Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.47.007483

Simple Protocol of L-Proline-Mediated Knoevenagel Condensation: A Sustainable Access to Coumarin-3-Carboxylic Ester

Mateusz Kowalski and Katarzyna Szwaczko*

Faculty of Chemistry, Marie Curie-Skłodowska University in Lublin, Gliniana St. Lublin, Poland

***Corresponding author:** Katarzyna Szwaczko, Department of Organic Chemistry, Institute of Chemical Sciences, Faculty of Chemistry, Marie Curie-Skłodowska University in Lublin, Gliniana St. Lublin, Poland

ARTICLE INFO

Received: November 14, 2022

Published: November 28, 2022

Citation: Mateusz Kowalski and Katarzyna Szwaczko. Simple Protocol of L-Proline-Mediated Knoevenagel Condensation: A Sustainable Access to Coumarin-3-Carboxylic Ester. Biomed J Sci & Tech Res 47(2)-2022. BJSTR. MS.ID.007483.

ABSTRACT

A convenient and simple methodology was developed for the synthesis of coumarin-3-carboxylic esters. A series of the C-3 substituted coumarins were obtained via L-proline mediated Knoevenagel condensation. The malonate esters with both saturated and unsaturated bonds worked well under the developed reaction conditions, thus providing good to very good yields (54–94%) of the corresponding coumarins. The mild reaction conditions and the fact that pure reaction product can be obtained without the need for column chromatography provide an attractive alternative to currently known methods. The reaction can also be readily adapted for synthesis on a multigram scale.

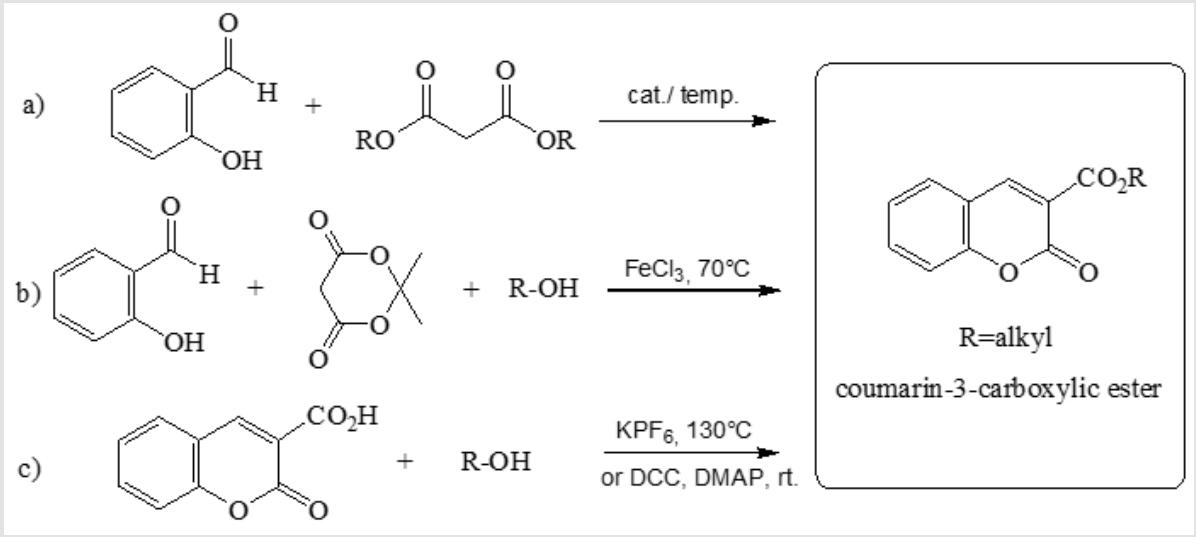
Keywords: Knoevenagel Condensation; L-proline; Coumarin-3-Carboxylic Ester

