New Syntheses of 3-Aroylflavone Derivatives; Knoevenagel Condensation and Oxidation versus One-Pot Synthesis

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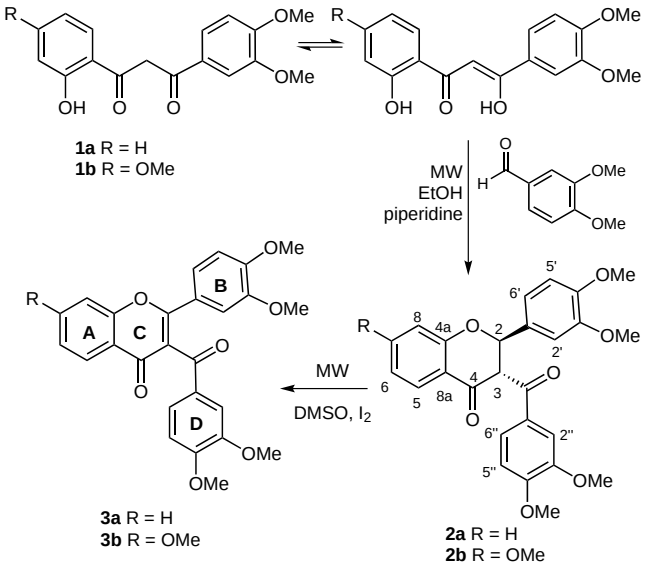
Abstract: Two syntheses of 3-aroylflavones have been established. In the first synthesis the use of microwave irradiation led to an improvement in the yields of both the Knoevenagel condensation of β-diketones with aldehydes to afford 3-aroylflavanones and of their oxidation to 3-aroylflavones. In the second and more general synthesis, a novel and efficient procedure for 3-aroylflavones involves a one-pot reaction between 2′-hydroxyacetophenones and aroyl chlorides in the presence of lithium bis(trimethylsilyl)amide.

Key words: Claisen condensation, Knoevenagel condensation, lithium bis(trimethylsilyl)amide, microwaves

Flavones constitute an important class of low molecular weight molecules widely distributed in the plant kingdom, where they impart interesting biological activities.[1] Among the naturally occurring flavones and their synthetic analogues, several compounds display anticancer,[2] anti-inflammatory[3] and antioxidant[4] activities, to mention a few examples. The presence of substituents at the flavone nucleus is considered to be an important structural feature. For instance, a few years ago we reported that 3-alkylflavones[5] and 3-(3,4-dihydroxybenzoyl)-3′,4′,5,7-tetrahydroxyflavone[5b] are potent antioxidant agents.

Recent growing interest in 3-aroylflavones has focused on other important pharmacological properties demonstrated by some derivatives, in particular the moderate antitubulin activity of 3-(3,4,5-trimethoxybenzoyl)-4′-methoxyflavone[6] and the potent topoisomerase I inhibitory activity of 3-(4-nitrobenzoyl)-7-benzoyloxy-4′-nitroflavone.[7] Consequently, a search for new or improved routes towards the synthesis of 3-aroylflavones is still a challenge. We have proven that microwave irradiation can dramatically improve the transformation of 2′,6′-bisaroyloxyacetophenones into the corresponding 3-aroylflavones through the Baker–Venkataraman rearrangement.[8] It was also reported that the Knoevenagel condensation of β-diketones (which exist in equilibrium with their enolic form) with aldehydes afforded 3-aroylflavanones, which were then oxidized to 3-aroylflavones, although in low overall yield.[6]

Following our interest in these compounds, we initiated a study on the synthesis of 3-aroylflavones and tried to improve this methodology by using microwave irradiation as an alternative source of energy (Scheme 1). 3-Aroylflavanones **2** were obtained in good yields (over 60%) (30 min at 300 W),[9–11] and their oxidation to 3-aroylflavones **3** were also performed in good yields (over 70%) (8 min at 500 W).[12–14]



Scheme 1

We then studied the one-pot synthesis of 3-aroylflavones by the reaction of 2′-hydroxyacetophenones with aroyl chlorides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base.[7] By treating acetophenone (1 equiv) with aroyl chloride (3 equiv) and DBU (3 equiv), in anhydrous pyridine at 70–80 °C (12–24 h), flavones were obtained as the main products (56–61%) and 3-aroylflavones as by-products (less than 5% yield).

