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SYNTHESIS AND CHROMATOGRAPHIC PROPERTIES OF CYANO-PHENYL ETHERS

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SUMMARY

A general route for the preparation of cyanophenyl ethers to be used as polar thermally stable liquid phases in gas chromatography is described. Electrophilic bromination with thallium acetate catalysis occurs exclusively at positions *para* to the ether bond. Under vigorous reaction conditions bromination at *ortho* positions in the terminal phenyl rings may also occur. On subsequent reaction with cuprous cyanide all *para* substituted bromine groups may be exchanged but those in *ortho* positions are resistant to reaction. To monitor the synthetic reactions effectively and to establish the isomeric purity of the final products high-performance liquid chromatography and proton nuclear magnetic resonance spectroscopy were used.

INTRODUCTION

The most common liquid phases used in gas chromatography (GC) are polymeric materials. These materials have a wide temperature operating range and a high maximum operating temperature. They have served the needs of chromatographers well. They have one major disadvantage; namely they are defined only in terms of an average molecular weight, a property which may vary from batch to batch. Once coated onto the column the weight fraction of the material may also change due to the selective evaporation of low-molecular-weight oligomers. Standardization in GC requires stationary phases having defined chemical structures, which can be operated without chemical change or evaporation from the column, within defined temperature operating ranges. Suitable substances combining high thermal stability ($>300°C$), polar functionality and a simple chemical structure reproducible by synthesis are not currently available.

Phenyl ethers of low ring number (*e.g.*, 5, 6, 7, etc.) have remarkable thermal stability and low volatility[1]. Because of this they find use as lubricants for engines operated in extreme environments, as diffusion pump fluids in vacuum apparatus and have also been used as stationary phases in GC. For the latter application they are considered to be moderately polar. To increase their polarity without adversely affecting their thermal stability we have investigated several reactions for the introduction of polar substituents at specific ring positions. Preliminary results indicate that most

reactions such as nitration, chloromethylation, acylation, bromination and cyanolation occur in an uncontrolled manner yielding products with a wide isomer distribution[2]. In this paper we report a successful electrophilic bromination reaction using thallium acetate catalysis which can be used to selectively introduce bromine into positions *para* to the ether bond[3,4]. The bromine groups may be replaced entirely by cyano groups using cuprous cyanide[5,6]. The stationary phase properties of the cyanophenyl ethers will be described in a subsequent paper[7].

The structures, abbreviations and systematic names for the bromophenyl and cyanophenyl ethers used in this study are given in Fig. 1. The compounds PPE-2, PPE-3 and PPE-4 were prepared for the first time. The synthesis of DPE-2, DPE-3 and DPE-4 is an improvement over literature syntheses of these compounds[8-11].
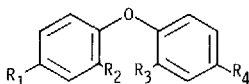
DPE-1 $R_1=R_2=R_3=R_4=H$; diphenyl ether
DPE-2 $R_1=R_4=Br$, $R_2=R_3=H$; 4,4'-dibromodiphenyl ether
DPE-3 $R_1=R_2=R_3=R_4=Br$; 2,2',4,4'-tetrabromodiphenyl ether
DPE-4 $R_1=R_4=CN$, $R_2=R_3=H$; 4,4'-dicyanodiphenyl ether
DPE-5 $R_1=R_2=R_3=R_4=CN$; 2,2',4,4'-tetracyanodiphenyl ether
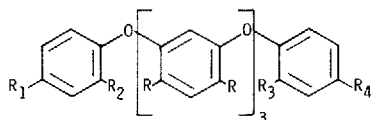
PPE-1 $R_1=R_2=R_3=R_4=R=H$; 1,3-bis(3-phenoxyphenoxy)benzene
PPE-2 $R_1=R_4=R=Br$, $R_2=R_3=H$; 1,3-dibromo-4,6-bis(2,4-dibromo-5(4-
        bromophenoxy)phenoxy)benzene
PPE-3 $R_1=R_2=R_3=R_4=R=Br$; 1,3-dibromo-4,6-bis(2,4-dibromo-5(2,4-
        dibromophenoxy)phenoxy)benzene
PPE-4 $R_1=R_4=R=CN$, $R_2=R_3=H$; 1,3-dicyano-4,6-bis(2,4-dicyano-5(4-
        cyanophenoxy)phenoxy)benzene
PPE-5 $R_1=R_2=R_3=R_4=R=CN$; 1,3-dicyano-4,6-bis(2,4-dicyano-5(2,4-
        dicyanophenoxy)phenoxy)benzene

Fig. 1 Structure and nomenclature of the phenyl ethers used or prepared in this study.

