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A Study on the Selective Phosphorylation and Phosphinylation of Hydroxyphenols

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ABSTRACT: *By choice of appropriate reaction conditions, the phosphorylation of hydroquinone by diethyl chlorophosphate gave predominantly the monophosphate (***2***). A similar reaction of phloroglucinol led to the mixture of the possible products (***6, 7***, and* ***8***). *The monophosphinylation of the above hydroxyphenols by diphenylphosphinyl chloride could be accomplished with a good selectivity to give product* ***4*** *or* ***9***, *the yields, however, being variable.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:126–130, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10006

INTRODUCTION

Organophosphorus compounds used as monomers or as additives form an important group of flame retardants [1]. Among the polyols, whose "Achilles' heel" is their stability, the phosphorus containing derivatives such as aryl phosphates are also potential candidates as starting materials for flame retardants [2]. It was a challenge for us to prepare hydroxyphenols with a phosphorus moiety in the aromatic ring that can be used as additives or starting materials in polycondensations to form flame retardants [3]. We wished to make available some monophosphorylated and monophosphinylated polyhydroxyphenols.

RESULTS AND DISCUSSION

According to the literature, the acetylation of hydroquinone by acetyl chloride or acetic anhydride gives a mixture of mono- and diacetylated products [4,5]. The use of acetic anhydride in acetic acid afforded, however, 4-acetoxyphenol in 65% yield [6]. Generally, monoacylation, including monophosphorylation, monophosphonylation, and monophosphinylation of dihydroxy compounds can be carried out efficiently only if the two hydroxy groups have different chemical natures, one of them being spatially open and the other being shielded [7]. Phosphorus triamides were, however, found to be suitable reagents to achieve a predominant monoacylation of dihydric phenols [8]. The phosphorylation of

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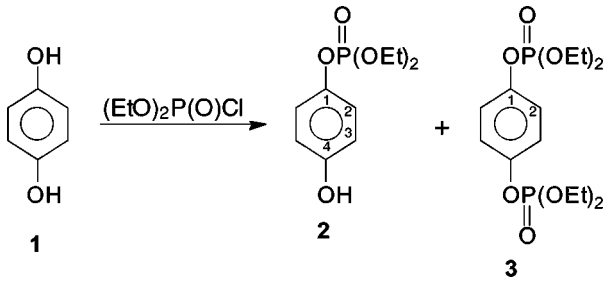


SCHEME 1

hydroxyphenols utilizing low-coordinate phosphorus fragments [9] did not seem to be a practical synthesis in this particular case.

In the first place, we studied the phosphorylation of hydroquinone by diethyl chlorophosphate under different conditions (Scheme 1, Table 1). When the phosphorylations in boiling ether or in acetonitrile were carried out in the presence of one equivalent of triethylamine, the proportion of the monophosphate (**2**) and the diphosphate (**3**) was found to be comparable according to ^{31}P NMR analysis of the crude mixtures (ca. 41 vs. ca. 45%, respectively). Formation of the tetraethyl pyrophosphate as a side product was inevitable (Table 1, entries 1 and 2). The best results were achieved by performing the phosphorylation in boiling acetone; the selectivity of the monophosphorylation was found to be 0.79. Obviously, because of the unremovable traces of the water, 28% of the pyrophosphate was formed (entry 3). No phosphorylation took place in the absence of triethylamine. The phase transfer catalytic method was proved not to be suitable, as the liquid–liquid two-phase reaction mixture containing aqueous sodium hydroxide led predominantly to diphosphorylation (entry 4).

The crude product obtained by using acetone as the solvent (entry 3) was refined by column chromatography. The first fraction was practically clean diphosphate **3**, while the second one contained monophosphate **2** in a purity of 86% and in 31% yield. The products (**2** and **3**) were identified by ^{31}P and ^{13}C NMR spectra, as well as mass spectroscopy including GC–MS for **2**. Compound **2** was also characterized by HR–MS. The δ_P shift of the 4-hydroxyphenyl diethyl phosphate was comparable with that of the corresponding phenyl derivative (−5.6 vs. −6.8) [11]. It is worth mentioning that diphosphate **3** is a valuable starting material in the synthesis of 1,4-disubstituted benzenes by a cross-coupling approach [12].

