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Synthesis and electrochemical properties of substituted *para*-benzoquinone derivatives

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ABSTRACT

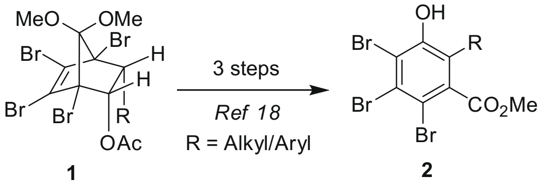
A facile transformation of pentasubstituted tribromophenol derivatives to the corresponding alkyl-substituted dibromo-*p*-benzoquinones has been achieved using PbO_2 as oxidizing agent in combination with 60% aq $HClO_4$ in acetone in 70–72% yields. The electrochemical properties of these quinones were studied by means of cyclic voltammetry and compared with *p*-benzoquinone (BQ) and 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) recorded under identical experimental conditions.

Synthesis and chemistry of quinones continue to draw the attention of chemists as they are important intermediates in organic synthesis[1,2] and are among the most abundant substructures found in numerous naturally occurring bioactive molecules.[3] Quinones constitute a large group of natural pigments,[1] exhibit interesting photochemistry,[4] function as intermediates in the biosynthesis of important antibiotics like tetracyclines,[5] display a broad spectrum of biological activities including antioxidative,[6] cytotoxic,[7] anticancer,[8] antidiabetic[9] and enzyme inhibitory activities.[10] They find applications in charge-transfer complexes[11] and chemical sensors.[12] The ease of reduction to hydroquinones and their re-oxidation enable them to play a vital role in the redox processes occurring in the living organisms. They act as electron-proton carriers in biochemical processes.[5] Besides, substituted quinones are used as oxidants and dehydrogenating agents[13] and as precursors for the synthesis of polycyclic compounds utilizing their inherent dienophilic character in the Diels–Alder reaction.[14] The versatility of quinones as useful building blocks in the synthesis of natural products and their biological activity led to the development of many synthetic methods.[15]

Benzoquinones are commonly prepared by oxidation of phenols[16] and alkoxybenzene derivatives[17] using a variety of oxidants. Earlier we had developed an easy access to highly substituted tribromophenol derivatives **2**, starting from Diels–Alder adducts **1** derived from 1,2,3,4-tetrabromo-5,5-dimethoxycyclopentadiene and β-substituted vinyl acetates using a three- step hydrolysis-oxidation-fragmentation strategy in high overall yield (Scheme 1).[18] It occurred to us that tribromophenols **2** could serve as excellent precursors to substituted benzoquinone derivatives. Herein we wish to report the synthesis of alkyl-substituted dibromo-*p*-benzoquinone derivatives from tribromophenols **2** and their electrochemical properties as exhibited by cyclic voltammetric studies.

Although a large number of reagents[16,17] are known to oxidize phenols to quinones, our initial attempts with **2** revealed the task to be arduous and required optimization. For this purpose, we first selected compound **2a** as the model substrate for carrying out the reaction employing few of the known oxidizing agents as depicted in Table 1. While [(diacetoxy)iodo]benzene (DAIB) and ceric ammonium nitrate (CAN) were able to convert **2a** to the corresponding *p*-quinone derivative **3a** *albeit* in low yields, other reagents such as lead tetraacetate (LTA) and [bis(triflouroacetoxy)iodo]benzene (BTIB) showed a deleterious effect on the yield of the reaction as trace amount of product was observed. On the other hand, PbO_2 in combination with 60% aq $HClO_4$ furnished **3a** in moderate yield. Reducing the amount of PbO_2 from 4 to 2 equiv improved the yield of **3a** to 72%.[19] Further decrease of PbO_2 to 1.2 equiv was fruitless as longer reaction time diminished the product yield with incomplete conversion of starting material. The reaction was also found to be sensitive to the amount of $HClO_4$ used. A systematic study in which the amount of $HClO_4$ was varied, keeping PbO_2 constant (2 equiv), revealed that 0.1 mL of 60% aq $HClO_4$ for 0.07 mmol of substrate gave the best results.

The reaction was also screened to determine the best solvent to obtain **3a** employing PbO_2 and 60% aq $HClO_4$ according to the optimized stoichiometry mentioned above. Almost all the commonly used solvents were found to furnish **3a** in varying yields except MeOH and benzene. Solvents such as AcOH, CH_2Cl_2, $CHCl_3$, CH_3CN,



Scheme 1. Synthesis of substituted tribromophenols.

