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Microwave-Assisted Esterification of Gallic Acid

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An efficient synthesis of alkyl gallates under microwave irradiation was described. The reaction took place in 6-10 mins, which was much shorter than the traditional synthetic methods, with almost quantitative yields.

Keywords: Esterification, Gallic acid, Microwave irradiation, Short reaction time, High yield.

INTRODUCTION

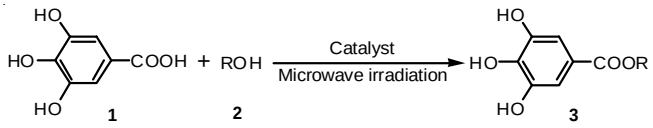
It is well established that living cells are constantly challenged by conditions that cause acute or chronic stress. Within the cell, reactive oxygen species (ROS) including hydrogen peroxide (H_2O_2), hydroxyl radical ($HO^{\bullet}$) and superoxide anion ($O_2^{\bullet-}$), are physiologically present at minimal concentration as by-products of aerobic metabolism and second messengers in many signal transduction pathways. In normal conditions, there is a steady state balance between pro-oxidants and antioxidants, which is necessary to ensure the optimal efficiency of antioxidant defenses. However, when the rate of free radical generation exceeds the capacity of anti-oxidant defenses, oxidative stress ensues with severe damage to the cell[1]. Excessive reactive oxygen species can cause damage of cardinal cellular components such as lipids, proteins and nucleic acids (*e.g.*, DNA), which lead to subsequent cell death by mode of necrosis or apoptosis[2]. Therefore, the use of radical scavengers should be of critical importance to prevent and cure many diseases such as ischemia-reperfusion injury, neurodegenerative disorders and surgical organ transplantation[3].

Recent evidence demonstrated alkyl gallates have a wide range of uses as antioxidants in food, cosmetics and pharmaceutical industries. In addition, gallic acid, which is an intermediary component of plant metabolism[4], is employed as a source material for inks, paints and colour developers[5]. Pharmacological studies performed with these compounds have shown that they possess many therapeutic potentialities, including antioxidant[6], antifungal[7], antibacterial[8], antitumoral[9], antiviral[10], and antiherpetic[11] activities. However, more interest has been devoted to the antioxidant activity of alkyl gallates due to their ability to scavenge and reduce reactive oxygen species formation[12-15].

The alkyl gallates could be synthesized through the method where the acid directly refluxed with alcohols in the presence of various catalysts, such as conc. sulfuric acid, hydrogen chloride, boron trifluoride, aluminum chloride, trifluoroacetic anhydride, polyphosphate ester, neodymium oxide, dicyclohexylcarbodiimide, graphite bisulfate, *etc*.[16-18] The disadvantages of using these catalysts, such as long reaction time, low yield, expensive reagents and tedious operation are difficult to avoid, as in the case of Savi *et al.* method[11], in order to obtain the alkyl gallates, the mixture of gallic acid, conc. sulphuric acid and alcohol in toluene must be heated under reflux for 8-12 h. Gallic acid is heat-sensitive and susceptible to oxidation, which makes enzymatic synthesis of its esters an attractive alternative to chemical synthesis[19]. However, these latter methods have many disadvantages including low yields, time consumption, solvent requirements, *etc*.

In recent years, microwave-assisted reactions have received a great deal of attention, because reactions under microwave irradiation are in general not only faster compared with the conventional heating reactions, but also potentially more efficient, cleaner and safer[20,21]. Further improvements have also been reported which can offer enhanced reaction rates, higher yields, and greater selectivity to the targeted product under milder reaction conditions[22].

The aim of this study was to establish an efficient strategy for synthesis of alkyl gallates (**Scheme-I**) through optimization of catalyst, reaction time, reaction temperature and the ratio of gallic acid to alcohol under the microwave irradiation.



Scheme-I: Esterification of gallic acid under microwave irradiation

EXPERIMENTAL

All the reagents are commercially available and used directly. The ^{1}H NMR spectra were recorded on a Bruker AV 300 spectrometer using DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in parts per million (ppm). The ESI-MS were obtained on Agilent 1946A-MSD.

General procedures for the esterification of gallic acid through microwave irradiation: To a stirring mixture of gallic acid (170 mg, 1 mmol) in alcohol (6 mmol) was added the *p*-toluenesulfonic acid (6.88 mg, 0.04 mmol), and the reaction mixture was heated in a sealed reaction vessel of discover (CEM, USA) under microwave irradiation, where the power was set at 200 W, the temperature was set at some centigrade which was 10 ºC above the boiling point of the alcohol, and the PSI was set at 180. All of the alkyl gallate are known compounds and were identified on the basis of ^{1}H NMR and ESI-MS spectral data.