EXPERIMENTAL

The 5-ring *meta*-linked polyphenyl ether (Santovac-5) was obtained from Monsanto (St. Louis, MO, U.S.A.). Diphenyl ether and thallium acetate sesquihydrate were obtained from Aldrich (Milwaukee, WI, U.S.A.) and copper(I) cyanide from Alfa Products (Danvers, MA, U.S.A.).

General methods for preparing substituted phenyl ethers

4,4'-Dibromodiphenyl ether (DPE-2). To diphenyl ether (17 g, 0.1 mol) in carbon tetrachloride (100 ml) was added in one portion thallic acetate sesquihydrate

(4.0 g). The mixture was stirred in the dark for 0.5 h and then a solution of bromine (32 g, 0.2 mol) in carbon tetrachloride (100 ml) was added dropwise. Midway through the reaction a further portion (0.5 g) of thallic acetate sesquihydrate was added. After the addition of all the bromine the mixture was stirred for *ca.* 1.0 h and the reaction terminated when high-performance liquid chromatography (HPLC) indicated a single product. The mixture was stirred into a saturated solution of sodium bicarbonate, the organic phase washed with sodium bicarbonate solution and water, and then dried over anhydrous sodium sulfate. The solvent was removed on a rotovapor to give a yellow waxy solid, m.p. 52.5–53°C (lit.[8], 48–50°C) in quantitative yield.

2,2′,4,4′-Tetrabromodiphenyl ether (DPE-3). To diphenyl ether (17.0 g, 0.1 mol) in carbon tetrachloride (100 ml) was added thallic acetate sesquihydrate (10.0 g). The mixture was stirred in the dark for 0.5 h and then a solution of bromine (64 g, 0.4 mol) in carbon tetrachloride (100 ml) was added dropwise. When the bromine addition was complete the mixture was heated to reflux for *ca.* 9 h and the reaction terminated when HPLC indicated a single product. The sample was worked-up as for DPE-2, m.p. 78–80°C in quantitative yield. $C_{12}H_6Br_4O$ requires Br = 65.79 %; found Br = 65.60 %. The nuclear magnetic resonance (NMR) spectrum is given in Fig. 3.

1,3-Dibromo-4,6-bis[2,4-dibromo-5(4-bromophenoxy)phenoxy]benzene (PPE-2). To the 5-ring *meta*-linked polyphenyl ether (PPE-1, 44.6 g, 0.1 mol) in carbon tetrachloride (200 ml) was added in one portion thallic acetate sesquihydrate (10.0 g). The mixture was stirred in the dark for 0.5 h and then bromine (128 g, 0.8 mol) in carbon tetrachloride (200 ml) was added dropwise over a period of time. In the early stages of the reaction further portions of thallic acetate sesquihydrate were added during the bromine addition whenever the reaction seemed to cease (persistence of bromine color). After all the bromine had been added the reaction mixture was stirred for 1.0 h at room temperature and then heated to reflux (66 h) until HPLC indicated the formation of a single product. The cool reaction mixture was poured into a saturated solution of sodium bicarbonate, the organic phase washed with sodium bicarbonate solution and water, and the solvent removed on a rotovapor. The crude residue was then boiled in water–methanol (9:1) until after several solvent changes the aqueous phase remained colorless. Cold water was added to the soft honey-comed mass which became brittle and could be powdered and air dried. PPE-2 was obtained in quantitative yield, m.p. 80–81°C, $(C_{30}H_{14}Br_8O_4$ requires Br = 59.31 %, found Br = 59.40 %). The NMR spectrum is given in Fig. 3.

1,3-Dibromo-4,6-bis[2,4-dibromo-5(2,4-dibromophenoxy)phenoxy]benzene (PPE-3). PPE-3 was prepared in a similar manner to PPE-2. The amount of bromine was increased to a 10:1 molar ratio and the reflux time extended to *ca.* 75 h. The reaction was stopped when HPLC indicated a single product was formed. PPE-3 was obtained as a glassy solid (m.p. 95–96°C) in quantitative yield [$C_{30}H_{12}Br_{10}O_4$ requires Br = 64.68 %; found Br = 64.01 %]. The NMR is given in Fig. 3.

