One-Pot Synthesis of 12-Hydroxy-12*H*-benzo[*b*]thioxanthene-6,11-diones from 1,4-Naphthoquinone and *o*-Acylbenzenethiols

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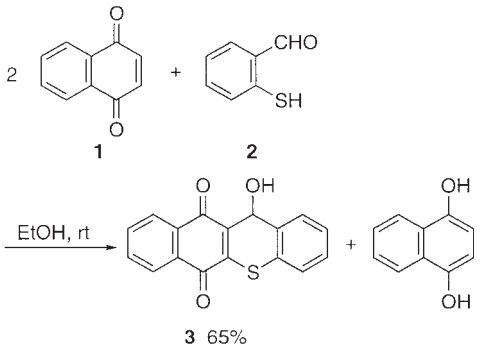
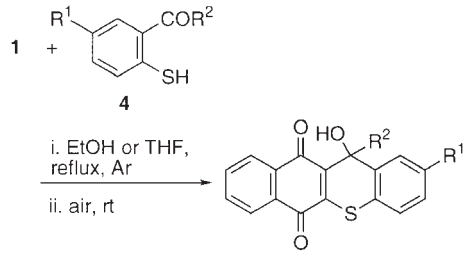
The title benzo[*b*]thioxanthenequinone derivatives could be prepared in one-pot via a sequential conjugate addition and an aldol-type reaction between 1,4-naphthoquinone and *o*-acylbenzenethiols, followed by oxidation with 1,4-naphthoquinone or air.

In recent years, we have been developing convenient methods to prepare biologically interesting heterocycle-fused quinone derivatives.[1] Compounds having the 12*H*-benzo[*b*]thioxanthene-6,11-dione skeleton are potentially interesting from biological and synthetic points of view. However, there have been few reports on methods for constructing this thioxanthenequinone derivative, though Chuang et al. have described a synthesis of diethyl 6,11-dihydro-6,11-dioxo-12*H*-benzo[*b*]-thioxanthene-12,12-dicarboxylates by a free radical reaction between 2-phenylthio-1,4-naphthoquinones with diethyl malonate initiated by manganese(III) acetate.[2] In this paper, we wish to report on a method for the synthesis of new thioxanthenequinone derivatives, 12-hydroxy-12*H*-benzo[*b*]thioxanthene-6,11-diones **3** and **5**, from 1,4-naphthoquinone (**1**) and *o*-acylbenzenethiols (**2** and **4**). The method is very simple; a sequential conjugate addition and aldol-type reaction between these starting materials takes place without any catalyst or initiator to give the desired products in one-pot.

First, in order to prepare 12-hydroxy-12*H*-benzo[*b*]thioxanthene-6,11-dione (**3**), 1,4-naphthoquinone (**1**) was allowed to react with 2-mercaptobenzaldehyde (**2**) (2:1 molar ratio) in ethyl alcohol at room temperature. The precipitated desired product **3** was collected by filtration in fair yield, as shown in Scheme 1.



Scheme 1.



a R^1 = H, R^2 = Ph
b R^1 = H, R^2 = *m*-Tol
c R^1 = H, R^2 = *p*-Tol
d R^1 = H, R^2 = *p*-ClC_6H_4
e R^1 = H, R^2 = *m*-$(MeO)C_6H_4$
f R^1 = H, R^2 = *p*-$(MeO)C_6H_4$
g R^1 = H, R^2 = Me
h R^1 = Cl, R^2 = Ph

5a	60%
5b	62%
5c	61%
5d	75%
5e	50%
5f	43%
5g	25%
5h	56%

Scheme 2.

