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SIMPLE AND EFFICIENT SYNTHESIS OF BIS-(4-HYDROXYCOUMARIN-3-YL)METHANE DERIVATIVES USING L-GLUTAMIC ACID AS CATALYST

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ABSTRACT

In the present study, we reports synthesis of bis-(4-hydroxycoumarin-3-yl)methaneby the one-pot-multicomponent reaction of different substituted aromatic aldehyde/heterocyclic aldehydes and 4-hydroxycoumarine in the presence of L-Glutamic acid (5mol %) as a catalyst in water : ethanol (1:1). The reaction mixture was stirred at reflux temperature for specified period of time. We found that this is a facile and efficient method for the synthesis of bis-(4-hydroxycoumarin-3-yl)methane. The prominent features of this method are the inexpensive reagents, simple and safe experimental procedure, easy and clean workup, short reaction times (05-40 min), excellent yield (52-99 %), no toxic waste and environmentally benign method.

KEYWORDS: 4-Hydroxycoumarine, bis(4-hydroxy coumarin-3-yl)methane, L-Glutamic acid.

INTRODUCTION

Coumarins constitute an intrinsic class of naturally occurring compounds in the area of natural products and synthetic organic chemistry. Bis-(4-hydroxycoumarin-3-yl) methane derivatives are of much interest because their wide range of biological activities which play very significant role as drug in the medicinal and pharmaceutical chemistry. Bis-4-hydroxycoumarine derivatives shows significant biological/pharmaceutical activity such as anticoagulant,[1] anti-microbial,[2] pesticides,[3] anticancer,[4] anti-inflammatory[5] activities.

These biological activities of coumarins raised our interest in synthesizing some new coumarins derivatives.

L-L-Glutamic acid is an amino acid which is acts as an efficient catalyst in the organic chemistry to synthesize various biologically important compounds such as, dihydropyrimidinones,[6] 1,2,4,5-tetrasubstituted imidazoles under thermal, solvent-free conditions,[7] polyfunctionalized dihydro-2-oxypyrroles[8] and 2,4,5-Triaryl-*1H*-imidazoles.[9]

The study of literature it reveals that, bis-(4-hydroxycoumarin-3-yl)methane derivatives are synthesized using catalysts and ionic liquids such as $RuCl_3 \cdot nH_2O$,[10] sulfated titania(TiO_2/SO_4),[11] SiO_2-OSO_3H NPs,[12] Nano silica chloride (nano SiO_2Cl),[13]n-Dodecylbenzene Sulfonic Acid (DBSA),[14]tungstate sulfuric acid (TSA),[15] choline chloride–oxalic acid,[16] Cobalt(II) chloride hexahydrate ($CoCl_2.6H_2O$),[17]succinimide-N-sulfonic acid,[18] $NaHSO_4/SiO_2$/Indion 190 resin,[19] Fe_3O_4 nanoparticles,[20] Nano TiO_2@KSF,[21]Phosphotungstic acid,[22] $[MIM(CH_2)_4SO_3H][HSO_4]$[23] andPOImD.[24]

However, most of these reported methods include disadvantages such as low yield, costly reagents or catalysts, drastic reaction conditions, environmental pollution, long reaction time, complicated operations. So to overcome these disadvantages we have developed a new simple, green and efficient method to synthesis of bis-(4-hydroxycoumarin-3-yl) methane by the one-pot reaction of 4- hydroxycoumarine and various substituted benzaldehyde on reflux in ethanol: water (1:1) as solvent.

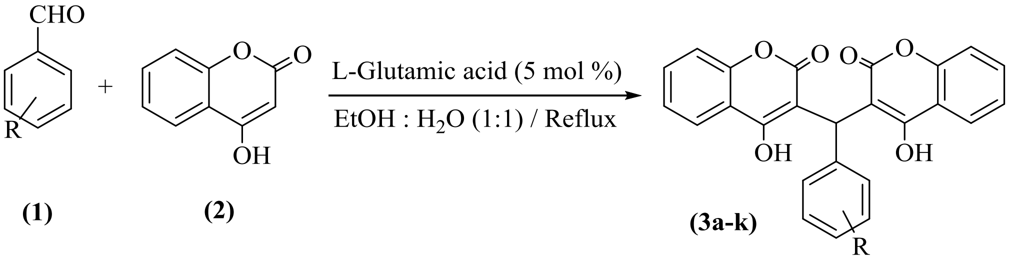
Experimental

a) Material and Methods

Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. All yields refer to isolated products unless otherwise stated. Melting points were determined in an open capillary. NMR spectrum recorded at 500 MHz with tetramethylsilane as internal standard and dimethylsulfoxide DMSO-d_6 as solvent on Bruker Avance Neo 500 MHz NMR spectrometer; Fourier transform infrared (IR) spectra were obtained as KBr discs on a Perkin Elmer spectrum 400 FT-IR/FT-FIR spectrometer and mass spectra on LCMS Water’s Synapt-XS Maldi TOF HDMS spectrometer.

