Heteroatom Chemistry
Volume 1, Number 3, 1990

Ambident Electrophilicity of *O*,*O*-Diethyl-*S*-phenyl Phosphorothiolate

Hendrik V. Garbers and Tomasz A. Modro*

Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

Received 28 November 1989.

ABSTRACT

Reaction between O,O-*diethyl-*S-*phenyl phosphorothiolate and lithium dialkylamides results in the displacement of the PhS substituent by the R_2N group. With Grignard reagents, the same substrate gives products of the nucleophilic substitution at both the phosphorus and the sulfur atom.*

Treatment of the *O*-phosphorylated phenols, ArO-$P(O)X_2$ (X = ArO, RO, R), with lithium diisopropylamide (LDA) results in the lithiation at the ortho position of the aromatic ring, followed by the migration of the phosphorus group to the ortho carbon, therefore it opens the synthetic route to the 2-hydroxyarylphosphonic systems [1]. This reaction operates also for *N*-arylphosphoroamidates, yielding, after the nitrogen-carbon migration of the $P(O)X_2$ group, the 2-aminoarylphosphonic, phosphinic, or phosphine oxide products [2]. We report now the results obtained when the same approach was applied to O,O-diethyl-*S*-phenyl phosphorothiolate (**1**), the potential precursor for the diethyl 2-mercaptophenylphosphonate [3].

RESULTS AND DISCUSSION

Treatment of (**1**) with LDA under conditions analogous to those applied for O-phosphorylated phenols, or *N*-phosphorylated anilines, gave no evidence for either the *o*-lithiation (quenching of the reaction mixture with D_2O gave no evidence for the incorporation of deuterium to the aromatic ring), or for the subsequent S-C migration. When the acid workup of the reaction product was replaced by careful neutralization, we found that the product consisted of diethyl *N*,*N*-diisopropylphosphoramidate (**2a**), thiophenol (**3**), and phenyl disulfide (**4**). The reaction was repeated using *N*-lithium derivatives of piperidine and 2,6-dimethylpiperidine; in all cases the reaction yielded the corresponding phosphoramidates **2** as the only phosphorus-containing products (Equation 1).

$$\underset{\mathbf{1}}{(EtO)_2P(O)SPh} + R_2NLi \rightarrow$$

$$(EtO)_2P(O)NR_2 + PhSLi/\underset{\mathbf{4}}{(PhSSPh)} \quad (1)$$

2a, R = iPr
2b $R_2 = (CH_2)_5$
2c $R_2 = (CHMeCH_2)_2CH_2$

It is clear that, with respect to **1**, LDA (generally considered as a strong, but weakly nucleophilic, base [5]) behaves in fact as a strong nucleophile attacking the "hard" phosphoryl center. It is worthwhile to point out that this $S_N2(P)$ substitution cannot be achieved by a free amine; **1** was recovered unchanged after treatment with iPr_2NH for 24 h at room temperature.

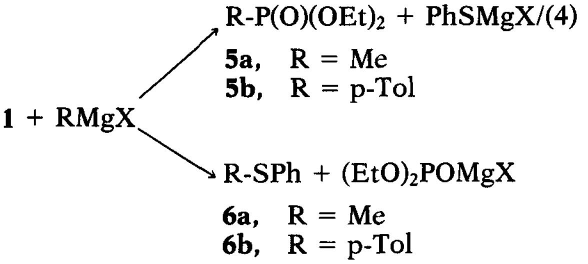
Reactions of **1** with Grignard reagents also did not result in the isomerisation, but in nucleophilic substitution. In this case, however, the reaction was much more complicated and led to the formation of a complex mixture of products. The nuclear magnetic resonance (NMR) (^1H and ^{31}P) spectroscopy, gas chromatography (GC) analysis of the reaction mixture, and comparison with the data obtained for the independently prepared standards, allowed qualitative and quantitative determination of the reaction products. The analysis showed the incorporation of Grignard reagents to the phosphorus (formation of diethyl phosphonic esters, **5**),

---

* To whom correspondence should be addressed.

1042-7163/90/$3.50 + .25

and to the sulfur atom (formation of phenyl thioethers, **6**) (Equation 2).



