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Solvent-Free Synthesis of Functionalized Flavones under Microwave Irradiation

Julio A. Seijas,* M. Pilar Vázquez-Tato,* and Raquel Carballido-Reboredo

Departamento de Química Orgánica, Universidad de Santiago de Compostela, Facultad de Ciencias, Aptdo. 280, 27080-Lugo, Spain

qoseijas@lugo.usc.es; pilarvt@lugo.usc.es

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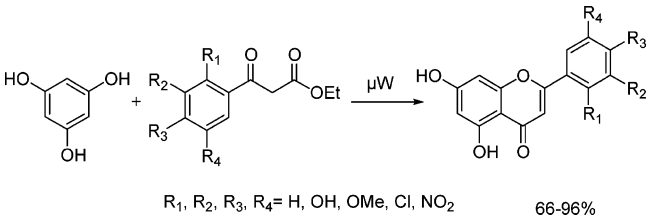

Eco-friendly direct solvent-free synthesis of flavones is achieved by microwave irradiation of phloroglucinol and β-ketoesters. Heating with microwaves versus under classical conditions was shown to be higher yielding, cleaner, and faster. The reaction goes through a cycloaddition of an α-oxo ketene intermediate followed by an uncatalyzed thermal Fries rearrangement.

Flavonoids are ubiquitous in plants, and researchers have been studying them for more than a century.[1] Despite their long presence in the organic chemistry field, there is still a constant interest in the isolation of new constituents[2] and in developing new synthetic approaches.[3] Most of the current syntheses for new flavonoids are based on the pioneer work developed by Robinson[4] and Venkataraman,[5] and despite the number of steps involved in both methods they constitute the most popular methodologies used nowadays for preparation of flavonoids. These synthetic efforts are due both to their chemotaxonomical interest as biological markers[6] and to the increasing importance of their multiple biological activities: leishmanicidal activity,[7] ovipositor stimulant phytoalexins,[8] antiHIV,[9] vasodilator,[10] antiviral,[11] antioxidants,[12] bactericidal,[13] DNA cleavage,[14] antiinflamatory,[15] antimutagenic,[16] antiallergic,[17] and anticancer.[18]

The microwave-assisted synthesis[19] offers considerable advantages over conventional heating because of rapid heating and substantial rate enhancements of a wide range of organic reactions. Cleaner reactions are also commonly achieved, together with improvement in yield and selectivity.[20] The increasing demand of clean and efficient chemical synthesis makes solvent-free reactions, which when combined with microwave irradiation give a more eco-friendly approach required from both economic and environmental standpoints. It is because of with this demand that different reports on the use of microwaves to enhance several solvent-free reactions have been published by our group.[21]

Recently there have been several reports on the application of microwave irradiation to the synthesis of flavonoids[22] and neoflavonoids or 4-substituted coumarins;[23] however, no attention has been paid to the development of a two-component single-stepped reaction to prepare flavones. Mentzer[24] reported the reaction between phenols and β-ketoesters to yield flavones under very harsh conditions (250 °C for long reaction times) and extended this method to a wide number or flavones, despite the low yield in these thermal cyclocondensations.

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TABLE 1. Yields and Reaction Times for Cyclocondensation of Phloroglucinol with β-Ketoesters under Microwave Irradiation

entry	R_1	R_2	R_3	R_4	product	irrad time (min)	yield (%)
1	H	H	H	H	**3a**[42]	3.0	96
2	H	H	OCH_3	H	**3b**[43]	3.5	81
3	H	OCH_3	OCH_3	H	**3c**[43]	3.5	77
4	H	H	OH	H	**3d**[44]	3.8	66
5	H	OCH_3	OCH_3	OCH_3	**3e**[42]	7.0	95
6	H	OCH_2O		H	**3f**[45]	3.5	91
7	OCH_3	H	H	H	**3g**[46]	2.0	86
8	H	H	Cl	H	**3h**[29d]	4.5	75
9	H	H	NO_2	H	**3i**[43]	12.0	68
10	H	H	CH_3	H	**3j**[29a]	2.3	80