4,4′-Dicyanophenyl ether (DPE-4). To DPE-2 (32.8 g, 0.1 mol) in N,N′-dimethylformamide (150 ml) under a nitrogen atmosphere at room temperature was added cuprous cyanide (21. g, 0.2 mol). The mixture was stirred at room temperature for 1.0 h and then heated to reflux for *ca.* 15 h. The progress of the reaction was monitored by HPLC and the reaction terminated when a single product was obtained. The hot solution was poured into concentrated hydrochloric acid containing a small quantity of N,N′-dimethylformamide and after stirring and cooling diluted

with a large volume of dilute hydrochloric acid and allowed to stand for several hours. The precipitate was removed by filtration and washed several times with dilute hydrochloric acid until the wash solution remained colorless. The crude residue was dried, powedered and purified by silica gel column chromatography. DPE-4 was eluted with hexane–ethyl acetate (7:3) in 86 % yield; m.p. 160–162°C (lit.[9], 176–178°C); IR: v(CN) = 225 cm^{-1}; NMR: 7.80 ppm (doublet) and 7.20 ppm (doublet).

1,3-Dicyano-4,6-bis[2,4-dicyano-5(4-cyanophenoxy)phenoxy]benzene (PPE-5). To PPE-2 (14.0 g, 0.013 mol) in N,N'-dimethylformamide (100 ml) was added in small portions over a period of time cuprous cyanide (19.6 g, 0.2 mol). After the addition was complete, the mixture was stirred for 1.0 h under nitrogen and then heated to reflux for *ca.* 30.0 h. The reaction was monitored by HPLC and terminated when no further changes in the product distribution occurred. The reaction mixture was poured into concentrated hydrochloric acid containing a small quantity of N,N'-dimethylformamide and after leaching for several hours was diluted with four to five volumes of dilute hydrochloric acid. The crude PPE-4 was removed by filtration, dried, powdered and taken up in acetonitrile. Insoluble material was discarded, the acetonitrile removed on the rotovapor and the residue redissolved in hexane–ethyl acetate (7:3) and filtered under vacuum through a bed of silica gel. The solvent was removed on the rotovapor and the residue purified by preparative HPLC. PPE-4 was obtained in 28 % yield; m.p. 90–91°C; $C_{38}H_{14}N_8O_4$ requires N = 17.33 %; found N = 17.50 %, Br = 0.0 %. IR: v(CN) = 2210 cm^{-1}; NMR: 5.40 ppm (singlet), 6.20 ppm (doublet), 6.80 ppm (doublet) and 6.82 ppm (singlet).

Sampling reaction mixtures

For the bromine-containing compounds a small volume of the reaction mixture (*ca.* 100 μl) was withdrawn by pipette and diluted with an equal volume of acetonitrile for injection (10 μl). If the sample was rich in free bromine this was removed by washing the carbon tetrachloride layer with dilute sodium bisulfite solution before diluting with acetonitrile.

For the cyano-containing compounds a small volume of the reaction mixture (100 μl) was added to an equal volume of concentrated hydrochloric acid. The precipitate formed was removed by filtration and redissolved in acetonitrile (200 μl). Alternatively, the acidic reaction mixture was diluted with four to five volumes of dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was dried with molecular sieves, evaporated to a residue and redissolved in acetonitrile (200 μl).

Analysis by high-performance liquid chromatography

Reversed-phase HPLC was used to monitor the progress of the synthesis of the above compounds and to establish the final product purity. A Varian 5000 gradient-elution liquid chromatograph with a variable-wavelength UV–visible detector was used. The column was a 30 cm × 4.0 mm I.D. Micro-Pak CH-10 octadecylsilane type, 10 μm particle diameter, from Varian. The separation conditions are given in the figure legends.

Preparative high-performance liquid chromatography

PPE-4 was purified by preparative reversed-phase HPLC using the Varian 5000 liquid chromatograph and a Partisil 10 ODS column, 25 cm × 9.4 mm I.D. from

Whatman (Clifton, NJ, U.S.A.). The mobile phase composition was water–acetonitrile (1:1), flow-rate 2.5 ml min^{-1} and the main fraction eluting between 17 and 24 min was collected manually.

Measurement of physical constants

Melting point measurements were made on a Thomas Hoover UniMelt capillary melting point apparatus and are uncorrected.

Infrared spectra were obtained on a Perkin-Elmer Model 283B spectrometer. Bromine-containing compounds were measured in carbon tetrachloride solution and the cyano-containing compounds as thin films smeared on sodium chloride plates.

