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# ONE-POT SYNTHESIS OF DIBENZOFURAN-1,4-DIONES

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*Dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday*

**Abstract** – One-pot synthesis of dibenzofuran-1,4-diones **8** from 4-methoxyphenols (or 4-methoxy-1-naphthols) **4** was achieved by oxidative dimerization over a semiconductor in heated, $O_2$-saturated toluene, followed by selective monodemethylation, and oxidative cyclization.

## INTRODUCTION

The dibenzofuran-1,4-dione core **1** is frequently found in natural products, such as popolohuanone E (**2**) and violet-quinone (**3**) (Figure 1),[1-4] and several methods have been reported for efficient construction of this structure.[5-8] In this context, we recently disclosed an efficient synthetic method of dibenzofuran-1,4-diones **8** having an oxygen functionality at C8, featuring a three-step sequence of oxidative dimerization of hydroquinone monomethyl ethers **4** leading to 2,2'-biarenyl-1,1'-quinones **6** via the 2,2'-biarenols **5**, followed by mono-demethylation of **6**, and oxidative cyclization of the quinone-arenols **7** (Scheme 1).[9]

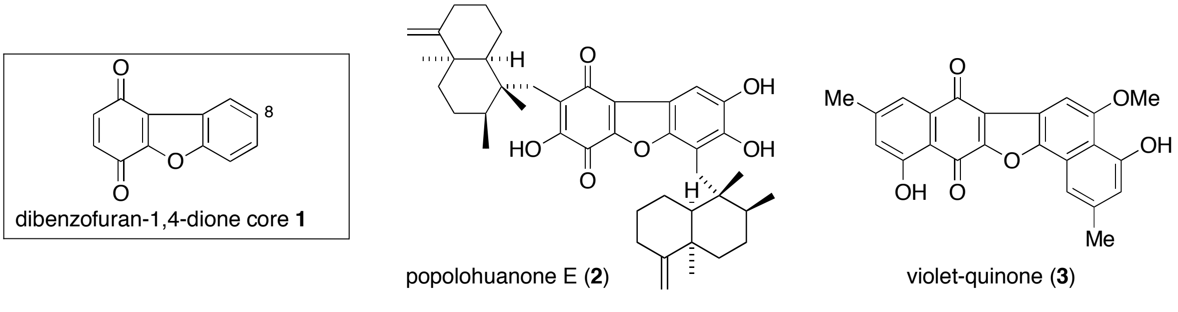
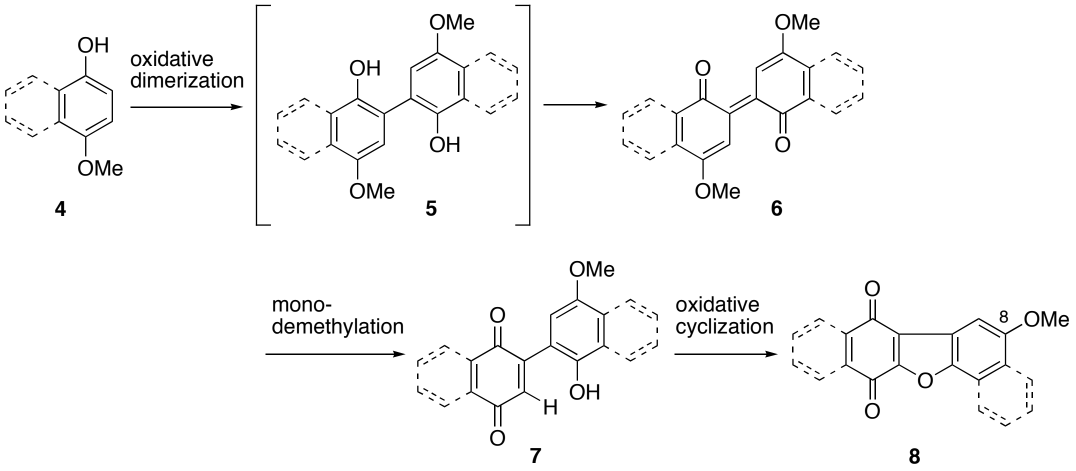


Figure 1

If the three-step sequence could be conducted in one pot, it would be very convenient for synthesizing a range of compounds **8** for studies on structure-activity relationships. We therefore sought appropriate oxidative conditions, and found that one-pot synthesis of several dibenzofuran-1,4-diones **8** from **4** could be achieved by employing a semiconductor and molecular oxygen.



