Metalation-Induced Migration of Phosphorus from Nitrogen to Carbon

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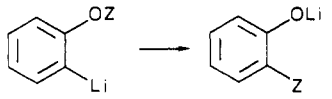
Phosphoric *N*-phenylamides undergo lithiation-induced rearrangement involving the fission of the P–N bond and the migration of phosphorus to the ortho aromatic carbon atom. In the *O*-phenyl *N*-phenylamido esters the migration to the phenolic ring preceeds that occurring at the aniline moiety. The reaction is illustrated by the preparation of the ortho-substituted aromatic phosphonic and phosphinic esters, as well as tertiary phosphine oxides. NMR (^{1}H, ^{13}C, ^{31}P) spectroscopic data are reported for all compounds studied.

Metalation-induced migration from oxygen to the aromatic carbon atom in the ortho-lithiated derivatives of phenol (eq 1) is a well-documented process for such electrophilic groups Z as R_3Si,[1] C(O)R,[2] or $C(O)NR_2$.[3] Single[4]



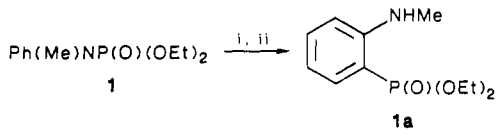
(1)

and double[5] migration of phosphorus in the ortho-lithiated derivatives of dialkyl aryl (Z = P(O)$(OR)_2$) and diaryl alkyl (Z = P(O)(OR)(OAr)) phosphates offers a convenient route to (2-hydroxyaryl)phosphonic and bis(2-hydroxyaryl)-phosphinic systems.

In this paper we report our results obtained by applying this methodology to *N*-arylphosphoramidate derivatives. In these compounds, the fission of the phosphorus–nitrogen bond and the formation of a phosphorus–carbon bond should lead to the preparation of the *o*-amino-substituted aromatic phosphonates, phosphinates, and tertiary phosphine oxides.

Results and Discussion

When diethyl *N*-methyl-*N*-phenylphosphoramidate (**1**) was treated with lithium diisopropylamide (LDA), diethyl [2-(*N*-methylamino)phenyl]phosphonate (**1a**) was obtained (eq 2); thus we have demonstrated the ability of phosphorus to undergo the metalation-induced migration from nitrogen to carbon atom. Although the IR and ^{1}H NMR

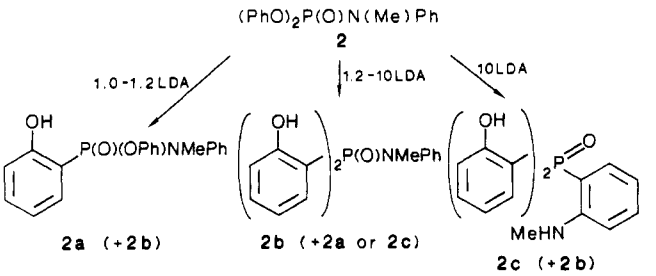


1 **1a** (2)

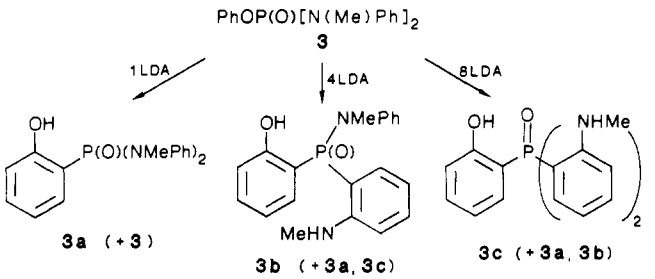
(i) LDA, THF; (ii) aqueous NH_4Cl

spectroscopy as well as MS and elemental analysis results obtained for the reaction product were consistent with the phosphonate structure (**1a**), the unambiguous structural evidence was obtained by the analysis of the ^{13}C NMR spectrum of the product and by comparing it with that reported[4b] for the diethyl (2-hydroxyphenyl)phosphonate (**1b**), obtained by the O→C migration in the corresponding phosphate ester (see Experimental Section).

