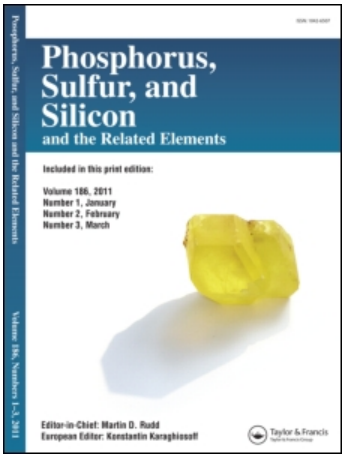

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SUBSTITUENT DIRECTIVE EFFECTS IN THE FRIEDEL-CRAFTS SYNTHESIS OF SUBSTITUTED PHENOXAPHOSPHINIC ACIDS

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Although meta-substituents on diphenyl ethers block attack at the para-position in the reaction with phosphorus trichloride and aluminium chloride, in some cases phosphorylation occurs in the even sterically more shielded ortho-position, leading to mixtures of isomeric phenoxaphosphinic acids. This effect and the obtained ratios of isomers can be explained by different substituent directive effects in a two step reaction mechanism.

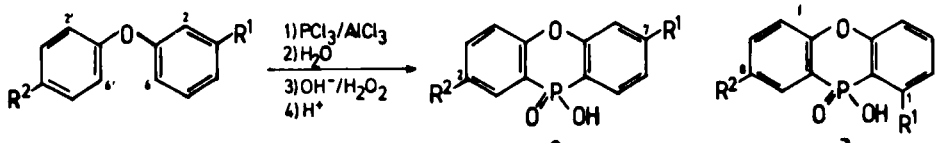
INTRODUCTION

Ring substituted 10-hydroxy-10H-phenoxaphosphine-10-oxides (phenoxaphosphinic acids) can only be synthesized by a Friedel–Crafts type reaction of diphenyl ethers with phosphorus trichloride and aluminium chloride, if the predominant formation of para-phenoxyphenylphosphonous dichloride in the initial step is prevented. This can be achieved by employing either para-substituted[1–5] or meta-substituted[6–8] diphenyl ethers. In the latter case, the para position is "indirectly" blocked by bulky methyl-, bromo- or chloro substituents.[6–8]

Surprisingly, we isolated considerable amounts of 1,8-disubstituted phenoxaphosphinic acids accompanying the expected cyclisation products when we caused to react 3,4′-disubstituted diphenyl ethers with phosphorous trichloride in the presence of aluminium chloride.[8] This intriguing result—blocking of the para position by the meta-substituent, but ring closure at the sterically more hindered ortho-position—prompted us to investigate the directive effects of the present substituent pattern of the diphenyl ethers.

RESULTS AND DISCUSSION

Under identical reaction conditions, diphenyl ethers **1a–c** were converted to phenoxaphosphinic acids in nearly identical amounts, but with distinctive different ratios of isomers **2** and **3**:



1

a	$R^1 = Cl$; $R^2 = CH_3$	
b	CH_3	CH_3
c	CH_3	Cl

2

a	49,4%
b	66,6%
c	74,2%

3

a	26,6%
b	7,4%
c	<1,0%

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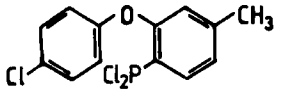
The isomeric phenoxaphosphinic acids **2** and **3** were separated and purified by crystallization. The structures were determined from the ^{1}H-NMR-spectra.[5,6] These results indicate that there are not only sterically directive effects of the diphenyl ether substituents as has been suspected by other authors.[6,7] We assume that in the first—presumably reversible—rate determininating reaction step the rather bulky electrophile "$PCl_2^+AlCl_4^-$" attacks the diphenyl ether either at the 6- or at the identical 2'/6'-positions, but not at the shielded 2-position analogous to the reaction of substituted anisoles with phosphorus trichloride.[9] It is reasonable that in the case of the chloro-methyl-substituted ethers **1c** and **1a** the reaction will take place in the more activated methyl-substituted benzene rings, leading to the dichlorophosphine intermediates **4** and **5** respectively:



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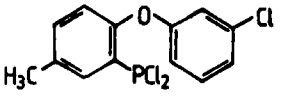

5

In the second, fast and probably irreversible reaction step, the tricyclic system is generated by cyclization of these dichlorophosphine intermediates. In this *intra*molecular step the dichlorophosphine group is able to attach even the sterically more shielded ortho-position, the ratio **2a** versus **3a** obtained from **5** therefore representing the preference of the less hindered position in this kinetically controlled reaction step. Cyclization of intermediate **4** however apparently leads to exclusively *one* cyclization product, which is converted to the 2,7-disubstituted phenoxyaphosphinic acid **2c**, neither NMR nor HPLC indicating the presence of isomeric acid **3c**. In dimethyl substituted diphenyl ether **1b**, there is no distinct preference for one of the phenyl rings to be attacked by the electrophile in the first reaction step. As a result both possible intermediates should be formed, resulting in a higher **2b** versus **3b** ratio after cyclization and conversion to the phenoxaphosphinic acids. The experimental findings confirm this prediction.