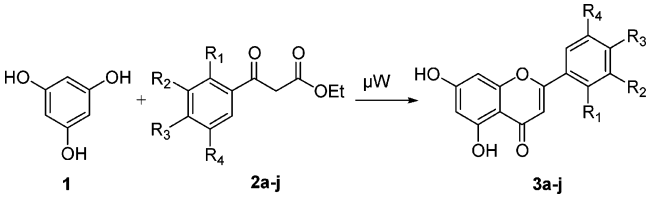

FIGURE 1. Cyclocondensation of phloroglucinol with β-ketoesters promoted by microwave irradiation.

For instance, chrysin (**3a**) and acacetin (**3b**) were obtained in 20 and 21% yield, respectively.[25]

This difficulty in itself constitutes a good challenge in proving the effectiveness of microwave irradiation. As proposed by Molho[26] this two-component reaction involves several steps: transesterification, thermal Fries rearrangement leading to a β-diketone, and cyclization to a γ-pyrone; these occur through dipolar transition states[27] and should favor the involvement of a microwave effect. As expected, when phloroglucinol (**1**) was irradiated for 3 min in the presence of ethyl benzoyl acetate (**2a**, $R_1 = R_2 = R_3 = R_4 = H$), chrysin (**3a**) was obtained in very good yield (Table 1, entry 1; Figure 1). With microwave heating, the temperature reached was similar to the one required under conventional conditions[25] (see Figure 2), but the reaction is faster, cleaner, and higher yielding as we have confirmed.

To see the scope of the reaction, several substituted β-ketoesters[28] were tried; they afforded flavones with different substituted patters in the B ring. Thus, natural

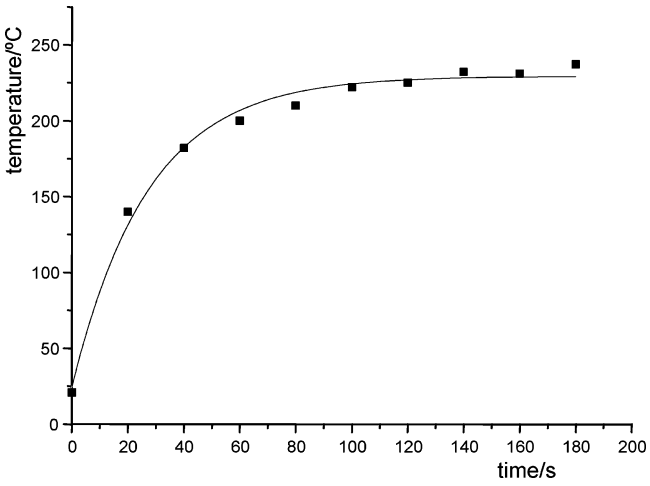

FIGURE 2. Variation of the temperature during microwave irradiation time of phloroglucinol and ethyl benzoyl acetate.

flavonoids such as acacetin (**3b**), luteolin 3′,4′-dimethyl ether (**3c**), apigenin (**3d**), tricetin trimethyl ether (**3e**), 5,7-dihydroxy-3′,4′-methylenedioxyflavone (**3f**), and 5,7-dihydroxy-2′-methoxyflavone (**3g**) were prepared from the corresponding ethyl benzoyl acetates and phloroglucinol for 3−4 min of irradiation (Table 1, entries 2−7) in 66−91% yields. In the case of the reaction with ethyl 3,4,5-trimethoxybenzoyl acetate, the reaction time required is longer than in the other cases because of the higher melting point of this compound (Table 1, entry 5). Due to the interesting properties of flavone derivatives[29] non-natural flavones were also prepared (**3h**−**j**).

