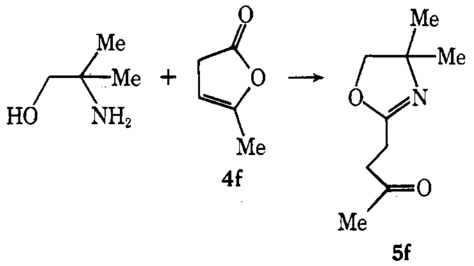
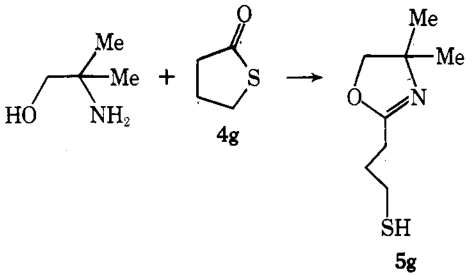


(3)



(4)

The recent work of Meyers and Mihelich[5] suggests the possible use of this procedure in the conversion of lactones to their alkylated forms and possibly in the preparation of asymmetric derivatives. For this purpose other amino alcohols may be of interest.[6]

Experimental Section

Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected. Ir spectra were recorded on a Beckman IR-10 spectrometer and NMR were recorded as 10–20% solutions in $CDCl_3$ at 90 MHz with a tetramethylsilane internal reference on a Bruker HFX-90 instrument.

All starting compounds and solvents were obtained from Aldrich Chemical Co. and were used without further purification.

The procedure below is typical. All reactions were monitored by infrared or by GC to determine the extent of reaction based on consumed lactone. Reactions were typically run for 48 h or until the volume of the aqueous layer in the Dean-Stark trap reached a maximum.

It was determined that the amino alcohol **1** was slowly distilling (bp 165 °C) as the reaction proceeded. This obviously could affect the percent conversion values (see Table I) when a 1:1 ratio of the amino alcohol:lactone is used. Actually, the effect was negligible with **4c** and **4f** owing to the high reactivity of the lactones. With the other lactones, even at an amino alcohol:lactone ratio of 2:1, the reactivities of the lactones were such that amino alcohol distillation affected percent conversion (Table I) as determined by the amount of lactone remaining (GC and quantitative ir measurements). This can be dealt with in two ways. In the case of γ-butyrolactone, with toluene as the solvent a successful reaction was achieved but at the expense of reaction time. On the other hand, the use of xylene allows a faster reaction (1–4 days for the range of lactones evaluated) and leads to no real losses since the amino alcohol, lactone, and xylene can be recycled by fractionation. Hence we prefer the latter method although one might want to explore the options for optimum conditions for an amino alcohol-lactone pair. We have not optimized conditions for any compounds reported here. A typical run for a 2:1 amino alcohol:lactone ratio is given below.

2-(3-Hydroxypropyl)-4,4-dimethyl-2-oxazoline (5a). To a 500-ml single-necked flask fitted with a magnetic stirrer, Dean-Stark trap, and condenser were added γ-butyrolactone (24.1 g, 0.29 mol), 2-amino-2-methyl-1-propanol (50.0 g, 0.56 mol), and xylene (100 ml). The mixture was stirred and refluxed gently, just allowing the xylene-water azeotrope to distill. The volume of the aqueous layer in the Dean-Stark trap with time was 5.5 ml at 5.75 h, 7.3 ml at 7.75 h, 12.3 ml at 15 h, 16.2 ml at 22 h, and 21 ml at 45 h. The reaction was stopped at 45 h. Analysis by GC indicated 80% conversion of the lactone. The xylene was removed on a rotary evaporator and the residue was distilled to yield 2-(3-hydroxypropyl)-4,4-dimethyl-2-oxazoline, bp 74–78 °C (0.5 mm), which still contained some lactone (GC). Distillation on an adiabatic spinning band column with a reflux ratio of 10/1 yielded 2-(3-hydroxypropyl)-4,4-dimethyl-2-oxazoline (65% yield based on conversion of lactone): bp 77–78 °C (0.5 mm); purity (GLC) 99.6%; ir (NaCl plates) 3310 (O–H), 2960, 2875, 1667 (C=N), 1460, 1363, 1164, 1065, 1038, 945, 819, and 775 cm^{-1}. Other analytical data are shown in Tables I and II.

