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# Efficient Liquid-Phase Synthesis of 2′-Hydroxychalcones

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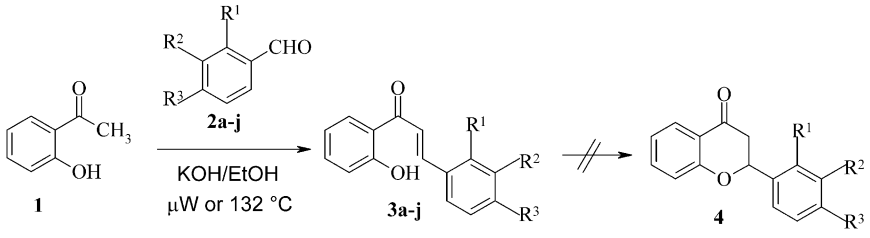
**Abstract**—The condensation of 2′-hydroxyacetophenone (**1**) with aromatic aldehydes (**2**) in a well closed vessel using microwave irradiation or classical heating at 132 °C, provides a fast and simple method for the liquid-phase synthesis of 2′-hydroxychalcones without formation of by-products. Antiproliferative activity of these compounds were evaluated using MCF-7 cells.


Natural chalcones and related synthetic analogues mediate a broad spectrum of biological responses including those that might be able to influence processes dysregulated during cancer development.[1,2] Many synthetic methods have been described to obtain 2′-hydroxychalcones.[3] Nevertheless, the Claisen–Schmidt condensation stays the most common method in homogeneous phase or in interfacial solid-liquid conditions using barium hydroxide catalyst (C-200).[4] Unfortunately 2′-hydroxychalcones always cyclized to flavanones.[5,6] One synthetic pathway to avoid this undesirable reaction is using protective group[7] or the Friedel–Crafts reaction of phenols with acyl halides.[8] This method request long reaction time and anhydrous conditions which limits the scope of its application.

In the last few years were published some microwave assisted methods for the synthesis of various chalcones.[9–11] These reaction procedures were not suitable for the preparation of 2′-hydroxychalcones. Our trials to reproduce some of them, which present the aldolic condensation between **1** and **2**,[9] gave a mixture of products and large amount of starting compounds. Obviously, the reaction conditions under μW needed more detailed investigation.

In this paper, we report convenient reaction procedure for the synthesis of 2′-hydroxychalcones with very good yields without formation of by-products (Scheme 1).

We applied successful microwave irradiation for the preparation of target molecules **3a**–**j**. The reaction took place in well closed pressure tube for 2 min with high yields (Table 1).[12] It is noteworthy to mention that all our trials to carry out the reaction in open vessel failed. A mixture of two products (**3** and **4**) and starting compounds was obtained in this case. Obviously, the well closed tube affords to reach temperatures much higher than boiling point of ethanol. The measured temperature in the reaction tube immediately after the irradiation was




**Scheme 1.**

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**Table 1.** Substituted 2′-hydroxychalcones prepared in this study

| Entry | $R^1$ | $R^2$ | $R^3$ | Observed MS[a] | Yield (%) |
|---|---|---|---|---|---|
| **3a** | H | H | H | 223 | 93 |
| **3b** | H | H | F | 241 | 93 |
| **3c** | H | H | Br | 301, 303 | 94 |
| **3d** | H | H | Me | 237 | 90 |
| **3e** | H | H | OMe | 253 | 89 |
| **3f** | H | OMe | OMe | 283 | 91 |
| **3g** | OMe | OMe | OMe | 313 | 87 |
| **3h** | H | H | $N(Me)_2$ | 266 | 93 |

Products show satisfactory H NMR[13] and MS data.
[a](M−1) peak. Negative electrospray experiments were conducted on Waters LCZ 2000 platform.

132 °C. To prove the microwave effect in this case we repeat the same experiments in the same vessel in oil bath at 132 °C. In these conditions reaction was complete for 3 min and also no by-products were detected, which means that the microwave irradiation is not important and could be replaced with classical heating at 132 °C for practically the same reaction time with the same yields. Longer irradiation as well as longer heating (more than 6 min) gave already a mixture of **3** and **4**.