b) General Procedure for the Synthesis of Bis-(4-hydroxycoumarin-3-yl) methane derivatives

In a 50 ml round bottom flask, a mixture of substituted aromatic aldehydes (1mmol), and 4-hydroxycoumarine (2 mmol) in the presence of catalytic amount of L-Glutamic acid (5 mol %) was stirred at reflux temperature in ethanol: water (1:1) (10 ml) for 5-40 minutes. The progress of the reaction was monitored by thin layer chromatography by using TLC plates at 70 % polarity (ethyl acetate: n-hexane) and TLC was observed under UV-lamp. After the appropriate time, the mixture was cooled then poured on ice cold water, the solidified product and filtered out 3(a-k). The crude solid material was purified by recrystallization from ethanol. Then the melting point of the product was determined by open capillary method and was uncorrected. Some principal products were characterized by FT-IT, FT-NMR, and LC–MS spectroscopic analysis from commercial agencies.



Spectroscopic analysis of compounds

3-((4-chlorophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-4-hydroxy-2H-chromen-2-one (3c)

M.F.: $C_{25}H_{15}O_6Cl$; Mol. Weight: 446.12, M.P. 257 °C; IR (KBr, cm^{-1}): 3415 (-OH), 3074, 2950, 2936 (Ar-H), 1668 (>C=O), 1565, 1490, 1404 (Ar-C=C), 1093(C-O), 816,782, 765 (C-Cl); ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.12 (s, 2H, -OH), 7.96-7.89 (m, 3H, Ar-H), 7.61-7.56 (m, 3H, Ar-H), 7.36-7.17 (m, 6H, Ar-H), 6.32 (s, 1H, CH); ^{13}C-NMR (500 MHz, DMSO-d_6, δ ppm): 166.35, 165.80, 164.52, 152.21, 139.65, 137.69, 131.65, 131.04, 129.85, 129.54, 128.63, 128.58, 127.76, 123.87, 123.46, 118.24, 115.77, 103.64, 35.61. (39.50 for DMSO solvent); LC-MS (m/z): 447 (M+1).

3, 3'-(3-Nitrophenyl)methylene)bis(2-hydroxy-4H-chromen-4-one) (3d)

M.F.: $C_{25}H_{15}NO_8$; Mol. Weight: 457.12, M.P. 237 °C; IR (KBr, cm^{-1}): 3414 (-OH), 3071, 2928, 2861 (Ar-H), 1641, 1617 (C=O), 1528, 1449 (Aromatic C=C), 1564, 1347 (NO_2), 1100 (C-O); ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 10.12 (s, 2H, OH), 8.22 -7.87 (m, 4H, Ar-H), 7.63 -7.51 (m, 4H, Ar-H), 7.34 -7.26 (m, 4H, Ar-H), 6.39 (s, 1H, CH); ^{13}C-NMR (500 MHz, DMSO-d_6, δ ppm): 173.14, 170.63, 166.69, 164.26, 152.37, 147.72, 144.33, 133.62, 131.46, 129.35, 124, 123.26, 121.07, 120.45, 118.87, 115.68, 102.90, 51.23, (39.58-39.25 for DMSO solvent), 36.20; LC-MS (m/z): 458 (M+1).

3, 3'-(4-Nitrophenyl)methylene)bis(2-hydroxy-4H-chromen-4-one) (3e)

M.Fo.: $C_{25}H_{15}NO_8$; Mol. Weight: 457.12, M.P. 230 °C; IR (KBr, cm^{-1}): 3414(OH), 2934, 2855,(Ar-H), 1618 (C=O), 1564, 1348, (NO_2), 1113 (C-O); ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 11.02 (s, 2H, OH), 7.95-7.93 (d, 2H, Ar-H), 7.62-7.60 (d, 2H, Ar-H), 7.37-7.25 (m, 5H, Ar-H), 6.88-6.73 (m, 3H, Ar-H), 6.53 (s, 1H, CH);^{13}C-NMR (500 MHz, DMSO-d_6, δ ppm): 166.01, 164.24, 152.18, 145.60, 131.77, 126.31, 124, 123.69, 123.52, 123.34, 118.27, 115.79, 104.13, (39.58, 39.42, 39.25 for solvent DMSO), 32.66.; LC-MS (m/z): 458 (M+1).