EXPERIMENTAL

The m.p.'s were determined with a Tottolli-apparatus (Büchi) and are uncorrected. The HPLC used LiChrosorb RP 18 5 μm 120 × 4,6 mm (Merck) as stationary phase and water/methanol (3:1.75, adjusted to pH 7.8 with sodium acetate) as mobile phase with UV-detection at 235 nm and 254 nm. The ^{1}H-NMR-spectra were recorded on a Bruker HX 90 (60 MHZ)-spectrometer with TMS as internal standard; chemical shifts are given in δ(ppm). Elemental analaysis were performed by the Analytical Department, Hoechst AG.

4-Chloro-3'-methyl diphenyl ether (**1c**). 4-bromo-1-chlorobenzene (40 g, 0.2 mole), potassium-meta-cresolat (16 g, 0.11 mole) and copper powder (0.5 g) were stirred and heated to 200°C in 80 ml 1-methyl-pyrrolidone(2) for 6 hours, then poured on 200 g ice and extracted twice with 200 ml hexane. The hexane layer was washed with water, concentrated and the residue distilled in vacuo to yield 11.7 g (49%) **1c** as colourless oil, bp 118°C/0.8 torr.

n_D^{25}: 1,5808 ^{1}H-NMR ($CDCl_2$): 2,25 (s. CH_3) 6.6–7.3 (m, arom. H)

Anal Calcd. for $C_{13}H_{11}ClO$: C, 71.4; H, 5.1; Cl, 16.2

Found C, 70.9; H, 4.8; Cl, 16.4

Phenoxaphosphinic acids **2a**, **2b**, **2c**, **3a** and **3b**.

GENERAL PROCEDURE

A mixture of diphenyl ether (0.1 mole), phosphorus trichloride (40 ml, 0.46 mole) and aluminium chloride (20 g, 0.15 mole) was refluxed under nitrogen for 24 hours. The cooled mixture was poured on ice (300 g), saturated with sodium chloride and extracted three times with 150 ml iso-butanol. The organic layer was washed with 100 ml saturated sodium chloride solution, concentrated, the crystalline residue dissolved in 2N sodium hydroxide solution (150 ml) and oxidized with hydrogen peroxide (30%, 4 ml). The solution was washed twice with ethyl acetate (100 ml each), acidified with 12N hydrochloric acid to pH 1.5–2.0, the precipitate collected and washed with water.

7-Chloro-2-methyl-10-hydroxy-10H-phenoxaphosphine-10-oxide (**2a**) *and 1-chloro-8-methyl-10-hydroxy-10H-phenoxaphosphine-10-oxide* (**3a**):[8] 3-chloro-4'-methyl diphenyl ether (**1a**), prepared from 3-bromo-1-chlorobenzene and p-cresol[8,10] (21.8 g, 0.1 mole) gave 21.4 g (76%) of a 13:7-mixture of **2a** and **3a**, (as determined by HPLC). Recrystallization from methanol yielded 9.2 g (33%) pure **2a**, mp 257°C. By concentrating the mother liqor and addition of acetone pure **3a**, (2.4 g, 9%), mp 298°C could be isolated.

2,7 Dimethyl-10-hydroxy-10H-phenoxaphosphine-10-oxide (**2b**) *and 1,8-dimethyl-10-hydroxy-10H-phenoxaphosphine-10-oxide* (**3b**). 3,4'-dimethyl diphenyl ether (**1b**), prepared from 4-bromotoluene and m-cresol,[10,11] (14.2 g, 0.072 mole) yielded 13.8 g (74%) of a 9:1-mixture of **2b** and **3b**, determined by HPLC. After recrystallization from ethanol/water 4.7 g (25%) **2b**, mp 244°C, were obtained. ^{1}H-NMR:(TFA) 2.45 (s, CH_3 at C-2), 2.51 (s, CH_3 at C-7), 7.1–8.1 (m, 6 arom. H)

Anal. Calcd. for $C_{14}H_{13}O_3P$: C, 64.6; H, 5.0; P, 11.9
Found C, 64.2; H, 5.1; P, 11.7

The mother liquor was concentrated and cooled, a precipitating mixed fraction discharged, further concentrated and the resulting residue recrystallized from methanol/acetone to yield 0.6 g (3.2%) pure **3b**, mp 251°C. ^{1}H-NMR (TFA) 2.47 (s, CH_3 at C-8); 2.84 (s, CH_3 at C-1); 7.0–7.9 (m, 6 arom. H).

Anal. Calcd. for $C_{14}H_{13}O_3P$: C, 64.6; H, 5.0; P, 11.9
Found C, 63.8; H, 5.0; P, 11.4

2-Chloro-7-methyl-10-hydroxy-10H-phenoxaphosphophosphine-10-oxide (**3c**). 4-chloro-3'-methyl diphenyl ether (**1c**, 4.6 g, 0.053 mole) gave 11.0 g (74%) **3c**, ^{1}H-NMR and HPLC showing no evidence of a second isomer. The crude product was recrystallized from methanol/acetone. 7.8 g (52.4%) as colourless crystals, mp 273°C. ^{1}H-NMR (TFA): 2.52 (s, CH_3 at C-7), 7.1–8.1 (m, 6 arom. H).

Anal. Calcd. for $C_{13}H_{10}ClO_3P$: C, 55.6; H, 3.6; Cl 12.6; P, 10.8
Found C, 55.2; H, 3.6; Cl 12.5; P, 10.8

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