Scheme 1

## RESULTS AND DISCUSSION

We recently reported that semiconductors, such as activated carbon, $ZrO_2$, $Nb_2O_5$, $TiO_2$, $SnO_2$, and $Ag_2O$, could be used for dimerization of 1-naphthols **4**, leading to the dimers **5** or **6**, and that $SnO_2$ effected mono-demethylation of **6**.[10] We initiated our investigation by examining the reaction of the naphthol **4a** with $SnO_2$ in the presence of various oxidants (Table 1). Since benzoquinone was found to be an excellent oxidant for dimerization of **4a** to **6a**,[11] $SnO_2$ and benzoquinone were used in combination. Heating a mixture of **4a**, $SnO_2$, and benzoquinone in toluene in a sealed tube at 100 °C gave a mixture of

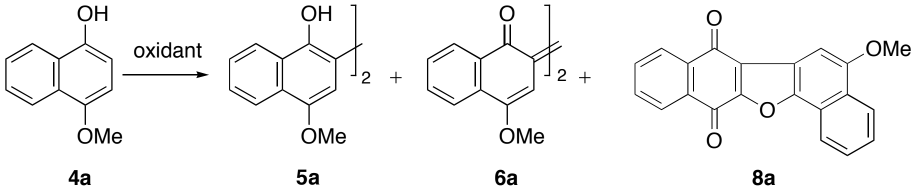
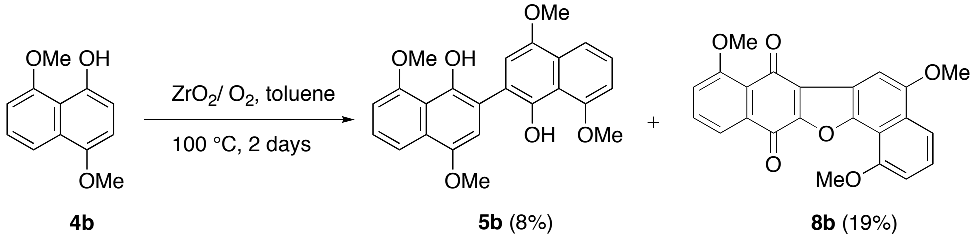


Table 1. One-pot synthesis of dibenzofuranquinone **8a** from **4a**.

| Entry | Conditions | Product (% yield) | | |
|---|---|---|---|---|
| | | **5a** | **6a** | **8a** |
| 1 | $SnO_2$/ benzoquinone (1.2 equiv.)<br>toluene, 100 °C, 7 h | 30 | 26 | 11 |
| 2 | $SnO_2$/ air, toluene, 100 °C, 21 h | | | 36 |
| 3 | $SnO_2$/ $O_2$, toluene, 100 °C, 7 h | | | 62 |

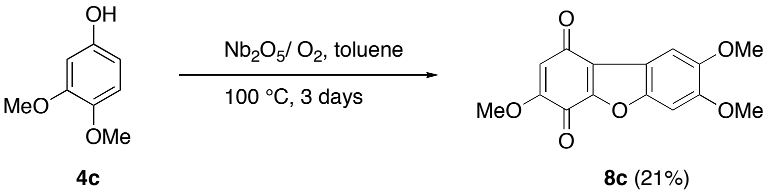
three products **5a**, **6a**, and the desired quinone **8a** in 30, 26, and 11% yields, respectively (entry 1). When the oxidation reaction was conducted in air-saturated toluene, the yield of **8a** was slightly improved (entry 2). The best result was obtained by the use of oxygen-saturated toluene as the solvent. Thus, on heating with $SnO_2$ in oxygen-saturated toluene, the naphthol **4a** underwent oxidative dimerization followed by cyclization to afford **8a** in 62% yield (entry 3).

Next, reaction of the naphthol **4b** was examined. Since the use of conditions similar to those employed for the reaction of **4a** ($SnO_2$/ $O_2$, toluene, 100 °C) gave a complex mixture, other semiconductors such as $TiO_2$, $Nb_2O_5$, and $ZrO_2$ were examined. Among them, $ZrO_2$ afforded **8b** in 19% yield, along with **5b** (8%) and unidentified products (Scheme 2).



