

REACTIVITY OF CONJUGATED PHOSPHAZENES DERIVED FROM DEHYDROASPARTIC ESTERS WITH ACYL HALIDES. SYNTHESIS OF 5(4*H*)-OXAZOLONE[‡]

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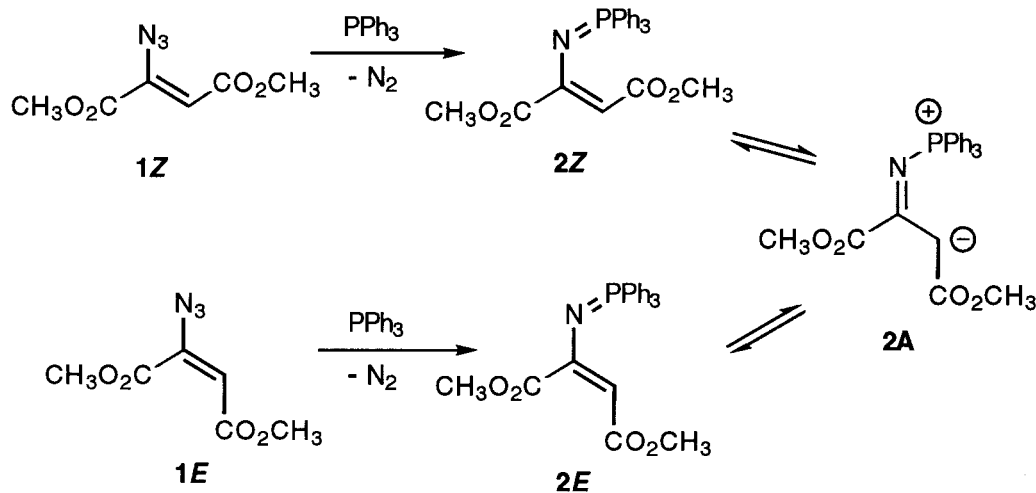
Abstract- The reactivity of *N*-vinyl phosphazenes derived from dehydroaspartic esters towards acyl halides is reported. Treatment of conjugated phosphazene with acyl halides led to the formation of *N*-acylated dehydroaspartic esters and alkenyl-5(4*H*)-oxazolones. When the reaction was performed in the presence of diethylamine, 1-diethylamino-3,4-dimethoxycarbonyl-2-aza-1,3-butadiene was obtained. Reaction of substituted 5(4*H*)-oxazolones with water, ethanol and amines gave *N*-acylated dehydroaspartic acid derivatives.

Phosphazenes¹ represent an important class of compounds and have attracted a great deal of attention in recent years because of their broad range of applications. Moreover, the utility of *N*-vinyl phosphazenes² has been demonstrated in the construction of carbon-nitrogen double bonds,^{3,4} and they are key intermediates in the preparation of heterocycles,³⁻⁹ and for the construction of the framework of pharmacologically active alkaloids.¹⁰ In recent years, we have been involved in the study of phosphazenes^{1b} and their usefulness in the preparation of acyclic^{3,4,11} and heterocyclic compounds.^{5,8,12} We have reported both the aza-Wittig reaction of conjugated phosphazenes³ and of phosphazenes derived from α -^{4e,f} or β -amino acids^{4a-c} with carbonyl compounds, and the use of these compounds as valuable intermediates in organic synthesis. Here we wish to explore the reactivity towards acyl halides of *N*-functionalized phosphazenes (**2**) derived from dehydroaspartic esters, having two methoxycarbonyl groups at the α and β positions (Scheme 1). We studied this reaction in order to establish the regioselectivity of the process (1,2- *versus* 1,4-addition) as well as their usefulness in the preparation of acyclic compounds such as *N*-acylated-dehydroaspartic ester derivatives (**5**) or 1-aminoazadiene (**8**) and of heterocyclic compounds such as 4-methylidene-5(4*H*)-oxazolones (**7**). Functionalized 2-azadienes have acquired great relevance as building blocks in organic synthesis¹³ while aspartic ester derivatives have been used in the preparation of peptides^{14a} and constrained scaffolds.^{14b,c} 5(4*H*)-Oxazolones can be used for the preparation of biologically active metal complexes,^{15a} α -amino acids,^{15b,c} peptides^{15d,e} and inhibitors of the herpes

