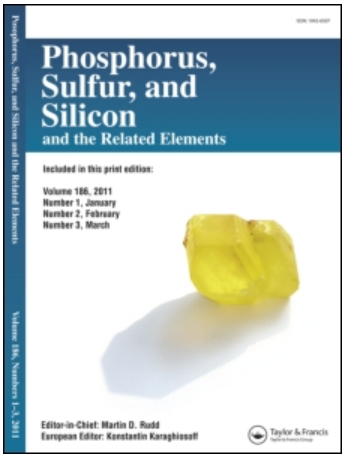

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Bifunctionalized Allenes. Part III. Bromination of 1-Substituted Phosphorylated Allenes

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BIFUNCTIONALIZED ALLENES. PART III. BROMINATION OF 1-SUBSTITUTED PHOSPHORYLATED ALLENES

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Various derivatives of the 2,5-dihydro-1,2-oxaphosphole were synthesized in good yields via *electrophile-induced cyclic reaction of 1-substituted (1-methyl-, 1-benzyl-, 1-allyl-, 1-propargyl-, 1-phenylthio- and 1-phenylseleno-) 1,2-alkadienephosphonates and -phosphine oxides **1** and **2**. Bromination of 1-substituted 1,2-alkadienephosphonates **1** leads to formation of 4-bromo-2,5-dihydro-1,2λ^5-oxaphosphol-2-oxides **3–8**, but the reaction with 1-substituted allenyl phosphine oxides **2** affords 4-bromo-2,5-dihydro-1,2-oxaphospholium bromides **9** and **10**.*

Keywords: 1-substituted 1,2-alkadienephosphonates; 1-substituted 1,2-alkadienyl phosphine oxides; 2,5-dihydro-1,2-oxaphospholium bromides; 2,5-dihydro-1,2λ^5-oxaphosphol-2-oxides; electrophile-induced cyclic reaction, bromination

INTRODUCTION

In the past three decades synthesis and use of allene derivatives have been rapidly expanded in preparative organic chemistry.[3–8] Reactions of electrophilic addition to allenes,[9–14] in which the double bonds are differently substituted presents the possibility of formation of eight different monoaddition products[13] depending on (1) which double bond is attacked; (2) whether an electrophile or nucleophile becomes attached to the central carbon; and (3) whether substituents on the remained double bond are *E* or *Z*. Moreover, the electrophilic addition to allenes can occur, as it does for alkenes, stereospecifically *syn* (suprafacial) or *anti* (antarafacial) and regioselectively with Markovnikov or anti-Markovnikov orientation.[14] On the other hand, the electrophile-induced cyclization of a variety of functionalized allenes to heterocyclic

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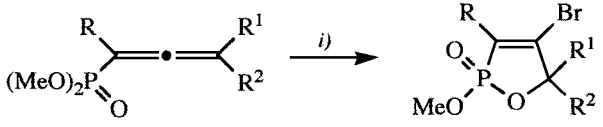
systems has received considerable attention due to its synthetic utility and remarkable stereoselectivity.[9–14]

Reactions of phosphorylated allenes with electrophilic reagents have been intensively investigated in the past 20 years. It has been shown[15–17] that depending on the structure of the starting allenic compound as well as the type of the electrophilic reagent, the reactions proceed with cyclization of the allenic system bearing a phosphoryl group (O=P–C=C=C) to give heterocyclic compounds in most cases. Thus, the reaction of electrophilic reagents with allenephosphonic dialkyl esters leads to 2,5-dihydro-1,2-oxaphospholes or 2,1- or 2,3-adducts, or a mixture of them, depending on the degree of substitution at the C^1 and C^3 atoms of the allenic system, on the nature of these substituents, and on the type of the reagents.[15,16]

As a part of our study on the synthesis[1,2] and electrophile-induced cyclization reactions of bifunctionalized allenes, we now report the results on the heterocyclization of 1-substituted phosphorylated allenes (phosphonates and phosphine oxides) in the reaction with bromine.

