Microwave-Assisted Efficient Synthesis of 2-Hydroxydeoxybenzoins from the Alkali Degradation of Readily Prepared 3-Aryl-4-hydroxycoumarins in Water

Zhong-Zhen Zhou,[#] Guang-Hua Yan,[#] Wen-Hua Chen,* and Xue-Mei Yang*

School of Pharmaceutical Sciences, Southern Medical University; Guangzhou 510515, China.
Received July 31, 2013; accepted August 19, 2013

This paper describes an operationally simple, green and efficient approach for the synthesis of 2-hydroxydeoxybenzoins bearing diverse substituents from the microwave-assisted alkali degradation of 3-aryl-4-hydroxycoumarins in water. The latter compounds were readily prepared from the intramolecular Claisen condensation reaction of methyl 2-(2-arylacetoxy)benzoates in the presence of Cs_2CO_3–acetone, in excellent yields and without laborious workup procedures. This method is highly atom-economic and thus applicable for the large-scale synthesis of 2-hydroxydeoxybenzoins.

Key words 3-aryl-4-hydroxycoumarin; atom economy; 2-hydroxydeoxybenzoin; microwave irradiation; water chemistry

2-Hydroxydeoxybenzoins (2-OH-DBOs, Fig. 1) are analogs of 2-hydroxydihydrochalcones and exhibit multiple pharmacological activities, including anti-microbial,[1–3] anti-oxidant,[4] anti-inflammatory,[5] vasodilator[6] and estrogenic effects.[7–9] 2-OH-DBOs are also key precursors for many drugs with promising pharmacological properties, such as 4-hydroxycoumarins,[10] 2,3-diaryl-2*H*-1-benzopyrans,[11] 3-arylflavones,[12] Schiff bases,[4] benzofurans,[13] isoflavones,[14,15] biaryl heterocycles,[16] isoquinolin-1(2*H*)-ones[17] and Landomycin A[18] (Fig. 1). In addition, 2-OH-DBOs are used industrially to manufacture fire-retardant polymers.[19] Therefore, considerable endeavors have been made to develop sophisticated approaches for the synthesis of 2-OH-DBOs.

Among the various methods to date, classic methods, such as Hoesch reactions,[20,21] Nencki reactions[22,23] and Friedel–Crafts acylation reactions[24,25] of polyphenols with substituted phenylacetonitriles or phenylacetic acids are attractive for the ready synthesis of polyhydroxydeoxybenzoins. However, these methods are only applicable for symmetrical polyphenols, such as resorcinol, phloroglucinol, benzene-1,2,3-triol, pyrocatechol and hydroquinone. The yields of 2-OH-DBOs from asymmetrical phenols are very low (<10%).[26]

An alternative approach for the synthesis of 2-OH-DBOs is the alkali degradation of 3-aryl-4-hydroxycoumarins in MeOH (only one citation in the Chemical abstracts database).[27] However, the synthetic procedures are tedious and time-consuming. It is reported that the alkali decarboxylation of coumarins can be also carried out under other conditions, such as dimethyl sulfoxide (DMSO)–H_2O,[28] H_2O/imidazole,[29] microwave-assisted H_2O–1-hexyl-3-methylimidazolium bromide,[30] $(CH_2OH)_2$,[28,31] H_2O–$(CH_2OH)_2$,[32] *N*,*N*-dimethylformamide (DMF)[33] and tetrahydrofuran (THF)–allylpalladium chloride dimer.[34] Herein we report the first efficient synthesis of 2-OH-DBOs **3** from the microwave-assisted alkali degradation of 3-aryl-4-hydroxycoumarins **2** in water, starting from methyl 2-(2-arylacetoxy) benzoates **1** (Chart 1).

Results and Discussion

Because methyl 2-(2-arylacetoxy)benzoates **1** are readily hydrolyzed under reported conditions[35–39] and 3-aryl-4-hydroxycoumarins **2** are key intermediates for the synthesis of 2-OH-DBOs **3**, we firstly revisited the intramolecular Claisen condensation reaction of methyl 2-(2-phenylacetoxy)benzoate **1a** in acetone as a model reaction to search for the optimized reaction conditions. The results are summarized in Table 1. Initially, we investigated the effect of bases and temperature (entries 1–9). As a result, compound **2a** was prepared in 88% yield in the presence of Cs_2CO_3 at room temperature (entry 5). However, it was not detected at room temperature in the presence of Na_2CO_3 (entry 1), K_2CO_3 (entry 3), or LiOH (entry 7). Stronger bases, such as KOH (entry 9), led to the complete hydrolysis of compound **1a**. Because of the hydrolysis of compound **1a**, raising the temperature was unfavorable, except in the presence of K_2CO_3 (entry 4). In addition, it is reported that 4-hydroxy-3-phenylcoumarins can be prepared from the phase transfer catalyst-mediated one-pot reaction of methyl 2-hydroxybenzoates with arylacetyl chlorides.[35,36] Therefore, we also carried out the reaction in the presence of ammonium salts (entries 10–13). Thus, compound **2a** was prepared in 47–75% yields in the presence of K_2CO_3–$BnEt_3NCl$. However, it was not detected in the presence of K_2CO_3–Et_4NBr. These results enabled us to conclude that the optimized condition was Cs_2CO_3–acetone at 20°C. This method avoids the use of poisonous pyridine.[10,37] More importantly, the hydrolysis of methyl 2-(2-arylacetoxy)benzoates **1** was rarely observed (except in the synthesis of compound **2j**, *vide infra*), which readily takes place under the reported conditions, such as K_2CO_3–refluxing acetone,[35,36] solvent-free Na at 200°C[38] and lithium bis(trimethylsilyl)amide (LiHMDS) (or NaHMDS)–THF at −20°C.[39]

This condition was applicable for a wide range of methyl 2-(2-arylacetoxy)benzoates **1** bearing both electron-donating and electron-withdrawing substituents (Table 2). For comparison, we also conducted the reactions in the presence of KOH–pyridine at room temperature, which is a classic method for the synthesis of 3-aryl-4-hydroxycoumarins **2**. It is clear from Table 2 that, compared with the outcomes (48–60% yields) under the conditions of KOH–pyridine at room temperature,

The authors declare no conflict of interest.

