Microwave assisted synthesis of coumarinocoumarins

José Crecente-Campo, M. Pilar Vázquez-Tato,* Julio A. Seijas*

Dpto. Química Orgánica. Facultad de Ciencias, Universidad de Santiago de Compostela. Campus de Lugo. Aptdo. 280. 27080 Lugo, Spain

Abstract:

Knoevenagel reaction under microwave irradiation of 2,2'-dihydroxybenzophenones and malonate esters lead to coumarocoumarins (8,12-dioxatetracyclo[8.8.0.02,7.013,18]octadeca-1(10),2,4,6,13,15,17-heptaene-9,11-diones) in good yields.

Coumarins are one of the most widespread classes of compounds in nature. They are quite common in the vegetal kingdom but they are also found in fungi and bacteria. Since substitutions can occur at any of the six available sites of their basic molecular moiety, coumarins are extremely variable in structure.[1-2]

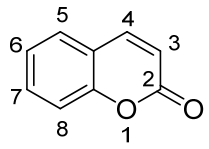


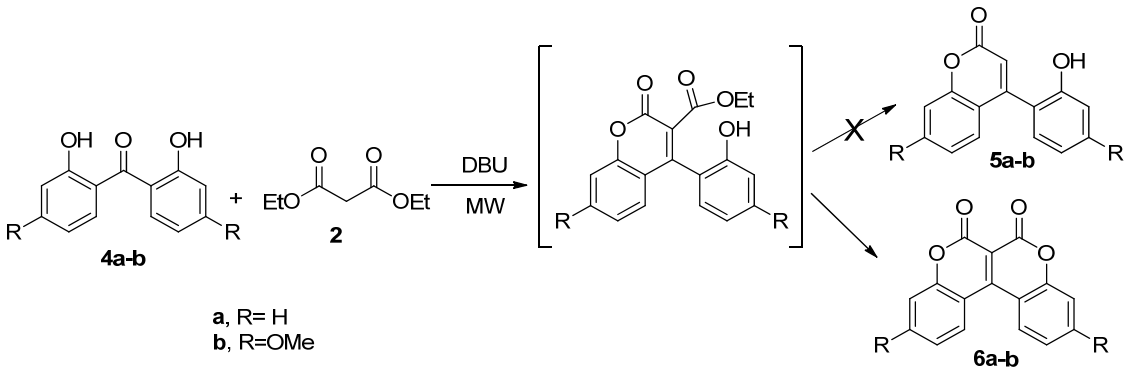
Figure 1. Coumarin

These compounds are within the most biologically active natural compounds[3] possessing multiple pharmacological activities such as anti-HIV,[4-6] antiproliferative[7] and antibiotic activities.[8-12] They can show anti-inflammatory activity,[13-16] antidiabetic,[17] antimalarial[18] and some of them present also vasodilator effects.[19] In many cases their activity is due to the inhibition of key enzymes of important metabolic routes.[20-25] Coumarins are structurally tightly related with flavonoids, another widespread class of compounds in nature. Like some flavonoids, coumarins can have important antioxidant[26-27] and

phytoestrogenic[28-29] activities. Moreover, they exhibit interesting fluorescence properties and can be used as environmentally-sensitive fluorescent probes.[30] Recently,[31] we have developed an efficient and versatile solvent-free synthesis for 4-arylcoumarins (**3**). The key step was a Knoevenagel-type reaction between 2-hydroxybenzophenones **1** and alkyl malonates **2**, using DBU as base, followed by a cyclization-decarboxylation process promoted by microwaves (Scheme 1).

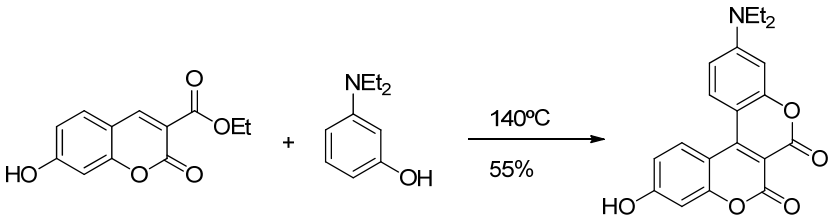
Scheme 1. Syntheses of 4-arylcoumarins from 2-hydroxybenzophenones.

In further studies we established that the decarboxylation step was blocked by the presence of a hydroxyl group in position 2' (**4a**) due to the transesterification of the second ester with this hydroxyl group, yielding an aryl coumarinocoumarin **6a** instead of the decarboxylated compound **5a**.

