

## Microwave-Accelerated Synthesis of Flavanones through Oxidative Cyclization of 2'-Hydroxychalcones Using Acetic Acid as a Sole Catalyst

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### Abstract

Under microwave irradiation conditions, 2'-hydroxy chalcones **1a-c** underwent AcOH-mediated cyclization in oxa-Michael addition manner to afford flavanones **2a-c** in acceptable yields (up to 82%). These reactions proceeded in a shorter reaction time (~ 30 min) through microwave activation; otherwise, the reaction would take several days and even weeks, if a conventional heating process was employed. For example, cyclization of (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (**1a**) has required 4 days of stirring with AcOH (0.25 M), under conventional heating at 100 °C, to produce 2-phenylchroman-4-one (**2a**), in 75% yield; while under microwave conditions, the reaction has yielded 82% of compound **2a**, after 30 min. Thus obtained products **2a-c** were fully characterized by recording of melting point together with UV, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectra.

**Keywords:** Catalysis, Flavonoids, Green chemistry, Michael reaction, Microwave synthesis, Oxygen heterocycles.

### Introduction

Naturally, flavanones are present in citrus plants such as lemons, orange, grapes, etc [1, 2]. Flavanones show strong antioxidant and radical scavenging activities; therefore, they are associated in reduction of chronic diseases, and

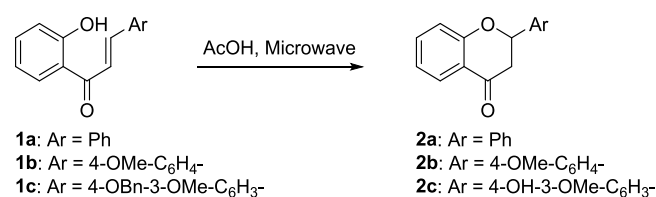
prevention of cardiovascular disorders and cancers [3]. Flavanones also exhibit antiviral, antimicrobial and anti-inflammatory activities; beneficial effects on capillary fragility; inhibition of human platelet aggregation; and antiulcer, antiallergenic and hypotensive properties [4, 5].

HLBT-100 (5,3'-dihydroxy-6,7,8,4'-tetramethoxy flavanone) has been shown to possess a high anticancer activity to inhibit brain cancer, breast cancer, leukemia, melanoma, and neuroblastoma [6].

Synthesis of flavanones **2** has been carried out by intramolecular cyclization of 2'-hydroxy chalcones **1** in the presence of acids [7, 8], bases [9, 10, 11], silica gel [12], MgO [13], Lewis acids [14, 15, 16], and under various conditions of photolysis [17], thermolysis [18] or electrolysis [19], etc. Recently, CH<sub>3</sub>SO<sub>3</sub>H, H<sub>3</sub>PO<sub>4</sub>, or piperidine is appeared as the most efficient acid or base catalyst for the cyclization of **1** into **2** [20, 21, 22, 23]. More recently, asymmetric synthesis of flavanones **2** from 2'-hydroxychalcones **1** has been achieved by using chiral quaternary ammonium salts and organocatalysts [24, 25, 26]. In nature, the enzyme chalcone isomerase catalyzes the cyclization to produce (2*S*)-flavanones [27, 28, 29, 30].

In the recent past, microwave-assisted synthesis has emerged as a new tool in organic synthesis [31, 32]. A shortened reaction time, higher yield, ease of manipulation, and cost economy are the major advantages. Earlier, household microwave ovens were used to demonstrate the microwave-assisted cyclization of 2'-hydroxy chalcones **1** to flavanones **2** in the presence of CF<sub>3</sub>CO<sub>2</sub>H or Et<sub>3</sub>N [33, 34]. Varma and Saini [35] have reported the microwave-assisted cyclization of nitrogen analogs of 2'-hydroxy chalcones (i.e. 2'-amino chalcones) to 2-aryl-1,2,3,4-tetrahydro-4-quinolones on montmorillonite K-10 clay surface. Herein, we report the AcOH-mediated cyclization of 2'-hydroxy chalcones **1** under microwave

irradiation to afford flavanones **2** in good to moderate yields (Scheme 1).



**Scheme 1.** Microwave-accelerated synthesis of flavanones (this work).

## Materials and Methods

### Chemicals and equipment

Acetic acid was distilled and stored under an argon atmosphere. All other chemicals purchased were of analytical grade and used without further purification. For reaction monitoring, pre-coated thin-layer chromatography (TLC) plates (Silica gel 60 F<sub>254</sub>) were procured from Merck. For column chromatography, silica gel (100–200 Mesh, Fisher Scientific) was used. A microwave synthesis reactor (Monowave 300, Anton Paar) was used for the synthesis. Melting point (M.p.) was determined by the open capillary method and was uncorrected. UV spectra were recorded with a Cary 60 UV-visible spectrophotometer (Agilent). <sup>1</sup>H- and <sup>13</sup>C- NMR spectra were measured using a JEOL JNM-ECS 400 and Bruker NMR spectrophotometers. Substrates 2'-hydroxy chalcones **1a-c** were synthesized following the reported procedure [36].

