Preparation of Chlorinated Phenoxyphenols

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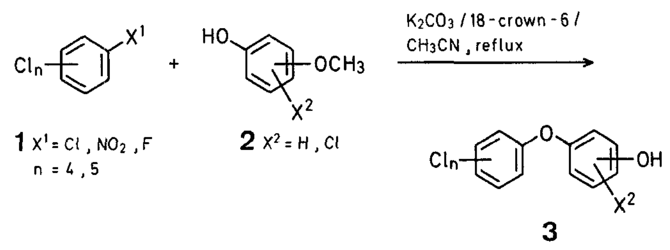
The appearance of polychlorophenoxyphenols in technical grade pentachlorophenol, a biocide used extensively in the wood products industry[1], stimulated a program to isolate and identify[2] and subsequently evaluate the toxicological and biochemical behavior of these contaminants[3]. Preliminary results have demonstrated that nonachloro-2-, and nonachloro-3-phenoxyphenols are acutely toxic to white mice[4]. In order to initiate further biological studies, a convenient synthetic scheme for the preparation of phenoxyphenols was required.

The reaction of a potassium phenoxide with an activated aromatic substrate, through nucleophilic aromatic substitution, is a common method of diaryl ether synthesis. The reaction is usually carried out at moderate temperatures (90–150 °C) in the presence of little or no solvent[5,6]. Under these conditions, the reactants frequently undergo only partial conversion to a complicated mixture of products, and the product yield is invariably poor[5,7].

The low yields observed in these reactions may be the result of inefficient solubilization of starting materials[7]. In many cases crown ethers have been employed as solid-liquid phase transfer catalysts to overcome solubility problems[8]. In fact, Sam and Simmons have employed the potassium methoxide/18-crown-6 complex to effect chloride ion displacement from *o*-dichlorobenzene to produce *o*-chloroanisole[9]. We have found that a modification of this reaction will produce polychloro-2-phenoxyanisoles.



Under our conditions, a methoxyphenol **2** (1.0 eq), an activated aromatic substrate **1** (1.0 eq), potassium carbonate, and 18-crown-6 (0.1–1.0 eq) are allowed to react in refluxing acetonitrile (Table). The reaction of guaiacol with hexachlorobenzene in acetonitrile produced 2-(2,3,4,5,6-pentachlorophenoxy)-anisole. The reaction did not occur in the absence of 18-crown-6 or if benzene was substituted as the solvent.

The reaction of 2,3,5,6-tetrachloronitrobenzene with 3,4-dichloroguaiacol under similar conditions gave 4,5-dichloro-2-(2,3,4,5-tetrachlorophenoxy)-anisole in 79% yield, and less than 2% starting material remained in the produce mixture. In the absence of 18-crown-6, the reaction proceeded at a much reduced rate; the half-life being twenty times greater than for the catalyzed reaction. 4,5-Dichloro-2-(2,3,4,5-tetrachlorophenoxy)-phenol was isolated in 41% overall yield following boron tribromide treatment of the anisole. The synthesis of this compound was reported previously[5], but the overall yield was only 13%.

The crown ether-catalyzed reaction of 3,4-dichloroguaiacol with pentachlorofluorobenzene produced 4,5-dichloro-2-(2,3,4,5,6-pentachlorophenoxy)-anisole in 88% yield. G.C.-M.S. analysis of the reaction mixture showed no fluorinated diphenyl ether. Again, the reaction was found to proceed at a reduced rate in the absence of 18-crown-6. Similar results (Table) were obtained for the synthesis of 3- and 4-(2,3,4,5,6-pentachlorophenoxy)-phenols from pentachlorofluorobenzene and *meta*- and *para*-methoxyphenols. In these examples, the use of 18-crown-6/acetonitrile as a solvent system for preparation of polychlorinated phenoxyanisoles through nucleophilic aromatic substitution increases the product yield and manageability.

