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Dihydrobenzofuran Derivatives via the Anodic Cycloaddition Reaction of *p*-Methoxyphenols and Vinyl Sulfides

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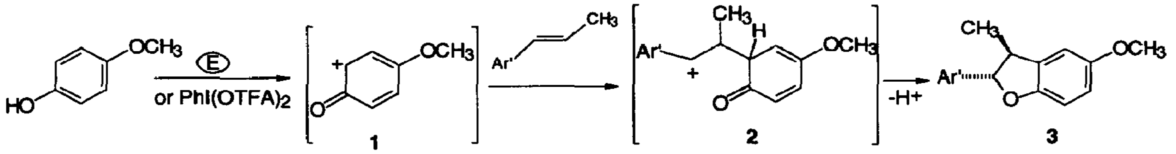
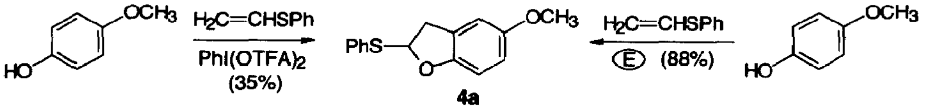
Abstract : The anodic oxidation of *p*-methoxyphenols in the presence of vinyl sulfides gives high yields of dihydrobenzofurans arising via a formal 1,3-cycloaddition reaction of the vinyl sulfide and the anodically generated phenoxonium ion.

The discovery of new, versatile, and efficient methods of forming carbon-carbon bonds is a prevalent theme in organic synthesis. It has recently been demonstrated that chemical and electrochemical oxidations of phenol derivatives provide relatively efficient means of effecting certain carbon-carbon bond-forming reactions.[1] One class of reactions affords substituted dihydrobenzofurans such as **3** via formal 1,3-cycloaddition reactions of electron-rich styrene derivatives to phenoxonium ions. Even though high yields of dihydrobenzofurans were often obtained, the scope of the olefinic component was limited to electron-rich styrene derivatives.[1,2] Dihydrobenzofurans analogous to **3** were not formed in the oxidative cyclization with other olefins (i.e., styrene, cyclohexene) even when the olefinic component was employed in large excess (5-10 equiv.).

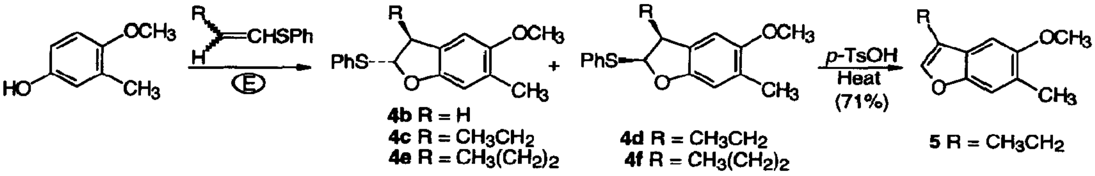


One goal of our current efforts has been to expand the versatility of the reaction by replacing the styrene component with other olefins, thus affording dihydrobenzofurans without aryl substitution at the 2-position. It has been reported that ethyl vinyl ether adds oxidatively to *p*-methoxyphenol to afford a dihydrobenzofuran.[3] Aside from low yields, a 20-fold excess of the vinyl ether was employed in the reaction. ***Furthermore, we have not been able to obtain even low yields of dihydrobenzofurans from electrochemical oxidation of p-methoxyphenol in the presence of 5-10 equivalents of several other vinyl ethers.*** One potential problem in using vinyl ethers as substrates in these reactions is their acid sensitivity. The phenol radical cation is highly acidic[4] and could be causing acid-catalyzed decomposition of the vinyl ether moiety. Vinyl sulfides are less sensitive to acids, yet could serve as electron-rich substrates to react with the chemically or electrochemically generated phenoxonium ions. We report herein the reaction of phenyl vinyl sulfides with phenoxonium ion intermediates. These reactions afford 2-thiophenyldihydrobenzofurans, often in excellent yields.[5]

