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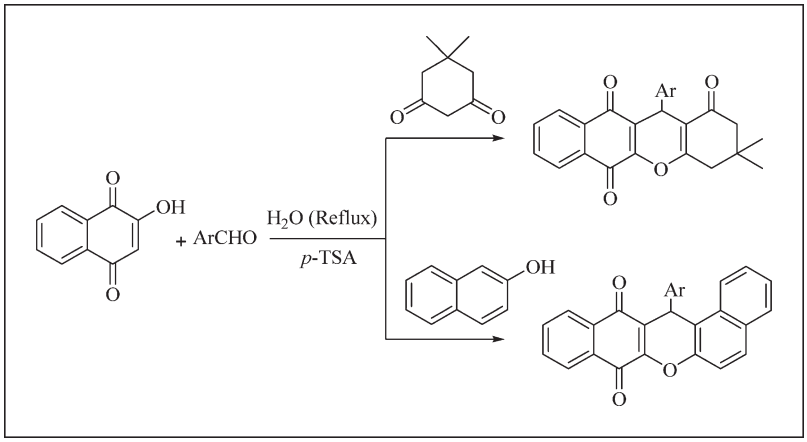

A clean, one-pot and three-component synthesis of new dibenzo[*a*,*i*]xanthene-diones derivatives by cyclo-condensation reaction of 2-hydroxynaphthalene-1,4-dione, aromatic aldehydes and dimedone or 2-naphthol in aqueous media is reported.

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INTRODUCTION

ortho-Quinone methides (*o*-QMs) are highly reactive intermediates that have been extensively harnessed by nature. Despite the general knowledge of *o*-QMs for over a century these intermediates still lie outside the synthetic mainstream [1,2]. Very recently, Pettus described the methods by which *o*-QMs are prepared, the benefits and limitations associated with each method as well as current applications in total synthesis [3]. The pseudo three-component condensation reaction of 2-naphthol with aldehydes in the presence of various catalysts to form xanthenes has been studied widely. The reaction proceeds through the *in situ* formation of *ortho*-quinone methides with 2-naphthol acting as a nucleophile [4]. However, the three-component condensation reactions of 2-naphthol and aldehydes with other nucleophiles is rarely reported in literature [5].

Xanthenes and benzoxanthenes have been reported to posses diverse biological and therapeutic properties, such as antibacterial [6], antiviral [7], and anti-inflammatory activities [8], as well as photodynamic therapy [9] and for antagonism of the paralyzing action of zoxazolamine [10]. The other useful applications of this heterocycles are as dyes [11], fluorescent materials for visualization of biomolecules [12], and in laser technologies [13]. Therefore, a number of methods have been reported for the preparation of xanthene derivatives [4,5f–h, 14–17].

Molecules with the naphthoquinone structure constitute one of the most interesting classes of compounds in organic chemistry, because of their biological properties, their industrial applications, and their potential as intermediates in the synthesis of heterocycles [18]. Naphthoquinone moiety occurs in different natural products, including β-lapachone **A**, α-xiloidone **B**, lambertellin **C**, WS-5995A **D**, and pyranokunthone B **E** [19]. Compounds **F** and **G** were extracted from marine actinomycete strain CNQ-525 bacteria; these bacteria were isolated from ocean sediments, which were collected at a depth of 152 m near La Jolla, California (Fig. 1). Compounds **F** and **G** possess significant antibiotic properties and cancer cell cytotoxicities activities [20].

In continuation of our previous works on synthesis of heterocycles containing naphthoquinone or xanthene moiety [21–25], herein we report a simple and efficient method for the preparation of benzo[*b*]xanthene-triones and dibenzo[*a*,*i*]xanthene-diones in aqueous media.

