Hz, 1H), 7.33 (t, $J = 10.5$ Hz, 1H), 7.51 (t, $J = 10$ Hz, 2H), 7.64 (t, $J = 10$ Hz, 1H), 8.13 (d, $J = 5$ Hz, 2H).

2-(cyclohexylamino)-1-(2,4-dimethoxyphenyl)-2-oxoethyl benzoate (4f): ^{1}H NMR, (500 MHz, $CDCl_3$): δ H (ppm) 1.11-1.15 (m, 1H), 1.22-1.26 (m, 2H), 1.36-1.43 (m, 2H), 1.63 (bs, 3H), 1.72 (m, 1H), 1.83-1.85 (m, 1H), 2.00-2.02 (m, 1H), 3.85 (s, 4H), 3.90 (s, 3H), 6.10 (bd, $J = 5$ Hz, 1H), 6.53 (s, 1H), 6.56 (d, $J = 5$ Hz, 1H), 7.47-7.52 (m, 3H), 7.60-7.61 (m, 1H), 8.14 (d, $J = 5$ Hz, 2H).

2-(cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl benzoate (4g): ^{1}H NMR, (500 MHz, $CDCl_3$): δ H (ppm) 1.15-1.30 (m, 4H), 1.37-1.45 (m, 2H), 1.61-1.67 (m, 1H), 1.73 (m, 2H), 1.98 (bd, 2H), 3.84-3.86 (m, 1H), 6.22 (bd, $J = 10$ Hz, 1H), 6.42 (s, 1H), 7.57 (t, $J = 10.5$ Hz, 2H), 7.71 (t, $J = 10.5$ Hz, 1H), 7.78 (d, $J = 10$ Hz, 2H), 8.15 (d, $J = 10$ Hz, 2H), 8.29 (d, $J = 5$ Hz, 2H).

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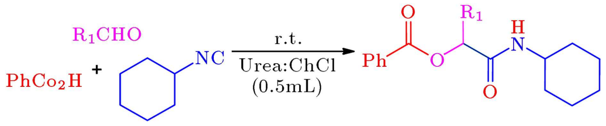
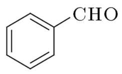
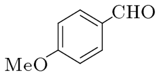
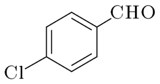
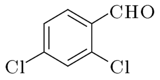
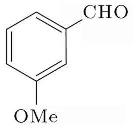
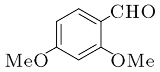
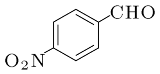
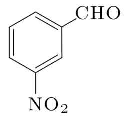
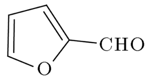
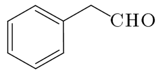
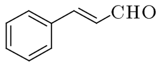
Table 2. Preparation of α-acyloxycarboxamides via urea choline chloride (2:1) based DES.



Entry	R1	Yield[a] (%)	product
1		90%	**4a**
2		83%	**4b**
3		79%	**4c**
4		67%	**4d**
5		80%	**4e**
6		71%	**4f**
7		84%	**4g**
8		81%	**4h**
9		65%	**4i**
10		66%	**4j**
11		81%	**4k**

[a] : Isolated yields.

istry, Science and Research Branch, Islamic Azad University is appreciated.

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Biographies

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Mohammad Mahmoudi Hashemi received his PhD degree from Nevada, in 1980, and post PhD from Iowa State, in 1981. He is currently a full professor at Islamic Azad University, Science and Research Branch. His research interests are organic synthesis, oxidation of organic compounds, solid supported reagents, and chemistry of aromatic compounds.