Scheme I



Scheme II



In order to determine the preference in the O→C vs N→C migration of the phosphoryl group in ortho-lithiated phenyl derivatives, we have next studied the behavior of two phosphoric amido esters: diphenyl *N*-methyl-*N*-phenylphosphoramidate (**2**) and phenyl *N*,*N*′-dimethyl-*N*,*N*′-diphenylphosphordiamidate (**3**). In both substrates the migration could occur at the phenol or *N*-methylaniline ring, and in both cases the reaction could involve single, double, and triple migration pathways. We have found that for both substrates all three migration steps can be achieved with large excess of LDA and that the N→C migration occurs only *after* the O→C migrations have been completed. Phosphoramidate **2** can, depending of the initial [LDA]/[**2**] ratio used, yield the corresponding phosphonic (**2a**), phosphinic (**2b**), and phosphine oxide (**2c**) derivatives (Scheme I).

The phosphordiamidate **3** reacted in a similar manner to **2** and yielded, depending on the initial amount of LDA, variable proportions of the products of a single, double, or triple migration (Scheme II). The relationship between the proportions of individual products obtained from **2** and **3** and the excess of LDA used is shown in Table I. After the isolation and purification of the individual products **2a–c** and **3a–c** their structure was elucidated from the ^{13}C and ^{31}P NMR spectra. In addition, the APT ^{13}C NMR spectra were recorded for products **2b** and **3b**. In agree-

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Table I. Product Composition (mol %)[a] for the Reaction of 2 and 3 with LDA as a Function of the [LDA]/[Substrate] Ratio

[LDA]/[substr]									
2	3	2	3	2a	3a	2b	3b	2c	3c
1.0	1.0	25	29	75	71				
1.2				61		39			
2.4						100			
3.6						100			
	4.0				20.3		76.0		3.7
4.8						ca. 100		trace	
	6.0				18.5		77.3		4.2
	8.0				15.8		79.2		5.0
10.0						85		15	

[a] Determined from the integration of the ^{31}P NMR signals in the spectrum of the reaction mixture; for the preparative yields, see Experimental Section. The follwing values of δ (relative to trimethyl phosphate, TMP) were used: (**2**) −5.9; (**2a**) 19.8; (**2b**) 41.0; (**2c**) 49.6; (**3**) 3.4; (**3a**) 26.0; (**3b**) 41.0; (**3c**) 48.3.

ment with the assignments made, in the APT spectrum of **2b** three quaternary carbon atoms (C_1, C_2, $C_{1''}$) gave positive signals, while the primary (NCH_3) and tertiary (C_3, C_4, C_5, C_6, $C_{2'',6''}$, $C_{3'',5''}$, $C_{4''}$) carbon atoms gave rise to the inverted signals. For **3b** the APT spectrum confirmed the presence of five quaternary carbon atoms (C_1, C_2, $C_{1'}$, $C_{2'}$, $C_{1''}$); resonances of two primary ($NHCH_3$, $PNCH_3$) and eleven tertiary (C_3, C_4, C_5, C_6, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{2'',6''}$, $C_{3'',5''}$, $C_{4''}$) carbon atoms appeared as inverted signals. ^{31}P NMR spectroscopy was also useful in structural determination, as the phosphorus atom becomes progressively more deshielded with each P–C bond introduced in the migration step (see Experimental Section).

In conclusion, we believe that the results of this work, together with those reported by Dhawan and Redmore[4b,5] provide an attractive route to aromatic phosphonic, phosphinic, and phosphine oxide systems with the hydroxy and/or alkylamino groups in the ortho positions. The metalation-induced migration of phosphorus can therefore serve as a synthetic method for the formation of the P–C bond, complementary to the general[7] routes based on the application of aromatic organometallic reagents or diazonium salts.