The crown ether-catalyzed reaction of 3,4,5-trichloroguaiacol with pentachlorofluorobenzene, however, yields less than 5% of 3,4,5-trichloro-2-(2,3,4,5,6-pentachlorophenoxy)-anisole and much unreacted starting material. Also under similar conditions, the reaction of tetrachloroguaiacol with pentachlorofluorobenzene results in only unreacted starting material and no detectable formation of 2-nonachlorophenoxyphenol. Apparently, reaction of a phenol with three or more chlorines leads to unfavorable steric interactions in the transition state and/or a phenoxide ion which possesses reduced nucleophilicity such that fluoride ion displacement is no longer facile.

Gas chromatography-mass spectrometry analyses were carried out on a Finnigan 4023 instrument. A Pyrex® gas chromatography column (0.32 cm × 4.88 m) packed with 3% OV-101 on 80/100 mesh high performance Chromosorb® W (Johns-Manville Co.) was used for separation. Nuclear magnetic resonance spectra were obtained on a Varian HA 100 spectrometer. Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus.

2-(2,3,4,5,6-Pentachlorophenoxy)-phenol (3a; 2-Hydroxy-2′,3′,4′,5′,6′-pentachlorodiphenyl Ether):

A mixture containing guaiacol (1.0 g, 8.0 mmol), hexachlorobenzene (Aldrich; 2.25 g, 8.0 mmol), dried potassium carbonate (2.0 g, 14.5 mmol), acetonitrile (50 ml), and 18-crown-6 (Aldrich; 50 mg, 0.190 mmol) is refluxed for two days. Following addition of guaiacol (0.2 g), the mixture is refluxed for one day more. The solvent is removed and the residue is partitioned between water (25 ml) and benzene (50 ml). The benzene layer,

0039-7881/81/0232-0133 $ 03.00

after being washed with water (3 × 25 ml), is dried with anhydrous sodium sulfate. Boron tribromide (1.0 ml) is added to the benzene solution and the solution is stirred for 24 h. The mixture is extracted with water (50 ml). The benzene layer is treated with 25% potassium hydroxide solution (20 ml) and the water is removed by azeotropic distillation. The resulting salt is filtered and washed with benzene (20 ml). The potassium salt is dissolved in water (100 ml), the solution is acidified to pH 1 with concentrated hydrochloric acid and extracted several times with chloroform (100 ml). The chloroform layer is backwashed with water (50 ml), dried with anhydrous sodium sulfate, and concentrated to yield a crude product (1.7 g). This product is chromatographed on a column (2 × 40 cm) containing neutral Silicar CC-7 special (Mallinckrodt), with chloroform as the eluent. Fractions (10 ml) are collected. Fractions 1-7 (each 10 ml) containing 2-(2,3,4,5,6-pentachlorophenoxy)-phenol, are combined and concentrated; yield: 0.78 g (27%); m.p. 154 °C.

$C_{12}H_5Cl_5O_2$	calc.	C 40.21	H 1.41	Cl 49.46
(358.4)	found	40.10	1.38	49.18

I.R. ($CHCl_3$): ν = 3560, 3010, 1600, 1490, 1180, 1200 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 5.74 (s, 1 H); 6.3-7.2 ppm (m, 4 H).

4,5-Dichloro-2-(2,3,5,6-tetrachlorophenoxy)-phenol (3b; 2-Hydroxy-2′,3′,4,5,5′,6′-hexachlorodiphenyl Ether):

