Microwave-assisted condensation of kojic acid with aldehydes

Pan-Pan Hu[a], Chun-Feng Zhu[b] and Tao Zhou[a]*

[a]*School of Food Science and Biotechnology, Zhejiang Gongshang University, Hangzhou, Zhejiang 310035, P. R. China*

[b]*College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China*

Kojic acid derivatives have been prepared in excellent yield by the condensation of two molecules of kojic acid and one molecule of an aldehyde using sodium carbonate as a base under microwave irradiation.

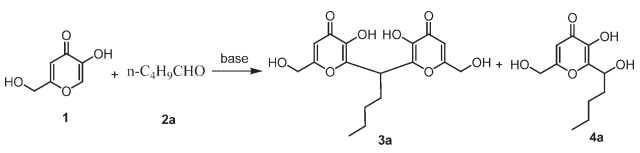
Keywords: kojic acid, aldehyde, microwave irradiation, condensation

Tyrosinase is a multi-functional copper-containing enzyme which is widely distributed in microorganisms, plants and animals.[1] It is a key enzyme in the biosynthesis of melanin and is responsible for melanization in animals and browning in plants.[2] Thus tyrosinase inhibitors have been widely used in the agricultural, food, cosmetic and medicinal fields.[3] Kojic acid, 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one (**1**) possesses appreciable inhibitory activity against tyrosinase by chelating copper, which is associated with its γ-pyrone structure containing an enolic hydroxyl group.[4] Kojic acid also exhibits free radical scavenging activity and prevents photodamage.[5] Kojic acid has been used as an ingredient in cosmetics and as an anti-browning agent in foods that change colour easily.[6,7] The synthesis of kojic acid derivatives have attracted considerable attention recently.[8–12] In attempts to seek better tyrosinase inhibitors, Barham *et al* reported[13] the reaction of kojic acid with aldehydes in the presence of ammonia in ethanol, which needed long reaction time (up to 48h) and a relatively complicated purification. Thus, a simple and efficient method for the preparation of the corresponding kojic acid derivatives is required.

In recent years, microwave-assisted organic reaction has become a widely-used and valuable technique in organic synthesis with considerable advantages over conventional thermal methods.[14] The beneficial effects of microwave radiation on performing organic reactions are well known, for example affording remarkable reductions in reaction time, improved yields and easier workups.[15–19] We report here a convenient and efficient synthesis of kojic acid derivatives by the condensation of kojic acid with aldehydes under microwave irradiation.

Results and discussion

Initially, we examined the reaction of kojic acid (**1**) and pentanal (**2a**) under different reaction conditions. In some cases, both the condensation product of two molecule of kojic acid with one molecule of pentanal (**3a**) and the condensation product of one molecule of kojic acid with one molecule of pentanal (**4a**) were detected (Scheme 1). However, in those cases, after work-up **3a** and **4a** were obtained as a mixture, which was difficult to separate by recrystallisation. In order to optimise the reaction conditions for the preparation of pure **3a**, we investigated the effects of several factors including the molar ratio of kojic acid to pentanal, reaction time, base and solvent on the products. The results are presented in Table 1.



Scheme 1

Two solvent systems, water/methanol and water/ethanol, were tested in the reaction. It was found that the reaction proceeded much better in water/methanol than in water/ethanol. The effect of volume ratio of water/methanol was also tested, and the best result was obtained when water/methanol ratio was 1:1. Among the tested bases, Na_2CO_3 was found to be best choice for the preparation of **3a**. The effect of molar ratio of starting materials kojic acid/pentanal on the reaction was investigated. In the case of molar ratio of 2:1 which is required for the formation of **3a**, the product which was obtained, was found to be contaminated by a small amount of unreacted kojic acid after work-up (entry 9). This is probably due to the side reactions which consumed some pentanal. Increasing the amount of pentanal to a molar ratio of 1:1 improved the yield of **3a** and the kojic acid reacted completely (entry 8). The yield of **3a** reached a maximum when molar ratio of kojic acid/pentanal was 1:1.5 (entries 10 and 11). A study on the effect of reaction time showed that the reaction was completed after 3h at 70 °C to give **3a** in good yield (entries 10 and 12). Thus, the optimal reaction conditions for the synthesis of **3a** at 70 °C are: water/methanol (1:1) as solvent, sodium carbonate as a base, molar ratio of kojic acid/pentanal 1:1.5, reaction time 3h.