[#] These authors contributed equally to this work.

* To whom correspondence should be addressed. e-mail: whchen@smu.edu.cn; xujp@smu.edu.cn

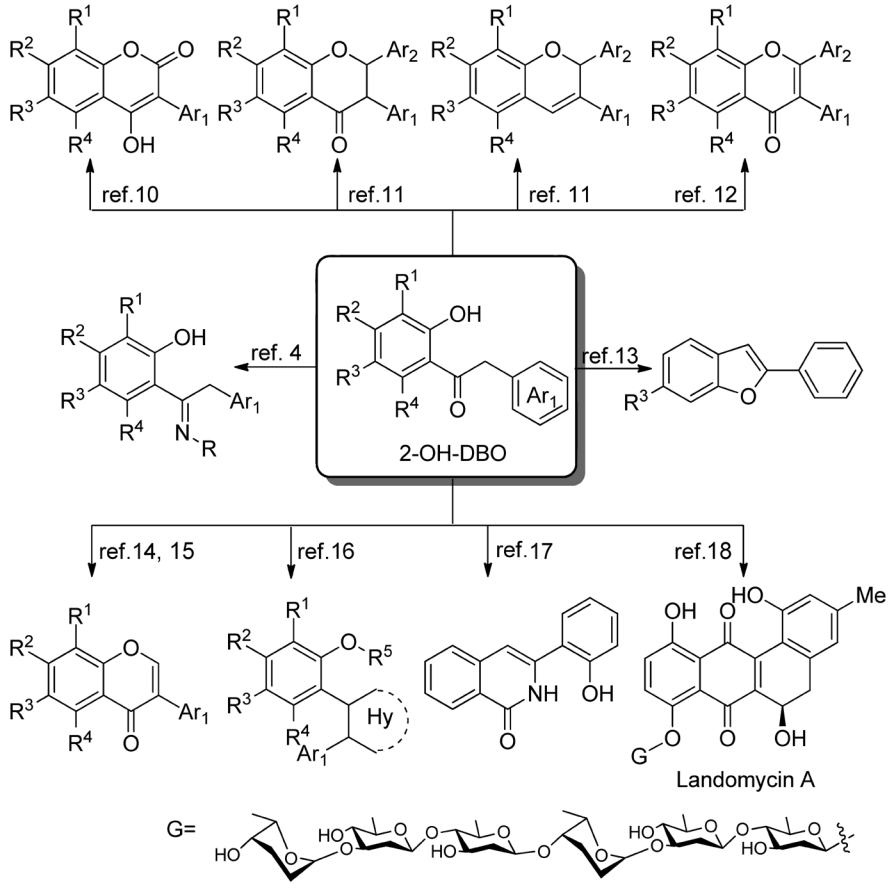


Fig. 1. Drugs That Are Synthesized from 2-OH-DBOs

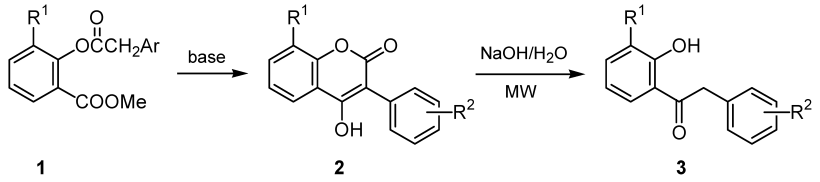


Chart 1. Synthetic Route for Compounds **3a**–**j**

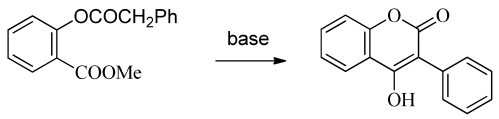
the yields of compounds **2** under our optimized condition (Cs_2CO_3–acetone at 20°C) increased by 15–37% and reached 63–94%.

With 3-aryl-4-hydroxycoumarins **2** readily available and with the aim to synthesize 2-OH-DBOs **3** bearing various substituents under mild conditions, we carried out the alkali degradation of 3-aryl-4-hydroxycoumarins **2** under microwave irradiation. The degradation of 4-hydroxy-3-phenylcoumarin **2a** was chosen as a model to optimize the effect of solvent, time and temperature. The results are summarized in Table 3.

