



CONDENSATION REACTION BETWEEN 3-ACETYLCOUMARINE AND ARYL ALDEHYDES IN THE PRESENCE OF *L*-PROLINE

Malihe Kamalpou^[a,b] and Farahnaz. K. Behbahani^{[a]*}

Keywords: 3-Acetylcoumarine, salicylaldehyde, ethyl amine, *L*-proline, chalcone.

3-Acetylcoumarine and a series of coumarin-chalcone hybrid compounds have been synthesized in good- to-excellent yields using a simple and efficient method. This method involved the one-pot reaction of salicylaldehyde, an α -ketoester to afford 3-acetylcoumarine and the product has been treated with an aromatic aldehyde using *L*-proline as a bioorganic catalyst to yield 1-(3'-coumarinyl)-3-aryl-2-propen-1-one (3-cinnamoylcoumarins).

* Corresponding Authors

Fax: 026 34418156

E-Mail: Farahnazkargar@yahoo.com

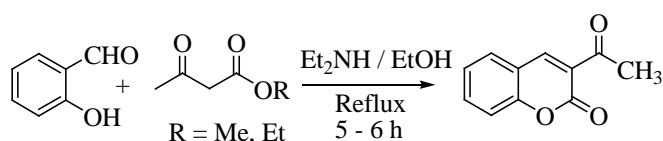
[a] Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran.

[b] Animal Science Research Institute of Iran, Agricultural research, Education and Extension Organization (AREEO), Karaj, Iran

INTRODUCTION

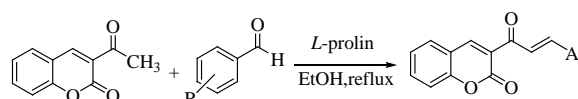
Recently, *L*-proline has gained importance as a versatile catalyst for effecting various organic transformations such as the synthesis of coumarone in ionic liquid¹ density functional study of the *L*-proline-catalyzed α -aminoxylation of aldehydes² unsymmetrical dihydro-1H-indeno[1,2-*b*]pyridines³ and 2-amino-4H-benzochromenes.⁴ Also, *L*-proline and *L*-proline derivatives were successfully used as organocatalysts in asymmetric aldol and Michael addition reactions.⁵ To the best of our knowledge, there was no attempt to use *L*-proline as a catalyst for the synthesis of 1-(3'-coumarinyl)-3-aryl-2-propen-1-one.

Diethylamine has recently been demonstrated to be an efficient organocatalyst in the various organic transformations such as synthesis of chromenes,⁶ Knoevenagel condensation,⁷ and aldol condensation and thia-Michael addition process.⁸ Also chromenes are an important class of compounds, widely present in plants, including edible vegetables and fruits.⁹ Numerous bioactive natural products have been identified, and the presence of the chromene-based structure has been associated with the capacity to prevent disease.¹⁰ In this study, diethylamine was used for the synthesis of 3-acetylcoumarine using alkyl acetoacetates and 2-hydroxy benzaldehyde in ethanol under reflux condition (Scheme 1).



Scheme 1. Synthesis of 3-acetylcoumarine using diethylamine.

Further, 3-acetylcoumarine and aromatic aldehydes, in the presence of *L*-proline, react under reflux condition in ethanol to yield 1-(3'-coumarinyl)-3-aryl-2-propen-1-one in good-to-excellent yields. The protocol represents a simple and efficient route, involving less hazardous solvent and easy separation (Scheme 2).



Scheme 2. Synthesis of 1-(3'-coumarinyl)-3-aryl-2-propen-1-one using *L*-proline.

EXPERIMENTAL

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer scanning between 4000–400 cm^{-1} . ¹HNMR spectra were obtained on Bruker DRX- 300 MHz NMR instrument.

Synthesis of 3-acetylcoumarin

A mixture of salicylaldehyde (20 mmol.), methyl acetoacetate or ethyl acetoacetate (30 mmol), ethanol (10 mL) and diethylamine (1 mL) were stirred under reflux condition at 4-5 h. After completion of the reaction, the mixture was cooled to afford yellow solid (92 %). The product was filtrated and then was washed with excess water and dried in air. M.p. 119–121 °C. ¹HNMR (300 MHz, CDCl_3) δ = 8.34 (s, 1H), 7.54–7.42 (m, 2H), 7.26–7.12 (m, 2H), 2.56 (s, 3H).

