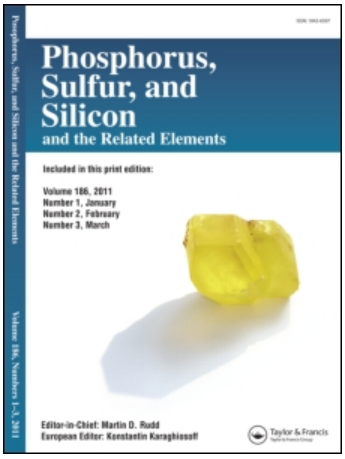

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METALATION INDUCED REARRANGEMENT OF DI-t-BUTYL(3-SUBSTITUTED PHENYL)PHOSPHATES

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METALATION INDUCED REARRANGEMENT OF DI-t-BUTYL(3-SUBSTITUTED PHENYL)PHOSPHATES

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Treatment of di-t-butyl(3,5-dimethylphenyl)phosphate **1b** with lithium diisopropylamide at −78°C followed by warming to rt yields di-t-butyl(2-hydroxy-4,6-dimethylphenyl)phosphonate **2b**. Di-t-butyl(3-methoxyphenyl)phosphate **1c** on similar treatment with LDA yields di-t-butyl(2-hydroxy-6-methoxyphenyl)phosphonate **2c**. Similarly di-t-butyl(3,5-dimethyloxyphenyl)phosphate **1d** rearranges to di-t-butyl(2-hydroxy-4,6-dimethoxyphenyl)phosphonate **2d**. Di-t-butyl(2-di-t-butoxyphosphinyl-3,5-dimethoxyphenyl)phosphate **3**, when treated with LDA, yields tetra-t-butyl(2-hydroxy-4,6-dimethoxy-1,3-phenylene)bis(phosphonate) **4**. The phosphonates **2c** and **2d** on treatment with trifluoroacetic acid in toluene are converted into the corresponding phosphonic acids **2e** and **2f** respectively.

Key words: Lithiation; phosphate-phosphonate rearrangement; phosphonic acids.

Dialkyl(2-hydroxyaryl)phosphonates **2** can be prepared in good yields by the metalation induced rearrangement of dialkyl aryl phosphates[1,2] **1**. Recently we showed that metalation induced rearrangement[3] of di-t-butyl(3-methylphenyl)phosphate **1a** yields di-t-butyl(2-hydroxy-4-methylphenyl)phosphonate **2a**. To see if the ortho position both to the methyl group and phosphate group is capable of undergoing metalation and migration of the di-t-butyl phosphinyl group to it, we prepared di-t-butyl(3,5-dimethylphenyl)phosphate **1b**. Di-t-butyl aryl phosphates **1** were prepared by the reaction of the sodium salt of a phenol with di-t-butyl phosphorochloridate. Treatment of **1b** with lithium diisopropylamide (LDA) gave di-t-butyl(2-hydroxy-4,6-dimethylphenyl)phosphonate **2b** in 73% yield. Thus although both the ortho positions to the phosphate ester group in **1a** are reactive, it is the least hindered ortho position to which the migration occurs. Our result is in agreement with the similar metalation induced migration of the carbamoyl group in (3-methylphenyl)diethylcarbamate which gives N,N-diethyl-2-hydroxy-4-methylbenzamide.[4]

Di-t-butyl(3-methoxyphenyl)phosphate **1c** on treatment with LDA undergoes clean rearrangement to give di-t-butyl(2-hydroxy-6-methoxyphenyl)phosphonate **2c** in 54% yield. The crude product exhibited only a single ^{31}P signal at 12.1 ppm. The structure of **2c** is based on the spectral data. In its ^{1}H NMR, **2c** exhibited a triplet at 7.3 ppm with $J_{H-H} = 9$ Hz assignable to the proton attached to C-4. As compared to the similar rearrangement of the carbamoyl group in (3-methoxyphenyl)diethylcarbamate[5] which gives a mixture of N,N-diethyl-2-hydroxy-6-methoxybenzamide and N,N-diethyl-2-hydroxy-4-methoxybenzamide, the rearrangement of **1c** is highly regioselective with the migration of the di-t-butylphosphinyl group occurring exclusively to the 'internal' ortho position. Thus both the ortho directing metalation groups, namely methoxy and phosphate ester groups, posi-

