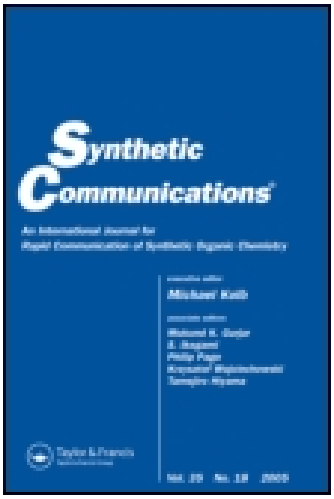

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MICROWAVE-ASSISTED EFFICIENT AND GREEN SYNTHESIS OF HYDROXYXANTHONE IN WATER

Xiao-Jin Zhang,[1,2] Suo-Fu Ye,[2] Yu Zhang,[2] Hu-Yan Meng,[2] Ming-Qian Zhang,[2] Wen-Lei Gao,[2] and Qi-Dong You[1,2]

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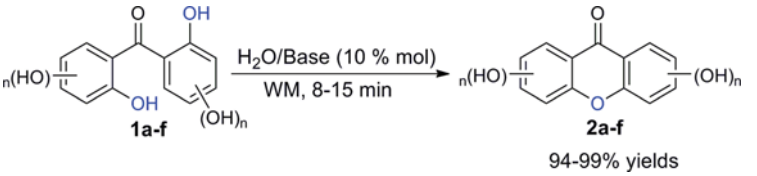
GRAPHICAL ABSTRACT



Abstract *An efficient and green procedure has been developed for the synthesis of hydroxyxanthones from substituted 2,2′-dihydroxybenzophenone precursors via microwave-assisted base-catalyzed cyclization in water. This method provides excellent yields of products in a short time, making it a useful strategy for the synthesis of structurally diverse hydroxyxanthones.*

Keywords Green synthesis; hydroxyxanthones; microwave; water

INTRODUCTION

Xanthones are oxygenated heterocyclic compounds with a dibenzo-γ-pyrone framework that are widely distributed in nature. The xanthone scaffold has been described as a "privileged structure" for biological profiles that vary depending on the nature and position of the substituents.[1] A large number of naturally occurring or synthetic xanthones that consist of the hydroxyxanthone scaffold have been reported, and these show a multitude of interesting biological activities, such as anti-Alzheimer, anticancer, and antimalarial activities and inhibition of Na/K-ATPase (Fig. 1).[2–5]

Generally, hydroxyxanthones can be achieved through condensation of the corresponding hydroxybenzoic acids with polyphenols by the Grover, Shah, and Shah (GSS) reaction.[6] However, this method is restricted to xanthones possessing

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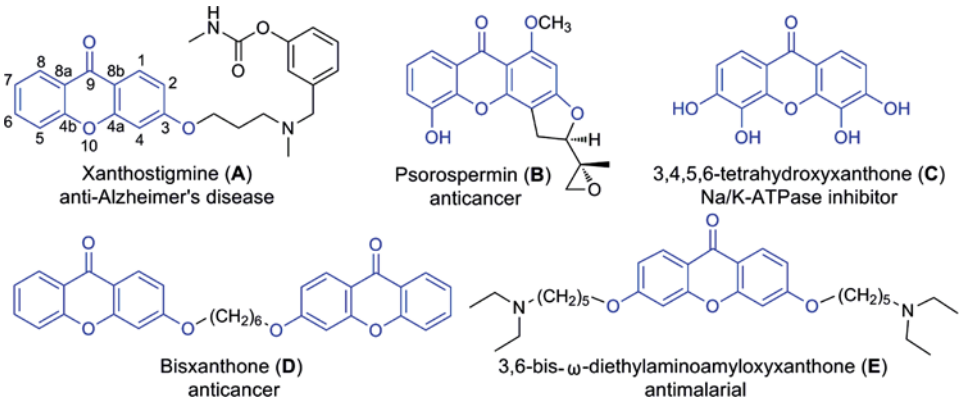