[‡] Dedicated to Professor T. Mukaiyama on the occasion of his 73rd birthday

proteases^{15f} and synthons in organic synthesis for the preparation of a wide range of acyclic and cyclic derivatives by means of their reaction with nucleophilic reagents^{16a-c} and as dienophiles or dipolarophiles in cycloaddition reactions.^{16d-e}

N-Vinyllic phosphazenes (**2**) were prepared, with a high yield, through the classical Staudinger reaction^{4b} of triphenylphosphine with dimethyl azidoethylenedicarboxylate in CH₂Cl₂ at -5°C. Although a *Z* configuration was observed in the phosphazene (**2Z**) obtained from the *Z*-vinyl azide, a progressive isomerization towards the *E* isomer (**2E**) was observed in solution at room temperature until a 30/70 mixture of isomers(**2Z**)/(**2E**) was obtained. Similar thermal isomerization has previously been described for conjugated phosphazenes.^{7c} Formation of the *E* isomer (**2E**) could be explained by means of the contribution of the **2A**-form containing a weak double-bond character.^{4d,7c} When the *E*-vinyl azide was used, and the reaction was performed at -5°C, only the formation of phosphazene (**2E**) was observed (Scheme 1). But an isomerization towards the *Z* isomer (**2Z**) was observed in solution at room temperature, and a 30/70 mixture of isomers(**2Z**)/(**2E**) was obtained. Since the thermal isomerization between isomers *E* and *Z* takes place easily, either every isomer or a mixture can be used for subsequent reaction giving similar results. The *E* and *Z* configurations of both isomers were assigned by means of ¹H NMR spectroscopy. The olefinic proton appeared at δ_H = 5.81 ppm as a doublet (⁴*J*_{PH} = 6.6 Hz) in compound (**2Z**) while in the *E* isomer appeared at δ_H = 4.71 ppm as a singlet.^{4b,7c}

