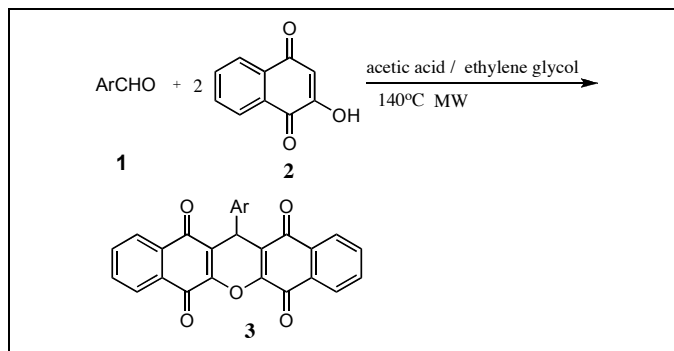


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A rapid and efficient method is developed to synthesize a series of benzoxanthene derivatives by the reaction of aldehydes and 2-hydroxynaphthalene-1,4-dione in mixed solvent of acetic acid and ethylene glycol under microwave irradiation. The method has the advantages of short synthetic route, operational simplicity and higher yields (70%~85%).

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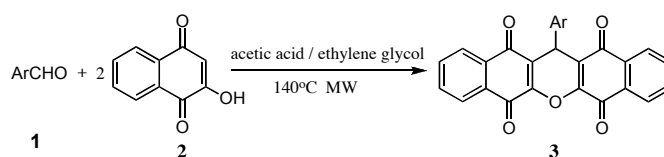
INTRODUCTION

Much attention has been paid to the development of new methods for the synthesis of heterocyclic compounds due to their potential importance in the fields of pharmaceutical and agricultural drugs. 4*H*-Benzo[*b*]pyrans and their derivatives have shown wide range of biological properties [1,2], such as spasmolytic, diuretic, anti-coagulant, anti-cancer and anti-ancaphylactia activities [3-5]. With 4*H*-Benzo[*b*]pyrans as structural unit, xanthenes and benzoxanthenes [6] are interesting compounds not only because of their pharmaceutical properties exemplified by anti-bacterial [7], antiviral [8] and anti-inflammatory activities [9], but also for their useful applications in dyes [10] and fluorescent materials [11]. As a result, the synthesis of new heterocyclic compounds containing xanthene and benzoxanthene scaffolds as well as the development of more rapid and efficient entry to these heterocycles have attracted considerable attention [12,13].

Microwave irradiation (MW) is a very useful technique in organic synthesis [14-17] since it is a simple, timesaving, high yielding, and environmentally friendly process. We have already reported the synthesis of heterocyclic compounds under microwave irradiation [18-20]. In continuation of our recent interest in the construction of heterocyclic scaffolds, we have developed a facile two-component reaction between aldehydes **1** and

2-hydroxynaphthalene-1,4-dione **2** under microwave irradiation to afford a series of new heterocyclic compounds, the aryl-substituted dibenzo[*b,i*]xanthene derivatives (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

To explore the scope and versatility of this method, various reaction conditions were investigated. Choosing an appropriate solvent is of crucial importance for the successful microwave-assisted synthesis. To search for the optimal solvent, the reaction of 3,4-dimethoxyphenyl aldehyde (**1i**) with 2-hydroxynaphthalene-1,4-dione **2** was examined using solvents of DMF, ethylene glycol, acetic acid and mixed solvent of acetic acid with ethylene glycol in different ratio, respectively. All the reactions were carried out at 140 °C with the maximum power of 300W and the results are summarized in Table 1.

As can be seen in Table 1, the reaction in mixed solvent of acetic acid with ethylene glycol (HOAc/ Ethylene glycol=2:1 V/V) gave the highest yield (Table 1, Entry 6).

This kind of mixed solvent was thus chosen as the solvent for all further reactions.

To optimize the reaction temperature, the same reaction of **1i** with **2** was carried out in above mixed solvent at temperature ranging from 100 °C to 150 °C, with the increment of 10 °C each time. The results are shown in Table 2.

