

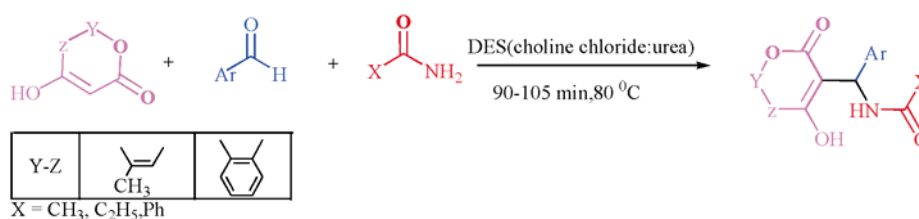
AN EFFICIENT AND GREEN PROTOCOL FOR THE ONE-POT SYNTHESIS OF 3-AMIDO-ALKYL-4-HYDROXYCOUMARIN DERIVATIVES BY CHOLINE CHLORIDE/UREA AS A DEEP EUTECTIC SOLVENT

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Received January 25, 2020

A green and highly efficient synthesis of some 3-amido-alkyl-4-hydroxycoumarin derivatives by one-pot, three-component reaction of aryl aldehydes, 4-hydroxycoumarin, or 4-hydroxy-6-methylpyran-1-one, and amides in deep eutectic solvent (DES) is reported. The DES system offers advantages in terms of environmental benign, biodegradable, short reaction times, and high yield. DES can be easily recovered and can be reused for other runs without any reduction in the activity.



INTRODUCTION

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity.¹ One of the ways to fulfill these goals is the development and use of multi-component reactions which consist of several simultaneous bond-forming reactions and allow the high efficient synthesis of complex molecules starting from simple substrates in a one-pot manner.²⁻⁴

A new generation of green solvents, namely deep eutectic solvents (DESs) had emerged an environmentally-benign media alternative to hazardous organic solvent in a variety of applications.⁵⁻⁷ Deep eutectic solvent is defined as a mixture of two or more components that are capable of self-association through hydrogen-bond

interactions, which result a large melting-point depression at a particular composition (the eutectic composition).⁸

DESs have some advantages, such as low price, negligible vapor pressure, non-flammability, simple reaction workup, low volatility, biodegradability and renewability. DESs are widely used in electrochemical applications and are promising alternatives for common organic solvents in industrial applications.^{9, 10}

Recently, we reported the reaction of 4-hydroxycoumarin, aromatic aldehydes, and acetonitrile in the presence of chlorosulfonic acid to produce 3-acetamido-alkyl-4-hydroxycoumarin derivatives.^{11,12} also we reported the reaction of 4-hydroxycoumarin, aromatic aldehydes and amides in the presence *p*-toluene sulfonic acid and ZnO NPs in solvent-free conditions to produce

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3-(α -amidobenzyl)-4-hydroxycoumarin derivatives,^{13,14} but these methodologies have been associated with some shortcomings such as long reaction times, and difficulty in recovery and reusability of the catalysts.

Considering the above reports and in continuation of our research on multi-component reactions,^{15,16} herein, we report an efficient approach for one-pot synthesis of 3-amido-alkyl-4-hydroxycoumarin derivatives **4** by a three-component reaction of 4-hydroxycoumarin, or 4-hydroxy-6-methylpyran-1-one **1**, aromatic aldehydes **2** and amides **3**, in the presence of deep eutectic solvent system based on choline chloride/urea (DES) as green and reusable catalyst in high yields (Scheme 1).

EXPERIMENTAL

Materials and methods

Products were characterized by comparison of their spectroscopic data (NMR and IR) and physical properties with those reported in the literature. Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ¹H and ¹³C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in DMSO-*d*₆ using TMS as internal standard. Chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Yields refer to isolated pure products.

Preparation of choline chloride-based deep eutectic solvents

Choline chloride-based deep eutectic solvents were prepared according to the literature^{17,18} and were used without further purification.

General procedure

A mixture of 4-hydroxycoumarin (0.25 mmol), aromatic aldehyde (0.25 mmol), and amide (0.25 mmol) were added to choline chloride/urea (1 mL). The resulting mixture was stirred and heated 80 °C for 90-105 min. (Table 2). After reaction completion, (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. All the products identified by IR, ¹H NMR and ¹³C NMR spectral data and by comparison of their melting points with literature reports.

