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

Francisco Palacios*, Marta Legido, Itziar Perez de Heredia, and Gloria Rubiales

Departamento de Química Orgánica, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain

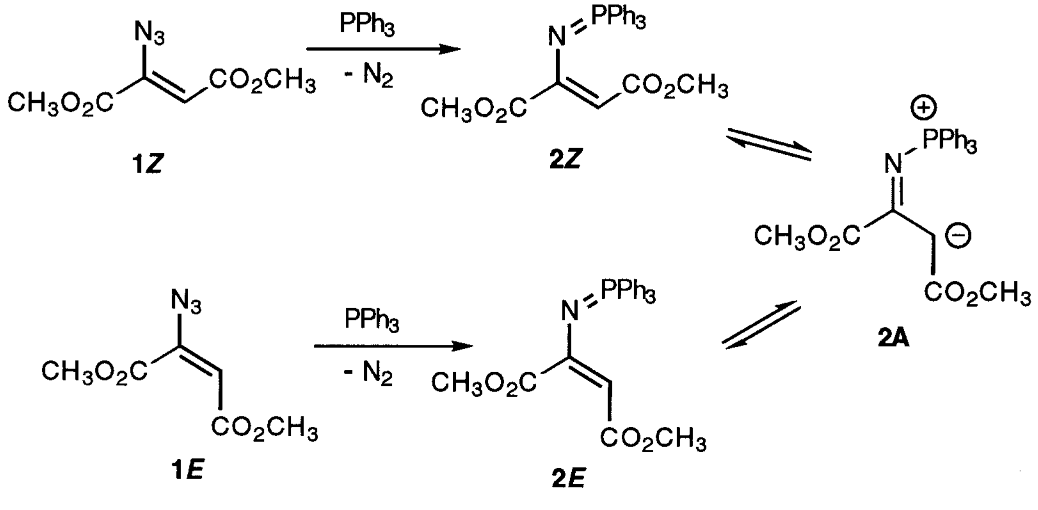
E-mail: qoppagaf@vf.ehu.es

Abstract- The reactivity of *N*-vinylic 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.

Phosphazenes[1] 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*-vinylic phosphazenes[2] 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 phosphazenes[3] 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 synthesis[13] 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-Vinylic phosphazenes (**2**) were prepared, with a high yield, through the classical Staudinger reaction[4b] of triphenylphosphine with dimethyl azidoethylenedicarboxylate in CH_2Cl_2 at -5°C. Although a *Z* configuration was observed in the phosphazene (**2*Z***) obtained from the *Z* -vinyl azide, a progressive isomerization towards the *E* isomer (**2*E***) was observed in solution at room temperature until a 30/70 mixture of isomers(**2*Z***)/(**2*E***) was obtained. Similar thermal isomerization has previously been described for conjugated phosphazenes.[7c] Formation of the *E* isomer (**2*E***) 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 (**2*E***) was observed (Scheme 1). But an isomerization towards the *Z* isomer (**2*Z***) was observed in solution at room temperature, and a 30/70 mixture of isomers(**2*Z***)/(**2*E***)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 ($^4J_{PH}$= 6.6 Hz) in compound (**2*Z***) while in the *E* isomer appeared at δ_H= 4.71 ppm as a singlet .[4b, 7c]

