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Reactions of 3-Carbomethoxy-2-Aza-1,3-Butadiene Derivatives with Dienophiles

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Abstract: The reactions of 1,1-diphenyl-3-carbomethoxy-2-aza-1,3-butadiene derivatives **1a-e** (on C4 : H,H or H,CH_3 or H,C_6H_5, both E and Z isomers), and of the C4 unsubstituted 1-phenyl-1-ethoxy analogue **2**, were studied with a number of electron-rich and electron-poor dienophiles, with results showing that **1a-e** give heterocycloadducts in Diels-Alder reactions with electron-poor dienophiles. Michael adducts were obtained from the $EtAlCl_2$ catalyzed reactions of these compounds with dimethyl acetylendicarboxylate. Compound **2** gave heterocyclic adducts as well but behaved like a nucleophile, at least in the case of the reactions with dimethyl acetylendicarboxylate and ethyl propynoate: these reactions afforded 2-azatrienes as Michael adducts that gave pyridine derivatives upon heating. The synthesis of the new 1-ethoxy-2-aza-1,3-butadiene **2** is also reported.

INTRODUCTION

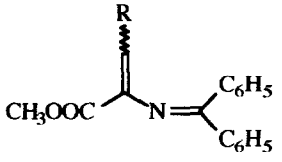
The activation energies of the Diels-Alder reactions of 2-aza-1,3-butadiene (2-AD) with several dienophiles have been recently calculated by computational methods and for the reaction with ethylene the values were similar[1,2] to those found in the case of 1,3-butadiene; these values were lowered by electron-withdrawing groups (e.g. cyano) bonded to the dienophilic reagents.[1] Experimentally, Cohen and co-workers[3] were the first to describe the use of 1-dimethylamino-2-aza-1,3-butadiene in the synthesis of pyridine derivatives by means of Diels-Alder reactions; thereafter, both acyclic and cyclic 2-azadienes have been studied to some extent as enophiles.[4a-d] These experimental and theoretical studies encourage the use of 2-AD in normal electronic demand hetero Diels-Alder reactions with both electrophilic and neutral dienophiles.

To date, the reactions of electron-poor 2-AD in inverse electronic demand Diels-Alder have been studied to a lesser extent: the few reports on this topic have dealt with compounds bearing one or more electron-withdrawing carbalkoxy substituents. These compounds are often unstable,[5] and either were prepared and trapped *in situ* with the enophiles[6] or were reacted intramolecularly.[7] 1-Phenyl-3,4-dicarbomethoxy-2-azadiene is an exception as it

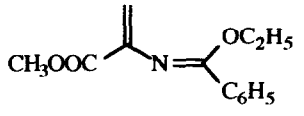
was isolated from a multigram preparation and treated with the electron-rich dienophile 1-pyrrolidino-1-cyclohexene to give a Diels-Alder cycloadduct.[8] Furthermore, stable poly-carbalkoxy (or cyano) substituted 2-AD, formally derived from 2,3-dehydroaminoacid esters, have recently been reported to give cycloadducts in good yields with trans-cyclooctene.[9]

The dehydroamino acid derivative 1-phenyl-3-carbomethoxy-2-aza-1,3-butadiene quickly cyclodimerizes at room temperature,[5] whereas the 1,1-diphenyl- **1** and the 1-phenyl-1-ethoxy-analogues have good thermal stability.[10a,b-11] Thus we studied the reactions of compounds **1a-e** and **2** with dienophiles within a research program on the synthesis,[10a,b] structural determination,[12] reactivity[11,13] and synthetic applications[14a,b,c] of amino acids related to 2-AD, giving special attention to the synthesis of new six-membered azaheterocycles.[15a,b]

a: R=H
b: R=CH_3 (E)
c: R=CH_3 (Z)
d: R=C_6H_5 (E)
e: R=C_6H_5 (Z)