As shown in Table 3, raising the reaction temperature from 100 to 140°C improved the yield of compound **3a** remarkably from 21 to 99% yields (entries 1–5). Further increases of the temperature above 140°C led to a decrease in the yield (entries 5–7). This may be due to the increasing instability of compound **3a** at high temperatures. On the other hand, the yields increased with time, *i.e.*, from 45% (1 min, entry 8) to 99% yields (10 min, entry 5). Extending the reaction time longer than 10 min did not change the yield significantly (entries 10–12). It should be noted that yield in MeOH was poor under microwave irradiation (entry 13). Taken together, we concluded that, under microwave irradiation, the optimized conditions were 140°C and 10 min in water. Thus, the microwave-assisted alkali degradation of 4-hydroxy-3-phenyl coumarin **2a** is characterized not only by the excellent yields and high efficiency, but also by the environmentally friendly reaction media (water).

Then, we extended these reaction conditions to other substrates (Table 4). As can be seen from Table 4, moderate to good isolated yields (16–84%) were achieved under conventional heating. However, the reactions were sluggish (180–1368 min) and highly dependent on the starting materials. Prolonging the reaction time did not significantly improve the yield. In sharp contrast, under microwave irradiation, the reactions were completed in 10–15 min and compounds **3a**–**j** were isolated in 62 to 99% yields. More importantly, this condition was applicable for the synthesis of a wide range of 2-hydroxydeoxybenzoins bearing both electron-donating and electron-withdrawing substituents, except compound **3j** because of some side reactions.

Table 1. The Effect of Bases and Temperature on the Yields of 4-Hydroxy-3-phenylcoumarin **2a**[a)]

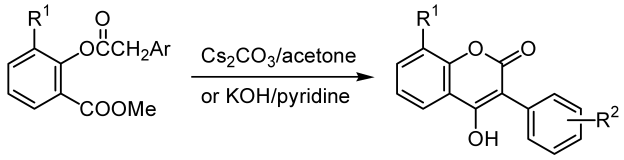


1a **2a**

No.	Base	T (°C)	t (h)	Isolated yield (%)
1	Na_2CO_3	20	5	—[b)]
2	Na_2CO_3	Reflux	3	Trace[c)]
3	K_2CO_3	20	5	—[b)]
4	K_2CO_3	Reflux	5	46
5	Cs_2CO_3	20	4	88
6	Cs_2CO_3	35	2	55
7	LiOH	20	5	—[b)]
8	LiOH	30	1.5	Trace[c)]
9	KOH	20	10	Trace[c)]
10	$K_2CO_3+Et_4NBr$	20	5	—[b)]
11	$K_2CO_3+Et_4NBr$	Reflux	2	Trace[c)]
12	$K_2CO_3+BnEt_3NCl$	20	2	75
13	$K_2CO_3+BnEt_3NCl$	Reflux	1	47

a) All the reactions were run with compound **1a** (1.0 mmol), base (5.0 mmol) and ammonium salt (1.0 mmol in the case of entries 10–13) in anhydrous acetone unless otherwise noted. *b*) No reaction was observed. *c*) Significant hydrolysis of **1a** was observed.

Table 2. Synthesis of 3-Aryl-4-hydroxycoumarins[a)]



1 **2**

Compound	R^1	R^2	Cs_2CO_3–Acetone		KOH–Pyridine	
			t (h)	Isolated yield (%)	t (h)	Isolated yield (%)
2a	H	H	4.0	88	2.0	56
2b	H	4′-F	4.5	72	2.0	55
2c	H	4′-MeO	7.5	78	2.5	48
2d	Me	H	4.5	88	6.0	48
2e	Me	2′-Cl	7.5	88	8.0	51
2f	Me	4′-F	7.5	94	6.0	57
2g	Me	2′-Cl-4′-F	6.0	83	7.5	60
2h	Me	4′-Cl	4.0	89	8.0	60
2i	Me	4′-MeO	6.0	89	5.5	60
2j	Me	3′,4′-diMeO	11.0	63	5.5	48

a) All the reactions were run with compounds **1** (1.0 mmol) and base (5.0 mmol) in acetone (3 mL) or pyridine (5 mL) at room temperature unless otherwise noted.

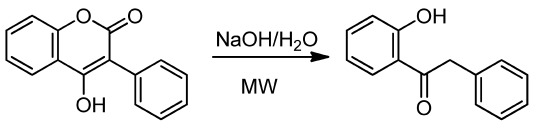
Concluding Remarks

In conclusion, we have developed a mild and practical approach for the synthesis of 2-hydroxydeoxybenzoins bearing diverse substituents from the alkali degradation of 3-aryl-4-hydroxycoumarins in water. This procedure is characterized by excellent yield, high efficacy and easy manipulation, and thus applicable for the large-scale synthesis of 2-hydroxydeoxybenzoins. Moreover, it reduces the use of organic solvents, minimizes the formation of waste, and improves energy consumption. In addition, we have also revisited the intramolecular Claisen condensation reaction of methyl 2-(2-arylacetoxy)benzoates as key starting materials for the synthesis of 2-hydroxydeoxybenzoins, and found that cesium carbonate/acetone at room temperature is an optimized reaction condition that boasts of excellent yields, little hydrolysis and simple workup procedures.