### General procedure for the cyclization of 2'-hydroxy chalcones to flavanones under conventional heating (reaction optimization)

Model substrate (*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (**1a**, 0.5 mmol, 112 mg)

and 10 mol% of the catalyst ( $\text{Pd}(\text{OAc})_2$ ,  $\text{PdCl}_2$ ,  $\text{Pd}(\text{CF}_3\text{CO}_2\text{H})_2$ ,  $\text{PtBr}_2$ ,  $\text{CuCl}_2$  or  $\text{CuCl}$ ) were taken in a Schlenk tube under argon atmosphere. To this was added AcOH (2 mL) *via* a syringe. The reaction mixture was stirred at 100 °C for several days (4–7 days) with continuous reaction monitoring by TLC (hexane/ethyl acetate, 4:1). Thereafter, the reaction mixture was cooled to room temperature, passed through a short column of silica gel using ethyl acetate as an eluent and then the solvent was evaporated. The residue obtained was purified by column chromatography using mixtures of hexane and ethyl acetate (99:1, 98:2, 95:5, and 90:10) to afford 2-phenylchroman-4-one (**2a**).

### General procedure for the cyclization of 2'-hydroxy chalcones to flavanones under microwave irradiation

In a microwave vial (G10) containing a magnetic stirrer, 2'-hydroxy chalcones **1** (0.5 mmol) and AcOH (2 mL). The vial was capped and then kept in the vial holder of Monowave 300. The reaction mixture was irradiated with microwave at 200 °C for 15 min. TLC monitoring (hexane/ethyl acetate, 4:1) showed incomplete conversion, hence the process was repeated for another 15 min. After cooling, the reaction mixture was transferred into a round bottom flask using ethyl acetate, and the solvent was evaporated using a rotary evaporator to obtain a residue. The residue was purified by column chromatography using mixtures of hexane and ethyl acetate (99:1, 98:2, 95:5 and 90:10) to afford corresponding flavanones **2**.

### Data analysis of the synthesized flavanones

*2-Phenylchroman-4-one, flavanone (2a)*: Yield 92 mg, 82%. M.p. 77 °C (reported 76 °C) [23].  $R_f$  = 0.64 (silica gel, hexane/ethyl acetate, 4:1). UV (MeOH)  $\lambda_{\text{max}}$  nm: 359, 247, 219.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 7.94 (dd,  $J$  = 8, 1.6 Hz, 1H), 7.54–7.37 (m, 6H), 7.08–7.04 (m, 2H), 5.48 (d,  $J$  = 13.2, 2.8 Hz, 1H), 3.10 (dd,  $J$  = 16.8, 13.2 Hz, 1H), 2.90 (dd,  $J$  = 17.2, 2.8 Hz, 1H) [37].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm: 192.20, 161.74, 138.91, 136.41, 129.05, 128.98, 127.25, 126.34, 121.81, 121.12, 118.32, 79.80, 44.88 [37].

*2-(4-Methoxyphenyl)chroman-4-one, 4'-methoxyflavanone (2b)*: Yield 70 mg, 55%. M.p. 92 °C (reported 93–94 °C) [21].  $R_f$  = 0.62 (silica gel, hexane/ethyl acetate, 4:1).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm: 7.88 (dd,  $J$  = 8, 1.8 Hz, 1H), 7.61–7.56 (m, 4H), 7.12–7.04 (m, 3H), 5.60 (dd,  $J$  = 13.1, 2.8 Hz, 1H), 3.87 (s, 3H), 3.22 (dd,  $J$  = 16.7, 13.1 Hz, 1H), 2.85 (dd,  $J$  = 17.2, 2.8 Hz, 1H) [38].  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm: 192.10, 162.54, 160.91, 136.81, 132.24, 128.98, 128.91, 127.45, 122.12, 121.91, 118.92, 114.88, 114.82, 80.20, 55.65, 44.88 [38].

