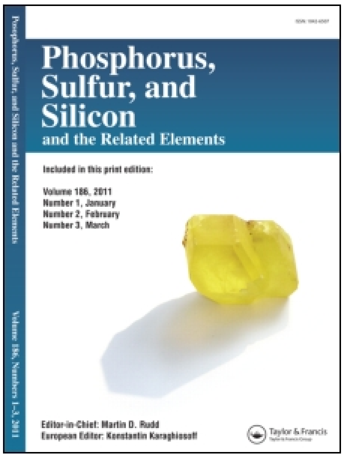

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2-CHLORO-1,3-ALKADIENYLPHOSPHONIC AMIDOESTERS AND THEIR 5,6-DIHYDRO-2H-1,2-OXAPHOSPHORINE CYCLIZATION IN REACTION WITH ELECTROPHILIC REAGENTS

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2-CHLORO-1,3-ALKADIENYLPHOSPHONIC AMIDOESTERS AND THEIR 5,6-DIHYDRO-2H-1,2-OXAPHOSPHORINE CYCLIZATION IN REACTION WITH ELECTROPHILIC REAGENTS

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The 2-chloro-1,3-alkadienylphosphonic amidoesters **2** and **3** have been prepared by the reaction of 2-chloro-1,3-alkadienylphosphonic dichlorides **1** with methanol and diethylamine or lithium bis(trimethylsilyl) amide. The synthesized amidoesters **2** and **3** have been cyclized to the 2-(N,N-diethylamido)-5,6 -dihydro-2H-1,2-oxaphosphorine 2-oxides **4** and 2-(N,N-trimethylsilylamido)-5,6-dihydro −2H-1, 2-oxaphosphorine 2-oxides **5** respectively in reaction with halogens and methylsulfenyl chloride.

Keywords: N,N-diethylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates; N,N-trimethylsilylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates; heterocyclization; 2-(N,N-diethylamido)- 5,6-dihydro-2H −1,2 -oxaphosphorine 2-oxides; 2-(N,N-trimethylsilylamido)-5,6-dihydro-2H- 1,2-oxaphosphorine 2-oxides

INTRODUCTION

It was shown that the reactions of the phosphorylated 1,3-alkadienes with electrophilic reagents[1] proceed with cyclization of the 1,3-alkadienylphosphonic system with formation of heterocyclic compounds in most cases. The reactions are studied with 1,3-dienylphosphonic dichlorides,[2] dialkyl esters,[3] acids,[4] as well as the corresponding phosphine oxides,[5] 1,3,2-dioxaphospholanes[6] and benzo[c]-1,3,2-dioxaphospholanes.[7] On the other hand, there are some publications concerning the synthesis of

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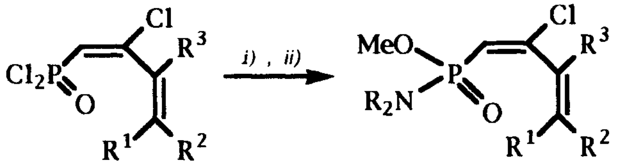
* Corresponding author

1,3-alkadienyl-1-phosphonic,[8a] 1-thiophosphonic[8b] and 2-phosphonic[8c] diamides. However, the synthesis and reaction with electrophiles of 1,3-alkadienylphosphonic amidoesters have not been investigated to date.

As a part of our continuing study on the chemistry of the phosphorylated 1,3-alkadienes, we now report the results on the synthesis of 2-chloro-1,3-alkadienylphosphonic amidoesters and their heterocyclization in the reaction with halogens and methylsulfenyl chloride.

RESULTS AND DISCUSSION

The N,N-diethylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates **2** and the N,N-trimethylsilylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates **3** were obtained in good yields (46–54%) by substitution reaction of the two chlorine atoms in the starting 2-chloro-1,3-alkadienylphosphonic dichlorides **1** with methanol in the presence of pyridine and diethylamine in the presence of triethylamine or lithium bis(trimethylsilyl) amide, respectively, according to Scheme 1:



1

2, 3

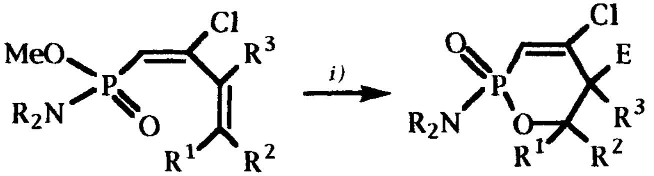
	R	R1	R2	R3
2a	Et	H	Me	Et
b	Et	H	-(CH2)4-	
c	Et	Me	Me	Me
3a	Me3Si	H	Me	Et
b	Me3Si	Me	Me	Me

