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Promoting hydrolysis of flavonoid glycosides by microwave- assistance

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ABSTRACT

The efficient hydrolysis of flavonoid glycosides hesperidin (1a), naringin (1b) and rutin (1c) to corresponding flavonoid aglycone hesperetin (2a), naringnin (2b) and quercetin (2c) respectively by employing microwave irradiation method was studied. The test was designed to investigate the influential factors of the hydrolysis process under a microwave-assistance such as power of microwave, reaction temperature and irradiation time. The results show that microwave-assistance can greatly accelerate the hydrolysis rate of flavonoid glycosides, shorten the reaction time, and increase the yield of flavonoid aglycone. The optimized parameters are: power 500-600 W, irradiation time 30-45 min, reaction temperature 80-90 °C.

KEYWORDS

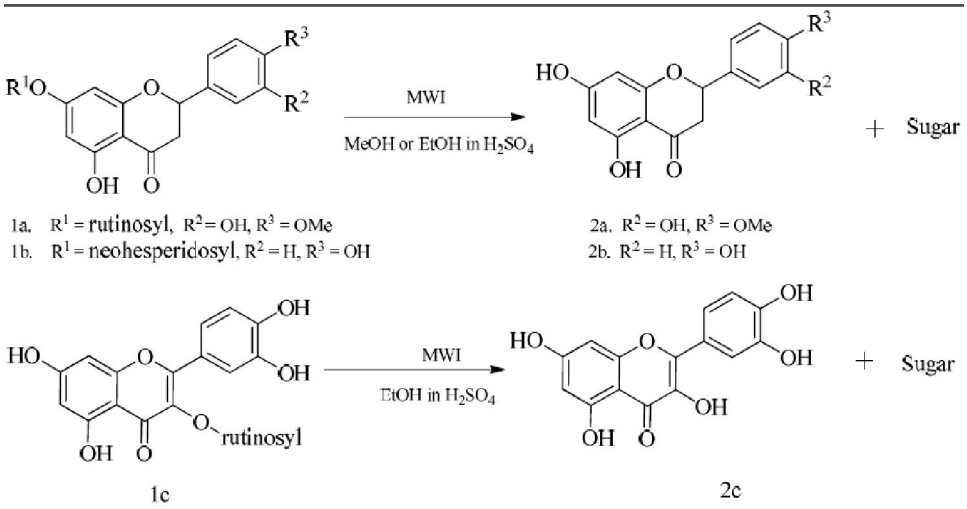
Flavonoid glycoside;
Flavonoid aglycone;
Hydrolysis;
Microwave-assistance

INTRODUCTION

Over the past two decades, there has been growing interest in applying microwave reactor to organic synthesis. Microwave synthesis method has been a good choice for studying chemical reactions due to its simple operation, spectacular accelerations, higher yields under milder reaction conditions and higher product purities[1-6].

Flavonoids are phenolic secondary metabolites widely distributed throughout the plant kingdom. They have been identified as antitumor agents, antiinflammatory agents, antioxidants and free radical scavengers[7-9]. Essentially, two forms of flavonoids are present in natural products: aglycone and glycosylated flavonoids. Compared to the glycosylated forms, the aglycones show a higher biological activity and bioavailability [10, 11].

Hesperidin (1a), naringin (1b) and rutin (1c) are three very abundant and inexpensive natural sources of flavonoid, consisting of an aglycone and an attached disaccharide. The acid hydrolysis of hesperidin, naringin or rutin by conventional heating manner have been reported[12-14], but the cleavage of glycosidic bond used conventional water bath heating usually takes a long time and affords low yields. Thus, we turned to microwave -assistance for removing of rutinosyl or neohesperidosyl. The influential factors of the hydrolysis process under microwave irradiation such as power of microwave, irradiation time and reaction temperature have been investigated. The results show that microwave -assistance can greatly accelerate the hydrolysis rate of flavonoid glycosides, shorten the reaction time and increase the yield of flavonoid aglycone.