In order to establish the general behaviour of this reaction under these conditions, several types of aromatic aldehydes **2** were studied (Table 1). We found out that both aldehydes with electon-withdrawing and electron-donating substituents react smoothly with 2′-hydroxyacetophenone (**1**). Secondary reactions, for example cyclisation of 2′-hydroxychalcone to flavanone, were not observed. This affords to avoid phenolic group protection as well as the use of interfacial solid-liquid catalyst such as barium hydroxide (C-200).

The growth inhibitory activity of the compounds was determined in the MCF-7 human breast cancer cell line using the MTT assay as described by Denizot et al.[14] and are reported in Figure. 1.

Compound **3c** showed interesting cytotoxic activity ($IC_{50} = 12.3\ \mu M$).

Our synthetic approach constitutes a simple and high yielding way for the development of flavonoid structurally-related compounds as pharmacological agents.[15,16]

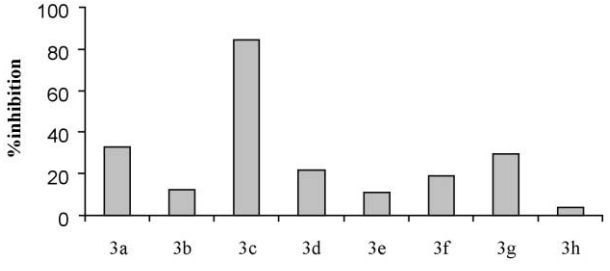


**Figure 1.** Antiproliferative activity: MCF-7 were incubated with chalcones at 20 μM for 6 days. Data points represent the mean values of three independent experiments and are expressed as percentage of control (untreated cells).

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12. In a typical procedure a mixture of 2′-hydroxyacetophenone (**1**) (1.36 g, 10 mmol) and the corresponding aromatic aldehyde **2** (10 mmol) in 20% KOH/EtOH (10 g) was filled into a 15-mL pressure tube (ALDRICH, with threaded type A plug, length 10.2 cm and additionally provided with a teflon ring) and placed in a beaker (200 mL). After irradiation in an ordinary domestic microwave oven (*Moulinex* CK3 with rotating plate) at 70 W for 2 min, or heating in oil bath at 132 °C for 3 min, the reaction mixture was cooled and poured into crushed ice water (100 mL). Then concd HCl (10 mL) was added and the reaction mixture was left to stay at 2–3 °C overnight. The separated solid was collected by filtration and recrystallized from methanol.