Scheme 2

One-pot oxidative dimerization-cyclization sequences of 4-methoxyphenols were also examined. Unfortunately, treatment of the phenol **4c** with $SnO_2$ in $O_2$-saturated toluene at 100 °C again resulted in the formation of a complex mixture. After extensive experimentation, the use of $Nb_2O_5$ in place of $SnO_2$ was found to afford the quinone **8c** in 21% yield although unidentified by-products were still produced (Scheme 3).



Scheme 3

In the case of **4d**, treatment with $SnO_2$ in $O_2$-saturated toluene at 100 °C gave the dibenzofuran-1,4-dione **8d** in 15% yield, along with unidentified products (Table 2, entry 1). Combined use of $ZrO_2$ and molecular oxygen appeared to be a milder oxidation system, and the starting **4d** was recovered despite the prolonged reaction time (entry 2). Addition of $K_2CO_3$ shortened the reaction time and improved the yield of **8d**, probably due to activation of substrate by conversion of the phenol **4d** to phenoxide (entry 3).

Finally, we attempted a one-pot synthesis of the dibenzofuran-1,4-dione **8e**, a model compound of popolohuanone E,[6b,9] from the phenol **4e**. However, the use of $ZrO_2$, $Nb_2O_5$, $TiO_2$, $SnO_2$, and $Ag_2O$ gave **8e** only in very low yield (<10%) although the reason remains unclear. For example, heating **4e** with $ZnO_2$ in $O_2$-saturated toluene at 100 °C gave only 6% yield of **8e** accompanied by many unidentified products.

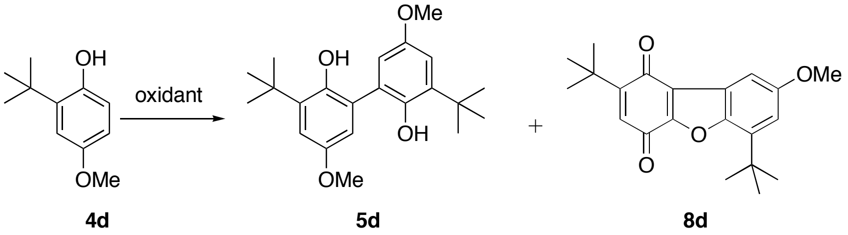
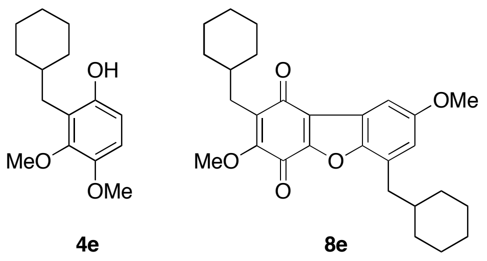


Table 2. One-pot synthesis of dibenzofuranquinone **8d** from **4d**.

| Entry | Conditions | Product (% yield) | |
|---|---|---|---|
| | | **5d** | **8d** |
| 1 | $SnO_2$/ $O_2$, toluene, 100 °C, 7 h | | 15 |
| 2 | $ZrO_2$/ $O_2$, toluene, 100 °C, 3 days | 18 | 15 |
| 3 | $ZrO_2$/ $O_2$, $K_2CO_3$, toluene, 100 °C, 19 h | 4 | 32 |



In summary, we examined the feasibility of one-pot synthesis of dibenzofuran-1,4-diones **8a-e** from 4-methoxyphenols (or 4-methoxy-1-naphthols) **4a-e** and found that the use of a combination of a semiconductor and molecular oxygen afforded the desired product **8** in some cases.

## EXPERIMENTAL

### General

Melting points are uncorrected. IR spectra were recorded with a Shimadzu FTIR-3200A spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were measured on JEOL JNM-AL300 and JEOL JNM-α-500 spectrometers. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 or a JEOL JMS-HX110 instrument. Column chromatography was performed on Silica gel 60 (0.040-0.063 mm) under pressure.

### 4,4'-Dimethoxy[2,2']binaphthalenyl-1,1'-diol (5a),
### 4,4'-Dimethoxy[2,2']binaphthalenylidene-1,1'-dione (6a),
### 5-Methoxydinaphtho[1,2-*b*;2',3'-*d*]furan-7,12-dione (8a) (Table 1).

