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SPIRO-ANNULATED CYCLOHEXA-2,5-DIENONES VIA ELECTROOXIDATION OF P-ARYL PHENOLS A NOVEL MODE OF ANODIC CARBON-CARBON BOND FORMATION

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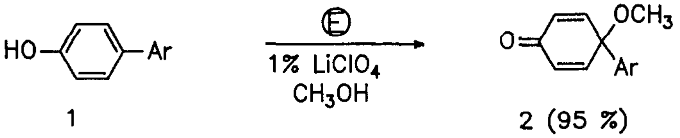
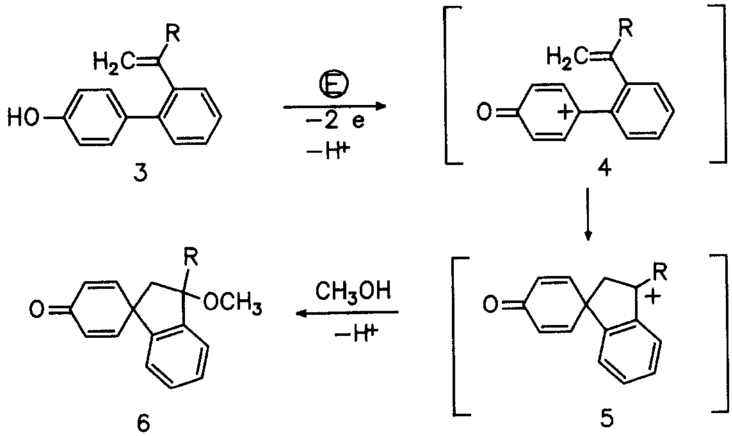
Summary: Intramolecular trapping of the reactive intermediate from anodic oxidation of 2'-alkenyl substituted p-*aryl phenols, followed by solvent capture, affords 4-aryl-4-alkyl-cyclohexa-2,5-dienones.*

Anodic addition reactions of oxygen nucleophiles to aromatic substrates serve as useful routes to oxygenated aromatic compounds, protected quinone derivatives, and *p*-quinols.[1] The synthetic utility of such anodic oxidations would be significantly enhanced if carbon rather than oxygen nucleophiles could be captured during the oxidation. However, with the exception of phenolic coupling processes and cyanation,[2] anodic carbon-carbon bond-forming reactions are uncommon.[3] We report herein the anodic oxidation of 2'-alkenyl substituted *p*-aryl phenols wherein a quaternary carbon-carbon bond is formed during the oxidation via an intramolecular cyclization process. The resulting products are 4,4-substituted cyclohexa-2,5-dienones, a class of compounds ubiquitous in natural product systems.[4]



Since the anodic oxidation of *p*-phenyl phenol 1 to the corresponding *p*-quinol ether 2 is an efficient and high-yield process,[5] this basic system was investigated for anodic carbon-carbon bond formation via the working hypothesis outlined in the scheme below. The 2-alkenyl substituent not only would serve to react with the intermediate from the oxidation of the phenol ring to produce a benzylic carbocation but would also sterically inhibit capture of solvent at the 4-position of the phenol: the 1 → 2 reaction. Trapping of the benzylic cation with methanol would furnish a spirodienone derivative which would be stable to further oxidation.

Initial studies focused on the oxidation of 3a (R = CH_3) under a variety of experimental conditions; the most pertinent results from this study are given in Table I. Under the conditions for the oxidation of *p*-phenyl phenol, anodic oxidation of 3a gave a modest yield (38%) of the spirodienone 6a (entry 1). The yield for this reaction is a function of the solvent system, current density, and anode material. A mildly acidic medium (compare entry 1 vs. 6 and 7) is especially beneficial to the yield of 6a. The effect of added acetic acid on



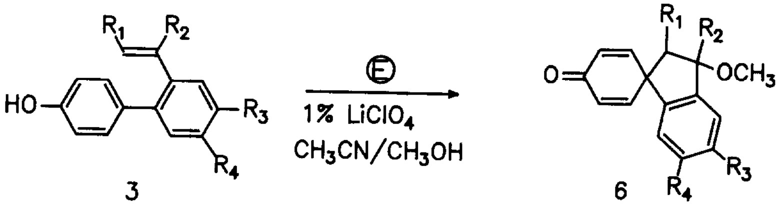
the yield of spirodienone is presumably due to the suppression of phenolic coupling processes under acidic conditions.[6] The above experiments demonstrated that high yields of spirodienones can be obtained from the anodic oxidation of phenols under well-defined experimental conditions.