*2-(4-Hydroxy-3-methoxyphenyl)chroman-4-one, 4'-hydroxy-3'-methoxyflavanone (2c)*: Yield 99 mg, 73%.  $R_f$  = 0.61 (silica gel, hexane/ethyl acetate, 4:1). UV (MeOH)  $\lambda_{\text{max}}$  nm: 379, 321, 280, 252, 222.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  ppm: 7.94 (dd,  $J$  = 9, x Hz, 1H), 7.51 (dt,  $J$  = 9, 3 Hz, 1H), 7.08–6.96 (m, 5H), 5.75 (s, 1H), 5.41 (dd,  $J$  = 12, 3 Hz, 1H), 3.94 (s, 3H), 3.11 (dd,  $J$  = 18, 12 Hz, 1H), 2.86 (dd,  $J$  = 18, 3 Hz, 1H) (Figure 1).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  ppm: 192.31,

161.71, 146.91, 146.31, 136.31, 130.74, 127.20, 121.72, 121.06, 119.73, 118.27, 114.68, 108.97, 79.83, 56.15, 44.81.

## Results and Discussion

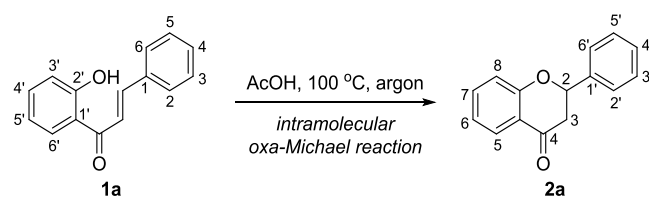
In the past few years, we have focused on the synthesis of flavonoids and evaluating their bioactivities [36, 39, 40, 41]. 2'-Hydroxychalcones **1**, members of a flavonoid group, possess  $\alpha,\beta$ -unsaturated ketone structural motif and can undergo intramolecular oxa-Michael reaction to provide cyclized product(s) – flavones and/or flavanones. First, we sought that transition metal or Lewis acid catalysts would efficiently promote the cyclization of **1** to afford flavones in accordance with a catalytic nucleophilic addition or oxidative cyclization involving carbon-carbon multiple bonds [42, 43]. Hence in our early attempts, we have treated the model substrate 2'-hydroxychalcone

(**1a**) with 10 mol% of Pd(OAc)<sub>2</sub> in AcOH under argon atmosphere (Table 1, entry 1). The reaction mixture was stirred at 100 °C for 5 days to afford flavanone (**2a**), in 70% isolated yield, and the corresponding flavone could not be

obtained. When the same reaction was performed in the presence of a stoichiometric amount of *p*-benzoquinone as an oxidant, the product **2a** was obtained in 75% yield, after 4 days (entry 2). The

reactions did not promote at all even after prolonged heating when toluene, isoamyl alcohol, DMF and nitromethane were used as solvents. Changing to other Pd(II) catalysts resulted inferior results (entries 3 and 4). We also screened some Lewis acid catalysts for the cyclization reaction; however, the result was not improved (entries 5–8). The cyclization reaction was proceeded in equal effectiveness even in the absence of a catalyst despite requiring of a longer reaction time (entry 9).

**Table 1.** Optimization of the reaction conditions for the cyclization of 2'-hydroxychalcone (**1a**) to flavanone (**2a**) under conventional heating



Entry	Catalyst (10 mol%)	Additive (1 equiv)	Time (days)	Isolated yield (%)
1	Pd(OAc) <sub>2</sub>	-	5	70
2	Pd(OAc) <sub>2</sub>	<i>p</i> -Benzoquinone	4	75
3	PdCl <sub>2</sub>	<i>p</i> -Benzoquinone	4	48
4	Pd(CF <sub>3</sub> CO <sub>2</sub> H) <sub>2</sub>	<i>p</i> -Benzoquinone	4	60
5	PtB <sub>2</sub>	-	7	69
6	CuCl	-	7	62
7	CuCl <sub>2</sub> ·2H <sub>2</sub> O	-	7	37
8	PtB <sub>2</sub> + CuCl <sub>2</sub>	-	7	43
9	No catalyst	-	4	75

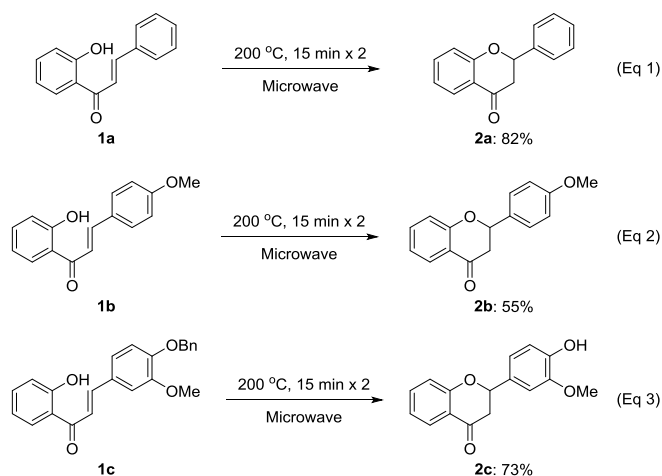
It has been reported that cyclization of 2'-hydroxychalcones **1** to flavanones **2** is proceeded in the presence of an acid or a base [44, 45]. In the acid-catalyzed cyclization, the chalcone is