Acknowledgment. S.P.M. acknowledges the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No.—**1**, 124-68-5; **4a**, 96-48-0; **4b**, 542-28-9; **4c**, 502-44-3; **4d**, 1679-47-6; **4e**, 108-29-2; **4f**, 591-12-8; **4g**, 1003-10-7; **5a**, 51849-54-8; **5b**, 58241-39-7; **5c**, 58241-40-0; **5d**, 58241-41-1; **5e**, 51849-55-9; **5f**, 58241-42-2; **5g**, 58241-43-3.

References and Notes

(1) (a) The University of Alabama in Huntsville; (b) Oakwood College; (c) Marshall Space Flight Center; (d) University of Alabama.

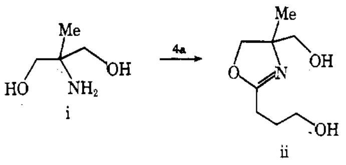
(2) J. H. Billman and E. E. Parker, U.S. Patent 2 556 791 (1951); *Chem. Abstr.*, **46**, 525 (1952).

(3) For a review of oxazoline chemistry, see J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).

(4) Polymerization of the lactone invalidates some of the conversion figures in Table I. Also, some amino alcohol was distilled with the water to give a low conversion; allowances were not made for this in the reaction stoichiometry in all cases; see the Experimental Section.

(5) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 1186 (1975).

(6) 2-Amino-2-methyl-1,3-propanediol (i) has been successfully employed in making diols such as (ii) by the same procedure employed here: S. P.



McManus and M. Ortiz, unpublished results; cf. M. Ortiz, M.S. Thesis, The University of Alabama in Huntsville, May 1973.

Trifluoromethylthiocopper.[1] A Reagent for the Introduction of the Trifluoromethylthio Group into Aromatic Nuclei

David C. Remy,* Kenneth E. Rittle, Cecilia A. Hunt, and Mark B. Freedman

Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486

Received December 29, 1975

The trifluoromethylthio and trifluoromethylsulfonyl groups are important nuclear substituents in the preparation of potential new dyes,[2] medicinal agents,[3] and novel heterocyclic systems.[4] At present, there are two standard procedures for the introduction of a trifluoromethylthio group into an aromatic nucleus. The first method requires a photoinitiated chlorination of an aryl methyl sulfide side chain, followed by reaction with antimony trifluoride[5] (eq 1).

$$ArSCH_3 + Cl_2 \xrightarrow{h\nu} ArSCCl_3 \xrightarrow{SbF_3} ArSCF_3 \quad (1)$$

The second method uses trifluoromethanesulfenyl chloride in either one of two ways. In one procedure[6] (eq 2), reaction of an aryl Grignard reagent with trifluoromethanesulfenyl chloride gives the desired aryl trifluoromethyl sulfide, while in the other procedure[7] (eq 3), reaction of activated aromatic derivatives, such as anilines, with trifluoromethanesulfenyl chloride leads to para-substituted aryl trifluoromethyl sulfides. When higher temperatures and Lewis acid catalysts are used, less activated aryl derivatives undergo reaction, but mixtures of aryl trifluoromethyl sulfide isomers are obtained.

