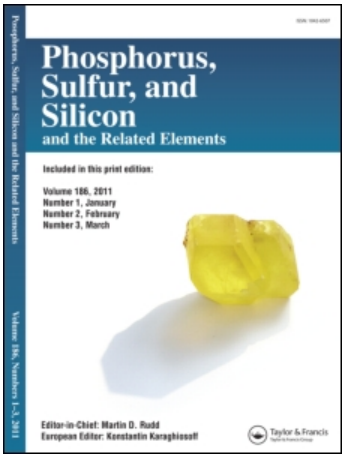

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Synthesis and Chemical Behavior of N-(2-Chloroethyl)O-alkyl-3-methyl-1,2-butadienephosphoniates

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Synthesis and Chemical Behavior of N-(2-Chloroethyl)-O-alkyl-3-methyl-1,2-butadienephosphoniates

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

Keywords 2-Chloroethylgroup; allenephosphonates; electrophilic addition

INTRODUCTION

Phosphorus amides substituted at nitrogen atom with 2-chloroethyl group, i.e. (N-phosphorylated mustards) or with ethylene groups i.e. (N-phosphorylated aziridines) exhibit biological activity responsible for the application of these compounds as chemosterilizing insecticides[1–4] or cytostatic agents.[2–7] The biology critical-alkylating reactivity of nitrogen mustards is attributed to the cyclization of the N(2-chloroethyl) function to aziridinium derivative followed by the cross-linking for the cellular nucleophile centers, which result in the inhibition of the cellular growth.

On the other hand, the 1,2-alkadienephosphonate amidoesters readily available from the corresponding 1,2-alkadienephosphonic dichlorides[8] 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.[9] We believe that the combination of these two above-mentioned effects for which the different groups are responsible in one molecule would increase the biological activity of the synthesized compounds.

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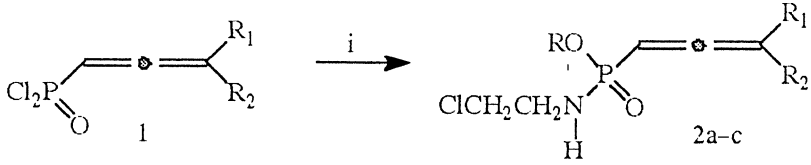
RESULTS AND DISCUSSION

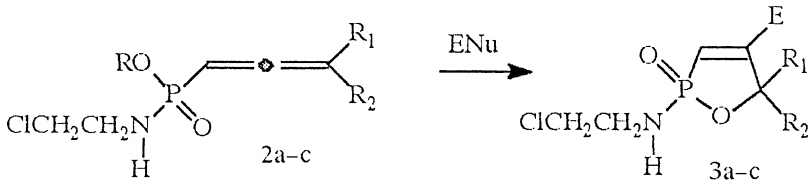
The reaction of the synthesis of the titled compounds was carried out following the procedure described by us earlier.[8] The interaction of 1,2-alkadienephosphonic dichlorides with aliphatic alcohols and N-(2-chloroethyl)ammonium chloride was performed in the presence of triethylamine in a nonpolar media under inert atmosphere and stirring (see Experimental section). The reaction follows Scheme 1:



i = 1. ROH; Et_3N
2. $ClCH_2CH_2NH_2.HCl$; Et_3N

SCHEME 1

The ^{1}H-NMR spectra of the isolated products exhibit signals for the proton at the C1 atom of the allenephosphonate system of double bonds as well as signals for the protons from the alkoxy- and 2-chloroethyl-groups. The chemical shift for ^{31}P corresponds to those for phosphorylated allenes (16.7–18.2 ppm). The isolated N-(2-chloroethyl)-O-alkyl-3-alkyl-1,2-alkadienephosphonates **2a–c** were investigated in the reactions with electrophilic reagenets. The reactions were performed in methylene chloride under inert atmosphere and stirring (see Experimental section). The solution of the appropriate electrophile was added dropwise to the solutions of **2a–c**, respectively. After one hour of work-up, evaporation of the solvent and recrystallization of the crude products 2,5-dihydro-1,2-oxaphosphole derivatives were isolated with good yields. The reaction follows Scheme 2:

