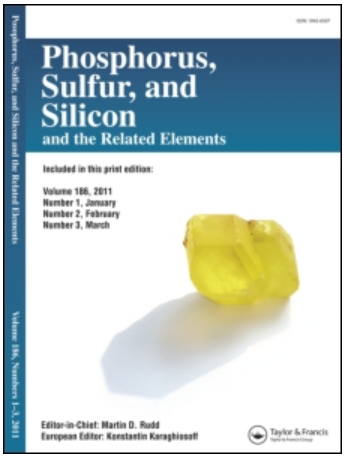

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SYNTHESIS OF 1-SUBSTITUTED PHOSPHORYLATED ALLENES

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SYNTHESIS OF 1-SUBSTITUTED PHOSPHORYLATED ALLENES

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Reaction of the lithio compounds **A**, generated *in situ* from the corresponding allene-phosphonates **1** and -phosphine oxide **2** and lithium diisopropylamide, with different electrophilic reagents leads to formation of the 1-benzyl-, 1-allyl-, 1-propargyl-, 1-phenylthio-, 1-phenylseleno-, 1-methylsulfinyl-, 1-trichloromethylsulfinyl- and 1-(trimethylsilyloxy)sulfonyl-1,2-alkadiene-phosphonates and -phosphine oxides **3–13**.

Keywords: allenephosphonates; allenephosphine oxides; lithium diisopropylamide; electrophilic reagents; 1-substituted 1, 2-alkadienephosphonates; 1-substituted 1, 2-alkadienyl phosphine oxides

INTRODUCTION

In the past three decades, synthesis and use of allene derivatives have rapidly expanded in preparative organic chemistry.[1] A most important aspect for applications of 1-acceptor substituted allenes is the relatively high acidity of the hydrogen atom at C-1 atom, for examples: 1-alkoxyallenes,[2] α-allenic esters,[3] 1-allene-sulfide,[4a] -sulfoxides,[4b] -sulfineamides,[4c] and -sulfone.[4d] The literature data show that the proton at C-1 atom from the allenic system is easy displaceable with different electrophilic reagents. On the other hand, α-metallation of an allenephosphine oxide (introduction of deuterium in the α-position) has been observed.[5a] Application of allenic phosphonates to the synthesis of structurally inter-

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esting molecules was made by R. S. Macomber[5b-5d] as shown in the construction of bicyclic cumulatriene as an elegant example.[5e]

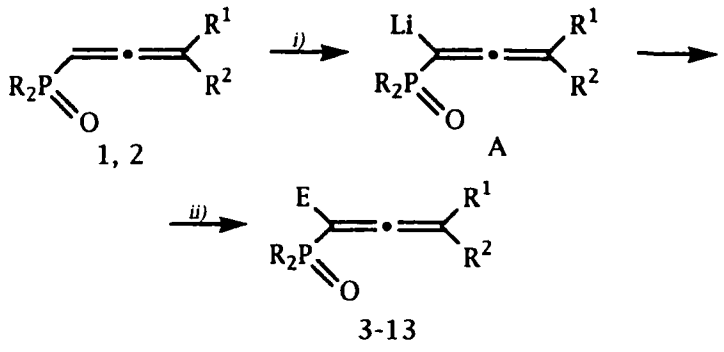
As a part of our research program on the chemistry of the heteroatom-containing highly unsaturated compounds, we required[12] a convenient method to introduce some electron-withdrawing groups at the α-position to the phosphorylated allenes. The thio-, seleno-, sulfinyl- and sulfonyl-group attact increasing attention as useful functionalities in organic synthesis. Of particular interest are the applications of these groups as temporary transformers of chemical reactivity of the allenic system in the synthesis of eventually heterocyclic compounds by the reactions with electrophilic reagents.[6]

RESULTS AND DISCUSSION

We found that the phosphorylated allenes **1** and **2** can smoothly be deprotonated at the α-position by lithium diisopropylamide (LDA) in THF under an argon atmosphere. The resulting lithio compounds **A** can react with different electrophiles leading to 1-substituted derivatives of **1** and **2** as benzyl-, allyl-, propargyl-, phenylthio-, phenylseleno-, methylsulfinyl-, trichloromethylsulfinyl- and (trimethylsilyloxy)-sulfonyl-1,2-alkadiene-phosphonates (**3, 5–7, 9–12**) and -phosphine oxides (**4, 8, 13**) according to the following reaction sequence outlined in the **Scheme**.

After a conventional work-up, the resulting 1-substituted 1,2-alkadiene-phosphonates and -phosphine oxides **3–13** were isolated by preparative TLC as light yellow oils or white crystals in moderate yields (41–65 %) and identified by ^{1}H NMR and IR spectra as well as elemental analysis. The low yield of the product **5** was due to the formation of unassignable polymeric material.