$$ArMgX + CF_3SCl \longrightarrow ArSCF_3 + (ArH + ArCl) \quad (2)$$

Table I. Preparation of Aryl Trifluoromethyl Sulfides

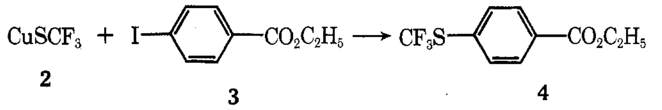
Example[a]	Starting material	Registry no.	Solvent; reaction temp, °C; time, h	Moles starting material/ moles $Hg(SCF_3)_2$/ moles Cu	Product[b]	Registry no.	% yield and (% purity, GLC) of isolated crude product	Product bp, °C (mm)	Product mp, °C, or $n^{25}D$
1	p-$IC_6H_4CO_2C_2H_5$	51934-41-9	DMF; 110–120; 3	1/2/0	None				
2	p-$IC_6H_4CO_2C_2H_5$		DMF; 110–120; 3	1/2/7.3[c]	p-$CF_3SC_6H_4CO_2C_2H_5$	587-19-9	90 (98.4)	81 (0.9) 106–110 (7)[d]	1.4845[d]
3	p-$IC_6H_4CO_2C_2H_5$		DMF; 110–120; 3	1/2/7.3[e]	p-$CF_3SC_6H_4CO_2C_2H_5$		88 (96.7)		
4	p-$IC_6H_4CO_2C_2H_5$		DMF; 110–120; 3	1/1/3.6[e]	p-$CF_3SC_6H_4CO_2C_2H_5$		98.5 (84)		
5	m-$IC_6H_4CO_2C_2H_5$	58313-23-8	DMF; 110–120; 2	1/2/7.3[e]	m-$CF_3SC_6H_4CO_2C_2H_5$[f]	58313-24-9	90 (92.5)		72–74[g]
6	o-$IC_6H_4CO_2C_2H_5$	1829-28-3	DMF; 110–120; 1	1/2/7.3[e]	o-$CF_3SC_6H_4CO_2C_2H_5$	58313-25-0	100 (97.9)	71 (0.7)	1.4879
7	p-$BrC_6H_4CO_2C_2H_5$	5798-75-4	Quinoline; 150–190; 10	1/2/7.3[e]	p-$CF_3SC_6H_4CO_2C_2H_5$		100 (88.6)		
8	p-$ClC_6H_4CO_2C_2H_5$	7335-27-5	Quinoline; 238; 4	1/2/7.3[e]	None				
9	p-$I_2C_6H_4$	624-38-4	DMF; 110–120; 2.5	1/4/14.5[e]	p-$(CF_3S)_2C_6H_4$	886-82-8	61.5 (96.9)	71–74 (15)	39–42[h]
10	p-$IC_6H_4NO_2$	636-98-6	DMF; 110–120; 2.5	1/2/7.3[e]	p-$CF_3SC_6H_4NO_2$	403-66-7	89 (82)	115–122 (20)[i]	
11	p-IC_6H_4Cl	637-87-6	DMF; 110–120; 2.5	1/4/14.5[e]	p-$CF_3SC_6H_4Cl$	407-16-9	78 (100)	173–175[j]	1.4900
12	p-$BrC_6H_4N(CH_3)_2$	586-77-6	HMPA[18]; 160–175; 12	1/3/10.9[e]	p-$CF_3SC_6H_4N(CH_3)_2$	2677-71-6	100 (89.2)	56–59 (0.10)[k]	1.5269[k]
13	3-IC_5H_4N	1120-90-7	DMF; 110–120; 3	1/3/10.9[e]	3-$CF_3SC_5H_4N$	58313-26-1	95 (83.5)	150–151	1.4676
14	p-$BrC_6H_4CH_3$	106-38-7	HMPA[18]; 160–180; 12	1/2/7.3[e]	p-$CF_3SC_6H_4CH_3$	351-60-0	79 (84.5)	67–85 (15)[l]	1.4657

[a] Example number corresponds to procedure number in Experimental Section. [b] All compounds exhibited ^1H and ^{19}F NMR spectra consistent with the assigned structure. [c] Trifluoromethylthiocopper was preformed. See Experimental Section. [d] Lit.[4]a bp 96–97 °C (5 mm), $n^{25}D$ 1.4812. [e] Trifluoromethylthiocopper was formed in situ during reaction. See Experimental Section. [f] Hydrolyzed by the procedure used to hydrolyze the ortho isomer; see Experimental Section, example 6. [g] Melting point of 3-(trifluoromethylthio)benzoic acid. Lit.[12] mp 75–76 °C. [h] Lit.[13] mp 42–43 °C. [i] Lit.[14] bp 115 °C (20 mm). [j] Lit.[15] bp 173–174 °C. [k] Lit.[7] bp 54 °C (0.15 mm), $n^{25}D$ 1.5309. [l] Lit.[16] bp 80 °C (15 mm).

Alkyl trifluoromethyl sulfides have been prepared from the reaction of bis(trifluoromethylthio)mercury[8] or trifluoromethylthiosilver[9,10] with alkyl iodides. Also, trifluoromethylthiosilver has been used to prepare benzyl trifluoromethyl sulfides from benzyl iodides.[10] As an extension of this type of reaction, we wish .to report that the reaction of trifluoromethylthiocopper with aryl bromides and iodides provides a convenient, one-step route to the synthesis of aryl trifluoromethyl sulfides. This procedure offers a number of advantages over existing processes, in that (1) the aromatic nucleus may contain electron-donating or electron-withdrawing groups, (2) Grignard sensitive groups may be present in the molecule, (3) pure ortho, meta, and para isomers are obtained from the reaction of trifluoromethylthiocopper with the respective ortho, meta, and para aromatic bromide or iodide derivative, (4) yields of products range from good (60%) to excellent (100%), and (5) selective halide displacements are possible since aromatic iodides react at a significantly lower temperature than do aromatic bromides while aryl chlorides do not react.