Figure 1. Some biological compounds with hydroxyxanthone scaffold. (Figure is provided in color online.)

a hydroxyl group at the 1-position. Thermal condensation of different methyl hydroxybenzoates with polyphenols has also been reported to directly give hydroxyxanthones in refluxing diphenyl ether, but the reactions are carried out in extremely harsh conditions and afford very poor yields.[7] Another method involving Friedel–Crafts acylation, cyclization, and demethylation has been described to provide diverse hydroxyxanthones, but it is stepwise and not environmentally friendly.[8,9] For these reasons, a facile, efficient, and environmentally benign procedure for the synthesis of this class of heterocyclic compounds is urgently needed.

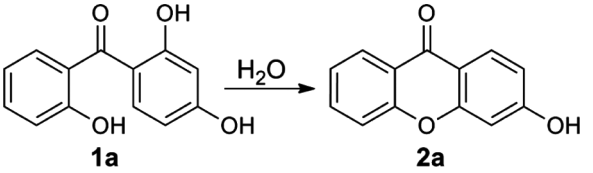
Nowadays, microwave-assisted organic synthesis (MAOS) has become a useful and important tool for rapid organic synthesis.[10] Some of the major advantages include spectacularly, reduced reaction time, improved conversions, and clean product formation.[11] Because water is very efficient at absorbing microwaves, and is obviously the cleanest and safest available solvent, numerous reports have recently focused on the combination of water as an environmentally friendly solvent for chemical transformations with the use of microwave irradiation (MWI) as an efficient heating method.[12]

Herein, we present a facile, efficient, and green method to synthesize hydroxyxanthones in a short time under MWI in water. To the best of our knowledge, this is the first time that synthesis of hydroxyxanthones in water by use of MWI has been reported.

RESULTS AND DISCUSSION

First, to investigate the effect of MWI on the cyclization reaction, hydroxybenzophenone **1a** was used as a test substrate. As shown in Table 1, the cyclization of hydroxybenzophenone **1a** to hydroxyxanthone **2a** under MWI at 100 °C in water as solvent was accomplished in 60 min with quantitative yield. On the other hand, when the reaction was carried out under conventional heating using the same sealed microwave tube at 100 °C for 24 h, only a trace amount of cyclization product **2a** was observed (entry 1, Table 1). Furthermore, a weak base, sodium acetate (NaOAc), was employed in trying to facilitate the deprotonation of the phenolic hydroxyl group and promote intramolecular nucleophilic cyclization. Fortunately,

Table 1. Microwave effect observed in the intramolecular cyclization of **1a** to **2a**



1a **2a**

			Microwave irradiation		Conventional heating	
Entry	Base (10 mol%)	Temp. (°C)	Time (min)	Yield (%)	Time (h)	Yield (%)
1	—	100	60	99	24	Trace[a]
2	NaOAc	100	12	99	24	8[b]

[a]The progress of the reaction was monitored by TLC.
[b]Isolated yield.

quantitative conversion of **1a** to **2a** was achieved in 12 min under MWI in the presence of NaOAc as a base catalyst, whereas only 8% conversion was detected in 24 h under conventional heating (entry 2, Table 1). All the evidence suggested that the cyclization reaction could be accelerated by MWI in water.

Subsequently, temperatures and basicity of catalysts were examined for their effects on the microwave-assisted cyclization of **1a** to **2a** (Table 2). The reaction time was significantly reduced from 15 min to 8 min when the temperature was raised from 90 °C to 120 °C. Further increase in temperature did not shorten the reaction time (entry 5, Table 2). Besides the relatively weak base NaOAc, moderate to strong bases such as Na_2CO_3 and NaOH were also applied as base catalysts. The results in Table 2 (entries 4, 6, and 7) showed that the reaction could complete rapidly in 8 min with excellent yields using different bases as catalysts, and the strength of basicity had no correlation with the reaction rate.