13. $^1$H NMR spectra were recorded in $CDCl_3$ using a Bruker 400 MHz spectrometer and $Me_4Si$ as internal standard. Compound **3a**: 6.95 (1H, ddd, 5′-H, $J_{5',6'} = 8.1$ Hz, $J_{5',4'} = 7.8$ Hz, $J_{5',3'} = 1.0$ Hz); 7.04 (1H, dd, 3′-H, $J_{3',4'} = 8.4$ Hz, $J_{3',5'} = 1.0$ Hz); 7.44 (3H, m, 3-, 4-, 5-H); 7.50 (1H, ddd, 4′-H, $J_{4',3'} = 8.4$ Hz, $J_{4',5'} = 7.8$ Hz, $J_{4',6'} = 1.5$ Hz); 7.67 (2H, m, 2- 6-H); 7.67 (1H, d, α-H, $J_{\alpha,\beta} = 15.4$ Hz); 7.93 (1H, d, β-H, $J_{\alpha,\beta} = 15.4$ Hz); 7.93 (1H, dd, 6′-H, $J_{6',5'} = 8.1$ Hz, $J_{6',4'} = 1.5$ Hz); 12.81 (1H, s, 2′-OH). Compound **3b**: 6.93 (1H, ddd, 5′-H, $J_{5',6'} = 7.9$ Hz, $J_{5',4'} = 7.7$ Hz, $J_{5',3'} = 0.8$ Hz); 6.94 (2H, d, 3- 5-H, $J_{3,2} = J_{5,6} = 8.7$ Hz); 7.02 (1H, dd, 3′-H, $J_{3',4'} = 8.0$ Hz, $J_{3',5'} = 0.8$ Hz); 7.49 (1H, ddd, 4′-H, $J_{4',3'} = 8.0$ Hz, $J_{4',5'} = 7.7$ Hz, $J_{4',6'} = 1.2$ Hz); 7.54 (1H, d, α-H, $J_{\alpha,\beta} = 15.5$ Hz); 7.90 (1H, d, β-H, $J_{\alpha,\beta} = 15.5$ Hz); 7.92 (1H, dd, 6′-H, $J_{6',5'} = 7.9$ Hz, $J_{6',4'} = 1.2$ Hz); 12.94 (1H, s, 2′-OH). Compound **3c**: 6.95 (1H, ddd, 5′-H, $J_{5',6'} = 8.1$ Hz, $J_{5',4'} = 7.6$ Hz, $J_{5',3'} = 0.8$ Hz); 7.04 (1H, dd, 3′-H, $J_{3',4'} = 8.4$ Hz, $J_{3',5'} = 0.8$ Hz); 7.51 (1H, ddd, 4′-H, $J_{4',3'} = 8.4$ Hz, $J_{4',5'} = 7.6$ Hz, $J_{4',6'} = 1.3$ Hz); 7.52 (2H, d, 2- 6-H, $J_{2,3} = J_{6,5} = 8.5$ Hz); 7.58 (2H, d, 3-, 5-H, $J_{3,2} = J_{5,6} = 8.5$ Hz); 7.64 (1H, d, α-H, $J_{\alpha,\beta} = 15.5$ Hz); 7.85 (1H, d, β-H, $J_{\alpha,\beta} = 15.5$ Hz); 7.90 (1H, dd, 6′-H, $J_{6',5'} = 8.1$ Hz, $J_{6',4'} = 1.3$ Hz); 12.73 (1H, s, 2′-OH). Compound **3d**: 2.40 (3H, s, 4-$CH_3$); 6.94 (1H, ddd, 5′-H, $J_{5',6'} = 7.9$ Hz, $J_{5',4'} = 7.7$ Hz, $J_{5',3'} = 1.0$ Hz); 7.02 (1H, dd, 3′-H, $J_{3',4'} = 8.4$ Hz,

