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A green synthesis of unsymmetrical 9-arylxanthenes in a one-pot cascade benzylation/annulation/dehydration strategy

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ABSTRACT

A green synthesis of unsymmetrical 9-arylxanthenones is described using $Ca(OTf)_2$ in one-pot cascade benzylation, annulation and dehydration strategy starting from readily accessible π-activated carbinols. 4-Hydroxycoumarin/cyclohexane-1,3-dione required to be refluxed in water with 2-(hydroxy(phenyl) methyl)phenol derivatives in the presence of 5 mol% of $Ca(OTf)_2$ to yield the unsymmetrical 9H-xanthenes, whereas α/β-naphthols reacted under solvent free-microwave irradiation conditions. Use of eco-friendly alkaline earth catalyst, water as the solvent, mw-irradiation, substrate scope and high yields make this methodology more amenable.

Pyran (a six membered oxygen heterocycle) is known to be the potential 'privileged structure' in the drug discovery and medicinal chemistry fields.[1] Amongst the several subclasses of pyrans, 9-aryl-xanthenes and 4-aryl-chromenes are widely distributed in nature and used as building blocks in the synthesis of molecules.[2,1a] In addition they are best known about their biological profiles. For example, 9-aryl-xanthenes possess antiviral,[3a] anti-inflammatory[3b] and antibacterial activities.[3c] They are also useful in photodynamic therapy,[4] used as fluorescent materials and dyes[5] (e.g., rhodamine B and rhodamine 6G). Xanthene derivatives are extremely useful in laser technology due to their interesting spectroscopic properties.[6] As a consequence of their importance, several synthetic methodologies have been developed for the synthesis of xanthenes (i) the most established method is the condensation of aldehydes with naphthols or 1,3-diones;[7] (ii) the cyclization of polycyclic aryl triflate esters;[8] (iii) condensation of aryloxy-magnesium halides with triethyl orthoformates;[9] (iv) reaction of xanthones with arylmagnesium halides or aryllithiums followed by subsequent conversion of the resulting carbinols;[10] and (v) coupling of arynes with aromatic aldehydes.[11] Nevertheless only method (iv) would provide the unsymmetrical 9-aryl-xanthene derivatives. But this method involves the xanthone as starting material which needs to be accessed in multistep process. Another attractive method was reported by Panda et al.[12a] using $FeCl_3$[12b] catalyzed intramolecular cyclization to access unsymmetrical 9-arylxanthenes from arenoxy carbinols, but the method is limited to dibenzoxanthenes. Hence it is still desirable to develop a general synthetic procedure to access unsymmetrical 9-aryl dibenzoxanthenes as well as 9-aryltetrahydrobenzoxanthenes using easily available reagents, environmentally benign catalyst and water as the solvent.

Since the past decade the chemists are more concern about the environment and health. Hence the focused research is being conducted in the area of green chemistry. One-Pot reactions, MCRs, Cascade/tandem processes with step economy & atom economy, microwave reactions, 'on-water' reactions and solvent-free reactions are part of the exploration towards the green chemistry for the sustainability.[13] In the recent years we have reported sustainable catalysis using environmentally benign alkaline earth catalyst which is more abundant, stable towards, moisture and air under solvent free reactions, water as the solvent (On-Water synthesis), microwave reactions and cascade MCRs with step & atom economy.[14] In continuation of our research aimed towards the development of sustainable synthetic protocols towards the biologically relevant molecules probably privileged structural motifs here in we report a benzopyran synthesis from the easily available benzylic alcohols with 1,3-diones and naphthols using $Ca(OTf)_2$.

