Ca(II)-catalyzed, one-pot four component synthesis of functionally embellished benzylpyrazolyl coumarins in water

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Graphical Abstract

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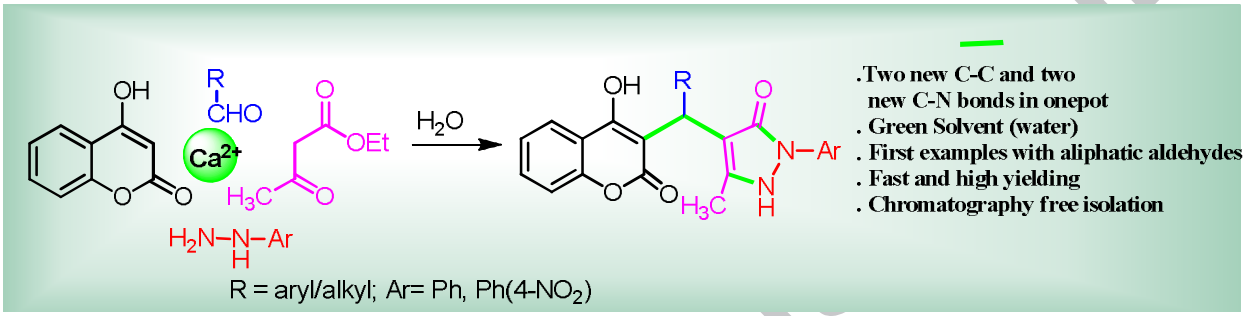

- Two new C-C and two new C-N bonds in onepot
- Green Solvent (water)
- First examples with aliphatic aldehydes
- Fast and high yielding
- Chromatography free isolation

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Ca(II)-catalyzed, one-pot four component synthesis of functionally embellished benzylpyrazolyl coumarins in water

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ABSTRACT

A facile one-pot, four-component synthesis of biologically important benzylpyrazolyl coumarins in water has been demonstrated using environmentally benign Ca(II) as the catalyst. Participation of aliphatic aldehydes has been described for the first time. Short reaction times, high yields and chromatography free isolation of the products, usage of eco-friendly catalyst and solvent are the key features of this method.

In the last two decades, enormous thrust and exploration towards the green chemistry practices has been taking place. Chemists, being more sensible to the society and human wellbeing, come up with various environmentally benign organic transformations, with minimization of chemical waste, atom economy, energy savings, easy work ups, alternative catalysts and procedures, chromatography free isolation of the products.[1-3] Multicomponent reactions are one of the major contributions to the green chemistry, in which several cascade one-pot transformations takes place in the same pot to yield the final product without isolating any intermediate.[4] Use of universal solvent (water) as an alternative to many of the organic solvents is a very good practice,[5] due to water being environmentally benign natural product, high abundance, being economical, high polarity and reactivity through hydrogen bonding interactions.

3-substituted coumarins, especially benzylcoumarins belongs to a broad class of biologically active heterocyclic compounds. They were also found in many of the natural products. For example as showed in the figure 1, warfarin, phenprocumene and coumatetralyl showed antibacterial, anti-HIV, antiviral, anticoagulant activities.[6] Similarly, pyrazolones are another important heterocyclic compounds (Figure 1, first row) with a broad spectrum of biological activities. To list a few phenazone, propphenazone and ampyrone (Figure 1, second row) are well known antipyretic and antianalgesic drugs. Pyrazolones are generally known for anti-fungal, antimycobacterial, antibacterial, anti-inflammatory, antitumor, antidepressant and anti-tuberculat activities.[7]

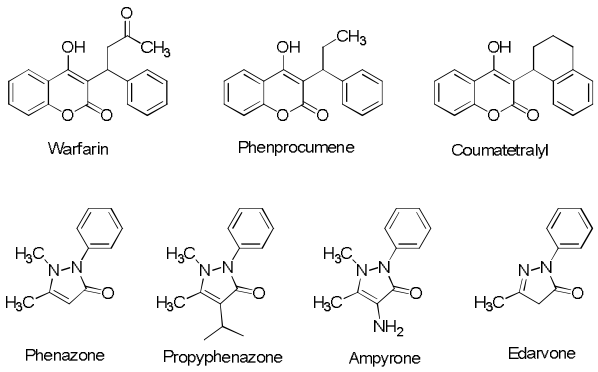

Figure 1. representative examples of biologically active 3-substituted coumarins (first row) and pyrazolones (second row)

