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# SYNTHESIS OF ACID-RESISTANT *P*-QUINONE MONOKETALS AND THERMALLY STABLE 4,4-DIALKOXYCYCLOHEXA-2,5-DIEN-1-OLS

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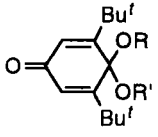
**Abstract:** Preparation and high resistance to acid hydrolysis of sterically hindered *p*-quinone monoketals **1a**, **1b** and **1c** are described. Thermal stability of ketal alcohols **2a** and **2b** derived from **1a** and **1c**, respectively, is also mentioned.

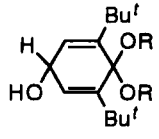


Quinone monoketals as versatile intermediates for organic synthesis[1] are susceptible to acid hydrolysis, giving benzoquinones. We herein report on synthesis of *p*-quinone monoketals which are highly resistant to acid hydrolysis. They are sterically hindered ketals **1a**, **1b** and **1c**. Thermal stability of ketal alcohols **2a** and **2b** obtained by reduction of **1a** and **1c**, respectively, is also mentioned.




**1**

**a**: R = R' = Me
**b**: R = Me, R' = Et
**c**: R = R' = Et




**2**

**a**: R = Me
**b**: R = Et

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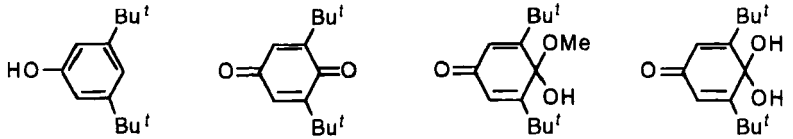
Recently, we have reported that $PbO_2$ in the presence of a strong acid (70% $HClO_4$) can rapidly oxidize various phenols to give *p*-benzoquinones.[2] Afterward this oxidation was applied to 3,5-di-*tert*-butylphenol (**3**). Thus, **3** was treated with $PbO_2$ in warm MeOH containing 70% $HClO_4$ for a short period, and we obtained quinone monoketal **1a** (28%) in addition to the anticipated product, 2,6-di-*tert*-butyl-*p*-benzoquinone (**4**) (15%). Extension of the reaction time did not alter the yields of **1a** and **4**. The result suggested that **1a** was stable under the strongly acidic reaction conditions and that **4** was formed not via **1a** but via hemiketal **5** and/or hydrate **6**.

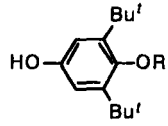



**3** **4** **5** **6**

Compound **1a** was yielded in higher yield (43%) when 70% $HClO_4$ was replaced by $CF_3SO_3H$ in the above reaction: only a small amount (2%) of **4** was formed in addition. It is noted that **1a** has been reported earlier. It has been obtained in not exceeding 23% overall yield from 2,6-di-*tert*-butylanisole, by its electrochemical methoxylation and subsequent spontaneous decomposition of the product *p*-quinone bisketal.[3,4]

Quinone monoketal **1c** was similarly prepared in 24% yield by oxidizing **3** with $PbO_2/CF_3SO_3H$ in EtOH. An attempt, however, was unsuccessful to produce **1** (R = R' = *i*-Pr) by treating **3** with $PbO_2/CF_3SO_3H$ in *i*-PrOH. Preparation of quinone monoketal **1b** was accomplished as follows. Reduction of **1a** with $NaBH_4$ gave ketal alcohol **2a**. Treatment of **2a** with 2N $H_2SO_4$ in DME afforded hindered

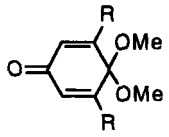
anisole **7a** in quantitative yield. Oxidation of **7a** with $PbO_2/CF_3SO_3H$ in EtOH gave the desired mixed ketal, **1b** in a quantitative fashion.