Scheme 1 : Synthesis routes of flavonoid aglycones from flavonoid glycosides by microwave-assistance hydrolysis

TABLE 1 : The yields of flavonoid aglycone hesperetin (2a), naringnin (2b) and quercetin (2c) from corresponding flavonoid glycosides by Microwave-assistance hydrolysis.

temp [°C]	Time (min)	Power/W 400 Product (%) 2a	500 2a	600 2a	700 2a	400 2b	500 2b	600 2b	700 2b	400 2c	500 2c	600 2c	700 2c
60	15	0	0	0	0	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0	0	0	0	0	0
	45	0	0	0	0	0	0	0	0	0	0	0	0
70	15	3	5	7	6	7	9	9	7	5	6	5	7
	30	13	16	17	15	12	15	13	15	13	17	15	19
	45	17	18	19	19	18	18	15	17	19	21	25	21
80	15	55	61	63	63	56	63	67	60	63	65	59	67
	30	82	83	89	83	72	80	89	87	87	90	93	78
	45	81	82	87	78	75	78	81	81	89	91	87	81
90	15	60	63	65	67	64	68	69	63	71	66	77	68
	30	88	87	90	87	73	79	88	87	87	91	95	86
	45	76	80	85	71	72	65	72	77	86	93	89	84

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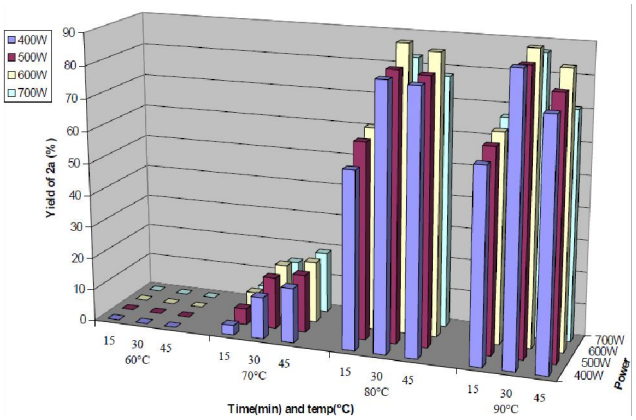

Figure 1 : Graph of speed optimization of time, temperature, capacity of the microwave- assistance in the reaction to hydrolysis the glycosidic bond of hesperidin (at 80 °C and 90 °C, in 30~45 min), afforded the product hesperetin in 90 % yield. Each column represents the average of three independent experiments.

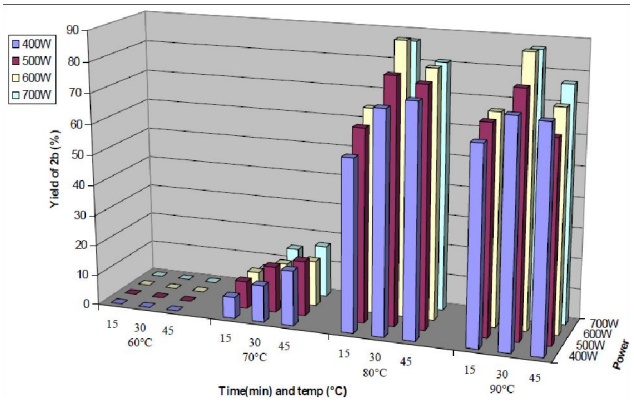

Figure 2 : Graph of speed optimization of time, temperature, capacity of the microwave- assistance in the reaction to hydrolysis the glycosidic bond of naringin (at 80 °C and 90 °C, in 30-45 min), afforded the product naringnin in 89% yield. Each column represents the average of three independent experiments.