A mixture of 3,4-dichloroguaiacol[10] (5.0 g, 26 mmol), 2,3,5,6-tetrachloronitrobenzene (Aldrich; 6.5 g, 25 mmol), dried potassium carbonate (10 g, 72.5 mmol), 18-crown-6 (Aldrich; 1.0 g, 3.8 mmol), and acetonitrile (300 ml) is refluxed for 6 h. The reaction mixture is cooled and filtered, and the filter cake is washed with chloroform (100 ml). The combined filtrate is concentrated, and the residue is refluxed for 14 h with tin(II) chloride (20 g), 95% ethyl alcohol (100 ml), water (35 ml), and concentrated hydrochloric acid (35 ml). Diethyl ether (200 ml) and water (200 ml) are added, the mixture is shaken, and the phases are separated. The aqueous layer is washed with ether (100 ml) and the combined ether layers are backwashed with water (100 ml) and saturated sodium chloride solution (50 ml). The ether layer is dried with anhydrous sodium sulfate, filtered, and evaporated to yield a solid (9.5 g) which is recrystallized from methanol/dichloromethane; yield: 5.47 g (51%). The recrystallized product (5.0 g) is refluxed in boron tribromide (6.0 ml) for 2.5 h, at which time water (100 ml) and dichloromethane (200 ml) are added. The mixture is shaken and the dichloromethane layer is separated, washed with water (50 ml), and saturated sodium chloride solution (50 ml), dried with anhydrous sodium sulfate, filtered, and concentrated. The solid is chromatographed on a column (2 × 40 cm) of Silicar CC-7 special (Mallinckrodt) with chloroform/hexane (1:1); yield: 4.2 g (41%); m.p. 152 °C (Lit.[5], m.p. 150.5 °C).

$C_{12}H_4Cl_6O_2$	calc.	C 36.69	H 1.03	Cl 54.14
(392.9)	found	36.43	0.95	53.68

I.R. ($CHCl_3$): ν = 3540, 3020, 1480, 1410, 1380, 1200 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 5.80 (s, 1 H); 6.48 (s, 1 H); 7.18 (s, 1 H); 7.62 ppm (s, 1 H).

4,5-Dichloro-2-(2,3,4,5,6-pentachlorophenoxy)-anisole (3c; 2-Methoxy-2′,3′,4,4′,5,5′,6′-heptachlorodiphenyl Ether):

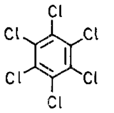
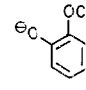
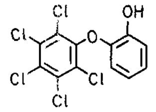
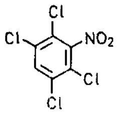
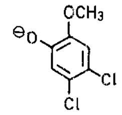
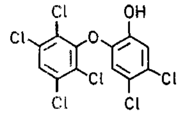
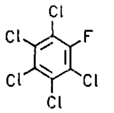
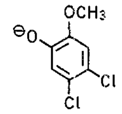
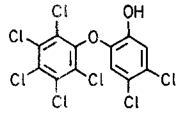
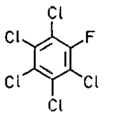
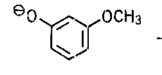
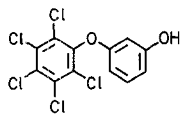
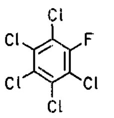
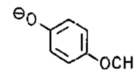
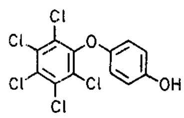
Pentachlorofluorobenzene[11] (1.4 g, 5.3 mmol), 3,4-dichloroguaiacol[10] (1.0 g, 5.2 mmol), dried potassium carbonate (4.0 g, 29 mmol), 18-crown-6 (0.1 g, 0.4 mmol), and acetonitrile (100 ml) are refluxed for 16 h. The reaction mixture is filtered and the residue is washed with hot acetonitrile (100 ml). The combined filtrate is concentrated to 60 ml and the product is allowed to crystallize; yield: 2 g (88%).

4,5-Dichloro-2-(2,3,4,5,6-pentachlorophenoxy)-phenol (3c; 2-Hydroxy-2′,3′,4,4′,5,5′,6′-heptachlorodiphenyl Ether):

3,4-Dichloro-2-(2,3,4,5,6-pentachlorophenoxy)-anisole (5.0 g), boron tribromide (10 ml), and dichloromethane (100 ml) are refluxed for 2 h. Dichloromethane (100 ml) and water (100 ml) are added and the mixture is shaken in a separatory funnel. The layers are separated and the water layer is extracted with dichloromethane (100 ml). The dichloromethane phase is dried with anhydrous sodium sulfate, filtered, and concentrated. The product is chromatographed on a column (2 × 40 cm) containing Silicar CC-7 special (Mallinckrodt). Hexane/chloroform (9:1) is passed through the column to remove impurities, followed by hexane/chloroform (1:1) to elute the product; yield: 4.1 g (84%); m.p. 216 °C.

