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Access to chromone-3-carboxylic acid via silver mediated coupling of 4-hydroxy coumarin and enol ester

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ABSTRACT

A silver-mediated aerobic approach to access 2-methyl-chromone-3-carboxylic acid from the reaction of 4-hydroxy coumarin and enol ester in the presence of base has been presented. Mechanistic investigation suggests that the base induced Michael-type addition reaction of 4-hydroxy coumarin to the enol ester resulting the sequential ring opening and closing with the liberation of acetone are the key-steps for the overall transformation. Theoretical calculation of energy of the intermediates by DFT supports the proposed reaction mechanism.

Introduction

Chromones (1,4-benzopyrones) are abundant in numerous natural products and medicinal compounds that exhibit a wide spectrum of biological activities including anti-inflammatory, antioxidant, antibacterial, and antitumor activities [1]. Because of substantial solubility and negligible toxicity to mammals, chromone motif is considered as a potential building block for the design of pharmacologically important compounds [2]. Among the members of the chromone family, *4H*-chromen-4-ones with a carboxylate group at C-3 position (i.e., chromone esters) are very interesting scaffolds, since they can act as both a Michael acceptor and a 1,3-diketone [3–5]. In fact, several strategies have been revealed for their synthesis. The conventional methods include the base-mediated coupling of β-ketoester or its surrogates with *o*-fluorobenzoyl chloride or salicycloyl chloride [6]. To minimize the number of steps with improved yield, transition-metal catalyzed pathways have been employed for chromone ester synthesis. Notably, coupling of salicylaldehydes with diazo-compounds through aldehyde C — H functionalization in the presence of various transition metal catalysts (Scheme 1a) [7–9] have been emerged as a straight forward and versatile pathway to access such chromone esters. For example, recently, Pawar and co-workers used Cp*Ir(III)-catalyzed C — H / O — H—bond functionalization of salicylaldehydes with α-diazocarbonyl compounds for the synthesis of chromones in methanol at room temperature [7]. Maji et al. also employed similar Ir-catalytic system for the synthesis of chromones with a ester substituent at C-3 position from salicylaldehydes and diazocarbonyl compounds in water medium [8]. Yao et al. used same reactants as well for the efficient transformation to chromone esters in the presence of a Rh-catalyst through C — H activation/annulation pathway [9]. Table 1.

One of our long-term objectives is directed at exploring the utility of enol ester in transition-metal catalyzed C—C and C—O bond formation reactions.[10,11] In a continuation of our research activity with enol esters, here we wish to report an unprecedented silver-mediated synthesis of 4-oxo-2-aryl-4*H*-chromene-3-carboxylic acid from 4-hydroxycoumarins and (*E*)-4-oxopent-2-en-2-yl benzoate (Scheme 1b).

Previously, we have observed an unprecedented transformation of enol ester of *o*-iodobenzoic acid to α-naphthol derivatives in the presence of copper catalyst [10]. The intra-molecular annulation of enol ester of *o*-iodobenzoic acid to isocoumarin derivatives in the presence of silver salt was also reported by us [11]. Reaction of *o*-halobenzoic acid with enol ester of benzoic acid also gave the isocoumarin derivatives in competent yield [11]. It has been proposed that in the presence of base, enol ester was cleaved into enolates; which subsequently react with the another equivalent of enol ester to afford the naphthol derivatives. In line with the mechanistic proposal, it occurred to us that enol esters of salicyclic acid

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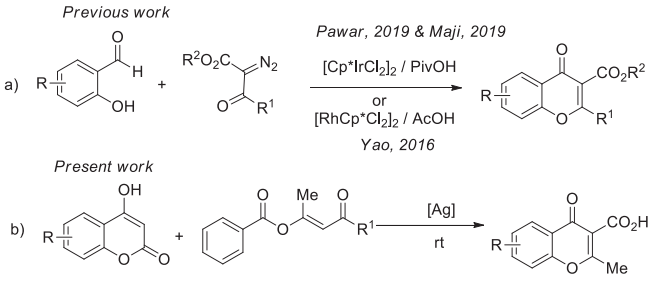
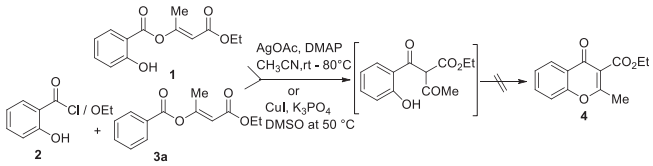


Scheme 1. Synthesis of chromone esters.