Next we considered the reaction of 2′-hydroxyacetophenones with aroyl chlorides in the presence of LiHMDS as base. This base was already used in the synthesis of β-diketones, from ketones and aroyl chlorides,[15] from *O*-silyl-protected methyl salicylate with acetophenones,[16] and also from hydroxylated 2′-hydroxyacetophenones with acid chlorides.[17] We started by investigating the reaction of 2′-hydroxyacetophenone (**4a**) with benzoyl chloride (**5a**). Optimal conditions were established as the reaction of **4a** with **5a** (3 equiv) and base LiHMDS (4 equiv), followed by treatment with hydrochloric acid (20%),[18] to give 3-aroylflavone **6a** in good yield (67%). With lower amounts of benzoyl chloride and/or base, 2-acetylphenyl benzoate (**7**) was obtained as the major product (72%; Scheme 2). These results contradict the results

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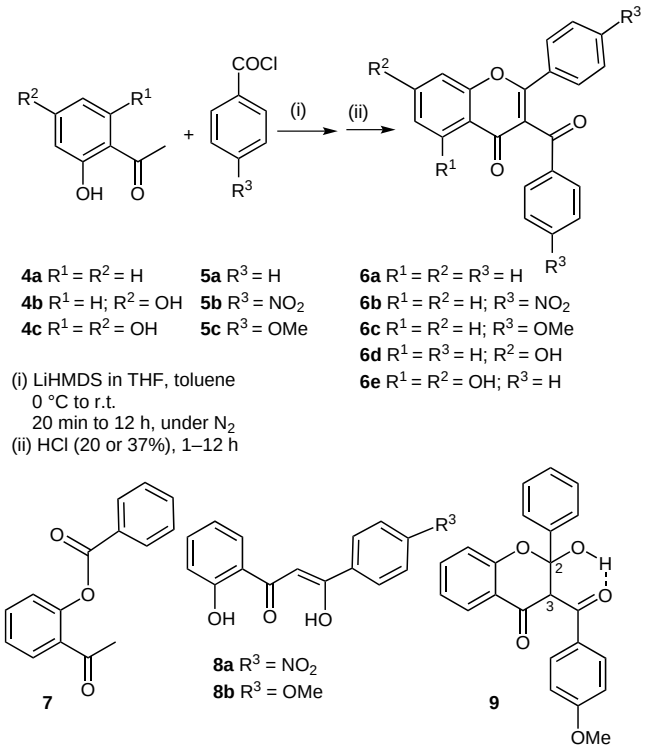
reported by Cushman and Nagarathnam,[17] who reported that C-2 aroylation of the acetophenone enolate took place rather than O-aroylation. Next, our study was extended to the use of *p*-nitro- and *p*-methoxybenzoyl chlorides (**5b** and **5c**). In these cases, a larger amount of the aroyl chloride derivative was necessary to obtain the desired 3-aroylflavones in good yields.[18] With lower amounts of LiHMDS or aroyl chloride, the (*Z*)-3-aryl-3-hydroxy-1-(2-hydroxyphenyl)prop-2-en-1-ones **8a** and **8b** were obtained as the major products (48–52%; Scheme 2).

Under the optimal conditions,[18] 4′-nitro-3-(4-nitrobenzoyl)flavone (**6b**) was obtained in very good yield,[19] but in the reaction of **4a** with *p*-methoxybenzoyl chloride (**5c**), the ^{1}H NMR spectrum of the obtained product showed, in addition to the 3-aroylflavone A, B and D ring proton resonances, two singlets at δ = 6.65 and 16.69 ppm.[20] The data indicate that we had not obtained the expected 3-aroylflavone **6c**, but, rather, the intermediate 2-hydroxy-3-(4-methoxybenzoyl)-2-(4-methoxyphenyl)chroman-4-one (**9**). The intramolecular hydrogen bond between the 2-hydroxyl proton and the 3-aroyl carbonyl group **9** deters water elimination (**9**; Scheme 2).[20] The referred singlets were assigned to the H-3 and 2-OH proton resonances, respectively.