In order to further improve the yield, we investigated the reaction of kojic acid and pentanal under microwave irradiation. The other optimised reaction conditions such as molar ratio of kojic acid:pentanal (1:1.5), sodium carbonate as a base and water:methanol (1:1) as solvent, were retained in this investigation. The effects of MW power and reaction time on the reaction were examined. The results are shown in Table 2. The best yield was obtained at 400W (entry 2). It was found that the yield of **3a** was improved significantly when the reaction time was prolonged to 40 min (85% yield) compared to 30 min (entries 2 and 5), but further extension of the reaction time did not improve the yield (entry 6). The optimal conditions for obtaining **3a** under microwave irradiation involved the use of 400 W power microwave at 70 °C and reaction time

Table 1 The reaction of kojic acid with pentanal under different reaction conditions[a]

Entry	Solvent	Base	Time /h	Ratio of **1**/**2a**	Yield/%[b]	
					3a	**4a**
1	H_2O/MeOH(1:1)	Na_2CO_3	2	1:1	52	12
2	H_2O/EtOH(1:1)	Na_2CO_3	3	1:1	28	15
3	H_2O/MeOH(1:2)	Na_2CO_3	2	1:1	32	12
4	H_2O/MeOH(2:1)	Na_2CO_3	2	1:1	35	16
5	H_2O/MeOH(1:1)	NaOH	5	1:1	42	15
6	H_2O/MeOH(1:1)	$NaHCO_3$	5	1:1	Trace	Trace
7	H_2O/MeOH(1:1)	K_2CO_3	3	1:1	70	None
8	H_2O/MeOH(1:1)	Na_2CO_3	3	1:1	72	None
9	H_2O/MeOH(1:1)	Na_2CO_3	3	2:1	69[c]	None
10	H_2O/MeOH(1:1)	Na_2CO_3	3	1:1.5	75	None
11	H_2O/MeOH(1:1)	Na_2CO_3	3	1:2	75	None
12	H_2O/MeOH(1:1)	Na_2CO_3	5	1:1.5	76	None

[a] All reactions were carried out at 70 °C.
[b] Yield based on kojic acid.
[c] Contaminated by trace amount of kojic acid.

* Correspondent. E-mail: taozhou@zjgsu.edu.cn

Table 2 The reaction of kojic acid with pentanal under microwave irradiation[a]

Entry	MW power W	Time/min	Product	Yield/%[b]
1	200	30	**3a**	ND[c]
2	400	30	**3a**	69
3	600	30	**3a**	66
4	800	30	**3a**	63
5	400	40	**3a**	85
6	400	50	**3a**	85

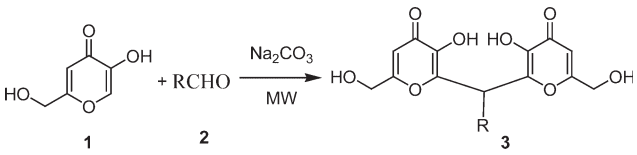
[a] All reactions were run with kojic acid (10mmol), pentanal (15mmol), Na_2CO_3 (10mmol), H_2O/MeOH (1:1, 20mL) at 70 °C.
[b] Isolated yield based on kojic acid.
[c] Not determined as a mixture of **3a** and **4a** was obtained.

40 min. In comparison with the conventional thermal method, the yield of **3a** was increased from 75 to 85% with the aid of microwave irradiation.

We investigated the scope of the reaction of kojic acid with a range of aldehydes including both aliphatic and aromatic aldehydes under the above optimal reaction conditions with microwave irradiation (Scheme 2). It was found that the reaction proceeded smoothly and gave the desired product **3** in excellent yields. The results are summarised in Table 3. As can be seen from Table 3, the longer carbon chain of the aliphatic aldehydes gave comparatively higher yields than the shorter ones (entries 1–5). Aromatic aldehydes, for example, benzaldehyde, 4-methoxybenzaldehyde and 4-methylbenzaldehyde could also react with kojic acid easily under the same reaction conditions (entries 6–8).