(**1**) may undergo intramolecular reaction to afford chromone esters. Thus, we began our investigation with the intramolecular transformation of enol esters of salicyclic acid (**1**) to chromone ester (**4**) under both Ag-catalysis [AgOAc (1 equiv), DMAP (2 equiv) in CH_3CN, rt – 80 °C] [11] and Cu-catalysis [CuI (10 mol %), K_3PO_4 (2 equiv) in DMSO at 50 °C] [10] as developed by us earlier (Scheme 2). Unfortunately, the desired chromone ester was not formed; rather, cleavage of enol ester to salicyclic acid was detected. Further attempts for an intermolecular reaction of ethyl salicylate or salicycloyl chloride (**2**) with enol ester of benzoic acid (**3a**) under similar reaction conditions were also failed to afford the desired chromone ester **4**.

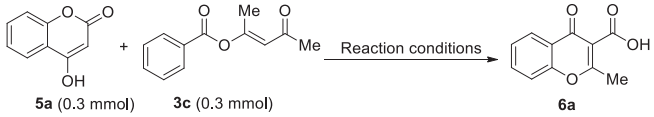
During our literature survey, we came across the report of Yao on alcohol mediated synthesis of flavon-3-carboxylate from the reaction of 4-hydroxy coumarins and β-nitroalkenes through a sequential Michael addition and alkoxide mediated rearrangement [12]. Because of the presence of an additional carbonyl group in the enol esters (e.g., **3**); we thought that our enol esters might serve as a potential Michael acceptor during reaction with 4-hydroxy coumarin in the presence of a base. With this in our mind, when 4-hydroxy coumarin (**5a**) was treated with the enol ester



Scheme 2. Attempts to chromone ester.

3a [(*E*)-4-ethoxy-4-oxobut-2-en-2-yl benzoate] in the presence of triethyl amine in ethanol, unfortunately, the desired chromone ester **4** was not formed; while **3a** was hydrolyzed to benzoic acid. Interestingly, the addition of 1 equiv. of AgOAc to the reaction mixture in acetonitrile gave an unmatched compound that was revealed to be 2-methyl-4-oxo-4*H*-chromene-3-carboxylic acid[6c] (**6a**) in 10 % yield. Structure of **6a** was evident from ^1H and ^{13}C NMR spectral data. Reaction of (*E*)-4-butoxy-4-oxobut-2-en-2-yl benzoate (**3b**) with **5a** also affords **6a** in 14 % yield. Furthermore, when **5a** was treated with (*E*)-4-oxopent-2-en-2-yl benzoate (**3c**) under similar silver-catalyzed reaction conditions, surprisingly the same chromone 3-carboxylic acid (**6a**) was formed in 20 % yield. For further illustration, single crystal X-ray diffraction study for the product generated from the reaction of 4-hydroxy-6-methyl-2H-chromen-2-one (**5b**) and **3c** was carried out, and the structure was confirmed to be 2,6-dimethyl-4-oxo-4*H*-chromene-3-carboxylic acid (**6b**) (Fig. 1) [13]. To recognize the optimum yield, we have screened the different parameters of the reaction process such as solvent, catalyst and base at room temperature by utilizing **5a** and **3c** as the model substrates. It has been observed that 2-methyl-4-oxo-4*H*-chromene-3-carboxylic acid (**6a**) was isolated in 90% yield when 4-hydoxy coumarin was treated with **3c** in the presence of AgOAc (1 equiv), DMAP (1.5 equiv) in acetonitrile for 5 h at room temperature. Other solvents such as EtOH, toluene, DMF, DMSO and THF did not afford appreciable yield. Further,

Table 1
Optimization of reaction conditions.[a]



