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Green and efficient synthesis of new *β*-amido-aroyl carbonyl derivatives catalyzed by choline chloride/urea as a deep eutectic solvent

ANITA BERJIS[1], BEHROOZ MIRZA[1]* and HOSSEIN ANARAKI-ARDAKANI[2]

[1]*Department of Chemistry, Islamic Azad University, Karaj Branch, Karaj, Iran and* [2]*Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, Iran*

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Abstract: A green and highly efficient synthesis of some new *β*-amido-aroyl carbonyl derivatives has been achieved through a one-pot, three-component reaction of dimedone/barbituric acid derivatives, arylglyoxals, and amides in choline chloride/urea as a deep eutectic solvent (DES). The use of biodegradable materials, short reaction time and high yields of products introduced this protocol as an efficient environmentally friendly method. The DES could be easily recovered and reused about four times with satisfied catalytic activity.

Keywords: deep eutectic solvents; green chemistry; multi-component reaction; β-amido-aroyl carbonyl compounds.

INTRODUCTION

Multicomponent reactions (MCRs) have been identified as one of the most efficient methods for the synthesis of heterocyclic compounds.[1,2] MCRs provide a powerful synthetic method in which a wide range of raw materials could react through one-pot reactions to produce valuable compounds. In general, most of the atoms in the substrates are also found in the structure of the newly-formed products.[3]

Green chemistry, as an essential and evolving research field, has focused on designing processes that reduce the consumption and production of environmentally harmful substances.[4]

Recently, deep eutectic solvents (DES) have been utilized as a new green solvent in research. DESs have received more attention due to their exciting properties, such as high thermal stability, high purity, high solubility, no water-reactivity, low cost, and simple preparation methods. Therefore, many valuable review articles examine the types and features of DES.[5] A deep eutectic solvent (DES) is defined as a mixture of two or more components with effective hydro-

* Corresponding author. E-mail: b_mirza@azad.ac.ir
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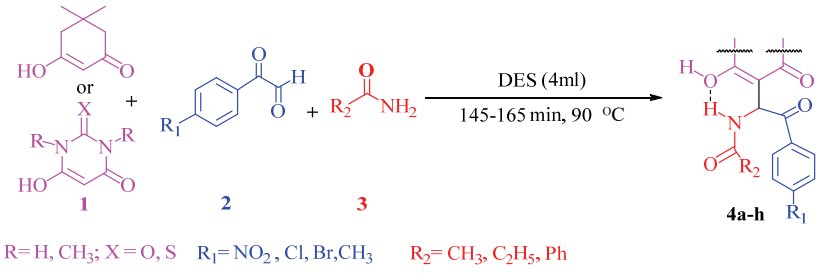
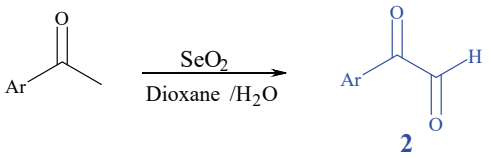
gen-bond interactions that result in the observed melting point being much lower than either of the individual components.[6–10] Choline chloride (ChCl) is one of the most common materials utilized in the synthesis of DESs. This quaternary ammonium salt has received more attention due to its special properties, such as low cost, biodegradability, environmental friendliness, and reusability. In addition, choline chloride exhibits high thermal and chemical stability.[11] ChCl as hydrogen bond acceptor (HBA) could produce DES in reaction with hydrogen bond donors (HBD), such as acids,[12] alcohols,[13] amines[14] or amides.[15]

β-Acetamido carbonyl compounds have been identified as precursors of 1,3-amino alcohols and *γ*-lactams.[16,17] They also exhibit biological and pharmaceutical activities[18] and are used to prepare of antibiotic drugs, such as nikkomycin or neopolyoxins.[19] The modified Dakin–West condensation of aromatic aldehyde, acetophenone and acetonitrile is highly recommended in the synthesis of *β*-acetamido carbonyl compounds.[20,21] Moreover, several efficient methods have been reported for the synthesis of *β*-acetamido ketones through three-component reactions of acetophenone, an aryl aldehyde, and acetyl chloride in acetonitrile using $CoCl_2$,[17] montmorillonite K-10 clay[22] and heteropoly acids[23] as useful catalysts. Three-component reactions of 1,3-dicarbonyl compounds, arylglyoxals, and heteroaryl amines/2-aminobenzimidazoles were reported in order to synthesis of 6,7-dihydrobenzofuran-4(5*H*)-one[24]/12-aroylbenzimidazo[2,1-*b*]-quinazolin-1(2*H*)-one[25] derivatives. Moreover, some reports have been found on the synthesis of *β*-amido-aryl carbonyl derivatives through three-component reaction of 1,3-dicarbonyl compounds, arylglyoxal, and benzamide.[26–28] Following previous works, herein an efficient approach is reported for the one-pot synthesis of *β*-amido-aroyl carbonyl derivatives (**4**) using three-component reactions of dimedone, barbituric/thiobarbituric acid derivatives (**1**), arylglyoxals (**2**) and amides (**3**), in the presence of choline chloride/urea as a deep eutectic solvent (DES), Scheme 1.