The second model reaction was the phosphinylation of hydroquinone by diphenylphosphinyl chloride. The acylation carried out in boiling ether, in the presence of one equivalent of triethylamine led to a mixture containing phosphinate **4** in 87% and tetraphenyl pyrophosphinate (δ_P ($CDCl_3$) 32.1, δ_P lit [13] 32.6) in 13% yields according to ^{31}P NMR spectroscopy (Scheme 2). Product **4** was identified by ^{31}P and ^{1}H NMR spectroscopy, as well as by mass spectra. The selectivity is probably the consequence of the poor solubility of the phosphinate (**4**) in ether.

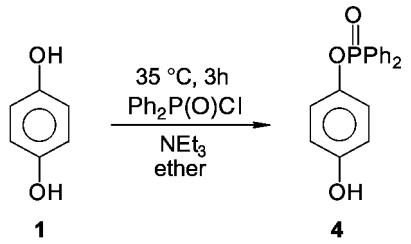
The phosphorylation of phloroglucinol with diethyl chlorophosphate at 35–82°C, in the presence of triethylamine, afforded a mixture of the mono-, di-, and triphosphates (**6, 7**, and **8**, respectively), no matter what was used as the solvent (Scheme 3, Table 2). No practical separation of the components could be achieved. Monophosphate **6** could, however, be separated from the experiment marked by *entry 1* in a poor yield. The phosphates (**6, 7**, and **8**) were characterized by ^{31}P NMR chemical shifts and mass spectroscopical data obtained by MS or by GC–MS.

The reaction of phloroglucinol with diphenylphosphinyl chloride in boiling ether, in the presence of a tertiary amine resulted mainly in

TABLE 1 Phosphorylation of Hydroquinone by Diethyl Chlorophosphate Under Different Conditions

				Reaction		*Product Composition[a] (%)*			
Entry	$\frac{n_{DECP}}{n_1}$	*Solvent*	*Base*	*Temp. (°C)*	*Time (h)*	***2***	***3***	*PP[b]*	***2/(2 + 3)***
1[c]	1.0	Ether	TEA	35	4.5	38	49	13	0.44
2[c]	1.0	MeCN	TEA	82	3	44	41	15	0.52
3[c]	1.0	Acetone	TEA	56	4.5	57	15	28	0.79
4[d]	1.1	CH_2Cl_2	NaOH/H_2O Tebac	26	4.5	3	62	35	0.05

Abbreviations: diethyl chlorophosphate (DECP); pyrophosphate (PP); triethylbenzylammonium chloride (Tebac).
[a]Determined on the basis of relative ^{31}P NMR intensities.
[b]δ_P ($CDCl_3$) − 12.9, δ_P [10] −13.0.
[c]For details see general procedure. The crude mixture obtained from the experiment marked by *entry 3* was refined.
[d]1.32 ml DECP was added dropwise to the stirred mixture of 1.0 g of **1** and 0.62 g of Tebac in 60 ml of CH_2Cl_2 and 3.6 g NaOH in 10 ml of water.



SCHEME 2

monophosphinylation. The acylation was, however, rather slow and even after prolonged heating at the boiling point, the yield of phosphinate **9** was only 17%. Some of the diphosphinylated product (**10**) could also be detected by GC–MS; the ratio of **9** and **10** was 5:1 (Scheme 4). Compounds **9** and **10** were characterized by ^{31}P NMR and mass spectroscopical data.

For the preparation of monophosphorylated and monophosphinylated hydroquinone, the reaction of *p*-benzoquinone with $(EtO)_2P(O)Na$ or with $Ph_2P(O)Li$ was also described that was not too efficient because of side reactions [14,15].

It can be concluded that while the monophosphinylation and the monophosphorylation of hydroquinone can be achieved selectively, similar reactions of phloroglucinol are rather complex: the monophosphorylation is not selective, while the monophosphinylation is fairly selective, but the yield is poor.

In the next stage of our work, the phosphorylated and phosphinylated hydroxyphenols will be incorporated into polymer composites in order to test their flame retarding effect.

EXPERIMENTAL

The ^{31}P NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 202.4 MHz. Chemical shifts are downfield relative to 85% H_3PO_4. GC–MS was performed on a Fisons GC 8000/MD 800 apparatus.

Phosphorylation of Hydroquinone by Diethyl Chlorophosphate

To 0.5 g (4.55 mmol) of hydroquinone and 0.63 ml (4.55 mmol) of triethylamine in 35 ml of the solvent (Table 1) was added 0.68 ml (4.71 mmol) of diethyl chlorophosphate, and the mixture was stirred at the boiling point for the time shown in Table 1. The solvent was evaporated and the residue taken up in a mixture of 20 ml of chloroform and 2 ml of water. The organic phase was dried (Na_2SO_4) and the solvent evaporated. The crude mixture was analyzed by ^{31}P NMR spectroscopy (Table 1).