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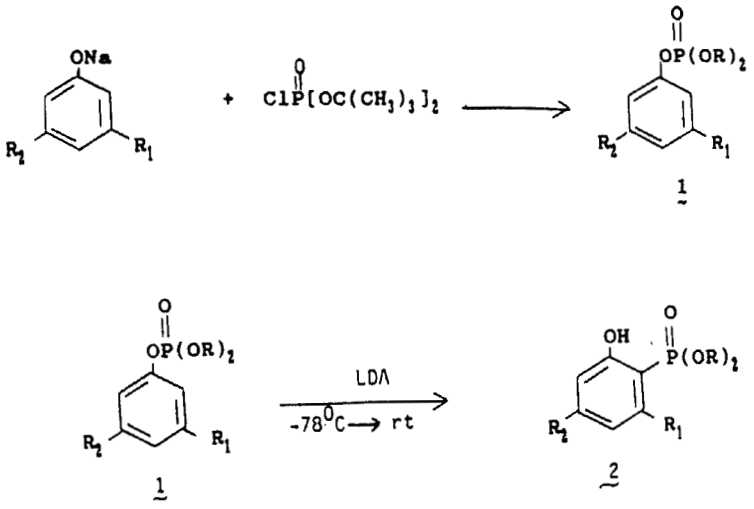
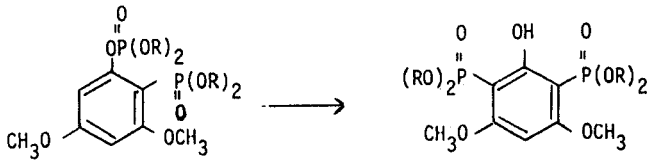


	R_1	R_2	R
a	H	CH_3	$C(CH_3)_3$
b	CH_3	CH_3	$C(CH_3)_3$
c	OCH_3	H	$C(CH_3)_3$
d	OCH_3	OCH_3	$C(CH_3)_3$
2e	OCH_3	H	H
2f	OCH_3	OCH_3	H

tioned meta to each other in **1c** cooperate fully in directing the metalation to the 'internal' ortho position. Similar treatment of di-t-butyl(3,5-dimethoxyphenyl) phosphate **1d** with LDA gave di-t-butyl(2-hydroxy4,6-dimethoxyphenyl)phosphonate **2d**.

Treatment of the di-t-butyl phosphonates **2c** and **2d** with trifluoroacetic acid in toluene resulted in de-t-butylation and gave the corresponding phosphonic acids **2e** and **2f** respectively. These were characterized by ^1H, ^{13}C and ^{31}P NMR and elemental analysis.

Treatment of the sodium salt of the phosphonate ester **2d** with di-t-butyl phosphorochloridate gave the phosphate-phosphonate **3** which, as expected, exhibited two signals at $+3.13$ and -16.78 ppm in its ^{31}P spectrum. Treatment of **3** with LDA gave tetra-t-butyl(2-hydroxy-4,6-dimethoxy-1,3-phenylene)bis(phosphonate) **4**. The structure of **4** was confirmed by ^1H, ^{13}C and ^{31}P NMR spectra. As expected from our earlier results,[3] the ^{13}C signal for $\underline{C}(CH_3)_3$ in **4** is a triplet with a visible splitting of 3.6 Hz. An unidentified isomer of **4** was also observed in minor amount in the crude product. The product **4** obviously results by the facile 1,3—O → C intramolecular migration of the di-t-butylphosphinyl group.



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R = $C(CH_3)_3$

EXPERIMENTAL

Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN and Petrolite Corporation, Analytical Section. ^{31}P spectra were obtained with a JEOL FX-60 spectrometer operating at 24.15 MHz. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) on a Varian Gemini-300 spectrometer, operational frequencies 300 (^1H) and 75 (^{13}C) MHz. The positive chemical shift values are downfield from H_3PO_4 (cap.) for ^{31}P spectra and from Me_4Si for ^1H and ^{13}C spectra.