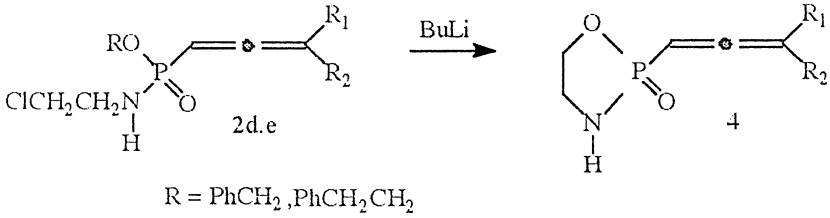


ENu = Cl_2, Br_2, MeSCl

SCHEME 2

Keeping in mind the results of other authors,[10] we try to investigate the synthesized by us compounds **2d**,**e**[11] in the reaction with some

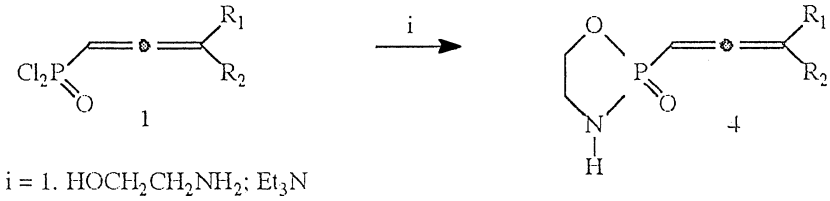
strong bases such as buthyllithium. In this case, the cyclization between N-(2-chloroethyl)- and aryoxygroups at phosphorus took place, obtaining the compound **4** (Scheme 3).



SCHEME 3

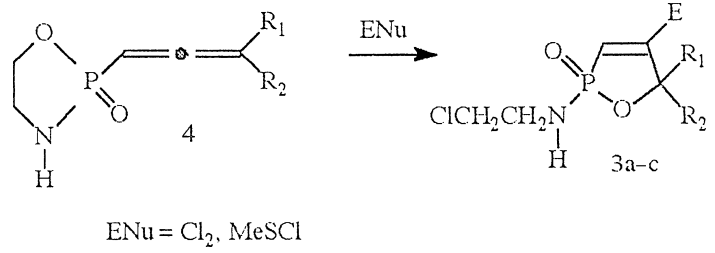
The isolation of **4** is due probably to the well-known nucleophilic assistance of the benzyloxy- and especially of the phenylethyloxy-groups. As we expected, the strong neighboring group effect of these two substituents promole the ring-closure reaction leading to 1,3,2-oxazaphosphole derivatives. The role of the aryloxy-substituents was confirmed by the fact that the same reaction failed in the case of presence of the alkoxy-substituents at the phosphorus atom.

To confirm our results, we successfully synthesized the same compound **4** using dichlorides of the 1,2-alkadienephosphonic acids and ethanolamine in the presence of triethylamine (Scheme 4):



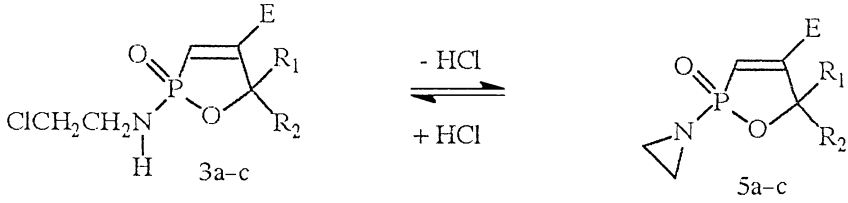
SCHEME 4

The reaction of **4** with different kinds of electrophilic reagents produce the compounds **3a**,**c**, following Scheme 5:



SCHEME 5

Following the procedure described earlier,[12] we try to investigate the reaction between **3a–c** and bases. As we expected, the aziridine cyclization reaction takes place in this case. The reaction follows Scheme 6:



SCHEME 6

The treating of compounds **5a–c** with LiCl in THF followed by aqueous work-up leads to an aziridine ring-opening reaction.

The structure of **5a–c** was determined by means of ^{1}H-NMR spectra. The formation of the aziridine ring was judged on the disappearance of the signals for the N(2-chloroethyl) group at 3.30–3.54 ppm and for the N—H proton at 3.80–3.85 ppm, and the appearance of new signals at 2.13–2.16 ppm with coupling constants in the range of 16.0–16.5 Hz, which corresponds to the aziridine ring protons reported by other authors.[12]

Furthermore, the ^{31}P chemical shift for **5a–c** shows that another cycle is attached to the phosphorus atom.

The results we obtained gave us a basis to assume that N-(2-chloroethyl)-O-alkyl-3-methyl-1,2-butadienephosphonates are suitable precursors for the synthesis of different kinds of cyclic organophosphorus compounds. The 1,3,2-oxazaphosphole and aziridine cyclization reactions have to be performed by means of variation of the kind of substituents at phosphorus.

