

agent 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 \times 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 $\text{Hg}(\text{SCF}_3)_2$, 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_D^{25} 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 $\text{C}_8\text{H}_5\text{F}_3\text{O}_2\text{S}$: 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_D^{25} 1.4676. The ¹H 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 $\text{C}_6\text{H}_4\text{F}_3\text{NS}$: 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.

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

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- (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

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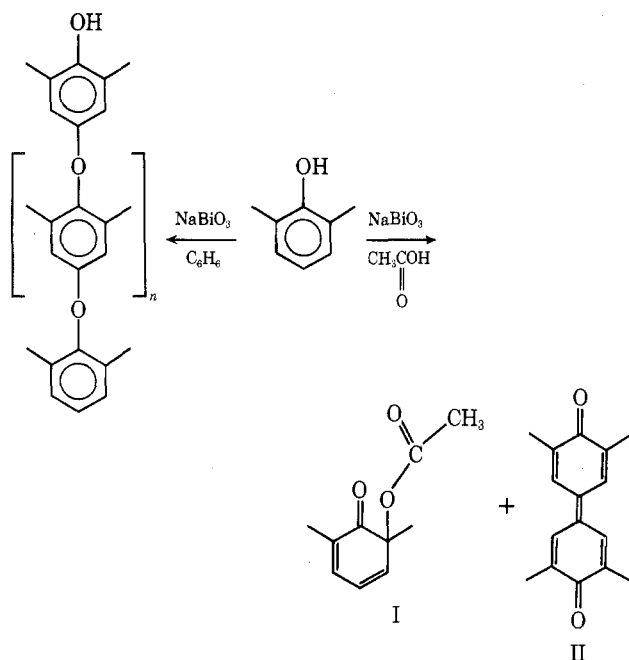
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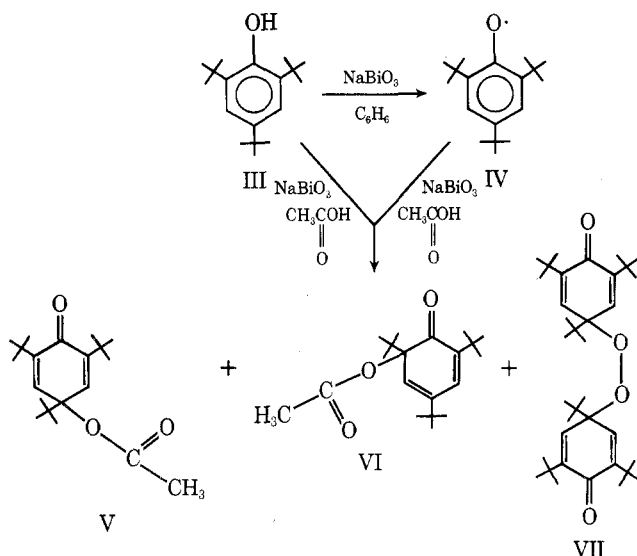
The oxidations of phenols in neutral aromatic solvents by sodium bismuthate has been shown to proceed by one-electron oxidation.¹ The principal products of such oxidations of 2,6-xyleneol and related phenols were the corresponding polyphenylene oxides. When the reaction solvent was changed to acetic acid, no polymer was detected. The oxidation products for 2,6-xyleneol were 2-acetoxy-2,6-dimethylcyclohexadien-3,5-one (I) and 3,3',5,5'-tetramethyl-diphenylquinone (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 acetoxyated 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-xyleneol 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-



creased to 20% and the yield of diphenoquinone II was 37%. Usually, little or no II was recovered from bismuthate oxidations in benzene. When the acetic acid content of the solvent was increased to 12%, the yield of II was 15% and the yield of isolated I was 64%. No polymer was detected. Approximately similar values were obtained when the solvent was glacial acetic acid.