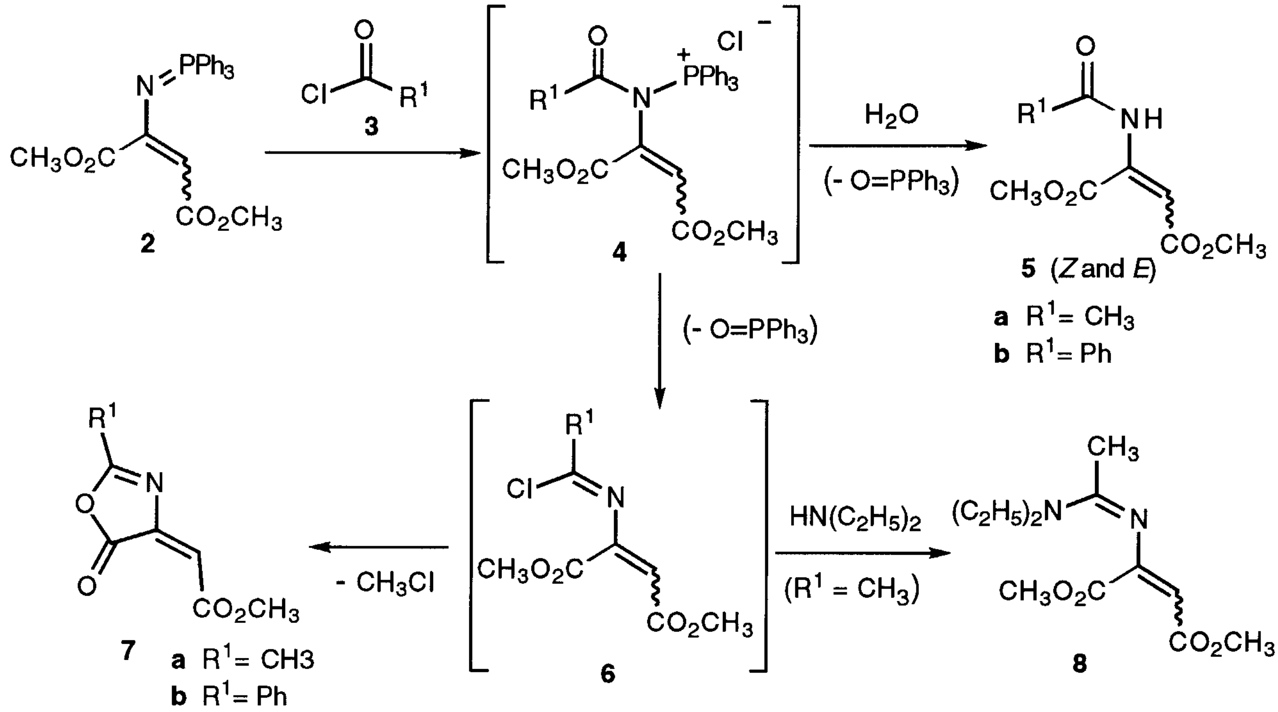


Scheme 1

After the synthesis of *N*-vinylic phosphazene (**2**), its reaction with acyl halides (**3**) was explored. When phosphazene (**2**) reacted with benzoyl chloride (**3**, R^1= Ph) at room temperature in CH_2Cl_2, 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*-vinylic 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.[4e] 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**).[4e] Cyclisation of compound (**6**) with loss of methyl chloride[17] may give oxazolones (**7**).



Scheme 2

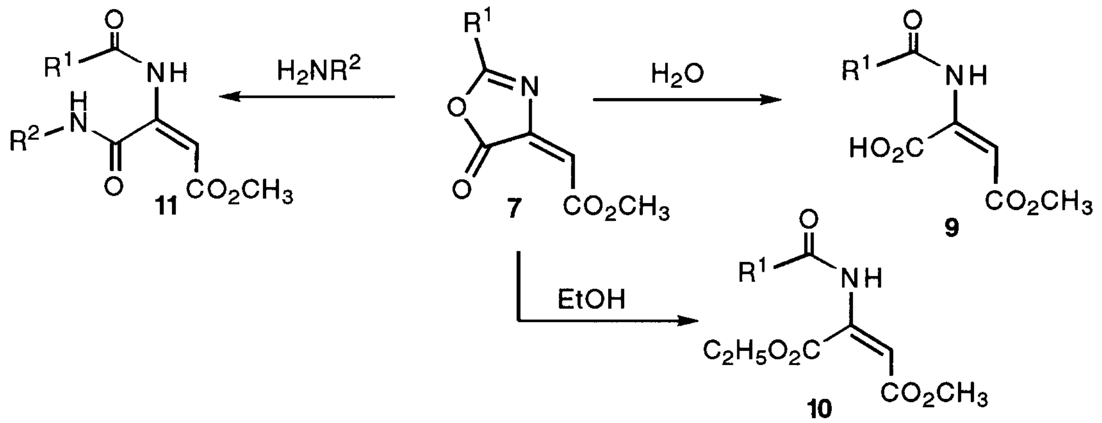
Table 1. Reaction of phosphazene (**2**) with acyl chlorides

Entry	R1	Solvent	T (°C)	time	Yield (%)	**5*Z*/5*E*/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 $(C_2H_5)_2NH$.