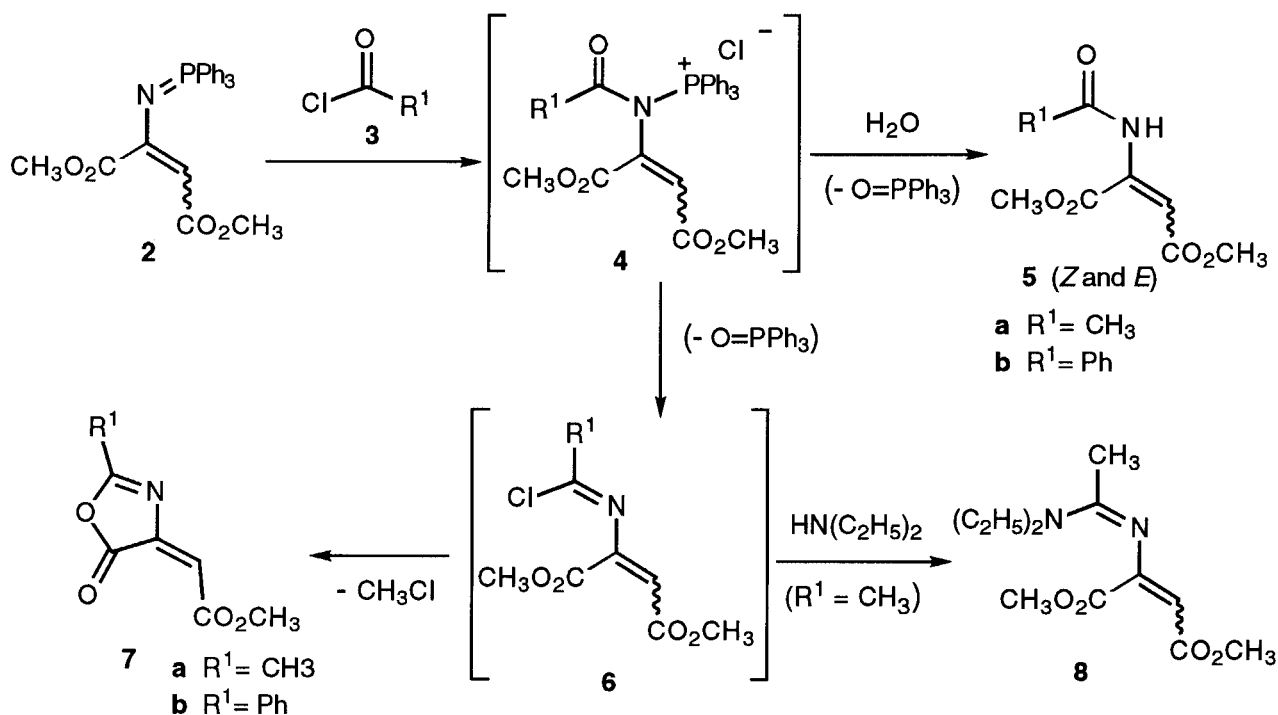


Scheme 1

After the synthesis of *N*-vinyllic phosphazene (**2**), its reaction with acyl halides (**3**) was explored. When phosphazene (**2**) reacted with benzoyl chloride (**3**, R¹ = Ph) at room temperature in CH₂Cl₂, a mixture of the *Z* and *E* *N*-acyl α,β-dehydroaspartic esters (**5**) was obtained (see Table 1, Entry 1), whereas in benzene the heterocyclic 5(4*H*)-oxazolone (**7b**) was also observed (see Table 1, Entry 2), but higher temperature (110°C) led mainly to the heterocyclic 5(4*H*)-oxazolone (**7b**) and a small quantity of the acyclic *E* *N*-acylated α,β-dehydroamino acid ester (**5**) (Table 1, Entry 3). In a similar way, when the reaction of *N*-vinyllic phosphazene (**2**) with acetyl chloride was performed in benzene, a mixture of *E* *N*-acylated α,β-dehydroaspartic ester (**5**) and the 5(4*H*)-oxazolone (**7a**) (see Table 1, Entry 4) was obtained, but higher temperature (110°C) led to the heterocyclic 5(4*H*)-oxazolones (**7a**) and a small quantity of the acyclic *E* *N*-

acylated α,β -dehydroamino acid ester (**5**) (Table 1, Entry 5). The heterocyclic compounds (**7**) were obtained as a single isomer. The configuration between the exocyclic methoxycarbonyl group and the imine group in the oxazolone ring was assigned as *trans* according to the configuration of products obtained by subsequent reactions of 5(4*H*)-oxazolone (**7**) and nucleophines (*vide infra*).

The formation of the *Z* and *E* *N*-acylated α,β -dehydroaspartic esters (**5**) can be explained by 1,2-addition of acyl halides to the phosphazene group followed by hydrolysis of the *N*-acylaminophosphonium salt (**4**). This is consistent with the reported behavior of *N*-vinylic phosphazenes derived from α -amino acids.^{4c} The formation of heterocycles (**7**) could also be explained by the initial formation of the same *N*-acylaminophosphonium salt (**4**) derived from the aspartic esters, followed by subsequent loss of Ph_3PO leading to the formation of haloimine (**6**).^{4c} Cyclisation of compound (**6**) with loss of methyl chloride¹⁷ may give oxazolones (**7**).



