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Facile construction of 4*H*-chromenes via Michael addition of phenols to benzylidene oxobutanoates and their successful conversion into pyranocoumarins

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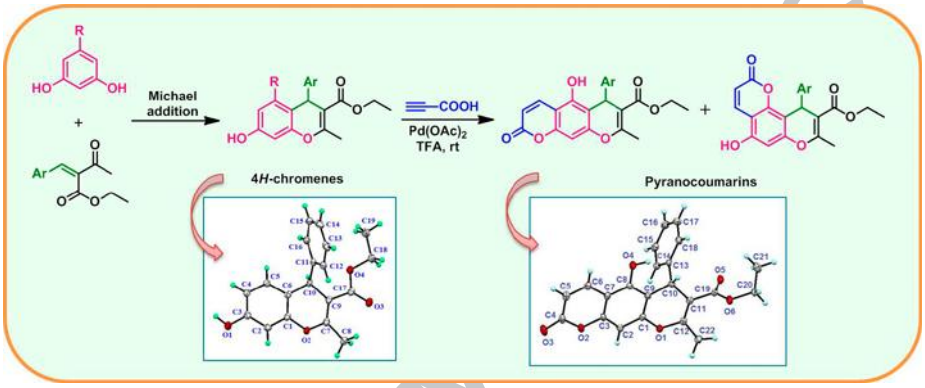

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Facile construction of 4*H*-chromenes via Michael addition of phenols to benzylidene oxobutanoates and their successful conversion into pyranocoumarins

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ABSTRACT

An efficient and simple approach for the synthesis of functionalized 4*H*-chromenes has been developed via acid catalyzed Michael addition of phenols to benzylidene oxobutanoates. Preliminary mechanistic studies were conducted, suggesting that intermediate chroman derivative is initially formed which on dehydration produces final 4*H*-chromene. The conversion of 4*H*-chromenes into linear and angular pyranocoumarins is also described. The structural arrangements between the pyran and coumarin rings have been established by X-ray crystallographic analysis and 2D NMR spectroscopy.

The 4*H*-chromene is an important class of structural motif found in various bioactive natural products and synthetic molecules.[1] This scaffold also serves as the intermediate in the preparation of other complex molecules of pharmaceutical and industrial importance.[2] A number of methods have been developed for the synthesis of 4*H*-chromenes in recent past such as benzylation and cyclization of *o*-hydroxybenzyl alcohols and 1,3-dicarbonyl compounds in the presence iron(III)chloride[3] or silica gel supported sodium bisulfate[4], Brönsted-acid catalyzed reaction of *o*-hydroxybenzyl alcohols with 1,3-dicarbonyl compounds,[5,6] three component reaction of 1,3-diketones, salicylaldehydes and nitrogen, sulphur or carbon based nucleophiles,[7,8,9] cycloaddition of propargylic alcohols or ketones with phenols,[10] $Bi(OTf)_3$-catalyzed tandem reaction of *β,γ*-unsaturated *α*-ketoesters with naphthols,[11] cesium carbonate-mediated reaction of 2-bromoallyl sulfones and ortho-hydroxychalcones,[12] ring closing metathesis reaction of aryl vinyl ethers,[13] coupling of aryl bromides with 1,3-dicarbonyl compounds in presence of copper catalyst[14] and many others.[15] Most of these methods produce 4*H*-chromenes unsubstituted in the benzene ring thus limiting their further functionalization and also require use of toxic reagents or solvents, high temperature and long reaction time. Therefore, it is highly desirable to explore new approach to the synthesis of functionalized 4*H*-chromenes.

Similarly, pyranocoumarins are also an interesting group of compounds that occur widely in natural products, for example, alloxanthoxyletin, xanthoxyletin, 5-methoxyseselin and (+)-calanolide and exhibit wide array of biological activities such as anti-cancer, anti-inflammatory, anti-HIV etc.[16-20] Depending upon the substitution pattern of coumarin and pyran rings these can be classified as angular and linear pyranocoumarins. Among them, pyrano[2,3-*c*]coumarins are the most widely studied class of compounds and various methods have been reported for their synthesis.[21] Despite the synthetic and medicinal significance of pyrano[2,3-*f*] and pyrano[2,3-*g*]coumarins, only limited synthetic routes are available in the literature. Literature methods reported for their synthesis either generally make use of preformed coumarins and/or require multistep sequence of reactions.[22-24] Thus, development of new strategies for the synthesis of these less explored class of pyranocoumarins remains an attractive field of research.

