A green and simple approach to α-acyloxycarboxamides

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Passerini reaction; α-acyloxycarboxamides; Deep eutectic solvent; Choline chloride; Green chemistry.

\textbf{Abstract.} In this study, a mild and sustainable three-component Passerini reaction in biodegradable deep eutectic solvent based choline chloride mixture (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 \cite{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 \cite{2}, which leads to their biodegradable \cite{3}, biocompatible \cite{4}, and non-toxic properties \cite{5}. Although there are limited reports on toxicity and biodegradability of DES \cite{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, refractive 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 \cite{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 \cite{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 \cite{11}. One of the most widely known and important isocyanide-based multi-component reactions (IMCRs) is the Passerini three-component reaction, known as a well suited domino reaction for combinatorial chemistry and potential drug candidate libraries \cite{12,13}. The classical reaction
is performed often in conventional organic solvents such as 
CH₂Cl₂ 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-acylamidoxoamide 
synthesis. Herein, an efficient and green one – 
pot approach for α-acylamidoxoamide synthesis via 
three-component passeri reaction in a choline chlo-
ride based DES – is developed. Its potential for 
application in green and fast multi component re-
cections 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 passeri reaction in DES as a 
green solvent and catalyst for α-acylamidoxoamide 
synthesis. Furthermore, the isolation and purification 
steps of this DES are very simple and easy. The 
three-component passeri 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-acylamidoxoamide was 
not produced which is probably related to isocyanide 
and PTSA reaction [26]. Thus, reaction of ben-
zaldehyde, 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 precip-
itated. 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 CH₂Cl₂, MeOH, CH₃CN, and three various 
DESs (Table 1).

The substrate scope was explored under opti-
mized condition and the representative results are sum-
arized in Table 2. Different aromatic and aliphatic 
aldehydes were transformed into the corresponding α-
acylamidoxoamides 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 NO₂, OMe, and 
halogens were tolerated.

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

3. Conclusion

In summary, a novel use of DES for three-component 
Passeri 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-
acylamidoxoamide 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 spectrom-
eter using CDCl₃ 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.
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-acyloxyarboxamides

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)-1-(3-methoxyphenyl)-2-oxoethyl benzoate (4e): 1H NMR, (500 MHz, CDCl3); δ H (ppm) 1.61-1.24 (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): 1H NMR, (500 MHz, CDCl3); 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 (d, 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): 1H NMR, (500 MHz, CDCl3); 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): 1H NMR, (500 MHz, CDCl3); 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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Figure 1. Proposed mechanism for three component Passerini reaction in DES as catalyst and solvent.
Table 2. Preparation of α-acyloxy carbamates via urea choline chloride (2:1) based DES.

<table>
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<th>Entry</th>
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<td>CHO</td>
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<td>4b</td>
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<tr>
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<td>CHO</td>
<td>79%</td>
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<tr>
<td>11</td>
<td>CHO</td>
<td>81%</td>
<td>4k</td>
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</table>

*: Isolated yields.

References


Biographies

Sahar Dezfooli received her PhD degree from the Science and Research Branch of Islamic Azad University, in 2013, under supervision of Professor Mohammad Mahmoudi Hashemi and Dr. Najmedin Azizi. Her research interests include green chemistry, especially deep eutectic solvents, and organic synthesis.

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