Experimental

General Electrospray ionization (ESI) and high resolution-electron ionization (HR-EI) mass spectra were measured on a water ultra performance liquid chromatography (UPLC)/Quattro Premier XE and Thremo High Resolution mass spectrometer (MAT95XP), respectively. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using Varian Mercury 400 spectrometers and tetramethylsilane (TMS) as an internal reference. Microwave-irradiated reactions were carried out

Table 3. Optimization of the Model Reaction under Microwave Irradiation[a)]

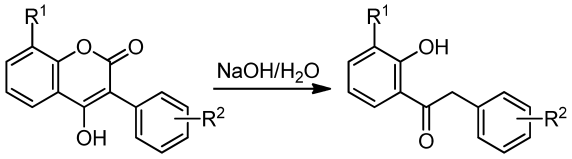


2a **3a**

No.	Solvent	T (°C)	t (min)	Isolated yield (%)
1	H_2O	100	10	21
2	H_2O	110	10	51
3	H_2O	120	10	62
4	H_2O	130	10	75
5	H_2O	140	10	99
6	H_2O	150	10	88
7	H_2O	160	10	86
8	H_2O	140	1	45
9	H_2O	140	5	83
10	H_2O	140	15	98
11	H_2O	140	20	95
12	H_2O	140	25	94
13	MeOH	140	10	Trace

a) All the reactions were run with compound **2a** (1.0 mmol) in 10% NaOH solution (5 mL) unless otherwise noted.

Table 4. Synthesis of 2-Hydroxydeoxybenzoins **3a–j** under the Condition of Microwave Irradiation and Conventional Heating



2 **3**

Compound	R^1	R^2	Microwave irradiation[a)]		Conventional heating[b)]	
			t (min)	Isolated yield (%)	t (min)	Isolated yield (%)
3a	H	H	10	99	180	84
3b	H	4′-F	10	82	330	40
3c	H	4′-MeO	10	88	360	72
3d	Me	H	10	88	360	39
3e	Me	2′-Cl	10	84	390	58
3f	Me	4′-F	10	92	552	81
3g	Me	2′-Cl-4′-F	10	74	510	57
3h	Me	4′-Cl	10	89	582	63
3i	Me	4′-MeO	10	79	690	56
3j	Me	3′,4′-diMeO	10	62	1368	16

a) All the reactions were run with compounds **2** (1.0 mmol) in 10% NaOH solution (5 mL) at 140°C for 10 min unless otherwise noted. *b*) The reactions were run under refluxing conditions in 10% NaOH solution (5 mL) for compounds **2a–i** (1.0 mmol), and in a mixture of 10% NaOH and methanol (5 mL, 4 : 1, v/v) for compound **2j** (1.0 mmol).

on a U.S.A. CEM Discover Focused Microwave Synthesizer (Serial Number DU8290), in sealed heavy-walled Pyrex tubes. During the reaction time, single mode microwave irradiation at constant temperature, pressure and irradiation power (100 W) was achieved by automatic power control.

General Procedures for the Preparation of 3-Aryl-4-hydroxycoumarins 2a–j in the Presence of KOH–Pyridine at Room Temperature 4-Hydroxy-3-phenylcoumarin **2a** as an example: to a solution of methyl 2-(2-phenylacetoxy) benzoate **2a** (270 mg, 1.0 mmol) in dry pyridine (5 mL) was added KOH (280 mg, 5 mmol). The resulting mixture was stirred at room temperature for 2 h. Then the reaction solution was poured into cold HCl (3 N, 20 mL). The formed solid was collected by filtration and recrystallized from ethanol to give compound **2a** (134 mg, 56%).

General Procedures for the Preparation of 3-Aryl-4-hydroxycoumarins 2a–j in the Presence of Cs_2CO_3–Dry Acetone at Room Temperature 4-Hydroxy-3-phenylcoumarin **2a** as an example: to a solution of compound **2a** (130 mg, 0.5 mmol) in dry acetone (3 mL) was added Cs_2CO_3 (815 mg, 2.5 mmol). The resulting mixture was stirred at room temperature for 4 h. Then the reaction solution was poured into cold HCl (3 N, 10 mL). The formed solid was collected by filtration and re-crystallized from ethanol to give compound **2a** (210 mg, 88%).

4-Hydroxy-3-phenyl-2*H*-chromen-2-one (**2a**)[10]: ^{1}H-NMR

(400 MHz, DMSO-d_6) δ: 7.33–7.47 (m, 7H), 7.67 (t, J=7.8 Hz, 1H), 8.05 (d, J=7.6 Hz, 1H), 11.42 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 106.55, 116.62, 116.83, 124.22, 124.35, 127.87, 128.38, 131.40, 132.47, 132.71, 152.70, 160.68, 162.31. ESI-MS m/z: 277.2 ([M+K]$^+$), 239.2 ([M+H]$^+$).

3-(4-Fluorophenyl)-4-hydroxy-2*H*-chromen-2-one (**2b**)[10]: ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.25 (t, J=8.2 Hz, 2H), 7.38–7.46 (m, 4H), 7.67 (t, J=7.8 Hz, 1H), 8.01 (d, J=7.6 Hz, 1H), 11.45 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 105.59, 115.20, 115.41, 116.65, 116.76, 124.13, 124.40, 128.65, 128.68, 132.78, 133.48, 133.56, 152.70, 160.76 (C–F), 160.84, 162.30, 163.18 (C–F). ESI-MS m/z: 279.4 ([M+Na]$^+$), 257.5 ([M+H]$^+$).

4-Hydroxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one (**2c**)[10]: ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.80 (s, 3H), 7.00 (d, J=8.8 Hz, 2H), 7.31–7.43 (m, 4H), 7.67–7.63 (m, 1H), 7.99 (dd, J=7.9, 1.2 Hz, 1H), 11.20 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 55.51, 106.22, 113.95, 116.56, 116.86, 124.03, 124.27, 124.33, 132.52, 132.58, 152.58, 159.07, 160.31, 162.46. Negative ESI-MS m/z: 268.0 ([M−H]$^-$).

