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An alum [KAl $(SO_4)_2.12H_2O$] catalyzed microwave assisted multicomponent synthesis of bioactive functionalized benzylpyrazolyl coumarin and quinolinone derivatives in PEG

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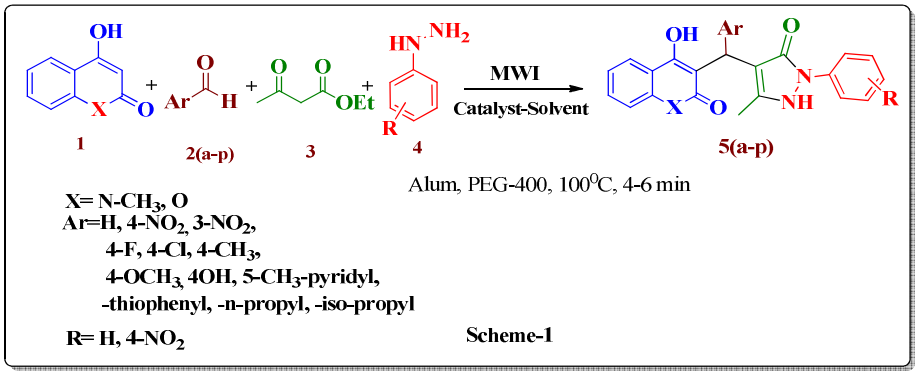
Abstract
An efficient and environmentally benign method has been developed for the synthesis of benzylpyrazolyl coumarin and quinolinone derivatives, hydroxy coumarin derivatives using Alum [KAl $(SO4)_2.12H_2O$] catalyst and Polyethylene glycol as green solvent under microwave condition.
Keywords: Knoevenagel, Michael addition reaction, coumarins, quinolinones, alum, polyethylene glycol, multicomponent microwave irradiation method.

1. Introduction

In recent years, multicomponent reactions (MCRs) are accepted worldwide as an important method for the synthesis of natural and medicinally important products.[1]These reactions avoid cost and time consuming processes for the purification of various precursors and isolation of intermediates of reaction.[2]
Now a day, polyethylene glycol (PEG) has emerged as a powerful phase transfer catalyst, and having extensive interest in research as environmentally benign solvents due to their favorable properties such as non-toxic, inexpensive, easy to handle, thermally stable and recyclable in various organic transformations,[3] such as for example, Heck reaction,[4] catalytichydrogenations,[5] asymmetric di-hydroxylation reaction,[6] Baylis-Hillman reaction,[7] Biginelli reaction,[8] Suzuki-Miyaura reaction, Stille cross-coupling reaction,[9] Wacker reaction[10] and asymmetric aldol reaction.[11] Alum ($KAl(SO_4)_2•12H_2O$), which is used for prominent organic transformations, such as the Biginelli[12] and Pechmann,[13] reactions and also used for the synthesis of 1,8-dioxo-octahydroxanthenes,[14] isoquinolonic acids,[15] trisubstituted dimidazoles,[16] 1*H*-spiro[isoindoline-1,2'-quinazoline]-3,4'(3*H*)-diones,[17] 1,3,4-oxadiazoles,[18] and 1,5-benzodiazepines,[19] This encouraged us to focus on the aspect of synthesis of biologically active benzylpyrazolyl coumarin and quinolinone derivatives under microwave irradiation. (Scheme **1**).

4-hydroxyquinolinone and its 3-substituted arylidine analogues having an excellent biological activity, such as hepatoprotative effects in human,[20] On the basis of biological evaluation 4-hydroxyquinolinone and its analogues has wide spectrum of pharmacokinetic usability, it constituent an important area of research because of their use as anti-oxidant, anti-angiogenic, Brain anti-tumor in vivo, analgesic, dye-stuff, herbicides, orally active antagonist and anti-inflammatory, anti-allergenic, anti-tubercles and cardiovascular agent, herbicidal[21-25] and competitive inhibitor.[26]4-hydroxycoumarin and its 3-substitutedarylidine derivatives are of much importanceas they exist in many natural products and exhibit a wide range of biological activities such as antibacterial, anti-HIV,[27] antiviral,[28] anticoagulant,[29] antioxidant,[30] and anticancer activities.[31]



Scheme 1: PEG mediated synthesis of benzylpyrazolyl coumarines and quinolinones.