Experimental Section

Melting points were measured on a Kohfler hotstage melting point apparatus and are uncorrected. Elemental analyses were performed with a Heraeus Universal combustion analyzer. ^{31}P, ^{13}C, and ^1H NMR spectra were obtained with a Varian VXR200 spectrometer operating at 200 MHz. All spectra were recorded in $CDCl_3$ with TMS (for ^{13}C and ^1H) and TMP (for ^{31}P) as internal standards. Mass spectra were recorded on a VG Micromass16F spectrometer coupled with a Carlo Erba gas chromatograph. Preparative TLC was performed on glass plates coated with Merck silica gel 60 F_{254}. Column chromatography was performed with either silica gel (Merck, 60 F_{254}) or aluminium oxide (Merck, 90 active, neutral).

THF was dried by refluxing over sodium wire in the presence of benzophenone and distilled. Diethyl ether was refluxed over P_4O_{10} and distilled. Commercially available reagents such as *N*-methylaniline, triethylamine, diphenyl phosphorochloridate, phenyl phosphorodichloridate, pyridine, and diisopropylamine were distilled immediately before use. All glassware was carefully flame-dried and purged with dry nitrogen. All joints were sealed with a septum and Parafilm. A syringe filled with anhydrous silica gel was used to release pressure. All reactions were carried out in an atmosphere of dry nitrogen.

Substrates. Diethyl *N*-Methyl-*N*-phenylphosphoramidate (1). Diethyl phosphorochloridate (12.9 g, 0.0748 mol) was added dropwise to a solution of *N*-methylaniline (8.0 g, 0.0738 mol) and triethylamine (9.42 g, 0.0933 mol) in THF (30 mL) at 0 °C with stirring and cooling. The mixture was then stirred overnight at room temperature and filtered, and the solvent was removed under reduced pressure. The crude product (17.4 g, 97%) was purified by distillation: 13.9 g, 78%, bp 70 °C (0.2 mm). ^1H NMR: δ 1.10 (6 H, t, J_{H-H} = 7.1 Hz, 2 × $OCCH_3$), 3.12 (3 H, d, J_{P-H} = 8.4 Hz, NCH_3), 3.90 (4 H, quint, J_{H-H} = J_{P-H} = 7.1 Hz, 2 × OCH_2), 7.00–7.30 (5 H, m, C_6H_5). ^{31}P NMR: δ 2.59. MS, *m/e* 243 (M^+). Anal. Calcd for $C_{11}H_{18}O_3NP$: C, 54.31; H, 7.05; N, 5.76. Found: C, 54.15; H, 7.1; N, 5.8.

Diphenyl *N*-methyl-*N*-phenylphosphoramidate (2) was prepared as **1** by using diphenyl phosphorochloridate (7.78 g, 0.029 mol), *N*-methylaniline (2.61 g, 0.024 mol), and triethylamine (5.08 g, 0.050 mol) in ether (20 mL). Crude **2** (94%) was purified by column chromatography (aluminium oxide, CH_2Cl_2/benzene, 1:1): oil, 87%. ^1H NMR: δ 3.20 (3 H, d, J_{P-H} = 10 Hz, NCH_3), 7.10–7.35 (15 H, m, 3 × C_6H_5). ^{31}P NMR: δ −5.87. MS, *m/e* 339 (M^+). Anal. Calcd for $C_{19}H_{18}O_3NP$: C, 67.25; H, 5.36; N, 4.13. Found: C, 67.3; H, 5.2; N, 4.15.