A plausible mechanism for the formation of the kojic acid derivative **3** is shown in Scheme 3. The enolate anion of kojic acid attacks the carbonyl of the aldehyde to generate **4**. The formation of **4** during the reaction has been confirmed by the results in Table 1. Under thermal conditions, **4** may generate intermediate **5**, which is easily attacked by the enolate anion of kojic acid to produce **3**.

In conclusion, we have developed a convenient and efficient method for the synthesis of kojic acid derivatives by microwave-assisted condensation of kojic acid with aldehydes. This method has advantages of high yield, simplicity of purification and short reaction time.



Scheme 2

Table 3 Microwave-assisted reaction of kojic acid with aldehydes[a]

Entry	R	Products	Yield/%[b]
1	n-Bu	**3a**	85
2	Et	**3b**	70
3	n-Hexyl	**3c**	90
4	n-Octyl	**3d**	88
5	n-Decyl	**3e**	92
6	C_6H_5	**3f**	80
7	4-$CH_3C_6H_4$	**3g**	88
8	4-$CH_3OC_6H_4$	**3h**	82

[a] All reactions were run with kojic acid (10mmol), aldehyde (15mmol), Na_2CO_3 (10mmol) in H_2O/MeOH (1:1, 20mL) with 400W power at 70 °C for 40 min.
[b] Isolated yield based on kojic acid.

Experimental

^{1}H NMR data were recorded on a Bruker Avance 400 spectrometer using DMSO-d_6 as the solvent with TMS as an internal standard. IR spectra were determined on NICOLET 380 IR spectrometer with KBr pallet. ESI-MS spectra were recorded on 4000Q mass spectrometer (Applied Biosystems, USA). High resolution mass spectra (HRMS) were obtained on a QTOF Micro using the ESI source. Melting points were measured on SGW X-4 micro melting point apparatus and are uncorrected. Microwave irradiation was carried out in a XH-MC-1 microwave synthesiser.

*Synthesis of 3,3′-dihydroxy-6,6′-bis(hydroxymethyl)-2,2′-(pentane-1,1-diyl)di-4H-pyran-4-one (***3a***)*

Under conventional thermal conditions: Pentanal (15 mmol) was added to a mixture of kojic acid (1.42 g, 10 mmol), sodium carbonate (1.06 g, 10 mmol) in water (10 mL) and methanol (10 mL) was added pentanal (15 mmol) at 70 °C. The reaction mixture was stirred at this temperature for 3h. After removal of about half the volume of the solvent, the solution was neutralised to pH1 with concentrated hydrochloric acid Dichloromethane (30 mL) was then added. The product **3a** precipitated after 30 min and was collected by filtration as an off-white solid (1.32, 75%). Further purification was achieved by recrystallisation from ethanol. M.p. 186.2–187.3 °C (lit.[13] 185.6–187.2 °C); IR (KBr) ν_{max}: 3443, 3304, 2925, 1647, 1617, 1571, 1450, 1322, 1221 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.87 (t, J = 8.0 Hz, 3H, CH_3), 1.20–1.34 (m, 4H, CH_2), 1.93 (q, J = 8.0 Hz, 2H, CH_2), 4.30 (s, 4H, CH_2), 4.70 (t, J = 8.0 Hz, 1H, CH), 5.66 (br, 2H, OH), 6.30 (s, 2H, C-5H in pyran ring), 9.10 (br, 2H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.7 (*C*H$_3$), 21.6 (*C*H$_2$), 28.5 (*C*H$_2$), 28.8 (*C*H$_2$), 35.5 (*C*H), 59.4 (*C*H$_2$), 108.7 (*C*5H in pyran ring), 142.0 (*C*2 in pyran ring), 148.0(*C*3 in pyran ring), 167.4(*C*6 in pyran ring), 173.4(*C*O in pyran ring). ESI-MS: *m/z* 353 (MH$^+$).

Under microwave irradiation: The aldehyde (15 mmol) was added to a solution of kojic acid (1.42 g, 10 mmol), sodium carbonate (1.06 g, 10 mmol) in water (10 mL) and methanol (10 mL) at 70 °C with a microwave power of 400 W. The reaction mixture was stirred at this temperature for 40min. The work-up procedures were the same as described above.