refluxed in the presence of HCl, H<sub>2</sub>SO<sub>4</sub>, H<sub>3</sub>PO<sub>4</sub> or CH<sub>3</sub>SO<sub>3</sub>H in water, acetic acid or ethanol as a solvent [22, 33]. However, this transformation usually suffered from incomplete conversion, formation of pairs of chalcone-flavanone isomers and also requires a long reaction time due to slow reactivity of the chalcone for the acceptable equilibrium shift. It did not surprise us that these acid-catalyzed Michael reaction proceeded smoothly due to their strong acidity (pK<sub>a</sub> values of HCl = -8, H<sub>2</sub>SO<sub>4</sub> = -3, H<sub>3</sub>PO<sub>4</sub> = 2.12 and CH<sub>3</sub>SO<sub>3</sub>H = -2.6) [46]. On the other hand, basic conditions are seldom used because of possibility of the product decomposition or retroaldol reaction. Therefore, finding of a milder reaction condition for this transformation allowing a good equilibrium shift in a forward direction is highly desirable. These facts encouraged us to study the scope of the reaction in AcOH, a mild organic acid with a pK<sub>a</sub> value of 4.76 [46].

A brief literature survey revealed that there are scarce examples of using of acetic acid for the cyclization of chalcones to obtain precious flavanone intermediates, particularly exemplified in the total synthesis of a few target molecules [47, 14]. As an example, Sagrera and Seoane [33] have mentioned that refluxing of 2'-hydroxy-4-methoxychalcone (**1b**) with AcOH for a long reaction time (3 days) produce 4'-methoxyflavanone (**2b**), albeit in a low yield (55%). The authors have further utilized CF<sub>3</sub>CO<sub>2</sub>H for the same transformation. Trifluoroacetic acid (pK<sub>a</sub> = -0.25) [46] is comparably a stronger acid with an acid ionisation constant approximately 34,000 times higher than acetic acid [48]. Therefore, it is not surprising that

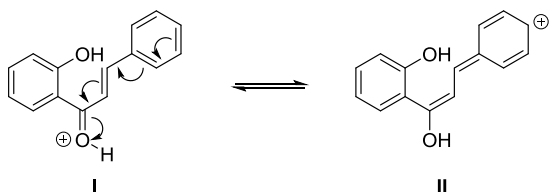
CF<sub>3</sub>CO<sub>2</sub>H has effectively promoted the cyclization of **1** to **2** under microwave irradiation with a maximum 2/1 ratio of 5.36 [33]. The reported reaction also received the synergistic benefit by using silica gel support, since silica gel alone can also promote the cyclization as reported by Sangwan *et al.* [12]. Therefore, we thought to perform a microwave synthesis in order to reduce the reaction time and increase the product yield in the present AcOH-mediated cyclization of 2'-hydroxychalcones **1**.

When 2'-hydroxychalcone (**1a**) and 2'-hydroxy-4-methoxychalcone (**1b**) in AcOH were irradiated with microwaves under program-controlled conditions using a Monowave 300, the corresponding cyclized products flavanone (**2a**) and 4'-methoxyflavanone (**2b**) were obtained in 82 and 55% isolated yields, respectively (Eqs 1 and 2). Under similar microwave conditions, 2'-hydroxy-4-benzyloxy-3-methoxychalcone (**1c**) underwent cyclization as well as deprotection of the benzyl group at the same time affording 4'-hydroxy-3'-methoxyflavanone (**2c**) in 73% yield (Eq 3).



Mechanistically, the present AcOH-mediated cyclization of 2'-hydroxy chalcones **1** to

flavanones **2** proceeds as follows. The carbonyl oxygen of 2'-hydroxy chalcone (**1a**) protonates by acetic acid to give its resonances **I** and **II**, which undergo a ring closure to produce flavanone (**2a**).



## Conclusion

In conclusion, we have shown the viability of the formation of flavanones **2** by oxa-Michael cyclization of 2'-hydroxychalcones **1** by heating solely with acetic acid under microwave conditions. In this present microwave-accelerated reaction, the products were obtained in up to 82% yield, within 30 min of reaction time; unless otherwise, it required several days under conventional heating procedure. A few demonstrated examples unveil a hitherto unfocused strategy to produce the valuable products. Further extension of this work by introducing heterocyclic rings is underway in our laboratory.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the work reported in this paper.

## Additional Information

No additional information is available for this paper.

## Author Contribution

Conceived and designed the experiments: GBB. Performed the experiments: RD, ST. Analyzed the data: GBB, RD, ST. Wrote the paper: GBB.

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