SUPPLEMENTARY MATERIAL

Microwave-assisted synthesis and pKa determination of umbelliferone: an experiment for the undergraduate organic chemistry laboratory

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CALIBRATION OF THE DOMESTIC MICROWAVE

The temperatures at the beginning and at the end of irradiation, for each level, were measured (Table 1S). Applying the results in Equation 1, it was possible to determine the corresponding experimental power related to each level.[1]

$$P = (Hc.n.\Delta T)/\ t \qquad (1)$$

P = Power; Hc = Heat capacity of water (75,312 $J.K^{-1}.mol^{-1}$); n = Number of mols of water; ΔT = Temperature variation; t = Time (s)

Table 1S. Initial and final temperatures obtained by heating 500g of water for 60 seconds and the corresponding level power of the domestic microwave

Microwave level	Initial temperature (To) (°C)	Final temperature (T) (°C)	Calculated power (W)
1	20.8	23.7	101
2	21.7	27.2	192
3	21.8	29.4	265
6	21.8	32.2	363
8	20.7	34.6	485
10	20.8	38.2	607

Unlike the one reported by Teixeira *et al.*,[1S] the domestic microwave oven used in our work has presented a linear power model, as it can be observed in Figure 2S. These results show the importance of previous determination of the real power of each domestic microwave oven.

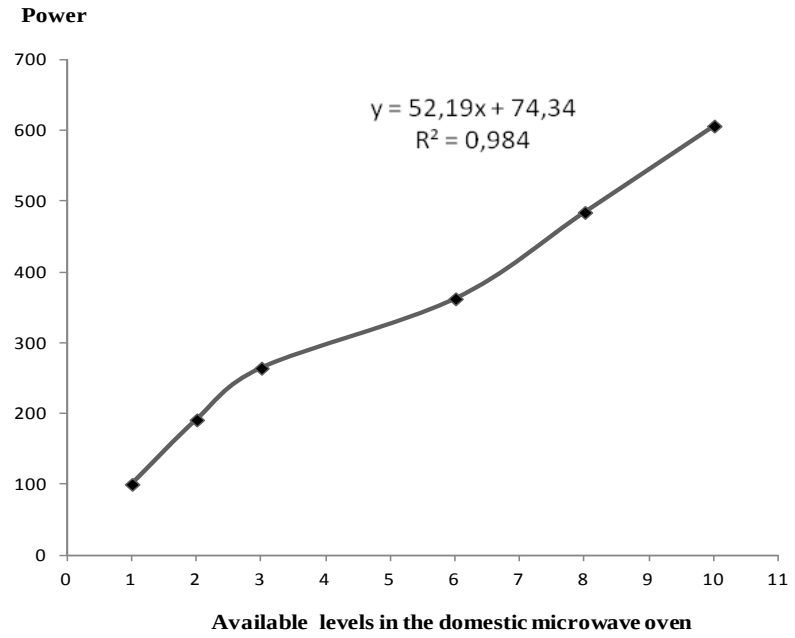
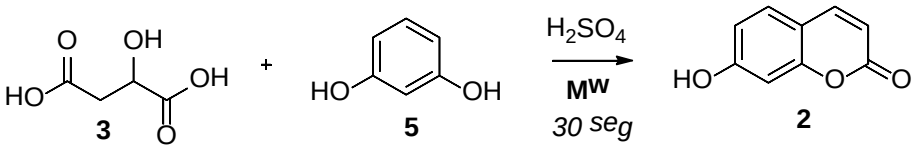


Figure 2S. *Experimental powers obtained in function of the different power levels of the microwave*

SYNTHESIS OF UMBELLIFERONE



Scheme 1S. *Experimental method of umbelliferone synthesis*

POWER AND TIME SELECTION TESTS

Resorcinol (20 mmol) and malic acid (20 mmol) were finely triturated and added in an Erlenmeyer flask (50 mL). Concentrated sulfuric acid (100 mmol) was gently added over the solids and a slow circular movement was applied in order to give a slurry. A glass funnel was adapted in the output of the flask, preventing eventual reaction projection.

