Vicarious Nucleophilic Aromatic Substitution via Trapping of an α-Ketosulfonium Ion Generated by Pummerer-Type Rearrangement of 2-(Phenylsulfinyl)phenols: Preparation of Biaryls

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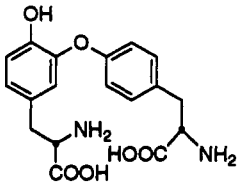
Summary: A new method for the nucleophilic substitution of phenols at the ortho position has been developed which uses as the key step the trapping of an α-ketosulfonium salt generated by a Pummerer rearrangement of 2-(phenylsulfinyl)phenols. In addition to preparing 2-halo- and 2-(acyloxy)phenols, this "vicarious substitution" also allows the preparation of biaryls in fair yield.

Our interest in the preparation of antibiotics containing the isodityrosine structure **1** as a subunit[3] has prompted us to examine various methods for the preparation of ortho-substituted phenols.[4] In particular, we have been interested in the internal trapping of the α-ketosulfonium salts formed by Pummerer-type rearrangement of the symmetrical bis(2-hydroxy-5-methylphenyl) sulfoxide.[5] We now report the successful nucleophilic trapping of a similar



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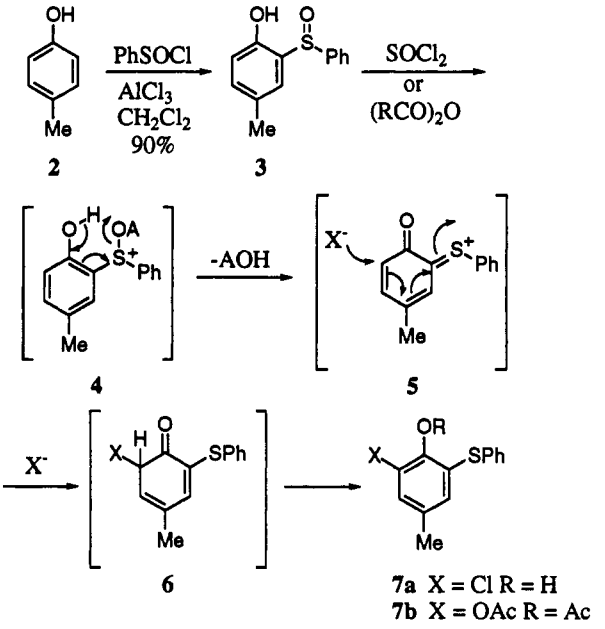
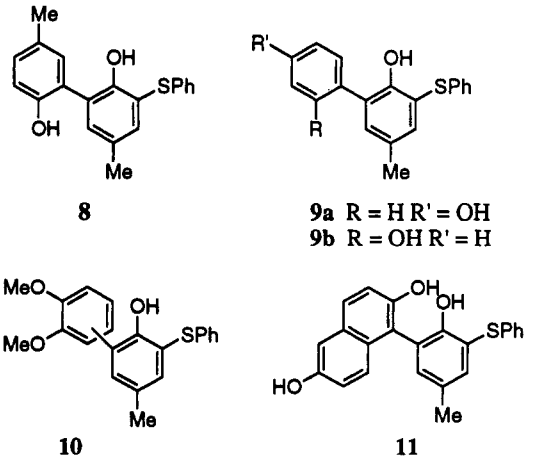
α-ketosulfonium salt at the 3-position of the phenyl ring leading to vicarious substitution of a nucleophilic group for a hydrogen atom, which permits the formation of biphenyl systems including biphenols.

Phenylsulfinylation of *p*-cresol **2** was carried out by treating **2** with phenylsulfinyl chloride and $AlCl_3$ to give **3** in 90% yield.[6] Reaction of **3** with a reactive electrophilic species such as an acid chloride or anhydride presumably produces the α-ketosulfonium salt **5** via elimination of a good leaving group from the activated sulfoxide **4**. Addition of a nucleophile to the unhindered carbon of **5** would generate the cyclohexadienone **6** which would aromatize by keto–enol tautomerization to give **7**. Thus, treatment of **3** with thionyl chloride at 25 °C for 30 min produced the 6-chlorophenol **7a** in an isolated yield of 78%. Likewise, treatment of **3** with acetic anhydride and sodium acetate produced the diacetate **7b** in 30% yield along with 54% of the acetate of **3**. When a mixture of **3** and *p*-cresol