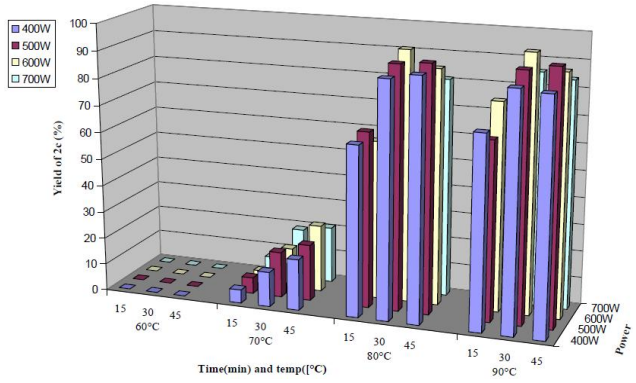

Figure 3 : Graph of speed optimization of time, temperature, capacity of the microwave-irradiated in the reaction to hydrolysis the glycosidic bond of rutine (at 80 °C and 90 °C, in 30-45 min), afforded the product quercetin in 95% yield. Each column represents the average of three independent experiments.

RESULTS AND DISCUSSION

Our present method provides an efficient synthesis of flavonoid aglycone hesperetin (2a), naringnin (2b) and quercetin (2c) from hesperidin (1a), naringin (1b) or rutin (1c), respectively, as depicted in Scheme 1.

From the process of hydrolysis of flavonoid glycosides hesperidin (1a), naringin (1b) and rutin (1c), it was found that the process did not happen at temperature below 60 °C, although we lengthened the time up to 45 minutes under microwave-assisted (initial power from 400 to 700 W). When the temperature was increased up to 70 °C, the glycosidic bond cleavage of compound 1a, 1b and 1c happened. However, the process took place at a low efficiency (shown in TABLE 1). Many sub-products were formed that lead to some difficulty in product separation.

The process of hydrolysis occurred smoothly when the temperature was up to 80 °C or 90 °C, especially at the microwave irradiation power of 500 W or 600 W, and during the time from 30 to 45 min. After finishing the reaction, the product was put into water immediately, followed by water washing. The average yields of flavonoid aglycone, each of which was obtained by averaging the data from three independent experiments, are shown in TABLE 1.

Each column represents the average of three the process of hydrolysis of flavonoid glycosides hesperidin did not happen at the temperature of 60 °C, or happened ineffectual at 70 °C. Even though the time was adjusted up to 45 min, the obtained product hesperetin did not exceed 20%. The hydrolysis of hesperidin gives 90% yield of hesperetin in 30 min by increasing the temperature up to 80 or 90 °C as depicted in Figure 1. While the conventional method which takes 6-7 hours affords a very low yield of product (*ca*. 65%) mixed with many impurities.

Independent experiments. To naringin, the hydrolysis of glycosidic bond was similar to the process of hydrolysis of hesperidin. Only an about 68% yield of naringnin was gained in traditional methods. But in our experiment as depicted in Figure 2, it was found that the process gave a higher yield of naringnin when metha-

nol was used because of the better solubility of hesperidin in methanol. At 45 min of time and 90 °C of temperature, the efficiency was, somewhat, lower than that of the process at 80 °C due to the elevated evaporation of solvent resulting in the higher acid and carbonation.

Similar to the two above processes, the results are described in Figure 3. The hydrolysis of rutine was done at 60 and 70 °C to give the corresponding aglycone quercetin and obtained a good result at 80 or 90 °C (95% yield)

EXPERIMENTAL

General experimental procedures

The ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on a Bruker AM-400 instrument, using tetramethylsilane as an internal standard, chemical shifts (δ) in ppm, coupling constants (J) in Hz, Mass spectra were determined with VG Autospec-3000 spectrometer by the EI method.. Melting points were determined by an XRC-1 apparatus and are uncorrected. Microwave-irradiation XH-MC-1 using in organic synthesis has power from 50 to 900 W was employed in experiment processes.