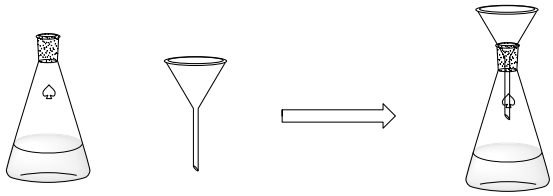


***Figure 3S**. Glassware protection apparatus*

The resulting mixture was irradiated at the edge of the microwave plate. Low (<3) and high (>6) power levels led to small product conversion or reaction degradation, respectively. Thus, intermediate powers were chosen to perform the synthesis and some experimental conditions employed are depicted in Table 2S. After each reaction time completion, crushed ice was directly added to the mixture to form a precipitate which was filtered out and dried to give umbelliferone.

Table 2S. Selection of the ideal experimental conditions

Entry	Power level; (W)	Time	Pulses	Isolated Yield* (%)
1	6; (363)	18 s	3 pulses of 6 seconds	20
2	6; (363)	30 s	3 pulses of 10 seconds	50
3	6; (363)	27 s	1 pulse of 15 s and 2 of 6 s	33
4	3; (265)	30 s	3 pulses of 10 s	40
5	2; (192)	30 s	3 pulses of 10 s	5

*Yields after filtration and dryness

OPTIMIZATION OF PRECIPITATION PROCESS WITH ADDITION OF HOT WATER

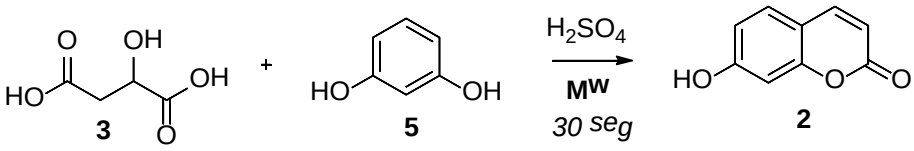
Even though we have found a good reactional condition (entry 2, Table 2S), the precipitation process was sometimes laborious due to the formation of a gelatinous material. Thus, we optimized this process: immediately after the irradiation (power level 6 and 3 pulses of 10 seconds), hot distilled water (approximately at 100 °C) (tested volumes in Table 3S) was added to dilute the reaction slurry and, after that, crushed ice was added into the erlemmeyer to force the precipitation. The precipitate was then filtered off under vacuum and dried at ambient temperature. This previous addition of hot water to the reaction vessel shown to be more suitable to allow the precipitation of umbelliferone.

Table 3S. Amount of hot water added to reactional slurry

Entry	Hot water (mL)	Isolation*	Yield (%)
1	10	easy	65
2	5	easy	77
3	2	difficult	52

*after precipitation with crushed ice, filtration and dryness.

STRUCTURAL ELUCIDATION OF UMBELLIFERONE



^{1}H NMR (500 MHz) DMSO / TMS (δ-ppm): H_3=6.21 (d, *J* = 9.4 Hz, 1H), H_4=7.94 (d, *J* = 9.5 Hz, 1H), H_5=7.54 (d, *J* = 8.5 Hz, 1H), H_6=6.79 (d, *J* = 8.5 Hz, 1H), H_8=6.72 (s, 1H), OH=10.60 (s, 1H), **^{13}C RMN (125 MHz) DMSO/ TMS (δ-ppm)**: C_2=161.75, C_3=113.5, C_4=145.02, C_5=130.20, C_6= 111.88, C_7=160.92, C_8=102.89, C_9=156.00, C_{10}= 111.75. Figure 4S and 5S.