The spectral and analytical data for the new compounds are as following:

N-((4-chlorophenyl) (4-hydroxy-2-oxo-2H-chromen-3-yl) methyl) benzamide (**4h**):

White powder, m.p. 189-191°C, IR (KBr) (ν_{\max} cm⁻¹): 3171 (NH), 1663, 1620, (2 C=O).

¹H NMR (300 MHz, CDCl₃): δ = 6.04 (1H, s, CH), 6.20 (1H, broad, NH), 7.13-8.04 (13 H, m, Ar), 11.35 (1 H, broad, OH).

¹³C NMR (62.90 MHz, CDCl₃): δ = 35.80 (CH), 93.35, 116.64, 124.40, 124.96, 17.33, 127.96, 128.60, 128.75, 131.96, 132.71, 133.00, 133.38, 133.88, 141.45, 152.41, 154.32 (carbons of Ar), 164.67, 169.53 (2C=O). Anal. Calcd. for C₂₃H₁₆ClNO₄: C, 68.07; H, 3.97; N, 3.45%. Found: C, 68.21; H, 3.81; N, 3.58 %.

N-((4-hydroxy-2-oxo-2H-chromen-3-yl)(4-methoxyphenyl)methyl)propionamide (**4i**):

White powder, m.p. 187-189°C, IR (KBr) (ν_{\max} cm⁻¹): 3348 (NH), 1682, 1619, (2 C=O).

¹H NMR (300 MHz, *d*₆-DMSO): δ = 0.92 (3 H, t, *J*_{HH} = 7.6 Hz, CH₃), 2.26 (2 H, q, *J*_{HH} = 7.6 Hz, CH₂), 3.65 (3H, s, OCH₃), 6.08 (1H, broad, CH), 6.28 (1 H, broad, NH), 7.20-8.05 (8H, m, Ar), 10.34 (1H, broad, OH). ¹³C NMR (75 MHz, *d*₆-DMSO): δ = 10.22 (CH₃), 28.69 (CH₂), 47.38 (CH), 106.72, 116.62, 116.68, 124.30, 124.51, 126.51, 126.98, 128.22, 132.87, 141.08, 152.80, 161.87 (carbons of Ar), 162.36, 174.34 (2C=O). Anal. Calcd. for C₂₀H₁₉NO₅: C, 67.98; H, 5.42; N, 3.96%. Found: C, 67.74; H, 5.61; N, 4.04%.

2-oxo-2H-pyran-3-yl) methyl) acetamide (**4j**):

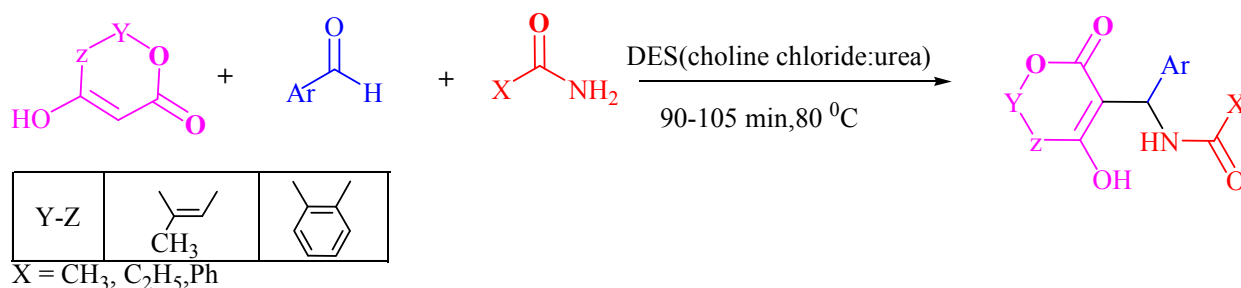
White powder, m.p. 177-179°C, IR (KBr) (ν_{\max} cm⁻¹): 3103 (NH), 1680, 1636, (2 C=O). ¹H NMR (300 MHz, CDCl₃): δ = 2.20 (3H, s, CH₃), 2.30 (3H, s, CH₃), 5.69 (1H, s, CH), 5.97 (1H, s, CH=C), 6.07 (1 H, broad, NH), 7.06-7.28 (4H, m, Ar), 10.94 (1H, broad, OH). ¹³C NMR (75 MHz, CDCl₃): δ = 19.66 (CH₃), 22.05 (CH₃), 34.40 (CH), 103.35, 127.90, 128.60, 132.49, 134.05, 152.38, 158.60 (carbons of Ar), 162.04, 170.10 (2C=O). Anal. Calcd. for C₁₅H₁₄ClNO₄: C, 58.55; H, 4.59; N, 4.55%. Found: C, 58.68; H, 4.64; N, 4.39%.