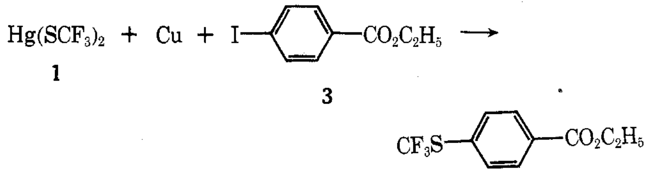
Ethyl p-(trifluoromethylthio)benzoate (**4**) is formed in 90% yield (98.4% pure by GLC) when ethyl p-iodobenzoate (**3**) is allowed to react with trifluoromethylthiocopper (**2**) formed by the reaction of copper with bis(trifluoromethylthio)mercury (**1**).[11] Bis(trifluoromethylthio)mercury, alone, does not

$$\underset{\mathbf{1}}{Hg(SCF_3)_2} + Cu \longrightarrow \underset{\mathbf{2}}{CuSCF_3} + Hg$$



2 **3** **4**

react with **3**. The copper reagent **2** does not need to be prepared prior to the condensation reaction. Indeed, a product of comparable yield and purity is obtained when **2** is formed in situ during reaction. Since the efficiency of preparing **2** from **1** is not known, excess copper and **1** (and, therefore, **2**) were



1 **3** **4**

used in the general reaction conditions. Empirically, it has been found that a ratio of 2 mol of **1** per mole of aryl iodide or bromide gives good to excellent yields of products. These products are often of sufficient purity to be used directly in subsequent reactions, as, for example, oxidation to the trifluoromethylsulfonyl derivatives. Both **1** and **2** are known to form very stable complexes with a variety of compounds, including amines.[11] For this reason, a ratio of 3 mol of **1** per mole of substrate was used for amines as in examples 12 and 13, Table I.

The scope and utility of the reaction of aryl iodides and bromides with trifluoromethylthiocopper is illustrated in Table I. Examination of Table I shows that the aromatic nucleus may contain electron-withdrawing or electron-donating groups. Pure ortho-, meta-, and para-substituted aryl trifluoromethyl sulfides are obtained from ortho-, meta-, and para-substituted aryl iodides or bromides. The yield and purity of the crude, isolated products are often greater than 90%. Also, disubstitution of p-diiodobenzene occurs readily as does selective replacement of iodine in p-chloroiodobenzene.

Because of the operational ease and efficiency of the process, trifluoromethylthiocopper appears to be a desirable reagent for the introduction of the trifluoromethylthio group into aromatic nuclei.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. NMR spectra were determined on a Varian T-60 spectrometer with $CDCl_3$ as a solvent. Proton chemical shifts are relative to tetramethylsilane as an internal standard, while fluorine chemical shifts are relative to fluorotrichloromethane. Gas–liquid chromatographic analyses were carried out on a Hewlett-Packard Model 5700 A/3370B gas chromatograph using a column (6 ft × 2 mm) packed with 1% OV-17 on 100/120 Gas-Chrom Q.

Copper metal (electrolytic dust), purified, was purchased from Fisher Scientific Co. Bis(trifluoromethylthio)mercury was prepared by the method of Man, Coffman, and Muetterties.[11] The mercuric fluoride used in this preparation was purchased from Ozark-Mahoning Company, Tulsa, Okla. *Caution: The toxicity of bis(trifluoromethylthio)mercury has been reported.*[11] *All reactions involving this reagent should be carried out in a well-ventilated hood.*

Ethyl-*p*-(trifluoromethylthio)benzoate. Example 2. An intimate mixture of 21.87 g (0.0543 mol) of bis(trifluoromethylthio)-mercury and 12.53 g (0.197 mol) of copper dust was heated at 80–100 °C until development of a bright orange color. Heating was continued at 150 °C for 0.5 h. After cooling, 7.50 g (0.027 mol) of ethyl *p*-iodobenzoate and 30 ml of DMF were added to the copper-colored residue, and the mixture was stirred and heated at 110–120 °C for 3 h. The cooled dark reaction mixture was poured into 500 ml of water and 200 ml of benzene. After stirring vigorously, the mixture was filtered through Celite, and the filter cake was washed with hot benzene. The combined benzene phases were washed with water, dried ($MgSO_4$), and filtered. The benzene was removed on a rotary evaporator to give 6.10 g (90%) of ethyl *p*-(trifluoromethylthio)benzoate that was 98.4% pure by GLC.