NMR analysis was performed on a Varian T-60 ^{1}H NMR spectrometer in carbon tetrachloride or deuterochloroform solutions using tetramethylsilane as internal standard.

Elemental analysis was provided by Spang Microanalytical Laboratory (Eagle Harbor, MI, U.S.A.).

RESULTS AND DISCUSSION

The chemical and physical properties demanded of a thermally stable polar reference stationary phase are very stringent. As well as meeting a broad spectrum of chromatographic demands the material must be a pure chemical compound with a clearly defined chemical structure capable of being reproduced exactly by systhesis. In a preliminary study, nitration, bromination, acylation, chloromethylation and cyanolation were investigated as possible reactive functional groups to provide growth points for the attachment of suitable substituted side chains to a phenyl ether backbone[2]. Of these reactions only electrophilic bromination employing thallium acetate as catalyst showed promising results as both its position of reaction and extent of reaction could be brought under control and products with a high chemical purity and isomer specificity obtained. The conditions needed to control this reaction and the subsequent replacement of bromine by the cyano group are discussed in this paper.

Bromination of polyphenyl ethers

The diphenyl ethers are useful model compounds for understanding the chemistry and reaction of the higher ring-number homologs. This information combined with HPLC to monitor the progress of reactions and ^{1}H NMR to assign structural configurations and isomer identification were important to this study.

The synthesis of DPE-2 by thallium acetate catalysed bromination proceeds smoothly under mild reaction conditions to give a quantitative yield of a single isomer (Fig. 2). NMR analysis of the final product indicates that the reaction is very specific and only *para* substitution occurs (Fig. 3). Under more vigorous conditions bromination may occur at both the *ortho* and *para* positions to form DPE-3 (Figs. 2 and 3). Fig. 2C illustrates that after 6 h of refluxing a mixture of starting material and the two brominated products DPE-2 and DPE-3 co-exist. By careful selection of the experimental conditions either DPE-2 (Fig. 2B) or DPE-3 (Fig. 2D) can be obtained as single products. Bromine enters the aromatic ring *para* to the phenyl ether bond preferentially but under vigorous reaction conditions this specificity is diminished and *ortho* substitution will also occur.
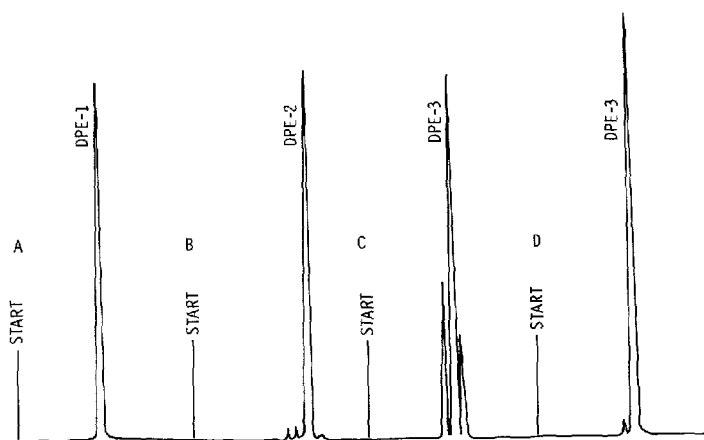
Fig. 2. HPLC analysis of the bromination products of DPE-1. Separation conditions: linear gradient water–acetonitrile (3:2) to acetonitrile over 20 min; flow-rate 1.2 ml min^{-1}; λ = 240 nm. A, DPE-1 (5.8 min); B, conversion of DPE-1 to DPE-2 (7.4 min), 6 h at room temperature; C, convesion of DPE-1 to DPE-3 (6.8 min), 6.0 h at reflux and D, 9.0 h at reflux.
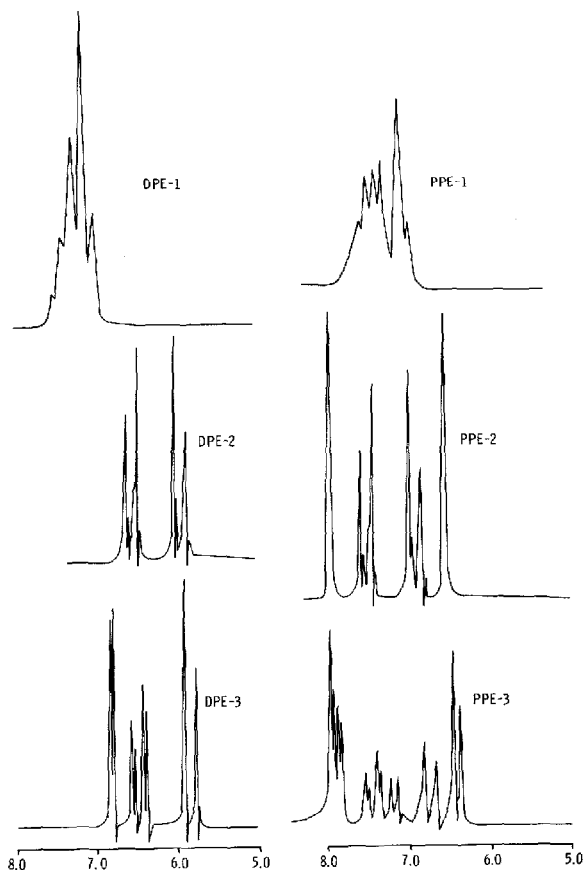