Scheme 2

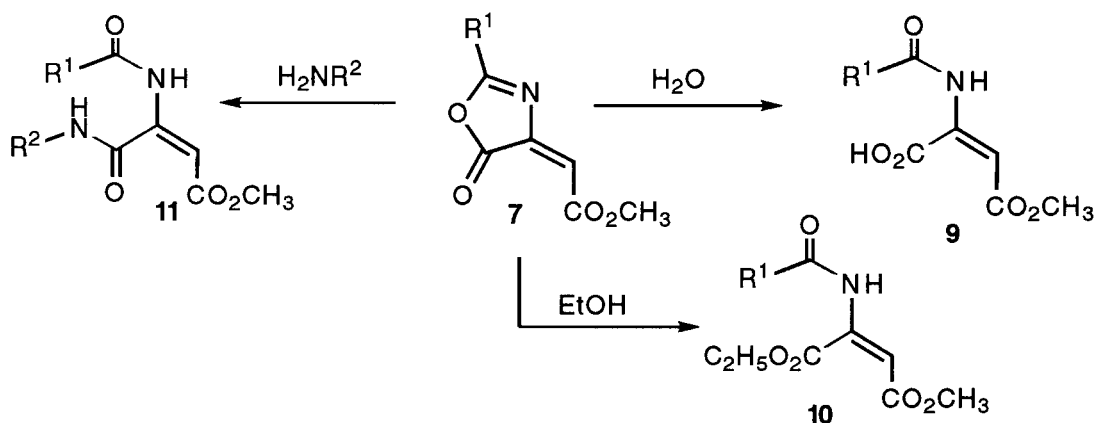
Table 1. Reaction of phosphazene (**2**) with acyl chlorides

Entry	R^1	Solvent	T ($^{\circ}\text{C}$)	time	Yield (%)	5Z/5E/7
1	Ph	CH_2Cl_2	r t	48 h	79	41/59/0
2	Ph	C_6H_6	r t	72 h	81	22/54/24
3	Ph	Tol.	110	16 h	87	0/22/78
4	CH_3	C_6H_6	r t	16 h	84	0/62/38
5	CH_3	Tol.	110	16 h	88	0/13/87
6	CH_3	Tol	110	20 h ^a	38	8

^a Reaction time of "one pot" reaction of **2** with acetyl chloride and $(\text{C}_2\text{H}_5)_2\text{NH}$.

In order to extent the synthetic usefulness of the acylation reaction of phosphazenes derived from aspartic esters and to test if the proposed halo imines (**6**) could be involved in the process, we explored this reaction in the presence of amines to obtain the not readily available 1-amino-2-azabuta-1,3-diene (**8**). Compound (**8**) was obtained after "one-pot" reaction of phosphazene (**2**) with acetyl chloride followed by addition of diethylamine (Scheme 1, Table 1, Entry 6). The formation of this heterodiene (**8**) containing an electron-donor and two electron-withdrawing groups can be assumed to proceed *via* the salt (**4**), leading to the chloro imine (**6**) and subsequent reaction with diethylamine.

The versatility of 5(4*H*)-oxazolones as reagents in organic chemistry is well known. They have been used in medicinal chemistry¹⁵ and for the preparation of acyclic and cyclic derivatives.¹⁶ In this context, the reactivity of oxazolones (**7**) towards some nucleophilic reagents such as water, ethanol and amines was studied. The ring opening of oxazolone (**7**) can be easily performed by addition of water affording the *E*-*N*-acyl aspartic monoester (**9**) (Table 2, Entries 1 and 2). When the reaction was performed using EtOH as solvent, the ring opening with addition of ethanol took place with formation of dehydroaspartic ester derivatives (**10**) containing different ester groups (Table 2, Entry 3). Finally, oxazolone (**7b**) was cleaved by treatment with amines at 50°C to give the methyl *E*-3-acylamino-3-carbamoylacrylates (**11**) (Scheme 3, Table 2, Entries 4-6).