Azole and its derivatives such as Pyrazolones phenazone, propyphenazone, ampyrone andmetamizole are useful for antipyretic and analgesicdrugs,[32] myocardial ischemia[33]. In addition, pyrazolones possess kinase inhibitory properties, particularly of enzymes which catalyze the phosphorylation of serine and threonine in proteins, and is also used for treating diseases related to these enzymes, such as rheumatoid arthritis, bone loss, cancer and other proliferative diseases like antimicrobial, antifungal,[34] antibacterial,[35] antiinflammatory,[36] antitumor,[37] gastricsecretionstimulatory,[38] antidepressant,[39] andanti-tubercularactivities.[40] The most commonly used synthetic methods for access in functionalized benzylpyrazolyl coumarin; quinolinone derivatives include Perkin, Knoevenagel, Reformatsky, Pechmann and Wittig reactions. Recently, a number of classical methods for the synthesis of benzyl pyrazolyl hydroxy coumarin, hydroxyl quinolinone derivatives have been reported in the literature in the presence of various catalysts like sulfuric acid, phosphorus pentoxide, aluminum chloride, iodine, and trifluoroacetic acid, sulfonic-acid-functionalized pyridinium chloride.[41-43] However, there are some disadvantages such as liquid acid catalysts, hazardous solvent and catalyst were used. In order to overcome these disadvantages, carry out this reaction an environmentally benign.

This method describes synthesis benzylpyrazolyl hydroxy coumarin, hydroxyl quinolinones in Alum-PEG as green catalyst and solvent under microwave irradiation technique. From our literature survey, there has been no any report synthesis of benzylpyrazolyl hydroxy coumarin, hydroxyl quinolinone derivatives, by alum catalyst in polyethylene glycol as solvent. As a part of our ongoing interest in MCRs.[44] We now report a simple and efficient procedure in alum and PEG-400 as an effective catalyst and solvent. (*Scheme 1*).

2. Result and Discussion

First**,** we choose alum as green catalyst for multicomponent, model reactions as hydrazine (1 mmol), ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol) and 4-hydroxycoumarin or 4-hydroxyquinolinone (1 mmol) to optimized reaction condition in different solvent, vary a temperature (80,100,120^{0}C) with different mole% of catalyst (5,10,15%), herein we observed that an excellent yield was obtained in very short reaction time in 10mol % of catalyst in minimum amount of solvent (Table **1**, entry 2) this is due to alum-PEG is good pair-emerged catalyst solvent for their solubility. Further, we optimized reaction condition and performed series of reactions with different acid catalyzed with selected solvent with variable temperature (Table **2**), we found that 97 % yield in 10 mole % catalyst at 100^{0}C temperature (Table **2,** entry 2). If we changed temperature, the product yield was decreases (Table **2**, entry 3, 4). The reaction did n't detect without catalyst even after 10 min at 120^{0}C (Table **2**, entry 1). Better yield was obtained in alum, Montmorillonite k-10 and Glacial acetic acid in short reaction time with same reaction condition (Table **2**, entry 2, 6, 9). Thus we decided reaction carried out in alum as green catalyst, and PEG as solvent, all example were tested reasonably good to excellent yields could be achieved in less time 4-6 min (Table **3**). An electronic effect was observed, electron withdrawing groups (Table **3**, entry 2-3, 10) and electron donating groups (Table **3**, entry 6-8, 11) to aryl aldehydes were well tolerate. The use of electron withdrawing NO_2 group on the aryl ring of the phenyl hydrazine was also successful and afforded the desired product in good yields (Table **3,** entry 9-11, 15-16). The reaction proceeded smoothly with hydrazine (Table **3**, entry 12). Five and six member heterocyclic aryl aldehyde gave corresponding yield (Table **3**, entry 13-16).

