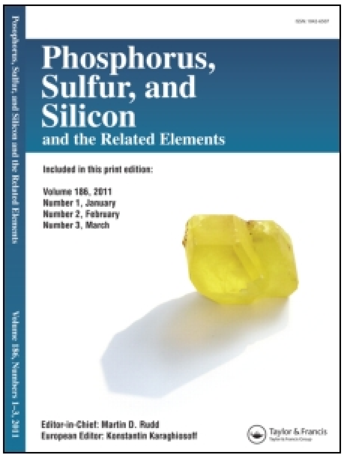

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Chemical Behavior of the N-Morpholino- O-Alkyl-3-Methyl-1,2-Butadienephosphonic Acid Esters

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To cite this Article Enchev, D. D.(2005) 'Synthesis and Chemical Behavior of the N-Morpholino- O-Alkyl-3-Methyl-1,2-Butadienephosphonic Acid Esters', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 9, 2131 — 2135
To link to this Article: DOI: 10.1080/104265090917637
URL: http://dx.doi.org/10.1080/104265090917637

Phosphorus, Sulfur, and Silicon, 180:2131–2135, 2005
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ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090917637

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Synthesis and Chemical Behavior of the N-Morpholino-O-Alkyl-3-Methyl-1,2-Butadienephosphonic Acid Esters

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The synthesis and the reactivity of the titled compounds towards electrophilic and nucleophilic reagents have been discussed.

Keywords 1,2-Butadienephosphonates; N-morpholino-O-alkyl-3-methyl-1,2-butadienephosphonates

INTRODUCTION

The 1,2-alkadienephosphonate amidoesters readily available from the corresponding 1,2-alkadienephosphonic dichlorides[1] by the substitution of the two chlorine atoms at phosphorus with ester- and dialkylamino groups, produced cyclic oxaphospholic derivatives in the reactions with a number of electrophilic reagents, in which derivatives exhibit strong biological effects.[2]

Until now, the synthesis of the titled compounds have been not reported. Now we wish to report the successful synthesis of the N-morpholine-O-alkyl-3-alkyl-1,2-alkadienephosphonates.

RESULTS AND DISCUSSION

The synthesis of the titled compounds was carried out following the procedure we described earlier, namely the interaction of 1,2-alkadienephosphonic dichlorides with aliphatic alcohols and morpholine in the presence of triethylamine, respectively, in nonpolar media

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Received February 18, 1998; accepted November 4, 2004.

Note from the editor: Due to unknown reasons, the manuscript was not published in 1998.

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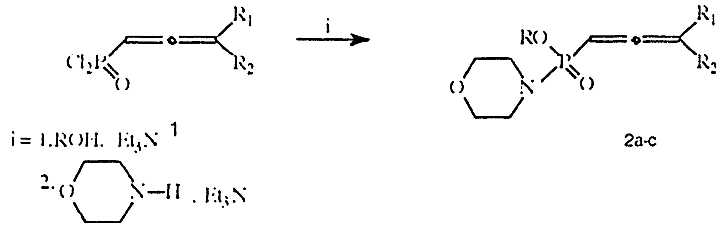
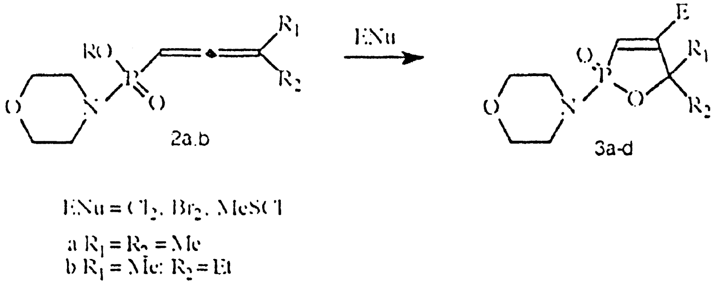
under inert atmosphere and strirring (see Experimental section). The reactions follow Scheme 1:



SCHEME 1

The ^{1}H-nmr spectra of the isolated products exhibits signals for the proton at the Cl atom of the allenephosphonate system of double bonds as well as signals for the protons from alkoxy- and morpholino- groups. The chemical shift for ^{31}P corresponds to those for phosphorylated allenes (16.7–18.2 ppm) (see Table I). The isolated compounds **2a–c** were investigated in the reactions with electrophilic and nucleophilic reagents. In the case of interaction with electrophilic reagents, the 2,5-dihydro-1,2-oxaphosphole 2-oxides were isolated with good yields. The reactions follow Scheme 2:



SCHEME 2

The interaction of the title compounds with nucleophilic reagents, i.e. secondary amines, results in the formation of β-ketaphsphonates 4a,b (Scheme 3):

The reactions with electrophilic[3] reagents were performed in methylene chloride under inert atmosphere and stirring (see Experimental section). The solution of an appropriate electrophile was added dropwise to the solutions of **2a–c**, respectively. After one hour and work-up, which included evaporization of the solvent and recrystallization of the crude products, 2,5-dihydro-1,2-oxaphosphole derivatives were isolated with good yields.

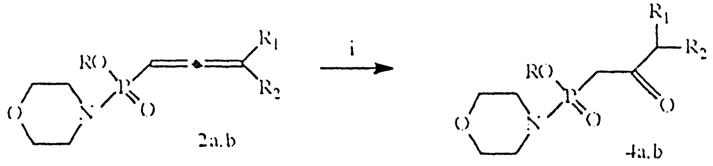
TABLE I Constants, Elemental Analysis Data and Spectral Characteristics for Compounds 2a–c

Constants and elemental analysis data for compounds 2a–c

N	R(R1) [R2]	Yield (%)	b.p. (°C)	Found (%)		Formula	Calcd (%)	
				P	N		P	N
2a	Me(Me) [Me]	75	137–8	13.38	6.0	$C_{10}H_{18}O_3PN$	13.41	6.06
b	Et(Me) [Me]	77	138–40	12.59	5.68	$C_{11}H_{20}O_3PN$	12.63	5.71
c	i-Pr(Me) [Me]	82	139–41	11.89	5.3	$C_{12}H_{22}O_3PN$	11.94	5.34

^1H, ^{31}P-NMR and IR spectral data for compounds 2a–c

		Chemical shift (ppm)				coupl. Const. (Hz)			IR (cm^{-1})	
N	R	H	Ha (Hb)	R	Me (Me)	^{31}P	H—P	R—P	P—O	C—C—C
2a	Me	5.04	2.87 (3.76)	3.48	1.68 (1.68)	18.2	7.5	11.2	1225	1957
b	Et	5.04	2.86 (3.76)	Me-1.20 CH2-3.87	1.68 (1.68)	17.1	7.0	11.6	1230	1958
c	i-Pr	5.04	2.87 (3.77)	Me-1.31 CH-2.56	1.68 (1.68)	16.7	6.8	11.5	1230	1956



2a,b

4a,b

R = Me, Et
R$_1$ = R$_2$ = Me
i = 1.Et$_2$NH, H$_2$O H

SCHEME 3

The spectral and elemental analysis data confirm our suggestions that an oxaphospholic cyclization of the allenephosphonate system of double bonds take place.

In the case of the reaction with secondary amines,[4] followed by the hydrolysis of the intermediate in acidity media, β-kelophosphonates **4a**,**b**, according to the results, reported earlier, have been isolated.

Thus, the high reactivity of the allenephosphonates have been confirmed arid the new phosphorus-containing compounds with eventual biological activity have been synthesized.

EXPERIMENTAL

Analytical Methods

^{1}H nmr spectra were determined on a Tesla BS(80 MHz) at a normal temperature as $CDCl_3$ solution with TMS as an internal standard. The IR spectra were recorded on an IR-72-spectrophotometer (Carl Zeiss Jena).

Starting Materials

The alkadienephosphonic dichlorides were prepared by the procedure described earlier.[5]

1. Synthesis of N-Morpholino-O-alkyl-3-alky-1,2-alkadienephosphonates 2a–c

General Procedure

To a solution of the appropriate dichloride of the 1,2-alkadienephosphonic acids in dry ether, a mixture of aliphatic alcohol and triethylamine dissolved in the same solvent at −8 to −10°C and stirring was added, followed by the addition of the mixture of morpholine and triethylamine at the same solvent and conditions. After an hour of stirring, the solvent was removed and the residue was distilled.

Yield 85–90%. The physical data are summarized in Table I.