Scheme 3

Table 2. Dehydroaspartic acid derivatives (**9-11**)

Entry	Compound	R ¹	Nucleophilic reagent	Yield (%) ^a	R _f
1	9a	CH ₃	H ₂ O	93	0.17 ^b
2	9b	Ph	H ₂ O	90	0.15 ^b
3	10	Ph	C ₂ H ₅ OH	76	0.42 ^c
4	11a	Ph	4-CH ₃ -Ph-NH ₂	62	0.40 ^d
5	11b	Ph	CH ₂ =CH-CH ₂ -NH ₂	70	0.21 ^c
6	11c	Ph	C ₂ H ₅ O ₂ C-CH ₂ -NH ₂	58	0.16 ^c

^a Yields of purified compounds isolated by column chromatography. ^b Eluent: AcOEt. ^c Eluent: 1/3 AcOEt/Hex. ^d Eluent: 1/1 AcOEt/Hex.

Table 3. Selected spectral data for compounds (**2**, **5-11**)

Compound	^1H NMR (CDCl_3) ^a δ (ppm)	^{13}C NMR (CDCl_3) ^a δ (ppm)	IR ^b ν (cm^{-1})	MS ^c (m/z)
2Z ^d	3.35 (s, 3H, $\text{CH}_3\text{-O}$), 3.73 (s, 3H, $\text{CH}_3\text{-O}$), 5.81 (d, 1H, $^4J_{\text{PH}} = 6.5\text{ Hz}$, =CH), 7.39-7.50 (m, 9H, Ar), 7.77-7.85 (m, 6H, Ar).	50.5 ($\text{CH}_3\text{-O}$), 52.1 ($\text{CH}_3\text{-O}$), 100.6 (d, $J_{\text{PC}} = 17.5\text{ Hz}$, =CH), 128.3-132.7 (m), 149.3, 166.7, 168.0.	1717 1694 1558	419 (M^+ , 8%) 404 ($\text{M}^+ - 15$, 12%) 360 ($\text{M}^+ - 59$, 53%)
2E ^e	3.29 (s, 3H, $\text{CH}_3\text{-O}$), 3.57 (s, 3H, $\text{CH}_3\text{-O}$), 4.71 (s, 1H, =CH), 7.36-7.48 (m, 9H, Ar), 7.61-7.68 (m, 6H, Ar).	50.5 ($\text{CH}_3\text{-O}$), 51.9 ($\text{CH}_3\text{-O}$), 94.8 (d, $J_{\text{PC}} = 16.1\text{ Hz}$, =CH), 128.3-132.7 (m), 168.4, 169.2.	1726 1676 1547	419 (M^+ , 6%) 404 ($\text{M}^+ - 15$, 8%) 360 ($\text{M}^+ - 59$, 37%)
5aE	2.10 (s, 3H, CH_3CO), 3.78 (s, 3H, $\text{CH}_3\text{-O}$), 3.70 (s, 3H, $\text{CH}_3\text{-O}$), 5.41 (s, 1H, =CH), 10.1 (s, 1H, NH)	23.4 (CH_3CO), 51.8 ($\text{CH}_3\text{-O}$), 53.0 ($\text{CH}_3\text{-O}$), 101.0 (=CH), 143.7 (C=), 164.2, 168.0, 168.3.	3310 1745 1685 1632	201 (M^+ , 5%),
5bZ	3.75 (s, 3H, $\text{CH}_3\text{-O}$), 3.82 (s, 3H, $\text{CH}_3\text{-O}$), 5.97 (s, 1H, =CH), 7.45-7.80 (m, 5H, Ar), 11.52 (s, 1H, NH)	52.0, 53.0, 101.3, 128.2, 128.6, 130.0, 133.2, 144.4, 164.4, 168.7, 170.8.	3300 1741 1680	263 (M^+ , 11%) 262 ($\text{M}^+ - 1$, 25%),