In summary, a new family of 1,1-disubstituted allenes was synthesized by reaction of the lithiated 1,2-alkadienephosphonates and -phosphine oxides with different electrophilic reagents. Synthetic application of the prepared 1-substituted phosphorylated allenes in the heterocyclization reactions with electrophilic reagents is now under investigation.



3-13	E	R	R^1	R^2
3	$PhCH_2$	MeO	Me	Me
4	$PhCH_2$	Ph	Me	Me
5	$CH_2{=}CHCH_2$	MeO	Me	Me
6	$CH{\equiv}CCH_2$	MeO	$-(CH_2)_5-$	
7	PhS	MeO	Me	Me
8	PhS	Ph	Me	Me
9	PhSe	MeO	$-(CH_2)_5-$	
10	MeS(O)	MeO	$-(CH_2)_5-$	
11	$CCl_3S(O)$	MeO	Me	Me
12	Me_3SiOSO_2	MeO	Me	Me
13	Me_3SiOSO_2	Ph	Me	Me

Reagents and Conditions:

i) LDA, THF, -78 °C, 1h;
ii) $PhCH_2Cl$ (3 and 4), allyl bromide (5), propargyl bromide (6), PhSCl (7 and 8), PhSeCl (9), MeS(O)Cl (10), $CCl_3S(O)Cl$ (11) or Me_3SiOSO_2Cl (12 and 13), THF, -78 °C to rt, 1-6 h.

SCHEME

EXPERIMENTAL

Method of analysis

^1H NMR spectra were obtained on a JEOL JNM-FX-60 spectrometer for solutions in $CDCl_3$ operating at 60 MHz. Chemical shifts are in parts per million downfield from internal TMS.

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. The reactions were carried out in ovendried glassware under an argon atmosphere and exclusion of moisture. All compounds were checked for their purify on TLC plates.

Starting materials

3-Methyl-1,2-butadienephosphonic (**1a**) and cyclohexylidene-ethenephosphonic (**1b**) dimethyl esters were synthesized from the corresponding dichlorides and methanol in the presence of pyridine according to the literature.[7,8] Diphenyl (3-methyl-1,2-butadienyl) phosphine oxide (**2a**) was prepared from the corresponding α-alkynol and diphenylchlorophosphine in the presence of triethylamine by a procedure described earlier.[9] Phenylsulfenyl chloride was prepared from diphenyl disulfide and sulfuryl chloride at –20 °C and used after distillation.[10] Methylsulfinyl chloride was synthesized from dimethyl disulfide and sulfuryl chloride in glacial acetic acid and used after distillation.[11]

Synthesis of 1-substituted phosphorylated allenes (3–13). General procedure

To a solution of lithium diisopropylamide (LDA), generated *in situ* from diisopropylamine (DIA) (1.11 g, 11 mmol) and n-butyl lithium (n-BuLi) (1.6 M in hexane, 6.25 ml, 10 mmol), in tetrahydrofuran (THF) (20 ml) was added a solution of allenephosphonate (**1a** or **1b**) or allenylphosphine oxide (**2a**) (10 mmol) in THF at -78 °C. The reaction mixture was stirred at this temperature for 1 h. After the addition of a solution of electrophilic reagent (10 mmol) in THF at –78 °C, the mixture was stirred at room temperature for 1–6h (see **Table**). After that the mixture was quenched with 2N HCl, extracted with ether or ethylacetate, washed with saturated NaCl, and dried over anhydrous sodium sulfate. After evaporation of the solvents, the residue was chromatographed on silica gel to give the pure 1-substituted phosphorylated allenes **3–13** with good yields (41–65%) (see **Table**).

TABLE Synthesis of 1-substituted phosphorylated allenes (3–13)

Entry	*Starting Allene*	E^+	*R*	R^1	R^2	*Reaction time*	*Product*	*Yield (%)*
1	**1a**	$PhCH_2$	MeO	Me	Me	5h[a]	**3**	52
2	**2a**	$PhCH_2$	Ph	Me	Me	6h[a]	**4**	49
3	**1a**	$CH_2{=}CHCH_2$	MeO	Me	Me	6h[a]	**5**	41
4	**1b**	$CH{\equiv}CCH_2$	MeO	$-(CH_2)_5-$		5h[a]	**6**	54
5	**1a**	PhS	MeO	Me	Me	3h	**7**	60
6	**2a**	PhS	Ph	Me	Me	4h	**8**	55
7	**1b**	PhSe	MeO	$-(CH_2)_5-$		4h	**9**	50
8	**1b**	MeS(O)	MeO	$-(CH_2)_5-$		3h	**10**	59
9	**1a**	$CCl_3S(O)$	MeO	Me	Me	2h	**11**	65
10	**1a**	Me_3SiOSO_2	MeO	Me	Me	1h	**12**	50
11	**2a**	Me_3SiOSO_2	Ph	Me	Me	1.5h	**13**	48

a. The reaction mixture was heated to 50 °C.