General procedure for the synthesis of 3-cinnamoyl coumarins using *L*-proline

A mixture of 3-acetylcoumarin (1 mmol.) and the corresponding aldehyde (1 mmol.) were mixed in the presence of *L*-proline (25 mol %) in ethanol (12 mL). The reaction mixture was stirred under reflux condition for a specified time.

The progress of the reaction was monitored by TLC (4:1 n-hexane:ethyl acetate). After completion of the reaction, the mixture was cooled and the product precipitated slowly after 8 h. The solid material was filtered off, washed with water, dried, and recrystallized from ethanol.

Recycling of the catalyst

The reusability of the catalyst was also investigated on the model reaction. After filtrating of the product, the liquor was evaporated under low pressure and the *L*-proline was washed with dichloromethane (15 mL), dried at 50 °C to provide an opportunity for recycling experiments. The separated catalyst was reused in the mentioned reaction for the synthesis of four times without considerable loss of its catalytic activity (entry 1, table 3; 90, 87, 83 and 78 %).

Spectra data for synthesized compounds

3-((E)-3-Phenylacryloyl)-2H-chromen-2-one (entry 1, table 3)

Brown solid. FTIR (KBr): 2978 (alkane, C-H str), 3037 (Ar, C-H str), 1715 (C=O), 1666 (C=O), 1607 (C=C) cm^{-1} . $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.61 (s, 1H, C-H), 7.90 (d, 1H, =C-H), 7.71-7.45 (m, 4H, Coumarin), 7.419-7.266 (m, 5H, Ar-H), 6.87 (d, 1H, =C-H).

3-((E)-3-(4-Chlorophenyl)acryloyl)-2H-chromen-2-one (entry 2, table 3)

Brown solid. FTIR (KBr): 3030 (Ar, C-H, str), 1717 (C=O), 1666 (C=O), 1610 (C=C) cm^{-1} . $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.61 (1H, s, C-H), 7.92 (d, 1H, =C-H, $J=15.72$), 7.84 (d, 1H, =C-H, $J=15.75$), 7.60-7.70 (m, 4H, Ar-H), 7.27-7.43 (m, 4H, Ar-H).

3-((E)-3-(4-Nitrophenyl)acryloyl)-2H-chromen-2-one (entry 3, table 3)

Brown solid. FTIR (KBr): 3042 (Ar, C-H), 1722 (C=O), 1666 (C=O), 1610 (C=C) cm^{-1} . $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.65 (s, 1H, C-H), 8.23-6.73 (m, 10H, Ar, CH=CH).

3-((E)-3-(3-Nitrophenyl)acryloyl)-2H-chromen-2-one (entry 4, table 3)

Brown solid, FTIR (KBr): 3078 (Ar, C-H str), 1728 (C=O), 1687 (C=O), 1608 (C=C) cm^{-1} . $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.69 (s, 1H, C-H), 8.49 (s, 1H, H-Ar), 8.21 (d, 1H, $J=7.63$, H-Ar), 7.78-7.26 (m, 8H, Ar, CH=CH).

3-((E)-3-(2-Furyl)acryloyl)-2H-chromen-2-one (entry 5, table 3)

Dark brown solid. FTIR (KBr): 3125 (Ar, C-H), 1739 (C=O), 1680 (C=O), 1607 (C=C) cm^{-1} . $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.58 (d, 1H, =C-H), 7.83 (d, 1H, =C-H), 7.70-7.60 (m, 4H, coumarin), 7.45-7.34 (m, 3H, furyl), 6.85 (d, 1H, =C-H).