Next, the reaction of 1,4-naphthoquinone (**1**) with 2-mercaptobenzophenone (**4a**) was carried out under the same conditions as described above. However, no reaction occurred. Heating of the mixture at reflux temperature resulted in the formation of an intractable mixture of products. Later, we found that the sequence leading to the desired 12-aryl-12-hydroxy-12*H*-benzo[*b*]thioxanthene-6,11-dione (**5**) could be accomplished as illustrated in Scheme 2. Thus, **1** and 2-mercaptobenzophenones **4** (an equimolar amount each) were mixed in ethanol at room temperature under argon. The mixtures were heated at reflux temperature for 8 h, and then the cooled reaction mixtures were exposed to air overnight. The precipitated desired benzothioxanthenequinone derivatives **5a–5f** and **5h** were collected by suction in moderate-to-good yields. The sequence between **1** and 2′-mercaptoacetophenone (**4g**) under the same conditions resulted in the formation of an intractable mixture, from which no more than a trace of the desired product was obtained. Using THF instead of ethanol as a solvent, the desired benzoxanthenequinone derivative **5g** was isolated from a rather complex reaction mixture by preparative TLC on silica gel in lower yield.

Experimental

Starting Materials. 2-Mercaptobenzaldehyde (**2**),[3] 2-mercaptobenzophenone (**4a**),[4] and 2′-mercaptoacetophenone (**4g**)[5] were prepared by appropriate literature methods. 2-Mercaptobenzophenones **4b–f** were prepared by the action of appropriate substituted phenyllithiums on 2-mercaptobenzoic acid according to a procedure in Ref. 5.

2-Mercapto-3′-methylbenzophenone (4b): mp 97–98 °C; IR (KBr disk) 2544, 1652 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.41 (3H, s), 4.21 (1H, s), 7.18 (1H, dt, J = 7.3, 1.3 Hz), 7.3–7.5 (5H, m), 7.54 (1H, d, J = 7.3 Hz), 7.61 (1H, s). Found: C, 73.52; H, 5.40; S, 14.02%. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.30; S, 14.04%.

2-Mercapto-4′-methylbenzophenone (4c): mp 83–84 °C; IR (KBr disk) 2541, 1652 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.44

Published on the web November 11, 2004; DOI 10.1246/bcsj.77.2095

(3H, s), 4.16 (1H, s), 7.18 (1H, td, $J = 7.3$, 1.3 Hz), 7.25–7.45 (5H, m), 7.69 (2H, d, $J = 8.2$ Hz). Found: C, 73.51; H, 5.40; S, 13.86%. Calcd for $C_{14}H_{12}OS$: C, 73.65; H, 5.30; S, 14.04%.

4′-Chloro-2-mercaptobenzophenone (4d): mp 73–74 °C; IR (KBr disk) 2534, 1657 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.17 (1H, s), 7.19 (1H, td, $J = 7.6$, 1.3 Hz), 7.36 (1H, td, $J = 7.6$, 1.3 Hz), 7.4–7.5 (4H, m), 7.72 (2H, d, $J = 8.9$ Hz). Found: C, 62.53; H, 3.73; S, 12.62%. Calcd for $C_{13}H_9ClOS$: C, 62.77; H, 3.65; S, 12.89%.

2-Mercapto-3′-methoxybenzophenone (4e): R_f 0.18 (1:10 AcOEt–hexane); IR (neat) 2548, 1651 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.86 (3H, s), 4.19 (1H, s), 7.1–7.55 (8H, m). Found: C, 68.55; H, 5.02; S, 12.87%. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.13%.

2-Mercapto-4′-methoxybenzophenone (4f): mp 87–88 °C; IR (KBr disk) 2538, 1645 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.89 (3H, s), 4.09 (1H, s), 6.95 (2H, d, $J = 8.9$ Hz), 7.19 (1H, td, $J = 7.3$, 1.6 Hz), 7.33 (1H, td, $J = 7.3$, 1.6 Hz), 7.35–7.45 (2H, m), 7.79 (2H, d, $J = 8.9$ Hz). Found: C, 68.72; H, 5.02; S, 13.00%. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.13%.