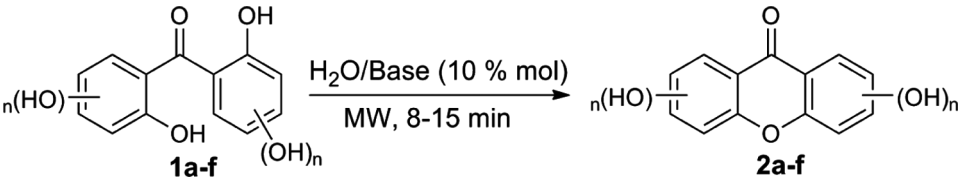
With the optimal reaction conditions (entry 4, Table 2) in hand, the scope of the cyclization reaction was extended to various hydroxybenzophenone substrates (Table 3). The hydroxybenzophenone precursors **1a–f** were conveniently prepared by Friedel–Crafts acylation of substituted benzoic acids with reactive polyphenols in the presence of phosphorus oxychloride and zinc(II) chloride according to

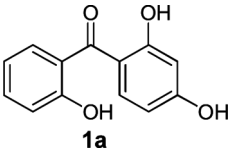
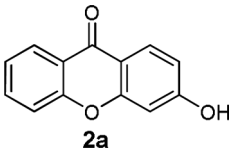
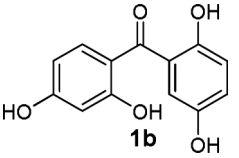
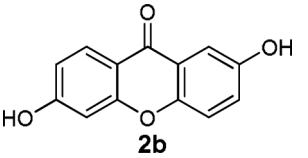
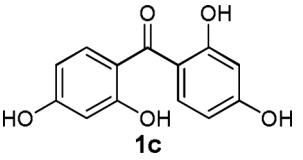
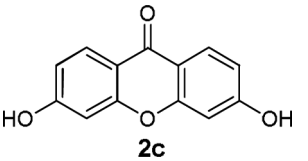
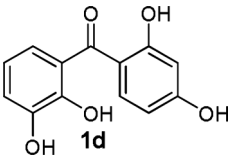
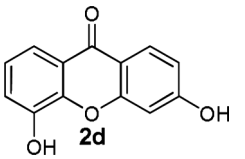
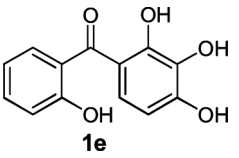
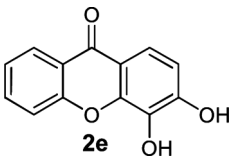
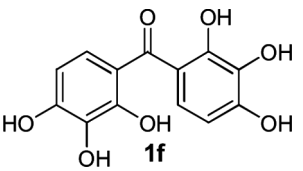
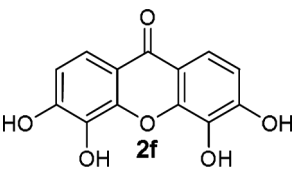
Table 2. The effects of the temperature and basicity of the cyclization of **1a** to **2a** under MWI

Entry	Base (10 mol%)	Temp. (°C)	Time[a] (min)	Yield[b] (%)
1	NaOAc	90	15	99
2	NaOAc	100	12	99
3	NaOAc	110	10	99
4	NaOAc	120	8	99
5	NaOAc	130	8	99
6	Na_2CO_3	120	8	98
7	NaOH	120	8	98

[a]The progress of the reaction was monitored by TLC.
[b]Isolated yields.

Table 3. Microwave-assisted synthesis of hydroxyxanthones from benzophenones in water



Entry[a]	Benzophenone	Hydroxyxanthone	Time (min)	Yield[b,c] (%)
1	 1a	 2a	8	99
2	 1b	 2b	8	98
3	 1c	 2c	8	99
4	 1d	 2d	8	99
5	 1e	 2e	12	96
6	 1f	 2f	15	94

[a]Run using P = 150 W.
[b]Isolated yields.
[c]All the hydroxyxanthones were characterized by ^{1}H NMR, ^{13}C NMR, IR, EI-MS, and HRESIMS (see Experimental section).