Finally, the product was confirmed by spectral data (IR, ^{1}HNMR and HRMS), presence of N-H form this is due to 3150-3165 cm^{-1}shows IR band, ^{1}HNMR shows at δ 2.1 and mechanistic path (Scheme **2**) and tautomeric form (figure **1**) and compared with reported method.[45-47]

Table **1**. Optimization of catalyst with different solvent for the synthesis of **5**

Entry	**Alum Catalyst (mole%)**			**Solvent**	**Time (min)**	**Yield[a] (%)**		
	a	**b**	**c**			**a**	**b**	**c**
1	5%	10%	15%	H_2O	6	58	83	83
2	5%	**10%**	15%	**PEG**	**4**	40	**97**	96
3	5%	10%	15%	EtOH	6	62	70	72
4	5%	10%	15%	MeOH	6	40	68	68
5	5%	10%	15%	CH_3CN	6	30	52	50
6	5%	10%	15%	Toluene	6	20	38	38
7	5%	10%	15%	DCM	6	25	42	40

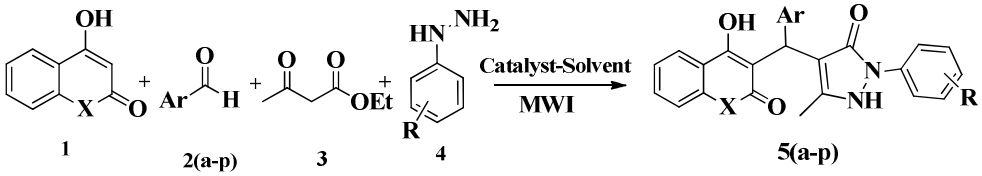
[a]Isolated yield
Reaction condition: Hydrazine (0.10g, 1 mmol), ethyl acetoacetate (0.13g, 1mmol), Aromatic aldehyde (1mmol), 4-hydroxy coumarin (0.16g, 1mmol) or 1-methyl 4-hydroxy quinolinone (0.17g, 1mmol) and Alum (10 mol %), PEG (4-6 mL) [b]Reaction condition used at 80^0C,100^0C and 120^0C for each solvent with alum catalyst.

Table 2. Optimization of reaction condition for the synthesis of **5**

Entry	**Catalyst (mol %)**	**Solvent**	**Temp. (^{0}C)**	**Time (min.)/Yield(%)[a]**
1	No catalyst	PEG	120	10/00
2	Alum (10)	PEG	100	**4/97**
3	Alum (10)	PEG	80	4/72
4	Alum (10)	PEG	120	4/86
5	Montmorillonite (05)	PEG	100	8/40
6	Montmorillonite(10)	PEG	100	4/84
7	Montmorillonite(15)	PEG	100	4/83
8	Glacial Acetic acid (05)	PEG	100	8/60
9	Glacial Acetic acid (10)	PEG	100	**4/89**
10	Glacial Acetic acid (15)	PEG	100	4/88

[a] Isolated yield.
Reaction condition: Hydrazine (0.10g, 1 mmol), ethyl acetoacetate (0.13g, 1mmol), Aromatic aldehyde (1mmol), 4-hydroxy coumarin (0.16g, 1mmol) or 1-methyl 4-hydroxy quinolinone (0.17g, 1mmol) and Alum (10 mol %), PEG (4-6 mL)

Table 3. Synthesis of benzyl pyrazolyl coumarin and quinolinone derivatives:



1 2(a-p) 3 4 5(a-p)