3, 3'-(Thiophen-2-ylmethylene)-bis-(4-hydroxy-2H-chromene-2-one) (3j)

M.F.: $C_{23}H_{14}SO_6$; Mol. Weight: 418.112, M.P. 214 °C; IR (KBr, cm^{-1}): 3474, 3414, (Ar-OH), 3114, 2928, 2726, 2600, (Ar-H), 1639, 1616 (C=O), 1565, 1495, 1449, (Aromatic C=C), 1097, 1050(C-O).; ^{1}H-NMR (500 MHz, DMSO-d_6, δ ppm): 11.53 (s, 2H, OH), 8.11-8.12 (d, 1H, Ar-H), 7.90-7.92 (d, 1H, Ar-H), 7.58-7.61 (m, 4H, Ar-H), 7.45-7.46 (d, 1H, Ar-H), 7.30-7.38 (m, 4H, Ar-H), 6.43 (s, 1H, CH); ^{13}C-NMR (500 MHz, DMSO-d_6, δ ppm): 166.30, 164.35, 152.34, 150.01, 145.47, 131.69, 127.99, 123.97, 123.44, 123.12, 118.44, 115.80, 103.23, (39.58, 39.42, 39.25 for DMSO solvent) 36.64; LC-MS (m/z): 419.06 (M+1).

RESULT AND DISCUSSION

In continuation of our previous studies on catalyzed organic reactions, we found that the condensation reaction of aromatic aldehyde (1) and 4-hydroxycoumarine (2) in the presence of catalytic amounts of L-Glutamic acid leads to formation of bis-(4-hydroxycoumarin-3-yl) methane derivatives (3) (Scheme-VIII).

Initially, we used 4-chlorobenzaldehyde (**1c**) and 4-hydroxycoumarine as the model reaction system to investigate the reaction at 0, 2.5, 5, 7.5 and 10 mol % of L-Glutamic acid in ethanol: water (1:1, v: v) at reflux temperature. The product (**3b**) was obtained in 0, 52, 99, 99 and 99 % yield, respectively. This indicates that the use of 5 mol % of L-Glutamic acid is sufficient to promote the reaction (Table-4.4).

Table 1: Optimization of amount of catalyst L-Glutamic acid for synthesis of compound (3c).

Entry	Amount of catalyst (mol %)	Time (min)	Yield (%)
1	0	30	0
2	2.5	30	52
3	5	30	99
4	7.5	30	99
5	10	30	99

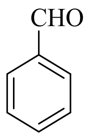
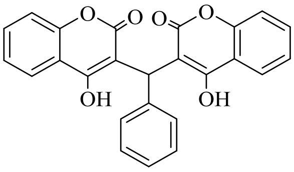
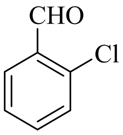
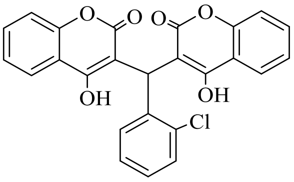
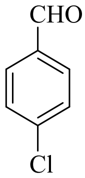
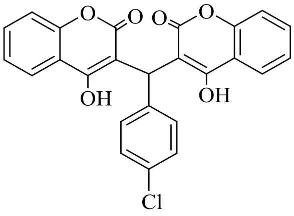
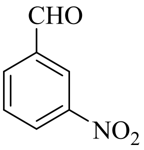
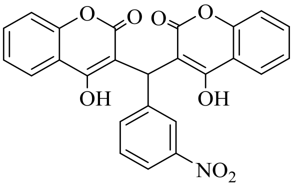
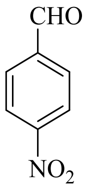
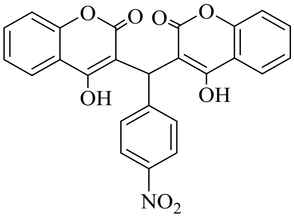
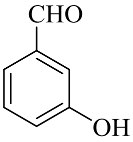
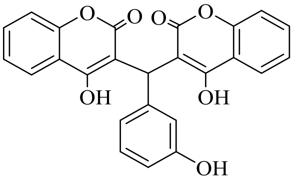
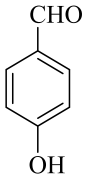
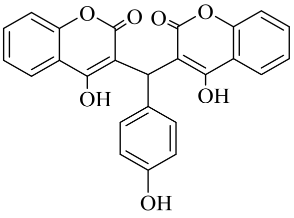
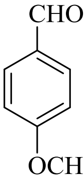
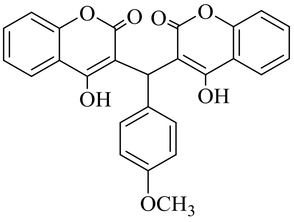
To determine the effect of solvent such as water, ethanol and mixture of water and ethanol at room temperature as well as reflux temperature to obtain varies yield. Ethanol: water (1:1) stand out as the best solvent system of choice among the solvents tested because of the rapid conversion and excellent yield (99 %) of desired product, where's the product formed in yields (52~99 %) by using other solvents (Table-2, Entry 1~10).