2 was treated with trifluoroacetic anhydride (TFAA), the biphenol **8** was obtained in an isolated crude yield of 60–74%. In like manner, the coupled products **9ab** (3:1 ratio), **10** (as a regioisomeric mixture), and **11** were produced by treatment of **3** with TFAA and the corresponding nucleophile, in yields of 80, 80, and 89%, respectively.[7] Thus, one can effect vicarious substitution of the hydrogen at C3 by a hetero or carbon nucleophile in high yield.



Reductive removal of the phenylthio group from these derivatives would lead to an overall substitution of a hetero or carbon nucleophile for an ortho hydrogen atom of a phenol. This could be accomplished easily but only in modest overall yields. Thus, treatment of **3** with *p*-cresol

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(1) UCLA McCoy Award recipient, 1991–92; UCLA Hanson-Dow Teaching Award recipient, 1992.

(2) Studienstiftung des deutschen Volkes Postdoctoral Fellow, 1992–3.

(3) Many naturally occurring compounds containing this subunit are known, e.g., piperazinomycin, K-13, bouvardin and deoxybouvardin, OF4949-I-IV, RA-I-VII, vancomycin, teicoplanin, and ristocetin. For references to their isolation, structure determination, and synthesis, see: (a) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. (b) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000. (c) Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481.

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(6) Chasar, O. W.; Pratt, T. M. *Phosphorus Sulfur* **1978**, *5*, 35.

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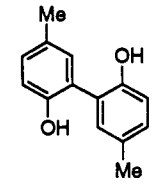
and TFAA followed by reductive desulfurization using Raney nickel or nickel boride affords the symmetrical biphenol 12[8] in 40–50% isolated yields for the two steps.



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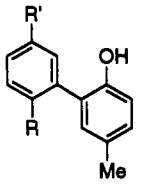
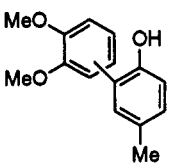


13a R = H R' = OH
13b R = OH R' = H



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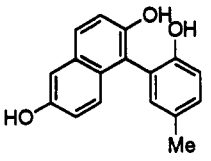

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In like fashion, the biaryls—**13ab** (3:1 ratio), **14** (as a regioisomeric mixture), and **15**—could be prepared from **3** and the corresponding arene in overall yields of 22%, 10%, and 14%, respectively. We believe that the problem in these desulfurization reactions is due to the presence of the phenolic hydroxyl group which perhaps strongly binds to the active metal catalysts. Protection of these hydroxyl groups permits much higher yields of desulfurization. For example, treatment of the diacetate of the biphenol **8** with Raney nickel in ethanol at pH 7 afforded in 87–96% isolated yield the diacetate of the symmetrical biphenol **12**, which afforded **12** in excellent yield on hydrolysis.

Thus, we have observed vicarious substitution of hetero and carbon nucleophiles for hydrogen in 2-(phenylsulfinyl)phenols under Pummerer-type conditions. It should be pointed out that this new method nicely complements the existing methods for biaryl and biphenol synthesis,[9] namely oxidative coupling of phenols and their derivatives[9a] and $S_{RN}1$ processes.[9b]

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Supplementary Material Available: General experimental procedures and characterization data for **3**, **7a**, **7b**, **8a**, and **12** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) *N,N*-Dimethylaniline also reacts with **3** in the presence of TFAA to give, after desulfurization, a mixture of the para and ortho isomers of the dimethylamino derivative corresponding to **13ab** in 10% overall yield. Moreover, the reaction of the pyrrolidine enamine of cyclohexanone with **3** and TFAA gives, after aqueous workup, a poorly separable mixture of products containing the desired α-arylcyclohexanone in poor yield.

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(9) (a) Whiting, D. A. Oxidative Coupling of Phenols and Phenyl Ethers. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.9, pp 659–703, especially pp 663–679. (b) Norris, R. K. Nucleophilic Coupling with Aryl Radicals. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, Chapter 2.2, pp 451–482, especially pp 469–471.