N-((4-chlorophenyl) (4-hydroxy-6-methyl-*N*-((4-chlorophenyl) (4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl) methyl) benzamide (**4k**):

White powder, m.p. 179-181°C, IR (KBr) (ν_{\max} cm⁻¹): 3300 (NH), 1679, 1619 (2 C=O). ¹H NMR (300 MHz, CDCl₃): δ = 2.27 (3H, s, CH₃), 5.74 (1H, s, CH), 6.06 (1H, s, CH=C), 6.25 (1H, broad, NH), 7.06-7.87 (8H, m, Ar), 10.94 (1 H, broad, OH). ¹³C NMR (75 MHz, CDCl₃): δ = 19.62 (CH₃), 34.33 (CH), 99.70, 101.56, 127.35, 127.91, 128.58, 132.02, 132.44, 133.24, 134.25, 144.34, 152.54, 158.90 (carbons of Ar), 161.77, 169.67 (2C=O). Anal. Calcd. for C₂₀H₁₆ClNO₄: C, 64.96; H, 4.36; N, 3.79%. Found: C, 64.82; H, 4.45; N, 3.86%.

N-((4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)(phenyl)methyl)benzamide (**4l**):

White powder, m.p. 176°C, IR (KBr) (ν_{\max} cm⁻¹): 3339 (NH), 1682, 1628 (2 C=O). ¹H NMR (300 MHz, CDCl₃): δ = 2.17 (3H, s, CH₃), 5.79 (1H, s, CH), 6.12 (1H, s, CH=C), 6.25 (1H, broad, NH), 7.06-7.86 (10H, m, Ar), 11.02 (1H, broad, OH). ¹³C NMR (75 MHz, CDCl₃): δ = 19.54 (CH₃), 34.21 (CH), 99.72, 102.32, 127.33, 128.01, 128.65, 132.06, 132.34, 133.29, 134.17, 144.32, 152.50, 157.96 (carbons of Ar), 161.83, 169.82 (2C=O). Anal. Calcd. for C₁₉H₁₆NO₄: C, 70.80; H, 5.00; N, 4.35%. Found: C, 70.65; H, 5.17; N, 4.43 %.



Scheme 1 – Synthesis of 3-amido-alkyl-4-hydroxycoumarin derivatives in DES as solvent and catalyst.

RESULTS AND DISCUSSION

At first, the reaction 4-hydroxycoumarin, benzaldehyde and acetamide were selected as model reaction. The model reaction was carried in various choline chloride (ChCl) - based DESs system like ChCl:PTSA, ChCl:ZnCl₂, ChCl:urea, ChCl: citric acid and ChCl:Oxalic acid in

different temperatures and the results are listed in Table 1. As indicated, the best yield was obtained in choline chloride and urea at 80 °C (Table 1, entry 7). A decrease in temperature gave lower yields (entry 6), and in the absence of the DES, only a 25% yield of the product was obtained (entry 5).

Table 1

Optimization of reaction in various choline chloride-based DES_s^a

Entry	DES	Temp(°C)	Time (min)	Yield (%) ^a
1	Choline chloride:ZnCl ₂ (1:2)	80	180	45
2	Choline chloride:PTSA(1:1)	80	180	40
3	Choline chloride: citric acid(1:1)	80	180	45
4	Choline chloride:oxalic acid(1:1)	90	180	55
5	--	100	240	25
6	Choline chloride:urea(1:2)	60	95	80
7	Choline chloride:urea(1:2)	80	95	90
8	Choline chloride:urea(1:2)	100	95	90