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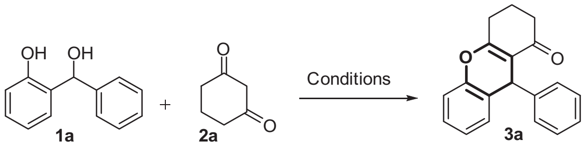
0040-4039/

Table 1
Optimization of reaction conditions for the synthesis of 4H-chromenes[a]



Entry	$Ca(OTf)_2$ (mol%)	Bu_4NPF_6 (mol%)	Solvent	T (°C)[c]	Time (h)	Yield (%)
1	10	10	MeCN	80	18	73
2	10	10	THF	80	9	86
3	10	10	H_2O	110	8	94
4	10	—	H_2O	110	15	65
5	10	5	H_2O	110	8	94
6	—	10	H_2O	110	18	55
7	—	—	H_2O	110	18	50
8[b]	5	5	H_2O	110	8	94
9	5	2	H_2O	110	8	85
10	5	5	H_2O	rt	24	35
11	5	5	—	110	12	30
12	5	5	DCE	80	2.5	94

[a] 1.0 equiv of **1a** and 1.2 equiv of **2a** were used.
[b] Optimum conditions.
[c] Oil bath temperature.

Our initial investigations (Table 1) began with the reaction of 2-(hydroxy(phenyl)methyl)phenol **1a** [which may be readily accessible through a Grignard (PhMgBr) or PhLi addition on salicylaldehyde] with cyclohexane 1,3-dione **2a** in acetonitrile at 80 °C in the presence of 10 mol% $Ca(OTf)_2/Bu_4NPF_6$.[15] As expected we could isolate 9-phenyl-2,3,4,9-tetrahydro-1H-xanthen-1-one **3a** after 18 h but with a 73% yield. The same reaction gave 86% of **3a** when refluxed in THF after 9 h, interestingly 94% yield of **3a** was isolated whilst refluxing in water after 8 h. The yields were not satisfactory when the reaction tried with $Ca(OTf)_2$ alone (entry 4) and Bu_4NPF_6 alone (entry 6). The attempts were made to decrease the catalyst loading and found that 5 mol% of catalyst and additive yielded 94% of **3a** after 8 h (entry 8). Under the same catalyst loading we tried to decrease the time and hence the reaction at ambient temperature could yield only 35% after 24 h and solvent-free conditions ended up with 30% yield (entries 10, 11).

Interestingly the reaction with 5 mol% of $Ca(OTf)_2/Bu_4NPF_6$ in 1,2 dichloroethane (DCE) gave **3a** in 94% yield after 2.5 h (entry 12, Table 1). Though this looks to be the best condition for the synthesis of unsymmetrical xanthene (yield is same in both water & DCE case but the time difference is there), we decided to use the green solvent as the medium (entry 8).

Having found the optimum conditions for the synthesis of unsymmetrical 9-arylxanthenes, we were interested in looking at

Table 2
Substrate scope of Ca(II) catalyzed 4H-chromene synthesis in water from benzylic alcohols & 1,3-diones[a]

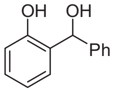
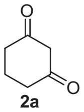
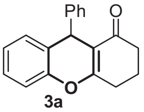
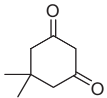
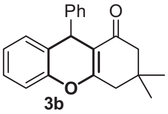
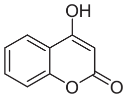
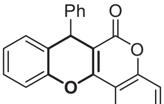
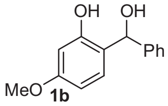
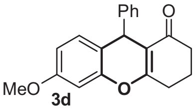
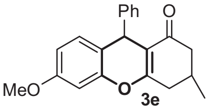
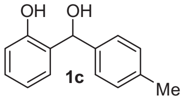
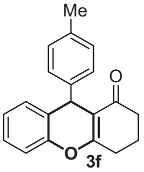
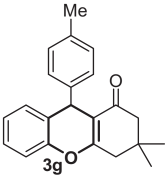
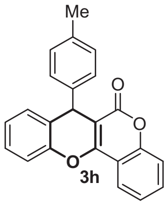
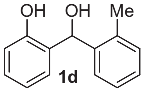
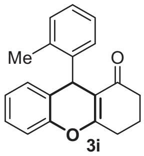
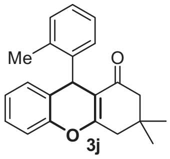
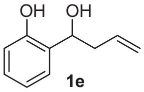
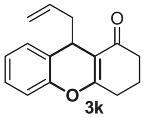
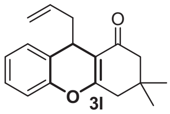
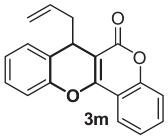
Entry	Benzylic alcohol (**1**)	Nucleophile (**2**)	4-Aryl-4H-chromene (**3**)	Yield (%)
1	 **1a**	 **2a**	 **3a**	94
2	**1a**	 **2b**	 **3b**	88
3	**1a**	 **2c**	 **3c**	94
4	 **1b**	**2a**	 **3d**	78
5	**1b**	**2b**	 **3e**	76
6	 **1c**	**2a**	 **3f**	89
7	**1c**	**2b**	 **3g**	82

