Steric and Electronic Effects in the Aryl Phosphate to Arylphosphonate Rearrangement

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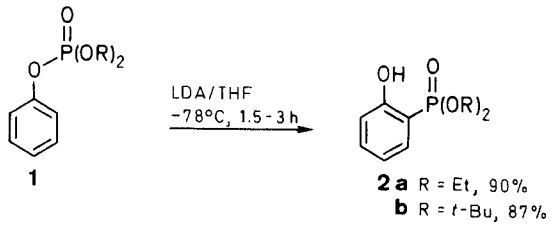
A number of carboxy substituted aryl phosphates have been prepared and subjected to anionic rearrangement conditions to provide the corresponding phenolic phosphonates. Steric effects of the phosphate ester group and the electronic effects of the aryl carboxy group can limit the scope of the rearrangement.

The base-promoted rearrangement of aryl phosphates is an effective method for the preparation of arylphosphonates when the aryl group is not highly substituted.[1-4] The mechanism is believed to involve phosphate directed *ortho*-metalation of the aromatic ring followed by phosphorus migration to the carbanionic center to give a phenolic phosphonate.[1,5] We sought to employ this approach in preparing a variety of phenols which also have carboxy and phosphonyl functionalities attached to the aromatic ring.

Diethyl phenyl phosphate (**1a**) and di-*tert*-butyl phenyl phosphate (**1b**) were easily prepared by phosphorylation of phenol. Diethyl phosphorochloridate is commercially available; the corresponding di-*tert*-butyl phosphorochloridate was prepared by the reaction of di-*tert*-butyl phosphite with carbon tetrachloride and base.[6] Both phosphates were then cleanly rearranged to phosphonates **2a** and **2b**, respectively, using lithium diisopropylamide in good yields[7] (Scheme **1**).



Scheme **1**

Application of the rearrangement strategy was then extended to the synthesis of carboxy substituted phenols starting from 4-hydroxybenzoic acid. The acid moiety was protected as its *tert*-butyl ester (**3a**) using standard conditions[8] and then was treated with di-*tert*-butyl phosphorochloridate to form the phosphate **4a**. Attempts to rearrange **4a** using the reported reaction conditions[1-3] were unsuccessful. Excess base (either butyllithium or lithium diisopropylamide), long reaction times, and elevated temperatures did not induce the compound to rearrange to **5a**. Rearrangement of the corresponding diethyl phosphate **4b** however, proceeded without difficulty although requiring more time (4 h) and providing diminished yields (40%) of **5b** (Scheme **2**).

Table 1. Aryl Phosphates **4a–g** Prepared

Product	Yield[a] (%)	Molecular Formula[b]	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS[b] m/z (%)
4a	70	$C_{19}H_{31}O_6P$ (386.4)	1369.8 (*t*-C_4H_9), 1705 (C=O)	1.51 (s, 18H, 2 × POC_4H_9-*t*), 1.58 (s, 9H, $CO_2C_4H_9$-*t*), 7.24 (d, 2H_{arom}, J = 8.6), 7.96 (d, 2H_{arom}, J = 8.6)	386 (7), 292 (100)
4b	53	$C_{15}H_{23}O_6P$ (330.3)	1369.5 (*t*-C_4H_9), 1716 (C=O)	1.36 (t, 6H, J = 7, 2 × CH_2CH_3), 1.58 (s, 9H, *t*-C_4H_9), 4.22 (dq, 4H, J = 7, 7, 2 × CH_2CH_3), 7.25 (d, 2H_{arom}), 7.98 (d, 2H_{arom})	330 (12), 148 (100)
4c	81	$C_{15}H_{25}BrO_4P$ (380.3)	1371 (*t*-C_4H_9)	1.52 (s, 18H, 2 × *t*-C_4H_9), 2.28 (s, 3H, CH_3), 7.02–7.07 (m, 1H_{arom}), 7.36–7.40 (m, 2H_{arom})	398 (17, M^+ + 17), 396 (14, M^+ + 17), 342 (97), 340 (100)
4d	66	$C_{10}H_{14}BrO_4P$ (309.1)		1.36 (t, 6H, J = 7, 2 × CH_2CH_3), 4.27 (dq, 4H, J = 7, 8, 2 × CH_2CH_3), 7.27–7.82 (m, 4H_{arom})	310 (10), 308 (8), 173 (100)
4e	66	$C_{14}H_{23}BrO_4P$ (366.2)	1371 (*t*-C_4H_9)	1.53 (s, 18H, 2 × C_4H_9), 6.86–7.60 (m, 4H_{arom})	367 (2.14), 365 (3), 255 (94), 253 (100)
4f	57	$C_{14}H_{22}Br_2O_4P$ (445.1)	1371 (*t*-C_4H_9)	1.53 (s, 18H, 2 × C_4H_9), 7.40 (s, 2H_{arom}), 7.71 (s, 1H_{arom})	447 (13), 445 (26), 443 (14), 333 (100)
4g	85	$C_{15}H_{21}Br_2O_6P$ (488.1)	1371 (*t*-C_4H_9), 1725 (C=O)	1.40 (t, 6H, J = 7, 2 × CH_2CH_3), 1.58 (s, 9H, *t*-C_4H_9), 4.34 (dq, 4H, J = 7, 7, 2 × CH_2CH_3), 8.13 (s, 2H_{arom})	492 (1.2), 490 (2), 488 (1), 429 (9), 290 (100)