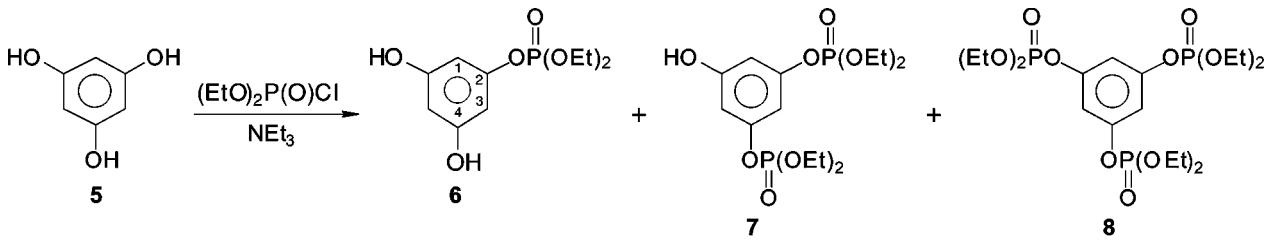
The crude mixture from the experiment marked by *entry 3* was subjected to column chromatography (silica gel, 3% methanol in chloroform) to give 0.14 (11%) of product **2** in a purity of 86% and 0.45 g (26%) of product **3** in a pure form.

2: ^{31}P NMR ($CDCl_3$) $\delta - 5.6$; ^{13}C NMR ($CDCl_3$) δ 15.6 ($J = 8.3$, CH_3CH_2), 64.2 ($J = 6.0$, CH_3CH_2), 120.2 (C_3), 120.7 ($J = 4.1$, C_2), 142.7 (C_4), 147.2 ($J = 6.6$, C_1); GC–MS, *m/z* (rel. int.) 246 (M^+, 47), 231 (M − 15, 4), 218 (M − 28, 23), 190 (218 − 28, 38), 137 ($(EtO)_2P(O)$, 2), 110 (M − $(EtO)_2P(O)$ + H, 100), 109 (M − $(EtO)_2P(O)$, 28); HRMS, $M^+_{found} = 246.0602$, $C_{10}H_{15}O_5P$ requires 246.0657.

3: ^{31}P NMR ($CDCl_3$) $\delta - 5.94$; ^{13}C NMR ($CDCl_3$) δ 15.8 ($J = 6.6$, CH_3CH_2), 64.5 ($J = 6.1$, CH_3CH_2), 120.9 ($J = 4.6$, C_2), 147.3 ($J = 6.6$, C_1); MS, *m/z* (rel. int.) 382 (M^+, 52), 367 (M − 15, 2), 354 (M − 28, 17), 326 (354 − 28, 12), 297 (326 − 29, 16), 246 (M − $(EtO)_2P(O)$ + H, 45), 228 (245 − 17, 27), 200 (245 − 45, 63), 110 (246 − $(EtO)_2P(O)$ + H, 68), 109 (246 − $(EtO)_2P(O)$, 100).

Phosphinylation of Hydroquinone with Diphenylphosphinyl Chloride

The reaction was carried out as the phosphorylations described previously using ether as the solvent and 0.87 ml (4.55 mmol) of diphenylphosphinyl chloride as the acylating agent. The precipitated material was filtered off and taken up in a mixture of 20 ml of



SCHEME 3

TABLE 2 Phosphorylation of Phloroglucinol by Diethyl Chlorophosphate in Different Solvents in the Presence of One Equivalent of TEA

		Reaction		*Product Composition* [a] *(%)*				
Entry	*Solvent*	*Temp. (°C)*	*Time (h)*	***6***	***7***	***8***	*PP*	***6/(6+7+8)***
1[b]	Ether	35	5	18	18	47	17	0.22
2[b]	MeCN	82	3	25	14	36	25	0.33
3[b]	Acetone	56	4.5	16	12	22	50	0.32

[a]Determined on the basis of relative ^{31}P NMR intensities.
[b]For details see general procedure. The crude mixture obtained from the experiment marked by *entry 2* was refined.

chloroform and 2 ml of water. The organic phase was dried (Na_2SO_4) and the solvent evaporated to give the phosphinate (**4**) in 90% yield, in a purity of ca. 90%. A small sample was recrystallized from chloroform to afford pure **4**. ^{31}P NMR ($CDCl_3$) δ 32.7; ^1H NMR ($CDCl_3$) δ 6.65–7.88 (m, 14H, ArH), 9.67 (s, 1H, OH); MS, *m/z* (rel. int.) 310 (M^+, 51), 201 ($Ph_2P(O)$, 100), 77 (Ph, 22).