GSS[6] and Davies and coworkers.[13] The data in Table 3 demonstrated that hydroxybenzophenones **1a–f** could successfully convert into structurally diverse hydroxyxanthones **2a–f** under MWI in a short time (8–15 min) with good to quantitative yields (94–99%). Meanwhile, it was observed that the introduction of additional hydroxyl groups to any benzene ring of the hydroxybenzophenones could result in more reaction times for the completely conversions (compare entry 1 to entry 5, and entry 3 to entry 6, Table 3). Presumably, the p-π conjugation effect of phenolic hydroxyl group led to an increase in the electron densities at the *ortho*- and *para*- positions, which hampered the process of the intramolecular nucleophilic substitution.

In conclusion, in this work we have demonstrated a facile, efficient, and green procedure for the synthesis of hydroxyxanthones from substituted 2,2′-dihydroxybenzophenone precursors under MWI in water with base catalysts. This method provides excellent yields and purities of products in a short time, making it a useful strategy for the synthesis of structurally diverse hydroxyxanthones.

EXPERIMENTAL

Microwave irradiation was carried out in Discover microwave synthesizer of CEM Corporation. Melting points (mp) were determined with a Melt-Temp II apparatus and are reported without any correction. Infrared (IR) spectra were obtained with Nicolet iS10 Fourier transform (FT) spectrophotometer using KBr film. The ^{1}H NMR and ^{13}C NMR spectra were collected on either a Brucker AMX300 or a Brucker AMX500 spectrometer (300 MHz for ^{1}H; 75 MHz or 125 MHz for ^{13}C) using dimethyl sulfoxide (DMSO-d_6) as solvent with tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on a Shimadzu GC-MS 2010 (EI-MS) or a LC/MSD TOF mass spectrometer (HRESIMS).

General Procedure for the Synthesis of Hydroxyxanthones 2a–f

A sealed 10-mL glass tube containing a suspension of the benzophenones (1 mmol) and base (10% mol) in water (4 ml) was introduced in the cavity of the CEM microwave reactor and irradiated for the appropriate time and temperature under magnetic stirring. The process of reaction was monitored by thin-layer chromatography (TLC). After cooling to room temperature by air flow, the tube was removed from the rotor, and the reaction mixture was diluted with water and filtered. The precipitate was washed with water and dried to give hydroxyxanthones ("one-spot" on TLC), which were further purified by silica-gel column chromatography.

3-Hydroxy-*9H*-xanthen-9-one 2a

White solid. Mp: 254–255 °C (lit.[14] mp: 254–255 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.91 (m, 2 H), 7.44 (t, $J = 7.5$ Hz, 1 H), 7.60 (d, $J = 8.4$ Hz, 1 H), 7.82 (t, $J = 7.8$ Hz, 1 H), 8.05 (d, $J = 8.6$ Hz, 1 H), 8.15 (d, $J = 7.9$ Hz, 1 H), 11.02 (br, 1 H).[15] ^{13}C NMR (DMSO-d_6, 125 MHz): δ 102.12, 113.99, 114.11, 117.83, 121.20, 124.07, 125.82, 127.97, 134.74, 155.54, 157.54, 164.00, 174.73.[15] IR (cm^{-1}, KBr): 3137, 1614, 1561, 1455, 1310, 844, 751. EI-MS (m/z): 212 (M^{+}). HRESIMS calcd. for $C_{13}H_8O_3$ $[M - H]^{-}$ 211.0395; found 211.0400.

