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Microwave Activation: Highly Efficient Hydrolysis of Hesperidin and Naringin and Synthesis of Their Aglycone Acetates Under Microwave Irradiation †

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Abstract: Acidic hydrolysis of Hesperidin and Naringin, furnishing their aglycone moieties Hesperetin and Naringenin, respectively, is reported using sulfuric acid and water as a solvent, under microwave irradiation. This new economical procedure provides flavanones in very good yields, ~90% better than that of acid hydrolysis in reflux. Furthermore, we describe for the first time an efficient synthesis of Hesperetin-triacetate and Naringenin-triacetate from the corresponding flavanones, in the presence of 4-(*N*,*N*-dimethylamino)-pyridine DMAP as a catalyst, under microwave irradiation.

Keywords: hesperidin; naringin; hesperetin; naringenin; DMAP; microwave

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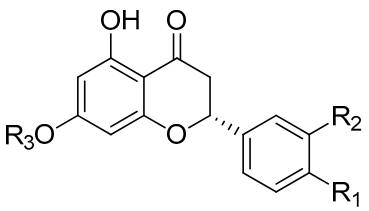
1. Introduction

Flavonoids are a group of naturally occurring polyphenolic compounds ubiquitously found in fruits and vegetables [1]. Citrus fruits such as *Citrus sinensis*, *Citrus x paradisi* L, *Citrus reticulata*, and *Citrus aurantium* are the major sources of flavonoids for humans [2]. Hesperidin (**1**) and Naringin (**2**) are inexpensive products (Figure 1) which occur almost exclusively in citrus fruits. A number of pharmacological properties of Hesperidin **1** and Naringin **2** have been reported.



1 R_1=R_4=OH, R_2=H, R_3=O-neohesperidose, **Hesperidin**
2 R_1=OCH_3, R_2=R_4=OH, R_3= O-rutinoside, **Naringenin**
3 R_1=R_2=R_3=R_4=OH, **Hesperitin**
4 R_1=OCH_3, R_2=R_3=R_4=OH, **Naringin**

Figure 1. Flavonoids and flavanones from *Citrus*.

Hesperidin (**1**) has been reported to have anti-cholesterol inhibition, antioxidant, antimutagenic, anti-hypertensive, diuretic, antidiabetic, and anti-carcinogenic properties [3–5].

Naringin (**2**) was also proven to have hypocholesterolaemic effects, hypoglycemic, and anti-inflammatory properties [6].

Hesperidin has been reported to have many biological activities, including antibacterial, anti-viral, immunomodulatory, and anti-cancer properties [7]. Hesperidin plays a beneficial role in disorders associated with the central nervous system and is an active antioxidant [8].

Naringenin has antidiabetic, anti-cancer, antimicrobial, anti-obesity, gastroprotective, immunomodulator, cardioprotective, nephroprotective, and neuroprotective properties [9].

2. Results and Discussion

Acidic hydrolysis of Hesperidin (**1**) and Naringin (**2**) has given their aglycone moieties Hesperetin (**3**) and Naringenin (**4**), respectively (Figure 2). The hydrolysis took place with sulfuric acid and water as a solvent, under microwave irradiation (Figure 2). This new economical procedure provides flavanones in very good yields, ~90% better than that of acid hydrolysis in reflux.

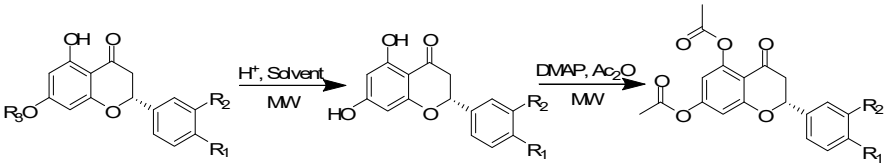


Figure 2. Hydrolysis and acetates formation under microwave irradiation.

Hesperetin and Naringenin are water soluble and their acetates are liposoluble. The formation of polyacetate makes it possible to increase the liposolubility of flavanones while being prodrugs, because the acetates are easily hydrolyzable into flavanones in living beings.

For thermal reactions, the products **5**–**6** were obtained after 24 h by mixing 5 mmol of flavanones **2**–**5** in 60 mL acetic anhydride with average yields. In contrast, the acylation reaction gives a sufficient yield using the microwave (600 W, 180 °C, 6.6 bars) better than in reflux, which increases the yield from 60–75% to about 90–95%).

Furthermore, we describe for the first time, an efficient synthesis of Hesperetin-triacetate (95%) and Naringenin-triacetate (97%) from the corresponding flavanones, in the presence of 4-(*N*,*N*-dimethylamino)-pyridine DMAP as a catalyst, under microwave irradiation (Figure 2).

DMAP is a known catalyst for alcohol esterification [10].

3. Experimental

3.1. Extractions of Flavonoids

Hesperidin **1** was extracted and purified from *Citrus sinensis* peels. Air-dried peels of *Citrus sinensis* (40 g) were extracted using a Soxhlet extractor with 500 mL of petroleum ether (40–60 °C) until the siphoned liquid became colorless for 2 h. After, the extraction was continued the second time and 300 mL of methanol was added over a period of 2 h. The methanol extract was evaporated at 65 °C in a vacuum and the solid residue was crystallized in aqueous acetic acid.

Naringin **2** was extracted with methanol and crystallized in water according to the literature [11].

*3.2. O**1** and Naringin **2***

Hesperetin **3** and Naringenin **4** were obtained by hydrolysis of 1 g of Hesperidin **1** or Naringin **2** in 10 mL of water with 0.5 mL of H_2SO_4 heated to 120 °C, irradiated by a microwave at 2450 MHz in a resonance cavity Anton Paar Monowave 300 for 10 min.

The yellow solutions were filtered and crystallized with ethanol to give the desired product, Hesperetin **3** or Naringenin **4**, respectively.

Under this condition, a significant increase in yield of **3** and **4** to 90% was observed in a very short reaction time in comparison to reflux conditions (yield about 70%).

3.3. Catalytic Esterification of Flavanones **2**–**5**

The acetates **5**, **6** were obtained from 1.6 mmol flavanones **3**, **4** with 10 mL of Ac2O in the presence of DMAP (0.1 mmol] as a catalyst under microwave irradiation for 5 min (monitored by TLC). The structures of products **5**, **6** were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS spectral data.

4. Conclusions

In conclusion, a new and original method, the efficient and economical use of acid hydrolysis of Hesperidin and Naringin to provide their aglycones in the presence of water as a solvent, has been described under microwave irradiation. The triacetates of their aglycones **5**, **6** were conveniently obtained with DMAP as a catalyst under microwave irradiation.

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Conflicts of Interest: The authors declare no conflicts of interest.

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