Phosphorylation of Phloroglucinol by Diethyl Chlorophosphate

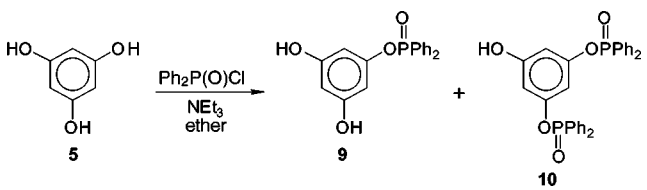
The reactions were carried out in the same manner as for the phosphorylations of hydroquinone described previously, 0.50 g (3.08 mmol) of phloroglucinol, 0.43 ml (3.08 mmol) of triethylamine, 0.45 ml (3.08 mmol) of diethyl chlorophosphate, and 25 ml of acetone or acetonitrile, or 60 ml of ether being used.

The crude mixture from the experiment marked by *entry 1* was characterized after flash column chromatography (as above). A second chromatography afforded monophosphate **6** in a pure form.

6: Yield: 5%; ^{31}P NMR ($CDCl_3$) δ −6.57; ^{13}C NMR ($CDCl_3$) δ 16.1 ($J = 6.4$, CH_3CH_2), 65.4 ($J = 6.2$, CH_3CH_2), 100.0 ($J = 4.8$, C_2), 100.7 (C_4), 151.8 ($J = 7.0$, C_1), 158.3 (C_3); MS, *m/z* (rel. int.) 262 (M^+, 34), 247 (M − 15, 10), 233 (M − 29, 6), 219 (247 − 28, 29), 205 (233 − 28, 5), 136 ($(EtO)_2P(O) - H$, 100), 126 (M − $(EtO)_2P(O)$ + H, 49), 108 (125 − 17, 13); HR–FAB, $(M+H)^+_{found} = 263.0614$, $C_{10}H_{16}O_6P$ requires 263.0684.

7: ^{31}P NMR ($CDCl_3$) δ −6.45; GC–MS, *m/z* (rel. int.) 398 (M^+, 49), 383 (M − 15, 11), 370 (M − 28, 10), 355 (383 − 28, 11), 341 (370 − 29, 10), 262 (M − $(EtO)_2P(O)$ + H, 21), 244 (261 − 17, 82), 233 (262 − 29, 25), 216 (261 − 45, 100), 188 (216 − 28, 23), 136 ($(EtO)_2P(O) - H$, 53); HR–FAB, $(M+H)^+_{found} = 399.0861$, $C_{14}H_{25}O_9P_2$ requires 399.0974.

8: ^{31}P NMR ($CDCl_3$) δ −6.64; GC–MS, *m/z* (rel. int.) 534 (M^+, 37), 519 (M − 15, 7), 506 (M − 28, 9), 491 (519 − 28, 5), 478 (506 − 28, 12), 398 (M − $(EtO)_2P(O)$ + H, 30), 380 (397 − 17, 100), 352 (397 − 45, 51), 324 (352 − 28, 52), 296 (324 − 28, 45), 216 (352 − $(EtO)_2P(O)$ + H, 38), 136 ($(EtO)_2P(O) - H$, 13); HR–FAB, $(M+H)^+_{found} = 535.1163$, $C_{18}H_{34}O_{12}P_3$ requires 535.1263.



SCHEME 4

Phosphinylation of Phloroglucinol with Diphenylphosphinyl Chloride

To 0.5 g (3.08 mmol) of phloroglucinol and 0.43 ml (3.08 mmol) of triethylamine in 60 ml of ether was added 0.59 ml (3.08 mmol) of diphenylphosphinyl chloride, and the mixture was stirred at the boiling point for 5 h. The precipitated material was filtered off and the filtrate evaporated to give a mixture containing 80% of the monophosphinate (**9**), 16% of the diphosphinate (**10**), and 4% of the pyrophosphinate.

9: ^{31}P NMR ($CDCl_3$) δ 32.0; GC–MS, *m/z* (rel. int.) 326 (M^+, 64), 201 ($Ph_2P(O)$, 100), 77 (Ph, 33).

10: ^{31}P NMR ($CDCl_3$) δ 32.7; GC–MS, *m/z* 526 (M^+).

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