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Synthesis of Novel 1-Aryl-9*H*-xanthen-9-ones

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Abstract: A novel route for the synthesis of 1-aryl-9*H*-xanthen-9-ones is reported. This methodology involves the condensation of 2-methylchromone with cinnamaldehydes leading to (*E*,*E*)-2-(4-arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones. The final steps involved electrocyclization and oxidation of the latter compounds, in an one-pot synthesis, giving the desired 1-aryl-9*H*-xanthen-9-ones.

Key words: 1-arylxanthones, 2-methylchromone, aldol condensation, electrocyclization, oxidation

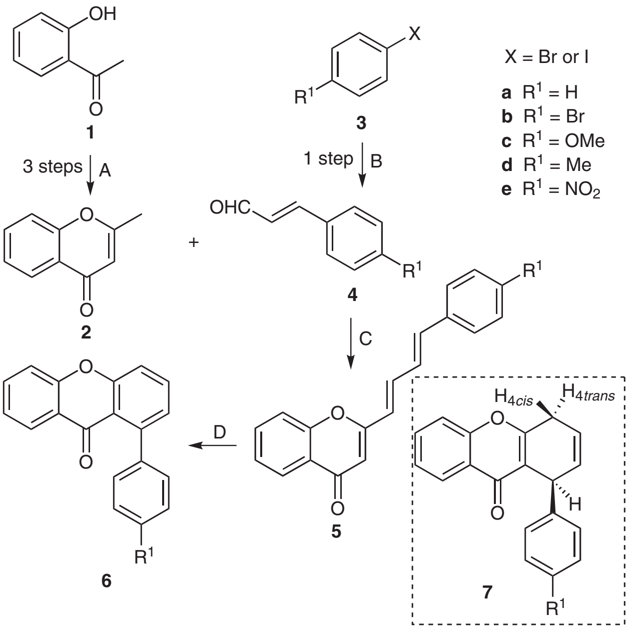
Xanthone or 9*H*-xanthen-9-one is the parent compound of an important class of oxygenated heterocycles with a dibenzo-γ-pyrone framework. This heterocyclic system is widespread in nature, commonly distributed in several higher plant families, such as *Gentianaceae*, *Guttiferae*, and *Polygalaceae*, and in a few families of fungi and lichens.[1]

Naturally occurring xanthones present different types of substituents (e.g., hydroxy, methoxy, and prenyl groups) in different positions of their scaffold leading to a large variety of analogues.[2] The presence of an aryl ring attached to the xanthone core has only been reported in some synthetic derivatives.[3–5] In our previous studies we have developed methodologies for the synthesis of xanthones bearing a 2,3-diaryl substitution pattern but, as far as we are aware, the introduction of a 1-aryl substituent in the xanthone nucleus has never been reported.[5]

In recent years, several studies have emphasized the biological and pharmacological properties of both natural and synthetic xanthones,[6] including anti-inflammatory,[7] cancer chemopreventive,[8] antimalarial,[9] and radical scavenging[10] activities, but also inhibition of cyclooxygenase, cholinesterase, and other enzymes.[6,11] Some xanthones even surpass the antimicrobial activity of traditional antibiotics.[12] These promising applications and the restricted chemical xanthone scaffolds have motivated the search for novel synthetic derivatives and the development of new synthetic routes for 9*H*-xanthen-9-one-type compounds.

The classical methods for the synthesis of xanthones are based on the formation of key intermediates, such as benzophenones, obtained by a Friedel–Crafts acylation or a Fries rearrangement, or diaryl ethers, prepared by intermolecular Ullmann condensation of phenolates with *ortho*-halobenzoic acids or by Smiles rearrangement of diaryl esters. To build more complex structures, several modifications on the traditional methods have been made and a great number of nonconventional approaches have emerged.[13]

In the present communication we report a new strategy for the synthesis of novel 1-aryl-9*H*-xanthen-9-ones **6a**–**e** (Scheme 1).



Scheme 1 *Reagents and conditions*: A. (i) MeCOCl, pyridine, r.t., 15 h; (ii) NaH, THF, reflux, 2 h; (iii) DMSO, I_2 (4 h) or *p*-toluenesulfonic acid (2 h), 100 °C; B. (i) dry DMF, $Pd(OAc)_2$, NBu_4OAc, K_2CO_3, KCl, 90 °C, 2–8 h; (ii) HCl, r.t., 10 min; C. Na, EtOH, r.t. D. 1,2,4-trichlorobenzene, I_2, reflux, 48 h.