In continuation of our efforts towards the development of bioactive molecules from the readily available substrates,[25] herein we report a new and efficient method for the synthesis of 4*H*-chromenes and their easy conversion into angular and linear pyranocoumarins in good yields.

Initially, the attempt was made towards the synthesis of substituted ethyl benzylidiene oxobutanoates **3a-j** by reaction between substituted aromatic aldehydes **1a-j** and ethylacetoacetate **2** in DMSO at 80 °C using different bases such as L-proline, triethyl amine, piperidine, diethylamine, pyridine. Among all these, 30 mol% of L-proline was found best in terms of clean reaction, easy work-up and high yields of the products (Scheme 1).

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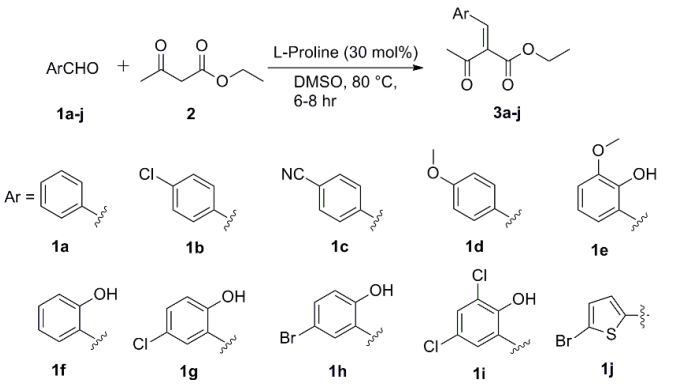


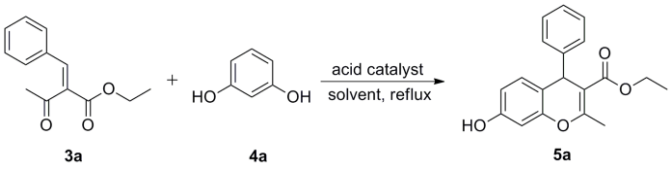
Scheme 1. Synthesis of substituted benzylidene oxobutanoate derivatives

Having successfully prepared the ethyl benzylidiene oxobutanoates, further studies were performed for the synthesis of 4*H*-chromenes. Ethyl-2-benzylidiene-3-oxobutanoate **3a** and resorcinol **4a** were selected as model substrates to optimize the reaction conditions. The results are summarized in **Table 1**. When L-proline was employed as catalyst, the reaction of **3a** and **4a** gave none of the desired product (Table 1, entry1). Different Lewis acids were then examined for this transformation in dichloromethane. The reaction did not proceed to completion even after 10 h stirring at reflux in the presence of $BiCl_3$, $ZnCl_2$, $FeCl_3$, and $AlCl_3$ as catalyst and resulted in the isolation of products in 26%, 22%, 10% and 30% yield, respectively (Table 1, entries 2-5). When reaction was carried out in presence of BF_3.etherate for 10 h, **5a** was obtained in 42% yield (Table 1, entry 6). Further, investigations were conducted with Bronsted acids using ethanol as solvent. With HCl the yield of reaction reached to only 32% (Table 1, entry 7). When reaction was carried out in presence of H_2SO_4 (0.5 mmol) for 8h, the yield of **5a** was increased upto 50% (Table 1, entry 8) and with 1mmol of H_2SO_4 only marginal increase in yield (53%) was detected (Table 1, entry 9); however no enhancement in yield was observed on further increasing the reaction time. The yield was improved to 58% when TFA was used as catalyst (Table 1, entry 12), changing the solvent from ethanol to nitromethane further increased the yield to 65% with 1 mmol loading (Table 1, entry 14). Further, the yield of product **5a** decreased with an increased catalyst loading of 2 mmol (Table 1, entry 15). When shifting the solvent to dichloromethane or toluene only trace or small amount of desired product was observed (Table 1, entry 16 and 17). As shown in entry 18 in the absence of catalyst, no cyclization product **5a** was observed. The structure of **5a** was confirmed by single crystal X-ray analysis (single crystals were grown from acetone solution of **5a** by slow evaporation method) as depicted in the ORTEP plot [Fig. 1(A)].[26]

With the optimized conditions in hand, we then turned our attention towards the scope of the reaction. The results are summarized in **Table 2.** First, a variety of ethyl benzylidiene oxobutanoates **3** bearing different substituents on the aromatic ring were allowed to react with resorcinol **4a** under the optimized reaction conditions. In all cases the corresponding benzopyran derivative **5** was obtained in good yield (Table 2, entries 1-10). Interestingly, the substrates bearing both electron-donating groups such as OMe and OH and electron-withdrawing substituents such as Cl, Br and CN were well tolerated in this transformation, thus providing good opportunities for further functionalization. Compound **3j** bearing heteroaromatic ring was also suitable substrate giving benzopyran **5j** in 64% yield (Table 2, entry 10).