Reagents and Conditions:
i) MeOH, pyridine, ether, -5 to -8 °C, rt, 1h;
ii) for **2**: Et_2NH, Et_3N, ether, 0-10 °C, 2h;
ii) for **3**: $(Me_3Si)_2NLi$, THF, -20 to -25 °C, rt, 1h;

SCHEME 1

The resulting 2-chloro-1,3-alkadienylphosphonic amidoesters **2** and **3** were isolated by column chromatography and characterized by ^1H NMR and IR spectra and elemental analysis. ^{1}H NMR spectra of **2** show a triplet and a multiplet signals for diethylamido group but the spectra of **3** show a singlet signal for bis(trimethylsilyl) amido group in addition to the signals of the protons due to the initial dichlorides **1**. Analysis of the ^{1}H NMR spectra of the amidoesters with different substituents at C^4 atom (**2a** and **3a**) shows that the compounds exist as mixtures of diastereoisomers in the ratio *E, Z* : *E, E* = 2.8–3.0 : 1. The IR spectra of **2** and **3** exhibit an additional characteristic absorption band due to the Me-O-P bonds (**Table II**). The data from elemental analysis confirm the structure of the compounds prepared (**Table I**).

The amidoesters **2** and **3** isolated in preparative amounts allowed us to study their chemical behavior in the reaction with chlorine, sulfuryl chloride, bromine and methylsulfenyl chloride. The interaction was carried out in 1,2-dichloroethane by heating at 55–60 °C. We established that in these conditions and irrespective of the type of the electrophilic reagent as well as the kind of the substituent in the amido group, a six-membered heterocyclization occured and only 2-(N,N-diethylamido)-5,6-dihydro-2H-1,2-oxaphosphorine 2-oxides **4** or 2-(N,N-trimethylsilylamido)-5,6-dihydro-2H-1,2-oxaphosphorine 2-oxides **5** were isolated in 46–58% yields as shown in **Scheme 2**:



2, 3 4, 5

	R	R^1	R^2	R^3	E
4a	Et	H	Me	Et	Cl
b	Et	H	-(CH$_2$)$_4$-		Br
c	Et	Me	Me	Me	Br
d	Et	Me	Me	Me	SMe
5a	Me$_3$Si	H	Me	Et	Cl
b	Me$_3$Si	Me	Me	Me	SMe

Reagents and Conditions:
i) E-Nu (Cl_2, SO_2Cl_2, Br_2 or MeSCl) $ClCH_2CH_2Cl$, 55 to 60 °C, 4h;

SCHEME 2

TABLE I. Yields and elemental analysis data of the N,N-diethylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates **2** and the N,N-trimethylsilylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates **3**

No.	*R* (*R*^{1})	*R*^{2} (*R*^{3})	*Yield %*	*Elemental analysis, %*						
				Found			*Formula*	*Calcd.*		
				N	*P*	*Cl*		*N*	*P*	*Cl*
2a	Et (H)	Me (Et)	54	5.14	11.03	12.88	$C_{12}H_{23}O_2NPCl$	5.01	11.07	12.67
b	Et (H)	$(CH_2)_4$	49	4.76	10.53	12.26	$C_{13}H_{23}O_2NPCl$	4.80	10.62	12.15
c	Et (Me)	Me (Me)	52	5.12	11.21	12.75	$C_{12}H_{23}O_2NPCl$	5.01	11.07	12.67
3a	Me_3Si (H)	Me (Et)	46	3.93	8.35	9.78	$C_{14}H_{31}O_2NPClSi_2$	3.81	8.42	9.64
b	Me_3Si (Me)	Me (Me)	47	3.88	8.56	9.80	$C_{14}H_{31}O_2NPClSi_2$	3.81	8.42	9.64

TABLE II. ^1H NMR and IR spectral data of the N,N-diethylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates **2** and the N,N-trimethylsilylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates **3**

No.		*=CH*	*^1H NMR spectra, δ, ppm*				*MeO*	*J, Hz*	*IR spectra, cm^{-1}*		
			R	*R^1*	*R^2*	*R^3*		*$^2J_{HP}$*	*Me-O-P*	*P=O*	*C=C-C=C*
2a	*E,E*	6.00d	Me1.23t	6.18m	1.88d	Me 1.06t	3.81d	11.9			
			CH_2 2.94m			CH_2 2.41m			1017	1274	1609, 1665
	E,Z	6.12d	Me 1.28t	1.85d	5.67m	Me 1.12t	3.81d	12.4			
			CH_2 2.99m			CH_2 2.41m					
b		5.78d	Me 1.18t	6.12m	2.33s	1.76s	3.75d	10.6	1009	1257	1604, 1654
			CH_2 2.93m								
c		5.89d	Me 1.19t	1.73s	1.79s	1.85s	3.72d	10.9	1012	1265	1598, 1650
			CH_2 2.96m								
3a	*E,E*	6.04d	0.32s	6.13m	1.80d	Me 1.09t	3.89d	12.3			
						CH_2 2.54m			1023	1277	1603, 1664
	E,Z	6.14d	0.32s	1.78d	5.65m	Me 1.14t	3.89d	12.9			
						CH_2 2.54m					
b		5.92	0.34s	1.75s	1.81s	1.88s	3.74d	11.3	1018	1273	1600, 1667