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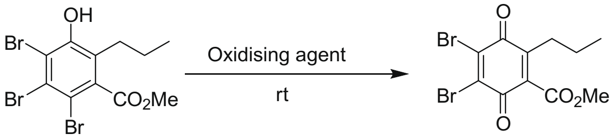
Table 1
Screening of oxidizing agents for conversion of **2a** to **3a**[a]



2a **3a**

Entry	Oxidizing agent	Equivalents	Solvent	Time (h)	Yield[b]
1	$Pb(OAc)_4$	2	Benzene	10	Trace[c]
2	$PhI(OCOCF_3)_2$	2.2	CH_3CN/H_2O (2:1)	12	Trace[c]
3	$PhI(OAc)_2$	3	TFA/AcOH (3:2):cat. H_2O	3.5	30%
4	$(NH_4)_2Ce(NO_3)_6$	3	CH_3CN/H_2O (7:3)	2.5	40%
5	PbO_2, 60% aq $HClO_4$	4	Acetone	2	60%
6	PbO_2, 60% aq $HClO_4$	2.5	Acetone	2	70%
7	PbO_2, 60% aq $HClO_4$	2	Acetone	2	72%
8	PbO_2, 60% aq $HClO_4$	1.2	Acetone	4	47%[d]

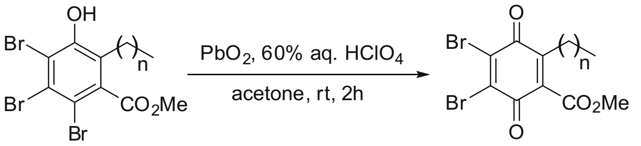
[a] All the reactions were carried out using 0.1 mmol of substrate.
[b] Isolated yield after column chromatography.
[c] On the basis of TLC monitoring against authentic product.
[d] Yield calculated on the basis of recovered starting material.

Et_2O and dioxane furnished **3a** in 38–45% yield in 3 h at room temperature. On the other hand, in THF, DMSO and DMF, reaction did not proceed to completion even after 16 h to furnish, respectively, 54%, 42% and 50% of **3a** (80–95% conversion). DME and acetone gave the best results (67% and 72% in 3.5 and 2 h, respectively). Thus acetone emerged as the solvent of choice for the reaction. Efforts to improve the yield further were not successful perhaps because of various competitive side reactions arising from the species produced under strongly acidic medium during the reaction. The reactions were deliberately carried out under dilute conditions (0.025 M) to minimize the competitive side reactions, mainly the coupling reactions which are common in quinone chemistry.[16e] Prolonging the reaction resulted in a proportionate increase in complexity of the reaction mixture and consequent decrease in the yield of the product.

All subsequent reactions were carried out using 2 equiv of PbO_2, 0.1 ml of 60% aq $HClO_4$ for 0.07 mmol of phenol derivatives **2** in acetone, maintaining a concentration of 0.025 M. For tribromophenols **2b–d**, reactions were completed within 2 h at room temperature, giving *p*-benzoquinone derivatives **3b–d** in 70–72% yields as the only isolable products,[19] with no indication of the formation of corresponding *o*-benzoquinones (Scheme 2).

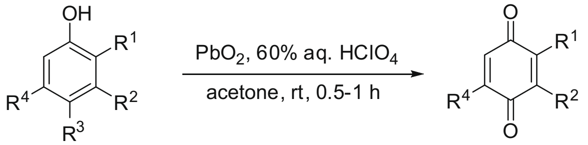
We then applied the optimized condition to few representative phenols **4a–c** to obtain quinones **5a–c** in 62%, 58% and 51% yields, respectively, as shown in Scheme 3.[16e]