Phenyl *N*,*N*'-dimethyl-*N*,*N*'-diphenylphosphordiamidate (3) was prepared as above, by using phenyl phosphorodichloridate (7.10 g, 0.034 mol), *N*-methylaniline (7.21 g, 0.067 mol), and pyridine (10.5 mL, 0.130 mol) in ether (15 mL). The crude product was purified by column chromatography (aluminium oxide, CH_2Cl_2/benzene, 1:1) and then by crystallization from ether/petroleum ether: 86%, mp 43–44 °C. ^1H NMR: δ 3.15 (6 H, d, J_{P-H} = 10.0 Hz, NCH_3), 7.20 (15 H, m, 3 × C_6H_5). ^{31}P NMR: δ 3.35. MS, *m/e* 352 (M^+). Anal. Calcd for $C_{20}H_{21}O_2N_2P$: C, 68.17; H, 6.01; N, 7.95. Found: C, 68.1; H, 6.0; N, 8.0.

Lithiation-Induced Rearrangements of Phosphoric Amido Esters. General Procedure. Required amount of butyllithium (1.6 M solution in hexane) was added to a solution of the equivalent amount of diisopropylamine in THF (1 mL per 2.85 × 10^{-4} mol of *i*-Pr_2NH) at −78 °C under N_2. The mixture was stirred at this temperature for 30 min, and the solution of the equivalent amount of the organophosphorus substrate in THF (1 mL per 0.00142 mol) was added by means of a syringe. The mixture was stirred at −78 °C for 1 h and then at room temperature for 18 h. Saturated aqueous solution of ammonium chloride (1 mL per 1.42 × 10^{-4} mol) and dichloromethane (1 mL per 8.11 × 10^{-5} mol) were added to the reaction mixture and stirred. The organic layer was separated, washed with water, and dried ($MgSO_4$). After removal of the solvent under reduced pressure the crude product was purified and identified.

Diethyl [2-(methylamino)phenyl]phosphonate (1a): purified by column chromatography (aluminium oxide, dichloromethane/benzene, 1:1), 63%, oil. ^1H NMR: δ 1.20 (6 H, t, J_{H-H} = 7.2 Hz, 2 × $OCCH_3$), 2.82 (3 H, d, J_{H-H} = 5.1 Hz, $NHCH_3$), 3.21 (4 H, quint, J_{H-H} = J_{P-H} = 7.2 Hz, 2 × OCH_2), 6.50–7.50 (4 H, m, C_6H_4). ^{13}C NMR (δ, J_{P-C}; for comparison, the values for the corresponding C atoms in **1b**, taken from ref 4b, are given in parentheses): $OCCH_3$, 16.2, 6.6 Hz (16.1, 7.8 Hz); $NHCH_3$, 29.9, s; OCH_2, 61.9, s (62.5, 5.9 Hz); C_1, 105.5, 178.0 Hz (109.0, 179.7 Hz); C_2, 152.6, 9.0 Hz (161.9, 7.8 Hz); C_3, 110.0, 12.2 Hz (117.4, 11.7 Hz); C_4, 134.1, s (135.1, s); C_5, 114.8, 14.0 Hz (119.4, 13.7 Hz); C_6, 113.2, 7.6 Hz, (131.6, 5.9 Hz). ^{31}P NMR: δ 19.9. MS, *m/e* 243 (M^+). Anal. Calcd for $C_{11}H_{18}O_3NP$: C, 54.31; H, 7.05; N, 5.76. Found: C, 53.8; H, 7.2; N, 6.1.

Phenyl *N*-methyl-*N*-phenyl(2-hydroxyphenyl)phosphonamidate (2a): purified by column chromatography (silica gel, ether/petroleum ether, 1:1), 35%, mp 90–91 °C. ^1H NMR: δ 3.20 (3 H, d, J_{P-H} = 9.5 Hz, NCH_3), 6.70–7.40 (14 H, m, 2 × C_6H_5, C_6H_4), 10.0 (1 H, s, OH). ^{31}P NMR: δ 19.7. MS, *m/e* 339 (M^+). Anal. Found: C, 67.3; H, 5.6; N, 4.1.

