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

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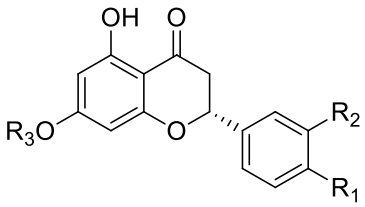
Abstract: Acidic hydrolysis of Hesperidin and Naringin, furnishing their aglycone moieties Hesperetin and Naringenin respectively, is reported using sulfuric acid and water as solvent, under microwave irradiation. This new economical procedure provides the flavanones in very good yields ~90%, better than 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 catalyst, under microwave irradiation.

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

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 Citrus x paradisi* L, *Citrus reticulata*, *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 agrumes. A number of pharmacological properties of Hesperidin **1** and Naringin **2** have been reported.

Hesperidin (**1**) has been reported to have anti-cholesterol inhibition, antioxidant, anti-mutagenic, 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].



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**

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4 R_1=OCH_3, R_2=R_3=R_4=OH, **Naringin**

Figure 1. Flavonoids and flavanones from *Citrus.*

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

Naringenin has antidiabetic, anticancer, antimicrobial, antiobesity, gastroprotective, immunomodulator, cardioprotective, nephroprotective, and neuroprotective properties [9].

2. Results and Discussion

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

Hesperetin and Naringenin are water soluble and theirs 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.

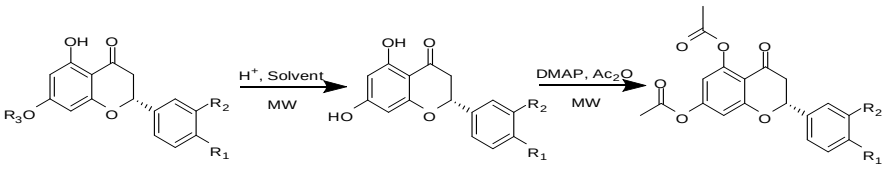

Figure 2. Hydrolysis and acetates formation under microwaves irradiation.

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 good yield using the microwave (600 W, 180 °C, 6.6 bars) better than in reflux which increases the yield of 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 catalyst, under microwave irradiation, in the presence of 4-(*N,N*-dimethylamino)-pyridine DMAP as catalyst, under microwave irradiation (Scheme 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 were. Air-dried peels of *Citrus sinensis* (40 g) were extracted using Soxhlet extractor with 500 mL of petroleum ether (40–60 °C) until the siphoned liquid become colorless for 2 h. After, the extraction was continued in second time 300 mL of methanol was added over a period of 2 h. The methanol extract was evaporated at 65 °C in vaccuum and the solid residue was crystallised in aqueous acetic acid.

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

3.2. Microwave-Assisted Hydrolysis of Hesperidin **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 microwave at 2450 MHz in a resonance cavity Anton Paar Monowave 300 for 10 min.

The yellow solutions were filtered, crystallized with ethanol to give a 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 Ac_2O in the presence of DMAP (0.1 mmol] as 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 original method, efficient and economical use of acid hydrolysis of Hesperidin and Naringin to provide their aglycones in presence of water as a solvent has been described under microwave irradiation. The triacetates of their aglycones **5**, **6** were conviently obtained with DMAP as catalyst under microwave irradiation.

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