Scheme 1. Synthesis of *β*-amido-aroyl carbonyl derivatives in DES as solvent and catalyst.

Aryglyoxals **2** were synthesized by the reported reaction of the corresponding acetophenone and SeO_2[29] (Scheme 2).



2

Ar = 4-Nitrophenyl, 4-Chlorophenyl, 4-Bromophenyl,4-CH_3-phenyl

Scheme 2. The synthesis of aryglyoxals.

EXPERIMENTAL

All used chemicals and solvents were purchased from Fluka (Buchs, Switzerland) and used without further purification. Melting points of the synthesized products were determined with an electrothermal 9100 apparatus. The IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker DRX-250 Avance spectrometer in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard. In addition, elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure for the synthesis of β-*amido-aroyl carbonyl derivatives*

A mixture of dimedone/barbituric acid derivatives (1 mmol), arylglyoxals (1 mmol), and amides (1 mmol) were added to choline chloride/urea (1:2, 4 mL). The resulting mixture was stirred and heated 90 °C for 145–165 min (Scheme 1). After completion of the reaction (TLC, ethyl acetate/*n*-hexane, 2:1), the reaction mixture was washed with water (10 mL) and the solid residue recrystallized from ethanol to obtain the pure product.

The spectral and analytical data for the new compounds are presented in the Supplementary material to this paper.

RESULTS AND DISCUSSION

First, the reaction of dimedone, 4-nitrophenylglyoxal, and benzamide was selected as a model reaction. Then the model reaction was performed in various DESs based on choline chloride (ChCl), and the results are listed in Table I. The mixture of choline chloride:urea (1:2) was identified as the best DES. Next, the reaction was tested at different temperatures to find the most suitable conditions, whereby the best reaction result was observed in the presence of choline chloride:urea (1:2) at 90 °C. Performing the reaction at lower temperatures reduced the reaction yields (Table I, entries 9–11). Furthermore only 20 % yield of the product was detected in the absence of any DES (Table I, entry 8).

In order to prove the efficiency of the method, several cyclic 1,3-diketones (**1**), various substituted arylglyoxal (**2**, including electron-donating and electron-withdrawing groups), and different amides (**3**) were employed in presence of choline chloride:urea (1:2) at 90 °C (Table II). Excellent yields of products and short reaction times were found as the advantages of the method.

Novel synthesized products (**4a**–**h**) were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectral data, as well as elemental analyses.

For example, the IR spectrum of **4a** showed absorptions at 3417 and 3258 cm^{-1} for OH and NH groups and at 1710, 1610 cm^{-1} for carbonyl groups, indi-

cating the presence of these functional groups in the proposed structure. The ^{1}H--NMR spectrum of **4a** exhibited two singlet signals at δ 0.63 and 0.99 ppm for methyl groups, and the methylene group was observed at δ 2.01 and 2.67 ppm. Additionally, a single signal was observed at δ 5.81 ppm for the methine group, and multiplet signals were observed at 7.50–8.27 ppm related to aromatic and NH hydrogens and finally a broad signals at δ 12.43 ppm related to the OH proton. The decoupled ^{13}C-NMR spectrum of **4a** showed 19 resonances that are consistent with the proposed structure. The elemental analysis confirmed the amounts of C, H and N in the final product.

TABLE I. Optimization of reaction in various choline chloride-based DESs; reaction conditions: dimedone (0.25 mmol), 4-nitrophenyl glyoxal (0.25 mmol) and benzamide (0.25 mmol) in DES (1 mL)

Entry	DES	*t* / °C	Time, min	Yield[a], %
1	Choline chloride	90	200	20
2	Choline chloride:$ZnCl_2$ (1:2)	90	200	40
3	Choline chloride:PTSA (1:1)	90	200	45
4	Choline chloride:malonic acid (1:1)	90	200	55
5	Choline chloride:succinic acid (1:1)	90	200	55
6	Choline chloride:citric acid (1:1)	90	200	50
7	Choline chloride:oxalic acid (1:1)	90	200	55
8	–	100	220	20
9	Choline chloride:urea (1:2)	70	150	70
10	Choline chloride:urea (1:2)	80	150	82
11	Choline chloride:urea (1:2)	90	150	90
12	Choline chloride:urea (1:2)	100	150	90

[a]Isolated yield

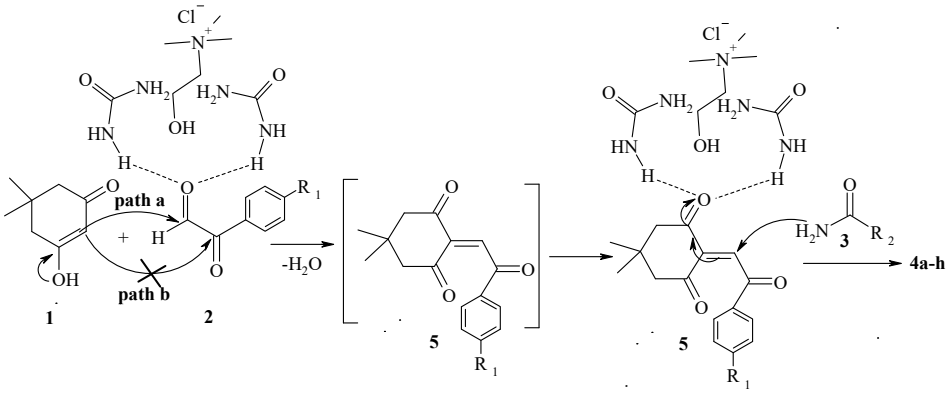
TABLE II. Three-component reaction of dimedone or barbituric acid derivatives, arylglyoxals, and amides in a deep eutectic solvent (DES); *MP* – melting point