Introduction

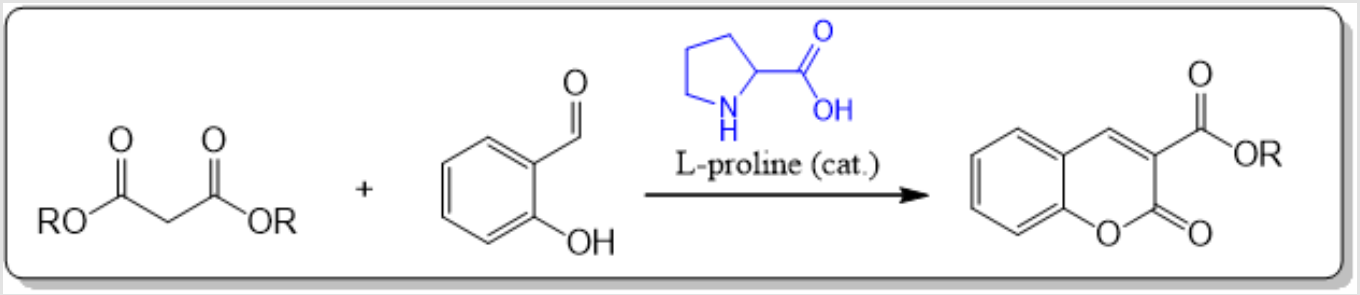
Coumarins represent an important family of naturally occurring oxygen-containing heterocyclic compounds. With their biological activity, they are an important structural element of many broad-spectrum drugs, exhibiting anti-inflammatory [1], anticoagulant [2], antifungal [3], anticancer [4] or antiviral [5]. The enormous utility of coumarins, combined with their relatively simple structure, means that interest in these compounds continues unabated. To date, a number of efficient methods for their synthesis have been developed, making coumarins more readily available synthetically. Thus, over the last decades, various protocols were reported to access coumarin scaffold [6,7]. They mainly include Perkin reaction, von Pechmann reaction, Baylis-Hillman condensation, Knoevenagel condensation, Michael addition, and the C-H bond activation [8-12]. The coumarin-3-carboxylic acid and its ester are important coumarin derivatives and an important intermediate for the synthesis of more complex molecules. They are readily available from the condensation reaction of salicylaldehyde to compounds with an active methylene group [13] and through the FeCl3-catalyzed multicomponent reaction of salicylaldehyde's, Meldrum acid and alcohols [14], (scheme 1 a & b).

These compounds can also be prepared from the coumarin-3-carboxylic acid and alcohols using DCC (N,N'-dicyclohexylcarbodiimide) with DMAP as the condensing reagent [15] or KPF6 (potassium hexafluorophosphate) [16], (scheme 1c). Unfortunately, many of these procedures are not ideal due to harsh reaction conditions and require the use of toxic and/or expensive catalysts. Coumarin derivatives are important to the pharmaceutical industry, so the development of simple, environmentally friendly, low-cost methods for their synthesis remains desirable. Searching for a universal and convenient method of synthesizing coumarins, we turned our attention to the traditional method of their preparation by Knoevenagel condensation. We also decided

to verify the catalytic potential of L-proline in this reaction. L-proline is an efficient bifunctional catalyst that is inexpensive and commercially available. It has two functional groups that can act as both acid or base which can facilitate chemical transformations and has already been widely used in numerous organic syntheses [17,18]. Here we describe the use of L-proline as a catalyst for the synthesis of coumarin-3-carboxylic esters from various substituted salicylaldehyde derivatives and the malonic acid esters (Scheme 2). The reaction products were obtained on a multi-gram scale in pure form without purification by column chromatography.



Scheme 1. The selected synthetic approaches towards coumarin-3-carboxylic esters.



Scheme 2. L-proline-mediated Knoevenagel condensation reaction.

Materials and Methods

General Information

The reagents and solvents were employed from commercial suppliers and used without further purification. All manipulations were performed under aerobic conditions. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV500 (1H 500 MHz, 13C NMR 126 MHz) spectrometer. All spectra were recorded in CDCl3 solutions, and the chemical shifts (δ) are expressed in ppm using internal reference to TMS. Coupling constants (J) were given in Hz. The abbreviations of signal patterns were as follows: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, b-broad.