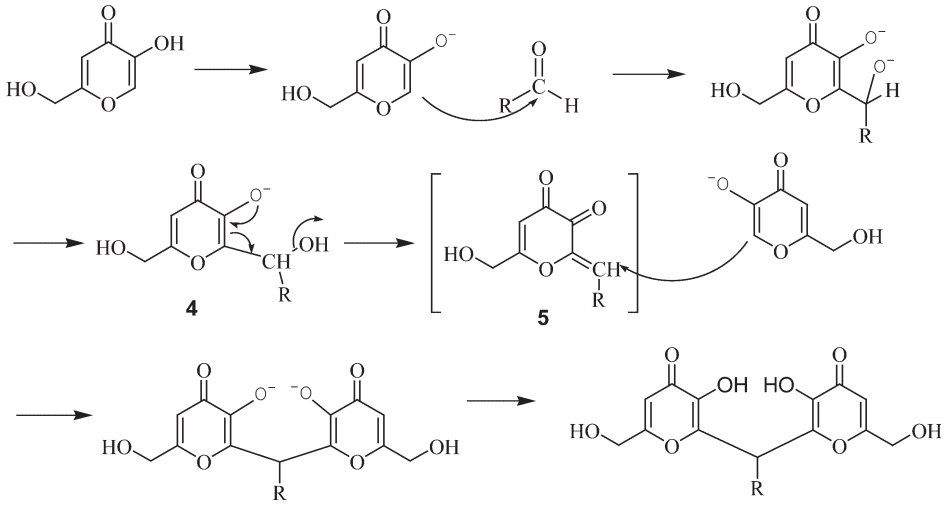
3,3′-Dihydroxy-6,6′-bis(hydroxymethyl)-2,2′-(pentane-1,1-diyl)di-4H-pyran-4-one (**3a**): 85% yield.

3,3′-Dihydroxy-6,6′-bis(hydroxymethyl)-2,2′-(propane-1,1-diyl)di-4H-pyran-4-one (**3b**): 70% yield; m.p. 214.5–216.1 °C (lit.[13] 217.5–218 °C); IR (KBr) ν_{max}: 3459, 3302, 2967, 1654, 1627, 1578, 1442, 1315, 1212 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.87 (t, J = 7.2 Hz, 3H, CH_3), 1.94 (m, 2H, CH_2), 4.27 (d, J = 6.0 Hz, 4H, CH_2), 4.59 (t, J = 7.2 Hz, 1H, CH), 5.72 (t, J = 6.0 Hz, 2H, OH), 6.29 (s, 2H, C-5H in pyran ring), 9.01 (s, 2H, OH); ESI-MS: *m/z* 325 (MH$^+$).

3,3′-Dihydroxy-6,6′-bis(hydroxymethyl)-2,2′-(heptane-1,1-diyl)di-4H-pyran-4-one (**3c**): 90% yield; m.p. 150.8–152.6 °C (lit.[13] 152.6–153.6 °C); IR (KBr) ν_{max}: 3402, 3302, 2930, 1655, 1618, 1578, 1458, 1315, 1214 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.84 (t, J = 7.2 Hz, 3H, CH_3), 1.23 (m, 8H, CH_2), 1.92 (q, J = 7.2 Hz, 2H, CH_2), 4.28 (d, J = 6.4 Hz, 4H, CH_2), 4.68 (t, J = 7.2 Hz, 1H, CH), 5.65 (t, J = 6.4 Hz, 2H, OH), 6.28 (s, 2H, C-5H in pyran ring), 9.01 (s, 2H, OH); ESI-MS: *m/z* 381 (MH$^+$).