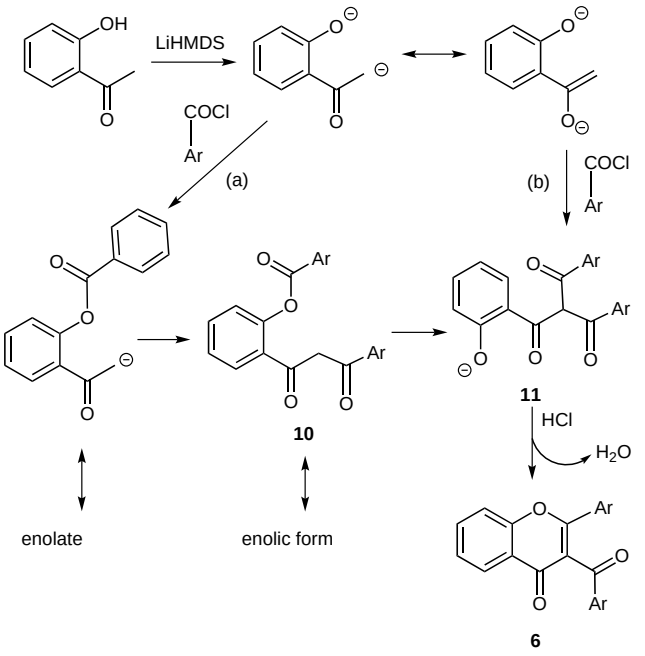
To overcome this problem we used commercial hydrochloric acid (37%), because we considered that the final acidification with 20% hydrochloric acid was not sufficient to induce water elimination. Under these conditions the desired 3-aroylflavone **6c** was obtained in good yield (72%), but only after stirring the reaction mixture at room temperature for eight hours (TLC analysis).



Scheme 2

The results indicate that both C- and O-aroylation may be occurring and an intermediate such as structure **10** can be formed (Scheme 3, path a). Compound **10** can be transformed into **11** through a base-catalyzed Baker–Venkataraman rearrangement; although structure **11** can also be obtained by bisaroylation of the C-2 acetophenone enolate (Scheme 3, path b). Finally, acid-catalyzed cyclization and water elimination leads to the expected 3-aroylflavones **6**.

The next step in our synthetic strategy was to use other 2′-hydroxyacetophenone derivatives **4b** and **4c** bearing extra hydroxyl groups, which give rise to important 3-aroylflavones that are suitable for biological evaluations. The desired products **6d** and **6e** were obtained in good yields (>50%), revealing the most challenging aspect of the work, which was the optimization of base and benzoyl chloride amounts and the reaction time needed to accomplish the synthesis. By this method it was possible to prepare polyhydroxy-3-aroylflavones without the need for protection and deprotection steps and also without the use of 2′,6′-dihydroxyacetophenone, which proceed through a bis-Baker–Venkataraman rearrangement.[8]



Scheme 3

In summary, we have established two successful methodologies to perform the synthesis of 3-aroylflavones. The first involves a Knoevenagel condensation followed by oxidation of the intermediate 3-aroylflavanones, under microwave irradiation. This methodology provides facile access to new derivatives in shorter reaction times and higher yields, although it is necessary to protect the hydroxyl groups of the starting material 2′-hydroxyacetophenone. The second approach constitutes a new and efficient one-pot synthesis of 3-aroylflavones, starting from hydroxylated 2′-hydroxyacetophenones and aroyl chlorides. To the best of our knowledge, this method rep-

resents the most efficient route for the synthesis of 3-aroylflavones. Application of this method in the synthesis of other pharmaceutically useful compounds is being pursued and the results will be disclosed in due course.