Table 1

Solvent optimization for the synthesis of **3i**

Entry	Solvent	Volume ratio	Time(min)	Yield(%)
1	DMF	—	6	trace
2	HOAc	—	6	46
3	Ethylene glycol	—	6	35
4	Mixed solvent ^a	1:2 (V/V)	6	62
5	Mixed solvent ^a	1:1(V/V)	6	70
6	Mixed solvent ^a	2:1(V/V)	6	85

^aThe mixed solvent of HOAc and Ethylene glycol

Table 2

Temperature optimization for the synthesis of **3i**

Entry	Power(W)	T (°C)	Time(min)	Yield (%)
1	300	100	9	62
2	300	110	8	68
3	300	120	7	71
4	300	130	6	73
5	300	140	6	85
6	300	150	6	85

The yield of product **3i** was increased with the increasement of temperature from 100 °C to 140 °C (Table 2, Entry 1-5). However, the yield leveled off when the temperatures was further increased to 150 °C (Table 2, Entry 6). So, the temperature of 140 °C was considered to be the most suitable for the reaction.

Under these optimized reaction conditions [140 °C, mixed solvent of acetic acid and ethylene glycol (HOAc/Ethylene glycol=2:1 V/V)], a series of products **3** were synthesized with this simple reaction procedure. The results are summarized in Table 3.

Moreover, we performed the synthesis of **3i** in the same mixed solvent at 140 °C under classical heating

conditions. The yield of **3i** is 78% and the reaction time is 8 h. Therefore, microwave irradiation exhibited obvious advantages over conventional heating by greatly reducing the reaction time and improving the reaction yield.

The electronic effect of aryl group on this reaction was also investigated. Under optimized reaction conditions, both electron-withdrawing and electron-donating substituents readily provided dibenzo[*b,i*]xanthene derivatives in higher yields (Table 3). Therefore, the electronic nature of the substrate has no significant effect on this reaction.

The formation of **3** is likely to proceed *via* initial condensation of aldehydes **1** with 2-hydroxynaphthalene-1,4-dione **2** to afford 3-arylidene-naphthalene-1,2,4(3*H*)-trione **4** which further undergoes Michael addition with 2-hydroxynaphthalene-1,4-dione **2** to furnish **5**, which upon intermolecular cyclization and dehydration gives rise to **3** (Scheme 2).

The structures of all the synthesized compounds were characterized by IR, ¹H NMR and elemental analysis. The IR spectrum of compound **3i** showed strong absorptions at 1697 and 1662 cm⁻¹ due to C=O groups. The ¹H NMR spectrum of **3i** showed a singlet at δ 5.07 due to CH.

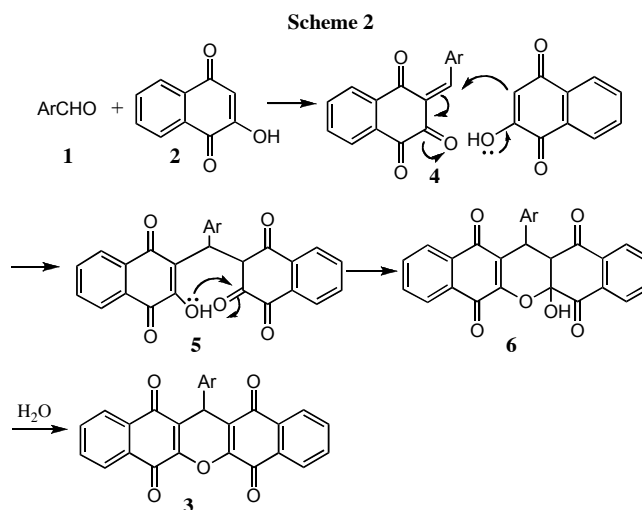


Table 3

Synthesis of Compounds **3**

entry	Compd	Ar	Time (min)	Temp. (° C)	Yield (%)	Mp (° C)
1	3a	4-NO ₂ C ₆ H ₄	7	140	76%	>300
2	3b	3-NO ₂ C ₆ H ₄	8	140	70%	>300
3	3c	4-OH-3-NO ₂ C ₆ H ₃	6	140	72%	>300
4	3d	4-ClC ₆ H ₄	7	140	72%	>300
5	3e	2-ClC ₆ H ₄	6	140	81%	>300
6	3f	3-BrC ₆ H ₄	7	140	78%	>300
7	3g	4-BrC ₆ H ₄	6	140	83%	>300
8	3h	4-OCH ₃ C ₆ H ₄	7	140	80%	>300
9	3i	3,4-(OCH ₃) ₂ C ₆ H ₃	6	140	85%	>300

In summary, we have demonstrated a rapid and direct method that offers a simple and efficient route for the synthesis of biologically important benzoxanthene derivatives in excellent yields. Particularly valuable features of this method included operational simplicity, increased safety for small-scale as well as short reaction time. Most importantly, the series of benzoxanthene derivatives may be interesting new lead compounds for biological activity evaluation.