The required starting material 2-methylchromone (**2**) was prepared by three-step Baker–Venkataraman sequence,[14] in good overall yields (Scheme 1) involving acetylation of 2′-hydroxyacetophenone (**1**) followed by the base-catalysed Baker–Venkataraman rearrangement[14] of the formed ester, leading to the formation of a 1,3-diketone derivative, which, after cyclodehydration afforded the desired 2-methylchromone (**2**). The last step was carried out with a catalytic amount of *p*-toluenesulfonic acid or iodine in DMSO. The results obtained seem to indicate that the cyclodehydration is favorable in the acidic medium, as previously reported for the synthesis of other chromone-type

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compounds.[15] The reaction of aryl bromides or iodides **3** with acrolein diethyl acetal in a palladium-catalyzed coupling reaction provided the required cinnamaldehydes **4b**–**e** (Scheme 1).[16]

The chemical reactivity of 2-methylchromones and further transformation into other biologically active analogues have been the subject of several works.[17] Among them is a number of condensation reactions with carbonyl compounds to afford new heterocyclic systems. For example, 2-styrylchromone derivatives have been synthesized from 2-methylchromones and these even find use as substrates in the preparation of new and remarkably bioactive xanthones.[10]

Focussing on this concept, optimization studies were carried out for the synthesis of the novel (*E*,*E*)-2-(4-arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones **5a**–**e**. The condensation of 2-methylchromone (**2**) with cinnamaldehydes **4a**–**e** using sodium methoxide, formed in situ from sodium and methanol, as base was ineffective. After several attempts we concluded that the base, its stoichiometry and the reaction time were very important to provide **5a**–**e** in good yields (Scheme 1, Table 1). (*E*,*E*)-2-(4-Arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones **5a**–**e** were thus obtained using four equivalents of base, sodium ethoxide, with the exception of the nitro derivative, which was prepared using only one equivalent of base but with longer reaction time (Table 1).[18,19]

Table 1 Conditions and Yields Obtained in the Formation of **5a**–**e** and Yields in the Synthesis of **6a**–**e**

Entry	Base (equiv)	Time (h)	Yield of **5** (%)	Yield of **6** (%)
1	4	4	**5a** 80	**6a** 55
2	4	8	**5b** 70	**6b** 56
3	4	4	**5c** 80	**6c** 70
4	4	4	**5d** 77	**6d** 67
5	1	55	**5e** 68	**6e** 50

Subsequently, extensive studies into the electrocyclization and oxidation reactions of (*E*,*E*)-2-(4-arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones **5a**–**e** were performed. In the first attempt, chromone **5a** was refluxed in 1,2,4-trichlorobenzene but, even after one week, no product was observed. However, when a catalytic amount of iodine was added to the reaction mixture, TLC analysis after 18 hours revealed the presence of three spots; the one with the lowest R_f value corresponding to the unreacted starting material **5a** (44%).The NMR spectra of the other two spots proved that the one with the highest R_f value was the expected 1-phenyl-9*H*-xanthen-9-one **6a** (15%) and the other one as the semioxidized intermediate of the final xanthone, 1,4-dihydro-1-phenyl-9*H*-xanthen-9-one (**7a**, 20%).[20] On extending the reaction time to 48 hours only the desired xanthone **6a** was isolated and the best yields were accomplished with these reaction conditions (Scheme 1, Table 1).[21,22] The extension of these conditions to compounds **5b**–**e** led to preparation of **6b**–**e** in good yields (50–70%). An extensive study on the referred electrocyclization and oxidation reactions, involving other solvents, temperature, and reaction time and even with irradiation with a high-pressure UV lamp, did not lead to better yields of **6a**–**e**.

The initial stereochemistry of the α,β,γ,δ,ε,ζ-unsaturated system (vide infra) of **5a**–**e** was clearly not appropriate for the ring closure in the attempted thermal electrocyclization, even at higher temperature. However, since it is well known that iodine is an efficient catalyst in the *trans*–*cis* isomerisation of alkenes,[23] a catalytic amount was enough to initiate reaction. A plausible mechanism for the described transformations invokes a thermal electrocyclization of the α,β,γ,δ,ε,ζ-unsaturated system of **5a**–**e** followed by a [1,3]-sigmatropic shift to give 1,4-dihydroxanthen-9-ones **7a**–**e**, which, after in situ oxidation, yield 1-aryl-9*H*-xanthen-9-ones **6a**–**e**.

