p-Quinols and p-Quinol Ethers from 2,4,6-Trialkylphenols

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Abstract: The oxidation of 2,4,6-trialkylphenols with lead(IV) oxide and 70% perchloric acid in water–acetone or in alcohols gives p-quinols or p-quinol ethers, respectively. Some nonmetallic oxidants serve the same purpose.

Key words: oxidations, 2,4,6-trialkylphenols, *p*-quinols, *p*-quinol ethers, lead(IV) oxide, perchloric acid, nonmetallic oxidants

A variety of oxidants have been exploited for the conversion of phenols into quinols and their derivatives, which are often important synthetic intermediates. The contribution of electrochemistry in achieving this purpose has also been extensive.² Herein, we report new oxidants for preparing such dienones from phenols.

The reactions of 2,4,6-trialkylphenols 1 as model substrates to yield the corresponding *p*-quinols or *p*-quinol ethers 2 were carried out with lead(IV) oxide and 70%perchloric acid in hydroxylic solvents (R³OH), and the results are summarized in Table $1.^3$ The reaction was mildly exothermic and rapidly completed. For instance, portionwise addition of a small excess of lead(IV) oxide to a stirred solution of 2,6-di-tert-butyl-4-methylphenol (1a) in methanol containing 70% perchloric acid readily gave quinol methyl ether 2al in 90% yield after column chromatography of the crude reaction product (Table 1, run 2).⁴ Omission of 70% perchloric acid resulted in the formation of the product of oxidative dimerization of 1a. Products 2 were generally obtained in high yields after column-chromatographic purification. In most cases, 2 could also be isolated by recrystallization of the crude reaction product. Some examples of the isolation by such recrystallization are also shown in Table 1. The yields of quinol tert-butyl ethers 2ao and 2co from the oxidations of 1a and 2,4,6-tri-tert-butylphenol (1c), respectively, in tert-butyl alcohol, a sterically hindered alcohol, were exceptionally low (Table 1, runs 5 and 11).

Among the effective oxidants for the conversion of phenols into quinols and their derivatives are periodic acid (H_5IO_6) ,⁵ (diacetoxyiodo)benzene [PhI(OAc)₂],⁶ and thallium(III) nitrate trihydrate [Tl(NO₃)₃·3H₂O; TTN].⁷ Oxidation of **1a** and/or **1c** with these reagents in methanol has been reported to provide **2al** and/or quinol methyl ether **2cl**, respectively, in good to high yields. Attempted preparation of quinol isopropyl ether **2an** by treatment of **1a**

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Table 1Preparation of 2 from 1 in the Presence of Lead(IV) Oxideand 70% Perchloric Acid

HO-	R ¹ R ² R ³ OH			$\begin{array}{c} \bullet O = \\ R^1 \\ R^2 \\ O R^3 \end{array}$	
1 a: R ¹ = <i>t</i> ·Bu, R ² = Me b: R ¹ = <i>t</i> ·Bu, R ² = Et c: R ¹ = R ² = <i>t</i> ·Bu d: R ¹ = R ² = Me					2 k: $R^3 = H$ l: $R^3 = Me$ m: $R^3 = Et$ n: $R^3 = i$ -Pr o: $R^3 = t$ -Bu
Run	1	Solvent	2	Yield ^a (%)	Mp (°C)
1	1a	H ₂ O-acetone	2ak	89 (78)	112–114 (Lit. ¹⁴ 113–114
2	1a	МеОН	2al	90 (79)	92.5-93 (Lit.15 94)
3	1a	EtOH	2am	83	_b
4	1a	<i>i</i> -PrOH	2an	83 (70)	_b
5	1a	t-BuOH	2ao ^c	30	_b
6	1b	H ₂ O-acetone	2bk	83 (69)	99-100 (Lit. ⁹ 99-100)
7	1b	MeOH	2bl	88	_b
8	1c	MeOH	2cl	90	56–57.5 (Lit. ⁹ 57–58)
9	1c	EtOH	2cm	84	40-42 (Lit. ⁹ 39-41)
10	1c	<i>i</i> -PrOH	2cn	85	oil ^d (Lit. ⁹ 30)
11	1c	t-BuOH	2co ^e	22	48-49.5 (Lit. ⁹ 37-39)
12	1d	MeOH	2dl	50	42-43 (Lit. ⁶ 42-44)

^a Yield of product purified by column chromatography. Yields shown in parentheses are of the products isolated by recrystallization of the crude reaction products.