Fig. 3. NMR spectra of bromine-containing phenyl ethers in ppm. DPE-1 and PPE-1 are unsubstituted; DPE-2 and PPE-2 are fully *para*-substituted; DPE-3 and PPE-3 are fully *para*-substituted with the terminal rings also *ortho* substituted.
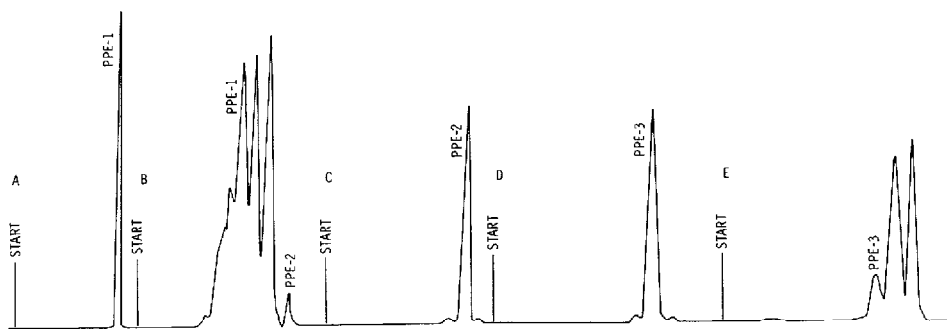
Fig. 4. HPLC analysis of the bromination products of PPE-1. Separation conditions: linear gradient water–acetonitrile (2:3) to acetonitrile over 20 min; B, after 15 h at reflux; C, PPE-2 (6.7 min) prepared by refluxing for 23 h; D, PPE-3 (7.4 min) prepared by refluxing for 75 h; E, product distribution after refluxing for 105 h.

The bromination of PPE-1 occurs in a similar manner to DPE-1 except that at room temperature the reaction is very slow and reflux conditions are required. The 5-ring phenyl ether has 8 exchangeable protons located *para* to the ether bond. When the bromine concentration is too low to allow replacement of all 8 protons or the reaction sampled at an intermediate time (Fig. 4B) a mixture of products is obtained. The first discernable single reaction product is PPE-2 (Fig. 4C) which contains 8 bromine atoms (elemental analysis) located in positions *para* to the ether link (NMR, (Fig. 3). This confirms the selectivity of the thallium acetate catalysed bromination reaction and PPE-2 can be recovered in quantitative yield if the reaction is stopped at this point. If the mixture is refluxed further in the presence of sufficient bromine for reaction a new product PPE-3 may be isolated. PPE-3 contains 10 bromine atoms (elemental analysis) of which 8 are located in positions *para* to the ether link and the remaining 2 are at *ortho* positions in the terminal phenyl rings (NMR, Fig. 3). Extending the reaction time further results in the introduction of bromine at unknown positions into PPE-1 and a mixture of isomeric products results. Thus, PPE-1 may be selectively brominated to obtain either PPE-2 or PPE-3 as single products of known orientation. Any other set of reaction conditions yields mixtures of isomerically substituted bromine-containing products which are not desirable for our purpose. Furthermore, the reaction occurs in a sequential manner in which the 8 protons para to the ether link are reacted first and in preference to the *ortho* protons in the two terminal phenyl rings. The reaction times given may vary with the experimental conditions but the reaction sequence remains the same and either PPE-2 or PPE-3 may be isolated from the reaction mixture in an isomerically pure form.

