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Graphical Abstract

Synthesis of 3-substituted carboxylate/carboxamide flavone derivatives from 4-hydroxycoumarin, β-nitrostyrene and alcohol/ amine using multicomponent reaction

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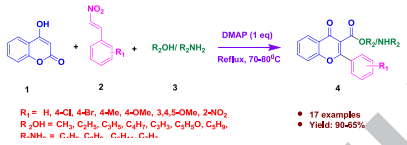

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Synthesis of 3-substituted carboxylate/carboxamide flavone derivatives from 4-hydroxycoumarin, β-nitrostyrene and alcohol/ amine using multicomponent reaction

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ABSTRACT

A wide range of 3-substituted carboxylate/carboxamide flavone derivatives were synthesized from 4-hydroxycoumarin, β-nitrostyrene and alcohol/amine using multicomponent reaction in presence of N,N-dimethyl-4-aminopyridine (DMAP). Good yield, short reaction time, atom economy, cost effective and use of non-toxic organo-catalyst are some of the remarkable advantages of the present protocol.

The most prevailing strategy for the synthesis of highly functionalized heterocyclic scaffolds is Multicomponent reaction (MCR).[1] It integrates three or more building blocks in an economic and ecofriendly manner to get the desired product in a single step. As a matter of fact, it has gained a significant position in organic synthesis.[2] The design of novel MCRs, based upon the synthesis of oxygen comprising heterocycles,[3] especially flavone[4] moieties are suitable synthetic targets for modern researchers. Flavones, a class of flavonoids also known as 2-aryl-4H-chromene-4-one, are widely distributed in nature, mainly found in cereals and herbs, and have an imperative aspect in pharmaceutical industries.[5] Figure 1 shows some of the naturally occurring pharmacologically active flavone scaffold.

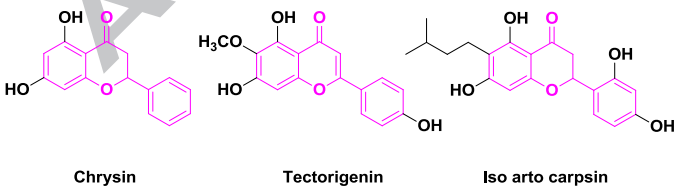
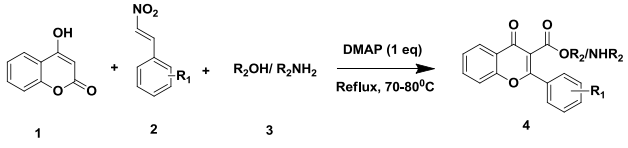


Figure 1: Some naturally occurring compounds containing flavone skeleton

A detailed analysis of the reported literature discloses that many strategies were developed for the synthesis of flavone moieties, but very few methods have known for the synthesis of 3-substituted carboxylate/carboxamide flavone derivatives. Classical methods were acylation of ester in presence of different catalytic conditions,[6] olefination of aldehydes with hydroxyphenylpropiolates,[7] acylation of anionic flavone,[8] solvent mediated reactions of 4-hydroxycoumarin with β-nitrostyrene, [9] cyclization of carbonates facilitated by the catalytic amount of PBu_3.[10] Though all the above mentioned protocols for the synthesis of substituted flavones are quite useful, but there are limitations like longer reaction time,[9] low yields,[9] uses of expensive catalyst,[7,10] and loading of excess catalyst.[9] The synthetic protocols were found unproductive for the synthesis of 3-carboxamide-flavone derivatives.[9,10] Consequently to develop an efficient synthetic route to overcome the shortcomings of the reported protocols are a valid exercise for the researcher.

N,N-dimethyl-4-aminopyridine (DMAP) is a Lewis base, extensively employed as a nucleophilic-catalyst for various organic reactions such as trans esterification,[11] acylation,[12] Michael's addition[13] and Baylise-Hillman reactions.[14] The catalyst has also been used for different multicomponent reactions for the synthesis of heterocycles by us[15] as well as by other research groups.[16]



Scheme 1: One-pot three-component synthesis of 3-substituted flavone derivatives

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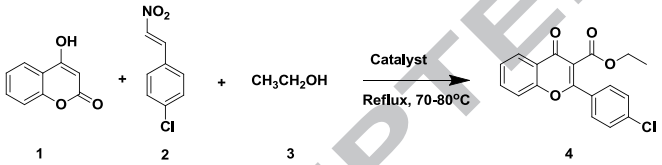
In continuation of our constant efforts in exploring DMAP for the construction of biologically active heterocycles, we hereby report a highly efficient one-pot three component reaction for the synthesis of 3-substituted-flavone derivatives from 4-hydroxycoumarin, β-nitro styrene and alcohol/ amine as shown in Scheme 1.