$C_{12}H_3Cl_7O_2$	calc.	C 33.73	H 0.71	Cl 58.08
(427.3)	found	33.94	0.74	57.64

Table. Chlorinated Phenoxyphenols prepared

Reactants 1	2	Product 3	No.	Yield [%]
			**3a**	27
			**3b**	41
			**3c**	78
			**3d**	85
			**3e**	88

I.R. ($CHCl_3$): ν = 3540, 3020, 1470, 1380, 1200, 920 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 5.76 (s, 1 H); 6.48 (s, 1 H); 7.18 ppm (s, 1 H).

3-(2,3,4,5,6-Pentachlorophenoxy)-phenol (3d; 3-Hydroxy-2′,3′,4′,5′,6′-pentachlorodiphenyl Ether):

A mixture of *m*-methoxyphenol (Aldrich; 1.68 g, 13.6 mmol), pentachlorofluorobenzene[11] (3.0 g, 11.3 mmol), dried potassium carbonate (3.12 g, 22.6 mmol), 18-crown-6 (0.1 g, 0.4 mmol), and acetonitrile (100 ml) is refluxed overnight. The reaction mixture is filtered and the cake is washed with hot acetonitrile (100 ml). The wash solutions and filtrate are combined and concentrated to cloudiness; crystallization yields 3.63 g and 0.88 g in two crops. The crystalline product is combined with boron tribromide (10 ml) in dichloromethane (100 ml) and refluxed for several hours. Water (100 ml) is added and the mixture is shaken in a separatory funnel. The phases are separated and the dichloromethane layer is dried with anhydrous sodium sulfate. After filtration, the solvent is removed and the product is chromatographed on a column (5 × 45 cm) containing Silicar CC-7 special (Mallinckrodt). Hexane/chloroform is passed through the column to remove impurities followed by 100% chloroform to elute the product; yield: 3.4 g (85%); m.p. 134 °C.

$C_{12}H_5Cl_5O_2$	calc.	C 40.21	H 1.41	Cl 49.46
(358.4)	found	40.13	1.43	49.50

I.R. ($CHCl_3$): ν = 3560, 1600, 1480, 1380, 1270, 1120, 990 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 5.04 (s, 1 H), 6.2-6.7 (m, 3 H), 7.0-7.2 ppm (m, 1 H).

4-(2,3,4,5,6-Pentachlorophenoxy)-phenol (3e; 4-Hydroxy-2′,3′,4′,5′,6′-pentachlorodiphenyl Ether):

A mixture of *p*-methoxyphenol (Aldrich; 1.68 g, 13.6 mmol), pentachlorofluorobenzene[11] (3.0 g, 11.3 mmol), dried potassium carbonate (3.12 g, 22.6 mmol), 18-crown-6 (0.1 g, 0.4 mmol), and acetonitrile (100 ml) is refluxed overnight. The workup and subsequent reactions are the same as for 3-(2,3,4,5,6-pentachlorophenoxy)-phenol except for the final elution of product from the Silicar column which in the present case is accomplished with hexane/chloroform (1:1); yield: 3.51 g (88%); m.p. 170 °C.

$C_{12}H_5Cl_5O_2$	calc.	C 40.21	H 1.41	Cl 49.46
(358.4)	found	40.21	1.42	49.44

I.R. ($CHCl_3$): ν = 3580, 1490, 1380, 1350, 1160 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 4.70 (s, 1 H); 6.76 ppm (s, 4 H).

This investigation was supported by grants from the National Institute of Environmental Health Sciences. (Individual Research Grant ES-01968, Program Project Research Grant ES-00040, and Center Grant ES-00210). Manuscript issued as Technical Paper No. 5294 from the Oregon Agricultural Experiment Station.

Received: April 22, 1980
(Revised form: September 26, 1980)

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