2. Synthesis of 4-Substituted-N-morpholino-2,5-dihydro-1,2-oxaphosphole-2-oxides 3a–d

General Procedure

To a solution of compounds **2a–c** in dry methylenechloride a solution of the appropriate electrophile was added at −5 to −0°C and stirring in an inert atmosphere. After an hour, the solvent was evaporized and the residue was recrystallized from heptane/benzene.

3a Yield % 75; m.p. °C uncorrect 88–9; Found % P, 12.20; Cl, 14.00; N, 5.52; $C_9H_{15}O_3$ PNCl Calcd. % P, 12.30; Cl, 14.08; N, 5.56; ^{1}H-nmr 6.34d (1H J_{HP} 23 Hz), 1.40 (3H), 1.58 (3H), 2.87, 3.76 m (morph.); ^{31}P 33.42; IR cm^{-1} ν_{P-O-C}, 998, 1030, ν_{P-O}, 1273 ν_{C-C}1584.

3b Yield % 78, m.p. °C uncorrect 89–90; Found % P, 10.00; Br, 25.82; N, 4.50; $C_{10}H_{16}O_3PNBr$ Calcd. % P, 10.02; Br, 25.85; N, 4.53; ^{1}H-nmr 6.1 1d (1H J_{HP} 23.2 Hz), 2.87, 3.76 m (morph.) 0.69, 1.64 (Et), 3.96 (Me); ^{31}P 34.12; IR cm^{-1} ν_{P-O-C}971, 1030, ν_{P-O}1260, ν_{C-C}1587.

3c Yield % 72, m.p. °C uncorrect 92–3 Found % P, 11.72; S, 12.15; N, 5.30; $C_{10}H_{18}O_3PNS$ Calcd. % P, 11.76; S, 12.17; N, 5.32; ^{1}H-nmr 6.25d (1H J_{HP} 23.2 Hz), 2.87, 3.76 m (morph.), 1.40 s (3H), 1.58 s (3H), 2.17 (MeS); ^{31}P 33.22; IR cm^{-1}, ν_{P-O-C}973, 1042, ν_{P-O}1263, ν_{C-C}1585.

3d Yield % 78, m.p. °C uncorrect 94–6 Found % P, 11.14; S, 11.53; N, 5.00; $C_{11}H_{20}O_3PNS$ Calcd. % P, 11.16; S, 11.56; N, 5.04; ^{1}H-nmr (6.20 d, J_{HP} 23 Hz), 2.87, 3.76 m (morph.) 0.68, 1.64 (Et), 3.90 (Me), 2.18 (MeS); ^{31}P 33.42; IR cm^{-1} ν_{P-O-C}974, 1039, ν_{P-O}1264, ν_{C-C}1575.

3. Synthesis of β-Ketophosphonats 4a,b

General Procedure

To a solution of the appropriate N-morpholino-O-alkyl-3-alkyl-1,2-alkadienephosphonate in ether at −8°C and stirring an equimolar amount of dialkylamine was added. After warm up to room temperature and additional stirring for an hour, 10% aqueous HCI was added. The organic phase was separated and the residue was extracted with $CHCl_3$. The organic phases were dried with $MgSO_4$, the solvents were evaporized, and the residue was distilled.

4a Yield 68%, b.p. °C 134–6; Found % P, 12.40; N, 5.59; $C_{10}H_{20}O_4$ PN Calcd. % P, 12.43; N, 5.62; ^{1}H-nmr 3.71–3.12 (2H J_{HP} 16.2 HZ), 2.30 (3H J_{HP} 2.7 Hz), 0.99, 1.07 (6H J_{HH} 7.0 Hz), 2.87, 3.77 (morph.); IR cm^{-1} ν_{P-O}1238, ν_{C-O} 1700.

4b Yield 68%; b.p. °C 134–6; Found % P, 11.72; N, 5.30; $C_{11}H_{22}O_4PN$ Calcd. % P, 11.76; N, 5.32; ^{1}H-nmr 3.71–3.12 (2H J_{HP} 16.2 Hz), 0.68, 1.64 (Et), 0.97, 1.06 (6H J_{HH} 7.0 Hz), 2.87, 3.77 (morph.); IR cm^1 ν_{P-O} 1238, ν_{C-O} 1700.

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