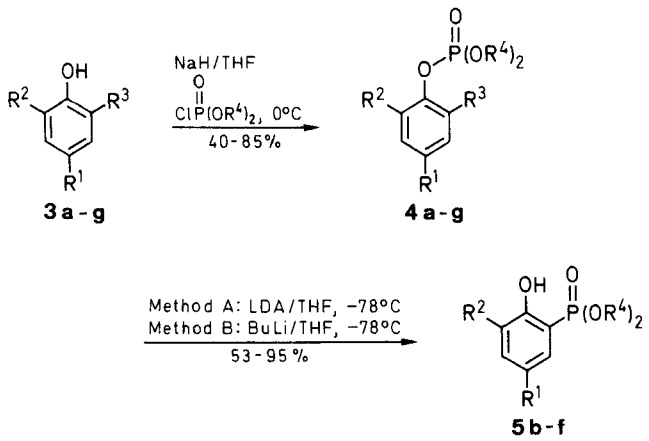
[a] Yield of isolated **4** based on **3**. All products except **4a** are oils and were purified by column chromatography on silica gel.
[b] Satisfactory microanalyses obtained for **4a**: C −0.32; H +0.07; P −0.07. Rest of the compounds gave HRMS values within ±0.0045 amu. The following instruments and techniques were used to record the MS and HRMS: MS (for **4a, c, g**): Delsi/Nermag R-10-10C, CI (NH_3); MS (**4b**): Trio-1, EI; MS/HRMS (**4d**), HRMS (**4b**): VGZABHF; MS/HRMS (**4e, 4f**), HRMS (**4c**): VG ZABHF (FAB, DTT/DTE matrix); HRMS (**4g**): VG ZABHF (FAB, 3-NBA matrix).

Table 2. Arylphosphonates **5b–g** Prepared

Product	Method	Time	Yield[a] (%)	Molecular Formula[b] or Lit. bp (°C)/Torr	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS[c] m/z (%)
5b	A	4 h	40	$C_{15}H_{23}O_6P$ (330.3)	1715 (C=O)	1.34 (t, 6H, J = 7, CH_2CH_3), 1.58 (s, 9H, $CO_2C_4H_9$-*t*), 4.15 (dq, 4H, J = 7, 7, CH_2CH_3), 6.90 (dd, 1H_{arom}, J = 3.6, 7.2), 8.10 (dd, 2H_{arom}, J = 3.6, 7.2)	330 (30), 218 (100)
5c	B	5 min	90	$C_{15}H_{26}O_4P$ (301.3)	1371 (*t*-C_4H_9)	1.48 (s, 18H, 2 × POC_4H_9-*t*), 2.30 (s, 3H, $ArCH_3$), 7.0 (m, 3H_{arom}), 10.34 (s, 1H, OH)	301 (74), 245 (100)
5d (≡**2a**)	A	1.5 h (from **1a**)	90	110–111/7[2]	–	–	
	B	5 min (from **4d**)	95				
5e (≡**2b**)	A	3 h (from **1b**)	87	oil[3]	–	–	
	B	5 min (from **4e**)	85				
5f	B	20 min	53	$C_{14}H_{22}BrO_4P$ (365.2)	1371 (*t*-C_4H_9)	1.49 (s, 18H, 2 × POC_4H_9-*t*), 6.79 (m, 1H_{arom}), 7.53 (m, 2H_{arom}), 10.57 (brs, 1H, OH)	364 (2), 366 (2), 254 (100)

[a] Yield of isolated product. All products are oils and were purified by chromatography.
[b] Satisfactory HRMS values within ±0.0025 amu obtained. **5b, f**: EI, **5c**: FAB (thioglycerol matrix) (VG ZABHF mass spectrometer).
[c] The MS of **5b** and **5f** were recorded as EI spectra on a Trio-1 and VG ZABHF instrument, respectively, while that of **5c** was obtained in CI mode (NH_3) on a Delsi/Nermag instrument.

It was clear from the rearrangement of **1b** that the presence of *tert*-butyl groups on the phosphate does not, by itself, prevent the rearrangement from occurring. The problem must therefore lie with the added carboxylate ester group on the ring. A combination of steric and electronic factors must be operating to prevent **4a** from undergoing the transformation to the phosphonate. In order to study this phenomenon more thoroughly, a series of aryl phosphates was prepared and the rearrangement of each under basic conditions was examined. The results of these studies are presented in Tables 1 and 2.