Table 1.

Optimization of reaction conditions for the synthesis of benzopyran 5a.[a]



Entry	Catalyst	Loading (mmol)	Solvent	Time (h)	Yield (%)[b]
1	L-Proline	0.3	DMSO	10	0
2	$BiCl_3$	0.3	CH_2Cl_2	10	26
3	$ZnCl_2$	0.3	CH_2Cl_2	10	22
4	$FeCl_3$	0.3	CH_2Cl_2	10	10
5	$AlCl_3$	0.3	CH_2Cl_2	10	30
6	BF_3.etherate	0.3	CH_2Cl_2	10	42
7	HCl	0.5	C_2H_5OH	8	32
8	H_2SO_4	0.5	C_2H_5OH	8	50
9	H_2SO_4	1	C_2H_5OH	8	53
10	H_2SO_4	1	toluene	8	traces
11	TFA	0.5	C_2H_5OH	8	56
12	TFA	1	C_2H_5OH	8	58
13	TFA	0.5	CH_3NO_2	8	60
14	TFA	1	CH_3NO_2	6	65
15	TFA	2	CH_3NO_2	7	56
16	TFA	1	toluene	8	10
17	TFA	1	CH_2Cl_2	8	traces
18	none	-	CH_3NO_2	8	0

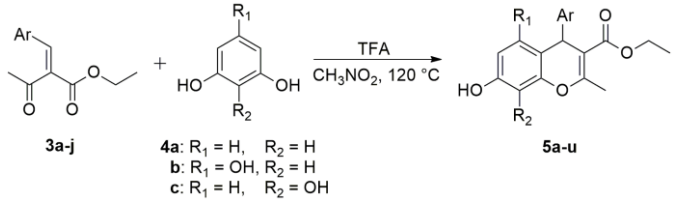
[a]Carried out with 1.2 mmol of **3a** and 1 mmol of **4a** in the presence of catalyst in 5 ml of solvent at reflux for given hours; [b]Isolated yields.

Next, the variability of resorcinol was checked by replacing it with trihydric phenols **4b** and **4c**. Thus the reaction of ethyl benzylidiene oxobutanoates **3a-j** with phloroglucinol **4b** in the presence of TFA in nitromethane at reflux afforded the corresponding benzopyrans **5k-t** in good yields (Table 2, entries 11-20). Similarly, **3a** (Table 2, entry 21) underwent cyclization with pyrogallol **4c** smoothly to furnish the desired benzopyran **5u** in 75% isolated yield. It was found that substrates **4b** and **4c** gave higher yields of **5** than those with **4a** (Table 2, entries 11-21 vs 1-10), indicating that electron-rich aromatic ring favored the reaction.

The possible mechanism for the present acid catalyzed benzopyran formation is outlined in **Scheme 2**. The mechanism is proposed on the established benzopyran chemistry [4,19] and the foregoing results. Michael addition of **4a** to **3a** in the presence of TFA affords intermediate **II**, which undergoes intramolecular cyclization to give intermediate **III**. Subsequent dehydration leads to the formation of benzopyran **5a**. The formation of chroman intermediate **III** gains stern support from the isolation of **III** in 16% yield from the reaction of **3a** with **4a** at reflux in the presence of catalyst $ZnCl_2$ during optimization process. Suitable crystals of intermediate **III** were obtained by slow evaporation of acetone solution and its structure was confirmed by single crystal X-ray diffraction [Fig. 1(B)].[27]

Table 2.

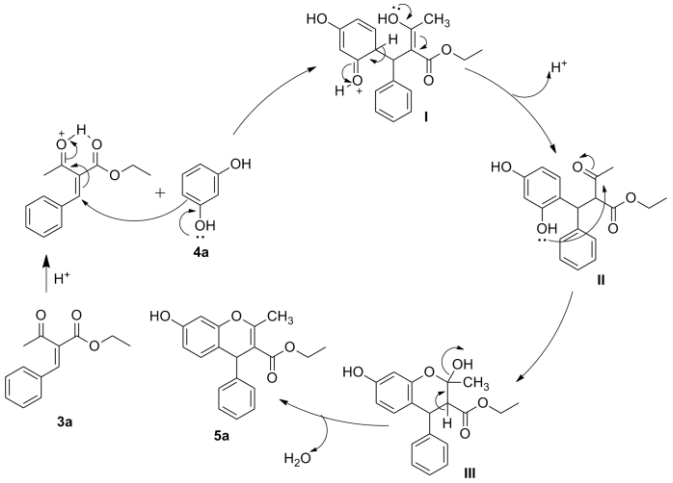
Reaction of ethyl benzylidene oxobuanoates **3a-j** with substituted phenols **4a-c.**[a]