4-Hydroxy-8-methyl-3-phenyl-2*H*-chromen-2-one (**2d**)[10]: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.50 (s, 3H), 6.47 (s, 1H), 7.22 (t, J=7.6 Hz, 1H), 7.43–7.48 (m, 4H), 7.53–7.56 (m, 2H), 7.75 (d, J=7.6 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.63, 106.32, 116.52, 121.77, 123.80, 125.44, 127.87, 128.41, 131.40, 132.51, 133.64, 150.99, 160.85, 162.24. ESI-MS m/z: 275.6 ([M+Na]$^+$), 253.5 ([M+H]$^+$).

3-(2-Chlorophenyl)-4-hydroxy-8-methyl-2*H*-chromen-2-one (**2e**): ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.41 (s, 3H), 7.30 (t, J=7.7 Hz, 1H), 7.37–7.46 (m, 3H), 7.56 (d, J=8.0 Hz, 2H), 7.87 (d, J=8.0 Hz, 1H), 11.59 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.64, 104.03, 116.22, 121.94, 123.93, 125.61, 127.55, 129.60, 130.22, 131.68, 133.76, 133.98, 135.07, 151.31, 161.44, 161.79. ESI-MS m/z: 309.8 ([M+Na]$^+$), 287.8 ([M+H]$^+$). HR-EI-MS for $C_{16}H_{11}ClO_3$ (M$^+$) Calcd: 286.0397; Found: 286.0392.

3-(4-Fluorophenyl)-4-hydroxy-8-methyl-2*H*-chromen-2-one (**2f**): ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.40 (s, 3H), 7.23–7.303 (m, 3H), 7.44 (dd, J=8.4, 5.6 Hz, 2H), 7.53 (d, J=7.2 Hz, 1H), 7.85 (d, J=8.0 Hz, 1H), 11.32 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.62, 105.34, 115.21, 115.42, 116.46, 121.79, 123.83, 125.47, 128.73, 128.76, 133.46, 133.55, 133.72, 150.98, 160.75 (C–F), 161.09, 162.24, 163.17 (C–F). ESI-MS m/z: 293.8 ([M+Na]$^+$), 271.9 ([M+H]$^+$). HR-EI-MS for $C_{16}H_{11}FO_3$ (M$^+$) Calcd: 270.0692; Found: 270.0685.

3-(2-Chloro-4-fluorophenyl)-4-hydroxy-8-methyl-2*H*-chromen-2-one (**2g**): ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.41 (s, 3H), 7.28–7.33 (m, 2H), 7.45 (t, J=7.4 Hz, 1H), 7.56 (t, J=7.4 Hz, 2H), 7.83 (d, J=8.0 Hz, 1H), 11.61 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.62, 103.01, 114.77, 114.98, 116.17, 116.82, 117.07, 121.91, 123.99, 125.63, 128.13, 128.16, 134.07, 135.16, 135.25, 136.07, 136.18, 151.34, 161.09 (C–F), 161.44, 162.09, 163.55 (C–F). ESI MS m/z: 327.5 ([M+Na]$^+$), 305.5 ([M+H]$^+$). HR-EI-MS for $C_{16}H_{10}ClFO_3$ (M$^+$) Calcd: 304.0303; Found: 304.0291.

3-(4-Chlorophenyl)-4-hydroxy-8-methyl-2*H*-chromen-2-one (**2h**)[40]: ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.40 (s, 3H), 7.28 (t, J=7.4 Hz, 1H), 7.42–7.55 (m, 5H), 7.85 (d, J=8.0 Hz, 1H), 11.43 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.62, 105.12, 116.44, 121.83, 123.87, 125.51, 128.45, 131.49, 132.53, 133.31, 133.83, 151.02, 161.25, 162.07. ESI-MS m/z: 325.8 ([M+K]$^+$), 309.9 ([M+Na]$^+$), 287.8 ([M+H]$^+$).

4-Hydroxy-3-(4-methoxyphenyl)-8-methyl-2*H*-chromen-2-one (**2i**)[10]: ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.39 (s, 3H), 3.80 (s, 3H), 7.00 (d, J=7.6 Hz, 2H), 7.28 (d, J=7.6 Hz, 1H), 7.33 (d, J=8.0 Hz, 2H), 7.51 (d, J=7.2 Hz, 1H), 7.83 (d, J=7.6 Hz, 1H), 11.11 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.62, 55.51, 113.95, 116.57, 121.71, 123.76, 124.37, 125.36, 132.57, 133.46, 150.86, 159.04, 160.60, 162.41. ESI-MS m/z: 321.9 ([M+K]$^+$), 283.9 ([M+H]$^+$).

3-(3,4-Dimethoxyphenyl)-4-hydroxy-8-methyl-2*H*-chromen-2-one (**2j**)[10]: ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.39 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 6.91–7.04 (m, 3H), 7.27 (t, J=7.7 Hz, 1H), 7.51 (d, J=7.3 Hz, 1H), 7.81 (d, J=7.4 Hz, 1H), 11.05 (s, 1H, OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.60, 55.90, 55.94, 106.12, 112.06, 115.21, 116.53, 121.71, 123.77, 123.96, 124.50, 125.32, 133.46, 148.73, 148.79, 150.90, 160.59, 162.31. ESI-MS m/z: 351.9 ([M+K]$^+$), 335.9 ([M+Na]$^+$), 313.9 ([M+H]$^+$).