5-Chloro-2-mercaptobenzophenone (**4h**) was synthesized by the action of phenyllithium on 5-chloro-2 mercaptobenzoic acid,[6] which was prepared from 2-amino-5-chlorobenzoic acid according to a method by Allen and MacKay.[7] **4h**: R_f 0.36 (1:5 AcOEt–hexane); IR (neat) 2555, 1652 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.15 (1H, s), 7.3–7.55 (5H, m), 7.62 (1H, t, $J = 7.6$ Hz), 7.78 (2H, d, $J = 8.3$ Hz). Found: C, 62.50; H, 3.74; S, 12.72%. Calcd for $C_{13}H_9ClOS$: C, 62.77; H, 3.65; S, 12.89%.

12-Hydroxy-12*H*-benzo[*b*]thioxanthene-6,11-dione (3). To a stirred solution of 1,4-naphthoquinone (**1**) (0.47 g, 3.0 mmol) in EtOH (15 mL) at room temperature was added dropwise an EtOH (5 mL) solution of 2-mercaptobenzaldehyde (**2**) (0.21 g, 1.5 mmol). Stirring was continued for 4 h at the same temperature. Filtration and washing with ethanol of the resulting precipitate gave pure **3** (0.29 g, 65%) as a red solid: mp 254 °C (decomp); IR (KBr disk) 3416, 1671, 1652 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.79 (1H, d, $J = 5.3$ Hz), 6.39 (1H, d, $J = 5.3$ Hz), 7.35–7.55 (3H, m), 7.65–7.85 (3H, m), 8.1–8.25 (2H, m). Found: C, 69.19; H, 3.50; S, 10.90%. Calcd for $C_{17}H_{10}O_3S$: C, 69.37; H, 3.42; S, 10.89%.

Typical Procedure for the Preparation of Benzothioxanthenediones 5. 12-Hydroxy-12-phenyl-12*H*-benzo[*b*]thioxanthene-6,11-dione (5a): To a stirred solution of 1,4-naphthoquinone (**1**) (0.16 g, 1.0 mmol) in EtOH (10 mL) at room temperature under argon was added a solution of 2-mercaptobenzophenone (**4a**) (0.21 g, 1.0 mmol) in EtOH (10 mL). After stirring for 5 min, the mixture was refluxed for 8 h. The cooled resulting mixture was exposed to the atmosphere and stirring was continued overnight. The red precipitate was collected by suction and recrystallized from hexane–CH_2Cl_2 to give pure **5a** (0.22 g, 60%) as a red solid; mp 208 °C (decomp); IR (KBr disk) 3415, 1658, 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.56 (1H, s), 7.1–7.4 (6H, m), 7.49 (2H, dd, $J = 7.9$, 1.3 Hz), 7.65–7.8 (3H, m), 7.95–8.05 (1H, m), 8.1–8.15 (1H, m). Found: C, 74.52; H, 3.78; S, 8.43%. Calcd for $C_{23}H_{14}O_3S$: C, 74.58; H, 3.81; S, 8.66%.

THF was used in place of EtOH for the preparation of **5g**, which was obtained after the usual workup, followed by purification using preparative TLC on SiO_2 (1:3 AcOEt–hexane).

12-Hydroxy-12-(3-methylphenyl)-12*H*-benzo[*b*]thioxanthene-6,11-dione (5b): mp 220 °C (decomp); IR (KBr disk) 3392, 1668, 1631 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.29 (3H, s), 6.48 (1H, s), 6.97 (1H, d, $J = 7.4$ Hz), 7.1–7.35 (6H, m), 7.65–7.8 (3H, m), 8.0–8.05 (1H, m), 8.1–8.2 (1H, m). Found: C, 74.97; H, 4.44; S, 8.36%. Calcd for $C_{24}H_{16}O_3S$: C, 74.98; H, 4.19; S, 8.34%.