3,3′-Dihydroxy-6,6′-bis(hydroxymethyl)-2,2′-(nonane-1,1-diyl)di-4H-pyran-4-one (**3d**): 88% yield; m.p. 106.3–106.8 °C; IR (KBr) ν_{max}: 3401, 3280, 2918, 1654, 1618, 1570, 1458, 1215 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.84 (t, J = 7.2 Hz, 3H, CH_3), 1.23 (m, 12H, CH_2), 1.92 (q, J = 7.2 Hz, 2H, CH_2), 4.28 (d, J = 6.0 Hz, 4H, CH_2), 4.69 (t, J = 7.2 Hz, 1H, CH), 5.62 (t, J = 6.0 Hz, 2H, OH), 6.28 (s, 2H, C-5H in pyran ring), 9.02 (s, 2H, OH); ESI-MS: *m/z* 409 (MH$^+$), HRMS: Found 431.1678 ([M+Na]$^+$); Calcd 431.1682 for $C_{21}H_{28}NaO_8$.

3,3′-Dihydroxy-6,6′-bis(hydroxymethyl)-2,2′-(undecane-1,1-diyl) di-4H-pyran-4-one (**3e**): 92% yield; m.p. 117–117.4 °C; IR (KBr) ν_{max}: 3249, 2915, 1656, 1619, 1583, 1453, 1313, 1210, 1090 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.84 (t, J = 6.8 Hz, 3H, CH_3), 1.24 (m, 16H, CH_2), 1.91 (q, J = 6.8 Hz, 2H, CH_2), 4.28 (d, J = 5.2 Hz, 4H, CH_2), 4.68 (t, J = 8.0 Hz, 1H, CH), 5.62 (t, J = 5.2 Hz, 2H, OH), 6.28 (s, 2H, C-5H in pyran ring), 9.01 (s, 2H, OH); ESI-MS: *m/z* 437 (MH$^+$); HRMS: Found 459.2007 ([M+Na]$^+$); Calcd 459.1995 for $C_{23}H_{32}NaO_8$.



Scheme 3

3,3'-Dihydroxy-6,6'-bis(hydroxymethyl)-2,2'-(phenylmethane-1,1-diyl)di-4H-pyran-4-one (**3f**): 80% yield; m.p. 244–245.3 °C (lit.[13] 242.4 °C, dec); IR (KBr) ν_{max}: 3434, 2925, 1654, 1619, 1570, 1443 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 4.25 (d, J = 3.2 Hz, 4H, CH_2), 5.65 (br, 2H, OH), 6.06 (s, 1H, CH), 6.32 (s, 2H, C-5H in pyran ring), 7.27–7.37 (m, 5H, Ph), 9.36 (s, 2H, OH); ESI-MS: *m/z* 373 (MH^+).

3,3'-Dihydroxy-6,6'-bis(hydroxymethyl)-2,2'-(4-methyl phenylmethane-1,1-diyl)di-4H-pyran-4-one (**3g**): 88% yield; m.p. 223–223.4 °C; IR (KBr) ν_{max}: 3322, 2925, 1655, 1619, 1570, 1457 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 2.27 (s, 3H, CH_3) 4.25 (d, J = 2.4 Hz, 4H, CH_2), 5.64 (br, 2H, OH), 6.01 (s, 1H, CH), 6.31 (s, 2H, C-5H in pyran ring), 7.16 (m, 4H, Ar), 9.33 (br, 2H, OH); ESI-MS: *m/z* 387 (MH^+); HRMS: Found 387.1081 ($[M+H]^+$) and 409.0904 ($[M+Na]^+$); Calcd 387.1080 and 409.0899 for $C_{20}H_{19}O_8$ and $C_{20}H_{18}NaO_8$, respectively.

3,3'-Dihydroxy-6,6'-bis(hydroxymethyl)-2,2'-(4-methoxyl phenylmethane-1,1-diyl)di-4H-pyran-4-one (**3h**): 82% yield; m.p. 235.8–236.7 °C (lit.[20] 248–250 °C); IR (KBr) ν_{max}: 3402, 3310, 2930, 1655, 1618 1577, 1458 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H, CH_3), 4.25 (d, J = 2.0 Hz, 4H, CH_2), 5.99 (s, 1H, CH), 6.31 (s, 2H, C-5H in pyran ring), 6.89 (d, J = 8.8 Hz, 2H, Ar), 7.21 (d, J = 8.8 Hz, 2H, Ar), 9.30 (s, 2H, OH); ESI-MS: *m/z* 403 (MH^+).

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