General Procedures for the Conventional Preparation of 2-Hydroxydeoxybenzoins 3a–j 2-Hydroxydeoxybenzoin **3a** as an example: to a stirring 10% NaOH solution (5 mL) was added compound **2a** (238 mg, 1.0 mmol). The resulting mixture was refluxed for 3 h. Then the reaction solution was poured into cold HCl (6 N, 5 mL) and extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with water (15 mL×3), dried over anhydrous $MgSO_4$ and concentrated. The obtained residue was purified by chromatography on a silica gel column, eluting with petroleum ether to afford compound **3a** (198 mg, 84%).

General Procedures for Microwave-Assisted Preparation of 2-Hydroxydeoxybenzoins 3a–j 2-Hydroxydeoxybenzoin **3a** as an example: compound **2a** (238 mg, 1.0 mmol) and 10% NaOH solution (5 mL) were added to a microwave tube. After sealed, the tube was microwave-irradiated at 140°C for 10 min. The reaction solution was poured into cold HCl (6 N, 5 mL) and extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with water (15 mL×3), dried over anhydrous $MgSO_4$ and concentrated to afford compound **3a** (210 mg, 99%).

1-(2-Hydroxyphenyl)-2-phenylethanone (**3a**)[41]: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.31 (s, 2H), 6.89–6.93 (m, 1H), 6.98–7.01 (m, 1H), 7.27–7.30 (m, 3H), 7.34–7.38 (m, 2H), 7.45–7.50 (m, 1H), 7.87 (dd, J=8.2, 1.4 Hz, 1H), 12.22 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 45.10, 118.63, 118.95, 119.02, 127.16, 128.75, 129.39, 130.38, 133.90, 136.52, 162.89, 203.85. Negative ESI-MS m/z: 211.5 ([M−H]$^-$).

2-(4-Fluorophenyl)-1-(2-hydroxyphenyl)ethanone (**3b**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.28 (s, 2H), 6.91 (t, J=7.6 Hz, 1H), 6.97–7.08 (m, 3H), 7.22–7.25 (m, 2H), 7.48 (t, J=7.8 Hz, 1H), 7.84 (d, J=8.0 Hz, 1H), 12.15 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 44.10, 115.51, 115.72, 118.70, 118.89, 119.01, 129.45, 129.49, 130.15, 130.96, 131.04, 136.64, 160.78 (C–F), 162.85, 163.22 (C–F), 203.53. Negative ESI-MS m/z: 229.6 ([M−H]$^-$). HR-EI-MS for $C_{14}H_{11}FO_2$ (M$^+$) Calcd: 230.0743; Found: 230.0733.

1-(2-Hydroxyphenyl)-2-(4-methoxyphenyl)ethanone (**3c**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.31 (s, 2H), 6.88–6.98 (m, 3H), 6.98–7.00 (m, 1H), 7.19 (dd, J=6.8, 2.0 Hz, 2H), 7.45–7.49 (m, 1H), 7.87 (dd, J=8.2, 1.4 Hz, 1H), 12.23 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 44.21, 55.21, 114.21, 118.61, 118.91, 118.97, 125.78, 130.32, 130.41, 136.44, 158.72, 162.87,

204.16. Negative ESI-MS *m/z*: 241.6 ([M−H]$^-$). HR-EI-MS for $C_{15}H_{14}O_3$ (M^+) Calcd: 242.0943; Found: 242.0938.

1-(2-Hydroxy-3-methylphenyl)-2-phenylethanone (**3d**)[26]: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 4.31 (s, 2H), 6.81 (t, J=7.8 Hz, 1H), 7.27–7.30 (m, 3H), 7.34–7.38 (m, 3H), 7.73 (dd, J=8.0, 1.2 Hz, 1H), 12.54 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.47, 45.15, 118.24, 118.28, 127.09, 127.69, 127.94, 128.71, 129.38, 134.11, 137.20, 161.38, 204.05. Negative ESI-MS *m/z*: 226.0 ([M−H]$^-$).

2-(2-Chlorophenyl)-1-(2-hydroxy-3-methylphenyl)ethanone (**3e**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H), 4.48 (s, 2H), 6.85 (t, J=7.6 Hz, 1H), 7.20–7.25 (m, 3H), 7.36–7.38 (m, 1H), 7.43–7.45 (m, 1H), 7.75–7.77 (m, 1H), 12.37 (d, J=0.4 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.50, 42.88, 118.34, 118.37, 126.94, 127.49, 127.72, 128.77, 129.52, 131.62, 132.53, 134.49, 137.30, 161.08, 202.65. ESI-MS *m/z*: 283.5 ([M+Na]$^+$), 261.5 ([M+H]$^+$). HR-EI-MS for $C_{15}H_{13}ClO_2$ (M^+) Calcd: 260.0604; Found: 260.0598.

2-(4-Fluorophenyl)-1-(2-hydroxy-3-methylphenyl)ethanone (**3f**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 4.28 (s, 2H), 6.82 (t, J=7.6 Hz, 1H), 7.02–7.06 (m, 2H), 7.21–7.25 (m, 2H), 7.36 (d, J=7.2 Hz, 1H), 7.70 (dd, J=8.0, 0.8 Hz, 1H), 12.46 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.47, 44.16, 115.48, 115.69, 118.15, 118.31, 127.72, 127.79, 129.68, 129.71, 130.94, 131.02, 137.32, 160.75 (C–F), 161.36, 163.19 (C–F), 203.74. ESI-MS *m/z*: 283.0 ([M+K]$^+$), 267.5 ([M+Na]$^+$), 245.4 ([M+H]$^+$). HR-EI-MS for $C_{15}H_{13}FO_2$ (M^+) Calcd: 244.0900; Found: 244.0895.

