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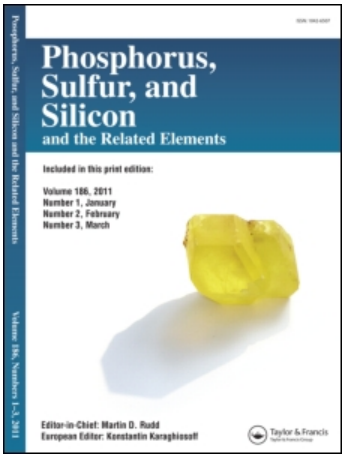

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
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To cite this Article Koziara, A. and Zwierzak, A.(1999) 'A NEW NITROGEN-TO-OXYGEN PHOSPHORYL MIGRATION', Phosphorus, Sulfur, and Silicon and the Related Elements, 149: 1, 15 — 21
To link to this Article: DOI: 10.1080/10426509908037018
URL: http://dx.doi.org/10.1080/10426509908037018

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Phosphorus, Sulfur and Silicon, 1999, Vol. 149, pp. 15-21
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A NEW NITROGEN-TO-OXYGEN PHOSPHORYL MIGRATION

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(Received 01 December, 1998)

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The reaction of diethyl N-acetyl-N-methylphosphoramidate **1** with aldehyde in the presence of LDA at −70°C results in the formation of the unstable oxyanion **6** which undergoes intramolecular rearrangement involving migration of a phosphoryl group from nitrogen to oxygen affording an amide anion **8.** Subsequent proton transfer in **8** followed by elimination of phosphate anion provides the respective α,β-unsaturated N-methylcarboxamide **4.** The formation of considerable amounts of diethyl N-methylphosphoramidate **5** is also always observed.

Keywords: Diethyl N-acetyl-N-methylphosphoramidate; phosphoryl migration; N-methylcarboxamides; diethyl N-methylphosphoramidate

INTRODUCTION

Migration of the phosphoryl group from oxygen to the vicinal hydroxyl group in the 1,2-diol system has been the subject of extensive studies[1,2]. A similar migration of the phosphoryl group from sulfur to oxygen has been observed in the reaction of oxiranes with phosphorus monothioacids[3,4], in the reactions of carbanions containing the thiophosphoryl group with carbonyl compounds[5], and by reduction of S-(β-oxoalkyl) thiophosphates with sodium borohydride[6] to give episulfides or olefines as the final result. Analogous transphosphorylations involving selenium-to-oxygen[7] and tellurium-to-oxygen[8] migrations have been also postulated. The migration of the intact phosphoryl group to a vicinal nucleophile was first satisfactorily rationalized by Hamer[3] on the assumption of a pentacovalent intermediate with the phosphorus at the

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centre of a trigonal bypyramid in which pseudorotation leading to location of the sulfur atom in the apical position and subsequent cleavage of the P-S bond is permitted. This mechanistic concept was then proposed also by other authors[9] and recently has been verified experimentally[10]. Transphosphorylation involving migration of a phosphoryl group from nitrogen-to-oxygen was also observed when N-diisopropylphosphoryl derivatives of serine and threonine methyl esters were refluxing with diluted hydrochloric acid[11]. To the best of our knowledge other rearrangements of this type have not been reported so far.