5bE	3.73 (s, 3H, $\text{CH}_3\text{-O}$), 3.85 (s, 3H, $\text{CH}_3\text{-O}$), 5.53 (s, 1H, =CH), 7.43-7.56 (m, 3H, Ar), 7.87 (m, 2H, Ar), 11.18 (s, 1H, NH)	51.8 ($\text{CH}_3\text{-O}$), 52.9 ($\text{CH}_3\text{-O}$), 101.1 (=CH), 127.7, 128.4, 129.6, 132.9, 144.4, 164.2, 164.7, 168.7.	3280 1739 1686	263 (M^+ , 20%) 262 ($\text{M}^+ - 1$, 100%),
7a	2.44 (s, 3H, CH_3), 3.89 (s, 3H, $\text{CH}_3\text{-O}$), 6.82 (s, 1H, =CH).	23.4 (CH_3), 53.1 ($\text{CH}_3\text{-O}$), 100.4 (=CH), 144.9 (C=), 164.2, 168.2, 171.2.	1740 1758	169 (M^+ , 9%)
7b	3.94 (s, 3H, $\text{CH}_3\text{-O}$), 6.87 (s, 1H, =CH), 7.43-7.59 (m, 3H, Ar), 8.23 (m, 2H, Ar).	53.3 ($\text{CH}_3\text{-O}$), 111.3 (=CH), 128.8, 128.9, 130.1, 133.9, 152.5, 158.3, 163.1, 164.8.	1747 1762	231 (M^+ , 31%)
8	1.14 (t, 6H, $^3J_{\text{HH}} = 6.7\text{ Hz}$, CH_3), 1.81 (s, 3H, CH_3), 3.36 (m, 4H, $^3J_{\text{HH}} = 6.7\text{ Hz}$, CH_2), 3.58 (s, 3H, $\text{CH}_3\text{-O}$), 3.71 (s, 3H, $\text{CH}_3\text{-O}$), 5.99 (s, 1H, =CH).	13.3 (CH_3), 15.6 (CH_3), 42.8 (CH_2), 50.8 ($\text{CH}_3\text{-O}$), 52.5 ($\text{CH}_3\text{-O}$), 103.2 (=CH), 151.1 (C=), 157.4, 166.5, 166.9.	1732 1709 1584	256 (M^+ , 7%) 225 ($\text{M}^+ - 31$, 7 %)
9a	2.06 (s, 3H, CH_3CO), 3.76 (s, 3H, $\text{CH}_3\text{-O}$), 5.52 (s, 1H, =CH), 10.3 (s, 1H, NH), 12.8 (s, 1H, COOH).	23.2 (CH_3), 52.7 ($\text{CH}_3\text{-O}$), 102.5 (=CH), 143.0 (C=), 164.5, 168.2, 169.1.	3500-2700 1745 1705 1632	187 (M^+ , 8 %)
9b	3.85 (s, 3H, $\text{CH}_3\text{-O}$), 5.53 (s, 1H, =CH), 7.38-7.46 (m, 3H, Ar), 7.82-7.87 (m, 2H, Ar), 11.0 (s, 1H, NH).	53.2 ($\text{CH}_3\text{-O}$), 100.0 (=CH), 128.9, 129.0, 129.1, 133.3, 146.3 (C=), 164.2, 164.6, 171.9.	3600-2700 1739 1679 1626	249 (M^+ , 13 %)

Table 3. (Continued)

