SOLVENT FREE, ALUM CATALYZED, MICROWAVE IRRADIATED SYNTHESIS OF 4-HYDROXY COUMARIN DERIVATIVES: A GREEN APPROACH

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Abstract : we developed an efficient and environmentally benign protocol for the synthesis of substituted coumarin derivatives using microwave irradiation under solvent free conditions by using a biodegradable and readily available alum catalyst. Overall process environmentally benign and synthetically more attractive.

Keywords: **Coumarin derivatives, alum catalyst, solvent free, MWI.**

I. INTRODUCTION

Coumarin was first isolated from natural source i.e. Tonka beans (Dipteryxodorata) in 1820 Coumarin is also found in extracts of Justicia pectoralis [1] [2]. afterword Coumarin was rediscovered in chemistry laboratory for the purpose of biological activities and there was born of new era i. e. Chemistry of Coumarin. [3] Coumarin and its derivatives have been studied for over a century owing to their diverse pharmacological activities. [4]

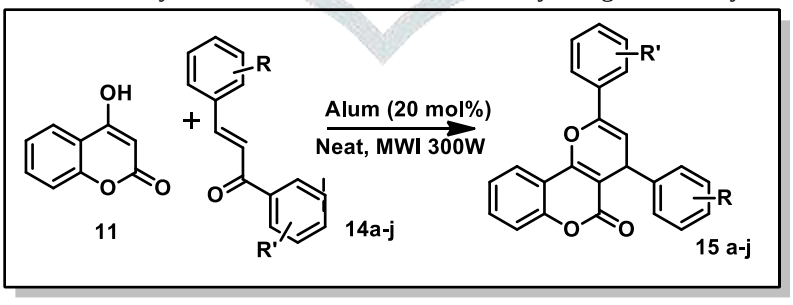
Coumarin and 4-hydroxy Coumarin are the types of simple molecules and these simple molecules does not show any specific types of biological activities but when these simple molecules with attached to one or more any electron donating or electron withdrawing groups, they become most biologically active molecules and shows antimicrobial, antiviral, anticoagulants, antagonistic, antifungal, in bio- fluorescence agent and in photochemistry, [5] [6] etc.

4- hydroxy coumarin is commonly called as Warfarin [7] and it is a synthetic derivative of dicoumarol, 4-hydroxy coumarin is first synthesized in chemistry laboratory more than a century ago by the scientist Mark A. Stahmann and its team [8] and make available as a drug. This is mostly used in US and European Countries due to their biological activities. [9]

α, β-Unsaturated ketones are commonly and chemically called as Chalcones, they display a wide range of pharmacological properties including cytotoxicity towards cancer cell lives, antimitotic, antimutagenic, antitumor, promoting activities, antibacterial, antiviral, anti-inflammatory, and hepatoprotective activities. [10-13] They are also useful in material sciences, fields such as non linier optics, optical limiting electrochemical censoring and they are well known reactive intermediates for synthesizing various heterocyclic compounds. [14]

Many of Researcher, Scientist and Pharmalogists are diverted for the synthesis of biological active heterocyclic compounds by using green solvent and green catalyst i.e. by green process. [15] Alum is one of the naturally occurring biodegradable economically very cheap, easily available and reactive catalyst. [16] Literature survey in the recent past reveals that alum is used as catalyst for synthesis of many heterocyclic molecules due to above reason, we decide to synthesize coumarin derivatives by using green catalyst alum under solvent free condition.[17][18]

Scheme 1. Synthesis of Coumarins derivatives by using alum catalyst.