***N*-Methyl-*N*-phenylbis(2-hydroxyphenyl)phosphinic amide (2b)**: purified by crystallization from ethanol, 70%, mp 179–181 °C. ^1H NMR: δ 3.10 (3 H, d, J_{P-H} = 10.3 Hz, $PNCH_3$), 6.70 (4 H, m, C_6H_4), 7.00 (10 H, m, 2 × C_6H_5), 11.40 (2 H, br s, 2 × OH). ^{31}P NMR: δ 41.0. MS, *m/e* 339 (M^+). Anal. Found: C, 67.4; H, 5.45; N, 4.1.

Bis(2-hydroxyphenyl)[2-(methylamino)phenyl]phosphine oxide (2c): purified by column chromatography (silica gel, di-

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chloromethane/benzene, 1:1), followed by preparative TLC (silica gel, ethyl acetate), 6%, mp 220–225 °C. ^{1}H NMR: δ 2.80 (3 H, d, J_{H-H} = 4.7 Hz, $NHCH_3$), 6.00 (1 H, br s, NH), 6.60–7.40 (12 H, m, 3 × C_6H_4), 11.30 (2 H, br s, 2 × OH). ^{31}P NMR: δ 49.6. MS, *m/e* 339 (M^+).

***N*,*N*′-Dimethyl-*N*,*N*′-diphenyl(2-hydroxyphenyl)phosphonic diamide (3a)**: purified by column chromatography (silica gel, ether/petroleum ether, 1:1), 51%, mp 122 °C. ^{1}H NMR: δ 3.08 (6 H, d, J_{P-H} = 9.4 Hz, 2 × NCH_3), 6.70–8.40 (14 H, m, 2 × C_6H_5, C_6H_4), 11.20 (1 H, br s, OH). ^{31}P NMR: δ 26.0. MS, *m/e* 352 (M^+). Anal. Found: C, 68.0; H, 5.7; N, 8.2.

***N*-Methyl-*N*-phenyl(2-hydroxyphenyl)[2-(methylamino)phenyl]phosphinic amide (3b)**: purified by column chromatography (silica gel, ether/petroleum ether, 1:1) followed by crystallization from ether/petroleum ether (1:1), 46%, mp 126 °C. ^{1}H NMR: δ 2.70 (3 H, d, J_{H-H} = 5.0 Hz, $NHCH_3$), 3.10 (3 H, d, J_{P-H} = 9.9 Hz, $PNCH_3$), 6.21 (1 H, m, NH), 6.50–7.30 (13 H, m, 2 × C_6H_4, C_6H_5), 11.20 (1 H, s, OH). ^{31}P NMR: δ 41.0. MS, *m/e* 352 (M^+). Anal. Found: C, 68.1; H, 5.7; N, 8.2.

(2-Hydroxyphenyl)bis[(*N*-methylamino)phenyl]phosphine oxide (3c): purified by crystallization from ether/petroleum ether (1:1), 25%, mp 246–247 °C. ^{1}H NMR: δ 2.80 (6 H, d, J_{H-H} = 4 Hz, 2 × $NHCH_3$), 6.30 (2 H, br s, 2 × NH), 6.50–7.50 (12 H, m, 3 × C_6H_4), 10.50 (1 H, br s, OH). ^{31}P NMR: δ 48.5. MS, *m/e* 352 (M^+). Anal. Found: C, 68.0; H, 6.0; N, 8.0.

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Supplementary Material Available: ^{13}C NMR spectroscopic data of substrates **2** and **3** and their rearrangement products (Table S-I) (2 pages). Ordering information is given on any current masthead page.

Selectivity in the Base-Catalyzed Hydrolysis of *p*-Nitrophenyl Esters within a Reversed-Phase Liquid Chromatography Column

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The $^-$OH-catalyzed hydrolyses of *p*-nitrophenyl acetate (**1**) and hexanoate (**2**) were performed with excess $^-$OH on a reversed-phase liquid chromatography column of macroporous 10-μm poly(styrene–divinylbenzene) under HPLC conditions to give pseudo-first-order rate constants k_ψ. The maximum value of k_ψ^1/k_ψ^2 was ≥25, and the reactivity difference was attributed to different rates of desorption of **1** and **2** from the polymer surface into the mobile phase, where $^-$OH was localized. The results demonstrated that a polymer-based, reversed-phase HPLC column can impart selectivity to the reactions of an ionic, inorganic reagent with neutral, organic substrates that have comparable intrinsic reactivities but different relative hydrophilic/lipophilic characters.