To find the optimal conditions for the synthesis of 3-substituted flavone derivatives, various reactions were tried out with 4-hydroxycoumarin (1 mmol), 4-chloro phenyl nitrostyrene (1 mmol) and ethanol (4 mmol). Initially, reaction has been carried out with 0.2 mmol of DMAP (Table 1; entry 1) furnished only 17% of the required product after 24 h of refluxing. The product was purified by chromatographic separation and found to be 3-substituted flavone **4aa**, as confirmed by IR, ^{1}H NMR and mass spectra. In ^{1}H NMR spectra of product **4aa**, quartet at δ 4.25 for 2H and triplet at δ 1.19 for 3H clearly indicate the presence of an ethoxy group into the molecule. Repeating the above experiment with 0.4 mmol, 0.6 mmol and 1 mmol of DMAP, the yield of the product was substantially increased from 30% to 80% accompanied by decrease of duration of the reaction from 24 h to 5 h. (Table 1; entries 2-4). Performing similar experiment with 1.5 mmol of DMAP, resulted in insignificant change in yield and time (Table 1; entry 5). The identical reaction was found unproductive at room temperature with no product formation (Table 1; entry 6). The same set of reactions was carried out with other basic catalysts like piperidine, DBU, DABCO and NaOH and was proved ineffective (Table 1; entries 7-10). No product was formed in the absence of catalyst (Table 1; entry 11). From these experimental outcomes, it was clear that catalyst played an important role in formation of the product **4aa**, and 1 mmol of DMAP was adequate enough to carry out the reaction in terms of efficacy of time and yield.

Table 1: Optimized condition for the synthesis of 3-substituted flavone derivatives

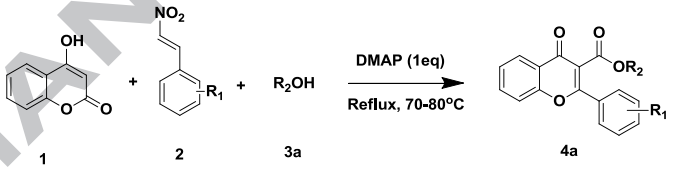


Entry	Catalyst	Mol%	Temp	Time (h)	Yield[b] %
1	DMAP	0.2	70°C	24	17
2	DMAP	0.4	70°C	24	30
3	DMAP	0.6	70°C	18	50
4	DMAP	1	70°C	5	80
5	DMAP	1.5	70°C	4.5	81
6	DMAP	1	RT	24	00
7	Piperidine	1	70°C	24	00
8	DBU	1	70°C	24	00
9	DABCO	1	70°C	24	00
10	NaOH	1	70°C	24	00
11	None	00	70°C	24	00

[a]The reactions were carried out with 4-hydroxycoumarin (1 mmol), 4-chloro phenyl nitrostyrene (1 mmol), and ethanol (4 mmol) in the presence of different catalyst at reflux. [b]Isolated yields.

To establish the optimal reaction conditions, we initially investigated a reaction with a mixture of 4-hydroxycoumarin, (E)-(2-nitrovinyl) benzene in ethanol under similar conditions, the desired product **4ab** was obtained in 85% yield (Table 2, entry 2). The scope and efficacy of the synthetic routes were explored by reacting 4-hydroxycoumarin with β-nitrostyrene having key functional groups such as halides, nitro, methyl, methoxy, etc. under optimized reaction conditions and the desired products were obtained in good yields. It was noted that, β-nitrostyrene having electron-donating group reacted faster and gave the better yield than β-nitrostyrene with electron-withdrawing groups (Table 2, entries 1, 3-7). Next, the protocol was examined by treating 4- hydroxycoumarin, 4- methyl nitrostyrene with various alcohols. Using alcohol with bigger aliphatic groups, the yields of the desired compounds were found to decrease. Reaction in methanol proceeds smoother and faster, and was able to produce the best yield (Table 2, entry 13) then any other alcohols in the series (Table 2, entries 8-13). The reaction with 4-penten-1-ol was slowest and produces the least yield (Table 2, entry 12). The protocol was found ineffective in cases of sterically hindered alcohols like t-butanol, 3-phenyl-1-propanol (Table 2, entries 14-15) as well as phenol (Table 2, entry 16).

