

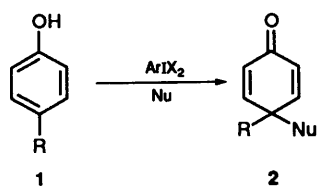
A Simple and Efficient Procedure for the Preparation of *p*-Quinols by Hypervalent Iodine Oxidation of Phenols and Phenol Tripropylsilyl Ethers

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Oxidation of *para*-substituted phenols with [bis(trifluoroacetoxy)iodo]benzene (BTIB) in aqueous acetonitrile at 0 °C gives *p*-quinols in moderate to good yields; higher yields are obtained when tripropylsilyl ethers of phenols are used.

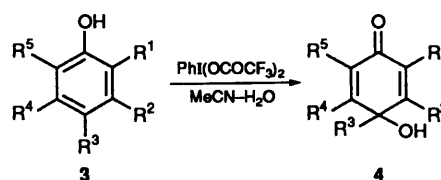
During our recent synthesis of aranorosin¹ we required a mild but efficient procedure for the oxidation of a *para*-substituted phenol to the corresponding *p*-quinol (4-substituted 4-hydroxycyclohexa-2,5-dienone). This transformation can be effected with a variety of reagents including peracetic acid,² potassium persulfate,³ thallium(III) salts,⁴ dimethyldioxirane⁵ and nitric acid;⁶ by oxygenation of phenols in the presence of Cu₄-Cl₄O₂(CuCN)₃,⁷ cobalt bis(salicylideneaminopropyl)amine⁸ or sodium amide and diethylamine;⁹ and by electrochemical methods.¹⁰ Alternatively, photooxidation¹¹ or hydrogen peroxide oxidation of phenols in the presence of various transition metals¹² or heteropolyacids¹³ gives 4-substituted 4-hydroperoxycyclohexa-2,5-dienones which can be reduced to *p*-quinols by triphenylphosphine, dimethyl sulfide or sodium iodide. Most of these procedures suffer from limitations. In particular, yields are often low, mixtures of products are common, and various side reactions are usually encountered with simple phenols.

During the last few years hypervalent iodine reagents have been widely used for the oxidation of phenols, and while no definitive mechanisms have been established for these reactions it is widely assumed that they proceed *via* some reactive intermediate which is electrophilic in nature. In keeping with this assumption, oxidation of 4-substituted phenols **1** in the presence of an appropriate nucleophile can constitute an effective synthesis of the 4,4-disubstituted cyclohexadienones **2**.



Oximes,¹⁴ alcohols,¹⁵ carboxylic acids,¹⁶ amides,¹⁷ fluoride ion¹⁸ and electron-rich aromatic rings¹⁹ have all been used successfully as nucleophiles, and dienone formation can occur by either inter- or intra-molecular reaction of the nucleophile.

We now report the extension of the general approach outlined in **1** → **2** to the preparation of *p*-quinols.²⁰ Thus, treatment of a variety of 4-substituted phenols **3** with [bis(trifluoroacetoxy)iodo]benzene (BTIB) in acetonitrile–water (4:1) at 0 °C followed by quenching with water after 5–15 min. gave the corresponding *p*-quinols **4** in moderate to good yields. In a number of other cases, however, and most notably with simple *p*-alkylphenols, the yields of *p*-quinols obtained in this way were poor to modest and overoxidation to tarry materials was a serious problem. *p*-Cresol, for example, gave 44% of 4-hydroxy-4-methylcyclohexa-2,5-dienone. Attempts were made



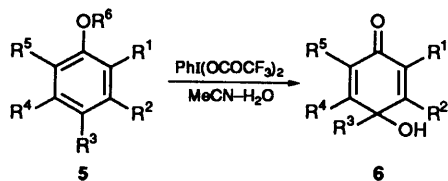
- a** R¹ = R⁵ = Bu^t, R² = R⁴ = H, R³ = Me, 78%
b R¹ = R³ = R⁵ = Bu^t, R² = R⁴ = H, 76%
c R¹ = R⁵ = Br, R² = R⁴ = H, R³ = Me, 78%
d R¹ = R⁵ = Br, R² = R⁴ = H, R³ = CH₂CO₂Et, 67%
e R¹ = R² = R⁴ = H, R³ = Me, R⁵ = CO₂Et, 30%

to optimise conditions for this conversion, for example by variation of reaction time and temperature, by use of different aryliodonium salts and solvent systems, and by addition of bases such as triton B or pyridine to the reaction medium. Despite an extensive investigation, however, the highest yield of *p*-quinol obtained from *p*-cresol was only 48%. Fortunately, this could be improved substantially by exploiting an observation made by Kita *et al.*,^{19c} during a recent synthesis of the alkaloid discorhabdin C. The Japanese workers needed to oxidise a 4-alkylphenol to a spirocyclic cyclohexadienone and used BTIB as reagent. They found that better yields of the cyclohexadienone were obtained when the phenol trimethylsilyl ether was used, rather than the free phenol.