RESULTS AND DISCUSSION

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In the course of our studies on the chemistry of N-acylphosphoramidates we decided to investigate nucleophilic addition of diethyl N-acetyl-N-methylphosphoramidate anion **1′** to aldehydes as a possible method of carbon chain elongation. Contrary to our expectations we did not observe the formation of β-hydroxyketones **3** as a result of nucleophilic addition of the enolate anion **1′** to the carbonyl group of aldehyde. Instead an intramolecular rearrangement involving P-N bond rupture took place and N-methyl-α,β-unsaturated carboxamides **4** were produced contaminated always with considerable amounts of diethyl N-methylphosphoramidate **5** (Scheme 1). When diethyl N-acetyl-N-methylphosphoramidate **1** was allowed to react at −70°C with an equimolar amount of LDA in tetrahydrofuran deprotonation at the acetyl group took place and the respective lithium enolate **1′** was obtained. The reaction of this salt with an aldehyde after usual work-up with aqueous ammonium chloride solution resulted in isolation and/or spectroscopic identification of a mixture of α,β-unsaturated carboxamide **4a-d** and diethyl N-methylphosphoramidate **5.** From the reactions of **1′** with benzaldehyde **2a** and p-nitrobenzaldehyde **2b** N-methylcinnamamide **4a** and N-methyl-p-nitrocinnamamide **4b** were isolated in pure form and identified by comparsion with authentic samples prepared by an independent procedure. N-Methylbutyramide **4c** and N-methylisobutyramide **4d** were identified by inspection of the ^{1}H NMR spectra of crude reaction products. N-Methylcarboxamides **4a-d** were always accompanied by large amounts of diethyl N-methylphosphoramidate **5** which could be easily identified spectroscopically (characteristic doublet of **NH-CH$_3$** protons at $\delta = 2.63$ ppm, $^3J_{P\text{-}H} = 12.0$ Hz). The

progress of the reaction between lithium enolate of diethyl N-acetyl-N-methylphosphoramidate **1′**and benzaldehyde **2a** could be easily followed by means of ^{31}P NMR spectroscopy in THF/$CDCl_3$ solution. The disappearance of the signal at $\delta = 3.53$ ppm characteristic for **1** was observed instantaneously after addition of LDA. The new signal of lithium enolate **1′** at 11.38 ppm vanished after addition of benzaldehyde and was replaced by a broad signal of high intensity at $\delta = 0.60$ ppm corresponding to lithium diethyl phosphate **10** and a weaker signal at $\delta = 10.91$ ppm which has been ascribed to the lithium salt of diethyl N-methylphosphoramidate **5′** by comparsion with an authentic specimen. After quenching the reaction mixture with aqueous ammonium chloride solution the organic phase contained only N-methylcinnamamide **4a** and diethyl N-methylphosphoramidate **5** (δ $^{31}P = 10.69$ ppm). On the basis of this experimental evidence we propose the following reaction mechanism presented in the Schemes 1 and 2. The first step is the nucleophilic attack of lithium enolate **1′** on the carbonyl group of the aldehyde **2** resulting in the formation of the oxyanion **6.** The intramolecular nucleophilic substitution at phosphorus results from the attack of the anionic oxygen atom on the phosphorus in the phosphoryl group of **6** and leads to the formation of the pentacoordinate system **7a** (Scheme 2). In order to fulfill the rule of apical entry and apical departure, the pseudorotation **7a** → **7b** is required, with the oxygen anion as a pivot. The pentacoordinate intermediate **7b** desintegrates then by opening the six-membered ring to give **8**, followed by proton transfer from the α-carbon to the anionic nitrogen with the formation of **9**, and finally by elimination of diethylphosphate anion affording **10** and **4.** Spontaneous decomposition of lithium enolate **1′**, probably undergoing partial fragmentation under the reaction conditions (Scheme 3), is the source of diethyl N-methylphosphoramidate **5.** It was found in an independent experiment that metalation of **1** with LDA at –70°C in tetrahydrofuran followed by heating **1′** thus formed to room temperature and quenching it with aqueous ammonium chloride solution gives a mixture containing ca. 40% of **1** and 60% of diethyl N-methyphosphoramidate **5.**

EXPERIMENTAL

^{31}P NMR spectra were recorded on a Bruker HFX-90 spectrometer operating at 36.43 MHz and on a Bruker AVANCE DPX-250 spectrometer at

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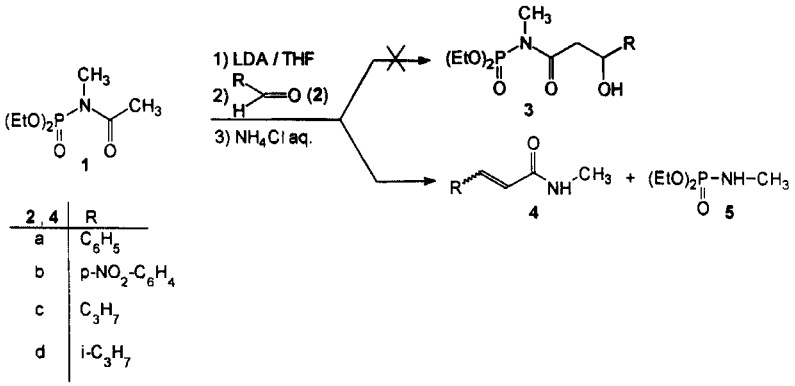