General Procedure for the Preparation of Neutral Aryl Trifluoromethyl Sulfides. Ethyl *o*-(Trifluoromethylthio)benzoate. Example 6. A mixture of 15.0 g (0.0543 mol) of ethyl *o*-iodobenzoate, 43.78 g (0.1087 mol) of $Hg(SCF_3)_2$, 25.07 g (0.395 mol) of copper dust, and 60 ml of DMF was stirred and heated at 110–120 °C for 1 h. The reaction mixture was worked up as in example 2 to give a quantitative yield of ethyl *o*-(trifluoromethylthio)benzoate that was 97.9% pure by GLC. The slight yellow color of this crude product was removed by distillation, bp 70–71 °C (0.7 mm), $n^{25}{}_D$ 1.4879.

A solution of 5.0 g of ethyl *o*-(trifluoromethylthio)benzoate, 30 ml of ethanol, and 20 ml of 10% sodium hydroxide was refluxed for 1.5 h. After cooling, the solution was acidified with 6 N hydrochloric acid. The product was collected by filtration, dried, and recrystallized from a mixture of 60% hexane–40% benzene to give *o*-(trifluoromethylthio)benzoic acid, mp 119–121 °C.

Anal. Calcd for $C_8H_5F_3O_2S$: C, 43.24; H, 2.27; F, 25.65. Found: C, 43.31; H, 2.30; F. 25.86.

General Procedure for the Preparation of Basic Aryl Trifluoromethyl Sulfides. 3-Trifluoromethylthiopyridine. Example 13. A mixture of 5.0 g (0.024 mol) of 3-iodopyridine,[17] 29.48 g (0.0732 mol) of bis(trifluoromethylthio)mercury, 16.96 g (0.267 mol) of copper dust, and 50 ml of DMF was stirred and heated at 110–120 °C for 3 h. After cooling in an ice bath, 100 ml of ether and 50 ml of 5 N sodium hydroxide were added and the mixture was stirred overnight at room temperature. The mixture was filtered through Celite, and the aqueous phase was separated and extracted with two 100-ml portions of ether. All of the ether phases were combined, washed with three 100-ml portions of water, dried ($MgSO_4$), and filtered, and the ether removed on a rotary evaporator. The yield of crude 3-trifluoromethylthiopyridine was 4.15 g (95%) that was 83.5% pure by GLC. The product was purified by distillation, bp 150–151 °C, $n^{25}{}_D$ 1.4676. The ^{1}H NMR ($CDCl_3$) showed three multiplets centered at δ 7.42 (1 H), 8.08 (1 H), and 8.83 (2 H), while the fluorine spectrum showed a sharp singlet at δ 41.9.

Anal. Calcd for $C_6H_4F_3NS$: C, 40.22; H, 2.25; N, 7.82; F, 31.82; S, 17.89. Found: C, 39.79; H, 2.42; N, 7.79; F, 31.53; S, 17.80.

Acknowledgments. The authors are indebted to Mr. A. Augenblick for the GLC analyses, Mr. W. Riley McGaughran for the NMR spectra, and Mr. K. Streeter and Mr. Y. Lee for the microanalytical data.

Registry No.—**1**, 21259-75-6; **2**, 3872-23-9; Cu, 7440-50-8; *o*-(trifluoromethylthio)benzoic acid, 37526-67-3.