Table 2: Substrate scope and yields of 3-carboxylate flavone derivatives (4a)[a]

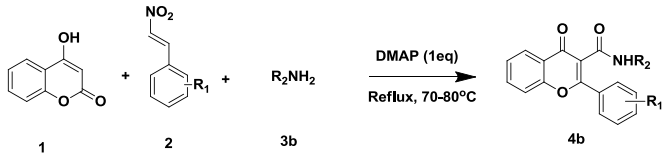


Entry	R^1	R^2OH	Time (h)	Yield[b] (%)	Product
1	4-Cl	Et OH	5	80	**4aa**
2	H	Et OH	4.5	85	**4ab**
3	4-Br	Et OH	5	79	**4ac**
4	4-Me	Et OH	2	86	**4ad**
5	4-OMe	Et OH	2.5	88	**4ae**
6	3-OMe-4-OMe-5-OMe	Et OH	3	87	**4af**
7	2- NO_2	Et-OH	5.5	79	**4ag**
8	4-Me	allyl-OH	6	77	**4ah**
9	4-Me	furfuryl-OH	8	72	**4ai**
10	4-Me	crotyl-OH	7	76	**4aj**
11	4-Me	Propargyl-OH	4	78	**4ak**
12	4-Me	4-pentene-OH	9	70	**4al**
13	4-Me	Me-OH	2	90	**4am**
14	4-Me	t-butanol	12	N.R	-
15	4-Me	3-phenyl-1-propanol	12	N.R	-
16	4-Me	Phenol	24	N.R	-

[a]The reactions were carried out with 4-hydroxycoumarin (1 mmol) β-nitrostyrene (1 mmol), and alcohol (4 mmol) in the presence of different catalyst at reflux. [b]Isolated yields.

On the lookout for further scope of the reaction, we investigated the nucleophilicity of the reaction by amine as shown in table 3. Various amine moieties like aliphatic, benzylic, cyclic amines were considered by conducting the reaction with 4-hydroxycoumarin and 4-methyl nitrostyrene, the desired products **4ba-4bd** were obtained in moderate yield. Unfortunately, reactions failed to give the desired product in case of aromatic amine like aniline and secondary amine, for example, diisopropyl amine (Table 3, entry 5 and 6) respectively.

Table 3: Substrate scope and yields of 3-carbamide flavone derivatives (4b)[a]



Entry	R^1	R^2NH_2	Time (h)	Yield[b] (%)	Product
1	4-Me	Butyl amine	12	65	**4ba**
2	4-Me	(s)-Phenyl ethyl amine	8	69	**4bb**
3	4-Me	Cyclohexyl amine	15	68	**4bc**
4	4-Me	Benzyl amine	6	66	**4bd**
5	4-Me	Aniline	24	N.R	-
6	4-Me	Diisopropyl amine	24	N.R	-

[a]The reactions were carried out with 4-hydroxycoumarin (1 mmol) β- nitro styrene (1 mmol), and ammine (4 mmol) in the presence of different catalyst at reflux. [b]Isolated yields

All the synthesized compounds were fully characterized by IR, NMR and Mass Spectra. In IR spectrum, compound **4aa-4am** and **4ba-4bd** showed two characteristic strong absorptions at the range of 1718-1732 cm^{-1} and 1590-1645 cm^{-1} due to the carbonyl group present in the molecule. The mass spectra of all the compounds exhibited molecular ion peaks at the appropriate m/z values. For further confirmation, the structure of the compound **4ad** was determined by single-crystal X-ray crystallography (Figure 2).

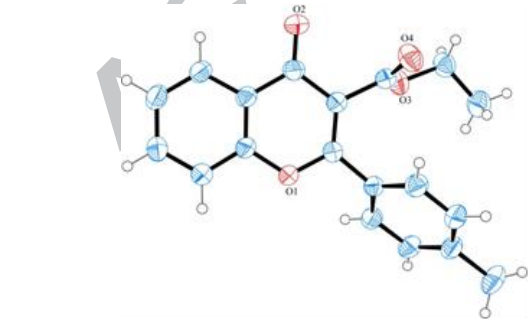
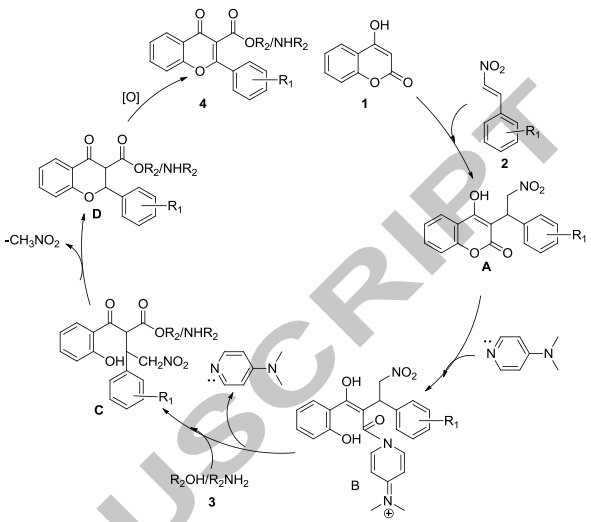