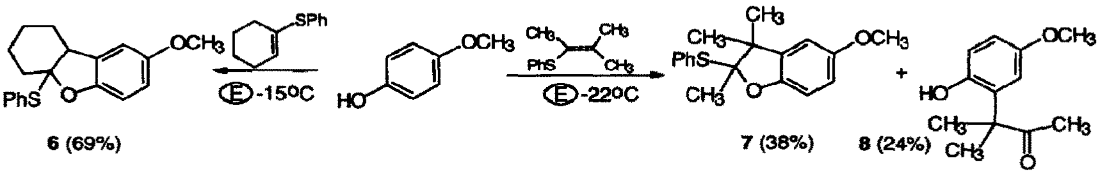
Addition of iodobenzene *bis*-trifluoroacetate (1 equiv.) to an acetonitrile solution of *p*-methoxyphenol (1 equiv.) and phenyl vinyl sulfide (2 equiv.) gave the dihydrobenzofuran **4a**, which was isolated by silica gel chromatography in 35% yield. Although this was our first successful example of a cycloaddition reaction of an oxidized phenol with something other than an electron-rich styrene derivative, the modest yield was disappointing. However, an 88% yield was obtained in this system when the reaction was conducted electrochemically. The constant current anodic oxidation of *p*-methoxyphenol was performed at 0°C in 8:1 acetonitrile/glacial acetic acid with lithium perchlorate as the supporting electrolyte in the presence of phenyl vinyl sulfide (2 equiv). The reaction progress was monitored by TLC (20% ethyl acetate/hexane) which showed essentially a spot-to-spot conversion with a current efficiency of 83%. The dihydrobenzofuran, **4a**, was obtained by crystallization (88%),[6] and the unreacted vinyl sulfide was recovered (80%) by simple chromatography of the mother liquors. Other reactions proceeded similarly,[6] except flash chromatography was used for purifying the product.



We next examined the effect of phenol and olefin substitution on the yield of the oxidative cycloaddition. Anodic oxidation of 3-methyl-4-methoxyphenol in the presence of phenyl vinyl sulfide gave **4b** (72%). The anodic cycloaddition of this phenol with a monosubstituted vinyl sulfide, 1-thiophenyl-1-butene (~ 4:1 *trans*/ *cis*) afforded a ~3:1 mixture of two inseparable dihydrobenzofuran derivatives **4c** and **4d** in 69% yield.[7] Both of these products were converted to the benzofuran **5** by heating with *p*-toluenesulfonic acid in benzene. The stereospecificity of this chemistry was examined using 1-thiophenyl-1-pentene,[8] enriched in the *cis*-isomer, in the anodic cycloaddition reaction. Thus, electrochemical oxidation of 3-methyl-4-methoxyphenol with a 3:1 *cis/trans* mixture of 1-thiophenyl-1-pentene mixture afforded a 3:1 *trans/cis* cycloadduct mixture, **4e** and **4f**.[8] This is nearly identical to the ratio of *trans* to *cis* isomers found in experiments in which the vinyl sulfide was mostly *trans*. Thus, this chemistry most reasonably proceeds in a stepwise manner via nucleophilic attack of the vinyl sulfide on the phenoxonium ion followed by ring closure and aromatization (see **1** → **2** → **3**). Furthermore, a 3-methyl group on the phenol has a small effect on the yield.