2,6-Dihydroxy-*9H*-xanthen-9-one 2b

Pale yellow solid. Mp: >300 °C (lit.[7] mp: >310 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.84(s, 1 H), 7.60 (d, J = 8.8 Hz, 1 H), 7.25 (m, 1 H), 7.47 (m, 2 H), 8.02 (d, J = 8.6 Hz, 1 H), 9.19 (br, 1 H), 10.84 (br, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 101.84, 118.67, 113.50, 113.84, 119.02, 121.78, 123.47, 127.84, 149.13, 153.63, 157.54, 163.60, 174.71. IR (cm^{-1}, KBr): 3280, 3185, 2932, 1632, 1460, 1293, 1151,795. EI-MS (m/z): 228 (M^+). HRESIMS calcd. for $C_{13}H_8O_4$ $[M-H]^-$ 227.0344; found 227.0348.

3,6-Dihydroxy-*9H*-xanthen-9-one 2c

White solid. Mp: >300 °C (lit.[6] mp:>330 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.85 (m, 2 H), 6.89 (m, 2 H), 8.00 (d, J = 8.6 Hz, 2 H), 10.82 (br, 2 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 112.02, 113.60, 113.98, 127.74, 147.44, 163.24, 173.93.[16] IR (cm^{-1}, KBr): 3385, 3138, 1614, 1457, 1276, 1174, 848. EI-MS (m/z): 228 (M^+). HRESIMS calcd. for $C_{13}H_8O_4$ $[M-H]^-$ 227.0344; found 227.0347.

3,5-Dihydroxy-*9H*-xanthen-9-one 2d

Pale yellow solid. Mp: >300 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.91 (m, 2 H), 7.24 (m, 2 H), 7.57 (d, J = 7.5 Hz, 1 H), 8.03 (d, J = 6.3 Hz, 1 H), 10.57 (br, 2 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 102.10, 113.83, 114.08, 115.17, 119.66 122.29, 123.67, 127.90, 145.02, 146.22, 15.27, 163.77, 174.97. IR (cm^{-1}, KBr): 3375, 3086, 1611, 1448, 1342, 1236, 745. EI-MS (m/z): 228 (M^+). HRESIMS calcd. for $C_{13}H_8O_4$ $[M-H]^-$ 227.0344; found 227.0347.

3,4-Dihydroxy-*9H*-xanthen-9-one 2e

White solid. Mp: 241–242 °C (lit.[8] mp: 237–239 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.95 (d, J = 8.7 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H), 7.60 (d, J = 9.0 Hz, 1 H), 7.83 (t, J = 7.8 Hz, 1 H), 8.15 (d, J = 8.2 Hz, 1 H), 9.91 (br, 2 H).[8] ^{13}C NMR (DMSO-d_6, 75 MHz): δ 103.03, 114.66, 116.52, 117.88, 120.77, 123.85, 125.81, 132.45, 134.69, 146.30, 151.37, 155.45, 175.22.[16] IR (cm^{-1}, KBr): 3550, 3121, 1613, 1460, 1349, 1062, 754. EI-MS (m/z): 228 (M^+). HRESIMS calcd. for $C_{13}H_8O_4$ $[M-H]^-$ 227.0344; found 227.0349.

3,4,5,6-Tetrahydroxy-*9H*-xanthen-9-one 2f

Yellow solid. Mp: >300 °C (lit.[8] mp: >300 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.92 (d, J = 8.4 Hz, 2 H), 7.53 (d, J = 8.5 Hz, 2 H), 9.42 (br, 4 H).[8] ^{13}C NMR (DMSO-d_6, 75 MHz): δ 112.99, 114.00, 116.15, 132.51, 145.23, 150.24, 174.70. IR (cm^{-1}, KBr): 3515, 3105, 1614, 1570, 1471, 1392, 1342, 1292, 1078, 1040, 770. EI-MS (m/z): 260 (M^+). HRESIMS calcd. for $C_{13}H_8O_4$ $[M-H]^-$ 259.0243; found 259.0248.

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