RESULTS AND DISCUSSION

We found that a mixture of 2-hydroxynaphthalene-1,4-dione **1**, 2-naphthol **2** and aromatic aldehydes **3a–i**,

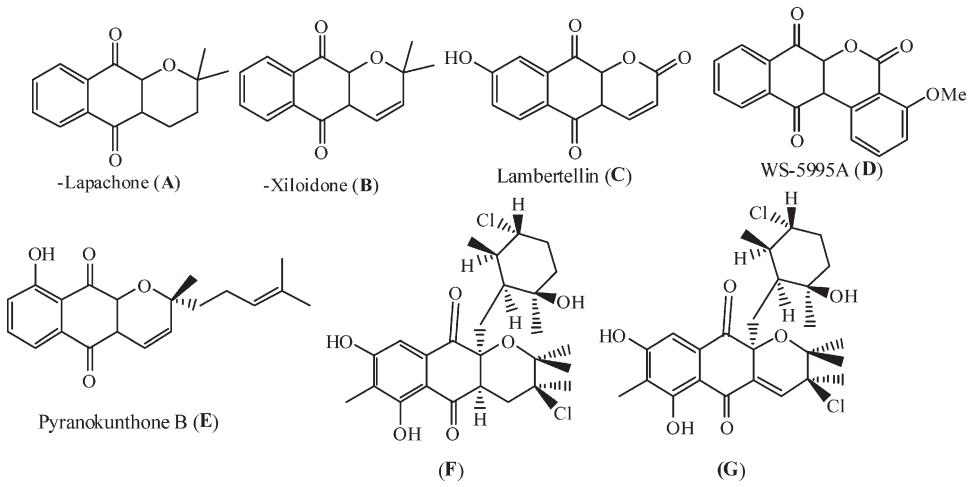


Figure 1. Examples of biologically active naphthoquinone derivatives.

in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and readily available catalyst at refluxing water for 8–10 h, afforded 14-aryl-8*H*-dibenzo[*a*,*i*]xanthene-8,13(14*H*)-diones **4a–i** in 83–91% yields (Scheme 1). The optimized results are summarized in Table 1. In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields.

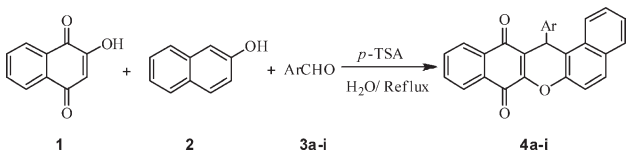
The results were good in terms of yields and product purity in the presence of *p*-TSA, while without *p*-TSA and over long period of time (24 h) the yields of products were low (<30%).

When this reaction was carried out with aliphatic aldehyde, such as butanal or pentanal, TLC and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products, the yield of the expected product was very poor.

By referring to the literature [4], the formation of products **4** can be rationalized by initial formation of *ortho*-quinone methides intermediate **5**. Subsequent addition of **1** to the intermediate **5**, followed by elimination of water afforded the corresponding products **4** (Scheme 2).

To further explore the potential of this protocol for xanthene synthesis, we investigated reaction of 1,3-cyclohexadione **6** instead of 2-naphthol **2** and obtained 3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione **7a–i**, in good yields for 14–16 h (Scheme 3). The optimized results are summarized in Table 2.

Scheme 1



The nature of the compounds **4** and **7** as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4** and **7** are stable solids whose structures are fully supported by IR, NMR spectroscopy, and elemental analysis.

In summary, a novel, simple, convenient, and practical method for the synthesis of substituted benzo[*b*]xanthene-triones and dibenzo[*a*,*i*]xanthene-diones has been reported by one-pot and three component reaction using *p*-TSA as an inexpensive and readily available catalyst. This protocol includes some important aspects like the use of water as a ''green'' reaction medium, high atom economy, mild reaction conditions, and excellent yields.

EXPERIMENTAL

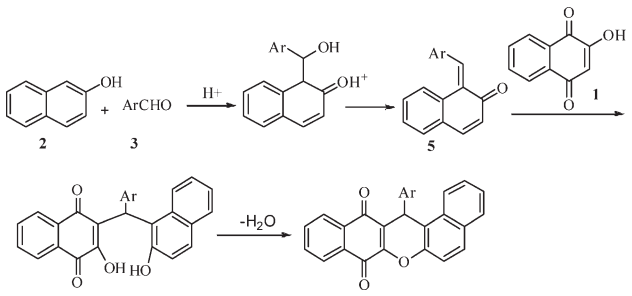
Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at

Table 1

Synthesis of dibenzo[*a*,*i*]xanthene-diones **4**.