Synthesis Of Malonate Esters

Malonic acid (10.0 g, 0.096 mol), Oxone (0.2 equiv.), and 20 ml of alcohol were placed in a Schlenk tube. The mixture was stirred at 80 °C for 48h. Then, the reaction mixture was diluted with EtOAc and washed with 5% NaHCO3 solution and H2O. The organic layer was dried with anhydrous Na2SO4, filtered, and concentrated in vacuo. The malonate esters were received with yield 58-87%. The 1HNMR and 13CNMR analyses are in agreement with literature data.

Dimethyl malonate (2a)

Colorless liquid, yield 80%, 1H NMR (500 MHz) δ 3.70 (s, 6H), 3.35 (s, 2H); 13C NMR (126 MHz) δ 166.6, 52.5, 41.1.

Diethyl malonate (2b)

Colorless liquid, yield 87%, 1H NMR (500 MHz) δ 5.03-5.98 (m, 2H), 3.25 (s, 2H), 1.20 (d, J = 6.3 Hz, 6H); 13C NMR (126 MHz) δ

166.4, 61.2, 41.5, 13. 8.

Diisopropyl malonate (2c)

Colorless liquid, yield 58%, 1H NMR (500 MHz) δ 5.98-5.90 (m, 4H), 3.38 (s, 2H), 1.27 (t, J = 7.5 Hz, 12H); 13C NMR (126 MHz) δ 166.1, 68.8, 42.2, 21. 5.

Dibenzyl malonate (2d)

Brown liquid, yield 70%, 1H NMR (500 MHz) δ 7.41-7.36 (m, 10H), 5.20 (s, 4H), 3.51 (s, 2H); 13C NMR (126 MHz) δ 166.1, 135.4, 128.9, 128.7, 128.5, 67.8, 42.0.

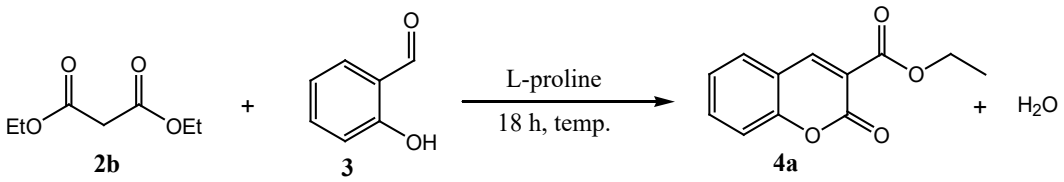
Diallyl malonate (2e)

Colorless liquid, yield 60%, 1H NMR (500 MHz) δ 5.91 (ddt, J = 17.0, 10.9, 5.6 Hz, 1H), 5.38 (ddd, J = 17.0, 2.8, 1.6 Hz, 1H), 5.27 (ddd, J = 10.4, 2.5, 1.2 Hz, 1H), 4.69 (ddd, J = 5.6, 2.8, 1.2 Hz 2H), 3.47 (s, 1H). 13C NMR (126 MHz) δ 166.1, 131.5, 119.0, 66.2, 41.6.

General Method for the Condensation of Malonate Esters with Salicylaldehyde

Salicylaldehyde (6.0g, 0.05mol), malonic acid esters (1.05equiv.), L-proline (10.0mol%) and the corresponding alcohol or acetonitrile (20ml), were placed in a Schlenk tube. The mixture was stirred at 80°C for 18h. Then the amount of the solvent was reduced by half and pure coumarin was prepared by crystallization at 4°C from EtOH or ACN or/and by precipitation with diethyl ether. The reaction efficiencies were 54-94% (Table. 1). The 1HNMR and 13CNMR analyses are in agreement with literature data.

Table 1: Optimization of reaction conditions[1].