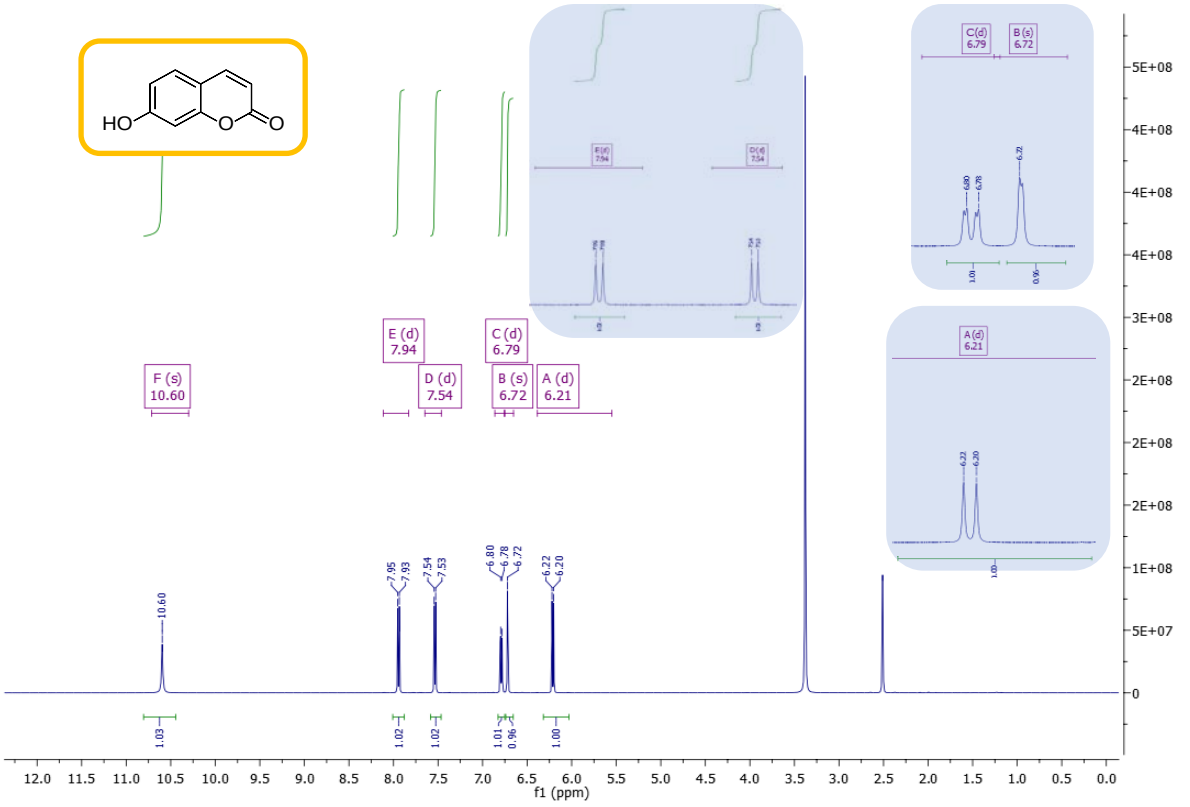


Figure 4S. *^{1}H NMR (500 MHz) spectra of* ***umbelliferone*** *in DMSO-d$_6$ (with enlargement in 6.15-6.29 ppm, 6.6-6.85 ppm and 7.51-7.99 ppm).*