3-((E)-3-(4-Bromophenyl)acryloyl)-2H-chromen-2-one (entry 6, table 3)

Brown, solid. FTIR (KBr): 3050 (Ar, C-H), 1707 (C=O), 1741 (C=O), 1607 (C=C) cm^{-1} . $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 8.57 (s, 1H, C-H), 7.90 (d, 1H, =C-H), 7.71-7.50 (m, 4H, coumarin), 7.40-7.16 (m, 4H, Ar-H), 6.59 (d, 1H, =C-H), 7.71-7.50 (m, 4H, Coumarin), 7.40-7.16 (m, 4H, Ar-H), 6.59 (d, 1H, =C-H).

RESULTS AND DISCUSSION

Initially, 3-acetylcoumarine was synthesized from the reaction of salicylaldehyde, an α -ketoester (methyl acetoacetate or ethyl acetoacetate) in ethanol with the addition of little amount of ethyl amine under reflux condition. On the base of our knowledge, the synthesis of 3-acetylcoumarine in the presence of diethyl amine have not been reported previously (Scheme 1).

Table 1. Optimization of the catalyst amount for the synthesis of 1-(3-coumarinyl)-3-(4'-chlorophenyl)-2-propen-1-one.

Entry	Catalyst, mol %	Yield, %
1	0	0
2	10	40
3	15	47
4	20	75
5	25	90
6	30	90

Reaction conditions: Benzaldehyde (1 mmol), 3-acetylcoumarin (1 mmol), solvent: ethanol (12 mL) under reflux

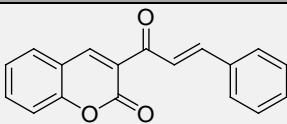
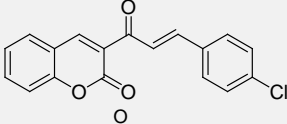
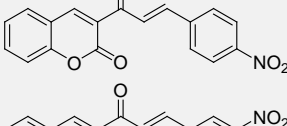
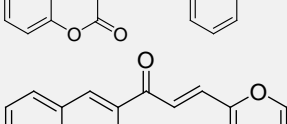
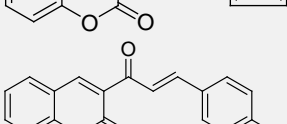
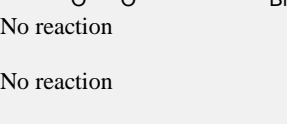
Thus synthesized 3-acetylcoumarine was used for the preparation of 3-cinnamoyl coumarins. In this case, initially, the optimization of the reaction conditions was studied for the synthesis of 3-((E)-3-phenylacryloyl)-2H-chromen-2-one. No product was obtained from the reaction of 3-acetyl coumarin and benzaldehyde in the absence of the catalyst under reflux condition in ethanol (Table 1, entry 1). The reaction was then performed in the presence of various amounts of *L*-proline to examine the catalytic activity (Table 1, entries 2-6). Among these amounts (25 mol %) of *L*-proline was found to be the most effective catalyst and afforded the desired product in 90 % yield (Table 1, entry 5).

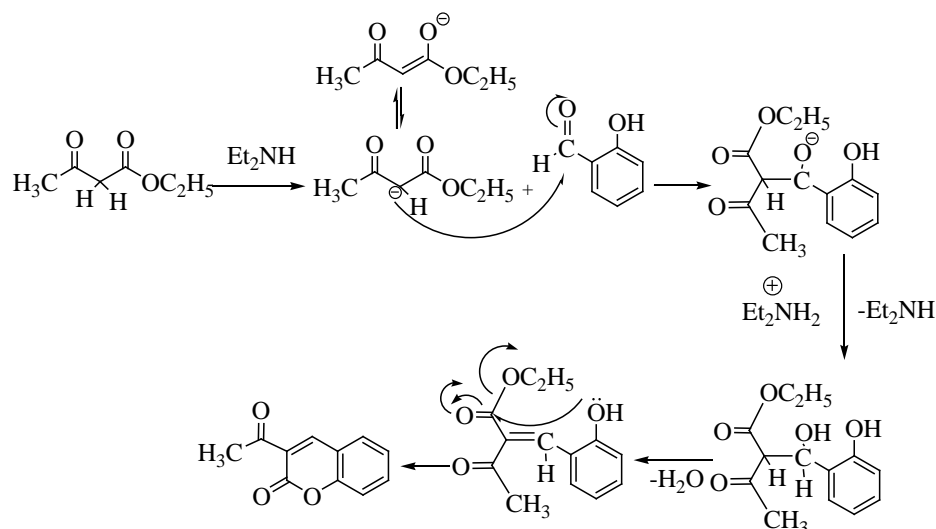
Also, different solvents were evaluated in the benchmark reaction. The results were revealed, that the catalyst more efficiently worked in ethanol under reflux conditions (Table 2).

