term k_{gb}[amine]^2[ester] as a general-base-assisted nucleophilic attack of amine at the ester carbonyl group.[10]

[10] This work was supported by a grant from the National Institutes of Health.

[11] Postdoctoral Fellow, Department of Chemistry, University of California at Santa Barbara.

Thomas C. Bruice, Stephen M. Felton[11]
Department of Chemistry
University of California at Santa Barbara
Santa Barbara, California 93106

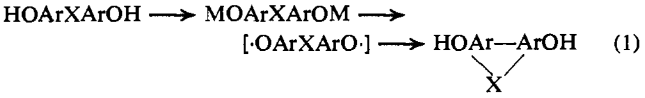
Received March 8, 1969

Intramolecular Oxidative Phenol Coupling. A New Method

Sir:

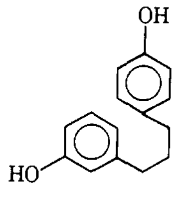
Intramolecular oxidative phenol coupling has long been recognized as the key step in the biosynthesis of phenolic alkaloids and other natural products.[1] The nonenzymic analog of this reaction can lead to elegantly simple *in vitro* syntheses of these compounds, but in practice often results in low yields of desired products, along with relatively large amounts of polymeric materials.[1a,2] We wish to report a new approach that shows considerable promise in alleviating this problem.[3]

In the belief that the above-mentioned difficulties result at least in part from the use of an "external" oxidizing agent (*e.g.*, potassium ferricyanide, ferric chloride, or manganese dioxide), we sought to devise a procedure whereby the oxidizing agent is incorporated into the diphenol molecule prior to actual oxidation. The electron-transfer step could then be carried out under conditions of high dilution, in an inert solvent, and in the absence of excess oxidizing agent (eq 1). The observation by Funk and coworkers[4] that treatment of vanadium oxytrichloride with phenols gave rise in certain cases to isolable phenoxyvanadium(V) compounds prompted us to investigate the use of this reagent in the above scheme.

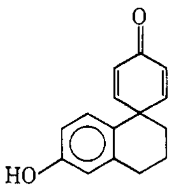


$$\mathrm{HOArXArOH} \longrightarrow \mathrm{MOArXArOM} \longrightarrow [\cdot\mathrm{OArXArO}\cdot] \longrightarrow \underset{\diagdown\,\mathrm{X}\,\diagup}{\mathrm{HOAr{-}ArOH}} \qquad (1)$$

The 1,3-bis(hydroxyphenyl)propane **1**, mp 75–77.5°, was prepared by standard methods from 3,4′-dimethoxychalcone.[5] The reaction of **1** with vanadium oxytrichloride was studied under a variety of conditions. In a typical experiment, a solution of 1.0 mol equiv of **1** in anhydrous ether was added slowly to a solution of 2.5 mol equiv of vanadium oxytrichloride in ether (dark red solution, probably due to a vanadium etherate[4]) at −78° under nitrogen. Hydrogen chloride evolution began immediately; the resulting dark blue solution (2.5×10^{-3} *M* in **1**) was stirred in the cold for 2.5 hr, then refluxed for 10 hr. After extraction of the dark green solution with water and evaporation of the ether there was obtained a crystalline crude product, from which the phenolic dienone **2** was isolated by recrystallization in 76% yield:[6] mp 221–222°; ir (KBr) 3.22, 6.07 μ; uv (C_2H_5OH) 237 mμ (ϵ 29,900), 280 mμ (ϵ 2570); nmr (DMSO-d_6) δ 1.80 (4 H), 2.10 (s, 1 H), 2.80 (2 H), 6.20 (d, 2 H, J = 10 Hz), 6.65 (m, 3 H), 7.16 (d, 2 H, J = 10 Hz); mol wt 226 (mass spectrum).[7]



1



2

Hydrolysis of the reaction mixture prior to refluxing yielded only starting material, indicating oxidation to be quite slow at −78°. The utilization of less than 2.5 mol equiv of vanadium oxytrichloride resulted in lower yields of **2**, along with appreciable amounts of unreacted starting material. As yet none of the isomeric *ortho–para* coupling product has been detected.

In order to provide a basis for comparison of the vanadium oxytrichloride results with traditional methods for effecting intramolecular oxidative phenol coupling, the following experiments were carried out. (1) Oxidation of **1** with aqueous alkaline potassium ferricyanide in chloroform gave rise to a mixture of at least six components, from which **2** was isolated in 4% yield. (2) Treatment of **1** with ferric chloride under a variety of conditions afforded, in the best case, a 7% yield of **2** (corrected for unreacted starting material). (3) Oxidation of **1** with the recently reported[3c] manganic tris(acetylacetonate) in refluxing acetonitrile gave rise to **2** in 10% yield. Again, in none of these experiments could the isomeric *ortho–para* coupling product be detected.

Studies on the application of this method to the biogenetic-type synthesis of phenolic alkaloids are in progress. Preliminary results indicate the formation of desired coupling products where no such products could be obtained with other oxidizing agents. Full details will be reported in due course.[8]

Acknowledgment. This work was supported by Public Health Service Grant CA-10136 from the National Cancer Institute.

---

[1] (a) A. I. Scott, *Quart. Rev.* (London), **19**, 1 (1965); (b) D. H. R. Barton, Pedler Lecture, *Chem. Brit.*, **3**, 330 (1967).

[2] See, for example, T. Kametani and K. Fukumoto, *Chem. Commun.*, 26 (1968).

[3] There has been considerable recent interest in new methods for phenol oxidation, dealing mainly, however, with intermolecular coupling: (a) M. L. Larson and F. W. Moore, *Inorg. Chem.*, **5**, 801 (1966); (b) J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind.* (London), 2127 (1966); (c) M. J. S. Dewar and T. Nakaya, *J. Am. Chem. Soc.*, **90**, 7134 (1968); (d) W. L. Carrick, G. L. Karapinka and G. T. Kwiatkowski, *J. Org. Chem.*, in press.

[4] H. Funk, W. Weiss, and M. Zeising, *Z. Anorg. Allg. Chem.*, **296**, 36, (1958).

[5] B. J. F. Hudson, *J. Chem. Soc.*, 754 (1946).

[6] Kwiatkowski and coworkers[3d] have very recently reported good yields (56–65%) in the intermolecular coupling of naphthols with vanadium oxytrichloride in carbon tetrachloride, but only polymer was obtained with *m*-cresol under the same conditions. We thank Dr. Kwiatkowski for communicating his results to us prior to their publication.

[7] The nmr spectrum of the tetrahydro derivative of **2** exhibited aromatic proton absorption consistent with a 3,4-disubstituted phenol moiety, thus establishing **2** as the *para–para* coupling product.

[8] All new compounds had satisfactory elemental analyses.

Martin A. Schwartz, Robert A. Holton, Steven W. Scott
Department of Chemistry, Florida State University
Tallahassee, Florida 32306

Received March 18, 1969