RESULTS AND DISCUSSION

We found that the electrophile-induced reaction of bromination of the 1-substituted 1,2-alkadienephosphonates[1] **1a–f** proceeds only with five-membered heterocyclization of the allenephosphonic system of double bonds (O=P–C=C=C) to give the 3-substituted 4-bromo-2,5-dihydro-1,2λ^5-oxaphosphol-2-oxides **3–8** according to the following reaction sequence outlined in the Scheme 1.



1a-f **3-8**

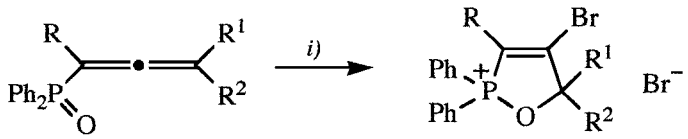
	R	R^1	R^2
1a, 3	Me	Me	Me
1b, 4	$PhCH_2$	Me	Me
1c, 5	CH_2=$CHCH_2$	Me	Me
1d, 6	CH≡CCH_2	- $(CH_2)_5$ -	
1e, 7	PhS	Me	Me
1f, 8	PhSe	- $(CH_2)_5$ -	

Reagents and Conditions:
i) Br_2, CH_2Cl_2, -5 to 0 °C, 1h, rt, 2-3h.

SCHEME 1

The resulting heterocyclic compounds **3–8** were isolated by preparative TLC as light yellow oils or white crystals in good yields (54–69%). Compounds **3–8** exhibited correct spectroscopic properties which are in good agreement with ^{1}H[18] and ^{13}C[19] NMR and IR[18] data reported for similar structures. The data from elemental analysis confirm the structure of the compounds prepared.

On the other hand, electrophile-induced interaction of the diphenyl (1-benzyl- or 1-phenylthio-3-methyl-1,2-butadienyl) phosphine oxides **2b,f** with bromine affords five-membered cyclic phosphonium salts, that is, 3-benzyl- or 3-phenylthio-4-bromo-2,2-diphenyl-2,5-dihydro-1,2-oxaphospholium bromides **9** and **10** (yield: 49% and 52%), according to the Scheme 2.



2b,f **9,10**

	R	R^1	R^2
2b, 9	$PhCH_2$	Me	Me
2f, 10	PhS	Me	Me

Reagents and Conditions:
i) Br_2, CH_2Cl_2, -5 to 0 °C, rt, 1h.

SCHEME 2

The salts **9** and **10** were air-stable crystals which were not dissolved in organic solvents, but dissolved in water and CF_3COOH. Formation of cyclic phosphonium salts only is a result which corresponded to that obtained in the reaction of 1-nonsubstituted allenyl phosphine oxides with electrophilic reagents.[20] The NMR and IR spectral data of **9** and **10** were fully in accord with data reported for similar structures.[20,21] These results again[20] confirm the assumption that the electrophile-induced heterocyclization reactions of 1,2-alkadienephosphonates probably proceed through a phosphonium intermediate.[15–18]

In summary, a new family of 3-substituted 4-bromo-2,5-dihydro-1,2-oxaphospholes was synthesized by reaction of 1-substituted 1,2-alkadienephosphonates and 1,2-alkadienyl phosphine oxides with bromine. The results of an initial investigation of the physiological activity of **3–10** were encouraging. The synthetic application and growth-regulating activity of the prepared 3-substituted 1,2-oxaphospholes are now under investigation.

EXPERIMENTAL

Method of Analysis

NMR spectra were obtained on a BRUKER WM-250 spectrometer for solutions in $CDCl_3$ or CF_3COOH operating at 250.1 (^1H) and 100.6 (^{13}C) MHz. Chemical shifts are in parts per million downfield from internal TMS (^1H and ^{13}C).

IR spectra were recorded with an IR-72 spectrophotometer (Carl Zeiss, Jena). Elemental analyses were carried out by the University of Shoumen Microanalytical Service Laboratory.

The melting points were measured in open capillary tubes and are uncorrected. The solvents were purified by standard methods. Reactions were carried out in oven-dried glassware under an argon atmosphere and exclusion of moisture. All compounds were checked for their purity on TLC plates.