2, 4	R
a	C_6H_5
b	p-NO_2-C_6H_4
c	C_3H_7
d	i-C_3H_7

SCHEME I

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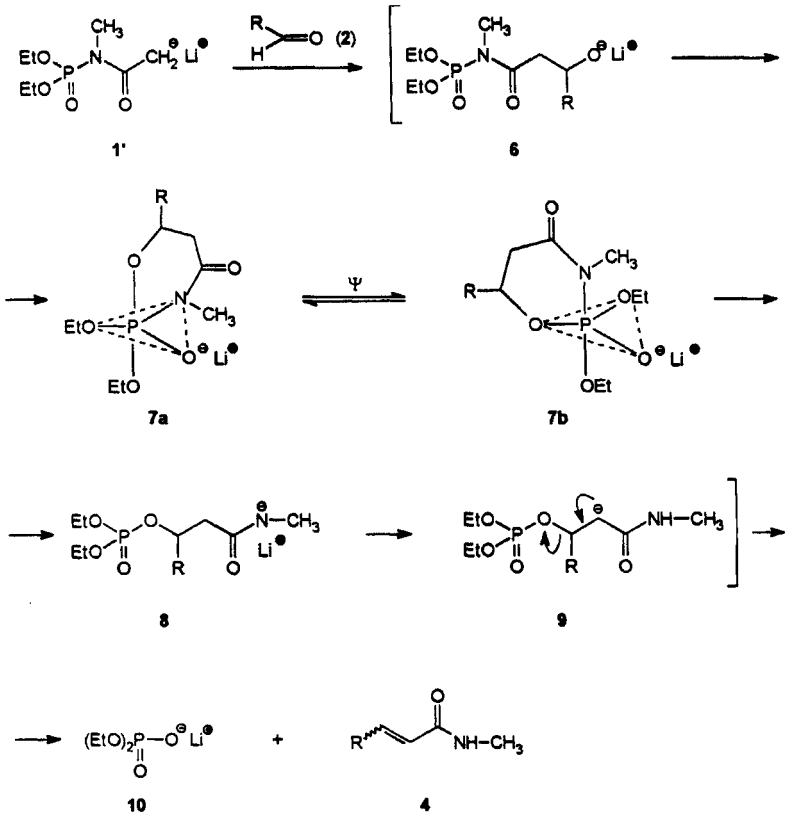
101.255 MHz (when progress of the reaction was followed). Positive chemical shifts are downfield from ext. H_3PO_4. ^1H NMR spectra were recorded at 80 MHz with a Tesla 587 FT spectrometer ($CDCl_3$ solns/TMS int.). Melting points were determined in open capillaries and were uncorrected.

Diethyl N-acetylphosphoramidate

Was prepared as described previously[12].

Diethyl N′-acetyl-N-methylphosphoramidate 1

A solution of diethyl N-acetyl-phosphoramidate (25.3 g, 0.13 mol) in benzene (250 mL) was slowly added dropwise with stirring to the suspension of sodium hydride (3.12 g, 0.13 mol) in benzene (250 mL). Tetrabutylammonium bromide (TBABr 2.09 g, 6.5 mmol) was then added and the mixture was stirred at room temperature until evolution of hydrogen ceased. Methyl iodide (7.68 g, 0.195 mol) was then added and the mixture was refluxed for 3h. It was then cooled to room temperature and water (30 mL) was added. The organic phase was separated, dried ($MgSO_4$), and evaporated. The residue was distilled *in vacuo*. B.p. 69–71 %/0.3 torr. Yield: 11.0 g (40%). The product was spectroscopially pure. ^{31}P NMR: δ=3.53 ppm.



SCHEME 2

Diethyl N-methylphosphoramidate 5

Was obtained following the procedure published earlier[13].