2b **3** **4a**

Entry	L-proline (mol %)	Solvent	Temp. [°C]	4a, yield [%]
1	0.5	EtOH	80	41
2	1.0	EtOH	80	80
3	5.0	EtOH	80	85
4	5.0	EtOH	80	872
5	10.0	EtOH	80	94
6	10.0	EtOH	RT	10
7	10.0	toluene	80	80
8	10.0	ACN	80	85
9	10.0	DMF	80	77
10	10.0	EtOH	60	88

Note: [1]Reaction condition: 3(2.0 g, 16.3 mmol), 2b(1.05 equiv.), L-proline, 18h; [2]Reaction condition: 3, 10.0 g (81.9 mmol), 2b (1.05 equiv.), L-proline (5.0 mol%) 48h;RT = room temperature.

Methyl 2-oxo-2H-chromene-3-carboxylate (4a)

White solid, mp 103-105 ˚C, yield 92%, [1]H NMR (500 MHz) δ 8.6 (s, [1]H), 7.69–7.60 (m, 2H), 7.42-7.30 (m, 2H), 3.40 (s, 3H); [13]CNMR (126 MHz) δ 163.5, 156.3, 155.0, 148.9, 134.5, 129.6, 124.9, 119.0, 117.9, 116.8, 52.8.

Ethyl 2-oxo-2H-chromene-3-carboxylate (4b)

White solid, mp 86-87 ˚C, yield 69%, 1H NMR (500 MHz) δ 8.56 (s, 1H), 7.69-7.63 (m, 2H), 7.40-7.35 (m, 2H), 4.44 (q, *J* = 6.9, 2H), 1.44 (t, *J* = 7.2, 3H); 13CNMR (126 MHz) δ 163.2, 156.6, 155.0, 148.8, 134.4, 129.6, 124.9, 118.6, 117.9, 116.8, 61.8, 14.4.

Isopropyl 2-oxo-2H-chromene-3-carboxylate (4c)

White solid, mp 113-114 ˚C, yield 56%, 1H NMR (500 MHz) δ 8.48 (s, 1H), 7.67-7.62 (m, 2H), 7.36-7.37 (m, 2H), 5.31-5.26 (m, 1H), 1.40 (d, J = 6.3, 6H); 13CNMR (126 MHz) δ 162.4, 158.6, 155.1, 148.2, 134.2, 129.4, 124.8, 118.7, 117.9, 116.8, 69.7, 22.8.

Benzyl 2-oxo-2H-chromene-3-carboxylate (4d)

Brown solid, mp 85-87 ˚C, yield 75%, 1H NMR (500 MHz) δ 8.56 (s, 1H), 7.69-7.65 (m, 1H), 7.63-7.61 (m, 1H), 7.52-7.50 (m, 2H), 7.44-7.34 (m, 5H), 5.42 (s, 2H); 13CNMR (126 MHz) δ 162.7, 156.6, 155.2, 148.9, 135.4, 134.5, 129.7, 128.7, 128.3, 124.9, 117.8, 116.7, 67.4.

Allyl 2-oxo-2H-chromene-3-carboxylate (4e)

White solid, mp 50-52 ˚C, yield 80%, ^{1}H NMR (500 MHz) δ 8.54 (s, ^{1}H), 7.65-7.60 (m, 2H), 7.34-7.31 (m, 2H), 6.00 (tdd, *J* = 16.4, 5.6, 1.9 Hz, ^{1}H), 5.47 (d, *J* = 16.0 Hz, 1H), 5.45 (d, J = 17.0 Hz, 1H), 4.85 (d, *J* = 5.6 Hz, 2H); 13CNMR (126 MHz) δ 162.6, 156.6, 155.1, 148.9, 134.5, 131.5, 129.6, 124.9, 119.0 , 117.8, 116.7, 66.3.

Allyl 3-oxo-3H-benzo[f]chromene-2-carboxylate (4ea)

Brown solid, mp 113-115 ˚C, yield 56%, 1H NMR (500 MHz) δ 9.34 (s, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 9.1 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.77 (t, *J* = 8.2 Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 6.13-6.08 (m, 1H), 5.54 (ddd, *J* = 17.2, 2.8, 1.6 Hz, 1H), 5.38 (ddd, *J* = 10.4, 2.5, 1.3 Hz, 1H), 4.93 (dt, *J* = 5.6, 1.6 Hz, 2H), 13CNMR (126 MHz) δ 163.2, 156.7, 156.1, 144.8, 136.3, 131.6, 130.2, 129.3, 129.2, 126.6, 121.4, 119.1, 116.7, 116.1, 112.2, 66.5.

Allyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (4eb)

White solid, mp 154-155 ˚C, yield 72%, 1H NMR (500 MHz) δ 8.48 (s, 1H), 7.78-7.74 (m, 2H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.09-6.01 (m, 1H), 5.51-5.45 (m, 1H), 5.36-5.34 (m, 1H), 4.88-4.86 (m, 1H), ^{13}CNMR (126 MHz) δ 163.2, 155.9, 154.0, 147.4, 137.1, 131.6, 131.3, 119.3, 118.6, 117.4, 66.56.

Allyl 6,8-dibromo-2-oxo-2H-chromene-3-carboxylate (4ec)

Brick solid, mp 154-155 ˚C, yield 54%, 1H NMR (500 MHz) δ 8.43 (s, 1H), 8.01 (d, *J* = 2.21 Hz, 1H), 7.72 (d, *J* = 2.2 Hz, 1H), 6.07-6.00 (m, 1H), 5.50 (ddd, *J* = 17.3, 3.1, 1.6 Hz, 1H), 5.36 (ddd, J = 10.4, 2.5, 1.2 Hz, 1H), 4.87 (dt, *J* = 5.7, 1.5 Hz, 2H), ^{13}CNMR (126 MHz) δ 162.5, 162.0, 157.9, 154.8, 147.0, 139.2, 131.2, 130.8, 120.0, 119.3, 117.3, 66.8.

Allyl 7-methoxy-2-oxo-2H-chromene-3-carboxylate (4ed)

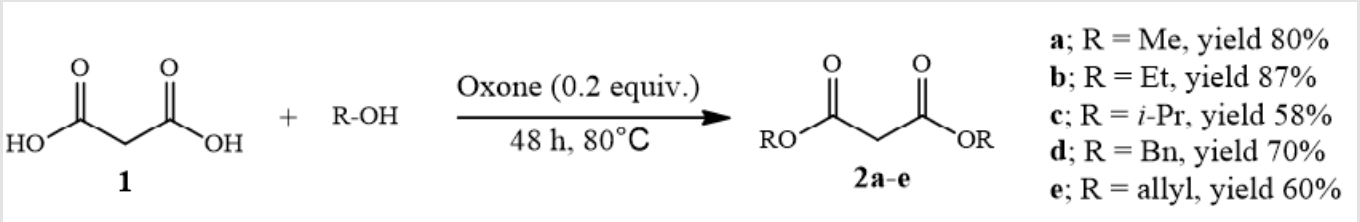
White solid, mp 100-103 ˚C, yield 90%, 1H NMR (500 MHz) δ 8.56 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.09-6.02 (m, 1H), 5.49 (ddd, *J* = 17.0, 2.8, 1.6 Hz, 1H), 5.33 (ddd, *J* = 10.4, 2.5, 1.2 Hz, 1H), 4.86 (dt, *J* = 5.7, 1.6 Hz, 2H), 3.93 (s, 3H), ^{13}CNMR (126 MHz) δ 165.2, 163.1, 157.6, 157.0, 149.3, 131.7, 130.8, 118.9, 113.7, 111.6, 100.4, 66.2, 56.0.

Allyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (4ee)

White solid, mp 95-96 ˚C, yield 70%, 1H NMR (500 MHz) δ 8.52 (s, 1H), 7.28-7.24 (m, 1H), 7.19-7.17 (m, 2H), 6.03-5.99 (m, 1H), 5.55 (ddd, *J* = 17.2, 2.8, 1.6 Hz, 1H), 5.32 (ddd, *J* = 10.4, 2.5, 1.2 Hz, 1H), 4.84 (dt, *J* = 5.7, 1.6 Hz, 2H), 3.97 (s, 3H), 13CNMR (126 MHz) δ 162.7, 156.0, 149.1, 147.0, 144.8, 131.5, 124.8, 120.6, 119.0, 118.4, 118.1, 116.0, 100.4, 66.4, 56.3.