Compound 3a[11]: White solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.75 (s, 3H), 6.94 (s, 2H), 8.94 (s, 1H), 9.26 (s, 2H); ESI-MS *m/z*: 185 $[M + H]^+$ (100).

Compound 3b[11]: White solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, 3H), 4.19 (q, 2H), 6.94 (s, 2H), 8.91 (s, 1H), 9.24 (s, 2H); ESI-MS *m/z*:199 $[M + H]^+$ (100).

Compound 3c[11]: White solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (t, 3H), 1.65 (m, 2H), 4.11 (t, 2H), 6.95 (s, 2H), 8.92 (s, 1H), 9.25 (s, 2H); ESI-MS *m/z*: 213 $[M + H]^+$ (100).

Compound 3d[19]: White solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (d, J = 6.3 Hz, 6H), 5.03 (m, 1H), 6.93 (s, 2H), 8.89 (s, 1H), 9.23 (s, 2H); ESI-MS *m/z*: 213 $[M + H]^+$ (100).

Compound 3e[11]: White solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (t, 3H), 1.44 (m, 2H), 1.64 (m, 2H), 4.16 (t, 2H), 6.94 (s, 2H), 8.92 (s, 1H), 9.25 (s, 2H); ESI-MS *m/z*: 227 $[M + H]^+$ (100).

Compound 3f[23]: White solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (d, J = 6.6 Hz, 6H), 1.97 (m, 1H), 4.03 (d, J = 7.1 Hz, 2H), 6.96 (s, 2H), 9.16 (s, 3H); ESI-MS *m/z*: 227 $[M + H]^+$ (100).

Compound 3g[11]: White solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (t, 3H), 1.36 (m, 4H), 1.64 (m, 2H), 4.12 (t, 2H), 6.92 (s, 2H), 9.08 (s, 1H); ESI-MS *m/z*: 241 $[M + H]^+$ (100).

Compound 3h[19]: White solid, ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.56 (m, 2H), 1.70 (m, 1H), 4.16 (t, 2H), 6.94 (s, 2H), 9.08 (s, 3H); ESI-MS *m/z*: 241 $[M + H]^+$ (100).

RESULTS AND DISCUSSION

In present research, ethanol (**2b**) was selected as a representative alcohol to optimize the reaction condition. For the reactant and solvent of this esterification were all the ethanol, which was a kind of polar solvent, it could absorb the microwave much more efficiently. Firstly, we tried this esterification without any catalyst where the gallic acid (**1**) reacted with the ethanol (**2b**) directly under the microwave irradiation at 200 W (Table-1, Runs 1-2). Unfortunately, the result was that there was no indication of the product even the reaction time had proceeded 20 min. To make this reaction much easier to proceed, we added the catalyst of conc. sulfuric acid into the reaction mixture. This time the esterification was found to be finished after 10 min at 88 ºC, in the presence of 10 mol % H_2SO_4 in ethanol, giving the corresponding ethyl gallate (**3b**) in 96 % (Table-1, Run 7). When the amount of H_2SO_4 was increased to 12 mol %, the yield of the product was reduced to 88 % (Table-1, Runs 8), this could be that the ethyl gallate was hydrolyzed in the presence of excessive H_2SO_4. However, when the amount of H_2SO_4 was decreased (2, 4, 6, 8 mol %), the reaction proceeded more slowly, and the yields of ethyl gallate (**3b**) were reduced into 58, 72, 88 and 92 %, respectively, even after the reaction mixture had proceeded 10 min at 88 ºC (Table-1, Runs 3-6). Subsequently, we selected *p*-toluenesulfonic acid as the catalyst to investigate this esterification, and it was found that this catalyst could make the esterification of gallic acid much more easily. From the report, it is observed that this esterification was finished after 10 min in 88 ºC, in the presence of 4 mol % *p*-toluenesulfonic acid in ethanol, giving the corresponding ethyl gallate (**3b**) in 96 % yield (Table-1, Run 10). Compared to the H_2SO_4, the demand of *p*-toluenesulfonic acid was much less to make this esterification proceed completely, so we chose *p*-toluenesulfonic acid as the catalyst in this microwave assisted esterification.