The experimental setup is always simple, just mixing the phenol and the β-ketoester in an open test tube and irradiating with microwaves (800 W output) without any solvent or solid. Reactions can be performed either under wattage control or temperature control (240 °C) with no significant differences in reaction times or yields. The reaction can be scaled up to multigram quantities in similar yields. For example, 6 g of chrysin (**3a**) was obtained from phloroglucinol and ethyl benzoyl acetate (98% yield) in one batch reaction. These features convert this procedure in an environmentally benign method for the production of flavones on a large scale.

To find evidence of the microwave effect in this solvent-free reaction, where the possible specific effects are not moderated or impeded by solvents, the reaction temperature was reduced both under conventional and microwave conditions; starting with a poorer yield made it possible to appreciate microwave activation. So, both experiments were done for the same amount of time (10 min) and in the same temperature ramp (25−152 °C); under these conditions the yield of flavonoid (chrysin), estimated by HPLC,[30] was 4-fold in the microwave

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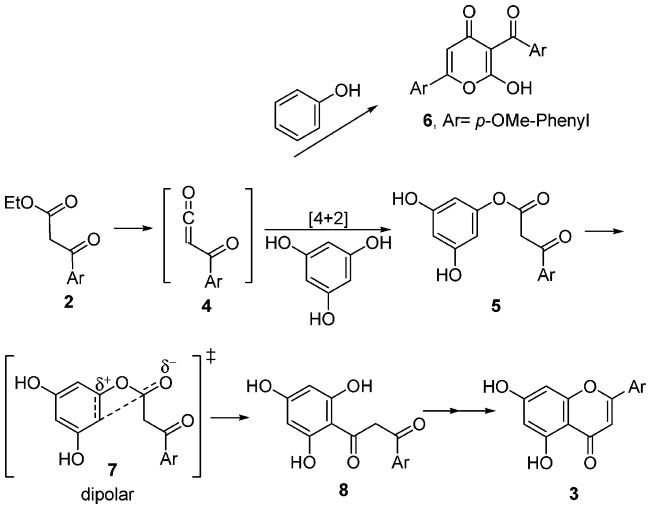
(30) The crude products were analyzed by HPLC using a Discovery HS PEG column, gradient 15% CH_3CN/85% water (10 mM ammonium acetate) to CH_3CN, flow rate= 1 mL min^{-1}. Absorbances were recorded at 268 nm.

SCHEME 1

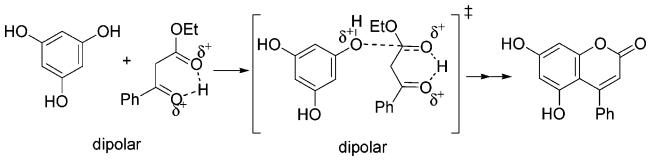


reaction. These results suggest that the better yields achieved with the use of microwave irradiation are perhaps not entirely a result of the rapid heating of the reaction media, since the speed of heating was the same for both experiments.

A reason for this enhancement can be found in the mechanism of this reaction. The first step initially proposed[26] was the formation of the ester through a transesterification; this step satisfies the requirements necessary to be enhanced by microwaves since it goes through a more polar transition state than the starting reagents.[31] However, this transesterification step does not coincide with our results for phloroglucinol irradiated in the presence of ethyl phenylpropionate for long periods, since both of the starting materials were recovered unchanged. On the other hand, it is well-known that β-ketoesters easily yield α-oxo ketenes when heated at high temperatures.[32] Of particular interest in these compounds is their tendency to undergo [4 + 2] cycloadditions, in contrast to the [2 + 2] cycloadditions characteristic of ketenes and vinylketenes.[33] So, the reaction should go through [4 + 2] cycloaddition of phloroglucinol and this α-oxo ketene **4** to give ester **5** (Scheme 1); this is similar to the addition of alcohols to acetylketene described by Birney et al.[34] In fact, the irradiation of phenol and benzoyl acetate confirmed the formation of α-oxo ketene intermediate with the detection of aroylketene dimer **6**[35] but no flavone could be isolated. The pseudopericyclic reaction step could be enhanced by microwaves since Diels−Alder reactions and 1,3-dipolar cycloadditions under uncatalyzed neat reaction conditions have been promoted in this way.[36]