TABLE III. Melting points, yields and elemental analysis data of the 2-(N,N-diethylamido)-5,6-dihydro-2H–1,2-oxaphosphorine 2-oxides **4** and the 2-(N,N-trimethylsilylamido)-5,6-dihydro-2H-1,2-oxaphosphorine 2-oxides **5**

						Elemental analysis, %				
No.	*R (R^1)*	*R^2 (R^3)*	*E*	*m.p. °C*	*Yield %*	*Found*		*Formula*	*Calcd.*	
						N (P)	*Hlg (S)*		*N (P)*	*Hlg (S)*
4a	Et	Me	Cl	83–4	56	4..73	23.88	$C_{11}H_{20}O_2NPCl_2$	4.67	23.62
	(H)	(Et)				(10.26)	(-)		(10.32)	(-)
b	Et	$(CH_2)_4$	Br	107–8	51	3.99	32.55	$C_{12}H_{20}O_2NPClBr$	3.93	32.35
	(H)					(1.11)	(-)		(8.69)	(-)
c	Et	Me	Br	100–1	53	4.03	33.37	$C_{11}H_{20}O_2NPClBr$	4.06	33.48
	(H)	(Me)				(9.07)	(-)		(8.99)	(-)
d	Et	Me	SMe	94–5	58	4.43	11.44	$C_{12}H_{23}O_2NSPCl$	4.49	11.37
	(H)	(Me)				(9.97)	(10.21)		(9.93)	(10.28)
5a	Me_3Si	Me	Cl	121–2	48	3.77	18.36	$C_{13}H_{28}O_2NPCl_2Si_2$	3.61	18.25
	(H)	(Et)				(7.90)	(-)		(7.97)	(-)
b	Me_3Si	Me	SMe	117–8	46	3.43	8.88	$C_{14}H_{31}O_2NSPClSi_2$	3.50	8.86
	(Me)	(Me)				(7.61)	(8.11)		(7.74)	(8.02)

TABLE IV. ^1H NMR and IR spectral data of the 2-(N,N-diethylamido)-5,6-dihydro-2H-1,2-oxaphosphorine 2-oxides **4** and the 2-(N,N-trimethylsilylamido)-5,6-dihydro-2H-1,2-oxaphosphorine 2-oxides **5**

No.	*=CH*	*^1H NMR spectra, δ, ppm*				*E*	*J, Hz $^2J_{HP}$ ($^3J_{HP}$)*	*IR, cm^{-1}*		
		R	*R^1*	*R^2*	*R^3*			*P-O-C*	*P=O*	*C=C*
4a	6.23d	Me 1.09t	4.85m	1.56d	Me 0.92t	-	8.1	995	1270	1590
		CH_2 2.95m			CH_2 2.08m		(6.3)			
b	6.15d	Me 1.03t	4.57m	2.13s	1.67s	-	8.4	991	1280	1596
		CH_2 3.02m					(6.5)			
c	6.19d	Me 1.04t	1.70s	1.75s	1.84s	-	8.0	989	1288	1590
		CH_2 3.00m								
d	6.08d	Me 1.06t	1.58m	1.64d	1.38s	2.12s	9.4	998	1273	1584
		CH_2 2.96m								
5a	6.24d	0.26s	4.75m	1.58d	Me 1.00t	-	8.5	995	1277	1596
					CH_2 2.02m		(6.2)			
b	6.16d	0.25s	1.62s	1.67s	1.40s	2.18s	9.7	994	1276	1588