Results and Discussion

The corresponding malonic acid esters (2a-e) were prepared by Oxone catalyzed esterification reaction (Scheme 3). The esterification was performed on a 10-gram scale (96.1 mmol of malonic acid, 1) in a Schlenk tube in the presence of at least 3.0 equiv. of the corresponding alcohol (15-20 ml) at 80 °C and for 48 hours. The alcohol played both as the reactant and solvent for the reaction while Oxone in amount of 0.2 equiv. was used as the catalyst. The reaction mixture was washed with 5% NaHCO3 solution and the product was extracted with ethyl acetate. After distillation of the excess alcohol, the pure malonic esters were isolated with very good yield (87-58%) and then applied in the synthesis of the coumarins. Initially, salicylaldehyde and diethyl malonate were chosen as the starting materials in the model L-proline catalyzed condensation. The reaction was performed in 20 ml reaction vials closed with an aluminum cap with the silicone/PTFE septa. Ethyl alcohol played as the solvent for the reaction while L-proline in amount of 10 mol% was used as the catalyst. At 80 °C and after a time of 18 hours, the reaction of 2b with salicylic aldehyde resulted in the isolation of the pure coumarin 4a yield of 94% (Table 1) entry 5.



Scheme 3. The esterification of malonic acid with the alcohols.

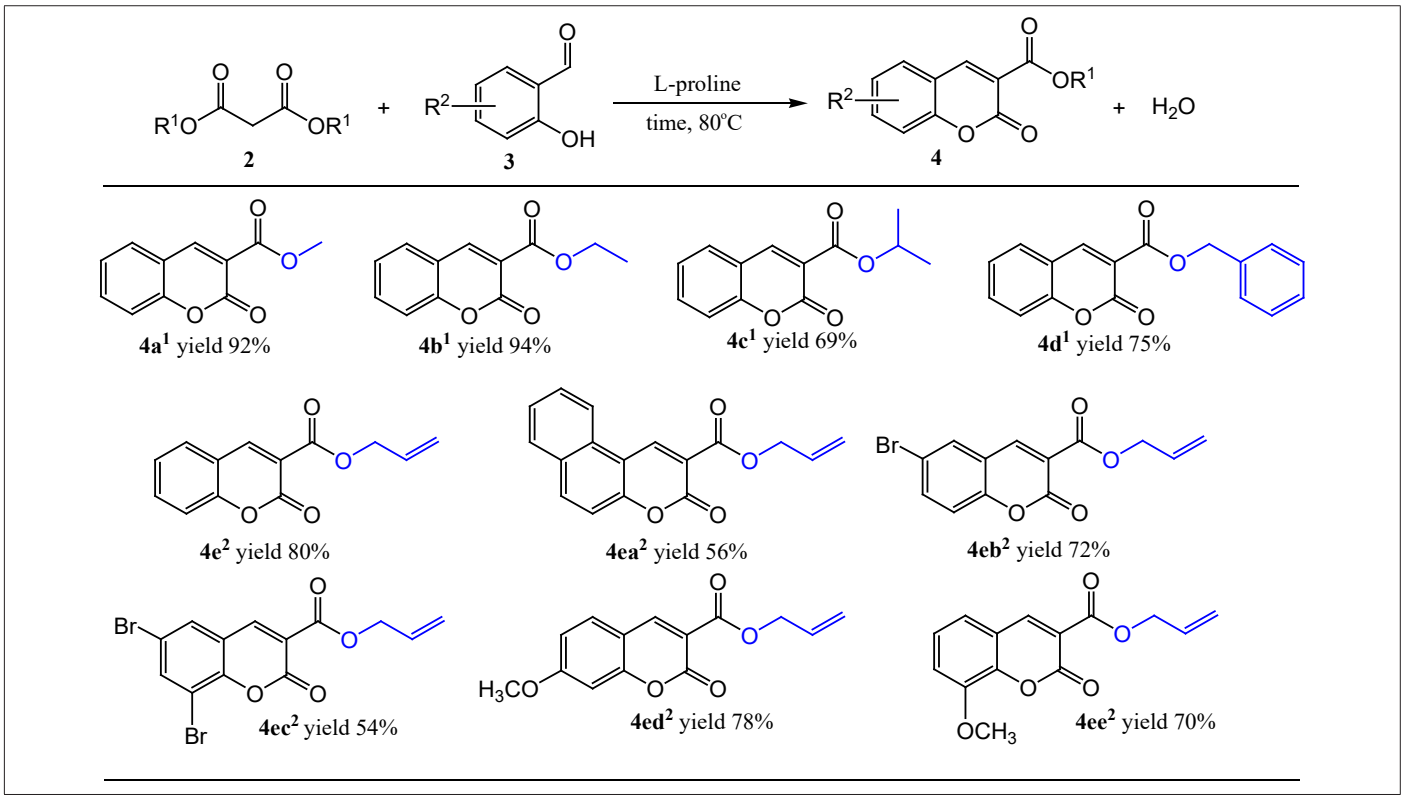
In order to determine the optimal reaction conditions, the influence of other reaction parameters, such as solvent addition, temperature, and amount of catalyst. When L-proline was used in an amount of 0.5 mol%, the product was obtained with an efficiency of 41%, and with an amount of 1.0 mol% and 5.0 mol% the efficiency were 80% and 85%, respectively. The effects of solvents other than alcohol was investigated, including toluene, dimethylformamide (DMF) and acetonitrile (ACN). Reactions in toluene and DMF yielded the reaction product with efficiencies of 80% and 77%, respectively. In ACN as the solvent, the product with 85 % of yield was observed. Thus, for the condensation reaction of diethyl malonate with salicylaldehyde, it is preferable to use alcohol