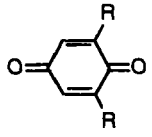
**7** **a**: R = Me
**b**: R = Et

Attempts were made to prepare **1** from **3** and **7a** by use of other alkoxylating agents for phenols; DDQ,[5] $Tl(NO_3)_3 \cdot 3H_2O$,[5,6] $PhI(OCOCF_3)_2$,[7] and $PhI(OAc)_2$.[8] The reaction of **3** with these reagents afforded no or little **1a** or **1c**. Ethoxylation of **7a** with them gave **1b** in the range of 7 to 49% yield. Therefore, these oxidants had no advantage over the $PbO_2/CF_3SO_3H$ reagent.

To show exceedingly high acid-resistant property of sterically hindered ketals **1a**, **1b** and **1c**, they and less hindered *p*-quinone monoketals **8a** and **8b** were subjected to hydrolysis by an acid, and their relative stabilities to the acid were compared (Table). Refluxing a solution of **8a** in DME containing 10% $H_2SO_4$ for 1 h totally consumed **8a** and yielded *p*-benzoquinone **9a**. Under the same conditions, hydrolysis of **8b** proceeded slower, yet a large part of **8b** was converted into *p*-benzoquinone **9b**. In sharp contrast, **1a** was recovered totally unchanged even when the reaction time was extended to 24 h. Ketals **1b** and **1c** were likewise stable to the acid. Compounds **1** may undoubtedly be among the most acid-resistant *p*-quinone monoketals ever known.



**8** **a**: R = Me
**b**: R = OMe



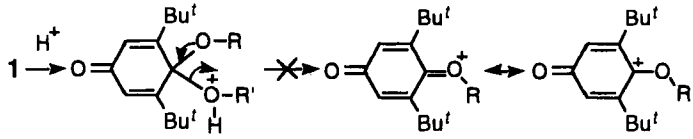
**9** **a**: R = Me
**b**: R = OMe

**Table. Acid Hydrolysis of *p*-Quinone Monoketals[a]**

| ketal | reaction time (h) | recovery of ketal (%) | product (yield, %) |
|---|---|---|---|
| **8a** | 1 | 0 | **9a** (90) |
| **8b** | 1 | 34 | **9b** (56) |
| **1a** | 24 | 100 | **4** (0) |
| **1b** | 24 | 100 | **4** (0) |
| **1c** | 24 | 100 | **4** (0) |

[a] See Experimental for experimental detail.

The extraordinary reluctance of **1** to undergo acid hydrolysis may be ascribed to difficulty in formation of oxonium ion **11** from protonated **1**, **10**: required planarity of the Bu$^t$—C—C=O$^+$—R skeleton in **11** may be interrupted due to severe steric repulsion between the Bu$^t$ group and the R group.

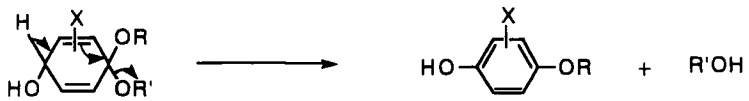


**10** **11**

( R, R' = Me or Et )

Thermal stability of **2a** as well as ketal alcohol **2b**, which was obtained by reduction of **1c** with $NaBH_4$, also deserves mentioning. Both **2a** and **2b** could be obtained in microanalytically pure states. In addition, they remained intact even when allowed to stand at room temperature for months. Simple ketal alcohols with general formula **13** are labile and tend to decompose spontaneously to yield *p*-

alkoxyphenols with loss of alcohols,[1a, 9] and we are not aware of **13** which have been reported to be microanalytically pure.