Entry	Substrate	Ar	R_2	Time, min	Yield[a], %	*MP* / °C
4a	Dimedone	4-NO_2-C_6H_4	Ph	150	90	200
4b	Dimedone	4-Cl-C_6H_4	Ph	160	89	205
4c	Dimedone	4-Br-C_6H_4	Ph	160	85	225
4d	Dimedone	4-Br-C_6H_4	CH_3	155	90	210
4e	Dimedone	4-NO_2-C_6H_4	CH_3	145	88	215
4f	Dimedone	4-Br-C_6H_4	C_2H_5	150	85	210
4g	1,3-Dimethylbarbituric acid	4-CH_3-C_6H_4	CH_3	165	80	200–203
4h	Thiobarbituric acid	4-Cl-C_6H_4	C_2H_5	165	78	215–217

[a]Isolated yield

A plausible mechanism for the synthesis of *β*-amido-aroyl carbonyl derivatives based on the previously reported[30,31] is presented in Scheme 3. First, a Knoevenagel condensation of enolic form of dimedone **1** with more electrophilic formyl group of the arylglyoxal **2** (path a) in the presence of DES is proposed to

give intermediate **5**.[28,29] Then Michael addition of amide **3** to intermediate **5** forms the *β*-amido-aroyl carbonyl derivatives products. DES activates all carbonyl groups *via* hydrogen bonding. (Scheme 3).



Scheme 3. Suggested pathway for the formation of compounds **4a**–**h**.

Finally, the reusability of the catalyst for the synthesis of *N*-[1-(2-hydroxy--4,4-dimethyl-6-oxo-cyclohex-1-enyl)-2-(4-nitro-phenyl)-2-oxo-ethyl]-benzamide (**4a**) was studied (Fig. 1). After completion of the reaction, the reaction mixture was washed with water and the solid residue recrystallized to obtain the pure product. The DES was recovered from the aqueous phase by evaporation at 80 °C under vacuum and prepared for the next run. It was applied for four runs without noticeable decrease in the catalyst activity (Fig. 1).

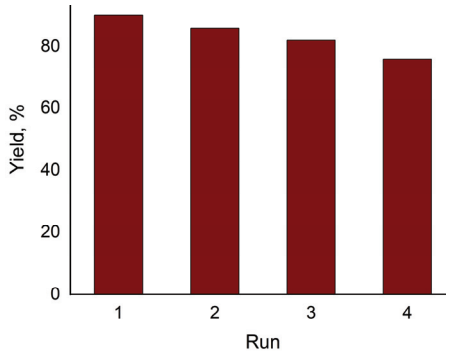


Fig. 1. Reusability of the DES.

CONCLUSIONS

In conclusion, a simple and efficient methodology for the synthesis of *β*--amido-aroyl carbonyl derivatives was successfully developed by the one-pot three-component reaction of dimedone/barbituric acid derivatives, arylglyoxals, and amides in the presence of choline chloride/urea as a green and eco-friendly

catalyst and solvent. Several noticeable advantages such as simplicity of operation, safe method, high yields of products, and biodegradable, non-toxic, inexpensive materials were found. Also, the deep eutectic solvent (DES) could be easily recycled and reused in at least four consecutive runs without significant loss of catalytic activity.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/index, or from the corresponding author on request.

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ИЗВОД

ЗЕЛЕНА И ЕФИКАСНА СИНТЕЗА НОВИХ *β*-АМИДО-АРОИЛ КАРБОНИЛНИХ ДЕРИВАТА У ЕУТЕКТИЧНОЈ СМЕШИ ХОЛИН-ХЛОРИД/УРЕА

ANITA BERJIS[1], BEHROOZ MIRZA[1] и HOSSEIN ANARAKI-ARDAKANI[2]

[1]*Department of Chemistry, Faculty of Science, Islamic Azad University, Karaj Branch, Alborz, Iran* и [2]*Department of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, Iran*

Зелена и веома ефикасна синтеза нових *β*-амидо-ароил карбонилних деривата постигнута је у једном реакционом кораку у тро-компонентној реакционој смеши која садржи димедон/деривате барбитурне киселине, арил-глиоксале и амиде у смеши холин хлорида/уреа као дубоком еутектичком растварачу (deep eutectic solvent, DES). Због употреба биодеградабилних материјала, кратког реакционог времена и високог приноса производа овај поступак припада ефикасним и еколошки прихватљивим методама синтезе. Еутектички растварач се лако може рециклирати и поново користити четири пута без губитка каталитичке активности.

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