Now a day an international trend is developed to carry out the chemical reaction under solvent free condition. [19] It helps us by different angle such as economical way, ecofriendly way and easy for workup, etc. [20] Conventional and non-conventional energy source are used for much chemical transformations. Many composition studies explain that non-conventional energy source is better than conventional one. Due to low reaction time, high purity, high yield, with easily handling. MWI is one of the most used non-conventional energy source for many reactions. This technic provides lot of heat in very short span of time to specific chemical bond which help to breaking and making of chemical bond.[21] [22]

To make things simpler, we envisaged developing an efficient and environmentally benign protocol for the synthesis of substituted coumarin derivatives using microwave irradiation under solvent free conditions by using a biodegradable and readily available alum catalyst. The employment of solvent free condition makes the overall process environmentally benign and synthetically more attractive (**Scheme 1**)

II. EXPERIMENTAL

General:

4-hydroxyl coumarin and other chemicals were obtained from commercial source and were used without further purification. Yields referred to isolated compounds, melting point of all the compounds were recorded by open head capillary method and uncorrected. IR spectra were recorded on Bruker v-22 spectrophotometer and in cm-1,1H- NMR &13C NMR spectra were recorded on Bruker AV -400 spectrophotometer with TMS as an internal standard. Chemical shift (δ) are expressed in parts per million (ppm) & coupling constant (J) are expressed in Hertz. TLC was performed on fluka® silica gel plates (F254).The mobile phase was ethyl acetate: n-hexane & detection was made using UV light.

General procedure for synthesis of chalcone derivatives:

A mixture of equimolar amount of aromatic aldehydes and aromatic ketones dissolved in minimum amount of absolute alcohol, stirred with 10 % aqueous solution of potassium hydroxide at room temperature for 6 hr. After completion of reaction monitored by TLC, poured this solution on crude ice, yellowish solid separate out, it was filtered, dried and recrystallization by ethyl alcohol to get pure product.

General procedure for synthesis of novel Coumarin derivatives by using Alum catalyst and solvent free condition:

In a 100 ml of round bottom flask, equimolar amount of 4-hydroxy coumarin, chalcone was added with 20 mol % of alum and mix all the content at room temperature. The mixture was subjected to microwave irradiation at the power of 300 watts, for appropriate time as shown in Table 5. The mixture was kept overnight at room temperature when the mixture was poured on cursed ice, solid get separated out, the product thus obtained was filtered and washed with cold water for 3 times and dried, the crude product was recrystallized by using hot solution of ethyl alcohol to get pure product in 75-89 % yields.

III. SPECTRAL CHARACTERIZATION DATA FOR REPRESENTATIVE COMPOUNDS

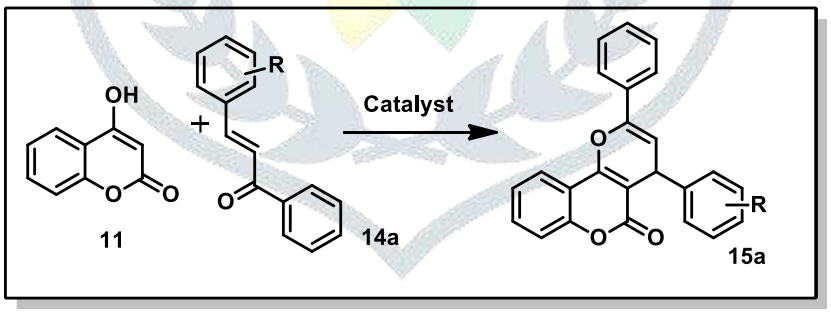
15b:2-(4-chlorophenyl)-4-phenylpyrano[3,2-c]chromen-5(4H)-one:whitish solid, mp: 136-138˚C, 1H NMR (400 MHz, CDCl3): δ 8.19 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 8 Hz, 1H), 7.76 (d, J = 8 Hz, 2H), 7.64–7.59 (m, 3H), 7.50–7.41 (m, 4H), 7.38 (d, J = 8 Hz, 1H), 5.81 (d, J = 4.5 Hz, 1H), 4.86 (d, J = 4.5 Hz, 1H); 13C NMR (CDCl3): δ 161.2, 156.6, 152.8, 150.5, 147.8, 147.1, 132.8, 132.1, 129.5, 129.4, 128.7, 124.6, 124.6, 123.8, 122.7, 117.1, 114.0, 102.3, 102.2, 36.7; IR (KBr): υmax 2924, 2852, 1722, 1515, 1347, 1017 cm-1.