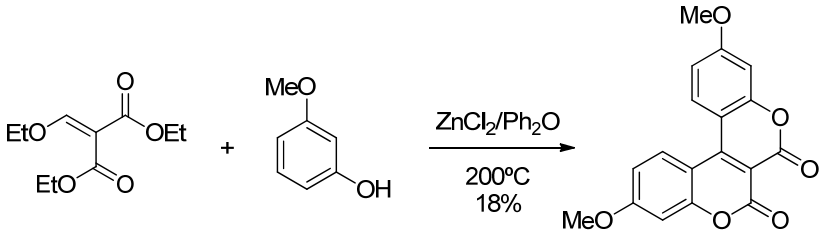


Scheme 2. Syntheses of coumarinocoumarins from 2,2'-dihydroxybenzophenones.

This shows a new route to fused biscoumarins, a type of compounds with a small number of representatives described,[32-33] being the only two previously published synthesis outlined in Schemes 3 y 4.



Scheme 3.[33]



Scheme 4.[34]

The scope of this new strategy of synthesis by microwave irradiation in a monomode oven was studied (Table 1), varying the ratio of the reactants and the solvent effect. Founding that when the reaction is carried out in the presence of solvent (DMF, DMSO, Table 1, entries 1 and 2), the coumarinocoumarin was not obtained, meanwhile solventless conditions rendered a 39% yield of **6a** after 8 minutes of irradiation at 150ºC (Table 1, entry 3). When the ratio of benzophenone to malonate was raised to 1:7 the yield was slightly better (43%, entry 4).

Similarly, the reaction of 4,4'-dimethoxybenzophenone derivative **4b** with ethyl malonate, yielded under analogous conditions the fluorescent compound **6b** in very good yield (82%, Table 1, entry 5).

Fluorescence spectra of both compounds synthesized are shown in Figures 2 and 3. The fluorescence of compound **6b** converts it in an interesting probe for fluorescence studies, with the advantage of its easy availability.

Table 1.

Entry	R	Molar ratio 4:2:DBU	Solvent	Irradiation time (min)	T (ºC)	Yield (%)
1	H	1:1.5:0.75	DMF	10	150	-
2	H	1:1.5:0.75	DMSO	30	160	-
3	H	1:4:0.3	-	8	150	39
4	H	1:7:0.3	-	8	150	43
5	OMe	1:7:0.3	-	10	150	82

The reactions were carried out in a monomode microwave in a sealed tube.

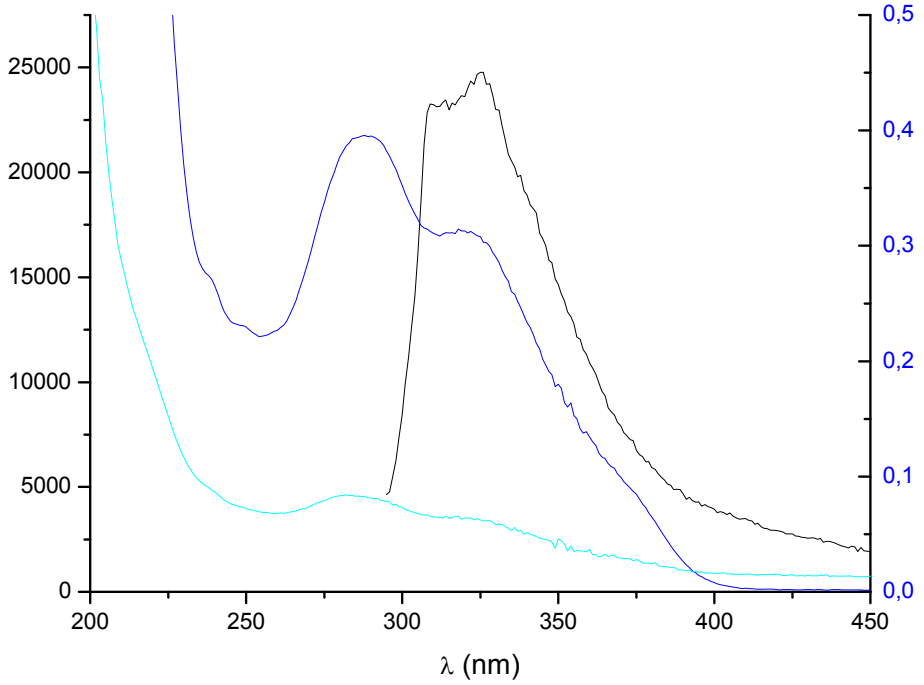


Figure 2. Absorption (blue and cyan lines) and emission (black line) spectra of compound **6a**.