^b For data, including mp data, of quinol ethyl ethers **2am**, **2an**, **2ao**, and **2bl**, see the experimental section.

^c In addition, 3,5-di-*tert*-butyl-4-hydroxybenzyl *tert*-butyl ether (31%) was obtained.

^d Attempts at obtaining crystals at r.t. (25 °C) were unsuccessful.¹⁶

^e In addition, **2ck** (72%) was obtained; mp 86–128 °C (Lit.^{4,17} 82–124).

with any of these oxidants in isopropyl alcohol, a moderately hindered alcohol, was, however, not quite successful (Table 2, runs 1–3), whereas the same oxidation with lead(IV) oxide and 70% perchloric acid afforded **2an** in high yield (Table 2, run 4). Similarly, the oxidation of **1a** in *tert*-butyl alcohol and of **1c** in isopropyl alcohol with

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section).8

 Table 2
 Preparation of 2an from 1a with Various Oxidants

Run	Oxidant	Solvent	Yield of 2an ^a (%)
1	H ₅ IO ₆	<i>i</i> -PrOH	47
2	PhI(OAc) ₂	<i>i</i> -PrOH	14
3	TTN	<i>i</i> -PrOH	33
4 ^b	PbO ₂ /70% HClO ₄	<i>i</i> -PrOH	83 (70)
5	NaIO ₃ /70% HClO ₄	<i>i</i> -PrOH	78 (68)
6	Br ₂ /NIS	<i>i</i> -PrOH–MeCN	79 (62)
7	$I_2/30\% H_2O_2$	<i>i</i> -PrOH	45 ^c

^a Yield of product purified by column chromatography. Yields shown in parentheses are of **2an** isolated by recrystallization of the crude reaction product.

^b Identical to run 4 in Table 1.

^c In addition, 2ak (32%) was obtained.

The above-cited results obtained by us and other workers appear to indicate that the ease of the oxyfunctionalization of **1** giving **2** with an oxidant and an alcohol, in general, tends to depend on the steric bulk of the alcohol. Regarding such dependency, it is worth adding that the thallium(III) nitrate trihydrate oxidation of **1c** in *tert*-butyl alcohol is reported to yield no **2co** (and a low yield of quinol **2ck**), as compared with a high yield of **2cl** from the same oxidation in methanol, the smallest alcohol,⁷ and that the yields of quinol ethers **2c** obtained by electrochemical oxidation of **1c** in alcohol–acetonitrile mixtures decrease in the order **2cl** (95%) > quinol ethyl ether **2cm** (78%) > **2cn** (62%) > **2co** (12%).⁹

Some nonmetallic oxidants (including the sodium salt) were explored for conversion of phenols into quinols and quinol ethers. As a model reaction, the conversion of 1a into **2an** was studied, and the results are also shown in Table 2. Treatment of 1a with sodium iodate and 70% perchloric acid in isopropyl alcohol for three hours yielded 2an (Table 2, run 5). No reaction of 1a took place if 70% perchloric acid was omitted.¹⁰ Addition of bromine followed by N-iodosuccinimide (NIS) to a solution of 1a in an isopropyl alcohol-acetonitrile solvent mixture also afforded 2an readily (Table 2, run 6).¹¹ The yields of 2an from the above two runs were almost as high as that from the oxidation with lead(IV) oxide and 70% perchloric acid. If carried out in methanol and in methanol-acetonitrile, respectively, the reactions of 1a with sodium iodate and 70% perchloric acid and with bromine and N-iodosuccinimide gave 2al in 87% and 85% chromatographic yields, respectively. Reaction of 1a with iodine and 30% hydrogen peroxide,¹² both of which are inexpensive, in isopropyl alcohol for 1.5 hours also produced 2an, although the yield was intermediate and formation of quinol **2ak** as a byproduct was substantial (Table 2, run 7).¹³ The similar oxidation of **1a** with iodine and 30% hydrogen peroxide in methanol gave **2al** in a chromatographic yield (82%) higher than that of **2an** obtained from the above-mentioned same oxidation in isopropyl alcohol. The reaction of **1c** with iodine and 30% hydrogen peroxide in methanol gave **2cl**, also in a good chromatographic yield (71%). Possibly, the oxidation with iodine and 30% hydrogen peroxide, which proved catalytic in nature with respect to iodine, can be improved by modifying the reaction conditions.