Di-t-butyl aryl phosphates. These were prepared as reported for di-t-butyl phenyl phosphate.[1,2]

Di-t-butyl(3,5-dimethylphenyl)phosphate (**1b**). Starting with 75 mmol of 3,5-dimethylphenol, the yield of the crude product **1b** was 18.5 g (78%). ^{31}P NMR −15.47. ^1H NMR 1.50 (s, 18H, $C(CH_3)_3$), 2.24 (s, 6H, CH_3), 6.72 (s, 1H, Ar), 6.82 (s, 2H, Ar). ^{13}C NMR 21.30 (CH_3) 29.87 (d, 3.91 Hz, $C(CH_3)_3$), 83.24 (d, 7.81 Hz, $C(CH_3)_3$), 117.52 (d, 3.91 Hz, $C_{2,6}$), 125.83, 139.08 ($C_{3,5}$), 151.55 (C_1).

Di-t-butyl(3-methoxyphenyl)phosphate (**1c**). Starting with 75 mmol of 3-methoxyphenol, the yield of the crude product was 17.1 g (72%). ^{31}P NMR −15.64. ^1H NMR 1.48 (s, 18H, $C(CH_3)_3$), 3.75 (s, 3H, OCH_3), 6.55–6.90 (m, 3H), 7.18 (t, J_{H-H} = 8 Hz, 1H). ^{13}C NMR 29.74 (d, 3.91 Hz, $C(CH_3)_3$), 55.06 (OCH_3), 83.24 (d, 7.81 Hz, $C(CH_3)_3$), 105.90 (d, 5.86 Hz), 109.99, 112.00 (d, 5.86 Hz), 129.73, 152.39 (d, 5.86 Hz), 160.51.

Di-t-butyl(3,5-dimethoxyphenyl)phosphate (**1d**). Starting with 60 mmol, the yield of the crude product was 16.0 g (77%). ^{31}P NMR −15.77. ^1H NMR 1.48 (s, 18H, $C(CH_3)_3$), 3.72 (s, 6H, OCH_3), 6.20 (t, 2.0 Hz, 1H), 6.44 (dd, $^4J_{P-H}$ = 1 Hz, $^4J_{H-H}$ = 2 Hz, 2H). ^{13}C NMR 29.74 (d, 3.9 Hz, $C(CH_3)_3$), 55.19 (OCH_3), 83.37 (d, 7.8 Hz, $C(CH_3)_3$), 96.62 (C_4), 98.50 (d, 5.86 Hz, $C_{2,6}$), 152.98 (d, 7.81 Hz, C_1), 161.16 ($C_{3,5}$).

Di-t-butyl(2-hydroxyaryl)phosphonates (**2**). The rearrangement of di-t-butyl aryl phosphates to di-t-butyl(2-hydroxyaryl)phosphonates was carried out as reported earlier.[2,3]

Di-t-butyl(2-hydroxy-4,6-dimethylphenyl)phosphonate (**2b**). Starting with 50 mmol of **1b**, the yield of **2b** was 11.3 g (73%), mp. 73.5°C (pet. ether). ^{31}P NMR +15.52. ^1H NMR 1.45 (s, 18H, $C(CH_3)_3$), 2.22 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.45–6.65 (m, 2H, Ar). ^{13}C NMR 21.30 (s, CH_3), 30.13 (d, 3.91 Hz, $C(CH_3)_3$), 83.50 (d, 7.81 Hz, $C(CH_3)_3$), 110.19 (d, 189.45 Hz), 115.38 (d, 13.67 Hz), 122.84 (d, 15.62 Hz), 141.35 (d, 5.86 Hz), 144.02, 161.61 (d, 9.76 Hz).

Analysis: Calcd for $C_{16}H_{27}O_4P$: C, 61.15; H, 8.60; P, 9.87.
Found: C, 61.49; H, 8.64; P, 9.85.