Product **4**	Ar	Time (h)	Yield (%)
a	C_6H_5	10	88
b	4-Cl—C_6H_4	9	83
c	4-Br—C_6H_4	10	89
d	4-F—C_6H_4	8	85
e	4-MeO—C_6H_4	10	84
f	4-Me—C_6H_4	10	87
g	4-HO—C_6H_4	10	78
h	3-NO_2—C_6H_4	8	91
i	2-Cl—C_6H_4	9	87

Scheme 2



300.13 and 75.47 MHz, respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for preparation of 14-phenyl-8*H*-dibenzo[*a*,*i*]xanthene-8,13(14*H*)-dione (4a). A mixture of benzaldehyde (0.11 g, 1 mmol), 2-naphtol (0.140 g, 1 mmol), 2-hydroxynaphthalene-1,4-dione (0.17 g, 1 mmol), *p*-TSA (0.1 g) was refluxed in water (5 mL) for 10 h (TLC). At the end of the reaction, the precipitate formed was collected by filtration and washed with ethanol to afford the pure product **4a**. Orange powder (88%); m.p. 294–297°C; IR (KBr) (ν_{max}/cm^{-1}): 3054, 1703, 1656; ^{1}H NMR (DMSO-d_6): δ_H 5.09 (1H, s, CH), 7.16–8.08 (15H, m, H-Ar). MS (*m*/*z*) 388 (M^+). Anal. Calcd (%) for $C_{27}H_{16}O_3$: C, 83.49; H, 4.15. Found C, 83.55; H, 4.10.

Selected Characterization Data.

14-(4-Chlorophenyl)-8H-dibenzo[a,i]xanthene-8,13(14H)-dione(4b). Yellow powder (83%); m.p. 281–284°C; IR (KBr) (ν_{max}/cm^{-1}): 3044, 1699, 1663; ^{1}H NMR (DMSO-d_6): δ_H 5.77 (1H, s, CH), 7.24 (2H, d, J = 7.4 Hz, H-Ar), 7.39 (2H, d, J = 7.4 Hz, H-Ar), 7.46–7.51 (2H, m, H-Ar). 7.67–7.74 (2H, m, H-Ar). 7.86 (1H, d, J=7.1 Hz, H-Ar), 7.90–8.02 (4H, m, H-Ar), 8.20 (1H, d, J=7.1 Hz, H-Ar). MS (*m*/*z*, %) 422 (M^+). Anal. Calcd (%) for $C_{27}H_{15}ClO_3$: C, 76.69; H, 3.58. Found C, 76.61; H, 3.52.

14-(4-Bromophenyl)-8*H*-dibenzo[*a*,*i*]xanthene-8,13(14*H*)-dione (4c). Yellow powder (89%); m.p. 294–298°C; IR (KBr) (ν_{max}/cm^{-1}): 3075, 1704, 1663; ^{1}H NMR (DMSO-d_6): δ_H 5.89 (1H, s, CH), 7.27–7.34 (4H, m, H-Ar), 7.45 (2H, t, J = 6.8 Hz, H-Ar). 7.50–7.62 (2H, m, H-Ar), 7.79 (1H, t, J = 7.6 Hz, H-Ar). 7.85–7.92 (3H, m, H-Ar), 8.11–8.18 (2H, m, H-Ar). MS (*m*/*z*, %) 468 (M^+ + 2), 466 (M^+). Anal. Calcd (%) for $C_{27}H_{15}BrO_3$: C, 69.39; H, 3.24. Found C, 69.30; H, 3.33.

Due to very low solubility of the product **4a–c**, we cannot report the ^{13}C NMR data for this product.