Starting Materials

The starting 1-substituted 1,2-alkadienephosphonic dimethyl esters **1a-f** and diphenyl (3-methyl-1,2-butadienyl) phosphine oxides **2b,f** were synthesized according to the established procedure.[1]

Bromination of the 1-substituted 1,2-alkadienephosphonates 1

General Procedure

To a solution of the 1-substituted 1,2-alkadienephosphonate **1** (10 mmol) in dry dichloromethane (15 ml) was added dropwise with stirring a solution of bromine (10 mmol) in the same solvent (10 ml) at −5–0°C. The reaction mixture was stirred at the same temperature for 1 h and then at room temperature for 3 h. The solvent was removed using a rotatory evaporater. The residue was chromatographed on preparative TLC (silica gel, Kieselgel Merck DGF_{254} 60) with a mixture of ethyl acetate and hexane as a eluent to give the pure 2,5-dihydro-1,2λ^5-oxaphosphol-2-oxides **3–8**. Yield: 54–69%. The products **3–8** had the following properties.

*4-Bromo-3-methyl-2-methoxy-5,5-dimethyl-2,5-dihydro-1,2λ^5-oxaphosphol-2-oxide (**3**).* Yield: 69%, oil; $C_7H_{12}O_3PBr$, Found, %: P 12.14, Br 31.33; Calcd., %: P 12.32, Br 31.48. IR spectra (neat), cm^{-1}: 1011 (Me—O—P), 1274 (P=O), 1594 (C=C). ^1H NMR spectra ($CDCl_3$), ppm: 1.56 (s, 6H, 2Me), 2.03 (d, $^3J_{HP}$ 14.69 Hz, 3H, Me), 3.74 (d, $^3J_{HP}$ 11.22 Hz, 3H, MeO). ^{13}C NMR spectra ($CDCl_3$), ppm: 9.89 (C-6, J_{CP} 14.09 Hz), 24.87 (C-5, J_{CP} 7.7 Hz), 27.45 (C-4, J_{CP} 7.7 Hz), 51.34 (C-7, J_{CP}

4.09 Hz), 80.38 (C-3, J_{CP} 14.21 Hz), 117.22 (C-1, J_{CP} 124.78 Hz), 144.55 (C-2, J_{CP} 34.13 Hz).

*3-Benzyl-4-bromo-2-methoxy-5,5-dimethyl-2,5-dihydro-1,2λ^5-oxaphosphol-2-oxide (**4**).* Yield: 63%, oil; $C_{13}H_{16}O_3PBr$, Found, %: P 9.35, Br 24.13; Calcd., %: P 9.31, Br 24.41. IR spectra (neat), cm^{-1}: 1007 (Me—O—P), 1276 (P=O), 1587 (C=C). ^1H NMR spectra ($CDCl_3$), ppm: 1.59 (s, 6H, 2Me), 3.24 (m, 2H, CH_2), 3.82 (d, $^3J_{HP}$ 11.43 Hz, 3H, MeO), 7.25–7.61 (m, 5H, Ph). ^{13}C NMR spectra ($CDCl_3$), ppm: 25.43 (C-5, J_{CP} 7.42 Hz), 27.86 (C-4, J_{CP} 7.42 Hz), 36.75 (C-7, J_{CP} 7.1 Hz), 50.62 (C-6, J_{CP} 5.12 Hz), 81.44 (C-3, J_{CP} 13.84 Hz), 123.51 (C-1, J_{CP} 126.84 Hz), 126.76 (C-13), 127.64 (C-9, C-10), 130.31 (C-11, C-12), 139.42 (C-2, J_{CP} 31.71 Hz), 143.32 (C-8).