All novel compounds synthesized have been characterized by NMR, MS, and elemental analysis. The most important feature in the ^{1}H NMR spectra of chromones **5a**–**e** are the singlets corresponding to the resonance of protons H-3, at $\delta_H = 6.24–6.31$ ppm. Other important characteristics are the $^3J_{H\alpha-H\beta}$ and $^3J_{H\gamma-H\delta}$ values of 15–16 Hz indicating a *trans-trans* configuration for the two vinylic systems. The assignments of vinylic protons and of their stereochemistry were confirmed by HMBC and NOESY spectra. Thus, in the HMBC spectrum of chromones **5a**–**e** it was possible to observe the connectivity of H-α with C-2 and C-3 and of H-γ and H-3′,5′ with C-1′. In the NOESY spectra it was possible to observe the close proximity of H-α with H-3 and H-γ and of H-β with H-δ (Figure 1).

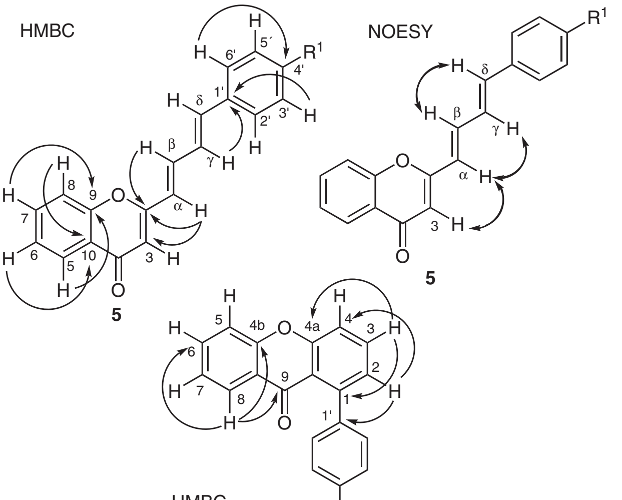

Figure 1 Main results obtained in the HMBC (connectivities) and NOESY (close proximity) spectra of compounds **5** and **6**

The main features in the ^{1}H NMR spectra of 1-aryl-9*H*-xanthen-9-ones **6a**–**e** are the double doublets corresponding to the protons H-8, resonating at higher frequency values ($\delta_H = 8.15–8.19$ ppm) due to the anisotropic and mesomeric deshielding effects of the carbonyl group, and the lowest frequency aromatic signals corresponding to the resonance of protons H-2, at δ_H = 7.13–7.18 ppm. The structure of xanthones **6a–e** was also supported by the main connectivities found in their HMBC spectra (Figure 1).

In conclusion, we have established a simple synthetic methodology for preparing 1-aryl-9*H*-xanthen-9-ones **6a–e**, by the electrocyclization and oxidation reactions of the new (*E*,*E*)-2-(4-arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones **5a–e**. The latter compounds were obtained by condensation of 2-methylchromone (**2**) with cinnamaldehydes **4a–e**.

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(18) **Typical Experimental Procedure**
Sodium (0.11 g, 4.8 mmol) was gradually added to dry EtOH (5 mL), and the mixture was stirred until it reached r.t. 2-Methylchromone (**2**, 0.2 g, 1.2 mmol) and the appropriate cinammaldehyde **4a–e** (1.5 mmol) were added and the reaction mixture allowed to stand at r.t. until complete disappearance of chromone **2** (TLC). The solution was then poured into ice (20 g) and H_2O (30 mL) and adjusted to pH 4 with dilute HCl. The solid was removed by filtration, dissolved in CH_2Cl_2, and purified by silica gel column chromatography using CH_2Cl_2 as eluent. The solvent was evaporated the residue were recrystallized from EtOH to give the (*E*,*E*)-2-(4-arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones **5a–e** in good yields (Table 1).

(19) **Physical Data of (*E*,*E*)-2-[-4-(4-methoxyphenyl)buta-1,3-dien-1-yl]-4*H*-chromen-4-one (5c)**
Mp 137–139 °C. ^{1}H NMR (300,13 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 6.24 (s, 1 H, H-3), 6.32 (d, 1 H, *J* = 15.3 Hz, H-α), 6.84–6.87 (m, 1 H, H-δ), 6.90 (d, 2 H, *J* = 8.8 Hz, H-3′,5′), 6.90–6.96 (m, 1 H, H-γ), 7.38 (ddd, 1 H, *J* = 8.2, 7.1, 0.9 Hz, H-6), 7.41–7.44 (m, 1 H, H-β), 7.43 (d, 2 H, *J* = 8.8 Hz, H-2′,6′), 7.49 (d, 1 H, *J* = 8.1 Hz, H-8), 7.67 (ddd, 1 H, *J* = 8.1, 7.1, 1.7 Hz, H-7), 8.18 (dd, 1 H, *J* = 8.2, 1.7 Hz, H-5). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 109.9 (C-3), 114.3 (C-3′-5′), 117.7 (C-8), 122.3 (C-α), 124.1 (C-10), 124.8 (C-6), 125.0 (C-γ), 125.5 (C-5), 128.5 (C-2′,6′), 128.6 (C-1′), 133.6 (C-7), 137.8 (C-β), 138.9 (C-δ), 140.4 (C-9), 160.3 (C-4′), 162.0 (C-2), 178.4 (C-4). ESI-MS: *m/z* (rel. int.) = 305 (100) $[M + H]^+$, 327 (110) $[M + Na]^+$, 343 (20) $[M + K]^+$, 631 (11) $[2 M + Na]^+$. Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.86; H, 5.30.