N-Methylcinnamamide 4a and N-Methyl-p-nitrocinnamamide 4b

The mixture of cinnamic or p-nitrocinnamic acid (3.4 mmol), O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TBTU, 1.2 g, 3.74 mmol), methylamine hydrochloride (0.253 g, 3.74 mmol), triethylamine (1.135 g, 11.2 mmol), and CH_2Cl_2(2 mL) was stirred ar room temperature for 24 h. It was then evaporated, the residue was dissolved in

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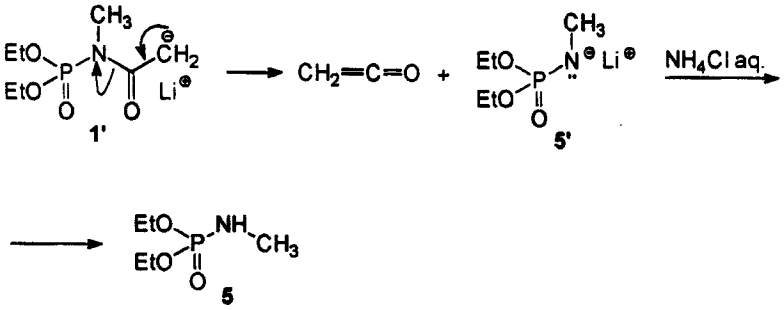

SCHEME 3

$CHCl_3$ (35 mL) and washed successively with 10% $NaHSO_4$ aq. (3 × 5 mL), $NaHCO_3$ aq. (3 × 5 mL), and water (3 × 5 mL). Evaporation of solvent left a crystalline residue which was washed with ether (20 mL). Yields: 55% for **4a** and 60% for **4b.**

N-Methylcinnamamide 4a

M.p. 109–110°C; lit[14] 111–112°C; ^{1}H NMR: δ = 2.94 (d, 3H, J = 4.85, $NHCH_3$), 6.09 (br s, 1H, NH), 6.42 and 7.63 (2d, 2H, J = 15.7, = CH), 7.26 – 7.48 (m, 5H, ArH).

N-Methyl-p-nitrocinnamamide 4b

M.p. 204 – 206°C; lit.[15] 203 – 204°C; ^{1}H NMR: δ = 2.97 (d, 3H, J = 4.85, NH-CH_3), 6.49 and 7.68 (2d, 2H, J = 15.6, = CH), 7.52–8.37 (m, 5H, ArH).

Reactions of diethyl N-acetyl-N-methylphosphroamidate anions 1′ with aldehydes 2 a-d.

General procedure

LDA Solution was freshly prepared by addition of a 1.6 M solution of butyllithium in hexane (16 mL, 25 mmol) to the solution of diisopropylamine (2,53g, 25 mmol) in THF (25 mL) at −70°C. The temperature was raised to −15°C for 15 min. and then the solution was cooled again to −70°C. The solution of diethyl N-acetyl-N-methylphosphoramidate **1** in

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THF (20 mL) was added dropwise with stirring at this temperature. Stirring was continued for 15 min., then aldehyde **4 a-d** (25 mmol) in THF (5 mL) was added and the mixture was stirred at −70°C for an additional 15 min. The temperature was then raised to 20°C and stirring was continued for 0.5 h. The resultant mixture was poured into saturated aqueous solution of NH_4Cl (100 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2(3 × 20 mL) and the extracts were combined with the organic phase. After removal of solvent under reduced pressure the residual crude products were analyzed by ^1H NMR spectroscopy. The amounts of N-methylcarboxamides **4 a-d** and diethyl N-methylphosphoramidates **5** were calculated by integration of the NH-CH_3 signals in **4** (at δ = 2.85 – 2.97 ppm) and in **5** (at δ = 2.63 ppm). The results were as follows: **4a : 5** = 54 : 46; **4b : 5** = 40 : 60; **4c: 5** = 55 :45; **4d : 5** = 42 : 58. Crude mixtures **4a + 5** and **4b + 5** partially crystallized on refrigeration. The crystals were filtered off and washed with ether. Yield of **4a:** 35%; m.p. 108–110°C. Yield of **4b:** 27% m.p. 204 – 206°C. Samples of **4a** and **4b** were identical with authentic specimens.

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Acknowledgements

Financial support by a grant Nr 22714,92.03 from the Polish Committee for Scientific Research (KBN) is gratefully acknowledged.

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