Structural assignment of the heterocyclic compounds **4** and **5** was clearly made by their ^1H NMR and IR spectra **(Table IV)** as well as elemental analysis data **(Table III)**. Formation of ring compounds is evident from the fact that in the ^1H NMR spectra of the crude reaction mixtures a singlet (δ 3.01–3.08 ppm) of the protons of methyl halide is observed and from the fact that the signal of the methoxy group is absent. Formation of six-membered ring was judged on the basis of the doublet signal of the =CH proton which appears at low field (δ 6.08–6.24 ppm). The coupling constant of this proton with phosphorus (^2JHP 8.0–9.7 Hz) is in agreement with data reported for similar structures.[2–7] In compounds **4a, 4b** and **5a** the proton at C^6 atom in the ring (δ 4.57–4.85 ppm) shows a considerable coupling constant (^3JHP 6.2–6.5 Hz) which is characteristic for the P-O-CH moiety. If the resulting products **4** and **5** were five-membered heterocycles or adducts, this proton would resonate in another region and no such coupling interaction would be observed. The IR spectra of **4** and **5** exhibit absorption bands characteristic for endocyclic double bond, for P=O group and for the ring P-O-C moiety (absence of a band for the Me-O-P function as is observed in the IR spectra of the 2-alkoxy substituted 5,6-dihydro-2H-1,2-oxaphosphorine 2-oxides[3]).

In summary, the 2-chloro-1,3-alkadienylphosphonic amidoesters are readily available compounds which can be used as precursors of 2-amido substituted 5,6-dihydro-2H–1,2-oxaphosphorine 2-oxides. Moreover, the above results again[1] show that the reactions of the various 2-chloro-1,3-alkadienylphosphonic derivatives[2–7] with electrophilic reagents proceed regiospecifically with formation of six- or five-membered heterocyclic compounds in most cases.

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. Reactions were carried out in oven-dried glassware under an argon atmosphere and exclusion of moisture. All compounds were checked for their purify on TLC plates.

Starting materials: 2-Chloro-1,3-alkadienylphosphonic dichlorides (**1**) were synthesized by chlorination reaction of allenylphosphonic dichlorides according to the literature.[9] The methylsulfenyl chloride was prepared from dimethyl disulfide and chlorine or sulfuryl chloride in 1,2-dichloroethane.

*Synthesis of N,N-diethylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates (**2**). General procedure:*

To a solution of the 2-chloro-1,3-alkadienylphosphonic dichloride (**1**) (50 mmol) in dry diethyl ether (100 ml) at –8 to –5 °C was added dropwise with stirring a solution of the mixture of methanol (50 mmol) and pyridine (51 mmol) in the same solvent (20 ml). The reaction mixture was stirred for an hour at room temperature and then to the reaction mixture was added a solution of the mixture of diethylamine (50 mmol) and triethylamine (51 mmol) in dry ether (30 ml) at 0-10 °C. The stirring was continued for 2h at the same temperature. Then the precipitate of pyridine and triethylamine hydrochlorides was filtered off, the solvent was removed using a rotatory evaporater and the residue was chromatographed on column (silica gel, Kieselgel Merck 60 F_{254}) with hexane/ethylacetate 1:1 as eluent to give the pure products as light yellow oils. Yield: 49–54 %.

*Synthesis of N,N-trimethylsilylamido-O-methyl-2-chloro-1,3-alkadienylphosphonates (**3**). General procedure:*

To a solution of the 2-chloro-1,3-alkadienylphosphonic dichloride (**1**) (20 mmol) in dry diethyl ether (40 ml) at –8 to –5 °C was added dropwise with stirring a solution of the mixture of methanol (50 mmol) and pyridine (51 mmol) in the same solvent (20 ml). The reaction mixture was stirred for an hour at room temperature and then the precipitate was filtered off. To the reaction mixture was added a solution of lithium bis(trimethysilyl) amide (20 mmol) in dry THF (10 ml) at –20 to –25 °C. The stirring was continued for 1h at room temperature. Then, the mixture was quenched with 2N HCl, extracted with ether, washed with saturated NaCl, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a column (silica gel, Kieselgel Merck 60

F_{254}) with ethylacetate as a eluent to give the pure products as light yellow oils, which had the following properties (**Table I** and **II**).

Synthesis of 2-(N,N-diethylamido)–5,6-dihydro-2H-1,2-oxaphosphorine 2-oxides (**4**) *and 2-(N,N-trimethylsilylamido)-5,6-dihydro-2H-1,2-oxaphosphorine 2-oxides* (**5**). *General procedure:*

A solution of 5 mmol of electrophilic reagent (Cl_2, SO_2Cl_2, Br_2 or MeSCl) in dry 1,2-dichloroethane (10 ml) was slowly added, with stirring at 55–60°C, to a solution of 5 mmol of N,N-diethylamido-O-methyl-2-chloro-1,3-alkadienylphosphonate (**2**) or N,N-trimethylsilylamido-O-methyl-2-chloro-1,3-alkadienylphosphonate (**3**) in the same solvent (10 ml). After stirring for 4 hs at the same temperature, the solvent was removed. The residue was recrystallized from hexane or heptane to give the pure products as white crystals, which had the following properties (**Table III** and **IV**).

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