Di-t-butyl(2-hydroxy-6-methoxyphenyl)phosphonate (**2c**). Starting with 50 mmol of **1c**, the yield of **2c** was 8.5 g (54%), mp. 80–81°C (pet. ether, bp. 35–60°C). ^{31}P NMR +12.13. ^1H NMR 1.42 (s, 18H, $C(CH_3)_3$), 3.80 (s, 3H, OCH_3), 6.25–6.60 (m, 2H, Ar), 7.30 (t, $^3J_{H-H}$ = 9 Hz, 1H, Ar), 11.55 (s, 1H, OH). ^{13}C NMR 30.13 (d, 3.91 Hz, $C(CH_3)_3$), 55.19 (OCH_3), 82.85 (d, 7.81 Hz, $C(CH_3)_3$), 101.03 (d, 7.81 Hz), 103.17 (d, 181.64 Hz), 110.0 6 (d, 13.67 Hz), 134.54, 161.68, 162.52 (d, 5.86 Hz).

Analysis: Calcd. for $C_{15}H_{25}O_5P$: C, 56.96; H, 7.91; P, 9.81.
Found: C, 57.22; H, 7.91; P, 9.81.

Di-t-butyl(2-hydroxy-4,6-dimethoxyphenyl)phosphonate (**2d**). Starting with 35 mmol of **1d**, the yield of **2d** was 9.10 g (75%), mp. 115–116°C (CH_2Cl_2-pet. ether). ^{31}P NMR +12.69. ^1H NMR 1.50 (s, 18H, $C(CH_3)_3$), 3.76 (s, 6H, OCH_3), 5.90 (dd, $^4J_{P-H}$ = 5 Hz, $^4J_{H-H}$ = 2 Hz, 1H), 6.0 (dd, $^4J_{H-P}$ = 5 Hz, $^4J_{H-H}$ = 2 Hz, 1H), 11.65 (s, 1H, OH). ^{13}C NMR 30.00 (d, 3.91 Hz, $C(\underline{C}H_3)_3$), 55.06 (OCH_3), 82.59 (d, 7.81 Hz, $\underline{C}(CH_3)_3$), 90.32 (d, 9.77 Hz), 93.50 (d, 11.72 Hz), 95.51 (d, 189.45 Hz), 162.72, 163.82 (d, 5.86 Hz), 165.31.

Analysis: Calcd. for $C_{16}H_{27}O_6P$: C, 55.49; H, 7.80; P, 8.96.
Found: C, 55.82; H, 7.96; P, 8.88.

2-Hydroxy-6-methoxyphenylphosphonic Acid (**2e**). Trifluoroacetic acid (1.8 g) was added to a solution of **2c** (3.0 g) in toluene (15 mL). After 1 h at rt, a solid began to separate. After 24 h stirring at rt, the crude product (1.9 g) was collected by filtration. The crude product was dissolved in methanol (50 mL), the solution was filtered and the filtrate was concentrated almost to dryness on a rotary evaporator. The residue when dissolved in methylene chloride slowly deposited a crystalline solid, mp. 113–115°C. ^{31}P NMR +17.08. ^1H NMR (D_2O) 3.88 (s, 3H, OCH_3), 6.50–6.80 (m, 2H, Ar), 7.50 (t, $^3J_{H-H}$ = 9 Hz, 1H, Ar). ^{13}C NMR (D_2O), 56.75 (OCH_3), 102.26 (d, 177.74 Hz), 103.50 (d, 7.81 Hz), 110.19 (d, 9.76 Hz), 136.22, 160.64 (d, 3.90 Hz), 162.59.

Analysis: Calcd. for $C_7H_9O_5P$: C, 41.18; H, 4.41.
Found: C, 40.53; H, 4.45

2-Hydroxy-4,6-dimethoxyphenylphosphonic Acid (**2f**). Starting with 11.5 mmol, the yield of **2f** was 2.7 g (91%), mp. 128–129°C. ^{31}P (CD_3COCD_3) +17.4. ^1H NMR 3.78 (s, 6H, OCH_3), 5.90–6.10 (m, 2H, Ar), 7.20 (b, 3H, OH, P(O) $(OH)_2$). ^{13}C NMR 55.88 ($\underline{O}CH_3$), 56.19 (OCH_3), 91.10 (d, 8.5 Hz), 94.65 (d, 12.3 Hz), 95.49 (d, 183.9 Hz), 164.67, 165.35 (d, 5.8 Hz), 166.86.

Analysis: Calcd. for $C_8H_{11}O_6P$: C, 41.02; H, 4.70; P, 13.25.
Found: C, 40.42; H, 4.58; P, 13.11.