(2)

The additional products of reaction (2) were ethyl phenyl sulfide, EtSPh, and some ionic, water-soluble phosphate products, resulting from the well-known [6] nucleophilic dealkylation of the P(O)OEt function by the thiophenolate ion. Although phosphonates **5** represented the major reaction products, the obtained results indicate that, with respect to organomagnesium reagents, **1** offers, in addition to the phosphorus atom, also the thiolate sulfur as an alternative electrophilic center. Similar ambident (P/S) electrophilicity in the Grignard reaction was reported for *S*-esters of diphenylphosphinothioic acid [7]. Thioethers **6** could, however, also result from a secondary reaction involving unreacted Grignard reagent and **4** (Equation 3), produced by the spontaneous oxidation of the thiophenolate ion, released upon the substitution at phosphorus.

$$\mathbf{4} + \mathrm{RMgX} \rightarrow \mathbf{6} + \mathrm{PhSMgX} \qquad (3)$$

Reaction (3) was in fact employed in this work for the preparation of the authentic samples of sulfides **6**. If **6** were to result from such subsequent reaction, the ratio **5**/**6** should *decrease* with the total conversion of **1**. We determined this ratio as a function of reaction progress by sampling the reaction mixtures and determining the **5**/**6** ratios by GC; the average value of 3.3 ± 1.1 was obtained, with no trend in the individual values of the ratio. We believe therefore that products **6** are the consequence of the ambident electrophilic character of substrate **1**, in which the phosphorus as well as sulfur atom (and, in some cases, the α-carbon atom of an ester group) offer reactive centers for a nucleophilic attack. The electrophilic reactivity of the aryl derivatives of phosphoric acid is therefore a limiting factor in the synthetic scope of the metalation/migration process.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AC 300 MHz spectrometer in $CDCl_3$ with TMS (or trimethyl phosphate in case of ^{31}P) as internal standard. GC analysis was carried out on a Carlo Erba Fractovap 2150 instrument using a 3% OV-17 (2m) column, and N_2 as a carrier gas. The oven temperature was 175–220°C. Melting points were obtained on a Gallenkamp apparatus, and are uncorrected. Mass spectra were recorded on a Varian MAT-212 double focusing direct inlet spectrometer at an ionization potential of 70 eV. Only the values for M^+ are given. "Bulb to bulb" distillations were performed on a Buchi GKR-50 apparatus. For column chromatography Merck Kieselgel 60 (0.063–0.200 mm) was used as a stationary phase. Thin-layer chromatography (TLC) was carried out using precoated Kieselgel 60 F254 aluminium plates. Solvents and commercially available substrates were purified by conventional methods immediately before use. All reactions involving organometallic reagents were carried out in an atmosphere of dry nitrogen. Authentic samples of compounds required for the comparison with the reaction products were prepared by the reported procedures; in all cases their properties agreed very well with those given in the literature.

O,O-Diethyl-*S*-phenyl phosphorothiolate (**1**) was prepared from phenyl disulfide and sodium diethyl phosphite according to the literature procedure [8]. We have found, however, that the product prepared according to [8] contained, after distillation, some phenyl disulfide and phenyl ethyl sulfide (the latter formed by deethylation by the PhS^- ion). When distillation of the crude product was replaced by column chromatography (chloroform), pure **1** was obtained as a second fraction with 64% yield. ^{1}H NMR: δ 1.22 (6H, t, J_{HH} 7.1 Hz, Me of EtO); 4.11 (4H, m, CH_2 of EtO); 7.26 (3H, m, H_{arom}); 7.49 (2H, m, H_{arom}). ^{31}P NMR; δ 20.5. MS: m/z 246 (M^+, 94%). Anal. Calcd for $C_{10}H_{15}O_3PS$ (246.3): C, 48.77; H, 6.14. Found: C, 48.9; H, 6.1%.

Reactions of 1 with Lithium Dialkylamides

n-BuLi (1.6 M solution in hexane) was added to the solution of the amine in THF at −78°C, stirred for 30 min, then the solution of **1** in THF was added, and the mixture was stirred for 18 h at −78°C, and for 24 h at room temperature. Aq. trifluoroacetic acid was added, most of THF was removed, and the product was extracted with dichloromethane. After drying and removal of the solvent, crude products were purified by distillation.

2a (65%), purified by "bulb to bulb" distillation (oven temp. 80–90°C/1 mm); ^{1}H NMR: 1.10 (12H, d, J_{HH} 6.7 Hz, Me of iPr); 1.18 (6H, t, J_{HH} 7.2 Hz, Me of OEt); 3.30 (2H, m, CH of iPr); 3.86 (4H, m, CH_2 of OEt). ^{31}P NMR: δ 5.99. MS: m/z 237 (M^+, 5%).

2b (53%), purified by "bulb to bulb" distillation (oven temp. 90–100°C/0.15 mm); ^{1}H NMR: δ 1.20 (6H, t, J_{HH} 7.1 Hz, Me of OEt); 1.44 (6H, m, CH_2 of piperidyl group); 2.98 (4H, m, NCH_2): 3.91 (4H, m, CH_2 of OEt). ^{31}P NMR: δ 6.56. MS: m/z 221 (M^+, 3%).