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 chemistry[15] 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]	Rf
1	**9a**	CH_3	H_2O	93	0.17 [b]
2	**9b**	Ph	H_2O	90	0.15 [b]
3	**10**	Ph	C_2H_5OH	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	$C_2H_5O_2C$-CH_2-NH_2	58	0.16 [c]

[a] Yields of purified compounds isolated by column chomatography. 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] υ (cm^{-1})	MS[c] (m/z)
2Z[d]	3.35 (s, 3H, CH_3-O), 3.73 (s, 3H, CH_3-O), 5.81 (d, 1H, $^4J_{PH}$= 6.5Hz, =CH), 7.39-7.50 (m, 9H, Ar), 7.77-7.85 (m, 6H, Ar).	50.5 (CH_3-O), 52.1 (CH_3-O), 100.6 (d, J_{PC}= 17.5 Hz, =CH), 128.3-132.7 (m), 149.3, 166.7, 168.0.	1717 1694 1558	419 (M^+, 8%) 404 (M^+-15, 12%) 360 (M^+-59, 53%)
2E[e]	3.29 (s, 3H, CH_3-O), 3.57 (s, 3H, CH_3-O), 4.71 (s, 1H, =CH), 7.36-7.48 (m, 9H, Ar), 7.61-7.68 (m, 6H, Ar).	50.5 (CH_3-O), 51.9 (CH_3-O), 94.8 (d, J_{PC}= 16.1 Hz, =CH), 128.3-132.7 (m), 168.4, 169.2.	1726 1676 1547	419 (M^+, 6%) 404 (M^+-15, 8%) 360 (M^+-59, 37%)
5aE	2.10 (s, 3H, CH_3CO), 3.78 (s, 3H, CH_3-O), 3.70 (s, 3H, CH_3-O), 5.41 (s, 1H, =CH), 10.1 (s, 1H, NH)	23.4 (CH_3CO), 51.8 (CH_3-O), 53.0 (CH_3-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, CH_3-O), 3.82 (s, 3H, CH_3-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 (M^+-1, 25%),
5bE	3.73 (s, 3H, CH_3-O), 3.85 (s, 3H, CH_3-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 (CH_3-O), 52.9 (CH_3-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 (M^+-1,100%),
7a	2.44 (s, 3H, CH_3), 3.89 (s, 3H, CH_3-O), 6.82 (s, 1H, =CH).	23.4 (CH_3), 53.1 (CH_3-O), 100.4 (=CH), 144.9 (C=), 164.2, 168.2, 171.2.	1740 1758	169 (M^+, 9%)
7b	3.94 (s, 3H, CH_3-O), 6.87 (s, 1H, =CH), 7.43-7.59 (m, 3H, Ar), 8.23 (m, 2H, Ar).	53.3 (CH_3-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, $^3J_{HH}$= 6.7 Hz, CH_3), 1.81 (s, 3H, CH_3), 3.36 (m, 4H, $^3J_{HH}$= 6.7 Hz, CH_2), 3.58 (s, 3H, CH_3-O), 3.71 (s, 3H, CH_3-O), 5.99 (s, 1H, =CH).	13.3 (CH_3), 15.6 (CH_3), 42.8 (CH_2), 50.8 (CH_3-O), 52.5 (CH_3-O), 103.2 (=CH), 151.1 (C=), 157.4 , 166,5, 166,9.	1732 1709 1584	256 (M^+, 7%) 225 (M^+-31, 7 %)
9a	2.06 (s, 3H, CH_3CO), 3.76 (s, 3H, CH_3-O), 5.52 (s, 1H, =CH), 10.3 (s, 1H, NH), 12.8 (s, 1H, COOH).	23.2 (CH_3), 52.7 (CH_3-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, CH_3-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 (CH_3-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)

Compound	^{1}H NMR ($CDCl_3$)[a] δ (ppm)	^{13}C NMR ($CDCl_3$)[a] δ (ppm)	IR[b] υ (cm^{-1})	MS[c] (m/z)
10	1.25 (t, 3H, $^{3}J_{HH}$= 7.1 Hz, CH_3), 3.85 (s, 3H, CH_3-O), 4.18 (q, 2H, $^{3}J_{HH}$= 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 (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_2C=), 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 (M^+-31, 10%)
11c	1.21 (t, 3H, $^{3}J_{HH}$=7.2 Hz, CH_3), 3.83 (s, 3H, CH_3-O), 4.03 (d, 2H, $^{3}J_{HH}$=5.2 Hz, CH_2-NH), 4.18 (q, 2H, $^{3}J_{HH}$=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 (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*-vinylic 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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