After successfully synthesizing the *p*-benzoquinone derivatives **3a**–**d**, our next task was to examine their electrochemical behavior as quinone–hydroquinone couples have been known to have been studied extensively over the years as the prototypical examples of organic redox systems.[20] The electrochemical properties of the quinones **3a**–**d** were evaluated by cyclic voltammetry (CV) in dry CH_2Cl_2 with 0.1 M *tetra-n*-butylammonium hexafluorophosphate ($^{n}Bu_4NPF_6$) as the supporting electrolyte.[21] The CV curves exhibited typically two cathodic polarographic waves corresponding to two single electron reductions to give semiquinone radical anion ($Q^{\cdot -}$) and hydroquinone dianion (Q^{2-}), respectively, in all the cases (Fig. 1). Cathodic to anodic peak separations were 140–260 mV for the first reduction waves (ΔE_1) and about 150–250 mV for the second reduction waves (ΔE_2) (Table 2). Although benzoquinone–hydroquinone redox couple is one of the known reversible electrochemical systems but the electrochemical reductions of quinones **3a–d** to first semiquinone radical anions ($Q^{\cdot -}$) and then to hydroquinone dianions (Q^{2-}) behave quasi-reversibly as the potential differences between cathodic and anodic peaks (ΔE_1, ΔE_2) are in between 140 and 260 mV which are higher than the value for a reversible process. Furthermore, the ratios between the cathodic and anodic peak currents of these electrochemical species range from 1.0 to1.04 for the first reduction potentials (i.e., Q–$Q^{\cdot -}$) establishing that the electro- generated species (i.e., semiquinone radical anions, $Q^{\cdot -}$) are stable in CV time scale and the concentration of oxidized and reduced species are the same suggesting reversible nature of the electrochemical response during the conversion of quinones **3** to corresponding semiquinone radical anions. On the other hand, in the second reduction process (i.e., $Q^{\cdot -}$ to Q^{2-}), the corresponding ratios between the cathodic and anodic peak currents vary from 1.0 to 1.3 showing depletion of reduced species before the reverse scan suggesting chemical instability of the reduced species (i.e., hydroquinone dianions, Q^{2-}) in CV time scale.



2b, n=3	**3b**, 70%
2c, n=4	**3c**, 70%
2d, n=5	**3d**, 72%

Scheme 2. Oxidation of tribromophenols **2b–d** to *p*-benzoquinone derivatives **3b–d**.



4a, R^1, R^2, R^4 = H; R^3 = Br	**5a**, 62%
4b, R^1, R^3 = H; R^2, R^4 = Me	**5b**, 58%
4c, R^1, R^2 = Me; R^3, R^4 = H	**5c**, 51%

Scheme 3. Oxidation of representative phenols **4a**–**c** to quinones **5a**–**c**.

To visualize the electrochemical effect of the substituents present in the aforementioned quinones **3**, the cyclic voltammograms were compared with that of two known 1,4-quinone

Table 2
Electrochemical parameters: reductions of quinones **3a**–**d**, BQ and DDQ

Entry	Quinone	ΔE_1 (mV)	$-E_{1/2}^{(1)}$ (V)	ΔE_2 (mV)	$-E_{1/2}^{(2)}$ (V)	$-\Delta E_{1/2}$ (V)
1	**3a**	260	0.18	250	0.95	0.77
2	**3b**	220	0.18	220	0.95	0.78
3	**3c**	160	0.19	170	0.95	0.77
4	**3d**	140	0.18	150	0.93	0.75
5	**BQ** (**5a**)	320	0.52	320	1.19	0.67
6	**DDQ**	80	0.31	220	0.97	0.66
7	**5b**	220	0.67	260	1.26	0.59
8	**5c**	210	0.66	250	1.16	0.50

Half wave or formal potential $E_{1/2} = (E_p^r + E_p^o)/2$, E_p^r = Reduction peak potential, E_p^o = Oxidation peak potential. Potential separation $\Delta E = (E_p^r - E_p^o)$. (1) and (2) stand for first and second reductions, respectively. $\Delta E_{1/2}$ = Separation in formal potentials.