Acknowledgment

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(9) The optimal conditions were established after a study of the reaction times, ranging from 5 to 30 minutes, and microwave (MW) irradiation power, ranging from 200 to 500 W. The obtained results indicate that higher MW irradiation power gave lower yields (40–50%) and more degradation even when shorter reaction times were used. When using MW irradiation power lower than 300 W with shorter reaction times the starting β-diketones **1a** and **1b** were recovered (depending on the time and power 10–25%).
(10) **Optimized Experimental Procedure for the Synthesis of Flavanones 2a and 2b**: A mixture of the appropriate 1-(2-hydroxyaryl)-3-(3,4-dimethoxyphenyl)propan-1,3-dione **1a**,**b** (0.5 mmol), 3,4-dimethoxybenzaldehyde (0.25 g, 1.5 mmol) and piperidine (0.4 mmol) in EtOH (15 mL), was poured in a two-necked glassware apparatus equipped with a magnetic stirring bar, fibre-optic temperature control and reflux condenser, and was then irradiated in an Ethos SYNTH microwave (Milestone Inc.) at 300 W constant power for 30 min. After that period, the reaction mixture was poured into a mixture of ice (10 g) and water (30 mL) and the pH was adjusted to 2 with dilute HCl (10%). Finally, the mixture was extracted with $CHCl_3$ (3 × 20 mL), dried over sodium sulfate, and evaporated to dryness. The obtained residue was purified by column chromatography (EtOAc–hexane, 1:1). After solvent evaporation, the obtained residue was recrystallized from EtOH to give the expected 3-aroylflavanones **2a** (134 mg, 60%) or **2b** (163 mg, 68%).
(11) **3′,4′,7-Trimethoxy-3-(3,4-dimethoxyphenyl)flavanone 2b**: Yellow solid; mp 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, 3′-OCH_3), 3.84 (s, 3 H, 4′-OCH_3), 3.85 (s, 3 H, 7-OCH_3), 3.89 (s, 3 H, 3″-OCH_3), 3.91 (s, 3 H, 4″-OCH_3), 5.06 (d, *J* = 11.9 Hz, 1 H, H-3), 5.91 (d, *J* = 11.9 Hz, 1 H, H-2), 6.51 (d, *J* = 2.3 Hz, 1 H, H-8), 6.63 (dd, *J* = 2.3, 8.9 Hz, 1 H, H-6), 6.80 (d, *J* = 8.4 Hz, 1 H, H-5′), 6.83 (d, *J* = 8.4 Hz, 1 H, H-5″), 7.00 (br s, 1 H, H-2′), 7.02 (br d, *J* = 8.4 Hz, 1 H, H-6′), 7.40 (d, *J* = 1.9 Hz, 1 H, H-2″), 7.45 (dd, *J* = 1.9, 8.4 Hz, 1 H, H-6″), 7.86 (d, *J* = 8.9 Hz, 1 H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6, 55.7, 55.8, 55.9, 56.0 (5 × O*C*H$_3$), 58.7 (C-3), 82.2 (C-2), 100.8 (C-8), 109.9 (C-2′), 110.4 (C-5″), 110.5 (C-5′), 110.6 (C-6), 111.0 (C-2″), 114.4 (C-4a), 123.8 (C-6″), 129.1 (C-5), 129.8 (C-1′), 131.1 (C-1″), 148.9 (C-4′), 149.0 (C-3″), 149.4 (C-3′), 157.7 (C-4″), 163.2 (C-8a), 166.5 (C-7), 188.6 (C-4), 194.5 (C=O). Anal. Calcd for $C_{27}H_{26}O_8 \cdot 1/2\ H_2O$: C, 66.66; H, 5.39. Found: C, 66.52; H, 5.46.
(12) The optimal conditions were established after a complete study of the reaction conditions. The amount of iodine was optimized in order to prevent the formation of iodinated derivatives. MW irradiation power was optimized to 500 W; with less power, a longer reaction time (30 min) was needed to perform the complete oxidation into flavones, without improvement in the obtained yields, and with higher power there was more degradation and consequently a lower yield (40–56%).
(13) **Optimized Experimental Procedure for the Synthesis of 3-Aroylflavones 3a and 3b**: Iodine (5 mg, 0.02 mmol) was added to a solution of the appropriate 3′,4′-dimethoxy-3-(3,4-dimethoxybenzoyl)flavanone **2a** and **2b** (0.2 mmol) in DMSO (5 mL). The mixture was poured into a two-necked glassware apparatus equipped with a magnetic stirring bar, fibre-optic temperature control and reflux condenser, and was then irradiated in an Ethos SYNTH microwave (Milestone Inc.) at 500 W constant power for 8 min. After that period, the reaction mixture was poured into a mixture of ice (10 g) and water (20 mL), and $Na_2S_2O_3 \cdot 5H_2O$ was added. Finally, the mixture was extracted with $CHCl_3$ (3 × 20 mL), dried over sodium sulfate, and the organic solvent was evaporated to dryness. The residue was purified by preparative TLC (EtOAc–hexane, 1:1), affording 3-aroylflavones **3a** (70 mg, 78%) or **3b** (71 mg, 75%).
(14) **3′,4′-Dimethoxy-3-(3,4-dimethoxyphenyl)flavone (3a)**: Orange solid; mp 150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, 3′-OCH_3), 3.89 (s, 3 H, 4′-OCH_3), 3.90 (s, 3 H, 4″-OCH_3), 3.92 (s, 3 H, 3″-OCH_3), 6.80 (d, *J* = 8.4 Hz, 1 H, H-5″), 6.84 (d, *J* = 8.4 Hz, 1 H, H-5′), 7.19 (d, *J* = 2.0 Hz, 1 H, H-2′), 7.34 (dd, *J* = 2.0, 8.4 Hz, 1 H, H-6′), 7.44 (br d, *J* = 7.0, 8.0 Hz, 1 H, H-6), 7.48 (dd, *J* = 2.0, 8.4 Hz, 1 H, H-6″), 7.60 (br d, *J* = 8.0 Hz, 1 H, H-8), 7.62 (d, *J* = 2.0 Hz, 1 H, H-2″), 7.75 (ddd, *J* = 1.7, 7.0, 8.0 Hz, 1 H, H-7), 8.24 (dd, *J* = 1.7, 8.0 Hz, 1 H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7, 55.9, 56.0 (4 × O*C*H$_3$), 110.2 (C-5″), 110.3 (C-2″), 110.9 (C-5′), 111.2 (C-2′), 118.0 (C-8), 121.7 (C-1′), 122.1 (C-6′), 123.2 (C-3), 124.1 (C-4a), 125.3 (C-6″), 125.4 (C-6), 126.0 (C-5), 130.4 (C-1″), 134.1 (C-7), 148.8 (C-3″), 149.3 (C-3′), 151.6 (C-4′), 153.9 (C-4″), 155.9 (C-8a), 161.6 (C-2), 176.5 (C-4), 192.4 (C=O). Anal. Calcd