2-(2-Chloro-4-fluorophenyl)-1-(2-hydroxy-3-methylphenyl)-ethanone (**3g**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H), 4.45 (s, 2H), 6.86 (t, J=7.6 Hz, 1H), 6.97–7.02 (m, 1H), 7.18–7.25 (m, 2H), 7.38 (d, J=7.2 Hz, 1H), 7.74 (d, J=8.0 Hz, 1H), 12.31 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.49, 42.09, 114.10, 114.31, 116.82, 117.06, 118.22, 118.42, 127.34, 127.80, 128.38, 128.42, 132.46, 132.55, 135.07, 135.17, 137.41, 160.56 (C–F), 161.08, 163.04 (C–F), 202.28. Negative ESI-MS *m/z*: 277.5 ([M−H]$^-$). HR-EI-MS for $C_{15}H_{12}ClFO_2$ (M^+) Calcd: 278.0510; Found: 278.0505.

2-(4-Chlorophenyl)-1-(2-hydroxy-3-methylphenyl)ethanone (**3h**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 4.28 (s, 2H), 6.82 (t, J=7.6 Hz, 1H), 7.20 (t, J=5.2 Hz, 2H), 7.31–7.37 (m, 3H), 7.68 (t, J=4.0 Hz, 1H), 12.43 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.47, 44.35, 118.13, 118.34, 127.70, 127.82, 128.85, 130.79, 132.47, 133.12, 137.38, 161.36, 203.43. Negative ESI-MS *m/z*: 259.5 ([M−H]$^-$). HR-EI-MS for $C_{15}H_{13}ClO_2$ (M^+) Calcd: 260.0604; Found: 260.0597.

1-(2-Hydroxy-3-methylphenyl)-2-(4-methoxyphenyl)-ethanone (**3i**)[42]: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 3.79 (s, 3H), 4.25 (s, 2H), 6.81 (t, J=7.8 Hz, 1H), 6.89 (dd, J=6.8, 2.0 Hz, 2H), 7.19 (dd, J=6.8, 2.0 Hz, 2H), 7.34 (d, J=7.6 Hz, 1H), 7.71–7.73 (m, 1H), 12.54 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.47, 44.26, 55.20, 114.17, 118.21, 118.23, 126.01, 127.66, 127.89, 130.41, 137.13, 158.67, 161.36, 204.38. Negative ESI-MS *m/z*: 255.5 ([M−H]$^-$).

2-(3,4-Dimethoxyphenyl)-1-(2-hydroxy-3-methylphenyl)-ethanone (**3j**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 3.86 (d, J=1.6 Hz, 6H), 4.24 (s, 2H), 6.78–6.85 (m, 4H), 7.34 (d, J=7.2 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 12.54 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.47, 44.73, 55.84, 111.36, 112.47, 118.22, 121.59, 126.47, 127.69, 127.88, 137.19, 148.16, 149.07, 161.37, 204.28. Negative ESI-MS *m/z*: 285.5 ([M−H]$^-$). HR-EI-MS for $C_{17}H_{18}O_4$ (M^+) Calcd: 286.1205; Found: 286.1200.

Acknowledgment This work was financially supported by the National Natural Science Foundation of China (No. 21002048).