Di-t-butyl(2-di-t-butoxyphosphinyl)-3,5-dimethoxyphenyl Phosphate (**3**). This was prepared as reported earlier for di-t-butyl 2-(di-t-butoxyphosphinyl)phenyl phosphate.[2] Starting with 30 mmol of **2d**, the yield of **3** was 12.5 g (77%), mp. 87–88°C. ^{31}P NMR +3.13 (d, 2.44 Hz), −16.78 (d, 2.44 Hz). ^1H NMR 1.45 and 1.50 (2 s, 36H, $C(CH_3)_3$), 3.78 and 3.80 (2 s, 6H, OCH_3), 6.20 (dd, $^4J_{H-P}$ = 4.5 Hz, $^4J_{H-H}$ = 2 Hz, 1H), 6.85–7.00 (m, 1H). ^{13}C NMR 30.02 (d, 4.4 Hz), 30.50 (d, 4.4 Hz), 55.51 (OCH_3), 56.17 (OCH_3), 81.95 (d, 7.3 Hz), 83.99 (d, 7.3 Hz), 95.38 (d, 9.3 Hz), 97.00 (d, 9.2 Hz), 105.60 (dd, 195.5 Hz, 10.5 Hz), 155.91 (d, 6.4 Hz), 163.87, 164.31.

Analysis: Calcd for $C_{24}H_{44}O_9P_2$: C, 53.53; H, 8.18; P, 11.52.
Found: C, 53.88; H, 8.28; P, 11.52.

Rearrangement of 3 on Treatment With LDA. n-Butyl-lithium (15.6 mL of 1.6 M in hexane, 25 mmol) was added to a stirred solution of diisopropylamine (2.5 g, 25 mmol) in THF (15 mL) at −78°C under an argon atmosphere. After 30 min., a solution of **3** (6.75 g, 12.5 mmol) in THF (15 mL) was added dropwise with a syringe. The mixture was stirred at −78°C for 1 h and then allowed to reach rt. After 2 h, the reaction mixture was carefully poured into a mixture of saturated aq. NH_4Cl (100 mL) and diethyl ether (150 mL). The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated on a rotary evaporator to dryness. ^{31}P NMR of the crude product showed two signals at +13.57 and +8.54 in 9:1 ratio.

Tetra-t-butyl(2-hydroxy-4,6-dimethoxy-1,3-phenylene)bis(phosphonate) (**4**). The crude product was dissolved in CH_2Cl_2 and pet. ether was added until it became turbid. The precipitated solid was collected by filtration and crystallized from CH_3CN. The yield was 4.0 g (59%), mp. 160–162°C (shrinks). ^{31}P NMR +13.60. ^1H NMR 1.36 (s, 36H, $C(CH_3)_3$), 3.78 (s, 6H, OCH_3), 5.5 (t, $^4J_{H-P}$ = 5 Hz, 1H). ^{13}C NMR 30.44, 54.92 (OCH_3), 80.51 (t, 3.6 Hz, $C(CH_3)_3$), 80.74 (t, 10.1 Hz), 101.80 (dd, 193.00 Hz, 10.5 Hz), 168.32, 177.80 (t, 8.0 Hz).

Analysis: Calcd for $C_{24}H_{44}O_9P_2$: C, 53.53; H, 8.18; P, 11.52.
Found: C, 53.24; H, 8.03; P, 11.46.

The filtrate from the CH_2Cl_2/pet. ether crystallization on standing deposited slowly a white solid, 0.4 g (6%, unidentified isomer of 4), mp. 145°C (effervesces). ^{31}P NMR +8.49. ^1H NMR 1.42 (s, 36H), 3.86 (s, 6H, OCH_3), 5.90 (t, 5 Hz, 1H). ^{13}C NMR 30.32 (d, 4.0 Hz), 55.59 (OCH_3), 82.59 (d, 7.3 Hz), 86.73 (t, 9.3 Hz), 99.30 (2 m, approx. J = 193.5 Hz, 7.5 Hz), 166.35 (t, 5.9 Hz), 167.39.

Analysis: Calcd. for $C_{24}H_{44}O_9P_2$: C, 53.53; H, 8.18; P, 11.52
Found: C, 53.42; H, 8.14; P, 11.41.

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