Com- pound	^1H NMR (CDCl_3) ^a δ (ppm)	^{13}C NMR (CDCl_3) ^a δ (ppm)	IR ^b ν (cm^{-1})	MS ^c (m/z)
10	1.25 (t, 3H, $^3J_{\text{HH}} = 7.1$ Hz, CH ₃), 3.85 (s, 3H, CH ₃ -O), 4.18 (q, 2H, $^3J_{\text{HH}} = 7.1$ Hz, CH ₂), 5.52 (s, 1H, =CH), 7.41-7.53 (m, 3H, Ar), 7.88 (m, 2H, Ar), 11.19 (s, 1H, NH).	14.1 (CH ₃), 53.1 (CH ₃ -O), 61.1 (CH ₂), 101.8 (=CH), 127.9, 128.9, 129.0, 131.9, 144.4 (C=), 164.43, 164.5, 168.4.	3283 1743 1681 1630	277 (M^+ , 3%) 204 ($\text{M}^+ - 73$, 71%)
11a	2.32 (s, 3H, CH ₃), 3.90 (s, 3H, CH ₃ -O), 5.51 (s, 1H, =CH), 7.14 (m, 2H, Ar), 7.41-7.60 (m, 5H, Ar), 7.76 (s, 1H, NH), 7.96 (m, 2H, Ar), 11.25 (s, 1H, NH).	21.2 (CH ₃), 53.4 (CH ₃ -O), 105.5 (=CH), 120.8, 128.3, 129.1, 129.9, 132.3, 133.1, 134.6, 135.2, 142.7 (C=), 165.3, 165.5, 168.7.	3374 1723 1653	338 (M^+ , 16%)
11b	3.82 (s, 3H, CH ₃ -O), 3.88 (m, 2H, CH ₂), 5.08-5.18 (m, 2H, H ₂ C=), 5.51 (s, 1H, =CH-CO), 5.73-5.8 (m, 1H, =CH), 6.01 (s, 1H, NH), 7.38-7.50 (m, 3H, Ar), 7.87-7.90 (m, 2H, Ar), 11.98 (s, 1H, HN-C=).	41.8 (CH ₂), 53.0 (CH ₃ -O), 104.7, 116.8, 127.9, 128.8, 132.8, 133.2, 141.8, 165.0, 165.3, 167.0.	3333 1738 1637	288 (M^+ , 5%) 257 ($\text{M}^+ - 31$, 10%)
11c	1.21 (t, 3H, $^3J_{\text{HH}} = 7.2$ Hz, CH ₃), 3.83 (s, 3H, CH ₃ -O), 4.03 (d, 2H, $^3J_{\text{HH}} = 5.2$ Hz, CH ₂ -NH), 4.18 (q, 2H, $^3J_{\text{HH}} = 7.2$ Hz, CH ₂), 5.51 (s, 1H, =CH), 6.20 (m, 1H, NH), 7.38-7.51 (m, 3H, Ar), 7.87-7.90 (m, 2H, Ar), 11.86 (s, 1H, HN-C=).	14.1 (CH ₃), 41.3 (CH ₂), 53.0 (CH ₃ -O), 61.8 (CH ₂), 103.5 (=CH), 128.0, 128.8, 132.1, 138.8, 142.6 (C=), 164.8, 167.1, 169.3.	3353 1743 1690 1652	334 (M^+ , 3%) 303 ($\text{M}^+ - 31$, 4%)

^a Obtained on a Varian VXR 300 Spectrometer. ^b Recorded in a Nicolet FTIR Magna 550. ^c Obtained on a Hewlett Packard 5890 Spectrometer. ^d ^{31}P NMR (CDCl_3): 8.7 ppm. ^e ^{31}P NMR (CDCl_3): 11.8 ppm.

In conclusion, a new approach to the formation of *N*-acylated dehydroaspartic esters (**5**), alkenyl-5(4*H*)-oxazolones (**7**) and 1-diethylamino-3,4-dimethoxycarbonyl-2-aza-1,3-butadiene (**8**), from *N*-vinyllic phosphazenes derived from dehydroaspartic esters and acyl halides is reported. Ring opening of 5(4*H*)-oxazolones with water, ethanol and amines gave *N*-acylated dehydroaspartic acid derivatives containing a free carboxylic acid (**9**), an ester (**10**) or an amide group (**11**) in the α -position.

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