Microwave-Induced hydrolysis of hesperidin, naringin and rutin

The solution of hesperidin (1a) or naringin (1b), rutin (1c) (500 mg) in methanol or ethanol (15 mL) and 1.5 mL concentrated sulfuric acid was refluxed with stirring under a microwave irradiation at 400, 500, 600 and 700 W for 15, 30 and 45 min with the corresponding temperature 60, 70, 80 and 90 °C respectively (the instrument adjust the heating power to keep this temperature constant and stable). The mixture was cooled to room temperature, and then poured into ice water. The resulting precipitate was filtered, then washed with water, drying, crystallized from methanol to give compounds 2a or 2b, 2c as depicted in TABLE 1.

Compound **(2a)**: Light-yellow solid; mp 236-237 °C (lit: 228-230 °C[15]); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.14 (s, 1H, 5-OH), 10.84 (s, 1H, 7-OH), 9.13(s, 1H, 4'-OH), 7.01 – 6.82 (m, 3H, 2'-H and 5'-H and 6'-H), 5.90 (d, J = 3.3 Hz, 2H, 6-H+ 8-H), 5.43 (dd, J= 17.1, 2.8 Hz, 1H, 2-H), 3.78 (s, 3H, 4'-OCH_3), 3,20 (dd, 1H, J= 17.1, 12.4 Hz, 3-H *trans*), 2.871 (dd, 1H, J= 17.1, 2.8 Hz, 3-H *cis*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.6 (C4), 167.1 (C7), 163.9 (C5), 163.2 (C8a), 148.3 (C4'), 146.9 (C3'), 131.6 (C1'), 118.2 (C6'), 114.5 (C5'), 112.4 (C2'), 102.3 (C4a), 96.3 (C8), 95.5 (C6), 78.7 (C2), 56.1 (4'-OCH_3), 42.5 (C3); EIMS: *m/z* 303 $(M+H)^+$.

Compound 2b: Light-yellow solid; mp 224-226 °C (lit: 225-226 °C [16]); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (s, 1H. 5-OH), 10.81 (s, 1H, 4'-OH), 9.62 (s, 1H, 7-OH), 7.32 (d, J= 8.2 Hz, 2H, 2'-H and 6'-H), 6.81 (d, J = 8.2 Hz, 2H, 3'-H and 5'-H), 5.91 (s, 2H, 5-H and 8-H), 5.43(d, J = 10.8 Hz, 1H, 2-H), 3.24 (m, 1H, 3-H *trans*), 2.69 (dd, J= 17.1, 2.2 Hz, 1H, 3-H *cis*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.8 (C4), 167.1 (C7), 163.9 (C5), 163.4 (C8a), 158.2 (C4'), 129.3 (C1'), 128.9 (C2' and C6'), 115.7 (C3' and C5'), 102.2 (C4a), 96.3 (C8), 95.5 (C6), 78.9 (C2), 42.4 (C3); EIMS: *m/z* 273 $(M+H)^+$.

Compound **(2c)**: Yellow solid; mp 315-316 °C (lit: 116.5 °C [17]); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.56 (s, 1H, 5-OH), 10.87 (s, 1H, 3-OH), 9.69 (s, 1H, 7-OH), 9.46 (s, 1H, 3'-OH), 9.40 (s, 1H, 4'-OH), 7.73 (s, 1 H, 6'-H), 7.60 (d, J = 10.3 Hz, 1H, 5'-H), 6.94 (d, J = 8.5 Hz, 1H, 2'-H), 6.47 (s, 1H, 6-H), 6.25 (s, 1H, 8-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.3 (C4), 164.3 (C7), 161.2 (C5), 156.6 (C8a), 148.1 (C4'), 147.3 (C5'), 145.5 (C2), 136.2 (C3), 122.4 (C1'), 120.5 (C2'), 116.1 (C3'), 115.5 (C6'), 103.5 (C4a), 98.6 (C8), 93.8 (C6); EIMS: *m/z* 303 $(M+H)^+$.

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