References and Notes

(1) Cuprous, [(trifluoromethyl)thio]-; trifluoromethanethiol, copper(I) salt.
(2) L. M. Yagupol'skii and M. S. Marenets, *Zh. Obshch. Khim.*, **25**, 1771 (1955); *Chem. Abstr.*, **50**, 5635 (1956).
(3) E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **25**, 60 (1960).
(4) (a) L. M. Yagupol'skii and M. S. Marenets, *Zh. Obshch. Khim.*, **24**, 887 (1954); *Chem. Abstr.*, **49**, 8172 (1955); (b) D. M. Mulvey and H. Jones, *J. Heterocycl. Chem.*, **12**, 597 (1975).
(5) O. Scherer, *Angew. Chem.*, **52**, 457 (1939); French Patent 820 796 (1937).
(6) W. A. Sheppard, *J. Org. Chem.*, **29**, 895 (1964).
(7) S. Andreades, J. F. Harris, Jr., and W. A. Sheppard, *J. Org. Chem.*, **29**, 898 (1964).
(8) U.S. Patent 3 062 894 (1962); *Chem. Abstr.*, **58**, 8907 (1963); J. F. Harris, *J. Org. Chem.*, **32**, 2063 (1967).
(9) H. J. Emeleus and D. E. MacDuffie, *J. Chem. Soc.*, 2597 (1961).
(10) V. V. Orda, L. M. Yagupol'skii, V. F. Bystrov, and A. U. Stepanyants, *Zh. Obshch. Khim.*, **35**, 1628 (1965); *Chem. Abstr.*, **63**, 17861 (1965).
(11) E. H. Man, D. D. Coffman, and E. L. Muetterties, *J. Am. Chem. Soc.*, **81**, 3575 (1959).
(12) L. M. Yagupol'skii and B. E. Gruz, *Zh. Obshch. Khim.*, **31**, 1315 (1961); *Chem. Abstr.*, **55**, 24720 (1961).
(13) L. M. Yagupol'skii and V. V. Orda, *Zh. Obshch. Khim.*, **34**, 1979 (1964); *Chem. Abstr.*, **61**, 8217 (1964).
(14) French Patent 820 796 (1937).
(15) U.S. Patent 2 108 606 (1938).
(16) L. M. Yagupol'skii, M. S. Marenets, and N. V. Kondratenko, *Zh. Obshch. Khim.*, **35**, 377 (1965); *Chem. Abstr.*, **62**, 14551 (1965).
(17) Sapon Laboratories.
(18) Hexamethylphosphoramide. A recent report, *Science*, **190**, 422 (1975), discusses the carcinogenic potential of hexamethylphosphoramide. *Caution should be used in handling this chemical.*
(19) NOTE ADDED IN PROOF. After this manuscript had been prepared, an article by Yagupol'skii appeared [L. M. Yagupol'skii, N. V. Kondratenko, and V. P. Sambur, *Synthesis*, 721 (1975)] in which an alternate synthesis of trifluoromethylthiocopper was described.

Phenolic Oxidations with Sodium Bismuthate in Acetic Acid

Emil Kon

Chemistry Department, Touro College,
New York, New York 10036

Edward McNelis*

Chemistry Department, New York University,
New York, New York 10003

Received November 21, 1975

The oxidations of phenols in neutral aromatic solvents by sodium bismuthate has been shown to proceed by one-electron oxidation.[1] The principal products of such oxidations of 2,6-xylenol and related phenols were the corresponding polyphenylene oxides. When the reaction solvent was changed to acetic acid, no polymer was detected. The oxidation products for 2,6-xylenol were 2-acetoxy-2,6-dimethylcyclohexadien-3,5-one (I) and 3,3′,5,5′-tetramethyldiphenoquinone (II). A two-electron oxidation may be inferred from the acetoxy product. Adler, Holmberg, and Ryrfors have reported that the oxidation of mesitol (2,4,6-trimethylphenol) in aqueous acetic acid with sodium bismuthate produced acetoxylated cyclohexadienone products, which were similar to those formed by periodate, a two-electron oxidant.[2] Adderley and Hewgill noted that sodium bismuthate in acetic acid and lead tetraacetate in nonpolar solvents had the same effects on the oxidations of 2-bromo-5(6)-*tert*-butyl-4-methoxyphenols.[3] Additional results on this change of sodium bismuthate from a one-electron oxidant to a two-electron oxidant are given to further clarify this drastic product change.

The oxidation of 2,6-xylenol in benzene by sodium bismuthate affords the polyphenylene oxide in yields of 70 to 80%.[1] When the phenol was dissolved in a 6% (w/v) solution of acetic acid in benzene and oxidized with sodium bismuthate at reflux temperature, the yield of polymer de-