1a-e



2

Scheme 1

RESULTS

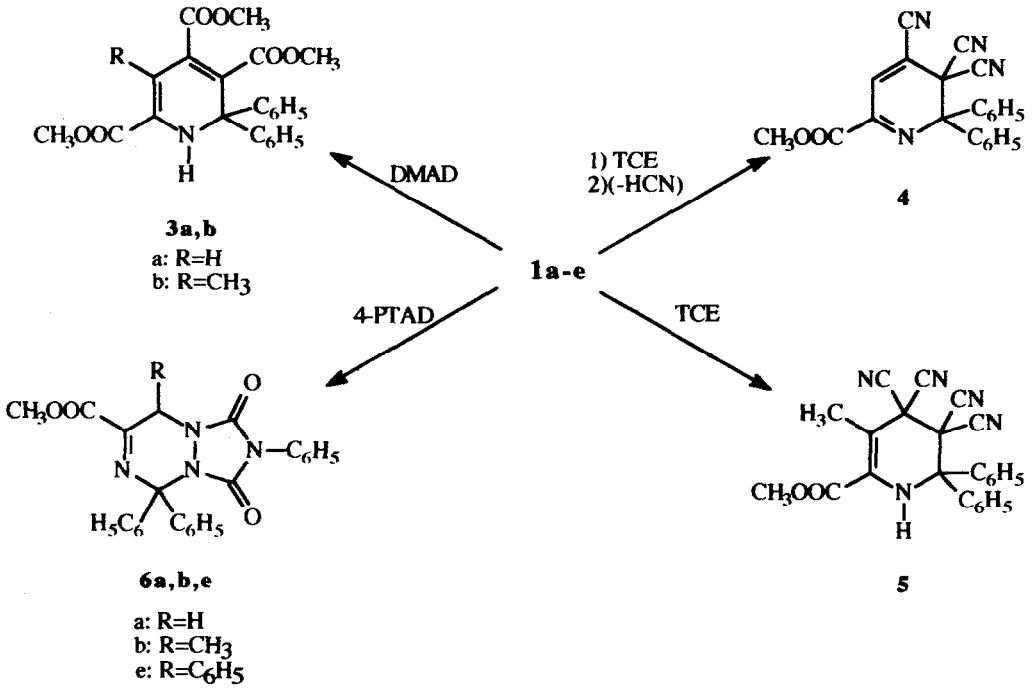
Reactions of 1,1-diphenyl-2-AD derivatives 1a-e.

Compounds **1a-e** undergo the reactions described in Scheme 2 and Table 1 with some of the most potent electron-poor dienophiles, such as dimethyl acetylenedicarboxylate (DMAD), tetracyanoethylene (TCE), 4-phenyl-1,2,4-triazolin-3,5-dione (4-PTAD). No reactions were observed with other electron-poor dienophiles, such as methyl propynoate, methyl acrylate and acrylic aldehyde, or with electron-rich dienophiles such as ethyl vinyl ether.

All of these reactions were attempted under a range of experimental conditions, changing temperatures and solvents. The yields listed in Table 1 were the best obtained and refer to isolated products. ^{1}H-NMR, MS and IR data for these new compounds are reported in Table 5. Both DMAD (0.02Mol; **1a-e** , 0.01Mol; Toluene; reflux; 8-72hr) and tetracyanoethylene (0.02Mol; **1a-e** 0.01Mol; $CHCl_3$; reflux; 3-40hr), gave cycloadditions only with **1a,b,c** in moderate to low yields; the Diels-Alder cycloadditions were followed by a prototropic rearrangement or, in the case of compound **4**, by the elimination of hydrogen cyanide, probably during the isolation step.

Good yields were found for the reactions of **1a,b,e** (0.01Mol; 4-PTAD 0.02Mol; $CHCl_3$ an.; r.t.; 1.5hr) with 4-PTAD, a potent dienophile used as a protective group for dienes, and under these conditions even the sterically congested cycloadduct **6e** was satisfactorily obtained. Compounds **1c,d** were not submitted to this reaction.

The reactions of **1** with 1-pyrrolidino-1-cyclohexene, a dienophile used successfully by others in Diels-Alder with similar 2-AD,[6,8] were attempted ($C_6H_5CH_3$; reflux.) under anhydrous conditions. No reaction was observed. Thus, the inability of compounds **1** to cycloadd to electron-rich dienophiles was confirmed.



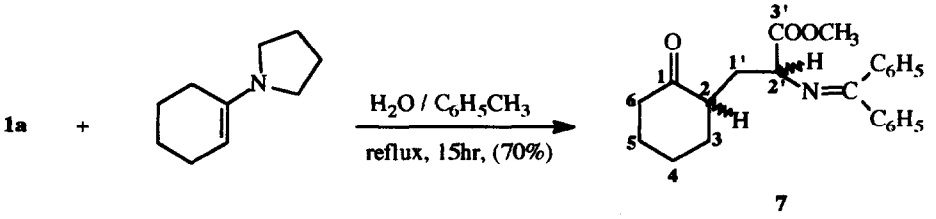
Scheme 2

2-aza-1,3-butadienes 1	R	dienophile	product	reaction time (hr)	Yield (%)	m.p.°C
a	H	DMAD	3a	8	41	214-215[a]
b	CH_3(E)	DMAD	3b	48	10	145[a]
c	CH_3(Z)	DMAD	3b	48	23	145[a]
a	H	TCE	4	3	69	145(dec)[b]
b	CH_3(E)	TCE	5	3	48	133(dec)[b]
c	CH_3(Z)	TCE	5	3	36	133(dec)[b]
a	H	4-PTAD	6a	1,5	90	186[c]
b	CH_3(E)	4-PTAD	6b	1,5	88	212-213
e	C_6H_5(Z)	4-PTAD	6e	1,5	67	183-184[c]

Crystallization from a: toluene; b: Et_2O-light petroleum; c: CH_2Cl_2-hexane.