In order to ascertain if acidic bismuthate could oxidize a possible radical intermediate in two one-electron oxidation steps, the oxidations of 2,4,6-tri-*tert*-butylphenol (III) were carried out. The corresponding stable phenoxyl (IV) was the product of bismuthate oxidation in benzene.¹ When the solvent was changed to glacial acetic acid, the oxidation products were 2,4,6-tri-*tert*-butyl-4-acetoxycyclohexadien-2,5-one (V), 2,4,6-tri-*tert*-butyl-6-acetoxycyclohexadien-2,4-one (VI), and bis(1,3,5-tri-*tert*-butyl-2,5-cyclohexadien-4-one) 1-peroxide (VII) in yields of 62, 22, and 5%, respectively. The molar oxidant to phenol ratio was 3:1.



When this same ratio was used in the generation of the blue phenoxyl IV in benzene under a nitrogen atmosphere, addition of acetic acid brought about a color discharge. Addition of acetic acid to benzene solutions of phenoxyl IV without the bismuthate gave no such color discharge. The isolated products and yields from the color discharging ex-

periment were V (54%), VI (19%), and VII (5%). The similar yield values support the possibility that the phenoxyl IV is an intermediate in the acidic oxidation. To test the notion that peroxide VII was not a precursor for V and VI by a reaction with acetic acid, VII was treated with acetic acid under the same conditions of the previous two experiments. The only product was 2,6-di-*tert*-butyl-1,4-benzoquinone (VIII) in 16% yield. Cyclohexadienones V and VI were not detected and the peroxide was recovered in 61% yield. The source of the oxygen for the peroxide was probably the decomposition of bismuthate during the reaction. This decomposition with oxygen evolution has been shown to be very vigorous at higher temperatures.¹

In order to test if acidic bismuthate delivered a hydroxyl radical to the phenoxyl IV to give intermediates such as 2,4,6-tri-*tert*-butyl-4-hydroxycyclohexadien-2,5-one (IX) which might have reacted with acetic acid to give V, authentic IX was treated with acetic acid. Compound IX was recovered in 89% yield.

The acetic acid medium is not acidic enough to induce an aryoxyl disproportionation to the corresponding cationic species, a source for V and VI, and a neutral phenol as proposed in a general way by Waters.⁴ Rather, there is an increase in oxidation potential of the oxidant. In this case, sodium bismuthate is converted to an unknown bismuth species which is able to remove an electron from the stable phenoxyl IV, whose intermediacy in an overall two-electron process is consistent with the observations.

Experimental Section

Materials and instruments were the same as those of the prior report.¹

2,6-Xylenol Oxidation. Sodium bismuthate (33.0 g, 0.118 mol) was added to a solution of 2,6-xyleneol (4.1 g, 0.033 mol) in 100 ml of glacial acetic acid. The mixture was stirred for 3 days at room temperature. The mixture was filtered and the residual sodium bismuthate was washed with small quantities of acetic acid. The combined acetic acid solutions were diluted with water to a volume of 500 ml and extracted several times with ether. The extracts were neutralized with dilute NaHCO₃ solution and dried. The ether was stripped to a crude oil (2.65 g) which was subjected to dry column chromatography (silica gel-chloroform). The main isolated band weighed 1.7 g (38% yield). It melted at 35 °C and its infrared spectrum was identical with that of I.⁵ The other bands were also compound I. The mass spectrum showed a base peak of *m/e* 36 and a parent ion of 5% *m/e* 180. The residual bismuthate was washed with ether, dried, and treated with concentrated HCl. A red solid weighing 0.63 g (15% yield) remained and was identified as II.⁶