We therefore converted *p*-cresol into the trimethylsilyl ether (92%) and oxidised this, as before, with BTIB in aqueous acetonitrile. This gave the *p*-quinol in 63% yield. A study was then made to determine the best silyl ether for this oxidation: nine further different silyl ethers of *p*-cresol were prepared (4-MeC₆H₄OSiR¹R²R³, R¹, R² and R³ combinations of Me, Et, Pr, Pr^t, Bu, Bu^t, Ph; yields 92–100%) and oxidised with BTIB under standard conditions. The tripropylsilyl ether was found to be best, and 4-hydroxy-4-methylcyclohexa-2,5-dienone was obtained in 73% yield. A series of experiments was then carried out to compare the oxidations of phenols and the corresponding tripropylsilyl ethers and the results are summarised as **5** → **6**. In all of the cases **5a–f** the yields of *p*-quinols **6a–f** were higher from the silyl ethers, significantly so in the cases of **5a** and **f**, and the oxidations were generally cleaner than when the phenols were used. Interestingly, attempts to further improve the yields of *p*-quinols by controlled addition of either 1 mol dm⁻³ hydrofluoric acid or tetrabutylammonium fluoride to mixtures of phenol tripropylsilyl ethers and BTIB were unsuccessful, and low yields were obtained.

In contrast to many other methods for the synthesis of *p*-quinols, the BTIB oxidations are relatively clean and pure products are easily obtained by chromatography. In only one instance, with 4-methyl-1-naphthol, was the yield of *p*-quinol lower with the tripropylsilyl ether (44%) than with the phenol (59%). Limitations to the methods that we encountered were: 1, the silyl ether approach is not useful for highly hindered phenols

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	R ⁶ = H (%)	R ⁶ = Pr ₃ Si (%)
a R ¹ = R ² = R ⁴ = R ⁵ = H, R ³ = Me	48	73
b R ¹ = R ³ = Me, R ² = R ⁴ = R ⁵ = H	60	73
c R ¹ = R ⁴ = R ⁵ = H, R ² = R ³ = Me	67	75
d R ¹ = R ³ = R ⁵ = Me, R ² = R ⁴ = H	67	78
e R ¹ = R ⁵ = H, R ² = R ³ = R ⁴ = Me	63	70
f R ¹ = R ² = R ⁴ = R ⁵ = H, R ³ = CH ₂ CO ₂ Me	27	59

(e.g., 2,4,6-tri-*tert*-butylphenol, ethyl 3,5-dibromo-4-hydroxyphenylacetate) or very acidic phenols (4-methyl-2-nitrophenol, ethyl 2-hydroxy-5-methylbenzoate) as the silyl ethers cannot be obtained by standard methods; oxidation of the free phenols, however, gives satisfactory results. 2, The tripropylsilyl ethers of certain 4-*tert*-butylphenols (4-*tert*-butylphenol, 4-*tert*-butyl-2-methylphenol) underwent complete decomposition on treatment with BTIB. 3, Oxidation of 4-benzylphenol gave 2-benzyl-1,4-benzoquinone as the only identifiable product (38%). 4, Oxidation of 4-ethylphenol gave 4-acetylphenol (15%) in addition to 4-ethyl-4-hydroxycyclohexa-2,5-dienone (48%). These limitations apart, BTIB oxidation of phenols and/or phenol tripropylsilyl ethers represents an extremely simple and efficient method for the preparation of a wide range of *p*-quinols, and is particularly useful for the preparation of simple cyclohexadienone natural products such as jacaranone **6f** and the related dibromo compound **4d**.²¹

Experimental

General Procedure for the BTIB Oxidation of para-Substituted Phenols to *p*-Quinols.—BTIB (1.1 mmol) was added to a stirred solution of the phenol (1.0 mmol) in acetonitrile–water (3:1; 4 cm³) at 0°C and stirring was continued until TLC analysis (diethyl ether) showed completion of the reaction after 5–15 min. The brown reaction mixture was quenched by addition of water (4 cm³) and the resulting mixture was extracted with dichloromethane (4 × 5 cm³). The combined extracts were dried (Na₂SO₄) and evaporated under reduced pressure to give a brown solid or oil. This crude product was purified by column chromatography [ether–light petroleum (b.p. 60–80°C)] followed by recrystallisation or Kugelrohr distillation.*

General Procedure for the BTIB Oxidation of Tripropylsilyl Ethers of para-Substituted Phenols to *p*-Quinols.—The same general procedure was used as described above, except that the reaction mixture was vigorously stirred throughout. Oxidations required 0.5–2 h to go to completion (TLC, ether), and products were isolated as described above.*

* Physical properties and spectroscopic data for known compounds were in complete agreement with literature data. Analytical and spectroscopic data for all new products were fully consistent with the assigned structures.

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