TABLE-1
OPTIMIZATION OF THE CATALYST FOR THE SYNTHESIS OF ETHYL GALLATE (**3b**)[a]

Run	Catalyst (mol %)	Time (min)[d]	Yield (%)[e]
1	0	10	0
2	0	20	0
3	2[b]	10	58
4	4[b]	10	72
5	6[b]	10	88
6	8[b]	10	92
7	10[b]	10	96
8	12[b]	10	88
9	2[c]	10	88
10	4[c]	10	96
11	6[c]	10	94
12	8[c]	10	87
13	10[c]	10	74
14	12[c]	10	67

[a]Reaction conditions: Gallic acid (**1**) (1 mmol), ethanol (**2b**) (5 mL), temperature 88 °C; [b]Conc. sulfuric acid as the catalyst; [c]*p*-Toluenesulfonic acid as the catalyst; [d]Monitored by TLC; [e]Isolated yield, purity confirmed by MS and ^{1}H NMR

Reaction temperature played a crucial role in this microwave-assisted esterification. It was reported that the yields of ethyl gallate might sometimes be dramatically affected by

changing the reaction temperature in the same reaction time. It is found that increasing the temperature remarkably accelerated the reaction (Table-2, Runs 1-5). A high yield was obtained when the esterification was carried out in ethanol at 88 °C within 10 min (Table-2, Run 5). The esterification at 48 °C for 10 min gave only the 40 % yield of desired product (Table-2, Run 1). However, for this esterification, higher temperature was unfavorable as the desired ethyl gallate (**3b**) was hydrolyzed (Table-2, Runs 6-7).

TABLE-2
OPTIMIZATION OF THE TEMPERATURE FOR THE SYNTHESIS OF ETHYL GALLATE (**3b**)[a]

Run	Temperature (ºC)	Time (min)[b]	Yield (%)[c]
1	48	10	40
2	58	10	56
3	68	10	78
4	78	10	88
5	88	10	96
6	98	10	91
7	108	10	85

[a]Reaction conditions: Gallic acid (**1**) (1 mmol), ethanol (**2b**) (5 mL), *p*-Toluenesulfonic acid (4 mol%); [b]Monitored by TLC; [c]Isolated yield, purity confirmed by MS and ^{1}H NMR

The effect of the reaction time was also examined (Table-3, Runs 1-6). It is observed that as the reaction time extended from 2 to 8 min, the yield of the desired product ethyl gallate (**3b**) improved from 32 to 96 % (Table-3, Runs 1-4). However, as the reaction time exceeded 8 min, the yield was not affected so much (Table-3, Runs 5-6).

TABLE-3
OPTIMIZATION OF THE REACTION TIME FOR SYNTHESIS OF ETHYL GALLATE (**3b**)[a]

Run	Time (min)[b]	Yield (%)[c]
1	2	32
2	4	58
3	6	88
4	8	96
5	10	95
6	12	95

[a]Reaction conditions: Gallic acid (**1**) (1 mmol), ethanol (**2b**) (5 mL), *p*-Toluenesulfonic acid (4 mol %), Temperature (88 ºC); [b]Monitored by TLC; [c]Isolated yield, purity confirmed by MS and ^{1}H NMR

Finally, we investigated the effect of mol ratio of gallic acid to ethanol in this esterification (Table-4, Runs 1-7). It was found that when the mol ratio was more 1 : 6, the desired product of ethyl gallate was obtained in almost quantitative yield (Table-4, Runs 6-8). Deceasing the ratio to 1 : 1, the ethyl gallate was obtained in only 30 % after this esterification had proceeded 8 min (Table-4, Run 1), and as the ratio of gallic acid to ethanol increased, the yield of ethyl gallate was also enhanced (Table-4, Runs 2-6).

After we have optimized the catalyst, temperature, reaction time and the mol ratio of gallic acid to alcohol in this esterification, then we applied this methodology for the reactions between gallic acid and other alcohols, and compared the efficiency of this microwave irradiation with that of the conventional heating. From the result (Table-5) we can see that all the reaction time of conventional heating was very

TABLE-4
OPTIMIZATION OF MOL RATIO OF GALLIC ACID TO ETHANOL FOR THE SYNTHESIS OF ETHYL GALLATE (**3b**)[a]

Run	Ratio (**1 : 2b**)	Time (min)[b]	Yield (%)[c]
1	1 : 1	8	30
2	1 : 2	8	55
3	1 : 3	8	86
4	1 : 4	8	90
5	1 : 5	8	94
6	1 : 6	8	96
7	1 : 7	8	97
8	1 : 8	8	96