References

1) Li H. Q., Xue J. Y., Shi L., Gui S.-Y., Zhu H.-L., *Eur. J. Med. Chem.*, **43**, 662–667 (2008).
2) Goto H., Kumada Y., Ashida H., Yoshida K., *Biosci. Biotechnol. Biochem.*, **73**, 124–128 (2009).
3) Xiao Z. P., Shi D. H., Li H. Q., Zhang L.-N., Xu C., Zhu H.-L., *Bioorg. Med. Chem.*, **15**, 3703–3710 (2007).
4) Ng L. T., Ko H. H., Lu T. M., *Bioorg. Med. Chem.*, **17**, 4360–4366 (2009).
5) Li H. Q., Luo Y., Lv P. C., Shi L., Liu C.-H., Zhu H.-L., *Bioorg. Med. Chem. Lett.*, **20**, 2025–2028 (2010).
6) Lu T. M., Kuo D. H., Ko H. H., Ng L.-T., *J. Agric. Food Chem.*, **58**, 10027–10032 (2010).
7) Fokialakis N., Lambrinidis G., Mitsiou D. Z., Aligiannis N., Mitakou S., Skaltsounis A.-L., Pratsinis H., Mikros E., Alexis M. N., *Chem. Biol.*, **11**, 397–406 (2004).
8) Papoutsi Z., Kassi E., Fokialakis N., Mitakou S., Lambrinidis G., Mikros E., Moutsatsou P., *Steroids*, **72**, 693–704 (2007).
9) Chandrasekharan S., Bhaskar B., Muthiah R., Chandrasekharan A. K., Ramamurthy V., *Steroids*, **78**, 147–155 (2013).
10) Tang L., Pang Y., Yan Q., Shi L., Huang J., Du Y., Zhao K., *J. Org. Chem.*, **76**, 2744–2752 (2011).
11) Sharma A. P., Saeed A., Durani S., Kapil R. S., *J. Med. Chem.*, **33**, 3222–3229 (1990).
12) Saeed A., Sharma A. P., Durani N., Jain R., Durani S., Kapil R. S., *J. Med. Chem.*, **33**, 3210–3216 (1990).
13) Chittimalla S. K., Chang T. C., Liu T. C., Hsieh H.-P., Liao C.-C., *Tetrahedron*, **64**, 2586–2595 (2008).
14) Gavande N., Karim N., Johnston G. A. R., Hanrahan J. R., Chebib M., *ChemMedChem*, **6**, 1340–1346 (2011). Selected papers for the synthesis of isoflavones from 2-OH-DBOs
15) Kumar M., Rawat P., Kureel J., Singh A. K., Singh D., Maurya R., *Bioorg. Med. Chem. Lett.*, **21**, 1706–1709 (2011). Selected papers for the synthesis of isoflavones from 2-OH-DBOs
16) Olivera R., SanMartin R., Churruca F., Dominguez E., *J. Org. Chem.*, **67**, 7215–7225 (2002).
17) Letcher R. M., Kwok N. C., Cheung K. K., *J. Chem. Soc., Perkin Trans. 1*, **14**, 1769–1771 (1992).
18) Yang X., Fu B. Q., Yu B., *J. Am. Chem. Soc.*, **133**, 12433–12435 (2011).
19) Moon S., Ku B., Emrick T., Coughlin B. E., Farris R. J., *J. Appl. Polym. Sci.*, **111**, 301–307 (2009).
20) Mays J. R., Hill S. A., Moyers J. T., Blagg B. S. J., *Bioorg. Med. Chem.*, **18**, 249–266 (2010). Selected papers on Hoesch reactions
21) Matin A., Gavande N., Kim M. S., Yang N. X., Salam N. K., Hanrahan J. R., Roubin R. H., Hibbs D. E., *J. Med. Chem.*, **52**, 6835–6850 (2009). Selected papers on Hoesch reactions
22) Kanagalakshmi K., Premanathan M., Priyanka R., Hemalatha B., Vanangamudi A., *Eur. J. Med. Chem.*, **45**, 2447–2452 (2010). Selected papers on Nencki reactions
23) Loewe W., Witzel S., Tappmeyer S., Albuschat R. X., *J. Heterocycl. Chem.*, **41**, 317–326 (2004). Selected papers on Nencki reactions
24) Yadav D. K., Gautam A. K., Kureel J., Srivastava K., Sahai M., Singh D., Chattopadhyay N., Maurya R., *Bioorg. Med. Chem. Lett.*, **21**, 677–681 (2011). Selected papers on Friedel–Crafts reaction
25) Luo Y., Li H.-Q., Zhou Y., Li Z.-L., Yan T., Zhu H.-L., *ChemMedChem*, **5**, 1110–1116 (2010). Selected papers on Friedel–Crafts reaction
26) Sharghi H., Kaboudin B., *J. Chem. Res.*, **10**, 628–629 (1998).

27) Rani B. S. U., Darbarwar M., *J. Indian Chem. Soc.*, **64**, 555–558 (1987).
28) Chang J. B., Wang S. Y., Shen Z. H., Huang G., Zhang Y. T., Zhao J., Li C. W., Fan F. F., Song C. J., *Tetrahedron Lett.*, **53**, 6755–6757 (2012).
29) Sinha A. K., Kumar V., Sharma A., WO Patent 07/110881 (2006) [*Chem. Abstr.*, **147**, 406534 (2006)].
30) Sharma A., Kumar R., Sharma N., Kumar V., Sinha A. K., *Adv. Synth. Catal.*, **350**, 2910–2920 (2008).
31) Tuhina K., Bhowmik D. R., Venkateswaran R. V., *Chem. Commun.* (Camb.), **38**, 634–635 (2002).
32) Roy A., Tuhina K., Biswas B., Venkateswaran R. V., *Tetrahedron*, **68**, 6575–6580 (2012), and references cited therein.
33) Lee C. W., Bloom S., WO Patent 12/026931 (2012) [*Chem. Abstr.*, **156**, 310668 (2012)].
34) Harayama T., Nishita Y., *Chem. Pharm. Bull.*, **44**, 1986–1988 (1996).
35) Sripathi S. K., Sivakamasundari S., *J. Indian Chem. Soc.*, **81**, 789–790 (2004).
36) Gandhidasan R., Neelakantan S., Raman P. V., Sripathi S. K., *Indian J. Chem. Sect B*, **27B**, 849 (1988).
37) Taksande K., Borse D. S., Lokhande P., *Synth. Commun.*, **40**, 2284–2290 (2010).
38) Stahmann M. A., Wolff I., Link K. P., *J. Am. Chem. Soc.*, **65**, 2285–2287 (1943).
39) Dittmer D. C., Li Q., Avilov D. V., *J. Org. Chem.*, **70**, 4682–4686 (2005).
40) Queval P., Falconet B., Susini-Garnier M. M., Krikorian-Manoukian M. A., Courmarcel D., Buu-Hoi N. P., *Chim. Ther.*, **7**, 300–306 (1972).
41) Park F. Y., Ullapu P. R., Choo H., Lee J. K., Min S.-J., Pae A. N., Kim Y., Baek D.-J., Cho Y. S., *Eur. J. Org. Chem.*, **32**, 5461–5469 (2008).
42) Martin R., Gros N., Bohmer V., Kmmerer H., *Monatsh. Chem.*, **111**, 81–92 (1980).