Figure 2. X-ray crystal structure of 3-carboxylate flavone derivative **4ad**

Although the mechanism of the reaction was not established experimentally, the product **4** can be believed formed by using the following mechanistic pathway: First 4-hydroxycoumarin undergoes Michael-addition reaction with nitro-olefin in presence of DMAP, resulting in an adduct A. DMAP being a strong nucleophile, attacks at the carbonyl center of A leading to the formation of the reactive amide center in B. The intermediate B cannot form any side products but immediately reacts with an alcohol or amine forming an intermediate C. Eventually intermediate C, undergoes an intramolecular cyclization by releasing nitro methane to form D, which undergoes an oxidation resulting in the final product 4 (Scheme 2).



Scheme 2. Plausible mechanism for the formation of 3-substituted flavone derivatives **4**

In summary, we have demonstrated a new synthetic protocol for the synthesis of 3-substituted flavone derivatives by using one pot three component reaction of 4-hydroxycoumarin, β-nitro styrene and alcohol/amine by utilizing an organo-catalyst DMAP. The present protocol is enhanced in terms of yield, reaction time and conditions as compared to the previous methods. Moreover, the protocol was successful for the synthesis of 3-carboxamide–flavone derivatives, which was not reported earlier.

Acknowledgments

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Supplementary Material

Supplementary data (X-ray crystallographic data (CIF files) of 4ad, spectral data of all compounds and copies of ^1H and 13C NMR spectra of products) associated with this article can be found, in the online version, at

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17. **General procedure for the formation of 3-substituted flavone derivatives (4aa-4am and 4ba-4bd):** 4-hydroxycumarin (1 mmol), different derivatives of β-nitrostyrene (1 mmol), various alcohols or amines (4 mmol) and DMAP (1 mmol) were taken in a round bottom flask. The reaction mixtures were refluxed at 70-80°C. The completion of the reaction (directed by the disappearing of starting material and formation of new spot) was observed by TLC of Ethyl acetate and hexane (15: 85%). After the formation of the product, the crude reaction mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with H_2O (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was chromatographed on silica gel (60–120 mesh) to afford the pure products in 65-90% yields (Table 2 and 3).

Ethyl 2-(4-chlorophenyl)-4-oxo-4H-chromene-3-carboxylate *(4aa)*:

Orange semi solid (0.262g, 80%),
IR (KBr): 1731, 1645, 1575, 1466, 1381, 1090, 1015, 761cm^{-1}.
^{1}H NMR (400 MHz, CDCl3): 8.22 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 6.8 Hz, 3H), 7.50-7.43 (m, 4H), 4.25 (q, *J* = 6.0 Hz, 2H), 1.19 (t, *J* = 6.8 Hz, 3H) ppm.
^{13}C NMR (100 MHz, CDCl3): 174.7, 164.8, 161.4, 155.5, 137.8, 134.4, 130.2, 129.3, 129.0, 125.8, 125.7, 122.8, 118.3, 118.0, 61.9, 13.8 ppm.
MS (ESI): [M+ H+], Calcd. For: $C_{18}H_{14}ClO_4$ (329.0575); Found: 329.0579.

Ethyl 4-oxo-2-phenyl-4H-chromene-3-carboxylate *(4ab)*:

Yellow solid (0.249 g, 85%), mp 80-81^{0}C.
IR (KBr): 1729, 1638, 1567, 1436, 1396, 1089, 760 cm^1.
^{1}H NMR (400 MHz, CDCl3): 8.23 (d, *J*= 7.2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.56-7.45 (m, 4H), 7.42 (t, *J*= 6.8 Hz, 1H), 4.25 (q, *J* = 6.8 Hz, 2H), 1.14(t, *J* = 7.2 Hz, 3H) ppm.
^{13}C NMR (100 MHz, CDCl3): 175.1, 165.1, 163.1, 155.8, 134.4, 131.9, 131.7, 128.8, 128.1, 126.1, 125.7, 123.2, 118.1, 61.9, 13.9 ppm.
MS (ESI): [M+ H+], Calcd. For: $C_{18}H_{15}O_4$ (295.0965); Found: 295.0970

.

- A wide range of 3-substituted carboxylate/carboxamide flavone derivatives were synthesized from 4-hydroxycoumarin, β-nitrostyrene and alcohol/amine using multicomponent reaction in presence of N,N-dimethyl-4-aminopyridine (DMAP).
- Good yield, short reaction time, atom economy, cost effective and use of non-toxic organo-catalyst are some of the remarkable advantages of the present protocol.