*3-Allyl-4-bromo-2-methoxy-5,5-dimethyl-2,5-dihydro-1,2λ^5-oxaphosphol-2-oxide (**5**).* Yield: 65%, oil; $C_9H_{14}O_3PBr$, Found, %: P 11.02, Br 28.43; Calcd., %: P 10.85, Br 28.67. IR spectra (neat), cm^{-1}: 1013 (Me—O—P), 1279 (P=O), 1592, 1632 (C=C). ^1H NMR spectra ($CDCl_3$), ppm: 1.59 (s, 6H, 2Me), 3.14 (m, 2H, CH_2), 3.81 (d, $^3J_{HP}$ 11.43 Hz, 3H, MeO), 4.93 (m, 1H, $H_aH_bC{=}CH_a$), 5.21 (m, 1H, $H_aH_bC{=}CH_a$), 6.03 (m, 1H, $H_aH_bC{=}CH_a$). ^{13}C NMR spectra ($CDCl_3$), ppm: 25.87 (C-5, J_{CP} 8.2 Hz), 27.05 (C-4, J_{CP} 8.2 Hz), 33.4 (C-7, J_{CP} 6.2 Hz), 49.51 (C-6, J_{CP} 5.3 Hz), 82.74 (C-3, J_{CP} 14.34 Hz), 113.76 (C-9, J_{CP} 36.16 Hz), 122.35 (C-1, J_{CP} 125.8 Hz), 127.8 (C-8, J_{CP} 7.3 Hz), 137.87 (C-2, J_{CP} 34.18 Hz).

*4-Bromo-2-methoxy-3-(2-propynyl)-1-oxa-2λ^5-phosphaspiro[4,5]dec-3-en-2-oxide (**6**).* Yield: 59%, oil; $C_{12}H_{16}O_3PBr$, Found, %: P 9.71, Br 25.04; Calcd., %: P 9.59, Br 25.34. IR spectra (neat), cm^{-1}: 1018 (Me—O—P), 1283 (P=O), 1594 (C=C) 2137 (C≡C). ^1H NMR spectra ($CDCl_3$), ppm: 1.22–1.69, 2.47–2.57 (mm, 10H, cyclohexyl), 2.41 (bs, 1H, HC≡), 3.18 (dd, $^3J_{HP}$ 12.64 Hz, $^4J_{HH}$ 3.2 Hz, 2H, CH_2), 3.74 (d, $^3J_{HP}$ 11.4 Hz, 3H, MeO). ^{13}C NMR spectra ($CDCl_3$), ppm: 20.72 (C-6, C-7), 22.18 (C-8), 25.5 (C-10), 34.9 (C-4, C-5), 51.0 (C-9, J_{CP} 15.4 Hz), 67.1 (C-12), 81.94 (C-11), 83.1 (C-3, J_{CP} 15.4 Hz), 122.13 (C-1, J_{CP} 127.2 Hz), 139.9 (C-2, J_{CP} 34.5 Hz).

*4-Bromo-2-methoxy-5,5-dimethyl-3-phenylthio-2,5-dihydro-1,2λ^5-oxaphosphol-2-oxide (**7**).* Yield: 54%, m.p. 86–87°C; $C_{12}H_{14}O_3SPBr$, Found, %: P 8.87, S 9.18, Br 22.88; Calcd., %: P 9.02, S 9.31, Br 22.94. IR spectra (nujol), cm^{-1}: 1003 (Me—O—P), 1287 (P=O), 1580 (C=C). ^1H NMR spectra ($CDCl_3$), ppm: 1.52 (s, 6H, 2Me), 3.68 (d, $^3J_{HP}$ 11.0 Hz, 3H, MeO), 7.08–7.57 (m, 5H, Ph). ^{13}C NMR spectra ($CDCl_3$), ppm: 25.1 (C-5), 28.44 (C-4), 50.8 (C-6, J_{CP} 15.75 Hz), 78.34 (C-3, J_{CP} 15.7 Hz), 124.5 (C-12), 127.32 (C-1, J_{CP} 97.2 Hz), 129.8 (C-8, C-9), 133.0 (C-10, C-11), 138.1 (C-7), 149.3 (C-2, J_{CP} 32.8 Hz).