Table 2 (*continued*)

Entry	Benzylic alcohol (**1**)	Nucleophile (**2**)	4-Aryl-4H-chromene (**3**)	Yield (%)
8	**1c**	**2c**	 **3h**	90
9	 **1d**	**2a**	 **3i**	83
10	**1d**	**2b**	 **3j**	81
11	 **1e**	**2a**	 **3k**	93
12	**1e**	**2b**	 **3l**	85
13	**1e**	**2c**	 **3m**	94

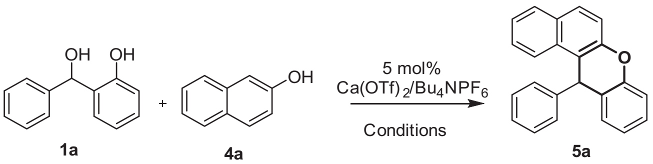
[a] Reaction conditions: stoichiometric amounts of **1** and **2** were refluxed in water at 110 °C using 5 mol% of $Ca(OTf)_2/Bu_4NPF_6$; reactions with **1a**, **2b** need 8–9 h; **2c** needs 2–3 h.

the scope of the various benzylic alcohols and 1,3-diones (Table 2). 5,5-dimethyl cyclohexane 1,3-dione (**2b**) reacted with **1a** under optimized conditions (Table 1, entry 8) and yielded the xanthene **3b** in 88% after 8.5 h (Table 2, entry 2). Another interesting dione, 4-hydroxy coumarin **2c** reacted with **1a** for 2 h to yield the respective xanthene **3c** in 94%. Similarly other benzylic alcohols **1b**, **1c**, **1d** and **1e** reacted with 1,3-dicarbonyls **2a**, **2b** and **2c** to yield the respective 9-arylxanthene derivatives in excellent yields (Table 2, entries 4–13).

Prompted by these results we sought to extend the methodology to synthesize the unsymmetrical dibenzoxanthene derivatives, for which we need to use naphthols as the nucleophilic counterparts (Table 3). As planned we refluxed the stoichiometric amounts of **1a** with β-naphthol (**4a**) in the presence of 5 mol% Ca(II)/additive in water but unfortunately the product was found to be not more than 5%. Hence we investigated the role of different solvents such as THF, DCE, EtOH & MeCN under reflux conditions and were glad to notice that reasonably good amount of the product formation was observed in all the cases (Table 3, entries 2–6).

To further improve the yield a reaction was tried under solvent free conditions at 110 °C and isolated the dibenzoxanthene **5a** in 90% yield after 15 h (Table 3, entry 7). However it is interesting to note that the reaction yielding better under solvent free conditions but the reaction took 15 h. To minimize the reaction time we opted the microwave conditions and after few efforts (Table 3, entries 8–11) we were able to optimize the reaction under mw irradiation for 15 min to yield 95% of unsymmetrical dibenzo-9-arylxanthene **5a** (entry 11, Table 3).