12-Hydroxy-12-(4-methylphenyl)-12*H*-benzo[*b*]thioxanthene-6,11-dione (5c): mp 215 °C (decomp); IR (KBr disk) 3434, 1657, 1633 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.25 (3H, s), 6.53 (1H, s), 7.08 (2H, d, $J = 7.9$ Hz), 7.2–7.35 (3H, m), 7.37 (2H, d, $J = 7.9$ Hz), 7.7–7.8 (3H, m), 8.0–8.05 (1H, m), 8.1–8.15 (1H, m). Found: C, 75.13; H, 4.46; S, 8.25%. Calcd for $C_{24}H_{16}O_3S$: C, 74.98; H, 4.19; S, 8.34%.

12-(4-Chlorophenyl)-12-hydroxy-12*H*-benzo[*b*]thioxanthene-6,11-dione (5d): mp 216 °C (decomp); IR (KBr disk) 3438, 1658, 1631 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.56 (1H, s), 7.2–7.4 (5H, m), 7.43 (2H, d, $J = 8.6$), 7.65–7.8 (3H, m), 7.95–8.05 (1H, m), 8.1–8.2 (1H, m). Found: C, 68.08; H, 3.17; S, 8.05%. Calcd for $C_{23}H_{13}ClO_3S$: C, 68.23; H, 3.24; S, 7.92%.

12-Hydroxy-12-(3-methoxyphenyl)-12*H*-benzo[*b*]thioxanthene-6,11-dione (5e): mp 235 °C (decomp); IR (KBr disk) 3438, 1670, 1632 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.76 (3H, s), 6.51 (1H, s), 6.70 (1H, dd, $J = 7.9$, 2.3 Hz), 7.05–7.35 (6H, m), 7.65–7.8 (3H, m), 8.0–8.05 (1H, m), 8.1–8.2 (1H, m). Found: C, 72.00; H, 4.04; S, 8.02%. Calcd for $C_{24}H_{16}O_4S$: C, 71.98; H, 4.03; S, 8.01%.

12-Hydroxy-12-(4-methoxyphenyl)-12*H*-benzo[*b*]thioxanthene-6,11-dione (5f): mp 216 °C (decomp); IR (KBr disk) 3466, 1684, 1658 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.72 (3H, s), 6.60 (1H, s), 6.79 (2H, d, $J = 8.9$ Hz), 7.15–7.35 (3H, m), 7.39 (2H, d, $J = 8.9$ Hz), 7.65–7.8 (3H, m), 8.0–8.05 (1H, m), 8.1–8.15 (1H, m). Found: C, 71.87; H, 4.12; S, 7.98%. Calcd for $C_{24}H_{16}O_4S$: C, 71.98; H, 4.03; S, 8.01%.

12-Hydroxy-12-methyl-12*H*-benzo[*b*]thioxanthene-6,11-dione (5g): mp 148 °C (decomp); IR (KBr disk) 3374, 1660, 1624 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.67 (3H, s), 6.65 (1H, s), 7.25–7.45 (3H, m), 7.7–7.85 (2H, m), 7.96 (1H, dd, $J = 7.9$, 1.3 Hz), 8.05–8.2 (2H, m). Found: C, 70.12; H, 4.22; S, 10.37%. Calcd for $C_{18}H_{12}O_3S$: C, 70.11; H, 3.92; S, 10.40%.

2-Chloro-12-hydroxy-12-phenyl-12*H*-benzo[*b*]thioxanthene-6,11-dione (5h): mp 237 °C (decomp); IR (KBr disk) 3400, 1663, 1631 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.59 (1H, s), 7.15–7.35 (5H, m), 7.45–7.5 (2H, m), 7.7–7.8 (3H, m), 8.0–8.05 (1H, m), 8.1–8.15 (1H, m). Found: C, 67.88; H, 3.34; S, 7.76%. Calcd for $C_{23}H_{13}ClO_3S$: C, 68.23; H, 3.24; S, 7.92%.

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