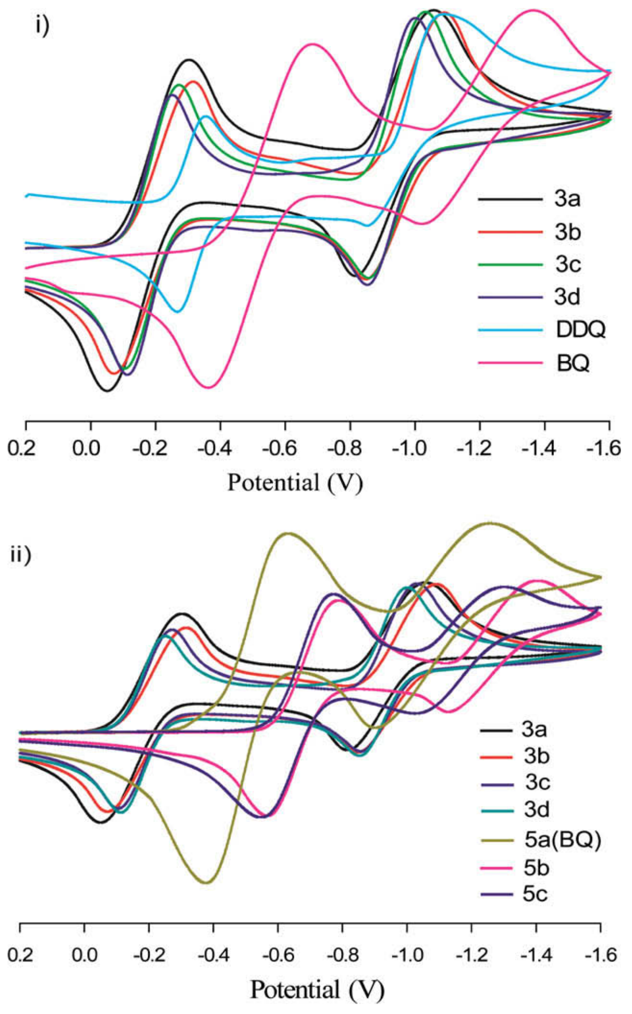


Figure 1. Comparison of cyclic voltammograms of **3a**–**d** with (i) BQ and DDQ and (ii) **5a** (BQ), **5b** and **5c** in dry CH_2Cl_2 with $^n Bu_4NPF_6$ (0.1 M) as the supporting electrolyte at a scan rate of 100 mVs^{-1}. The reference electrode was Ag/AgCl.

systems, *p*-benzoquinone (BQ) and 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) recorded under identical experimental conditions. All the electrochemical parameters associated with the cyclic voltammograms are tabulated in Table 2.

A decrease in $E_{1/2}$ value is associated with electron- withdrawing nature of the substituents on the benzoquinone core thereby facilitating reduction and vice versa. On going from **3a**→**d**, no appreciable change was observed in the $E_{1/2}$ values of first and second reduction with increase of alkyl chain as substituent ($E_{1/2}^{(1)} = -0.18 \rightarrow -0.19$ V, $E_{1/2}^{(2)} = -0.93 \rightarrow -0.95$ V) indicating electronic environment remaining almost undeterred. However, these values are found to be very much lower with respect to that of BQ ($E_{1/2}^{(1)} = -0.52$ V, $E_{1/2}^{(2)} = -1.19$ V) suggesting easy two- step reduction of quinones **3a–d** to corresponding hydroquinones compared to that of BQ (Fig. 1(i), Table 2). Moreover, in spite of the second reduction potentials being almost comparable to that of DDQ ($E_{1/2}^{(2)}$ values for **3a**–**d** $= -0.95 \rightarrow -0.93$ V; $E_{1/2}^{(2)}$ for DDQ = -0.97 V), the much lower first reduction potentials of **3a**–**d** ($E_{1/2}^{(1)} = -0.18 \rightarrow -0.19$ V) in comparison to that of DDQ ($E_{1/2}^{(1)} = -0.31$ V) indicate quinones **3** as comparable or relatively better electron acceptors than DDQ (Fig. 1(i), Table 2). These results may be explained on the basis of electronic environment around the benzoquinone skeleton. The combined electron- withdrawing effects of the ester (COOMe) as well as two bromine substituents generate an overall electron pump away from benzoquinone core making their reduction easier. With increasing number of carbons in the alkyl substituent ($C_3 \rightarrow C_6$, **3a**–**d**), electron- donating property does not change significantly. As a result, no appreciable alteration in the reduction potentials was observed.

Cyclic voltammograms of quinones **5**, obtained from the commercially available phenols **4** (Scheme 3) were also recorded and compared with that of quinones **3** (Fig. 1(ii)). Quinones **5** exhibited distinctly different voltammograms with respect to quinones **3**. It is clear from the voltammograms (Fig. 1(ii), Table 2) that both the first and second reduction potentials of **5** are higher than that of **3**.

In conclusion, synthesis of alkyl-substituted dibromo-*p*-benzoquinones has been accomplished from pentasubstituted tribromophenol derivatives using PbO_2 as oxidizing agent in combination with 60% aq $HClO_4$ in acetone in 70–72% yields. A detailed optimization study revealed a major dependency of the outcome of the reaction on solvent, stoichiometry of the oxidant and the amount of acid used. Title compounds exhibited interesting electrochemical properties as revealed from cyclic voltammetric studies.