EXPERIMENTAL

Microwave irradiation was carried out with microwave oven Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a TENSOR 27 spectrometer in KBr and reported in cm^{-1} . ^1H NMR spectra were measured on a Bruke DPX 400 MHz spectrometer in DMSO- d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument.

General Procedure for the synthesis of 14-Aryl-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone. The reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 10 mL Emrys™ reaction vial, an aldehyde **1** (1 mmol), 2-hydroxynaphthalene-1,4-dione **2** (1 mmol), acetic acid (1.0 mL) and ethylene glycol (0.5 mL) were mixed and then capped. The mixture was irradiated for 6–8 min at 300 W power and 140 °C. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was filtered to give the crude product, which was further purified by recrystallization from EtOH (95%) (**3a-3i**). All the products were characterized by IR, ^1H NMR and elemental analysis.

14-(4-nitrophenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3a). This compound was obtained according to above general procedure; ir (potassium bromide): CO 1681, 1667 cm^{-1} ; ^1H nmr: δ 8.13-8.16 (m, 2H, ArH), 8.10-8.12 (m, 2H, ArH), 8.03 (d, 2H, ArH, J = 8.4 Hz), 7.95-7.97 (m, 2H, ArH), 7.88-7.92 (m, 2H, ArH), 7.80 (d, 2H, J = 8.4 Hz), 5.25 (s, 1H, CH). *Anal* calcd. for $\text{C}_{27}\text{H}_{13}\text{NO}_7$: C, 69.98; H, 2.83; N, 3.02. found C, 69.77; H, 2.98; N, 3.22.

14-(3-nitrophenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3b). This compound was obtained according to above general procedure; ir (potassium bromide): CO 1680, 1663 cm^{-1} ; ^1H nmr: δ 8.26-8.28 (m, 1H, ArH), 8.21-8.23 (m, 1H, ArH), 8.14 (d, 2H, ArH, J = 8.4 Hz), 8.03-8.05 (m, 2H, ArH), 7.96-8.01 (m, 2H, ArH), 7.88-7.90 (m, 2H, ArH), 7.77 (d, 1H, ArH, J = 8.0 Hz), 7.58-7.60 (m, 1H, ArH), 5.26 (s, 1H, CH). *Anal* calcd. for $\text{C}_{27}\text{H}_{13}\text{NO}_7$: C, 69.98; H, 2.83; N, 3.02. found C, 69.72; H, 2.67; N, 3.19.

14-(4-hydroxy-3-nitrophenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3c). This compound was obtained according to above general procedure; ir (potassium bromide): CO 1681, 1667 cm^{-1} ; ^1H nmr: δ 10.90 (s, 1H, OH), 8.11 (d, 2H, ArH, J = 8.0 Hz), 8.03 (d, 1H, ArH, J = 8.0 Hz), 7.95-7.98 (m, 2H, ArH), 7.88-7.91 (m, 3H, ArH), 7.76 (d, 1H, ArH, J = 8.0 Hz), 7.66 (d, 1H, ArH, J = 8.0 Hz), 7.02 (d, 1H, ArH, J = 8.4 Hz), 5.10 (s, 1H, CH). *Anal* calcd. for $\text{C}_{27}\text{H}_{13}\text{NO}_8$: C, 67.65; H, 2.73; N, 2.92. found C, 67.91; H, 2.83; N, 2.76.

14-(4-chlorophenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3d). This compound was obtained according to above

general procedure; ir (potassium bromide): CO 1682, 1665 cm^{-1} ; ^1H nmr: δ 8.10-8.14 (m, 2H, ArH), 8.03 (d, 1H, ArH, J = 7.6 Hz), 7.96-7.99 (m, 2H, ArH), 7.88-7.92 (m, 2H, ArH), 7.76 (d, 1H, ArH, J = 7.6 Hz), 7.50 (d, 2H, ArH, J = 8.4 Hz), 7.32 (d, 2H, ArH, J = 8.4 Hz), 5.12 (s, 1H, CH). *Anal* calcd. for $\text{C}_{27}\text{H}_{13}\text{ClO}_5$: C, 71.61; H, 2.89. found C, 71.82; H, 2.73.