Once the ester is formed, it suffers an uncatalyzed thermal Fries rearrangement as Molho has proved for

SCHEME 2



α-naphthol acetoacetate when it was heated to 200 °C. This reaction could also be enhanced by microwaves, because it is a unimolecular reaction where the intramolecular addition generates an increment in the polarity of the transition state (**7**), although no entropic contribution should be expected.[37] The final hemiketal and dehydration steps must be very easy under the reaction conditions (Scheme 1).

On the contrary, no increase in yield for the reaction of β-ketoesters and phenols in an acidic medium (von Pechmann condensation) was observed for microwaves versus conventional heating.[38] In fact, phloroglucinol and ethyl benzoylbenzoate under reflux in trifluoroacetic acid, render 4-phenylcoumarine in 85% yield.[39] For polar starting materials, such as protonated ketoester (Scheme 2), microwave intrinsic effects on the reaction should not be expected, but ordinary thermal effects should be. A microwave-enhanced Pechmann reaction illustrates this last effect (Scheme 2).[40]

In summary, we have developed an efficient solvent-free method for the synthesis of flavones, where the irradiation with microwaves proves to be an efficient enhancer for the access to these bioactive compounds. This method is valid for flavones with or without substitution in the B ring, the latter compounds being known cyclooxygenase-2 inhibitors.[41] Moreover, this is the first time that α-oxo ketenes have been obtained from β-ketoesters by irradiation with microwaves in absence of solvents. The successful use of microwave irradiation in providing this rapid and direct route to flavones in comparison to classical procedures contributes to confirming the participation of specific effects in some microwave-assisted organic synthesis.

Experimental Section

Typical Procedure. Preparation of Chrysin (3a). A mixture of ethyl benzoyl acetate (384 mg, 2 mmol) and phloroglucinol (126 mg, 1 mmol) was irradiated with microwaves (ETHOS D, Millestone, at 80% of a total output of 1000 W or with the temperature control set to 240 °C) for 3 min. The crude was dissolved in 10% aq NaOH (20 mL) and washed with diethyl ether (2 × 20 mL), and the product was precipitated by adding concentrated aq HCl. The product was filtered, washed with water and vacuum-dried to give chrysin (**3a**) (243 mg, 96%), pure as per NMR: mp 288−290 °C (dichloromethane−methanol) (lit.[42] mp 290 °C); ^{1}H NMR (DMSO-d_6), δ 12.8 (s, H, OH-5), 11.0 (s, H, OH-7), 8.07 (br d, 2H, H-2′, H-6′, J = 8.1 Hz), 7.63−7.57 (m, 3H, H-3′, H-4′, H-5′), 6.98 (s, 1H, H-3), 6.56 (d, 1H, H-8, J = 2.1

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Hz), 6.25 (d, 1H, H-6, J = 2.2 Hz); ^{13}C NMR (DMSO-d_6), δ 181.8 (C4), 164.6 (C7), 163.1 (C2), 161.3 (C5), 157.3 (C9), 131.9 (C4′), 130.7 (C1′), 129.1 (C2′,C6′), 126.3 (C3′, C5′), 105.1 (C3), 103.8 (C10), 99.1 (C6), 94.1 (C8); ν_{max} (KBr): 3527 (OH-7), 3083 (OH-5), 1656 (C=O), 1609, 1580, 1556, 1445 (C=C) cm^{-1}; MS (EI) *m/z* 254 (M^+, 100), 226 (72), 152 (50), 105 (12), 102 (17), 77 (20).

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Supporting Information Available: Characterization data for all flavones. This material is available free of charge via the Internet at http://pubs.acs.org.

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