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 by us earlier.[8]

1. Synthesis of N-(2-chloroethyl)-O-alkyl-3-alkyl-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, which was dissolved in the same solvent at −8 to −10°C, was stirred and added, followed by the addition of the mixture of N-(2-chloroethyl)ammonium chloride and triethylamine at the same solvent and conditions. After an hour of stirring, the solvent was removed and the residue was purified by washing with heptane/benzene.

2a. Yield 75%, oil, $C_8H_{15}O_2PNCl$; Found %: P, 13.83°Cl, 15.83; N, 6.22; Calcd. %: P, 13.85; Cl, 15.85; N, 6.26; ^{1}H-NMR 5.04 d (1H $^2J_{HP}$ 7.2 Hz), 3.05–3.80 m (NCH_2CH_2Cl), 3.89(1H), 3.47(MeO); ^{31}P, 16.8; IR cm^{-1} 1230$\nu_{(P=O)}$, 1958$\nu_{(C=C=C)}$.

2b. Yield 77%, oil, $C_9H_{17}O_2PNCl$; Found %: P, 13.00; Cl, 14.90; N, 5.87; Calcd. %: P, 13.03; Cl, 14.91; N, 5.89; ^{1}H-NMR 5.04 d (1H $^2J_{HP}$ 7.0 Hz), 3.10–3.80 m (NCH_2CH_2Cl), 3.82(1H), 1.20, 3.87 (EtO) ^{31}P 17.3; IR cm^{-1} 1235$\nu_{(P=O)}$, 1960$\nu_{(C=C=C)}$.

2c. Yield 82%, oil, $C_{10}H_{19}O_2PNCl$; Found %: P, 12.27; Cl, 14.03; N, 5.53: Calcd. %: P, 12.30: Cl, 14.08; N, 5.56; ^{1}H-NMR 5.04 d(1H $^2J_{HP}$ 7.2 Hz), 3.05–3.85 m (NCH_2CH_2Cl), 3.87(1H), 1.31, 2.56(I-PrO), ^{31}P 17.8; IR cm^{-1} 1230$\nu_{(P=O)}$, 1958$\nu_{(C=C=C)}$.

2. Synthesis of 4-Substituted-N-(2-chloroethyl)-2,5-dihydro-1,2-oxaphosphole-2-oxides 3a–e

General Procedure

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

3a. Yield 82%, m.p. uncorrect 85–7°C, $C_7H_{12}O_2PNCl_2$; Found %: P, 12.64; Cl, 28.99; N, 5.70; Calcd. %: P, 12.69; Cl, 29.05; N, 5.73; ^{1}H-NMR 588 d (1H $^2J_{HP}$ 24.2 Hz), 3.05–3.85 m (NCH_2CH_2Cl), 3.87 (1H); ^{31}P 28.3; IR cm^{-1} 1230$\nu_{(P=O)}$, 1590$\nu_{(C=C)}$.

3b. Yield 80% m.p. uncorrected 91–2°C, $C_7H_{12}O_2PNClBr$: Found %: P, 10.69; Cl, 12.18; N, 4.81; Br, 27.63; Calcd. %: P, 10.73; Cl, 12.28; N, 4.85; Br, 27.69; ^{1}H-NMR 588 d(1H $^2J_{HP}$ 22.4 Hz),

3.05–3.85 m (NCH_2CH_2Cl), 3.87 (1H); ^{31}P 27.9; IR cm^{-1} 1235$\nu_{(P=O)}$, 1588$\nu_{(C=C)}$.

3c. Yield 83%, m.p. uncorrected 95–7°C, $C_8H_{15}O_2PNClS$; Found %: P, 11.94; Cl, 13.68; N, 5.39; S, 12.33; Calcd. %: P, 11.97; Cl, 13.70; N, 5.41; S, 12.39; ^{1}H-NMR 588 d (1H $^2J_{HP}$ 22.4 Hz), 3.05–3.85 m (NCH_2CH_2Cl), 3.87(1H), 2.17s(MeS), ^{31}P 32.3; IR cm^{-1} 1237$\nu_{(P=O)}$, 1587$\nu_{(C=C)}$.

3. Synthesis of 2-(1,2-Alkadienyl)-2-oxo-1′,3,2-oxazaphospholane 4

General Procedure 1

To a solution of the appropriate N-(2-chloroethyl)-O-benzyl-3-alkyl-1,2-alkadienephosphonate **2d** or N-(2-chloroethyl)-O-ethylphenyl-3-alkyl-1,2-alkadienephosphonate **2e** in THF at −78°C and inert atmosphere a required amount of BuLi(1.6 M solution in hexane) was added. After warming up to room temperature and additional stirring for 1 h, 10% aqueous NH_4Cl was added, followed by water. 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.