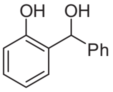
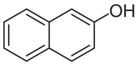
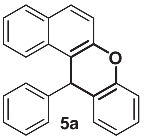
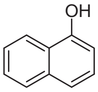
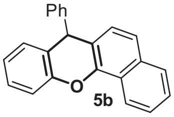
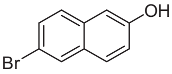
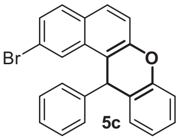
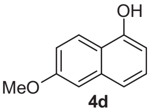
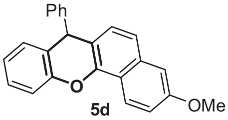
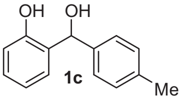
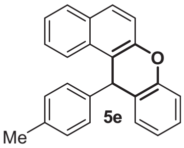
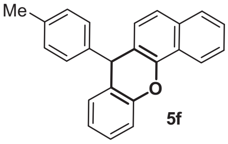
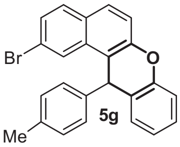
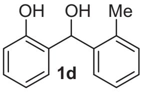
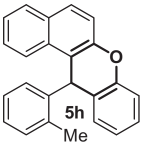
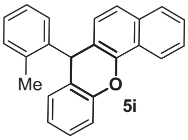
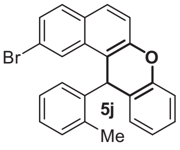
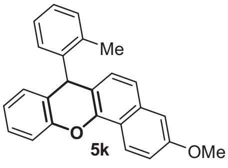
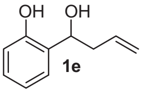
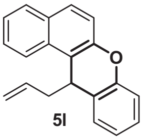
Table 3
Optimization of solvent & temperature towards the xanthenone synthesis[a]



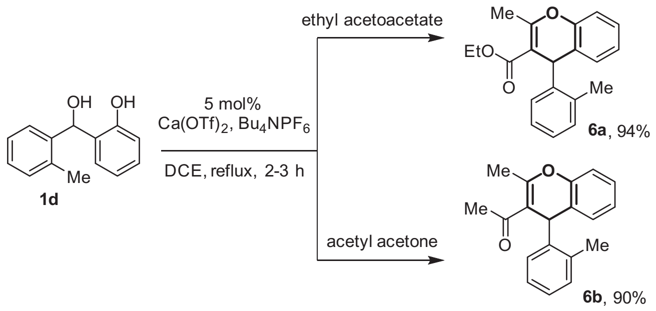
Entry	Solvent	Temperature (°C)	Time	Yield[b] (%)
1	H_2O	110	15 h	5
2	THF	70	20 h	70
3	DCE	80	12 h	85
4	EtOH	70	12 h	60
6	MeCN	80	14 h	75
7	Neat	110	15 h	90
8	Neat	110	3 min, mw	10
9	Neat	110	5 min, mw	30
10	Neat	110	10 min, mw	50
11[c]	Neat	110	15 min, mw	95

[a] Stoichiometric amounts of **1a** and **4a** were used.
[b] Isolated yields.
[c] Optimum conditions.

Table 4
Substrate scope of mw assisted Ca(II) catalyzed xanthene synthesis under solvent free conditions[c]

Entry	Benzylic alchol (**1**)	Nucleophile (**4**)	4-Aryl-4H-xanthene (**5**)	Yield (%)
1	 **1a**	 **4a**	 **5a**	95
2	**1a**	 **4b**	 **5b**	93
3	**1a**	 **4c**	 **5c**	91
4	**1a**	 **4d**	 **5d**	86
5	 **1c**	**4a**	 **5e**	94
6	**1c**	**4b**	 **5f**	92
7	**1c**	**4c**	 **5g**	83
8	 **1d**	**4a**	 **5h**	93
9	**1d**	**4b**	 **5i**	94
10		**4c**	 **5j**	87
11	**1d**		 **5k**	82
12	 **1e**	**4a**	 **5l**	88

[a] Reaction conditions: stoichiometric amounts of **1** and **4** were treated under mw along with 5 mol% $Ca(OTf)_2/Bu_4NPF_6$ for 15 min at 110 °C.