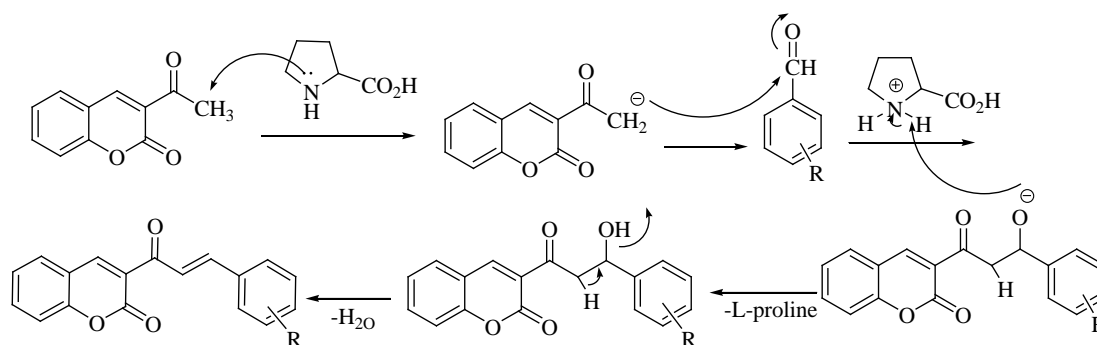
Table 2. The effect of solvent at different temperatures on the yield of the synthesis 1-(3-coumarinyl)-3-(4'-chlorophenyl)-2-propen-1-one.

Entry	Solvent	Temp., °C	Time, h	Yield, %
1	EtOH	25	48	60
2	H ₂ O	25	48	-
3	EtOH	Reflux	17	90
4	H ₂ O	Reflux	48	-
5	None	100	10	25

Table 3. The synthesis of 1-(3-coumarinyl)-3-aryl-2-propen-1-one using *L*- proline as a catalyst.

Entry	Aldehyde	Products	Time, h	Yield, %	M.P., °C Found/Reported(ref.)
1	Benzaldehyde		17	88	180-178/180-182 ¹¹
2	4-Chloro-benzaldehyde		17	90	188-190/188-190 ¹¹
3	4-Nitro-benzaldehyde		15	88	152-154/154-156 ¹¹
4	3-Nitro-benzaldehyde		15	87	205-207/205-207 ¹¹
5	Furan-2-carbaldehyde		20	78	93-95/101-103 ¹¹
6	4-Bromo-benzaldehyde		17	88	179-182/189-191 ¹¹
7	2-Hydroxy-benzaldehyde	No reaction	48	-	-
8	4-Dimethylamino-benzaldehyde	No reaction	48	-	-


Scheme 3. Proposed mechanism for the synthesis of 3-acetylcoumarine.



Scheme 4. Proposed mechanism for the synthesis of 1-(3-coumarinyl)-3-aryl-2-propen-1-ones.

To generalize optimized model reaction, several aromatic aldehydes and 3-acetylcoumarins in ethanol under the same conditions were used for the synthesis of 1-(3-coumarinyl)-3-(4-chlorophenyl)-2-propen-1-one. All aldehydes possessing electron withdrawing and electron releasing groups reacted in good-to-excellent yields under mild condition. An important feature of this procedure is the survival of variety of functional groups such as nitro groups, halides and heterocyclic aldehyde under the reaction conditions (Table 3).

Proposed mechanism for the synthesis of the preparation of 3-acetyl coumarine and 3-cinnamoyl coumarins have been shown in schemes 3 and 4.