[a]Reaction conditions: Gallic acid (**1**) (1 mmol), *p*-Toluenesulfonic acid (4 mol %), Temperature (88 ºC); [b]Monitored by TLC; [c]Isolated yield, purity confirmed by MS and ^{1}H NMR

long, and the reaction time became much longer as the atom numbers of the alcohol turned to be much more, this could be seen from the case of **2b**, **2c**, **2e** and **2g**, where the reaction time were 8, 12, 16 and 20 h, respectively. For alcohols with same atom numbers, the reaction time for the alcohol with branched carbon chains was much longer than those with lined carbon chains, such as the reaction time of **2c** was 12 h, where the reaction time of **2d** was 18 h (Table-5, Runs 3-4). Another interesting phenomenon was that the yields of the alkyl gallate turned to be much lower as the atom numbers of the alcohol became much more, as in the case of **2b** (81 %) and **2c** (77 %) (Table-5, Runs 2-3), and the yield of the alkyl gallate with branched alkyl chains was much lower than those with lined alkyl chains, which could be seen from the case of **2c** (77 %) and **2d** (71 %) (Table-5, Runs 3-4). All of these have changed as we applied the microwave irradiation in this esterification. Firstly, all the reaction time could be reduced into several min, even for the alcohols with long carbon chains and those with side chains, as in the case of **2g** and **2h** (Table-5, Runs 7-8), the reaction time for synthesis of these two gallate were only 10 min through the microwave irradiation, especially for **2h**, the reaction time could be reduced from 24 h into 10 min. Secondly, all the yields of synthesis of alkyl gallate could be achieved above 90 %, such as in the case of **2h**, which was very difficult to react through the conventional heating, while the yield could be enhanced from 62 into 91 % under the microwave irradiation.

Conclusion

In summary, an efficient microwave-assisted esterification of gallic acid with alcohols was developed with high yields for the first time. There are two advantages to this methodology *i.e.*, high yields and short reaction times.

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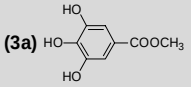
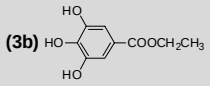
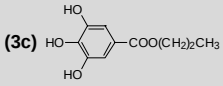
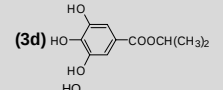
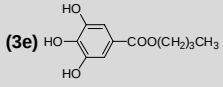
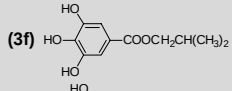
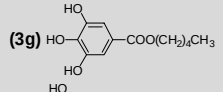
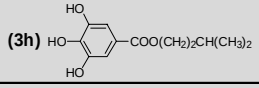
TABLE-5
SYNTHESIS OF ALKYL GALLATE UNDER CONVENTIONAL HEATING AND MICROWAVE IRRADIATION

Run	Substrate	Products	Conventional heating[a]			Microwave irradiation[b]		
			Temp.	Time[c]	Yield[d]	Temp.	Time[c]	Yield[d]
1	CH_3OH (**2a**)	 **(3a)**	Reflux	8 h	78[11]	75 ºC	6 min	95[11]
2	CH_3CH_2OH (**2b**)	 **(3b)**	Reflux	8 h	81[11]	88 ºC	8 min	96[11]
3	$CH_3(CH_2)_2OH$ (**2c**)	 **(3c)**	Reflux	12 h	77[11]	107 ºC	8 min	94[11]
4	$(CH_3)_2CHOH$ (**2d**)	 **(3d)**	Reflux	18 h	71[19]	92 ºC	8 min	93[19]
5	$CH_3(CH_2)_3OH$ (**2e**)	 **(3e)**	Reflux	16 h	73[11]	128 ºC	9 min	93[11]
6	$(CH_3)_2CHCH_2OH$ (**2f**)	 **(3f)**	Reflux	20 h	66[23]	118 ºC	9 min	92[23]
7	$CH_3(CH_2)_4OH$ (**2g**)	 **(3g)**	Reflux	20 h	68[11]	148 ºC	10 min	92[11]
8	$(CH_3)_2CH(CH_2)_2OH$ (**2h**)	 **(3h)**	Reflux	24 h	62[19]	142 ºC	10 min	91[19]

[a]Reaction conditions: **1** (1 mmol), alcohol (5 ml), *p*-Toluenesulfonic acid (4 mol%); [b]Reaction conditions: **1** (1 mmol), alcohol (6 mmol), *p*-Toluenesulfonic acid (4 mol%); [c]Monitored by TLC; [d]Isolated yield, purity confirmed by MS and ^{1}H NMR

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