12-phenyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (7a). Orange powder (82%); mp: 263–265°C. IR (KBr) (ν_{max}/cm^{-1}): 2926, 1678, 1606. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.94 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.15 and 2.31 (2H, AB system, J = 16.2 Hz, CH_2), 2.67 (2H, s, CH_2), 4.88 (1H, s, CH), 7.10–7.15 (1H, m, H-Ar), 7.21–7.32 (2H, m, H-Ar), 7.43–7.46 (2H, m, H-Ar). 7.80–7.91 (3H, m, H-Ar) 7.99–8.07 (1H, m, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 26.9, 28.9, 32.4, 32.7, 40.1, 113.6, 124.2, 126.2, 126.5, 127.2, 128.7, 128.8, 129.0, 130.9, 131.4, 134.6, 135.0, 143.2, 149.5, 163.4, 177.5, 183.2, 196.3. MS (*m*/*z*) 384 (M^+). Anal. Calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24;%. Found: C, 78.21; H, 5.29%.

Scheme 3

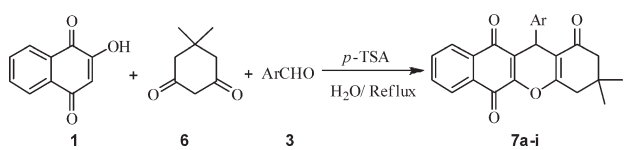


Table 2

Synthesis of dibenzo[*a*,*i*]xanthene-diones **7**.

Product **7**	Ar	Time (h)	Yield (%)
a	C_6H_5	16	82
b	4-Cl—C_6H_4	15	90
c	4-Br—C_6H_4	16	86
d	4-F—C_6H_4	14	82
e	4-NO_2–C_6H_4	14	84
f	4-Me—C_6H_4	16	83
g	2-Cl—C_6H_4	16	87
h	3-NO_2—C_6H_4	15	81
I	3-Br—C_6H_4	16	80

12-(4-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (7b). Yellow powder (90%); mp: 282–284°C. IR (KBr) (ν_{max}/cm^{-1}): 2932, 1663, 1618, 1594. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.94 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.15 and 2.31 (2H, AB system, J = 16.2 Hz, CH_2), 2.67 (2H, s, CH_2), 4.89 (1H, s, CH), 7.28–7.37 (4H, m, H-Ar), 7.83–7.90 (3H, m, H-Ar), 8.03–8.06 (1H, m, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 26.9, 29.0, 32.5, 33.7, 33.5, 50.5, 113.7, 124.2, 126.2, 126.5, 127.2, 128.6, 129.1, 130.9, 131.4, 134.6, 135.0, 143.2, 149.5, 163.4, 183.3, 196.4. MS (*m*/*z*) 418 (M^+). Anal. Calcd for $C_{25}H_{19}ClO_4$: C, 71.69; H, 4.57%. Found: C, 71.78; H, 4.50%.

12-(4-Bromophenyl)-3,3-dimethyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione (7c). Yellow powder (86%); mp: 268–270°C. IR (KBr) (ν_{max}/cm^{-1}): 2957, 1660, 1616, 1579. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.94 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.15 and 2.31 (2H, AB system, J = 15.9 Hz, CH_2), 2.67 (2H, s, CH_2), 4.88 (1H, s, CH), 7.10–7.12 (2H, d, J = 8.4 Hz, H-Ar), 7.42–7.45 (2H, m, H-Ar), 7.83–7.90 (3H, m, H-Ar), 8.03–8.06 (1H, m, H-Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 27.3, 29.0, 32.4, 33.7, 40.7, 50.5, 113.3, 123.8, 123.9, 126.6, 126.8, 129.7, 130.4, 131.4, 134.1, 134.7, 146.9, 149.3, 149.6, 163.4, 177.5, 196.0. MS (*m*/*z*) 464 (M^+), 462 (M^+). Anal. Calcd for $C_{25}H_{19}BrO_4$: C, 64.81; H, 4.13%. Found: C, 64.73; H, 4.20%.

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