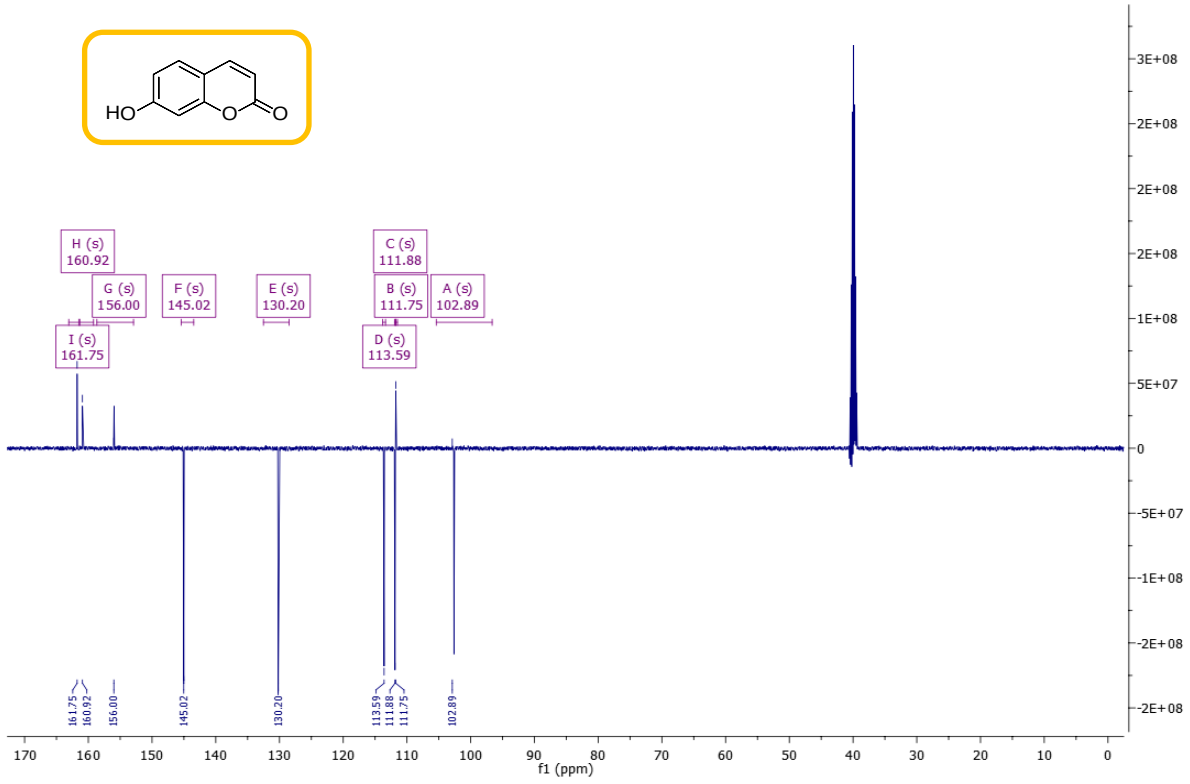


Figure 5S. *^{13}C NMR (125 MHz) spectra of* ***umbelliferone*** *in DMSO-d$_6$*

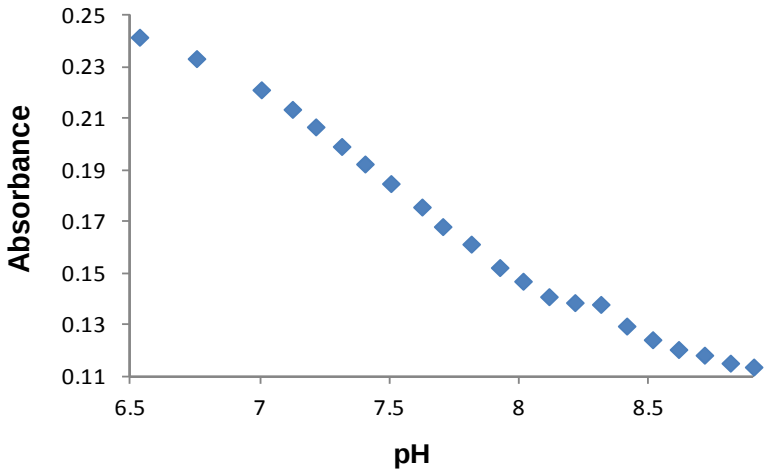


Figure 6S. *Spectra of pH versus absorbance in 323 nm*

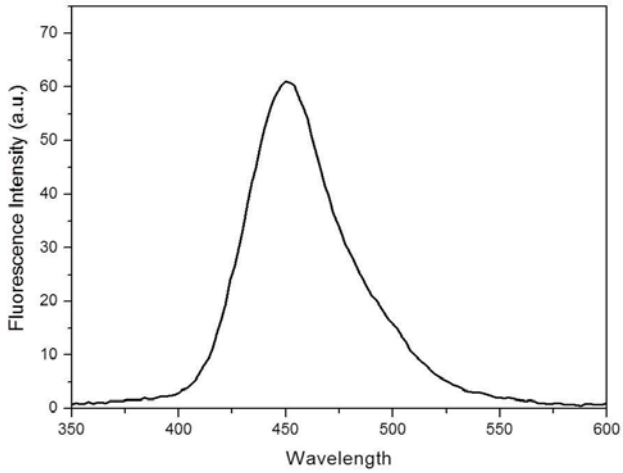


Figure 7S. *Fluorescence spectra of umbelliferone*

QUESTIONS

1) Propose a coherent mechanism pathway for the synthesis of umbelliferone, using resorcinol and malic acid in the presence of H_2SO_4.
2) What is the reason for the appearance of foam during the reaction for the synthesis of umbelliferone? Write the reaction that describes this phenomenon.
3) If we replace malic acid with ethyl acetoacetate, what would be the final product of the reaction? Suggest a mechanism.

4) Why there is a change in the fluorescence behavior of umbelliferone after addition of NaOH in aqueous solution?
5) Explain why umbelliferone (pka7.6) is more acid than phenol (pka~10) and alcohols (pka ~ 16)? Use draws to answer.

REFERENCES

1S. Teixeira, E. F.; Santos, A. P. B.; Bastos, R. S.; Pinto, A. C.; Kümmerle, A. E.; Coelho, R. R.; *Quim. Nova* **2010**, *33*, 1603.