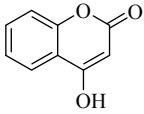
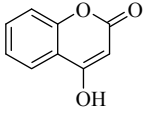
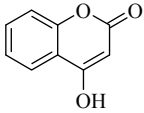
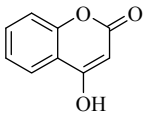
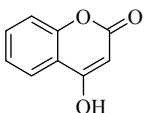
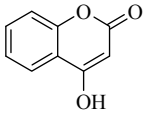
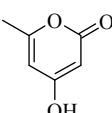
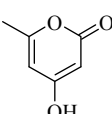
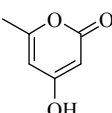
^b Isolated yield.^a Reaction condition: 4-hydroxycoumarin, (0.25mmol), benzaldehyde (0.25mmol) and acetamide (0.25 mmol) in DES (1 mL).

Table 2

Three-component reaction of aryl aldehydes, 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-1-one and amides in deep eutectic solvent (DES)

Entry	Substrate	Ar	X	Time(min)	Yield(%)	mp °C
4a		C ₆ H ₅	CH ₃	95	90	184(184-186) ^[13-14]
4b		4-Cl-C ₆ H ₄	CH ₃	100	92	176 (175-177) ^[13-14]
4c		4-Br-C ₆ H ₄	CH ₃	100	90	172-175(172-174) ^[13-14]

Table 2 (continued)

4d		4-NO ₂ -C ₆ H ₄	CH ₃	90	91	182(179-182) ^[13-14]
4e		3-CH ₃ O-C ₆ H ₄	CH ₃	105	88	202-204(203-206) ^[13-14]
4f		2-OH-C ₆ H ₄	CH ₃	100	85	147-148(146-148) ^[13-14]
4g		C ₆ H ₅	C ₂ H ₅	95	87	185(184-186) ^[13-14]
4h		4-Cl-C ₆ H ₄	Ph	100	85	189-191
4i		4-CH ₃ O-C ₆ H ₄	C ₂ H ₅	105	84	187-189
4j		4-Cl-C ₆ H ₄	CH ₃	90	92	177-179
4k		4-Cl-C ₆ H ₄	Ph	90	90	179-181
4l		C ₆ H ₅	Ph	100	90	176

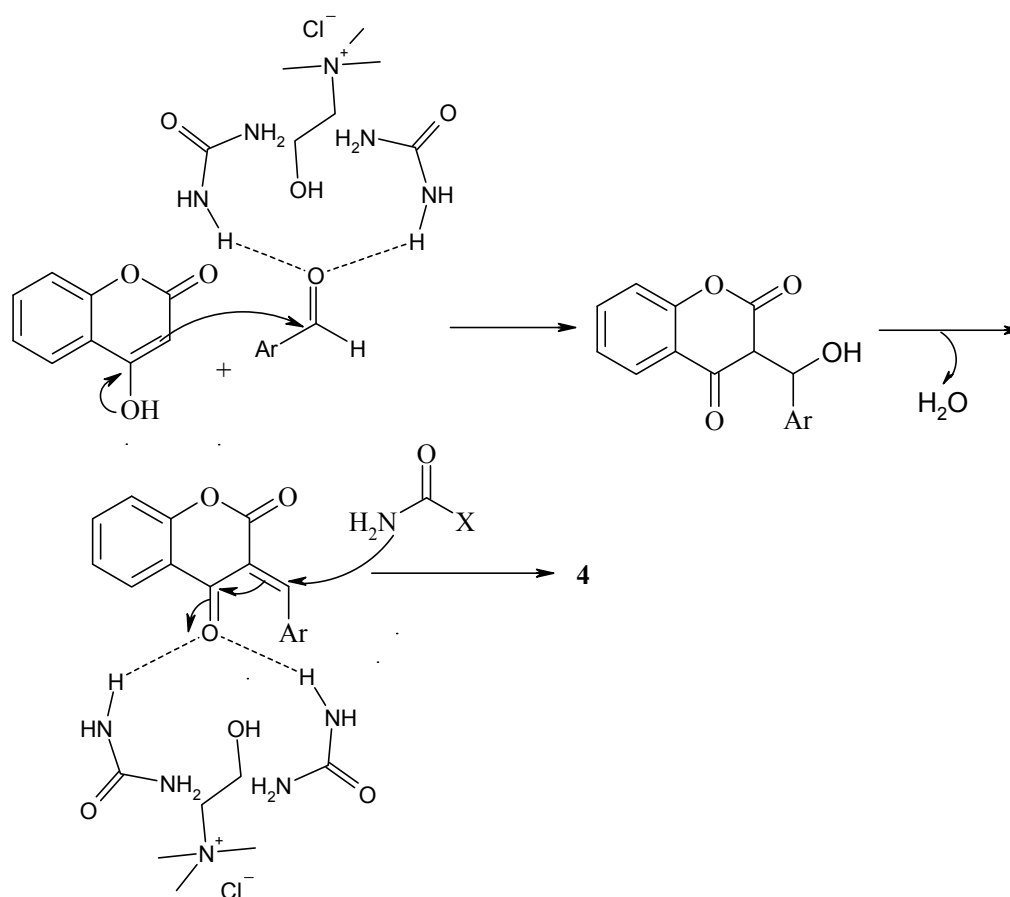
To study the scope and limitations of the reaction, various aromatic aldehydes, cyclic 1,3-diketone and amides were employed. The results are shown in Table 2. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields (Table 2).