**13** ( R, R' = alkyl )

Finally, treatment of **2b** with an acid provided hindered phenetole **7b** quantitatively. 2,6-Di-*tert*-butylphenetole itself can be obtained by the reaction of potassium 2,6-di-*tert*-butylphenoxide with EtI in poor yield.[10]

## Experimental

$^1$H NMR (90 MHz) and IR spectra were taken in $CDCl_3$ and in $CHCl_3$, respectively. TLC was run on $SiO_2$. 4,4-Dimethoxy-3,5-dimethylcyclohexa-2,5-dien-1-one (**8a**) was prepared according to the reported method.[8] 3,4,4,5-Tetramethoxycyclohexa-2,5-dien-1-one (**8b**) was obtained from 3,4,5-trimethoxyphenol by adaptation of the method reported for methoxylation of phenols[8]: mp 121-122 °C (lit.[7] mp 121.5-123 °C). 2,6-Di-*tert*-butyl- (**4**), 2,6-dimethyl- (**9a**) and 2,6-dimethoxy-*p*-benzoquinone (**9b**) obtained in our previous study[2] were used as authentic samples for product identification with $^1$H NMR spectroscopy and TLC.

**4,4-Dimethoxy-3,5-di-*tert*-butylcyclohexa-2,5-dien-1-one (1a).** To a stirred solution of **3** (2.060 g, 10 mmol) and $CF_3SO_3H$ (7 mL, 79 mmol) in MeOH (30 mL) at 40 °C, $PbO_2$ (9.57 g, 40 mmol) was added portionwise over a period of ca. 7 min. The mixture was stirred for 3 min and filtered. The filter cake

was washed with acetone into the flask containing the filtrate. The contents of the flask were diluted with water and extracted with ether. The extract was washed with water, dried (anhydrous $Na_2SO_4$) and evaporated. Recrystallization of the semi-crystalline residue from diisopropyl ether provided **1a** (557 mg) as colorless crystals: mp 166-167 °C (lit.[3] mp 143.5-145 °C); $^1$H NMR δ 6.48 (s, 2H), 3.14 (s, 6H), 1.34 (s, 18H); IR 1662, 1619 cm$^{-1}$. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.87; H, 9.71. The filtrate from the recrystallization was evaporated, and the residue was chromatographed on $SiO_2$. Elution with petroleum ether/benzene (5:1) gave **4** (44 mg, 2%): deep yellow crystals from MeOH; mp 65-68 °C (lit.[2] mp 66-68 °C). Elution with petroleum ether/benzene (1:1) yielded an additional crop of **1a** (588 mg, 43% in total).

The reaction of **3** carried out similarly with 70% $HClO_4$ (10 mL, 0.12 mol) (in place of $CF_3SO_3H$) gave **1a** (28%) and **4** (15%). A similar reaction of **3** carried out with 70% $HClO_4$ for 60 min (in place of 3 min) gave **1a** (28%) and **4** (14%).

**4,4-Dimethoxy-3,5-di-*tert*-butylcyclohexa-2,5-dien-1-ol (2a).** To a stirred solution of **1a** (2.660 g, 10 mmol) in DME (100 mL), a solution of $NaBH_4$ (1.9 g, 50 mmol) in $H_2O$ (20 mL) was added dropwise over a period of 20 min, and the mixture was stirred for 30 min. Aqueous AcOH was added dropwise to the reaction mixture until it became weakly acidic. The mixture was poured into water and extracted with petroleum ether. The extract was washed with water, dried and evaporated under reduced pressure to afford **2a** (2.630 g, 98%): colorless crystals from hexane; mp 128-130 °C; $^1$H NMR ($CDCl_3$ + $D_2O$) δ 6.29 (d, J = 3.5 Hz, 2H), 4.47 (t, J = 3.6 Hz, 1H), 3.05 (s, 3H). 3.01 (s, 3H), 1.28 (s, 18H); IR 3575, 3440 cm$^{-1}$. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.36; H, 10.76.

**4-Methoxy-3,5-di-*tert*-butylphenol (7a).** A solution of **2a** (1.800 g, 6.7 mmol) in a mixture of 2N $H_2SO_4$ (10 mL) and DME (100 mL) was allowed to

stand at 50 °C for 2h. The mixture was poured into water and extracted with petroleum ether. The extract was washed with water, dried and evaporated to leave **7a** (1.595 g, quantitative): colorless crystals from hexane; mp 91-93 °C; $^1$H NMR δ 6.71 (s, 2H), 4.38 (s, 1H), 3.65 (s, 3H), 1.40 (s, 18H); IR 3576, 3340 cm$^{-1}$. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C,76.19; C, 76.19; H, 10.53.