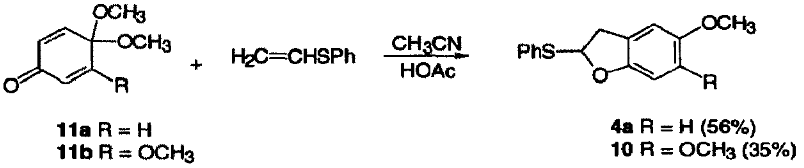


Initial experiments with di- and trisubstituted vinyl sulfides using the reaction conditions noted above gave somewhat lower yields of the respective dihydrobenzofuran. However, the yield of dihydrobenzofuran, **6**, from *p*-methoxyphenol and 1-thiophenylcyclohexene increased from 43% when the reaction was conducted at 0 °C to 69% at a reaction temperature of -15 °C. In the reaction of 2-thiophenyl-3-methyl-2-butene and *p*-methoxyphenol performed at -22 °C, a mixture **7** and **8** was obtained in a total yield of 62%. In these two examples, the highly substituted dihydrobenzofuran formed in the reaction apparently undergoes loss of thiophenol under the reaction conditions, leading to either benzofurans or ring-opened product. The products arising from loss of thiophenol (e.g., **8**) would undergo further oxidation under the reaction conditions. The loss of thiophenol should be minimized at a lower temperature, accounting for the temperature dependence on the yield noted above.



Although a 3-methyl group on the phenol had only a minimal effect on the yield of the dihydrobenzofuran (3-methyl-4-methoxyphenol→ **4b-f**), an electron-donating group at this position had a marked effect on yield. Reaction of 3,4-dimethoxyphenol, **9**, with phenyl vinyl sulfide gave a low yield of the dihydrobenzofuran, **10**, even when 15 equivalents of the vinyl sulfide were used.[10] The results recorded for 3-methyl-4-methoxyphenol suggest that this is not a steric effect. One possibility for the low yields of dihydrobenzofuran, **10**, is that this product is unstable under the oxidation conditions. Whereas **4a** is more difficult to oxidize than *p*-methoxyphenol ($E_{p/2}$= 1.18 V vs. 1.06 V relative to Ag/AgCl), **10** has virtually the same oxidation potential as 3,4-dimethoxyphenol ($E_{p/2}$= 0.94 V vs. 0.95 V relative to Ag/AgCl). Indeed, **10** is rapidly consumed when it is reacted separately under the oxidation conditions.

If the low yield of dihydrobenzofuran, **10**, arose solely from its further oxidation under the reaction conditions, then a non-oxidative generation of the phenoxonium ion intermediate would increase the yield of the reaction. Ionization of quinone monoketals serves as a complementary route to phenoxonium ion intermediates.[1b] Thus, when a mixture of 4,4-dimethoxy-2,5-cyclohexadienone, **11a**, and phenyl vinyl sulfide (2 equiv.) in acetonitrile/acetic acid (10:1) was heated at 55 °C, **4a** was isolated in 56% yield. Although **4a** was formed in significantly lower yield than that obtained via the anodic oxidation route, this non-oxidative chemistry was examined for generating the phenoxonium ion from **11b**. In this case, the dihydrobenzofuran, **10**, was formed in only 35% yield. Thus, the quinone ketal ionization route does complement the anodic cyclization method in cases in which the oxidative stability of the product is a problem. However, the lower yield of **10** (35%) versus **4a** (56%) suggests that the 3-methoxyl group also lowers the inherent reactivity of the phenoxonium ion in the cycloaddition reaction.



Since the thiophenyl group can be easily removed from the 2-thiophenyldihydrobenzofuran, the scope of the anodic cycloaddition reaction is markedly expanded by using vinyl sulfides as the olefinic component. The reaction proceeds cleanly with *p*-methoxyphenol derivatives lacking a 3-alkoxyl group using two equivalents of vinyl sulfide: the unreacted vinyl sulfide can be recovered in high yield. Performing the anodic cycloaddition with one equivalent of the vinyl sulfide leads to a 10-15% reduction in the yield. When the dihydrobenzofuran produced is stable to the anodic oxidation conditions, the anodic oxidation protocol is preferred to either the iodobenzene *bis*-trifluoroacetate oxidation or the quinone ketal ionization route (e.g., **11a** → **4a**). However, for the production of dihydrobenzofurans such as **10** (see **11b** → **10**), the quinone ketal ionization route serves as an alternative procedure.[11]

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3. Shizuri, Y.; Nakamura, K.; Yamamura, S. *J. Chem. Soc., Chem. Comun.* **1985**, 530.