X= N-CH_3, O

Entry	Compound[a]	Aldehyde	Hydrazine	Ethyl Aceto Acetate(EAA)	Yield(%)[b]/Time(min) (%Yield: Lit.)[45-47]
1	**5a**	C_6H_5	C_6H_5	$C_6H_{10}O_3$	89/04
2	**5b**	4-$NO_2C_6H_4$	C_6H_5	$C_6H_{10}O_3$	**97/04**
3	**5c**	3-$NO_2C_6H_4$	C_6H_5	$C_6H_{10}O_3$	90/04
4	**5d**	4-FC_6H_4	C_6H_5	$C_6H_{10}O_3$	83/06
5	**5e**	4-ClC_6H_4	C_6H_5	$C_6H_{10}O_3$	83/06
6	**5f**	4-$CH_3C_6H_4$	C_6H_5	$C_6H_{10}O_3$	82/06
7	**5g**	4-$OCH_3C_6H_4$	C_6H_5	$C_6H_{10}O_3$	88/06
8	**5h**	4-OHC_6H_4	C_6H_5	$C_6H_{10}O_3$	70/06
9	**5i**	C_6H_5	4-$NO_2C_6H_4$	$C_6H_{10}O_3$	83/06
10	**5j**	3-$NO_2C_6H_4$	4-$NO_2C_6H_4$	$C_6H_{10}O_3$	90/04
11	**5k**	4-$OCH_3C_6H_4$	4-$NO_2C_6H_4$	$C_6H_{10}O_3$	86/06
12	**5l**	C_6H_5	H_2NNH_2	$C_6H_{10}O_3$	86/06
13	**5m**	5-$CH_3C_5H_3N$	C_6H_5	$C_6H_{10}O_3$	82/06
14	**5n**	C_4H_3S	C_6H_5	$C_6H_{10}O_3$	73/06
15	**5o**	C_3H_7	4-$NO_2C_6H_4$	$C_6H_{10}O_3$	80/06
16	**5p**	C_3H_7	4-$NO_2C_6H_4$	$C_6H_{10}O_3$	82/06

[a] Isolated yield

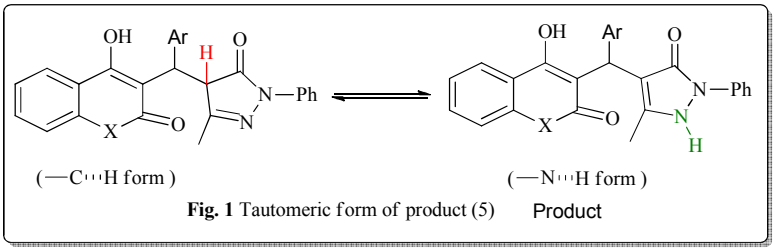
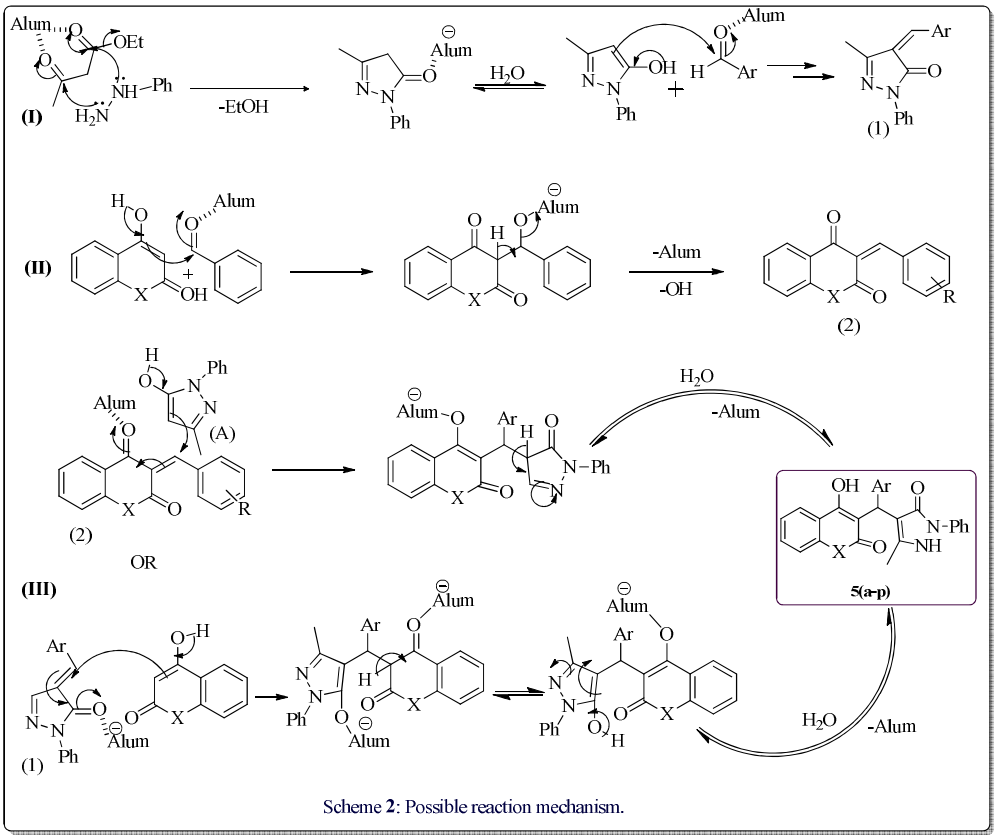