Table I. Experimental Variables on the Yields of the Anodic Cyclization of 3a

Entry	Solvent	Current Dens. (mA/cm^2)	Anode	Additive	Yield (HPLC) (%)
1	CH_3OH	0.42	Pt	none	38
2	CH_3OH	0.42	Pt	2,6-lutidine	29
3	CH_3OH	0.42	C	AcOH (5 equiv)	37
4	CH_3CN/CH_3OH (4:1)	3.36	Pt	AcOH (5 equiv)	13
5	CH_3CN/CH_3OH (4:1)	1.68	Pt	AcOH (5 equiv)	26
6	CH_3CN/CH_3OH (4:1)	0.84	Pt	AcOH (5 equiv)	76
7	CH_3CN/CH_3OH (4:1)	0.42	Pt	AcOH (5 equiv)	83

Having established reaction conditions for the high-yield anodic cyclization of **3a** to **6a**, further investigations focused on the generality of the oxidation. The effect of substituents on both the alkenyl side-chain and the *p*-aryl ring of the phenol was studied. Anodic oxidation of the cyclopentenyl system **3b** using the optimum conditions developed for **3a** (Table 1, entry 7) gave **6b** (69%). We were especially interested in spirodienones having oxygenated aryl rings since such compounds could be precursors to natural products of similar oxygen substitution. Although such substitution could complicate the anodic cyclization of the **3** → **6** type, this is not the case. For both **3c** and **3d**, anodic oxidation furnished high yields of **6c** and **6d**, establishing that methoxylated *p*-aryl phenols would furnish spirodienones for use in natural products synthesis.

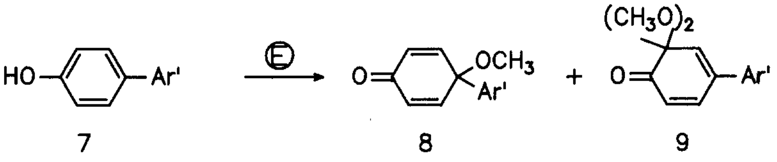
Table II. Spiro-annulated Cyclohexa-2,5-dienones from *p*-Aryl Phenols



		Yield 6 (%)	CE* (%)
3a:	R_1, R_3, R_4 = H; R_2 = CH_3	65	91
b:	R_3, R_4 = H; R_1 = R_2 = $-(CH_2)_3-$	69	93
c:	R_1, R_2 = H; R_3, R_4 = OCH_3	70	79
d:	R_1 = H; R_2 = CH_3; R_3, R_4 = OCH_3	92	92
e:	R_1, R_2, R_3, R_4 = H	17	57
f:	R_1, R_3, R_4 = H; R_2 = C_6H_5	22	52

*Current efficiency for formation of 6.

Under these solvent/electrolyte conditions, the limitation of the 3 → 6 transformation may be related to the nucleophilicity of the alkenyl side-chain. For phenols 3c and 3d the *p*-methoxy group would enhance the nucleophilicity of the olefinic moiety and high yields of spirodienones were obtained. In contrast, phenols 3e and 3f give spirodienones in much lower yields and current efficiencies. The 70% yield of 6c from 3c is in marked contrast to the 17% yield of 6e obtained from 3e. In all of these oxidations, good mass balances were obtained, but the remaining material was a mixture of higher molecular weight products; no appreciable amounts of quinols analogous to 2 were observed. For phenols having less nucleophilic side chains, the lower yields and current efficiencies for the 3e,f oxidations are probably due to a competing anodic addition of solvent at the 2-position, followed by aromatization, and further oxidation to an *o*-quinone monoketal. The *o*-quinone monoketal moiety, unless appropriately substituted, is known to be unstable,[7] accounting for the inability to characterize other products from the reactions of 3e and 3f. In support of this proposal, the anodic oxidation of 4-(2-biphenyl)phenol, 7, afforded in good yield a 1:1 mixture of *p*-quinol ether 8 and *o*-quinone monoketal 9.



This study establishes that intramolecular nucleophilic capture of the reactive intermediate generated from anodic oxidation of *p*-aryl phenols leads to formation of the spirodienones of structure **6**, often in good yield. The formation of quaternary carbon-carbon bonds between an aryl ring and an alkenyl substituent is rare and could have important mechanistic as well as synthetic implications. Significantly, the high-yield formation of oxygenated spirodienones such as **6c** and **6d** makes this chemistry applicable to synthesis of natural products[4] of similar substitution either directly or via dienone-phenol rearrangement. Further efforts will focus on conditions for effecting this transformation in high yields for compounds having less nucleophilic side chains and the bimolecular version of this reaction for both *p*-alkyl and *p*-aryl phenols.

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(8) The following is representative of the anodic oxidations. A solution of **3a** (0.5 g) in CH_3CN/CH_3OH (4:1, 300 mL) containing HOAc (0.75 mL) and 1% $LiClO_4$ by weight was anodically oxidized at 0 °C in a single cell at a constant current of 0.05 A using a cylindrical platinum electrode (1.3 cm diameter x 5 cm high) and a copper wire cathode for 180 minutes. Standard workup and flash chromatography on silica gel (2% Et_2O/hexane as eluant) gave **6a** (0.4 g, 65%, mp 109-110 °C).

(9) The preparation of the starting phenols, which involved as a key step the addition of aryllithium reagents to 4,4-dimethoxy-2,5-cyclohexadienone,[1d] will be detailed in our full manuscript. All compounds employed in this work showed acceptable exact mass measurement or combustion analysis. The melting points for all solid compounds are: **3b**, 107.5-109 °C; **3c**, 130-132 °C; **3d**, 110-111 °C; **6a**, 110-111 °C; **6b**, 118-120 °C; **6d**, 147-149 °C; **6g**, 145.5-147 °C; **8**, 128-130 °C.

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