1-Benzyl-3-methyl-1,2-butadienephosphonic dimethyl ester (3)

The compound was synthesized from the lithio derivative **A** of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1a** and benzyl chloride by heating to 50°C for 5h. Eluent for preparative TLC: hexane:ethylacetate = 3:1. Oil, $C_{14}H_{19}O_3P$, Calcd., %: P 11.63; Found, %: P 11.76. IR spectra (neat), cm^{-1}: 1017 (Me-O-P), 1277 (P=O), 1956 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 1.76 (s, 6H, 2Me), 2.68–2.87 (m, 2H, CH_2), 3.57 (d, $^3J_{HP}$ 10.9 Hz, 6H, 2MeO), 7.8–8.5 (m, 5H, $\underline{Ph}CH_2$).

Diphenyl (1-benzyl-3-methyl-1,2-butadienyl) phosphine oxide (4)

The compound was synthesized from the lithio derivative **A** of the diphenyl (3-methyl-1,2-butadienyl) phosphine oxide **2a** and benzyl chloride by heating to 50°C for 6h. Eluent for preparative TLC: benzene:ethylacetate = 2:1. M.p. 75–76 °C; $C_{24}H_{23}OP$, Calcd., %: P 8.64; Found, %: P 8.81. IR spectra (nujol), cm^{-1}: 1168 (P=O), 1959 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 1.81 (s, 6H, 2Me), 2.71–2.90 (m, 2H, CH_2), 7.54–7.64 (m, 10H, 2Ph-P), 8.0–8.6 (m, 5H, $\underline{Ph}CH_2$).

2-Methyl-2,3,6-heptatriene-4-phosphonic dimethyl ester (5)

The compound was synthesized from the lithio derivative **A** of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1a** and allyl bromide by heating to 50°C for 6h. Eluent for preparative TLC: hexane:ethylacetate = 3:1. Oil, $C_{10}H_{17}O_3P$, Calcd., %: P 14.33; Found, %: P 14.24. IR spectra (neat), cm^{-1}: 1001 (Me-O-P), 1286 (P=O), 1953 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 1.79 (s, 6H, 2Me), 2.66–2.87 (m, 2H, CH_2), 3.60 (d, $^3J_{HP}$ 10.8 Hz, 2MeO), 4.80–6.17 (m, 3H, $CH{=}CH_2$),

1-Cyclohexylidene-1-pentene-4-yne-2-phosphonic dimethyl ester (6)

The compound was synthesized from the lithio derivative **A** of the cyclohexylidene-ethene-phosphonic dimethyl ester **1b** and propargyl bromide by heating to 50°C for 5h. Eluent for preparative TLC: hexane:ethylacetate = 3:1. Oil, $C_{13}H_{19}O_3P$, Calcd., %: P 12.18; Found, %: P 12.14. IR spectra (neat), cm^{-1}: 1032 (Me-O-P), 1288 (P=O), 1952 (C=C=C), 2103 (C≡C), 3308 (HC≡). ^1H NMR spectra ($CDCl_3$), δ: 1.61 and 2.23 (s, s, 6H and 4H, cyclohexylidene), 2.54 (s, 1H, HC≡), 2.72–2.89 (m, 2H, CH_2), 3.57 (d, $^3J_{HP}$ 11.0 Hz, 6H, 2MeO).

3-Methyl-1-phenylthio-1,2-butadienephosphonic dimethyl ester (7)

The compound was synthesized from the lithio derivative **A** of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1a** and phenylsulfenyl chloride. Eluent for preparative TLC: hexane: ethylacetate = 2:1. Oil, $C_{13}H_{17}O_3SP$, Calcd., %: P 10.89, S 11.28; Found, %: P 10.74, S 11.47. IR spectra (neat), cm^{-1}: 1008 (Me-O-P), 1274 (P=O), 1956 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 1.79 (s, 6H, 2Me), 3.54 (d, $^3J_{HP}$ 10.9 Hz, 6H, 2MeO), 7.38–7.59 (m, 5H, PhS).