$J_{3',5'} = 1.0$ Hz); 7.24 (2H, d, 3-, 5-H, $J_{3,2} = J_{5,6} = 8.1$ Hz); 7.49 (1H, ddd, 4′-H, $J_{4',3'} = 8.4$ Hz, $J_{4',5'} = 7.7$ Hz, $J_{4',6'} = 1.4$ Hz); 7.56 (2H, d, 2-, 6-H, $J_{2,3} = J_{6,5} = 8.1$ Hz); 7.62 (1H, d, α-H, $J_{\alpha,\beta} = 15.5$ Hz); 7.91 (1H, d, β-H, $J_{\alpha,\beta} = 15.5$ Hz); 7.92 (1H, dd, 6′-H, $J_{6',5'} = 7.9$ Hz, $J_{6',4'} = 1.4$ Hz); 12.87 (1H, s, 2′-OH). Compound **3e**: 3.87 (3H, s, 4-$OCH_3$); 6.93 (1H, ddd, 5′-H, $J_{5',6'} = 8.0$ Hz, $J_{5',4'} = 7.8$ Hz, $J_{5',3'} = 0.8$ Hz); 6.95 (2H, d, 3-, 5-H, $J_{3,2} = J_{5,6} = 8.8$ Hz); 7.02 (1H, dd, 3′-H, $J_{3',4'} = 8.4$ Hz, $J_{3',5'} = 0.8$ Hz); 7.49 (1H, ddd, 4′-H, $J_{4',3'} = 8.4$ Hz, $J_{4',5'} = 7.8$ Hz, $J_{4',6'} = 1.4$ Hz); 7.54 (1H, d, α-H, $J_{\alpha,\beta} = 15.4$ Hz); 7.63 (2H, d, 2-, 6-H, $J_{2,3} = J_{6,5} = 8.8$ Hz); 7.90 (1H, d, β-H, $J_{\alpha,\beta} = 15.4$ Hz); 7.92 (1H, dd, 6′-H, $J_{6',5'} = 8.0$ Hz, $J_{6',4'} = 1.4$ Hz); 12.93 (1H, s, 2′-OH). Compound **3f**: 3.94* (3H, s, 4-$OCH_3$); 3.97* (3H, s, 3-$OCH_3$); 6.92 (1H, d, 5-H, $J_{5,6} = 8.3$ Hz); 6.94 (1H, ddd, 5′-H, $J_{5',6'} = 8.0$ Hz, $J_{5',4'} = 7.7$ Hz, $J_{5',3'} = 0.9$ Hz); 7.02 (1H, dd, 3′-H, $J_{3',4'} = 8.3$ Hz, $J_{3',5'} = 0.9$ Hz); 7.17 (1H, d, 2-H, $J_{2,6} = 1.9$ Hz); 7.27 (1H, dd, 6-H, $J_{6,5} = 8.3$ Hz,$J_{6,2} = 1.9$ Hz ); 7.49 (1H, ddd, 4′-H, $J_{4',3'} = 8.3$ Hz, $J_{4',5'} = 7.7$ Hz, $J_{4',6'} = 1.4$ Hz); 7.52 (1H, d, α-H, $J_{\alpha,\beta} = 15.4$ Hz); 7.89 (1H, d, β-H, $J_{\alpha,\beta} = 15.4$ Hz); 7.93 (1H, dd, 6′-H, $J_{6',5'} = 8.0$ Hz, $J_{6',4'} = 1.4$ Hz); 12.92 (1H, s, 2′-OH); [* HMBC data were used to assign proton resonances]. Compound **3g**: 3.90* (3H, s, 3-$OCH_3$); 3.93* (3H, s, 4-$OCH_3$); 3.98* (3H, s, 2-$OCH_3$); 6.74 (1H, d, 5-H, $J_{5,6} = 8.8$ Hz); 6.94 (1H, ddd, 5′-H, $J_{5',6'} = 8.1$ Hz, $J_{5',4'} = 7.7$ Hz, $J_{5',3'} = 0.9$ Hz); 7.02 (1H, dd, 3′-H, $J_{3',4'} = 8.4$ Hz, $J_{3',5'} = 0.9$ Hz); 7.40 (1H, d, 6-H, $J_{6,5} = 8.8$ Hz); 7.49 (1H, ddd, 4′-H, $J_{4',3'} = 8.4$ Hz, $J_{4',5'} = 7.7$ Hz, $J_{4',6'} = 1.4$ Hz); 7.72 (1H, d, α-H, $J_{\alpha,\beta} = 15.5$ Hz); 7.92 (1H, dd, 6′-H, $J_{6',5'} = 8.1$ Hz, $J_{6',4'} = 1.4$ Hz); 8.10 (1H, d, β-H, $J_{\alpha,\beta} = 15.5$ Hz); 12.97 (1H, s, 2′-OH); (* HMBC data were used to assign proton resonances). Compound **3h**: 3.06 (6H, s, 4-$N(CH_3)_2$); 6.70 (2H, d, 3-, 5-H, $J_{3,2} = J_{5,6} = 8.8$ Hz); 6.92 (1H, ddd, 5′-H, $J_{5',6'} = 8.6$ Hz, $J_{5',4'} = 7.6$ Hz, $J_{5',3'} = 0.9$ Hz); 7.00 (1H, dd, 3′-H, $J_{3',4'} = 8.4$ Hz, $J_{3',5'} = 0.9$ Hz); 7.46 (1H, ddd, 4′-H, $J_{4',3'} = 8.4$ Hz, $J_{4',5'} = 7.6$ Hz, $J_{4',6'} = 1.2$ Hz); 7.46 (1H, d, α-H, $J_{\alpha,\beta} = 15.2$ Hz); 7.57 (2H, d, 2- 6-H, $J_{2,3} = J_{6,5} = 8.8$ Hz); 7.92 (1H, d, β-H, $J_{\alpha,\beta} = 15.2$ Hz); 7.93 (1H, dd, 6′-H, $J_{6',5'} = 8.6$ Hz, $J_{6',4'} = 1.2$ Hz); 13.19 (1H, s, 2′-OH).

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