Entry 1: Argon gas was bubbled into a solution of 4-methoxy-1-naphthol (**4a**) (50 mg, 0.29 mmol) in toluene (15 mL) until saturation. Stannic oxide (5 g) and 1,4-benzoquinone (38 mg, 0.35 mmol) were added to the solution, and the mixture was heated in a sealed tube at 100 °C for 7 h, then filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with $CH_2Cl_2$-hexane (1:1) to give **5a** (15 mg, 30%), **6a** (13 mg, 26%), **8a** (5.2 mg, 11%). **5a**: Colorless needles, mp 223.0-224.0 °C (benzene). IR (KBr): 3435 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 3.99 (6H, s), 5.44 (2H, s), 6.73 (2H, s), 7.58-7.61 (4H, m), 8.28-8.30 (4H, m); MS *m/z* 346 ($M^+$); HRMS calcd for $C_{22}H_{18}O_4$ 346.1200, found 346.1222. **6a**: Deep blue needles, mp 257-258 °C (benzene); IR (KBr) 1605, 1585 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 4.08 (6H, s), 7.48 (2H, t, *J* = 7.7 Hz), 7.61 (2H, t, *J* = 7.7 Hz), 7.79 (2H, d, *J* = 7.7 Hz), 8.17 (2H, d, *J* = 7.7 Hz), 8.42 (2H, s); MS *m/z* 344 ($M^+$); HRMS calcd for $C_{22}H_{18}O_4$ 344.1044, found 344.1029. **8a**: $^1$H NMR ($CDCl_3$) δ 4.12 (3H, s), 7.48 (1H, s), 7.61-7.80 (4H, m), 8.22-8.45 (4H, m); $^{13}$C NMR ($CDCl_3$) δ 56.2, 95.9, 119.3, 121.0, 121.5, 123.6, 125.3, 126.7, 126.97, 127.03, 127.6, 128.1, 132.9, 133.4, 133.86, 133.90, 149.1, 152.6, 155.0, 174.4, 182.1. These $^1$H and $^{13}$C NMR spectra were consistent with those reported.[9]

Entry 3: Oxygen gas was bubbled into a solution of 4-methoxy-1-naphthol (**4a**) (50 mg, 0.29 mmol) in toluene (15 mL) until saturation. Stannic oxide (5 g) was added to the solution, and the mixture was heated in a sealed tube at 100 °C for 7 h, then filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with $CH_2Cl_2$-hexane (1:1) to give **8a** (29.5 mg, 62%).

### 4,4',8,8'-Tetramethoxy[2,2']binaphthalenyl-1,1'-diol (5b) and 1,5,8-trimethoxydinaphtho-[1,2-*b*;2',3'-*d*]furan-7,12-dione (8b).

Using a procedure similar to that for **8a** (Table 1, entry 3), 4,8-dimethoxy-1-naphthol (**4b**) (50 mg, 0.25 mmol) was treated with zirconium oxide (5 g) in oxygen-saturated toluene (15 mL). After work-up, the crude material was chromatographed on silica gel with $CH_2Cl_2$ to give **5b** (4.0 mg, 8%) and **8b** (9.2 mg, 19%). **5b**: Colorless needles, mp 207.0-209.0 °C ($CHCl_3$-hexane); IR (KBr) 3350 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 3.95 (6H, s), 4.03 (6H, s), 6.87 (2H, d, *J* = 8.6 Hz), 6.92 (2H, s), 7.35 (2H, t, *J* = 8.6 Hz), 7.89 (2H, d, *J* = 8.6 Hz), 9.87 (2H, s); $^{13}$C NMR ($CDCl_3$) δ 56.0, 56.1, 105.2, 109.4, 115.7, 116.0, 119.4, 125.0, 127.6, 144.7, 147.6, 156.2. These $^1$H and $^{13}$C NMR spectra were consistent with those reported.[10b] **8b**: IR (KBr) 1665, 1580 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.081 (3H, s), 4.085 (3H, s), 4.16 (3H, s), 7.10 (1H, d, *J* = 7.9 Hz), 7.35 (1H, d, *J* = 8.2 Hz), 7.55 (1H, dd, *J* = 7.9, 8.2 Hz), 7.67 (1H, s), 7.70 (1H, dd, *J* = 7.3, 8.2 Hz), 7.96 (2H, m); $^{13}$C NMR ($CDCl_3$) δ 56.1, 56.2, 56.5, 97.1, 107.6, 113.7, 115.4, 118.4, 119.9, 120.5, 120.7, 125.6, 127.8, 128.7, 134.9, 135.7, 148.7, 150.9, 154.4, 155.4, 160.4, 173.6, 182.3. These $^1$H and $^{13}$C NMR spectra were consistent with those reported.[9]