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19. *General procedure for oxidation of tribromophenols 2 to dibromo-p-benzoquinone derivatives* **3**. *Methyl 4,5-dibromo-3,6-dioxo-2-propylcyclohexa-1,4-dienecarboxylate* **3a**: To a magnetically stirred heterogeneous mixture of PbO_2 (98 mg, 0.41 mmol, 2 equiv) in acetone (2.6 mL) was added dropwise a solution of 60% aq $HClO_4$ (0.3 mL) followed by a solution of **2a** (88 mg, 0.2 mmol) in acetone (5.4 mL) over a period of 10 min at room temperature and the resulting mixture was stirred for 2 h. After disappearance of the starting material (as indicated by TLC monitoring) the reaction mixture was filtered through Whatman filter paper to a conical flask containing water (2 mL) and the filter cake was washed thoroughly with dichloromethane. The contents of the flask were then transferred to a separatory funnel and the aqueous portion was extracted with dichloromethane (3 × 10 mL). The combined organic layers were then washed first with water followed by brine and finally dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuo to leave a residue which was chromatographed on silica gel (using 1–2% EtOAc in hexane) to afford the quinone derivative **3a**. $R_f = 0.5$ (5% EtOAc in hexane); yield: 53 mg; 72%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, COOMe), 2.40 (t, $J = 7.7$ Hz, 2H), 1.52–1.42 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1 (C=O), 174.6 (C=O), 163.5 (C=O of COOMe), 146.1, 139.8, 138.8, 136.9, 53.1, 30.9, 22.7, 14.2; IR (neat): 2900, 1720 (C=O), 1660 (C=O), 1560, 1420, 1240, 1140, 1080 cm^{-1}. ESI-HRMS: *m*/*z* calcd for $C_{11}H_{11}Br_2O_4$ $(M+H)^+$: 364.9024, found: 364.9023. *Methyl 4,5-dibromo-2-butyl-3,6-dioxocyclohexa-1,4-dienecarboxylate* **3b**: $R_f = 0.5$ (5% EtOAc in hexane); yield: 70% from **2b**, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, COOMe), 2.42 (t, $J = 7.8$ Hz, 2H), 1.44–1.37 (m, 2H), 1.34–1.25 (m, 2H), 0.84 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1 (C=O), 174.6 (C=O), 163.5 (C=O of COOMe), 146.4, 139.8, 138.8, 136.7, 53.1, 31.3, 28.7, 22.8, 13.6; IR (neat): 2900, 1720 (C=O), 1660 (C=O), 1560, 1420, 1220, 1120, 1080 cm^{-1}. ESI-HRMS: *m*/*z* calcd for $C_{12}H_{13}Br_2O_4$ $(M+H)^+$: 378.9181, found: 378.9185. *Methyl 4,5-dibromo-3,6-dioxo-2-pentylcyclohexa-1,4-dienecarboxylate* **3c**: $R_f = 0.5$ (5% EtOAc in hexane); yield: 70% from **2c**, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 3H, COOMe), 2.46 (t, $J = 7.9$ Hz, 2H), 1.49–1.46 (m, 2H), 1.32–1.29 (m, 4H), 0.87 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2 (C=O), 174.8 (C=O), 163.6 (C=O of COOMe), 146.5, 139.9, 138.9, 136.8, 53.2, 31.9, 29.0, 28.9, 22.2, 13.9; IR (neat): 2900, 1720 (C=O), 1660 (C=O), 1560, 1420, 1220, 1120, 1080 cm^{-1}. ESI-HRMS: *m*/*z* calcd for $C_{13}H_{15}Br_2O_4$ $(M+H)^+$: 392.9337, found: 392.9335. *Methyl 4,5-dibromo-3,6-dioxo-2-hexylcyclohexa-1,4-dienecarboxylate* **3d**: $R_f = 0.5$ (5% EtOAc in hexane); yield: 72% from **2d**, yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.92 (s, 3H, COOMe), 2.47 (t, $J = 7.9$ Hz, 2H), 1.49–1.44 (m, 2H), 1.36–1.24 (m, 6H), 0.87 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1 (C=O), 174.6 (C=O), 163.5 (C=O of COOMe), 146.4, 139.7, 138.8, 136.6, 53.1, 31.2, 29.4, 29.2, 29.0, 22.4, 13.9; IR (neat): 2900, 1720 (C=O), 1660 (C=O), 1560, 1420, 1220, 1140, 1080 cm^{-1}. ESI-HRMS: *m*/*z* calcd for $C_{14}H_{17}Br_2O_4$ $(M+H)^+$: 406.9494, found: 406.9490.
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21. Cyclic voltammetric studies were performed on a BAS Epsilon electrochemical workstation in dichloromethane using 0.1 M $^nBu_4NPF_6$ as the supporting electrolyte. The reference electrode was Ag/AgCl and the concentrations of the compounds were used in the order of 10^{-3} M. The ferrocene/ferrocenium couple occurs at $E_{1/2} = +0.45$ (65) V versus Ag/AgCl under the same experimental conditions.