Compounds **4h-l** were new and their structures were deduced by elemental and spectral analysis. Other compounds (**4a-g**) were known and their structures were deduced by comparison of melting points and spectral data with authentic samples.^{13,14}

The suggested mechanism for the formation of the products is shown in Scheme 2. The reaction of 4-hydroxycoumarin with aromatic aldehyde in the

presence of DES is proposed to give 3-benzylidene-chroman-2,4-diones. Then 3-benzylidene-chroman-2,4-diones, generated *in situ*, react with amide to form the 3-acetamido-alkyl-4-hydroxycoumarin products, DES activates all carbonyl groups via hydrogen bonding (Scheme 2).

The reusability of the catalyst for the synthesis of *N*-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)acetamide (**4a**) was investigated (Figure 1). The DES was recovered from the aqueous phase by evaporation at 80 °C under vacuum and tested for its activity in the subsequent run was recycled for the next reaction. DES was tested for 4 runs. It was seen that the catalyst activity displayed very good reusability (Figure 1).



Scheme 2 – Suggested pathway for the formation of compounds 4a-l.

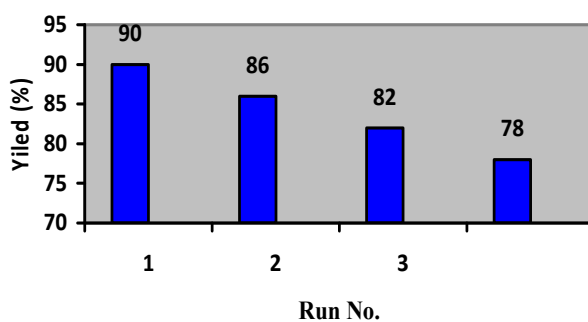


Fig. 1 – Reusability of the DES.

Table 3

Comparison of different methodology for the synthesis of compound 4a

Entry	Conditions	Temp (°C)	Time(min)	Yield (%) ^a	Ref
1	P-TSA (5 mol%), Solvent-free	115	300	85	[13]
2	ZnO NP, Solvent-free	110	130	85	[14]
3	This work	80	95	90	-

^a Isolated yield.

Finally, in order to access the efficiency and generality of this methodology, we compared this method with previous reported catalysts in the synthesis of compound **4a** (Table 3). From comparison with the results depicted in Table 3, it was found that DES is the most efficient catalyst with respect to reaction times, temperature, yield of the products and reusability of the catalyst.

CONCLUSIONS

In conclusion, we have successfully developed a simple and efficient methodology for the synthesis of 3-amido-alkyl-4-hydroxycoumarin derivatives by the three-component reaction of aryl aldehydes, 4-hydroxycoumarin, or 4-hydroxy-6-methylpyran-1-one, and amides in the present of deep eutectic mixture as green catalyst /solvent. Prominent among the advantages of this method are operational simplicity, mild reaction condition, short reaction times, higher yields, safe environmentally, also inexpensive and recyclable nature of DES.

Acknowledgements. We are thankful to the Islamic Azad University, Mahshahr branch, for the support of this work.

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