**3,7,8-Trimethoxydibenzofuran-1,4-dione (8c).**

Using a procedure similar to that for **8a** (Table 1, entry 3), 3,4-dimethoxyphenol (**4c**) (50 mg, 0.32 mmol) was treated with niobium(V) oxide (5 g) in oxygen-saturated toluene (15 mL). After work-up, the crude material was chromatographed on silica gel with $CH_2Cl_2$-AcOEt (10:1) to give **8c** (10.4 mg, 21%). IR (KBr) 1680, 1645, 1605, 1560 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.90 (3H, s), 3.98 (3H, s), 3.99 (3H, s), 5.86 (1H, s), 7.07 (1H, s), 7.47 (1H, s); $^{13}C$ NMR ($CDCl_3$) δ 56.47, 56.53, 57.0, 95.2, 102.5, 106.8, 114.9, 123.7, 149.5, 149.7, 152.8, 153.2, 159.8, 170.1, 183.5. These $^1H$ and $^{13}C$ NMR spectra were consistent with those reported.[9]

**3,3'-di-*tert*-Butyl-5,5'-dimethoxybiphenyl-2,2'-diol (5d) and 2,6-Di-*tert*-butyl-8-methoxydibenzofuran-1,4-dione (8d) (Table 2, entry 3).**

Using a procedure similar to that for **8a** (Table 1, entry 3), 3-*tert*-butyl-4-hydroxyanisol (**4d**) (50 mg, 0.28 mmol) was treated with zirconium oxide (5 g) and potassium carbonate (383 mg, 2.8 mmol) in oxygen-saturated toluene (15 mL). After work-up, the crude material was chromatographed on silica gel with $CH_2Cl_2$-AcOEt (8:1) to give **5d** (2 mg, 4%) and **8d** (15 mg, 32%). **5d**: Colorless powder, mp 228.5-229.5 °C ($CH_2Cl_2$); IR (KBr) 3420 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.43 (18H, s), 3.78 (6H, s), 5.01 (2H, s), 6.63 (2H, d, $J = 3.1$ Hz), 6.96 (2H, d, $J = 3.1$ Hz); $^{13}C$ NMR ($CDCl_3$) δ 27.5, 33.2, 53.8, 109.7, 113.3, 121.2, 136.9, 143.9, 151.2; MS (*m*/*z*) 358 ($M^+$); HRMS calcd for $C_{24}H_{22}O_6$ 358.2136, found 358.2133. **8d**: $^1H$ NMR ($CDCl_3$) δ 1.38 (9H, s), 1.49 (9H, s), 3.90 (3H, s), 6.60 (1H, s), 7.04 (1H, d, $J = 2.6$ Hz), 7.45. (1H, d, $J = 2.6$ Hz); $^{13}C$ NMR ($CDCl_3$) δ 29.7, 34.6, 35.6, 55.9, 100.5, 116.9, 123.4, 124.1, 131.0, 137.9, 150.1, 151.0, 156.9, 158.3, 177.6, 184.5. These $^1H$ and $^{13}C$ NMR spectra were consistent with those reported.[9]

**2,6-Bis-cyclohexylmethyl-3,7,8-trimethoxydibenzofuran-1,4-dione (8e).**

Using a procedure similar to that for **8a** (Table 1, entry 3), 2-cyclohexylmethyl-3,4-dimethoxyphenol (**4e**) (50 mg, 0.20 mmol) was treated with zirconium oxide (5 g) oxygen-saturated toluene (15 mL). After work-up, the crude material was chromatographed on silica gel with hexane-AcOEt (20:1) to give **8e** (2.7 mg, 6%). $^1H$ NMR ($CDCl_3$) δ 0.95-1.75 (22H, m), 2.43 (2H, d, $J = 7.2$ Hz), 2.81 (2H, d, $J = 7.3$ Hz), 3.88 (3H, s), 3.95 (3H, s), 4.08 (3H, s), 7.41 (1H, s). The signals were consistent with reported data.[9]

## ACKNOWLEDGEMENTS

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