In view of their biological activities and structural features, a new hybrid molecule (benzylpyrazolylcoumarins) has been designed by combining 3-benzylcoumarins and pyrazolones for the improved activity.[8-10] Till date there are only three reports available on the synthesis of these benzylpyrazolylcoumarins.[8-10] The first report describes the usage of glacial acetic acid in water under reflux conditions,[8] second one is ZrO_2 nanoparticles catalyzed synthesis[9] and the last one is ZnO nanoparticles as the catalyst.[10] Owing to the wide natural abundance, stability, inexpensive and non-toxic natures alkaline earth metal catalysts (especially calcium salts bearing a hard conjugate base such as triflate ion) have been demonstrated as an alternative to transition

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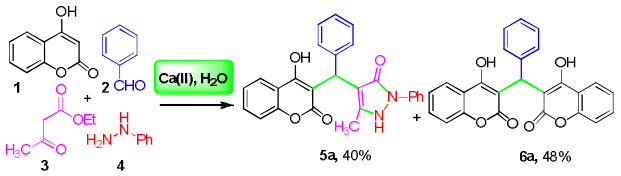
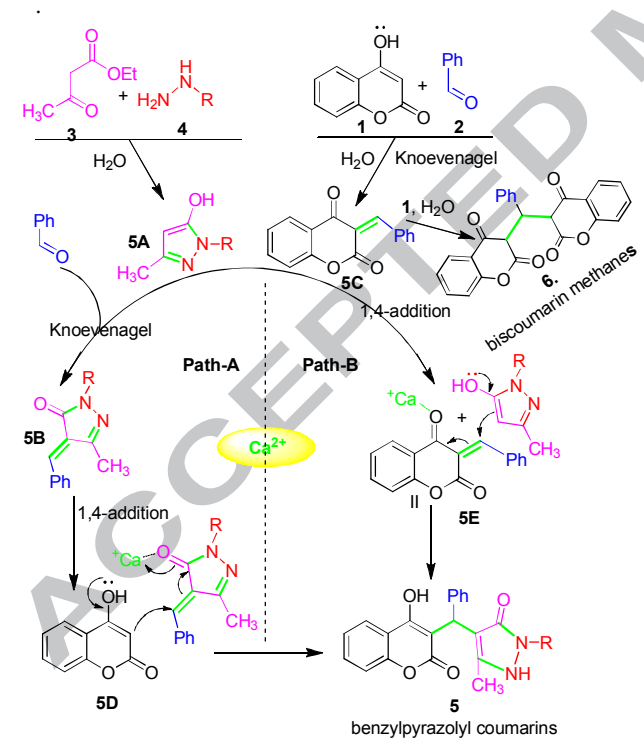
metal and lanthanide based catalysts.[11] In continuation our interest in exploring the environmentally benign Ca(II) as the green catalyst for the synthesis of several biologically important heterocyclic compounds,[12] here in we report a facile one-pot multicomponent reaction for the synthesis of various benzylpyrazolyl coumarins in water.



Scheme 1. Initial reaction for the synthesis of benzylpyrazolyl coumarins.[a]
[a].all the reactants weighed together in stoichiometric amounts and refluxed in water with 5 mol% of catalyst for 4 h

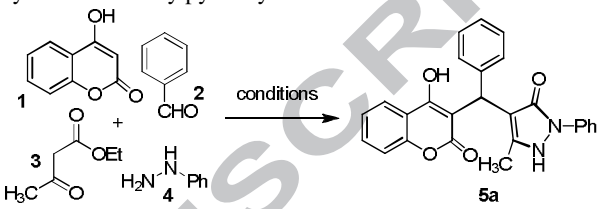
We commenced our synthesis with the stoichiometric amounts of all four reactants (4-hydroxycoumarin, ethylacetoacetate, phenylhydrazine and benzaldehyde) in presence of 5 mol% $Ca(OTf)_2$ in water under reflux at 100 °C. After completion of the reaction (4 h, monitored by TLC), we could isolate 40% of the expected benzylpyrazolyl coumarin **5a** along with 48% of benzyl biscoumarin **6a** (Scheme 1). In order to circumvent this undesired product (**6a**), we conducted several experiments and isolated the intermediates **5A**, **5B** and **5C** (Scheme 2), based on the isolated intermediates (also literature reports),[8,9] we propose that there could be two reaction pathways existing for the formation of 4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one **5** (benzylpyrazolyl coumarin).