Entry	catalyst	base	solvent	isolated yield of 6a(%)
1.		–	Et_3N	EtOH
2.	AgOAc	Et_3N	EtOH	0
3.	AgOAc	Et_3N	CH_3CN	20
4.	**AgOAc**	**DMAP**	**CH_3CN**	**90**
5.	AgOAc	DMAP	DMF	25
6.	AgOAc	DMAP	DMSO	0
7.	AgOAc	DMAP	THF	0
8.	AgOAc	DMAP	DCE	0
9.	AgOAc	DMAP	toluene	35
10.	AgOAc	K_3PO_4	CH_3CN	10
11.	AgOAc	K_2CO_3	CH_3CN	20
12.	AgOAc	NaOAc	CH_3CN	0
13.	AgOAc	Py	CH_3CN	15
14.	AgOAc	DBU	CH_3CN	10
15.	CuI	K_3PO_4	DMSO	0
16.	$Pd(OAc)_2$	DMAP	CH_3CN	0
17.	CuOAc	DMAP	CH_3CN	0
18.	$Ni(OAc)_2$	DMAP	CH_3CN	0
19.	$FeCl_3$	DMAP	CH_3CN	0
20.	AgOAc	DMAP	CH_3CN	70[b]
21.	Ag_2O	DMAP	CH_3CN	46
22.	$AgNO_3$	DMAP	CH_3CN	25
23.	Ag_2CO_3	DMAP	CH_3CN	35

[a] Reaction conditions: A mixture of **5a** (0.3 mmol), enol ester, **3c** (1 equiv), catalyst (1 equiv) and base (1.5 equiv) was stirred at rt for 7 h.
[b] 30 mol% of AgOAc was taken.

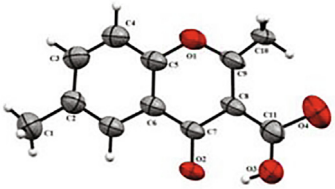


Fig. 1. ORTEP diagram for **6b.**

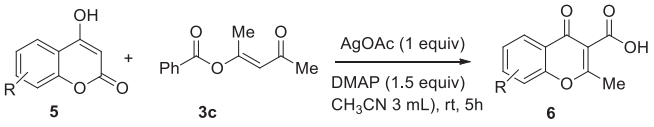
among the tested bases (i.e., K_2CO_3, K_3PO_4, NaOAc, Pyridine, Et_3N, DMAP, DBU) DMAP enabled the best yield of **6a**. Catalysts such as CuI, CuOAc, $Pd(OAc)_2$, $Ni(OAc)_2$, $FeCl_3$ did not produce chromone derivative, while silver salts [Ag_2O, Ag_2CO_3, $AgNO_3$] somehow afford the **6a** in variable yields. Besides, we noticed that the addition of 30 mol % of AgOAc gave 70% conversion of **5a** over a period of 48 h with complete decomposition of enol ester. Additionally, heating of the reaction mixture at 50–70 °C with 30 mol % of AgOAc was also not fruitful, as on heating enol ester was hydrolyzed more frequently.