*4-Bromo-2-methoxy-3-phenylseleno-1-oxa-2λ^5-phosphaspiro[4,5]dec-3-en-2-oxide (**8**).* Yield: 57%, m.p. 126–128°C (decomp.); $C_{15}H_{18}O_3$ PBrSe, Found, %: P 7.10, Br 18.32; Calcd., %: P 7.03, Br 18.53. IR spectra (nujol), cm^{-1}: 1005 (Me—O—P), 1284 (P=O), 1585 (C=C). ^{1}H NMR spectra ($CDCl_3$), ppm: 1.26–1.67, 2.37–2.51 (mm, 10H, cyclohexyl), 3.64 (d, $^3J_{HP}$ 11.1 Hz, 3H, MeO), 7.32–7.75 (m, 5H, Ph). ^{13}C NMR spectra ($CDCl_3$), ppm: 14.2 (C-6, C-7), 17.82 (C-8), 35.3 (C-4, C-5), 51.3 (C-9, J_{CP} 15.3 Hz), 82.4 (C-3, J_{CP} 14.6 Hz), 125.26 (C-1, J_{CP} 116.8 Hz), 131.8 (C-2, J_{CP} 4.8 Hz), 126.2, 130.0, 131.2, 131.7 [C-10 to C-15 (phenyl)].

Bromination of the 1-substituted diphenyl (3-methyl-1,2-butadienyl) phosphine oxides 2

General Procedure

To a solution of 1-substituted diphenyl (3-methyl-1,2-butadienyl) phosphine oxide **2** (5 mmol) in dry dichloromethane (7 ml) was added dropwise with stirring a solution of bromine (5 mmol) in the same solvent (5 ml) at −5–0°C. The stirring was continued at room temperature for 1 h. The resulting upper oily layer was separated and dried in vacuo. After drying, the products were crystallized. The salts **9** and **10** were not dissolved in organic solvents, but were dissolved in water and CF_3COOH. The pure samples were obtained by washing with organic solvents and drying in a vacuum desiccator. Yield: 49% and 52%. The products **9** and **10** had the following properties.

*4-Bromo-3-benzyl-5,5-dimethyl-2,2-diphenyl-2,5-dihydro-1,2-oxaphospholium bromide (**9**).* Yield: 49%, m.p. 112–114°C (decomp.); $C_{24}H_{23}OPBr_2$, Found, %: P 5.98, Br 30.84; Calcd., %: P 6.04, Br 30.99. IR spectra (nujol), cm^{-1}: 1553 (C=C). ^{1}H NMR spectra (CF_3COOH), ppm: 1.56 (s, 6H, 2Me), 3.35 (d, $^3J_{HP}$ 12.3 Hz, 2H, CH_2), 7.11–7.83 (m, 15H, 3Ph). ^{13}C NMR spectra (CF_3COOH), ppm: 24.8 (C-5), 25.22 (C-4), 34.4 (C-6, J_{CP} 6.6 Hz), 83.3 (C-3, J_{CP} 15.7 Hz), 135.64 (C-2, J_{CP} 34.2 Hz), 124.3, 127.1, 128.2, 128.7, 129.6, 130.8, 132.4, 134.0, 138.8 [C-7 to C-24 (phenyl)], 155.8 (C-1, J_{CP} 127.5 Hz).

*4-Bromo-5,5-dimethyl-2,2-diphenyl-3-phenylthio-2,5-dihydro-1,2-oxaphospholium bromide (**10**).* Yield: 52%, m.p. 122–123°C (decomp.); $C_{23}H_{21}OSPBr_2$, Found, %: P 5.84, S 5.73, Br 30.04; Calcd., %: P 5.78, S 5.98, Br 29.80. IR spectra (nujol), cm^{-1}: 1558 (C=C). ^{1}H NMR spectra (CF_3COOH), ppm: 1.69 (s, 6H, 2Me), 7.19–8.23 (m, 15H, 3Ph). ^{13}C NMR spectra (CF_3COOH), ppm: 27.7 (C-5), 29.51 (C-4), 82.4 (C-3, J_{CP} 15.5 Hz), 124.4, 127.5, 127.9, 128.7, 129.3, 130.2, 131.72, 132.21, 136.7 [C-6 to C-23 (phenyl)], 138.14 (C-2, J_{CP} 34.0 Hz), 142.62 (C-1, J_{CP} 89.7 Hz).

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