Facile Coupling of Sterically Hindered 2,6-Dialkylphenols with Periodic Acid[1]

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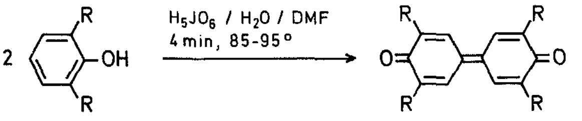
Oxidative coupling of sterically hindered 2,6-dialkylphenols can be performed with any one of a series of reagents, e.g. alkaline hexacyanoferrate(III), neutral iron(III) chloride, transition-metal compounds (MnO_2, Ce^{IV}), or lead(IV) oxide in neutral media[2–10], or nitric acid[11].

Recently, very effective silver carbonate on Celite[12], moisture-sensitive vanadium tetrachloride or vanadium oxytrichloride[13,14], lead dioxide in polar solvents[15], or anodic coupling[16] have been used.

This note describes an application of paraperiodic acid (H_5JO_6) to the oxidative coupling of sterically hindered 2,6-dialkylphenols, a reagent that has thus far been little used for coupling of alkyl-substituted phenols[17].

Although sodium periodate in aqueous or 80% aqueous acetic acid has been extensively used for oxidation of 2,6-dimethyl-[18] or 2,6-dimethoxy-[19] phenols, the oxidation products were found to be mainly mixtures of quinones and Diels-Alder type adducts[18], and to contain only ~7% of the coupling product[19].

Mixing of 2,6-dialkylphenols (**1a**–**1e**) in dimethylformamide with an aqueous solution of periodic acid at 85–95° for a few minutes generally produces the desired product (3,3′,5,5′-tetraalkyldiphenoquinones, **2a**–**2e**) in 60 to 94% yield (see Table). This is a simple and rapid laboratory procedure for obtaining coupling products from 2,6-dialkylphenols in yields comparable to those given by other longer methods[5,6,7,12].



1 **2**

a R = *t*-C_4H_9
b R = *sec*-C_4H_9
c R = *i*-C_3H_7
d R = CH_3
e R = OCH_3

Generally, one half equivalent or one equivalent of the oxidant was needed; however, good yields of the coupling product were obtained by using up to 4 equivalents of periodic acid per mole of the substrate. Usually, the coupling product crystallizes out from the reaction medium in high purity and does not require recrystallization; however, its purity can be checked by T.L.C. [Silica Gel G, with 8:1:1 (v/v heptane/dichloromethane/methanol or 3:1:1 (v/v heptane/acetone/methanol]. Using refluxing methanol as the reaction medium and an aqueous solution of periodic or iodic acids as the oxidant, high yields (55 to 90%) of the coupling products were also obtained; however, the product contained 2 to 6% of a quinone impurity (T.L.C.)[20].

By analogy with other oxidants[5–7,10], the mechanism of the coupling reactions described involves a radical intermediate and, as shown by E.S.R. studies, apparently proceeds by two, successive, one-electron transfers (periodic and iodic acids are two-electron oxidants); moreover, a direct involvement of dimethylformamide in a radical reaction is also apparent[17,21]. However, a partial involvement of a phenoxonium ion in the phenol couplings remains a strong possibility[16]. These studies show that the nature of the solvent and the electrophilic strength of the oxidizing species (periodic or iodic acids or their ions) in this solvent are very important factors in the formation of product, and that use of a solvent that is more, or less, nucleophilic usually causes a different reaction-path, e.g. an oxidative dealkylation[17,19].

Coupling of 2,6-Dialkylphenols; General Procedure:

The 2,6-dialkylphenol (10 mmol) is dissolved in dimethylformamide (10 ml), an aqueous 4*M* solution of periodic acid (3.5 g, 4 ml) is added, and the solution is stirred at 85–95° (hot water bath) for 4–5 min. Usually, colored product partially crystallizes out by this time. After 5–10 min at room temperature, the reaction mixture is diluted with 50% aqueous methanol (8–10 ml), and the product is isolated by filtration and washed with cold methanol. Gradual dilution of the filtrate with water gives a second crop of product; further dilution usually gives some by-products (quinones or purple-colored condensation products, T.L.C.).

Table. Preparation of 3,3′,5,5′-Tetraalkyldiphenoquinones from 2,6-Dialkylphenols and Periodic Acid via Coupling

Phenol	Oxidant	Yield of **2a–2e**[a] (%)	m.p.	Lit. m.p.
1a	Periodic acid	94	245–247°[b]	240–241°[4], 245–247°[2], 248°[12]
1b	Periodic acid	92	203–205°[c]	
1c	Periodic acid	92	202–203°[c]	199–203°[11], 200–201°[12],
1d	Periodic acid	60	216–218°[d] (shrinks at 205°)	205°[3], 215°[8], 217–218°[12]
1e	Periodic acid	94	290–292°[e]	293° (dec)[7]
3[g]	Periodic acid	90	135–137°[f]	
3[g]	Iodic acid	95	135–137°[f]	

[a] Coupling of phenol and yields of product were determined by ^{1}H-N.M.R. spectrometry. The spectral data of all compounds prepared were identical with those of authentic samples prepared by the known methods, cf. Ref.[5,6,7,12].

[b] Can be recrystallized from acetone or aqueous acetone (brown-red needles).

[c] Can be recrystallized from methanol or isopropanol (lustrous purple-red plates).

[d] Can be recrystallized from dichloromethane (red microcrystals).

[e] Can be recrystallized from nitromethane or 1:1 nitromethane/nitrobenzene (steel-blue needles).

[f] The product is 2,6-di-*t*-pentylbenzoquinone; yellow needles from methanol.

[g] The starting material (**3**) is 1,4-dihydroxy-2,6-di-*t*-pentylbenzene.

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[20] Mixing of methanol solutions of 2,6-dialkylphenols with periodic acid proceeds with substantial evolution of heat (an indication of complex-formation[17]), and the mixture sometimes requires external cooling (5–10°). For example, the exothermic reaction observed for the phenols used is in the order **1c**>**1b**>**1a**>**1e**>**1d**.

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