Diphenyl (3-methyl-1-phenylthio-1,2-butadienyl) phosphine oxide (8)

The compound was synthesized from the lithio derivative **A** of the diphenyl (3-methyl-1,2-butadienyl) phosphine oxide **2a** and phenylsulfenyl chloride. Eluent for preparative TLC: hexane: ethylacetate:ether = 2:1:1. M.p. 103–104 °C; $C_{23}H_{21}OPS$, Calcd., %: P 8.23, S 8.52; Found, %: P 8.14, S 8.47. IR spectra (nujol), cm^{-1}: 1270 (P=O), 1958 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 1.83 (s, 6H, 2Me), 7.43–7.55 (m, 5H, PhS), 7.51–7.63 (m, 10H, 2Ph-P).

Phenylseleno-cyclohexylidene-ethenephosphonic dimethyl ester (9)

The compound was synthesized from the lithio derivative **A** of the cyclohexylidene-ethene-phosphonic dimethyl ester **1b** and phenylselenenyl chloride. Eluent for preparative TLC: chloroform:ethylacetate: ether = 2:1:1. M.p. 110–111 °C; $C_{16}H_{21}O_3PSe$, Calcd., %: P 8.34; Found, %: P 8.21. IR spectra (nujol), cm^{-1}: 986 (Me-O-P), 1286 (P=O), 1952 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 1.58 and 2.2 (s, s, 6H and 4H, cyclohexylidene), 3.61 (d, $^3J_{HP}$ 10.7 Hz, 6H, 2MeO), 7.36–7.51 (m, 5H, PhSe).

Methylsulfinyl-cyclohexylidene-ethenephosphonic dimethyl ester (10)

The compound was synthesized from the lithio derivative **A** of the cyclohexylidenylethene-phosphonic dimethyl ester **1b** and methanesulfinyl chloride. Eluent for preparative TLC: hexane:ethylacetate = 2:1. Oil, $C_{11}H_{19}O_4PS$, Calcd., %: P 11.13, S 11.52; Found, %: P 11.05, S 11.64. IR spectra (neat), cm^{-1}: 991 (Me-O-P), 1071 (S=O), 1286 (P=O), 1950 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 1.6 and 2.18 (s, s, 6H and 4H, cyclohexylidene), 2.69 (s, 3H, MeS=O), 3.53 (d, $^3J_{HP}$ 11.3 Hz, 6H, 2MeO).

3-Methyl-1 -(trichloromethyl)sulfinyl-1,2-butadienephosphonic dimethyl ester (11)

The compound was synthesized from the lithio derivative **A** of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1a** and trichloromethanesulfinyl chloride. Eluent for preparative TLC: hexane:ethylacetate = 4:1. Oil, $C_8H_{12}O_4SPCl_3$, Calcd., %: P 9.07, S 9.39, Cl 31.14; Found, %: P 9.04, S 9.44, Cl 30.96. IR spectra (neat), cm^{-1}: 988 (Me-O-P), 1059 (S=O), 1266 (P=O), 1952 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 1.77 (s, 6H, 2Me), 3.49 (d, $^3J_{HP}$ 11.1 Hz, 6H, 2MeO).

3-Methyl-1-(trimethylsilyloxy)sulfonyl-1,2-butadienephosphonic dimethyl ester (12)

The compound was synthesized from the lithio derivative **A** of the 3-methyl-1,2-butadienephosphonic dimethyl ester **1a** and trimethylsi-

lylchlorosulfate. Eluent for preparative TLC: chloroform: ethylacetate = 2:1. Oil, $C_{10}H_{21}O_6SPSi$, Calcd., %: P 9.43, S 9.76; Found, %: P 9.54, S 9.82. IR spectra (neat), cm^{-1}: 849 (Si-O-S), 1004 (Me-O-P), 1186 (v_s SO_2), 1274 (P=O), 1319 (v_{as} SO_2), 1954 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 0.23 (s, 9H, Me_3SiO), 1.79 (s, 6H, 2Me), 3.59 (d, $^3J_{HP}$ 11.3 Hz, 6H, 2MeO).

Diphenyl [3-methyl-1-(trimethylsilyloxy)sulfonyl-1,2-butadienyl] phosphine oxide (13)

The compound was synthesized from the lithio derivative **A** of the diphenyl (3-methyl-1,2-butadienyl) phosphine oxide **2a** and trimethylsilylchlorosulfate. Eluent for preparative TLC: hexane:ethylacetate:ether = 3:1:1. M.p. 96–97 °C; $C_{20}H_{25}O_4PSSi$, Calcd., %: P 7.37, S 7.63; Found, %: P 7.54, S 7.82. IR spectra (nujol), cm^{-1}: 853 (Si-O-S), 1191 (v_s SO_2), 1278 (P=O), 1317 (v_{as} SO_2), 1958 (C=C=C). ^1H NMR spectra ($CDCl_3$), δ: 0.23 (s, 9H, Me_3SiO), 1.85 (s, 6H, 2Me), 7.55–7.63 (m, 10H, 2Ph-P).

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