IV. RESULTS AND DISCUSSION

In continuation of our studies [23] for the development of new coumarin derivatives, the reaction was extensively studied under different reaction conditions, to find out the best method giving the product in higher yield and short reaction time with operational simplicity. As shown in **Tables 1, 2, 3, and 4.**

Initially we use 4-hydroxy coumarin and simple chalcones (without any substituted) as a model reaction system to investigate systematically the reaction condition including effect of temperature, type of catalyst, and concentration of catalyst etc. for good to excellent yield as shown in **Table 5** and **Scheme 2.**

Scheme 2. Model reaction for synthesis of coumarin derivatives.



At first, we screened various mole % of catalysts (**Table 1 and 2**) with different solvents under conventional and microwave method (**Table 3 and 4**). Practically we observed that moderate to good yield was obtained in 20 mol % of alum as catalyst (**Table 1, 2** entry no. 5 and 5 respectively) in solvent free condition (**Table 3**, entry 6) using conventional method. If we increase mole % of catalyst more than 20 % there is no more significant effect was observed on the yield of product of reaction (**Table 2**, entry 6 and 7).

Table 1. Optimization of reaction condition w.r.t. Catalyst for synthesis of coumarin derivatives (15a) by conventional method.

Entry	**Catalyst (Mol %)**	**Time (hr)**	**Yields (%)[ab]**
1	Glacial AcOH	2	63
2	Mont-K-10	3	62
3	SiO_2	3	57
4	PMA	3	58
5	**Alum**	**2**	**72**
6	AcOH and Sod. Acetate	3	60

[a]Isolated yield, [b]Reaction condition: 4 hydroxy Coumarin, Simple Chalcone compound, reflux condition, Catalyst (20 mol %).

First, different catalyst such as Glacial AcOH, Mont-K-10, SiO2, PMA, alum and AcOH and Sod. Acetate (buffer) among these, we found that good yield (72 %) in alum catalyst under conventional heating method (**Table 1**, entry 5). Thus we decided to carry out all the reactions in alum catalyst.

Table 2. Optimization of Catalyst for synthesis of coumarin derivatives (15a) by conventional method.

Entry	Alum Catalyst (Mol %)	Time (hr)	Yields (%)[ab]
1	--	4	NR
2	5	4	NR
3	10	2	30
4	15	2	45
5	**20**	**2**	**72**
6	25	2	73
7	30	2	80

[a]Isolated yield, [b]Reaction condition: 4 hydroxy Coumarin, Simple Chalcone compound, Reflux condition, Alum Catalyst in different mole %

Second, different mole % of catalyst were tried for the same reaction, herein we observed that better yield in 20 mole % of catalyst (**Table 2**, entry 5).

Further, we optimized various solvents as DCM, Ethanol, THF, Toluene, Water, Neat, aq Ethanol, conventional at 120 ºC there was no reaction found in THF, water and aq Ethanol (**Table 3**, entry no. 3, 5 and 7). A very low yield was obtained in DCM, ethanol and Toluene (**Table 3**, entry no. 1, 2 and 4). Herein we obtained moderate to good yield in solvent free condition (**Table 3**, entry no. 6).

Table 3. Optimization of reaction condition w.r.t. solvent effect for synthesis of coumarin derivatives (15a) by conventional method.

Entry	Alum Catalyst (Mol %)	Solvents	Reaction Condition	Yields (%)[ab]
1	20	DCM	Reflux / 2hr / 120 ºC	20
2	20	Ethanol	Reflux / 2hr / 120 ºC	35
3	20	THF	Reflux / 2hr / 120 ºC	NR
4	20	Toluene	Reflux / 2hr / 120 ºC	10
5	20	Water	Reflux / 2hr / 120 ºC	NR
6	**20**	**Neat**	Reflux / 2hr / 120 ºC	**72**
7	20	aq. EtOH	Reflux / 2hr / 120 ºC	NR

[a]Isolated yield, [b]Reaction condition: 4 hydroxy Coumarin, Simple Chalcone compound, Reflux condition, Alum Catalyst (20 mol %).