Introduction of the cyano group into phenyl ethers

The reaction of DPE-2 with cuprous cyanide proceeds smoothly in which both *para*-substituted bromine atoms are replaced by the cyano group (Fig. 5A). However, a single product could not be obtained from the reaction with DPE-3, even after prolonged reaction times (Fig. 5B). The product distribution of the mixture formed after 32 h of reflux remained constant even after the addition of fresh reagent and further refluxing for 16 h. This alerted us to the fact that *ortho*-substituted bromine groups may not be as easily replaced by cyano groups as the *para*-substituted bro-
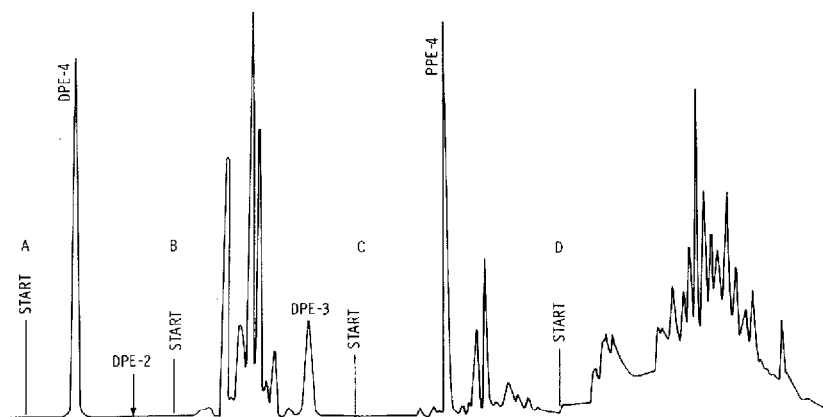
Fig. 5. HPLC analysis of the products obtained from the reaction between bromophenyl ethers and cuprous cyanide. Separation conditions for A and B are the same as Fig. 2. For C and D a linear gradient from acetonitrile–water (3:1) to acetonitrile over 20 min and a flow-rate of 1.2 ml min^{-1} was used. Retention time for DPE-4 was 5.2 min and PPE-4 7.3 min.

mines or that the introduction of bromine into *ortho* positions diminishes the re-activity of *para*-substituted bromine. In either case an isomerically pure material will not result from the reaction.

The completely *para* substituted PPE-2 can be converted into the cyano-substituted analogue PPE-4 in high yield (Fig. 5C). The desired product (PPE-4) may be isolated as the isomerically pure compound by preparative liquid chromatography. As might be anticipated from the results obtained with the model compound DPE-3, the reaction with PPE-3 would not be expected to give a single product. Fig. 5D indicates the product distribution observed after 120 h of refluxing. This remained virtually constant independently of whether the reaction time was increased, fresh reagents added, the crude reaction products isolated and the reaction restarted with fresh reagents, or different solvents used for the reaction. Thus, brominated phenyl ethers with bromine substituted in *ortho* positions to the ether bond are not suitable for preparing cyanophenyl ethers in high yield and with isomeric purity.

It should be noted that the cyanopolyphenyl ether PPE-4 binds copper very strongly and the complex formed during the reaction was not broken-up by the usual methods of sample work-up used for this reaction[5,6]. Saturated potassium cyanide, ammonium hydroxide solution, ferric chloride solution, formaldehyde and ethyl-enediaminetetraacetic acid gave very low yields of copper-free material. The method using concentrated hydrochloric acid described in the experimental section is drastic but essential to obtain a high yield of copper-free product. The cyanophenyl ether (PPE-4) is very resistant to acid hydrolysis and the product isolated does not contain any carboxylic acid groups.

CONCLUSIONS

The reaction between bromine and phenyl ethers in the presence of thallium acetate occurs specifically in the position *para* to the ether bond. Under vigorous reaction conditions substitution in the *ortho* position may also occur. However, *ortho*

bromine-substituted phenyl ethers are not quantitatively converted into cyanophenyl ethers by reaction with cuprous cyanide. Phenyl ethers substituted with bromine exclusively in the *para* position are suitable for preparing cyanophenyl ethers in high yield. The progress of the above reactions and the purity of the final products is conveniently monitored by HPLC.

The properties of the cyanophenyl ethers as stationary phases in gas–liquid chromatography will be described in a subsequent paper[7].

ACKNOWLEDGEMENTS

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