3–5	R^1	R^2	R^3	R^4
a	CO_2Bu-*t*	H	H	*t*-Bu
b	CO_2Bu-*t*	H	H	Et
c	Me	H	Br	*t*-Bu
d	H	H	Br	Et
e	H	H	Br	*t*-Bu
f	Br	H	Br	*t*-Bu
g	CO_2Bu-*t*	Br	Br	Et

Scheme **2**

We believed that the failure in the rearrangement of **4a** was due its inability to form the *ortho* anion by direct *ortho* lithiation. Reaction of **4a** with lithium diisopropylamide followed by a deuterium oxide quench showed no change in **4a**; there was no incorporation of deuterium detected by either ^1H- or ^2H-NMR. The aryl anion was not formed at postions either *ortho* to the phosphate or *ortho* to the carboxy group.

In an attempt to overcome this difficulty, an alternate method of generating the aryl anion was explored. Halogen–metal exchange, using compounds containing an *ortho* bromine, was the next choice.[9] Compounds **4c**, **4d**, and **4e** rearranged smoothly to the aryl phosphonates in a short time when treated with butyllithium. The rearrangement of **4f** to **5f** (di-*tert*-butyl 5-bromo-2-hydroxyphenylphosphonate) demonstrates that the reaction is indeed characterized by *ortho* stabilization of the anion since no regioisomeric product (such as di-*tert*-butyl 3-bromo-4-hydroxyphenylphosphonate) was detected. In addition, no debrominated starting material nor debrominated product was detected in the reaction mixture. Compound **4g** does rearrange, but only in very low yields (8–10%). The difference in the reactions between **4b** and **4g** may be attributable to steric congestion near the phosphate in **4g**.

Both steric and electronic effects appear to be important in the rearrangement of aryl phosphates to arylphosphonates. Compounds with phosphate *tert*-butyl esters do not rearrange as well as those with ethyl esters; even when allowed to react for longer periods of time, the yields are not as good as in the ethyl phosphate cases, most likely a result of steric hindrance. The rearrangement is also hindered by the presence of electron-withdrawing groups such as esters in the *para* position on the aryl ring. When both steric hindrance and electronic deactivation are present in the same system, such as in compound **4a**, rearrangement is completely suppressed.

In conclusion, the aryl phosphate rearrangement remains a general route to arylphosphonates, but the electronic nature of substituents on the aryl ring and the size of the ester groups on the phosphate will have a direct influence on the ability of phosphorus to migrate.

Aryl Phosphates 4; General Procedure:
Phenol **3**[10] (1 equiv) in THF (15 mL) is treated with NaH (1.1 equiv, 50% in mineral oil). After H_2 evolution has ceased, the flask is cooled in an ice bath and stirred under N_2 for 5 min. One equivalent of diethyl phosphorochloridate or di-*tert*-butyl phosphorochloridate in THF (5 mL) is slowly added. The reaction is stored in the cold for 72 h and then warmed to r.t. The solvent is removed by evaporation and the residue is partitioned between CH_2Cl_2 (30 mL) and water (10 mL). The organic layer is then washed with water (10 mL) followed by 5% aq NaOH (10 mL). The organic layer is dried (Na_2SO_4) and evaporated to give the crude phosphate. The products are purified by flash chromatography on silica gel using mixtures of EtOAc in hexanes (from 20–50%) as eluent.

2-Hydroxyphenylphosphonates 5; General Procedures:
Method A, *Rearrangement of* **4** *by ortho Lithiation:* To a cold (−78 °C) solution of *i*-Pr_2NH (2 mmol) in THF (30 mL) is added a solution of BuLi (2 mmol, 2.4 M in hexanes). After stirring for 30 min under N_2, phosphate **4** (1 mmol) dissolved in THF (30 mL) is added. The mixture is stirred in the cold for 1 h and then allowed to warm to r.t. over 3 h. The mixture is partitioned between CH_2Cl_2 (100 mL) and sat. aq NH_4Cl (30 mL). The organic layer is dried (Na_2SO_4) and evaporated to give a yellow oil. The product phosphonate **5** is purified by radial or flash chromatography on silica gel using EtOAc/hexane mixtures as the eluent. Yields range from 40–90% (Table 2).

Method B, *Rearrangement of* **4** *by Halogen-Metal Exchange:* A solution of BuLi (1.6 mmol, 2.4 M in hexanes)[11] is added to a cold (−78 °C) solution of the phosphate **4** (1 mmol) in THF (30 mL) under N_2. After 15 min, the cold bath is removed and the mixture is partitioned between CH_2Cl_2 (100 mL) and sat. aq NH_4Cl (30 mL). The organic layer is dried (Na_2SO_4), and evaporated to give an oil. The product phosphonate **5** is purified by radial or flash chromatography using EtOAc/hexane mixtures as the eluent. Yields range from 53–95% (Table 2).

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(10) All the phenols used in this study were obtained from Aldrich Chemical Co., and esterified using standard conditions.[8]
(11) Only 1 equivalent of base was used in the case of compounds **4f** and **4g**.