for $C_{26}H_{22}O_7 \cdot 1/2\ H_2O$: C, 68.56; H, 5.09. Found: C, 68.43; H, 5.10.

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(18) **Optimized Procedure for the Synthesis of 3-Aroylflavones 6a–e:** The appropriate acetophenone **4a–c** (1 mmol) was dissolved in toluene (5 mL) in a screw cap vial equipped with a magnetic stirring bar and sealed with a septum. The solution was cooled at 0 °C under nitrogen and LiHMDS (4.2 mL in THF, 4.2 mmol) was quickly added by using a syringe. The solution was stirred for approximately 5 min before the addition of aroyl chlorides **5a–c** (4 mmol) in one portion. The solution was then removed from the ice bath and stirred at room temperature [20 min (**6a**,**b**), 8 h (**6c**) and 12 h (**6d**,**e**)]. After that period, HCl (4 mL) [20% (**6a**,**b**) or 37% (**6c–e**)] was added and the resulting solution was stirred for 1 h (**6a**,**b**) or 8 h (**6d**,**e**) and then extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was then washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was purified by column chromatography (4:1, hexane–EtOAc; in the case of **6d**,**e** the eluent was CH_2Cl_2). After solvent evaporation and residue crystallization from EtOH, the expected 3-aroylflavones **6a–e** were obtained (**6a**: 218 mg, 67%; **6b**: 287 mg, 69%; **6c**: 278 mg, 72%; **6d**: 195 mg, 57%; **6e**: 183 mg, 51%).