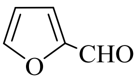
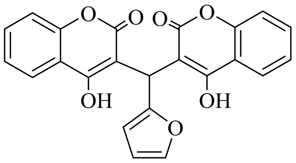
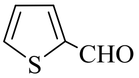
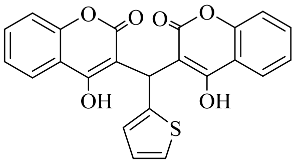
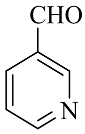
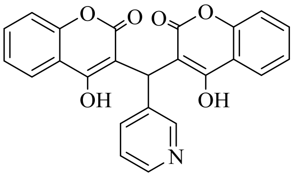
Table-2: Screening of solvents for the synthesis of bis-(4- hydroxycoumarin-3-yl)methane (3c).

Entry	Solvents	Temp	Amount of catalyst(mol %)	Time	Yield (%)
1	Ethanol	R.T.	5 mol%	22 Hrs	75
2	Water: Ethanol (1:1)	R.T.	5 mol%	6:30 Hrs	69
3	Water	R.T.	5 mol%	3 Hrs	79
4	Ethanol	Reflux	5 mol%	35 min	77
5	Water	Reflux	5 mol%	25 min	82
6	Water: Ethanol (1:1)	Reflux	5 mol%	5 min	99
7	Water: Ethanol (1:2)	Reflux	5 mol%	5 min	77
8	Water: Ethanol (1:3)	Reflux	5 mol%	5 min	70
9	Water: Ethanol (1:4)	Reflux	5 mol%	5 min	67
10	Water: Ethanol (1:5)	Reflux	5 mol%	5 min	62

To study the generality of this process, variety of examples were illustrated for the synthesis of bis-(4- hydroxycoumarin-3-yl) methane derivatives (3a-k) and the results are summarized in Entry-1-11, Table-3. The reaction is compatible for various substituents such as $–NO_2$, -OH, $-OCH_3$, -Cl and hetero cyclic aldehyde. The formation of desired product has been confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic analysis techniques and compared with the corresponding literature data.

Table 3: L-Glutamic acid catalysed synthesis of bis-(4-hydroxycoumarin-3-yl)methane (3a-k).

Entry	**Aldehyde**	**Product**	**Time (min)**	**Yield (%)**	**MP (°C) Found**	**MP (°C) Reported**
1		 3a	05	76	226	228-230[22]
2		 3b	05	78	225	224-226[19]
3		 3c	05	99	256	258-259[23]
4		 3d	20	91	236	234-236[13]
5		 3e	23	88	228-230	232-234[13]
6		 3f	30	81	262	256-258[24]
7		 3g	34	72	219	222-224[13]
8		 3h	40	73	248	247-249[13]

9		 3i	40	52	210	199-201[22]
10		 3j	25	85	212-214	212[22]
11		 3k	08	90	>300	-

[a]*Reaction conditions:* 1 (2 mmol), 2 (1 mmol), L-Glutamic acid (5%) ethanol at reflux temperature;

[b] Isolated yields

CONCLUSION

L--Glutamic acid is an easily available, inexpensive and efficient catalyst for the synthesis of Bis-(4-hydroxycoumarin-3-yl) methane derivatives from various substituted benzaldehyde (1 mmol) and 4-hydroxycoumarine (2 mmol) in the presence of L-Glutamic acid (5 mol %) as a catalyst was refluxed with magnetic stirring in ethanol: water (1:1) (10 ml) solvent for 05-40 minutes. The remarkable advantages of this method are the, short reaction times, easy work up, catalyst is simple and safe to handle and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of Bis-(4- hydroxycoumarin-3-yl) methane derivatives.

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