3a-j **4a**: R_1 = H, R_2 = H; **b**: R_1 = OH, R_2 = H; **c**: R_1 = H, R_2 = OH **5a-u**

Entry	R_1	R_2	Ar	Product 5	Time h	Yield %
1	H	H	C_6H_5	**5a**	6	65
2	H	H	4-Cl-C_6H_4	**5b**	6	60
3	H	H	4-CN-C_6H_4	**5c**	7	58
4	H	H	4-OMe-C_6H_4	**5d**	6	65
5	H	H	2-OH-3-OMe-C_6H_3	**5e**	7	64
6	H	H	2-OH-C_6H_4	**5f**	5	70
7	H	H	2-OH-5-Cl-C_6H_4	**5g**	6	68
8	H	H	2-OH-5-Br-C_6H_4	**5h**	6	66
9	H	H	2-OH-3,5-Cl_2-C_6H_4	**5i**	6	65
10	H	H		**5j**	6	64
11	OH	H	C_6H_5	**5k**	5	75
12	OH	H	4-Cl-C_6H_4	**5l**	4	72
13	OH	H	4-CN-C_6H_4	**5m**	5	70
14	OH	H	4-OMe-C_6H_4	**5n**	4	78
15	OH	H	2-OH-3-OMe-C_6H_3	**5o**	5	74
16	OH	H	2-OH-C_6H_4	**5p**	4	78
17	OH	H	2-OH-5-Cl-C_6H_4	**5q**	4	74
18	OH	H	2-OH-5-Br-C_6H_4	**5r**	4	76
19	OH	H	2-OH-3,5-Cl_2-C_6H_4	**5s**	5	70
20	OH	H		**5t**	5	74
21	H	OH	C_6H_5	**5u**	5	75

[a]reaction conditions: **3a-j** (1.2 mmol), **4a-c** (1 mmol), TFA (1 mmol), nitromethane 5 mL, reflux, 4-7 h.



Scheme 2. Proposed mechanism

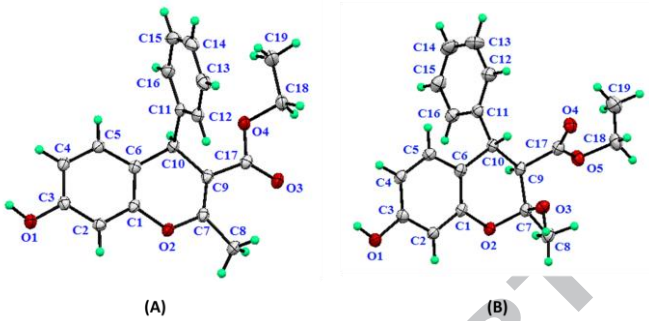


Fig. 1. (A) Crystal structure of compound **5a**; (B) Crystal structure of intermediate **III** with 30 % probability level.

Next, to extend the synthetic utility of this protocol obtained 4*H*-chromenes with phloroglucinol **5k-r** and pyragallol **5u** core were converted to pyranocoumarins *via* hydroarylation reaction with propiolic acid under transition metal catalysis, as this reaction is generally limited to electron rich phenols. Initially, reaction of benzopyran **5k** (1mmol) and propiolic acid **6** (1.5 mmol) was conducted in TFA in presence of $Pd(OAc)_2$ (5 mol%) at room temperature for 30 h. The two regioisomers which were formed in a ratio of 1:3.3 (Table 3, entry 1) were separated by column chromatography as colourless solids. The suitable crystals of less polar minor isomer **7a** could be grown in dichloromethane and its linear pyrano[3,2-*g*]coumarin pattern was unambiguously confirmed by X-ray single crystal analysis (Fig. 2)[28] whereas more polar major isomer **8a** was characterized as angular pyrano[2,3-*f*]coumarin. Its structure was unequivocally confirmed by HMBC and HSQC spectra. The HMBC spectrum of **8a** showed cross-peaks between H-6 proton and the carbon atoms C-4a, C-8 (both three bond couplings) and C-5, C-7 (both two bond couplings) while C-5 displayed three bond correlation with H-4 and two bond correlation with H-6. These observations excluded the formation of other angular isomer **9**. Notably, in comparison to other methods,[29,30] not only this method displays better regioselectivity but also offers a valuable route for the preparation of linear pyranocoumarins.