2d. ^{1}H-NMR 5.02 d(1H $^2J_{HP}$ 6.7 Hz), 1.68 d(6H), 7.70 m, 4.13 m, 3.05–3.85 m (NCH_2CH_2Cl); ^{31}P 17.8; IR cm^{-1} 1234$\nu_{(P=O)}$, 1960$\nu_{(C=C=C)}$.

2e. ^{1}H-NMR 5.05 d(1H $^2J_{HP}$ 7.0 Hz), 1.68 d(6H), 7.70 m, 4.13 m, 4.35 m, 3.05–3.85 m (NCH_2CH_2Cl); ^{31}P 16.8; IR cm^{-1} 1236$\nu_{(P=O)}$, 1960$\nu_{(C=C=C)}$.

4. Yield %: 68, b.p. 158–9°C, $C_7H_{12}O_2PN$; Found %; P, 17.84; N, 7.98; Calcd. %: P, 17.88; N, 8.08; ^{1}H-NMR 5.04 d (1H $^2J_{HP}$ 7.2 Hz), 4.15–4.18 m(NCH_2CH_2O), 2.73 d(1HJ_{HP}10.0 Hz NH); ^{31}P 16.8; IR cm^{-1} 1230$\nu_{(P=O)}$, 1958$\nu_{(C=C=C)}$.

4. Synthesis of 2-(1,2-Alkadienyl)-2-oxo-1,3,2-oxazaphospholane 4

General Procedure 2

To a solution of 1,2-alkadienephosphonic dichloride in dry ether at −10−−8°C and stirring, a mixture of equimolar amount of 2-aminoethanol and two equivalents of triethylamine dissolved in the same solvent was added. After an hour of stirring of the reaction mixture, the precipitate was filtered off, the solvent was removed, and the residue was distilled.

5. Synthesis of 2-N-aziridine-2,5-dihydro-1,2-oxaphosphole 2-Oxides 5a–c

General Procedure

To a solution of **3a–c** in dry THF at −78°C a solution of BuLi (1.6 M in hexane) was added, allowing the mixtute to warm-up to room temperature. Ten percent aqueous NH_4Cl was added, followed by water, and the mixture was extracted with CH_2Cl_2, dried, evaporizied, and examined by NMR.

The reaction with LiCl was carried out in THF by stirring of the substrate and BuLi. The solvent was filtered, evaporated, and examined by NMR.

5a. Yield % 56, oil, $C_7H_{11}O_2PNCl$; Found %: P, 14.89; Cl, 17.00; N, 6.70; Calcd. %: P, 14.91; Cl, 17.07; N, 6.74; ^{1}H-NMR 5.88d (1H J_{HP} 24.2 Hz), 2.13 d(4H J16.1 Hz); ^{31}P 37.0.

REFERENCES

[1] J. C. Paris and B. W. Arthur, *J. Econ. Etomol.*, **58,** 699 (1965).
[2] P. B. Morgan and G. C. La Brecque, *ibid.*, **57,** 896 (1964).
[3] M. M. Crystal, *ibid.*, **57,** 726 (1964).
[4] S. C. Chang, P. H. Terry, and A. B. Borkovec, *Science*, **144,** 57 (1964).
[5] W. J. Stec, In *Specialist Periodical Report: Organophosphorus Chemistry*. London: Royal Society of Chemistry, vol. 13 (1982).
[6] T. W. Engle, G. Zon, and W. Egan, *J. Med. Chem.*, **25,** 1347 (1982).
[7] R. W. Kinas and W. J. Stec, *Phosphorus, Sulfur, and Silicon, and the Related Elements*, **51–52,** 400 (1990).
[8] Ch. M. Angelov and D. D. Enchev, *ibid.*, **34,** 163 (1987).
[9] Ch. M. Angelov and D. D. Enchev, *Bulgarian Patent N* 41902/15.09 (1987).
[10] S. Baumeister, A. Modro, and T. A. Modro, *Tetrahedron Lett.*, **30,** 2141 (1989).
[11] D. D. Enchev, *Phosphorus, Sulfur and Silicon*, **122,** 101 (1997).
[12] Ch. le Roux, S. Baumeister, and T. A. Modro, *J. Chem. Res. (S)*, 372 (1993).