2,4,6-Tri-*tert*-butylphenol Oxidation. The reaction conditions and ratios were as above for 2,6-xyleneol. The filtrate was mixed with 150 ml of benzene and 150 ml of water. The benzene layer was washed with a NaHCO₃ solution. The dried benzene was removed to give an oil which was chromatographed on silica gel with petroleum ether and benzene as eluents. The first band was identified as V by an infrared spectrum⁷ and weighed 6.59 g (62% yield), NMR (CDCl₃) δ 0.95 (s, 9 H), 1.21 (s, 18 H), 2.05 (s, 3 H), and 6.45 (s, 2 H). The base peak in the mass spectrum was *m/e* 220; no parent peak was observed. A second band weighed 2.30 g (22% yield) and melted at 97.5–99 °C after crystallization from methanol–water. It was identified as VI, NMR (CDCl₃) δ 0.98 (s, 9 H), 1.12 (s, 9 H), 1.21 (s, 9 H), 2.05 (s, 3 H), 5.8 (d, 1 H), and 6.85 (d, 1 H). The base peak in the mass spectrum was *m/e* 222; a parent peak at *m/e* 320 (1%) was observed. The dried recovered sodium bismuthate was dissolved in concentrated HCl. The residue weighed 0.45 g (5% yield) and was identified as peroxide VII, which after methanol crystallization melted at 142–144 °C.⁸

2,4,6-Tri-*tert*-butylphenoxyl Oxidation. Sodium bismuthate (66.0 g, 0.236 mol) was added to a solution of 2,4,6-tri-*tert*-butylphenol (8.73 g, 0.033 mol) in 100 ml of benzene. The mixture was held under a nitrogen atmosphere while being stirred for 20 h at room temperature. To this mixture was added 250 ml of glacial acetic acid while the nitrogen atmosphere was maintained. After 20 min the dark blue color faded completely to a pale green. The mixture was worked up in the same manner as above to give 5.75 g of V (54%), 2.02 g of VI (19%), and 0.470 g of VII (5.4%).

Stability of 2,4,6-Tri-*tert*-butylphenol in Acetic Acid. Sodium bismuthate (33.0 g, 0.118 mol) was added to a solution of III (8.73 g, 0.033 mol) in 50 ml of benzene. The mixture was stirred for 6 h at room temperature under nitrogen. The mixture was filtered rapidly. The dark blue filtrate was mixed with 100 ml of glacial acetic acid and kept under nitrogen for 2 weeks. The color persisted until the nitrogen supply was exhausted.

Stability of Hydroxycyclohexadienone IX in Acetic Acid. Compound IX was prepared from 2,4,6-tri-*tert*-butyl-4-nitrocyclohexadien-2,5-one⁹ by the method of Müller and Ley.¹⁰ In 5 ml of glacial acetic acid was dissolved 0.330 g of IX. The solution was kept at room temperature for 3 days. The solution was poured into 75 ml of water. The precipitate was filtered, dried, and weighed at 0.294 g (89%) and found to be identical with the starting material by an infrared spectrum and mixture melting point determination.

Registry No.—I, 7218-21-5; II, 4906-22-3; III, 732-26-3; IV, 2525-39-5; V, 20778-61-4; VI, 20778-58-9; VII, 1975-14-0; VIII, 719-22-2; IX, 4971-61-3; sodium bismuthate, 12125-43-8; 2,6-xylene, 576-26-1; 2,4,6-tri-*tert*-butyl-4-nitrocyclohexadien-2,5-one, 1665-87-8.

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A Two-Step Synthesis of (*E*)-4-Chloro-2-methylcrotonaldehyde from Isoprene. An Unprecedented Oxidative Chlorination of a 1,3-Diene Monoepoxide by Cupric Chloride

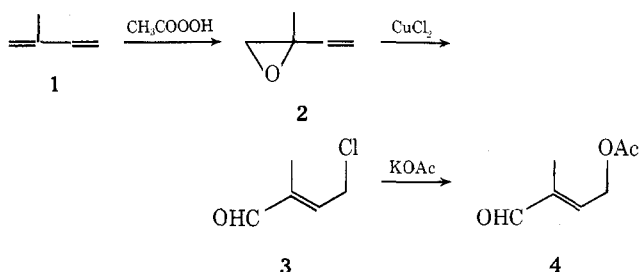
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A key intermediate in the Pommer industrial synthesis of vitamin A acetate from β -ionone is (*E*)-4-acetoxy-2-methylcrotonaldehyde (4).¹ However, the known syntheses of the latter derivative are multistep and/or low-yield procedures.¹⁻⁴