as a solvent, although acetonitrile and toluene are also suitable. Finally, the reaction scale was increased 5 times. Starting with 10 grams of 3 in the presence of diethyl malonate and L-proline in the amount of 5.0 mol % after a time of 48 hours at 80 °C, the pure coumarin 4a crystallized from the reaction mixture (Figure 1) and the total yield was 87%. (Table 1), entry 4. After optimizing various parameters for Knoevenagel condensation of the malonate ester 2b with salicylic aldehyde, the best result of 94% was obtained under the following conditions: L-proline (10 mol%), EtOH as the solvent, temperature 80 °C, reaction time 18 hours (Table 1), entry 5.

Figure 1: Coumarin 4a crystals in the mixture after the reaction.

With these optimized reaction conditions in hand, the activity of various salicylic aldehydes with malonate acid esters 2a-e was investigated (Table 2). We found that both saturated and unsaturated malonate esters gave desirable condensation products 4. The highest yields of isolated coumarin were obtained for dimethyl malonate and diethyl malonate at 92% and 94%, respectively. To our delight, good product yields were also achieved with dibenzyl malonate (yield 75%) and diisopropyl malonate (yield 69%). In order to prepare allyl coumarin-3-carboxylate (4e) with satisfactory efficiency of 80%, the reaction time was extended to 48 hours. Then, various structurally diverse salicylaldehyde's were subjected to the condensation reactions with diallyl malonate in the presence of L-proline. Regardless of the electron nature of the substituent in the aromatic ring and steric hindrance, the target coumarin derivatives were obtained with good yields of up to 78%. The lowest reaction yields were reported for the 3,5-dibromobenzaldehyde and 2-hydroxy-1-naphthaldehyde.

Table 2: Condensation reaction of different malonic esters with salicylic aldehyde (3).