The present results indicate that there are cases where lead(IV) oxide with 70% perchloric acid and the new nonmetallic oxidants are better reagents than the previously employed oxidants in preparing p-quinols and p-quinol ethers, possibly especially the sterically hindered ethers, from phenols.

¹H NMR (90 MHz) spectra were obtained of samples in CDCl₃ with TMS as reference on a Hitachi R-1900 spectrometer. IR spectra were recorded of samples in CHCl₃ on a Shimadzu FTIR-8300 spectrophotometer. Column chromatography was conducted on Merck silica gel 60. Unless otherwise specified, reagents were purchased from WAKO and used as received.

Preparation of 2 from 1 by Use of Lead(IV) Oxide and 70% Perchloric Acid (Table 1); General Procedure

 PbO_2 (1.195 g, 5 mmol; Aldrich) was added portionwise over 3 min to a stirred soln of **1** (4 mmol) in an alcohol R³OH (30 mL) containing 70% HClO₄ (1 mL), after which the mixture was kept stirring for 5 min. In runs 1 and 6 (Table 1), a mixture of H₂O (3 mL) and acetone (27 mL) was employed in place of the alcohol. The mixture was filtered, and the filtrate was poured into H₂O and subjected to extractive workup with Et₂O. The crude product thus obtained was chromatographed to give **2**. Runs 1, 2, 4, and 6 were repeated, and the crude reaction products were recrystallized from hexane or MeOH to give **2ak**, **2al**, **2an**, and quinol **2bk**, respectively.

2,6-Di-*tert*-butyl-4-ethoxy-4-methylcyclohexa-2,5-dienone (2am)

Colorless crystals (MeOH); mp 69.5–71 °C.

IR (CHCl₃): 1663, 1643 cm⁻¹.

¹H NMR (90 MHz, CDCl₃): δ = 1.15 (shoulder, t, *J* = 7.0 Hz, 3 H), 1.24 (s, 18 H), 1.36 (s, 3 H), 3.28 (q, *J* = 7.0 Hz, 2 H), 6.46 (s, 2 H). Anal. Calcd for C₁₇H₂₈O₂: C, 77.22; H, 10.67. Found: C, 76.94; H, 10.68.

2,6-Di-*tert*-butyl-4-isopropoxy-4-methylcyclohexa-2,5-dienone (2an)

Colorless crystals (MeOH); mp 70–73.5 $^{\circ}\text{C}.$

IR (CHCl₃): 1661, 1643 cm⁻¹.

¹H NMR (90 MHz, CDCl₃): δ = 1.09 (d, *J* = 6.1 Hz, 6 H), 1.24 (s, 18 H), 1.33 (s, 3 H), 3.39 (sept, *J* = 6.1 Hz, 1 H), 6.48 (s, 2 H).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.35; H, 10.68.

2,6-Di-*tert*-butyl-4-*tert*-butoxy-4-methylcyclohexa-2,5-dienone (2ao)

Colorless crystals (EtOH); mp 64.5–66.5 °C.

IR (CHCl₃): 1659, 1639, 1630 cm⁻¹.

¹H NMR (90 MHz, CDCl₃): δ = 1.19 (s, 9 H), 1.23 (s, 18 H), 1.29 (s, 3 H), 6.69 (s, 2 H).

Anal. Calcd for C₁₉H₃₂O₂: C, 78.03; H, 11.03. Found: C, 77.77; H, 10.95.

2,6-Di*-tert*-**butyl**-**4**-**methoxy**-**4**-**ethylcyclohexa**-**2,5**-**dienone** (**2bl**) Colorless crystals (MeOH); mp 46.5–48 °C.

IR (CHCl₃): 1665, 1643 cm⁻¹.