14-(2-chlorophenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3e). This compound was obtained according to above general procedure; ir (potassium bromide): CO 1701, 1665 cm^{-1} ; ^1H nmr: δ 8.13 (d, 2H, ArH, J = 8.0 Hz), 8.02 (d, 1H, ArH, J = 7.6 Hz), 7.99 (d, 1H, ArH, J = 7.6 Hz), 7.92-7.94 (m, 1H, ArH), 7.88-7.91 (m, 2H, ArH), 7.73-7.77 (m, 1H, ArH), 7.46-7.48 (m, 1H, ArH), 7.37-7.40 (m, 1H, ArH), 7.19-7.22 (m, 2H, ArH), 5.51 (s, 1H, CH). *Anal* calcd. for $\text{C}_{27}\text{H}_{13}\text{ClO}_5$: C, 71.61; H, 2.89. found C, 71.79; H, 2.71.

14-(3-bromophenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3f). This compound was obtained according to above general procedure; ir (potassium bromide): CO 1681, 1663 cm^{-1} ; ^1H nmr: δ 8.12 (t, 2H, ArH, J = 8.00 Hz), 8.03 (d, 1H, ArH, J = 7.6 Hz), 7.95-7.99 (m, 2H, ArH), 7.89-7.91 (m, 2H, ArH), 7.75 (t, 1H, ArH, J = 7.6 Hz), 7.65 (s, 1H, ArH), 7.50 (d, 1H, ArH, J = 8.0 Hz), 7.38 (d, 1H, ArH, J = 8.0 Hz), 7.23 (t, 1H, ArH, J = 8.0 Hz), 5.11 (s, 1H, CH). *Anal* calcd. for $\text{C}_{27}\text{H}_{13}\text{BrO}_5$: C, 65.21; H, 2.63. found C, 65.03; H, 2.81.

14-(4-bromophenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3g). This compound was obtained according to above general procedure; ir (potassium bromide): CO 1681, 1663 cm^{-1} ; ^1H nmr: 8.14–8.16 (m, 2H, ArH), 8.11 (d, 1H, ArH, J = 8.0 Hz), 8.03 (d, 1H, ArH, J = 7.6 Hz), 7.94-7.98 (d, 2H, ArH), 7.90-7.92 (m, 2H, ArH), 7.75–7.77 (m, 1H, ArH), 7.45 (s, 3H, ArH) 5.09 (s, 1H, CH). *Anal* calcd. for $\text{C}_{27}\text{H}_{13}\text{BrO}_5$: C, 65.21; H, 2.63. found C, 65.42; H, 2.49

14-(4-methoxyphenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3h). This compound was obtained according to above general procedure; ir (potassium bromide): CO 1701, 1662 cm^{-1} ; ^1H nmr: δ 8.09-8.13 (m, 2H), 8.02 (d, 1H, ArH, J = 7.6 Hz), 7.94-7.97 (m, 2H, ArH), 7.88-7.91 (m, 2H, ArH), 7.74 (t, 1H, ArH, J = 7.6 Hz), 7.36 (t, 2H, J = 8.4 Hz), 6.81 (d, 2H, J = 8.4 Hz), 5.07 (s, 1H, CH), 3.67 (s, 3H, OCH₃). *Anal* calcd. for $\text{C}_{28}\text{H}_{16}\text{O}_6$: C, 75.00; H, 3.60. found C, 75.23; H, 3.45.

14-(3,4-dimethoxyphenyl)-14H-dibenzo[*b,i*]xanthene-1,6,8,13-tetraone (3i). This compound was obtained according to above general procedure; ir (potassium bromide): CO 1697, 1681 cm^{-1} ; ^1H nmr: δ 8.10-8.14 (m, 2H, ArH), 8.03 (d, 1H, ArH, J = 8.0 Hz), 7.97-7.99 (m, 2H, ArH), 7.88-7.91 (m, 2H, ArH), 7.74 (t, 1H, ArH, J = 8.0 Hz), 6.99 (d, 1H, J = 8.0 Hz), 6.94 (d, 1H, J = 8.0 Hz), 6.81 (d, 1H, J = 8.0 Hz), 5.07 (s, 1H, CH), 3.67 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃). *Anal* calcd. for $\text{C}_{29}\text{H}_{18}\text{O}_7$: C, 72.80; H, 3.79. found C, 72.99; H, 3.52.

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