Scheme 2. plausible mechanism for the synthesis of benzylpyrazolylcoumarins

As shown in the scheme 2, first ethylacetoacetate and phenylhydrazine will react to give the pyrazolone **5A**, which will undergo knoevenagel condensation with aldehydes to give the adduct **5B**. Owing to the presence of nitrogen atom next to the carbonyl carbon in the **5B**, nucleophile cannot add to it via a 1,4-conjugate manner. But when the Ca^{2+} is present in the reaction, it chelates with the carbonyl oxygen and enhance the electrophilicity of carbonyl carbon and thus facilitates the Michael addition by 4-hydroxycoumarin (**5E**) to form the final product **5**. Alternatively, this reaction may also proceed via path-B, where 4-hydroxycoumarin and benzaldehyde can react to give a Knoevenagel adduct **5C**. In the next step pyrazolone 5A and Knoevenagel adduct **5C** will undergo Ca-catalyzed Michael addition (as depicted in **5E**) to form the final product **5**. However during this procedure **5C** may also react with 4-hydroxycoumarin (1,4-addition) to yield biscoumarin methane (**6**)

Table 1. Optimization of reaction conditions for the cascade Knoevenagel condensation and Michael addition for the synthesis of benzylpyrazolyl coumarins.[12]



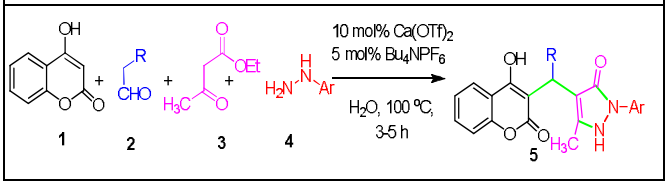
Entry	Ca(OTf)$_2$, mol%	Bu_4NPF_6, mol%	Solvent	Time (h)	Temp (°C)	Yield[a]
1	5	0	H_2O	4	100	65
2	5	5	H_2O	4	100	80
3	5	5	-	6	100	50
4	0	0	H_2O	5	100	trace[b]
5	0	0	-	8	100	trace[c]
6	10	0	H_2O	4	100	83
7[d]	**10**	**5**	**H_2O**	**3.5**	**100**	**92**
8	10	5	EtOH	4	100	90
9	10	5	H_2O+EtOH	3.5	100	92
10	10	5	H_2O	16	rt	78
11	10	5	H_2O	12 min	110,mw	90
12	10	5	CH_3CN	5	90	40
13	10	5	THF	5	80	45
14	10	5	Toluene	5	110	70
15	10	5	CH_2Cl_2	6	55	40