4. (a) Dixon, W. T.; Murphy, D. *J. Chem. Soc. Faraday Trans. 2* **1978**, *74*, 432. (b) Holton, D. M.; Murphy, D. *Ibid.* **1979**, *75*, 1637. (c) Waters, W. A. *J. Chem. Soc. B.* **1971**, *47*, 2026 and references cited therein.

5. This work has been presented at the 185th meeting of the Electrochemical Society, San Francisco, CA., May 22-27, Abstract # 748.

6. A 0°C solution of 4-methoxyphenol (0.199 g, 1.61 mmol), phenyl vinyl sulfide (0.438 g, 3.22 mmol), and $LiClO_4$ (0.25 g) in $CH_3CN/HOAc$ (8:1, 54 mL) was anodically oxidized at 80 mA in a single cell for 69 min. A circular platinum gauze anode (25 mm high x 23 mm diameter) was used and a circular platinum sheet (15 mm diameter) was the cathode. The colorless solution was then neutralized by adding a saturated $NaHCO_3$ solution (40 mL) followed by solid $NaHCO_3$. Standard workup and removal of solvent in vacuo yielded a clear light yellow oil which was crystallized from hexane/Et_2O to afford **4a** as white, fluffy crystals (0.367 g, 88%): mp 66.5-67°C; IR (KBr) 1489 (s), 1225 (s), 1179 (s), 930 (s) cm^{-1}; ^1H NMR δ 7.5-7.6 (m, 2 H), 7.2-7.4 (m 3 H), 6.65-6.85 (m, 3 H), 6.19 (dd, $J = 4.8, 9.1$ Hz, 1 H), 3.76 (s, 3 H), 3.62 (dd , $J = 9.1, 16.7$ Hz, 1 H), 3.15 (dd, $J = 4.8, 16.7$ Hz, 1 H). Exact mass calculated for $C_{15}H_{14}O_2S$: m/z 258.0715, obsd 258.0717.

7. (a) The *trans*-isomers, **4c** and **4e**, showed the hydrogen alpha to the thiophenyl group as a doublet ($J = 4.1$ Hz) at $\delta \sim 5.8$, while this signal for the *cis*-isomers, **4d** and **4f**, occurred at $\delta \sim 6.1$ (d, $J = 7.5$ Hz). (b) The anodic cycloaddition of *p*-methoxyphenol and 1-thiophenyl-1-butene (~4:1 *trans/cis*) also gave a ca. 3:1 mixture of the corresponding *cis*- and *trans*-dihydrobenzofurans in 89% yield.

8. This was prepared from the corresponding *cis*-bromide,[9a] by conversion to the lithium compound and subsequent reaction with diphenyldisulfide.[9b]

9. (a) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Amer. Chem. Soc.* **1973**, 95, 6456. (b) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839.

10. A low yield (19%) was also obained in the anodic reaction of 4-methoxy-3-thiomethylphenol with phenyl vinyl sulfide.

11. All new compounds showed either a correct combustion analysis or exact mass measurement. The vinyl sulfides were prepared via the procedure of Bartles[12a] except for 2-phenylthio-2-methyl-2-butene. The compound was obtained by heating a solution of 3-methyl-2-butanone (1 equiv.), thiophenol (1 equiv), and phosphorous pentoxide (2 equiv.) in methylene chloride.[12b] The following compounds were obtained as crystalline solids: **4a**, mp 66.5-67 °C; **5**, mp 36-39 °C; **9a**, 78.5-79.0 °C; **9b**, 104.0-106.0 °C. The remaining compounds were colorless oils.

12. (a) Bartels, B.; Hunter, R.; Simon, C. D.; Tomlinson, G. D. *Tetrahedron Lett.* **1987**, *28*, 2985. (b) Trost, B. M.; Lavoie, A. *J. Amer. Chem. Soc.* **1983**, **105**, 5075.

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