¹H NMR (90 MHz, CDCl₃): δ = 0.73 (t, *J* = 7.5 Hz, 3 H), 1.25 (s, 18 H), 1.71 (q, *J* = 7.5 Hz, 2 H), 3.16 (s, 3 H), 6.36 (s, 2 H).

Anal. Calcd for C₁₇H₂₈O₂: C, 77.22; H, 10.67. Found: C, 76.95; H, 10.66.

3,5-Di-tert-butyl-4-hydroxybenzyl tert-Butyl Ether

Colorless crystals (hexane); mp 68–69.5 °C.

IR (CHCl₃): 3641 cm⁻¹.

¹H NMR (90 MHz, CDCl₃): δ = 1.29 (s, 9 H), 1.43 (s, 18 H), 4.33 (s, 2 H), 5.09 (s, 1 H), 7.13 (s, 2 H).

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.78; H, 11.30.

Preparation of 2an from 1a by Use of Various Oxidants (Table 2)

Run 1: A soln of H_5IO_6 (913 mg, 4 mmol) in *i*-PrOH (20 mL) was added in one portion to a soln of **1a** (881 mg, 4 mmol) in *i*-PrOH (20 mL) in a bottle under N₂. The bottle was screw-capped and the mixture was allowed to stand at 20 °C for 24 h in the dark. The mixture was poured into aq NaHSO₃, and extractive workup with Et₂O afforded a residual crude product.

Run 2: PhI(OAc)₂ (1.29 g, 4 mmol; Aldrich) was added portionwise over 20 min to a soln of **1a** (4 mmol) in *i*-PrOH (35 mL) in a bottle under N₂. The bottle was screw-capped, and the mixture was stirred at 20 °C for 40 min. The mixture was evaporated under reduced pressure to give a residue.

Run 3: TTN (1.79 g, 4 mmol) was added in one portion to a stirred, cooled (-20 °C) soln of **1a** (4 mmol) in *i*-PrOH (30 mL). After 2 min, the stirred mixture was allowed to warm to r.t. PE was added to the mixture, the resulting mixture was filtered, and the filtrate was evaporated under reduced pressure to leave a residue.

Run 5: NaIO₃ (1.59 g, 8 mmol) was added in one portion to a soln of **1a** (4 mmol) in *i*-PrOH (30 mL) containing 70% HClO_4 (1 mL), and the mixture was stirred for 3 h at 20 °C. The mixture was poured into aq NaHSO₃, and extractive workup with Et₂O afforded a residual crude product.

Run 6: A soln of Br₂ (640 mg, 4 mmol) in MeCN (10 mL) was added dropwise over 2 min to a stirred soln of **1a** (4 mmol) in a mixture of *i*-PrOH (6 mL) and MeCN (54 mL) at 18 °C. After 1 min, NIS (900 mg, 4 mmol; TCI) was added in one portion to the stirred mixture. After 3 min, the mixture was poured into aq NaHSO₃, and extractive workup with Et₂O left a residual crude product.

Run 7: A soln of I₂ (2.03 g, 8 mmol) in *i*-PrOH (60 mL) containing 30% H₂O₂ (2 mL) was added in one portion to a soln of **1a** (4 mmol) in *i*-PrOH (20 mL), and the mixture was stirred for 1.5 h at 20 °C. The mixture was poured into aq NaHSO₃, and extractive workup with Et₂O left a residual crude product.

The residue from each run was chromatographed to afford **2an**. A small amount (11%) of **1a** was recovered unchanged from run 2. Runs 5 and 6 were repeated. The crystalline residue from run 5 was washed with cold hexane, the washing was evaporated, and the residue was recrystallized (MeOH), yielding **2an**. The crystalline residue from run 6 was recrystallized (MeOH) to yield **2an**.

The reactions of **1a** with H_5IO_6 , PhI(OAc)₂, and TTN in *t*-BuOH in place of *i*-PrOH gave **2ao** in 0%, 21%, and <3% chromatographic

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yields, respectively. The reactions of **1c** (1.050 g, 4 mmol) in place of **1a** with H_5IO_6 , PhI(OAc)₂, and TTN in *i*-PrOH gave **2cn** in 22%, 25%, and 4% chromatographic yields, respectively.

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- (17) For purification and identification of the product, see ref. 4.