CONCLUSION

The synthesis of potential bioactive hybrid molecules obtained from naturally occurring coumarin-chalcone moieties using *L*-proline as a highly efficient catalyst has been achieved. This method has the advantages of low cost, short reaction time, high atom economy, convenience and efficiency. It also offers a selective approach to the synthesis of coumarins, a structural motif found in a large number of natural products, pharmaceuticals and functionalized materials. Such a selective procedure offers energy saving advantages and reduces the expense of the purification process.

REFERENCES

- ¹Khurana, J. M., Nand, B., Saluja, P., DBU: a highly efficient catalyst for one-pot synthesis of substituted 3,4-dihydropyrano[3,2-*c*]chromenes, dihydropyrano[4,3-*b*]pyranes, 2-amino-4*H*-benzo[*h*]chromenes and 2-amino-4*H*-benzo[*g*]chromenes in aqueous medium, *Tetrahedron*, **2010**, *66*, 5637. doi.org/10.1016/j.tet.2010.05.082
- ²Wang, H., Yang, C., Han, K., Density functional study of the *L*-proline-catalyzed α -aminoxylation of aldehydes reaction: The reaction mechanism and selectivity, *Struct. Chem.*, **2006**, *17*, 97. doi.org/10.1007/s11224-006-9001-9

- ³Behbahani, F. K., Alaei, H. S., *L*-proline-catalysed synthesis of functionalized unsymmetrical dihydro-1*H*-indeno[1,2-*b*]pyridines. *J. Chem. Sci.*, **2013**, *125*, 623. doi.org/10.1007/s12039-013-0419-5
- ⁴Behbahani, F. K., Ghorbani, M., Sadeghpour, M., Mirzaei, M., *L*-proline-catalysed synthesis of functionalized unsymmetrical dihydro-1*H*-indeno[1,2-*b*]pyridines. *Lett. Org. Chem.*, **2013**, *10*, 191. doi.org/10.2174/1570178611310030008
- ⁵Liu, Y., Zhiwei, M., Chuanchuan, W., Jingchao, T. Research Progress in Supported Proline and Proline Derivatives as Recyclable Organocatalysts for the Asymmetric C-C Bond Formation Reactions, *Chinese J. Catal.*, **2011**, *32*, 1295. doi.10.3724/SP.J.1088.2011.10344
- ⁶Kulkarni, M. A., Pandit, K. S., Desai, U. V., Lad, U. P., Wadgaonkar, P. P., Diethylamine: A smart organocatalyst in eco-safe and diastereoselective synthesis of medicinally privileged 2-amino-4*H*-chromenes at ambient temperature. *C. R. Chimie.*, **2013**, *16*, 689. doi.org/10.1016/j.crci.2013.02.016
- ⁷Ye, W., Jiang, H., Yang, X.-C., Diethylamine functionalized polyethylene glycol as a novel and efficient catalyst for Knoevenagel condensation., *J. Chem. Sci.*, **2011**, *123*, 331. doi.org/10.1007/s12039-011-0085-4
- ⁸Abae, M. S., Cheraghi, S., Navidipoor, S., Mojtahedi, M. M., Forghani, S., An efficient tandem aldol condensation-thiamichael addition process. *Tetrahedron Lett.*, **2012**, *53*, 4405. doi.org/10.1016/j.tetlet.2012.06.040
- ⁹Curini, M., Cravotto, G., Epifano, F., Giannone, G., Chemistry and biological activity of natural and synthetic prenyloxycoumarins, *Curr. Med. Chem.*, **2006**, *13*, 199. doi.org/10.2174/092986706775197890
- ¹⁰O'Kennedy, P., Thornes R. D., (Eds.), *Coumarins: Biology, Applications and mode of action*, John Wiley & Sons, Chichester, U.K, **1997**.
- ¹¹Abd El Aleem, M., Ali. El-Remaily, A.A., Bismuth triflate: A highly efficient catalyst for the synthesis of bio-active coumarin compounds via one-pot multi-component reaction, *Chin. J. Catal.*, **2015**, *36*, 1124. doi.org/10.1016/S1872-2067(14)60308-9

Received: 28.07.2019.
Accepted: 22.09.2019