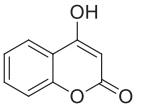
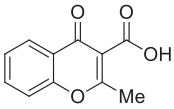
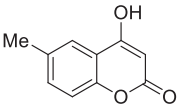
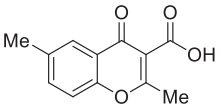
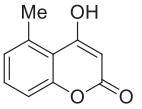
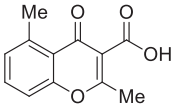
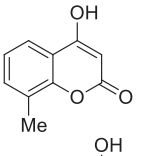
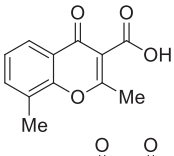
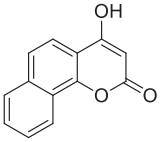
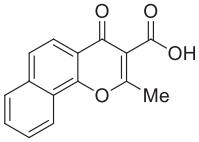
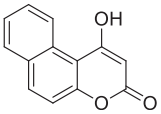
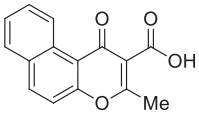
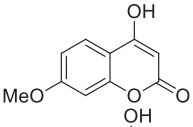
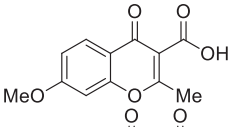
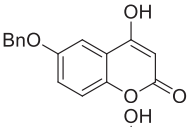
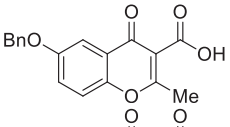
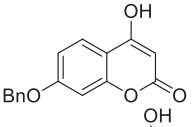
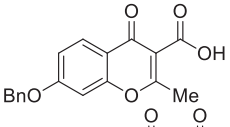
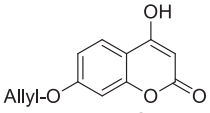
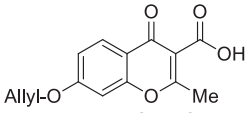
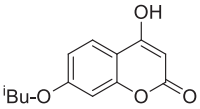
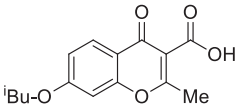
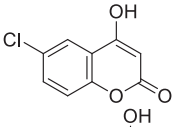
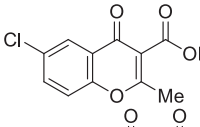
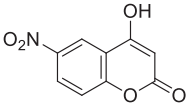
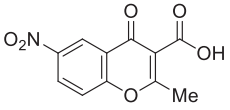
Having the optimized reaction conditions, we examined the substrate scope (Table 2). To our pleasure, a series of coumarins underwent the silver-mediated transformation to 2-methyl-4-oxo-4*H*-chromene-3-carboxylic acids (**6**) in moderate to good yield. In general, 4-hydroxy coumarins with donating substituents at the aromatic ring gave the chromone-carboxylic acid with appreciable yield. On the other hand, as a limitation, 4-hydroxy coumarins with an electron-withdrawing group such as – Cl and $–NO_2$, did not provide the desired product (**6l** and **6m**) may be due to ring deactivation at the C3 position. In such case, 4-hydroxy coumarin derivatives (**5l** and **5m**) were recovered back with the concordant hydrolysis of the enol ester to benzoic acid.

To enlighten the reaction pathway, some control experiments were performed (Scheme 3). Notably, when 4-hydroxy-3-acetyl coumarin (**A**) was treated under the optimized reaction conditions, the expected chromone **6a** was not formed (Scheme 3a); which indicates that initial attack of the base, i.e., DMAP did not occur and **A** cannot be a suitable intermediate to afford the chromone derivative **6a**. Next, when **5a** was treated with acetyl acetone under the optimized reaction conditions, nucleophilic attack to the carbonyl group of acetyl acetone did not happen to afford **D** via the intermediate **C** (Scheme 3b). Further, it is also apparent from the reaction of **5a** with more reactive acetyl chloride that under our reaction conditions, the base catalyzed C-CO bond formation did not occur to afford **A** (Scheme 3c). As reaction of **5a** with **3c** enables the same product **6a**, that we are getting from the reaction of **5a** and **3a** or **3b**; there must be the loss of an acetone molecule under the optimized reaction conditions.

In line with the above observation, we proposed the following reaction pathway for the overall transformation of 4-hydroxy coumarin (**5a**) to chromone-3-carboxylic acid **6a** (Scheme 4). The plausible mechanism involves the early silver-mediated Michael-addition of the C-3 carbon of **5a** to the enol ester **3c** to form the intermediate **I**, which subsequently releases the benzoate to afford **II**. Next, DMAP mediated coumarin ring opening affords α, β-unsaturated ketone **IV**. Subsequent intramolecular oxa-Michael addition of **IV** causes ring closer to form **V**. Later, removal of the acetone and hydrolysis of the amide bond enable the desired chromone acid selectively. In support of the above pathway, density functional theory (DFT) [14] was utilized to calculate the energy of the intermediates (Fig. 2). For instance, the Michael adduct (**I**) forms from the reaction of **5a** and **2b** is unstable with 89.5 $KJmol^{-1}$ energy. With the exclusion of benzoic acid, the intermediate II forms, and is indeed 13.48 $KJmol^{-1}$ more stable than **I**. Nucleophilic attack of DMAP at the carbonyl carbon of **II** is an endothermic process