Scheme 1. Synthesis of 4-aryl-4H-chromenes using Ca (II).

After discovering the suitable conditions (Table 3, entry 11) for the unsymmetrical dibenzoxanthene (**5a**) synthesis from **1a** and **4a** we extended this methodology to various benzylic alcohols and naphthols (Table 4) to show the substrate scope of the methodology. α-Naphthol (**4b**) reacted with **1a** under neat-mw conditions and yielded the xanthene **5b** in 93% yield. Similarly other benzylic alcohols **1c**, **1d** & **1e** reacted with naphthols to produce the respective dibenzoxanthene derivatives in good yields (Table 4, entries 5–12).

To further extend the scope of the methodology towards the synthesis of 4-aryl-4H-chromenes which are very well known for their biological profiles, we refluxed **1d** with ethyl acetoacetate using 5 mol% of Ca(II)/Bu_4NPF_6 in water for 6 h, unfortunately the reaction could not lead to the chromene formation. However the ethyl 2-methyl-4-(o-tolyl)-4H-chromene-3-carboxylate **6a** was achieved in 94% within 2 h when DCE was used as solvent. Encouraged by this result we synthesized 1-(2-methyl-4-(o-tolyl)-4H-chromen-3-yl)ethan-1-one **6b** in 90% yield by treating 1d with acetyl acetone (Scheme 1).

All the synthesized compounds are fully characterized by the spectral data (^{1}H NMR, ^{13}C NMR, mass and melting point) and the known compounds were matched with the previously reported data and thus confirmed.[16,17]

In summary, we described a novel one pot tandem benzylation/cyclization/dehydration strategy for the high yielding synthesis of novel unsymmetrical 9-aryl-tetrahydro benzoxanthenes, dibenzoxanthenes and 4-aryl 4H-chromenes using alkaline earth catalyst starting from readily available benzylic alcohols, 1,3-diones and naphthols. The methodology offers important green synthetic protocols such as on water synthesis, microwave reaction, solvent-free reaction, large substrate scope and atom & step economy. In view of these highlights, we believe that our protocol will be more amenable for the synthesis of unsymmetrical xanthene derivatives amongst the existing ones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.016.

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15. Based on our previous observations we knew that Bu_4NPF_6 is required as an additive along with the Ca(II) catalyst. The additive helps to bring the species together to facilitate the faster reaction.
16. *General experimental experimental procedure for the synthesis of unsymmetrical 9-aryl-9H-xanthene derivatives*: Synthesis of xanthene **3**: A mixture of benzylic alcohol **1** (1.0 equiv), cyclic 1,3-dione (**2**) (1.0 equiv), $Ca(OTf)_2$ (5 mol%) and additive-Bu_4NPF_6 (5 mol%) was refluxed in water at 110 °C for 8–9 h. After the completion of the reaction (monitored by TLC) the reaction was brought to rt and extracted into ethyl acetate, organic layer was evaporated and the crude product was purified by column chromatography using ethyl acetate and hexanes as the eluents to yield the desired unsymmetrical xanthene derivatives (**3**); Synthesis of dibenzoxanthenes **5**: A mixture of benzylic alcohol **1** (1.0 equiv), naphthol (**4**) (1.0 equiv), $Ca(OTf)_2$ (5 mol%) and additive-Bu_4NPF_6 (5 mol%) was subjected to microwave irradiation (domestic mw with mwo output 900 W) for 15 min at 110 °C. After the completion of the reaction (monitored by TLC), the crude reaction mass was purified by column chromatography on silica gel using ethyl acetate and hexanes as the eluents to yield the desired unsymmetrical xanthene derivatives (**5**).
17. See the Supporting information for the spectral data and copies of ^{1}H and ^{13}C NMR spectra.