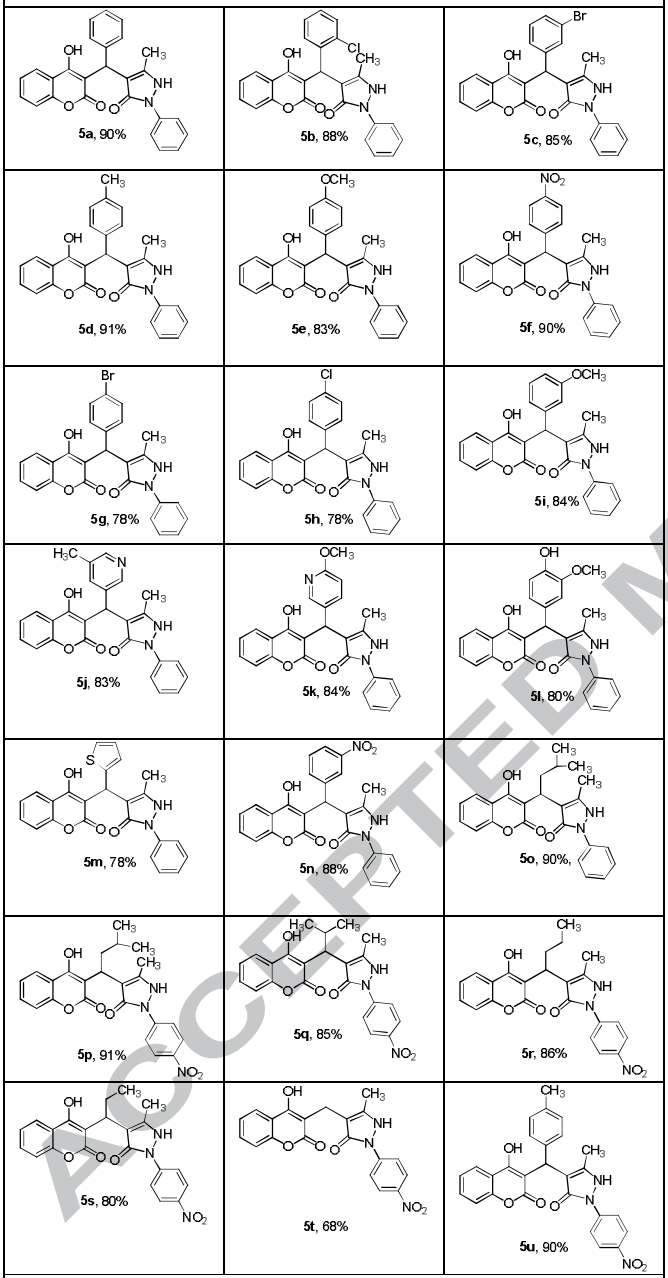
[a].Isolated Yields after filtration; [b].trace amount of product and >90% of biscoumarin compound was observed; [c]. trace amount of product and 20% of biscoumarin was observed; [d].optimum conditions

Scheme 2 evidences that the formation of biscoumarinmethane **6** could be avoided if the reaction proceeds via path-A, based upon this hypothesis we modified our experimental procedure.[12] stoichiometric amounts of phenylhydrazine, ethylacetoacetate and benzaldehyde were refluxed in water using 5 mol% of $Ca(OTf)_2$ for 1 h (formation of Knoevenagel product was observed by TLC), then 4-hydroxycoumarin was added and the reflux was continued for 2 more hours and we were glad to notice the formation of benzylpyrazolyl coumarin alone in 65% yield. Our next target was to increase the yield of the product for which we conducted several experiments using different conditions as shown in Table 1. Entry 4, 5 (Table 1) evidences the importance and necessity of the catalyst to accelerate the reaction. Entry 2, tells that the yield of the product increases when additive (Bu_4NPF_6) is added. It is also observed that the protic solvents enhance the product formation (Entries 7-11 versus 12-15). Over all, entry **7** shows the optimum condition for the green synthesis of benzylpyrazolyl

coumarin **5a** in 92% (use of 10 mol% of Ca(II), 5 mol% of additive, reflux in water for 3.5 h).

Table 2. Substrate scope in the Ca(II) catalysed one-pot 4-component synthesis of benzylpyrazolylcoumarin derivatives.[12]

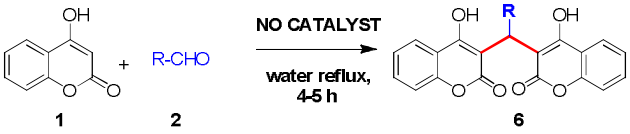




Isolated yields after filtration, all reactants are taken in stoichiometric amounts

After successful mechanistic studies and optimization of reaction conditions, we extended our methodology to utilize various aldehydes in the Ca(II) catalyzed four component synthesis of banzylpyrazolyl coumarins in water (Table 2). Halogen substituted aryl aldehydes like *o*-chloro benzaldehyde, *m*-bromo benzaldehyde, *p*-chloro and *p*-bromo benzaldehydes have been successfully participated in the multicomponent synthesis and produced corresponding benzylpyrazolyl coumarins **5b** (88%), **5c** (85%), **5g** (78%) and **5h** (78%) respectively. Similarly, benzaldehydes with electron donating groups like *p*-methyl, *p*-methoxy and *m*-methoxy groups also reacted under the similar conditions to yield corresponding benzylpyrazolyl coumarins **5d** (91%), **5e** (83%), **5i** (84%) in good yields. *p*-Nitrobenzaldehyde and *m*-nitrobenzaldehydes (with electron withdrawing groups) gave the benzylpyrazolyl coumarins **5f** (90%) and **5n** (88%). Encouraged by the participation of diversely substituted aryl aldehydes, we extended our methodology to check the participation of substituted pyridine aldehydes, thiophenaldehyde and found all these were equally participating to yield the products in good to excellent yields (entries **5j**, **5k**, **5m**, Table 2). To check the utility of aliphatic aldehydes (so far no example of aliphatic aldehyde participation is reported), we commenced with the reaction of 4-hydroxycoumarin, ethylacetoacetate, phenyl hydrazine with isovaleraldehyde and glad to isolate the product **5o** in 90% yield after 8 h. Encouraged by this result we extended this protocol to other aliphatic aldehydes, isobutyraldehyde, butyraldehyde, propanaldehyde and formaldehyde with 4-nitrophenyl hydrazine and isolated the corresponding pyrazolyl coumarins **5p**, **5q**, **5r**, **5s** and **5t** in good to excellent yields (Table 2). It is important to notice that in case of aromatic aldehydes reaction completes in 3-5 h, whereas in case of aliphatic aldehydes it is taking 7-10 h.