Finally, the same reaction was carried out under the microwave irradiation technique, herein we compared both these method, and better yield was obtained under the Microwave irradiation method, power at 300 W (**Table 4**, entry no. 8) in very less time for reaction.

Thus all the derivatives of coumarin were reasonably synthesized in 20 mole % of alum catalyst in solvent free condition under the microwave irradiation technique in good to better yield 75-89% (**Table 5**).

Table 4. Comparision of reaction condition w.r.t. conventional and non-conventional energy source for synthesis of coumarin derivatives. (15a)

Entry	Alum (Mol %)	Solvent	Reaction Condition	Yields (%)[ab]
1	20	Neat	Reflux / 1hr / 120 ºC	34
2	20	Neat	Reflux / 2hr / 120 ºC	**72**
3	20	Neat	Reflux / 3hr / 120 ºC	72
4	20	Neat	Reflux / 4hr / 120 ºC	74
5	20	Neat	Reflux / 5hr / 120 ºC	74
6	20	Neat	MWI / 100 W / 3min	42
7	20	Neat	MWI / 200 W / 3min	72
8	**20**	**Neat**	**MWI / 300 W / 3min**	**88**
9	20	Neat	MWI / 400 W / 3min	88

[a]Isolated yield, [b]Reaction condition: 4 hydroxy Coumarin, Simple Chalcone compound, Reflux and MWI condition, Alum Catalyst (20 mol %).

Table 5. Physical Charecterisation data of coumarin derivatives catalyzed by green alum catalyst under solvent free condition with MWI technique[b].

Sr No.	Comp.d	R	R'	Mol. Formula	Time in (min.)	M.P.in (^{0}C)	Yield[a] in (%)[ab]
1	15a	H	H	$C_{24}H_{16}O_3$	3.00	170-172	88
2	15b	H	4-Cl	$C_{24}H_{15}ClO_3$	2.50	136-138	88
3	15c	H	4-Br	$C_{24}H_{15}BrO_3$	2.40	132-133	86
4	15d	H	4-NO_2	$C_{24}H_{15}NO_5$	4.00	217-219	89
5	15e	H	3-OMe	$C_{24}H_{16}O_3$	2.40	177-179	83
6	15f	H	4-OMe	$C_{25}H_{18}O_4$	3.00	180-181	81
7	15g	4-Br	4-OMe	$C_{25}H_{17}BrO_4$	2.40	220-221	75
8	15h	4-Br	4-Cl	$C_{24}H_{14}BrClO_3$	3.35	128-130	85
9	15i	3-Br	4-OMe	$C_{25}H_{17}BrO_4$	3.30	215-217	77
10	15j	3-Br	4-Cl	$C_{24}H_{14}BrClO_3$	3.30	127-129	83

[a]Isolated yield, [b]Reaction condition: 4 hydroxy Coumarin, Simple Chalcone compound, MWl at 300 Watt, Alum Catalyst (20 mol %), Solvent free condition.

V. Conclusions

In summary, it is evident that coumarin and coumarin related compounds are a plentiful source of potential active drugs candidate in relation to their safety and efficacy. In present study, we have developed a novel, practically efficient, environmentally benign protocol for the synthesis of substituted coumarin derivatives under solvent free condition of 4 hydroxy coumarin with unsaturated ketone (chalcone) in presence of green, biodegradable, easily available, cheap alum catalyst under non-conventional energy source i.e. microwave irradiation method in good to excellent yields.

The present protocol offers several advantages such as operational simplicity, short reaction time, and easy workup with purification of product by simple recrystallization.

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VII. References

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