Figure 1.Tautomeric (-C---H & -N---H) form of benzyl pyrazolylcoumarin and quinolinone **5**



Scheme 2: Possible reaction mechanism.

Scheme 2: Possible reaction mechanism

3. Experimental

3.1 *Materials and Methods.*

All chemicals were purchased from Sigma Aldrich and Rankem and used without further purification. Melting pointswere obtained on Buchi Melting Point B540 and are uncorrected. ^{1}H NMR spectra were recorded in solvent $CDCl_3$, at 400 MHz using TMS as the internal standard on a Bruker AM-400 spectrometer. Analytical thin-layer chromatography ($CHCl_3$: MeOH) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light. All other solvents and reagents were used as obtained from commercial sources and used without further purification.

3.2 General Procedure for preparation of benzylpyrazolyl hydroxy quinolinone, hydroxy coumarin derivatives 5(a-p)

A mixture of phenyl hydrazine (0.10g, 1 mmol), ethyl acetoacetate (0.13g, 1mmol), aldehyde (1mmol), 4-hydroxy coumarin (0.16g, 1mmol) or 1-methyl 4-hydroxy quinolinone (0.17g, 1mmol) were added in alum (10 mol%) and 4-6mL of PEG, mixture were subjected to microwave irradiation at 400W. After completion of the reaction was monitored by TLC, reaction mass was added in water to precipitate a solid compound. The precipitated crude product was purified by recrystallization from hot ethanol. Melting range of **5a &5b** (observed: 230°C-233, reported 232-234°C. All the isolated compounds were further characterized by FT-IR, ^{1}H NMR and MS-Spectrometry, and compared with reported method [45-47].

3.3 Spectral data of compounds

(5a):4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2phenyl-1H-pyrazol-3(2H)- one:

White solid, m.p. 2320C, IR (KBr cm-1): 3155, 3060-3150, 3050, 2865, 1730-1775, 1697,1460-1560.

1HNMR (400 MHz, CDCl3): δ2.21 (s, 1H, -NH), 2.25 (s, 3H, -CH3); 6.02 (s, 1H, CH-Ar); 16.72 (s, 1H, -OH); 7.40-7.80 (m, 4H, CH-Ar); 7.20-7.35 (m, 5H, -CH-Ar); 6.90-7.68 (m, 5H, CH-Ar).

LRMS: m/z for (Coumarins) $C_{26}H_{19}NO_4$ [M+H] +Calcd 424.0

HRMS: m/z for (Coumarins) $C_{26}H_{20}NO_4$ [M+H] +Calcd 424.1

Anal.Calcd (Coumarins): for $C_{26}H_{20}NO_4$ [M+H] + C,73.57; H,4.75; N,6.60; O,15.08; Found: C, 73.64; H,4.68; N, 6.52; O,15.1