It is surprising to notice that entry 4 in Table 1, illustrates the catalyst free synthesis of biscoumarin methanes in water with high yields. When we looked into the literature reports for the synthesis of biscoumarin methanes, we noticed that due to the broad biological array of these compounds several methods were reported using various catalytic systems.[14] But no report was there in which water mediated catalyst free synthesis of biscoumarins under conventional heating. Although Gong et al., has reported the similar synthesis of biscoumarins under microwave irradiation,[14] but no example with aliphatic aldehyde has been reported by them. Hence we are also reporting herewith the catalyst free synthesis of biscoumarin methanes in water under conventional heating. Not only aromatic aldehydes (with variety of electronic and steric functionalities), aliphatic aldehydes like acetaldehyde, formaldehyde and isobutyraldehydes (**6m**, **6n**, **6o**, Scheme 3) have been taking part in the reaction to produce high yielding biscoumarin methanes as shown in Scheme 3



Scheme 3 Catalyst-free synthesis of biscoumarin metanes in water under conventional heating

List of biscoumarins prepared (Scheme 3): **6a.** R = Ph, 95%; **6b.** R = Ph (4-NO_2), 93%; **6c**. R = Ph (4-Br), 93%; **6d**. R = Ph (4-Cl), 94%; **6e**. R = Ph (4-OMe), 82%; **6f**. R = Ph (4-OH), 88%; **6g**. R = Ph (3,4,5-trimethoxy), 79%; **6h**. R = Ph (3-OH, 4-OMe), 80%; **6i**. R = Ph (2-OH), 92%; **6j**. R = Ph (3-OMe), 91%; **6k**. R = Ph (2-Cl), 88%; **6l**. R = Ph (3-Br), 81%; **6m**. R = CH_3, 65%; **6n**. R = CH_2, 68%, **6o**. R=isobutyl, 86%.

All compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, Mass, IR and melting point data.[12]

In summary, a facile one-pot multicomponent approach for the synthesis of array of biologically important benzylpyrazolylcoumarins has been described using environmentally benign catalyst (Ca^{2+}) and solvent (water). Participation of aliphatic aldehydes has been described for the first time. This reaction endures a variety of aromatic aldehydes bearing electron withdrawing and donating groups, aliphatic aldehydes and hydrazines as the reacting partners. Owing to its simple reaction, work-up and isolation procedures, short reaction times and high yields we believe that this methodology will be amenable over the existing methods.

Acknowledgments

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13. *General Experimental Procedure:* a mixture of aryl aldehyde (1.0 equiv), phenyl hydrazine (1.0 equiv.) and ethyl acetoacetate (1.3 equiv.), $Ca(OTf)_2$ (10 mol%) and additive Bu_4NPF_6 (5 mol%) were weighed into a round bottom flask and refluxed in water at 100 ^oC for 1.5-2 h (monitored by TLC), then 4-hydroxycoumarin (1.0 equiv.) was added to the above reaction and reflux was continued for 1-1.5 h (monitored by TLC). After completion of the reaction, cold water was added to the reaction mixture and filtered through a Buchner flask washed 2-3 times with cold water and the obtained solid was dried to get the final product. If necessary the obtained solid was recrystallized with hot ethanol. ^1H NMR copies of selected compounds are given in the supporting information.
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