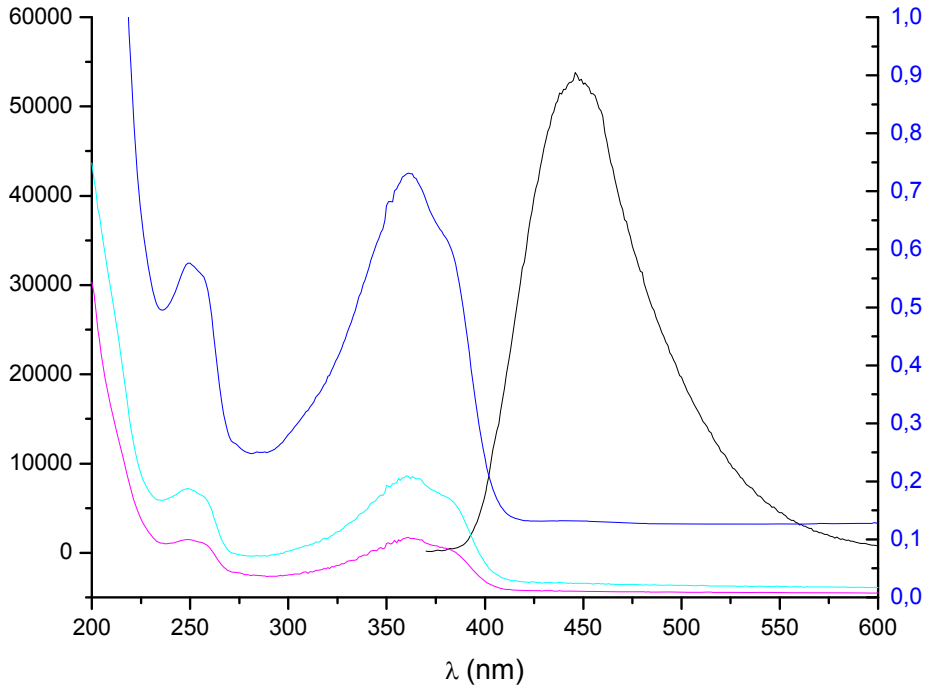


Figure 3. Absorption (blue, cyan and magenta lines) and emission (black line) spectra of compound **6b**.

General Procedure.

Synthesis de 6H,7H-[1]Benzopyrano[3,4-c]benzopyran-6,7-dione ***(6a).*** A mixture of 2,2'-dihydroxybenzofenone (428 mg, 2 mmol), diethyl malonate (2.24 g, 14 mmol) and DBU (91 mg, 0.6 mmol) was irradiated with microwaves (monomode oven Personal Chemistry *Emrys Creator*, 300 W) at 150 ºC (measured with a IR sensor) in a sealed tube, during 4 min. The resulted solid was washed with cold methanol and dried, obtaining … (208 mg, 49%) as a yelow solid. M.p. 291.9-294.5 ºC. UV λ_{max} (MeOH): 203, 239, 298, 326 nm. IR (*Golden-Gate*^{TM}): 1759 (C=O), 1703, 1595, 1524, 1377, 1238, 1095, 978, 766, 746, 604 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48-7.54 (m, 4H, Ar<u>H</u>), 7.84 (t, 2H, J_{ortho}= 7.6 Hz, Ar<u>H</u>), 8.42 (d, 2H, J_{ortho}= 8.2 Hz, Ar<u>H</u>). ^{13}C NMR (75 MHz, DMSO) δ 110.0 ((Ar)$_2$C=<u>C</u>), 115.9, 118.2, 125.6, 130.0, 135.6 (C_{Ar}), 152.9 (C_{Ar}O), 155.0 (C=O), 155.6 ((Ar)$_2$<u>C</u>=C). MS m/z (%): 264 (M^+, 100), 263 (M^+-1, 84), 236 (11), 208 (24), 180 (58), 179 (33), 152 (23), 151 (17). Anal. Calcd for $C_{16}H_8O_4$: C, 72.73; H, 3.05. Found C, 72.67; H, 2.70.

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