(19) **4′-Nitro-3-(4-nitrophenyl)flavone (6b):** Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (ddd, *J* = 0.7, 7.2, 7.9 Hz, 1 H, H-6), 7.64 (br d, *J* = 7.9 Hz, 1 H, H-8), 7.81 (d, *J* = 7.0 Hz, 2 H, H-2″, H-6″), 7.85 (ddd, *J* = 1.6, 7.2, 7.9 Hz, 1 H, H-7), 8.08 (d, *J* = 7.0 Hz, 2 H, H-2′,6′), 8.24 (dd, *J* = 1.6, 7.9 Hz, 1 H, H-5), 8.27 (d, *J* = 7.0 Hz, 2 H, H-3″5″), 8.30 (d, *J* = 7.0 Hz, 2 H, H-3′,5′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.3 (C-8), 123.1 (C-4a), 123.2 (C-3), 124.1 (C-3″,5″), 124.2.0 (C-3′,5′), 126.2 (C-6), 126.6 (C-5), 129.7 (C-2″,6″), 130.2 (C-2′,6′), 135.3 (C-7), 137.1 (C-1′), 141.0 (C-1″), 149.4 (C-4″), 150.8 (C-4′), 156.0 (C-8a), 161.3 (C-2), 176.0 (C-4), 191.6 (C=O). MS (ESI$^+$): *m*/*z* (%) = 439 (100) [M + Na]$^+$. Anal. Calcd for $C_{22}H_{12}N_2O_7$: C, 63.47; H, 2.91; N, 6.73; Found: C, 63.60; H, 3.19; N, 6.27.

(20) **2-Hydroxy-4′-methoxy-3-(4-methoxyphenyl)flavanone (9):** Yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OC*H*$_3$), 3.88 (s, 3 H, OC*H*$_3$), 6.65 (s, 1 H, H-3), 6.80 (d, *J* = 8.3 Hz, 2 H, H-3″,5″), 6.98 (d, *J* = 8.8 Hz, 2 H, H-3′,5′), 7.29 (dd, *J* = 1.3, 7.9 Hz, 1 H, H-8), 7.39 (ddd, *J* = 1.3, 7.6, 7.7 Hz, 1 H, H-6), 7.56 (ddd, *J* = 1.8, 7.6, 7.9 Hz, 1 H, H-7), 7.67 (d, *J* = 8.3 Hz, 1 H, H-2″,6″), 7.93 (dd, *J* = 1.8, 7.7 Hz, 1 H, H-5), 8.20 (d, 8.8 Hz, 2 H, H-2′,6′), 16.69 (1 H, 2-O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4 (O*C*H$_3$), 55.5 (O*C*H$_3$), 96.4 (C-3), 105.0 (C-2), 113.7 (C-3″,5″), 114. 0 (C-3′,5′), 121.5 (C-1′), 123.9 (C-8), 126.2 (C-6), 127.9 (C-1″), 129.3 (C-2″,6″), 129.5 (C-4a), 129.8 (C-5), 132.5 (C-2′,6′), 149.0 (C-8a), 163.1 (C-4″), 164.1 (C-4′), 182.4 (C-4), 186.2 (C=O). MS (ESI$^+$): *m*/*z* (%) = 427 (100) [M + Na]$^+$. Anal. Calcd for $C_{24}H_{10}O_6$: C, 71.28; H, 4.98; Found: C, 70.95; H, 4.99.