2c (45%), purified by "bulb to bulb" distillation (oven temp. 110–120°C/1.5 mm); ^{1}H NMR: δ 1.21 (6H, t, J_{HH} 7.1 Hz, Me of OEt); 1.21 (6H, d, J_{HH} 6.4 Hz, Me of 2,6-dimethylpiperidyl group); 1.34–1.76

(6H, m, CH_2 of piperidyl ring); 3.73 (2H, m, 2 × CH of piperidyl ring); 3.92 (4H, m, CH_2 of OEt). ^{31}P NMR: δ 7.62. MS: m/z 249 (M^+, 2%).

4 was purified by column chromatography (benzene/acetone, 9 : 1), and by crystallization from ethanol; mp 61–62°C. All products gave satisfactory elemental analysis (C, H, N), and their spectroscopic and GC characteristics were identical to those obtained for independently prepared samples.

*Reactions of **1** with Grignard Reagents*

The reactions were carried out in a standard way, and the crude products were examined by NMR (^1H and ^{31}P) spectroscopy and subjected to GC analysis. The individual products were identified and quantitatively determined by comparison with the independently prepared standards.

5a (43%); ^1H, NMR: δ 1.05 (6H, t, J_{HH} 7.1 Hz, Me of EtO); 1.18 (3H, d, J_{HP} 17.5 Hz, MeP); 3.82 (4H, m, CH_2 of EtO). ^{31}P NMR: δ 28.01.

5b (53%); ^1H NMR: δ 1.62 (6H, t, J_{HH} 7.1 Hz, Me of EtO); 2.32 (3H, s, MeAr); 3.94 (4H, m, CH_2 of EtO); 7.11 (2H, m, H_{arom}); 7.54 (2H, m, H_{arom}). ^{31}P NMR: δ 17.10.

6a (24%); ^1H NMR: δ 2.49 (3H, s, MeS); 7.20 (5H, m, PhS). MS: m/z 124 (M^+, 17%).

6b (16%); ^1H NMR: δ 2.42 (3H, s, MeAr); 7.19–7.42 (9H, m, H_{arom}). MS: m/z 200 (M^+, 12%).

Ethyl phenyl sulfide (5–10%); ^1H NMR: δ 1.44 (3H, t, J_{HH} 7.3 Hz, Me of EtS); 2.95 (2H, q, J_{HH} 7.3 Hz, CH_2 of EtS); 7.20 (5H, m, Ph).

*Determination of the **5b/6b** Ratio as a Function of Reaction Time*

An equimolar amount of **1** was added to the solution of *p*-tolymagnesium bromide in ether under nitrogen during 5 min. Samples of the reaction solution were withdrawn at certain time intervals, and followed by the workup involving adding the sample to an equal volume of 5% aq. HCl, separation, drying, and the removal of the solvent. The residue was then dissolved in $CHCl_3$ and subjected to the GC analysis. The following values of the **5b/6b** ratio were obtained after different times (in min): 5.3 (20); 3.4 (80); 2.2 (200); 2.1 (305); 2.5 (1305); 3.7 (1485); 4.0 (1595).

ACKNOWLEDGMENT

Financial assistance of the University of Pretoria and the Foundation for Research Development (CSIR) is gratefully acknowledged.

REFERENCES

[1] L. S. Melvin, Tetrahedron Lett., 2, 1981, 3375; B. Dhawan, D. Redmore, J. Org. Chem., 49, 1984, 4018; 51, 1986, 179; Synth. Comm., 17, 1987, 465.
[2] D. Hellwinkel, G. Hoffman, F. Lammerzahl, Tetrahedron Lett., 1977, 3241; Chem. Ber., 116, 1983, 3375; A. M. Jardine, S. M. Vather, T. A. Modro, J. Org. Chem., 53, 1988, 3983.
[3] Unknown compound. The analogous S-C migration of the Me_3Si group was reported for the ortho-lithiated phenyltrimethylsilyl sulfide [4].
[4] F. P. Bailey, R. Taylor, J. Chem. Soc. B, 1971, 1446; J. Heinicke, E. Nietzschmann, A. Tzschach, J. Organomet. Chem., 1983, 243, 1; D. Hellwinkel, R. Lenz, Chem. Ber., 1985, 118, 66.
[5] B. J. Wakefield, Organolithium Methods. Academic Press, London, 1988, Chapter 3.2. See, however, exceptions: J. L. Herrmann, G. R. Kieczykowski, R. H. Schlessinger, Tetrahedron Lett., 1973, 2433.
[6] G. W. Daub, E. E. van Tamelen, J. Am. Chem. Soc., 99, 1977, 3526.
[7] K. Goda, R. Okazaki, K. Akiba, N. Inamoto, Bull. Chem. Soc. Jpn., 51, 1978, 260.
[8] J. Michalski, J. Wasiak, J. Chem. Soc., 1962, 5056.