Reversed-phase high-performance liquid chromatography (HPLC) columns are used routinely in analytical and preparative separations. However, they have been employed only infrequently as reaction media.[1] Recently, we reported a study[2] of the aromatic chlorination of a series of alkyl phenyl ethers by chlorine water on a reversed-phase column of an alkylsilane-bonded silica; substrate and regioselectivity were obtained. Herein, we report a study of the $^-$OH-catalyzed hydrolyses of *p*-nitrophenyl acetate (**1**) and hexanoate (**2**) to *p*-nitrophenoxide and acetate/hexanoate on a 15 cm × 4.1 mm (i.d.) column of macroporous 10-μm poly(styrene–divinylbenzene) (PRP-1)[3] under HPLC conditions.

The HPLC reaction procedure for an individual ester, summarized in Figure 1, is as follows. First, at 23 ± 1 °C the column was equilibrated with a MeCN–H_2O mixture or H_2O. Then, at time (t) = 0, 5.0 μL of 0.030 M **1** (**2**) in MeCN was injected, and the eluant at a flow rate of 0.5 mL/min was changed to 100% H_2O, if necessary, to ensure immobilization of **1** (**2**) within the column by its sorption to the polymer. At t = 13 min, 2.0 mL of aqueous 0.50 M NaOH was injected, and the flow rate was either left at 0.5 mL/min or changed to a value between 0.30 and 4.0 mL/min. At t = 20 min, the flow rate was returned to 0.5 mL/min, and the MeCN content of the eluant was increased linearly to 60% (v/v) during 6 min for **1** or to 100% during 10 min for **2**, in order to elute unreacted ester. The same procedure was used for competition runs, except that at t = 0, 5.0 μL of a MeCN solution 0.015 M each in **1** and **2** was injected, and at t = 20 min the MeCN content was increased to 100% MeCN during 15 min. With these procedures, *p*-nitrophenoxide eluted first, followed by

Table I. Individual Hydrolyses of 1 and 2[a]

entry	substrate	equilibration solvent (v/v)	retention time of 1/2, min[b]	10^3k_ψ, s^{-1}[c]
1	1	H_2O	45.6	5.0 ± 0.3
2	1	10:90 MeCN–H_2O	45.3	4.3 ± 0.3
3	1	25:75 MeCN–H_2O	45.4	4.0 ± 0.3
4	1	40:60 MeCN–H_2O	41.7	11 ± 0.6
5	1	50:50 MeCN–H_2O	40.8	16 ± 0.8
6[d]	1	10:90 MeCN–H_2O	31.5	12 ± 0.6
7[d]	1	50:50 MeCN–H_2O	56.5	4.9 ± 0.3
8	2	H_2O	44.7	2.0 ± 0.2
9	2	25:75 MeCN–H_2O	44.5	1.4 ± 0.2
10	2	40:60 MeCN–H_2O	44.2	0.4 ± 0.1
11	2	50:50 MeCN–H_2O	44.4	0.4 ± 0.1
12	2	70:30 MeCN–H_2O	42.8	0.7 ± 0.1
13	2	80:20 MeCN–H_2O	40.7	0.9 ± 0.1

[a] The procedure of Figure 1 was used unless noted otherwise. [b] For each entry, the value represents the average of the retention times from t = 0 for the separate runs in the kinetic determination; average deviation 0.9 min for entry 6 and ≤0.3 min for the others. [c] Averages of duplicate determinations. [d] A modification of the program of Figure 1 was used; see the text for details.

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