(20) **Physical Data of 1,4-Dihydro-1-phenyl-9*H*-xanthen-9-one (7a)**
Yellow oil. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.76 (ddd, 1 H, *J* = 18.6, 5.8, 1.3 Hz, H-4_{trans}), 3.01 (ddd, 1 H, *J* = 18.6, 9.7, 2.8 Hz, H-4_{cis}), 4.56 (d, 1 H, *J* = 9.7 Hz, H-1), 6.39 (dd, 1 H, *J* = 9.7, 2.8 Hz, H-2), 6.44–6.51 (m, 1 H, H-3), 7.14–7.26 (m, 3 H, H-3′,4′,5′), 7.33–7.35 (m, 2 H, H-2′,6′), 7.33–7.37 (m, 1 H, H-7), 7.45 (d, 1 H, *J* = 7.9 Hz, H-5), 7.62 (ddd, 1 H, *J* = 7.9, 7.7, 1.6 Hz, H-6), 8.17 (dd, 1 H, *J* = 7.9, 1.6 Hz, H-8). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 31.5 (C-4), 33.4 (C-1), 116.6 (C-9b), 117.9 (C-5), 121.9 (C-2), 124.3 (C-8a), 124.8 (C-7), 125.9 (C-8), 125.9 (C-4′), 127.1 (C-2′,6′), 128.4 (C-3′,5′), 133.1 (C-6), 138.4 (C-3), 143.3 (C-1′), 155.4 (C-4b), 159.3 (C-4a), 176.4 (C-9).

(21) **Typical Experimental Procedure**
Iodine (18 mg, 0.07 mmol) was added to a solution of the appropriated chomone **5a–e** (0.35 mmol) in 1,2-4-trichlorobenzene (5 mL), and the mixture was refluxed for 48 h. After this period the solution was directly purified by silica gel column chromatography using light PE as eluent to remove 1,2,4-trichlorobenzene and then CH_2Cl_2 to recover the product. The solvent was evaporated to dryness and the residue were recrystallized from EtOH to give the 1-aryl-9*H*-xanthen-9-ones **6a–e** in moderated yields (Table 1).

(22) **Physical Data of 1-Phenyl-9*H*-xanthen-9-one (6a)**
Mp 177–179 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.18 (dd, 1 H, *J* = 7.2, 1.2 Hz, H-2), 7.31 (ddd, 1 H, *J* = 7.8, 7.5, 1.1 Hz, H-7), 7.33–7.36 (m, 2 H, H-2′,6′), 7.41–7.45 (m, 3 H, H-3′,4′,5′), 7.48 (d, 1 H, *J* = 8.6 Hz, H-5), 7.53 (dd, 1 H, *J* = 8.4, 1.2 Hz, H-4), 7.67–7.80 (m, 2 H, H-3 and H-6), 8.18 (dd, 1 H, *J* = 7.8, 1.7 Hz, H-8). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 117.4 (C-5), 117.7 (C-4), 119.3 (C-9b), 122.7 (C-8a), 123.8 (C-7), 127.0 (C-8), 127.1 (C-4′), 127.2 (C-2), 127.5 (C-3′,5′), 128.4 (C-2′,6′), 133.4 (C-3), 134.5 (C-6), 141.8 (C-1′), 144.2 (C-1), 155.4 (C-4b), 157.3 (C-4a), 176.9 (C-9). ESI-MS: *m/z* (rel. int.) = 273 (100) $[M + H]^+$, 295 (76) $[M + Na]^+$, 311 (12) $[[M + K]^+$, 567 (4) $[2 M + Na]^+$. Anal. Calcd for $C_{19}H_{12}O_2$: C, 83.81; H, 4.44. Found: C, 83.57; H, 4.13.

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