(5a):4-hydroxy-1-methyl-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1Hpyrazol-4yl) (phenyl)methyl)quinolin-2(1H)-one:
White solid, m.p. 2320C, IR (KBr cm-1): 3155, 3060-3150, 3050, 2865, 1697,1460-1560.
1HNMR (400 MHz, CDCl3): δ3.41 (s, 3H, -CH3), 2.21 (s, 1H, -NH), 2.25 (s, 3H, -CH3); 6.02 (s, 1H, CH-Ar); 16.72 (s, 1H, -OH);7.40-7.80 (m, 4H, CH-Ar); 7.20-7.35 (m, 5H, -CH-Ar); 6.90-7.68 (m, 5H, CH-Ar).
LRMS: m/z for (Quinolinone) $C_{27}H_{22}N_3O_3$ [M+H] +Calcd 437.0
HRMS: m/z for (Quinolinone) $C_{27}H_{23}N_3O_3$ [M+H] +Calcd 437.1
Anal.Calcd (Quinolinone): for $C_{27}H_{23}N_3O_3$ [M+H] + C, 74.12; H, 5.30; N, 9.60; O, 10.97; Found: C, 74.18; H, 5.26; N, 9.66; O, 11.3

(5b):4-((4-hydroxy-2-oxo-2H-chromen-3-yl) (4-nitrophenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one:
IR (KBr cm^{-1}): 3155, 3060-3150, 3050, 2865, 1730-1775, 1697, 1460-1560, 1490-1537 .
^{1}HNMR (400 MHz, $CDCl_3$):δ 2.21 (s, 1H, -NH), 2.25 (s, 3H, $-CH_3$); 6.03 (s, 1H, CH-Ar); 16.72 (s, 1H, -OH); 7.4-7.80 (m, 4H, CH-Ar);6.90-7.65 (m, 5H, -CH-Ar); 8.11 (d, 2H, CH-Ar); 7.50 (d, 2H, CH-Ar).
LRMS: m/z for (Coumarins) $C_{26}H_{18}N_3O_6$ [M+H] $^+$Calcd 469.0
HRMS: m/z for (Coumarins) $C_{26}H_{19}N_3O_6$ [M+H] $^+$Calcd 469.1
Anal.Calcd (Coumarins): for $C_{26}H_{19}N_3O_6$ [M+H] $^+$C, 66.52; H, 4.08; N, 8.95; O, 20.45; Found: C, 66.57; H,4.1;N, 8.99; O, 20.51
(5b):4-hydroxy-1-methyl-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(4-nitrophenyl)methyl)quinolin-2(1H)-one:
IR (KBr cm^{-1}): 3155, 3060-3150, 3050, 2865, 1697, 1460-1560, 1490-1537 .
^{1}HNMR (400 MHz, $CDCl_3$): δ 3.40 (s,3H, $-CH_3$) 2.21 (s, 1H, -NH), 2.25 (s, 3H, $-CH_3$); 6.03 (s, 1H, CH-Ar); 16.72 (s, 1H, -OH); 7.4-7.80 (m, 4H, CH-Ar); 6.90-7.65 (m, 5H, -CH-Ar); 8.11 (d, 2H, CH-Ar); 7.50 (d, 2H, CH-Ar).LRMS: m/z for (Quinolinone) $C_{27}H_{21}N_4O_5$ [M+H] $^+$Calcd482.0
HRMS: m/z for (Quinolinone) $C_{27}H_{22}N_4O_5$ [M+H] $^+$Calcd 482.1
Anal.Calcd (Quinolinone): for $C_{27}H_{22}N_4O_5$ [M+H] $^+$C, 67.21; H, 4.60; N, 11.61; O, 16.58; Found: C, 67.26; H,4.54; N, 11.73; O,16.63

4. Conclusion

In conclusion, we have developed an efficient and facile method to synthesis of benzyl pyrazolyl hydroxy coumarin and quinolinone derivatives by using Alum-PEG as an environmentally benign catalyst-solvent. The advantages of this protocol over other cleaner reaction profile, higher yields in short reaction time, simple reaction conditions, easy isolation of product are additional features of this methodology, beside better recyclability of PEG.

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6. Supplementary materials

Supplementary materials for this article are attached with manuscript and available to http://www.chem.mat.research.connect.com

7. References and notes

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