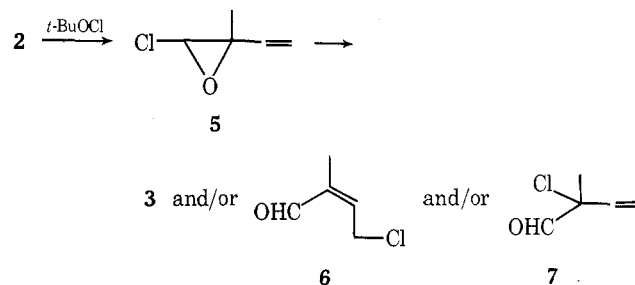
The scope of the present paper is to report a more efficient route to 4 involving epoxidation of isoprene (1) with peracetic acid to 3,4-epoxy-3-methyl-1-butene (2) followed by oxidative chlorination of the latter with cupric chloride to afford (*E*)-4-chloro-2-methylcrotonaldehyde (3), a known direct precursor of 4.²



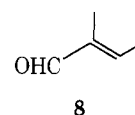
Although the peracetic acid epoxidation of 1 to 2 has been already described, the yield claimed is only 42%.⁵ By using a modified procedure, i.e., carrying out the reaction at about 5 °C in chloroform solution in the presence of so-

dium bicarbonate (to neutralize the acetic acid formed which otherwise gave side reactions with 2),⁶ we could, however, increase the yield of 2 to 80% (VPC analysis of the reaction mixture). Furthermore, the resulting reaction mixture, containing also some residual 1 (87% conversion⁷), could be used, after filtration from the salts, directly for the reaction with cupric chloride.

In preliminary attempts to convert 2 to useful precursors of 4 we speculated that 2, by free-radical reaction with *tert*-butyl hypochlorite, could give 4-chloro-3,4-epoxy-3-methyl-1-butene (5)⁸ and that the latter, by rearrangement (possibly in situ),⁹ could afford either 3 or its *Z* stereoisomer (6) or the constitutional isomer 2-chloro-2-methyl-3-butenal (7).



In fact, after gas-phase reaction¹⁰ over alumina of an equimolar mixture of 2¹¹ and *tert*-butyl hypochlorite (added dropwise, from the top, to a heated (125 °C) column charged with alumina pellets, using nitrogen as carrier gas and collecting the product at the bottom of the column in a liquid air cooled trap), VPC analysis of the reaction mixture revealed formation of a product (37% yield) with the same retention time as 3. The same analysis revealed also formation of a product (37% yield) with retention time as for (*E*)-2-methylcrotonaldehyde (8). Structures 3 and 8 for



these two products were confirmed by the NMR and IR spectra and the boiling points of the compounds isolated, in low yields, by fractionation. Derivative 8, the rearrangement product of 2, was obtained in quantitative yields when the gas-phase reaction of 2 over alumina was carried out in the absence of the hypochlorite. On the other hand, when 8 was treated with the hypochlorite under the conditions used for 2, no 3 was produced, supporting the intermediate formation of 5, rather than 8, in the reaction of 2 with the hypochlorite to give 3.

Although it is known that by oxidative chlorination with cupric chloride 8 can be converted to 3 in moderate yields,⁴ we thought that a more direct and possibly more efficient synthesis of 3 (or 6) from 2 might be achieved by reaction of 2 itself with cupric chloride. To our knowledge, oxidative halogenation of an epoxide with a cupric halide has no precedent in the literature.¹² We speculated, however, that reaction of 2 with cupric chloride could afford 3 (or 6), either via rearrangement in situ (cupric chloride acting as a Lewis acid catalyst) of 2 to 8 (or to its *Z* stereoisomer) or via cupric alcoholate 9.

In fact, when the chloroform solution of 2 obtained from the peracetic acid epoxidation of 1 was treated, after addition of an equal volume of ethyl acetate,¹³ with cupric chloride in the presence of lithium chloride,¹⁴ VPC analysis of the organic extracts revealed formation of a major product (80% yield) with the same retention time as 3. The retention time of the only by-product (20% yield) was as for 8.