**4-Ethoxy-4-methoxy-3,5-di-*tert*-butylcyclohexa-2,5-dien-1-one (1b).** A similar procedure described above for **1a** was followed, with use of **7a** (472 mg, 2 mmol) (in place of **3**), $PbO_2$ (4 mmol), $CF_3SO_3H$ (1.5 mL) and EtOH (10 mL) (in place of MeOH), to yield **1b** (545 mg, 97%): colorless crystals from hexane; mp 93.5-95.5 °C; $^1$H NMR δ 6.46 (s, 2H), 3.26 (q, J = 7.0 Hz, 2H), 3.14 (s, 3H), 1.34 (s, 18H), 1.23 (t, J = 7.3 Hz, 3H); IR 1659, 1618 cm$^{-1}$. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.72; H, 10.06.

**4,4-Diethoxy-3,5-di-*tert*-butylcyclohexa-2,5-dien-1-one (1c).** The reaction was conducted and the reaction mixture was worked up, in the manner described above for **1a**, except that EtOH (30 mL) replaced MeOH. Column chromatography of the oily residue on $SiO_2$ with petroleum ether/benzene (5:1) gave **1c** (719 mg, 24%): colorless crystals from hexane; mp 129-130 °C; $^1$H NMR δ 6.44 (s, 2H), 3.27 (q, J = 7.0 Hz, 4H), 1.34 (s, 18H), 1.24 (t, J = 7.2 Hz, 6H); IR 1658, 1618 cm$^{-1}$. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.45; H, 10.46.

**4,4-Diethoxy-3,5-di-*tert*-butylcyclohexa-2,5-dien-1-ol (2b).** A similar procedure described above for **2a** was followed, with use of **1c** (500 mg, 1.70 mmol) (in place of **1a**), $NaBH_4$ (9 mmol), DME (50 mL) and $H_2O$ (20 mL), to yield **2b** (498 mg, 99%): colorless crystals from hexane; mp 163-165 °C; $^1$H NMR ($CDCl_3$ + $D_2O$) δ 6.25 (d, J = 3.8 Hz, 2H), 4.44 (t, J = 3.6 Hz, 1H), 3.32 (q, J = 7.0 Hz, 2H), 3.13 (q, J = 7.0 Hz, 2H), 1.27 (s, 18H), 1.22 (t, J = 7.2 Hz, 3H),

1.20 (t, J = 7.2 Hz, 3H); IR 3575, 3420 $cm^{-1}$. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 72.71; H, 11.01.

**4-Ethoxy-3,5-di-*tert*-butylphenol (7b).** A similar procedure described above for **7a** was followed, with use of **2b** (500 mg, 1.69 mmol) (in place of **2a**), 2N $H_2SO_4$ (4 mL) and DME (25 mL), to yield **7b** (426 mg, quantitative): colorless crystals from hexane; mp 90-92 °C; $^1H$ NMR δ 6.70 (s, 2H), 4.48 (s, 1H), 3.73 (q, J = 7.0 Hz, 2H), 1.39 (s, 18H), 1.36 (t, J = 7.0 Hz, 3H); IR 3575, 3330 $cm^{-1}$. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.53; H, 10.61.

**Acid Hydrolysis of *p*-Quinone Monoketals (Table).** A solution of a quinone monoketal (0.25 mmol) in a mixture of 10% $H_2SO_4$ (2 mL) and DME (10 mL) was refluxed for the time indicated in the table. The progress of the reaction was followed by TLC. The reaction mixture was poured into water and extracted with ether or $CH_2Cl_2$. The extract was washed with water, dried and evaporated. The amounts of the unreacted quinone monoketal and the corresponding *p*-benzoquinone in the residue were estimated by $^1H$ NMR spectroscopy.

## Acknowledgment

The author is thankful to Michiko Kidouchi and Miyoko Matsuura (students) for experimental contributions.

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