Note: [1]Reaction condition: 3 (2.0 g), 2 (1.05 equiv.), L-proline (10 mol%), 18h, 80 °C; [2]Reaction condition: 3 (2.0 g), 2 (1.05 equiv.), L-proline (10 mol%), 48h, 80 °C

Conclusion

In conclusion, an efficient method, also for the large-scale synthesis, have been developed for the preparation of the coumarin-3-carboxylic ester derivatives without using expensive and toxic catalysts. For this purpose, L-proline was used as a cheap and commercially available reagent. The corresponding pure reaction products were obtained by crystallization omitting additional purification by column chromatography. It should be noted that this protocol was simple in operation, highly practical and efficient in the preparation of the suitable coumarin skeletons.

References

1. Sharma A (2016) Chapter 6-Anti-inflammatory agents. Advances in structure and activity relationship of coumarin derivatives Academic Press Boston Pp. 119-136.
2. Satish G (2016) Chapter 8-Anticoagulant agents. Advances in structure and activity relationship of coumarin derivatives, Academic Press Boston Pp. 151-159.
3. Kathiravan MK, Salake AB, Chothe AS, Dudhe PB, Watode RP, et al. (2012) The biology and chemistry of antifungal agents: A review. Bioorg Med Chem 20(19): 5678-5698.
4. Emami S, Dadashpour S (2015) Current developments of coumarin-based anti-cancer agents in medicinal chemistry. Eur J Med Chem 102: 611-630.
5. Hassan MZ, Osman H, Ali MA, Ahsan MJ (2016) Therapeutic potential of coumarins as antiviral agents. Eur J Med Chem 123: 236-255.
6. Bouhaoui A, Eddahmi M, Dib M, Khouili M, Aires A, et al. (2021) Synthesis and biological properties of coumarin derivatives. A review Chem. Select 6(24): 5848-5870.
7. Dalpozzo R, Mancuso R (2021) Copper-catalyzed synthesis of coumarins. A mini-review. Catalysts 11(11): 1382.
8. Ansary I, Taher A (2020) One-pot synthesis of coumarin derivatives. In book: Phytochemicals in human health. Intech Open.
9. Heravi MM, Khaghaninejad S, Mostofi M (2014) Pechmann reaction in the synthesis of coumarin derivatives. Adv Heterocycl Chem 112: 1-50.
10. Francisco CS, Francisco CS, Constantino AF, Neto ÁC, Lacerda Jr V (2019) Synthetic methods applied in the preparation of coumarin-based compounds. Curr Org Chem 23(24): 2722-2750.
11. Szwaczko K (2022) Coumarins synthesis and transformation via C–H bond activation—A review. Inorganics 10(2): 23
12. Dinparast L, Hemmati S, Zengin G, Alizadeh AA, Bahadori MB, et al. (2019) Rapid, efficient, and green synthesis of coumarin derivatives via Knoevenagel condensation and investigating their biological effects. Chemistry Select 4(31): 9211-9215.
13. Vekariya RH, Patel HD (2014) Recent advances in the synthesis of coumarin derivatives via Knoevenagel condensation: A review. Synth Commun 44(19): 2756-2788.
14. He X, Shang Y, Zhou Y, Yu Z, Han G, et al. (2015) Synthesis of coumarin-3-carboxylic esters via FeCl3-catalyzed multicomponent reaction of

salicylaldehyde's, Meldrum's acid and alcohols. Tetrahedron 71(5): 863-868.

15. Bogdal D, Galica M (2019) Novel terpolymers containing carbazole, coumarin and Alq3 complexes. Pure Appl Chem 91(3): 497-508.
16. Shinde SVN, Kumar A (2022) KPF6-Mediated esterification and amidation of carboxylic acids. J Org Chem 87(5): 2651-2661.
17. Thoran BR, Mali SN, Wavhal SS, Bhagat DS, Borade RM, et al. (2022) L-Proline: A Versatile organo-catalyst in organic chemistry, Comb. Chem. High Throughput Screen.
18. Elnagdi NMH, Al-Hokbany NS (2012) Organ catalysis in synthesis: L-proline as an enantioselective catalyst in the synthesis of pyrans and thiopyrans. Molecules 17(4): 4300-4312.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.47.007483

Katarzyna Szwaczko. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php