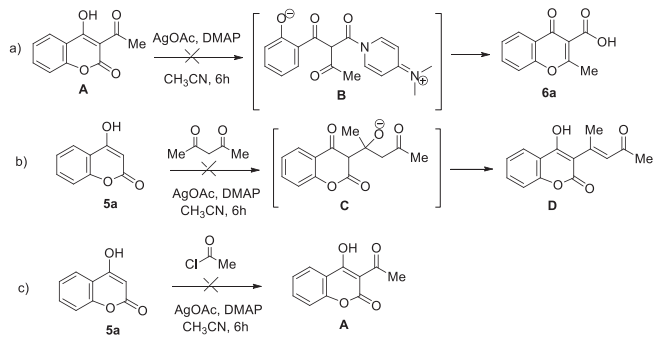
Table 2
Synthesis of chromone-3-carboxylic acid (**6**).[a]



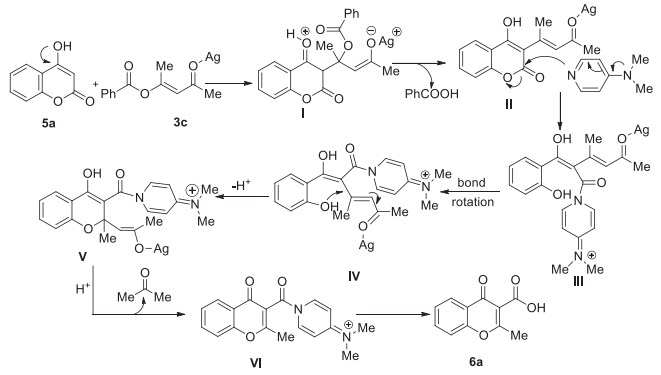
Entry	Substrate (**5**)	Product (**6**)	% yield
1.			90
2.			90
3.			48
4.			79
5.			95
6.			92
7.			50
8.			69
9.			59
10.			52
11.			58
12.			0
13.			0

[a] Reaction conditions: A mixture of **5** (0.6 mmol), enol ester **3c** (0.6 mmol), AgOAc (0.6 mmol), DMAP (0.9 mmol) in acetonitrile (2 mL), rt, 7 h.

followed by the ring opening affords the intermediate **III** through a transition state. Ring closing of **IV** through Michael's addition gave the stabilized intermediate **V** (91.7 $KJmol^{-1}$). Interesting to



Scheme 3. Control experiments.



Scheme 4. Plausible reaction pathway.

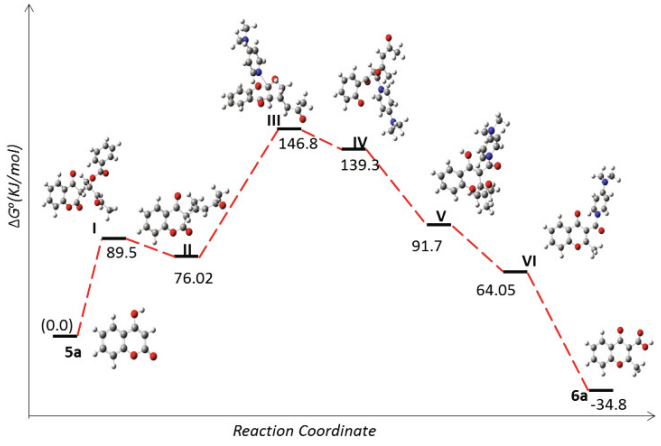


Fig. 2. Free energy profile (KJ/mol) for the conversion of 4-hydroxycoumarin (**5a**) to 2-methyl-4-oxo-4*H*-chromene-3-carboxylic acid (**6a**).

note that the acetone elimination from **V** is a forward reaction as intermediate amide **VI** is having 27.65 KJmol^{-1} lesser energy than that of **V**. Lastly, the hydrolysis process of **VI** is highly exothermic and is responsible for the formation of **6a**.

In summary, an alternative strategy for direct access to chromone-3-carboxylic acid from the reaction of 4-hydroxy coumarin and enol ester was developed. Silver salt in combination with DMAP was standout to be a proof-of catalytic system for the C—C bond formation via selective C3-H activation of coumarin ring. Most importantly, the reaction proceeds at ambient temperature and there is no need for any inert atmosphere for the success of the reaction. A plausible mechanism involving the early Michael addition reaction followed by acetone removal was proposed based on the control experiments. DFT calculations further supported the proposed mechanism.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153206.

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