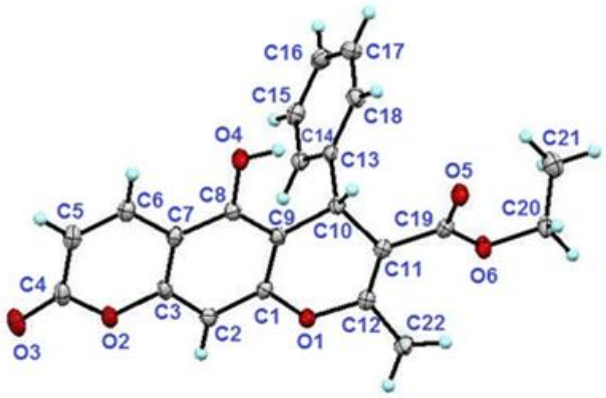
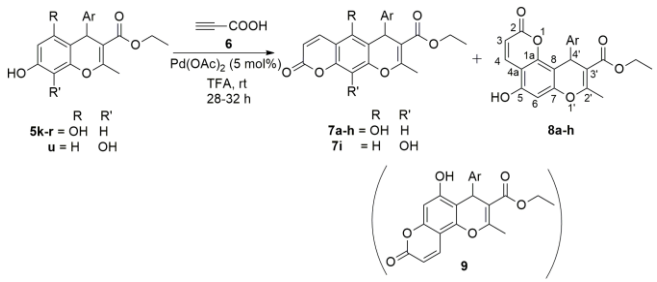


Fig. 2. Crystal structure of compound **7a** with 30% probability level.

Table 3.

Synthesis of pyranocoumarins from benzopyrans **5k-r** and **5u** and propiolic acid.



Entry	**5**	Ar	Time h	**7+8** (%) (**7**:**8**)[a]
1	**5k**	C_6H_5	30	60 (1:3.3)
2	**5l**	4-Cl-C_6H_4	30	59 (1:3.2)
3	**5m**	4-CN-C_6H_4	32	56 (1:3.6)
4	**5n**	4-OMe-C_6H_4	30	61 (1:3.7)
5	**5o**	2-OH-3-OMe-C_6H_3	32	57 (1:3.4)
6	**5p**	2-OH-C_6H_4	28	60 (1:3.3)
7	**5q**	2-OH-5-Cl-C_6H_4	30	61 (1:3.3)
8	**5r**	2-OH-5-Br-C_6H_4	28	62 (1:3.1)
9	**5u**	C_6H_5	30	64[b]

[a]The product ratio was determined by isolated yields; [b]isolated yield of **7i**.

Next, the hydroarylation reaction could be successfully extended to other substituted benzopyrans **5l-r**, affording the desired pyranocoumarins **7b-h** and **8b-h** in good yields. These compounds were separated by column chromatography using methanol/chloroform (1:99) as eluent as colorless solids. The reaction time and overall yields with product ratios of compounds are given in Table 3 (entries 2-8). Similarly, benzopyran **5u** bearing pyrogallol core underwent hydroarylation reaction smoothly and afforded pyrano[3,2-*g*]coumarin **7i** in 64% yield (Table 3, entry 9).

In conclusion, we have disclosed a simple protocol for the synthesis of benzopyrans in good yields from the corresponding phenols and benzylidene derivatives via Michael addition. The reaction features mild reaction conditions, broad substrate scope and good functional group tolerance. The cyclization strategy proceeds through the intermediate chroman derivative and is well supported by its X-ray structure. The synthetic utility of this protocol was demonstrated by a facile synthesis of angular and linear pyranocoumarins. The 4*H*-chromenes synthesized herein contain valuable functional groups that can be transformed into other functional groups of synthetic importance. It is hoped that this strategy may find applications in the synthesis of various bioactive 4*H*-chromenes and pyranocoumarins.

Acknowledgments

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A. Supplementary Material

Experimental details and spectra for selected synthesized compounds are given (PDF).

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26. CCDC 1402647 contains the supplementary crystallographic data for compound **5a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
27. CCDC 1402653 contains the supplementary crystallographic data for intermediate **III**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
28. CCDC 1570784 contains the supplementary crystallographic data for compound **7a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Highlights:

- Simple and efficient protocol for the synthesis of 4*H*-chromenes.
- Reaction proceeds via Michael addition of corresponding phenols and benzylidene oxobutanoates.
- Reaction features broad substrate scope and good functional group tolerance.
- Extended synthetic utility of protocol by synthesis of angular and linear pyranocoumarins.
- Structures of pyranocoumarins confirmed by XRD analysis and 2D NMR.