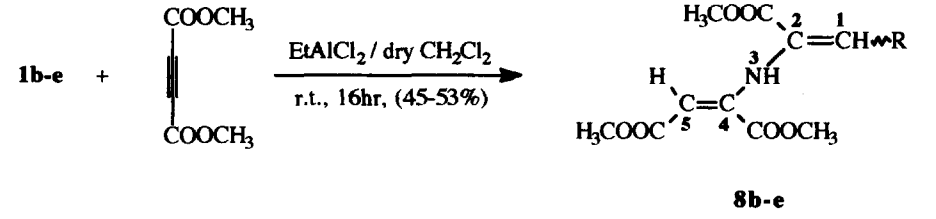
Table 1. Reactions of 1a-e with Dienophiles.

In the presence of water, a diasteroisomeric mixture of Michael adduct 7 was recovered in good yield from the reaction of **1a** and 1-pyrrolidino-1-cyclohexene (Scheme 3). Under the same conditions, **1b-e** did not react.



Scheme 3

Many unsuccessful attempts were made to improve the yields of the cycloadditions of 2-AD **1b-e** with DMAD and to react **1a-e** with dienophiles correlated to DMAD, *e.g.* methyl propynoate and maleic anhydride. In the course of these experiments, the Lewis acid $EtAlCl_2$ was employed as catalyst: with a mechanism which remains to be clarified, *cis*-additions of the dehydroamino acid moieties to the triple bond of DMAD took place producing enamines **8b-e** (Scheme 4 and Table 2). The stereochemistry of the double bond of the starting azadiene **1** was retained. Stoichiometric amounts of benzophenone were isolated by chromatography during the working-up of all these reactions. Under the same reaction conditions, compound **1a** dimerized as described previously.[11]



Scheme 4

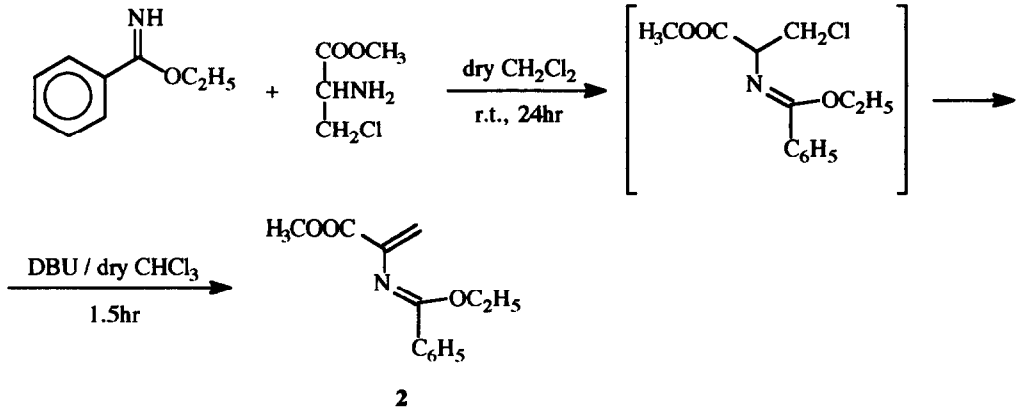
product	R 1,8b-e	Yield (%)	m.p.°C[a]	IR cm^{-1}	MS m/z	^{1}H-NMR ($CDCl_3$)
8b (E,E)	CH_3(E)	45	oil	3270, 1740, 1720[b]	257, 138	2.01 (d, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.73 (s, 6H, OCH_3), 5.33 (s, 1H, H5), 5.83 (q, 1H, H1), 9.33 (br s, 1H, NH).
8c (1Z,4E)	CH_3(Z)	50	oil	3270, 1740, 1720, 1660[c]	257, 138	1.83 (d, 3H, CH_3), 3.70 (s, 9H, OCH_3), 5.46 (s, 1H, H5), 6.42 (q, 1H, H1), 9.31 (br s, 1H, NH).
8d (E,E)	C_6H_5(E)	48	110	3280, 1725, 1665, 1610[c]	319, 260	3.64 (s, 3H, OCH_3), 3.76 (s, 6H, OCH_3), 5.52 (s, 1H, H5), 6.56 (s, 1H, H1), 7.24-7.32 (m, 5HArom), 9.61 (br s, 1H, NH).
8e (1Z,4E)	C_6H_5(Z)	53	105	3250, 1730, 1660, 1610[d]	319, 260	3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.60 (s, 1H, H5), 7.11 (s, 1H, H1), 7.26 (m, 3HArom), 7.60 (d, 2HArom), 9.64 (br s, 1H, NH).

[a]Crystallization from CH_2Cl_2-hexane. [b] film. [c] $CHCl_3$. [d] nujol.

Table 2. Yields, Physiochemical and Spectroscopic Data of Compounds 8b-e.

Reactions of 1-phenyl-1-ethoxy-3-carboxymethyl-2aza-1,3-diene.

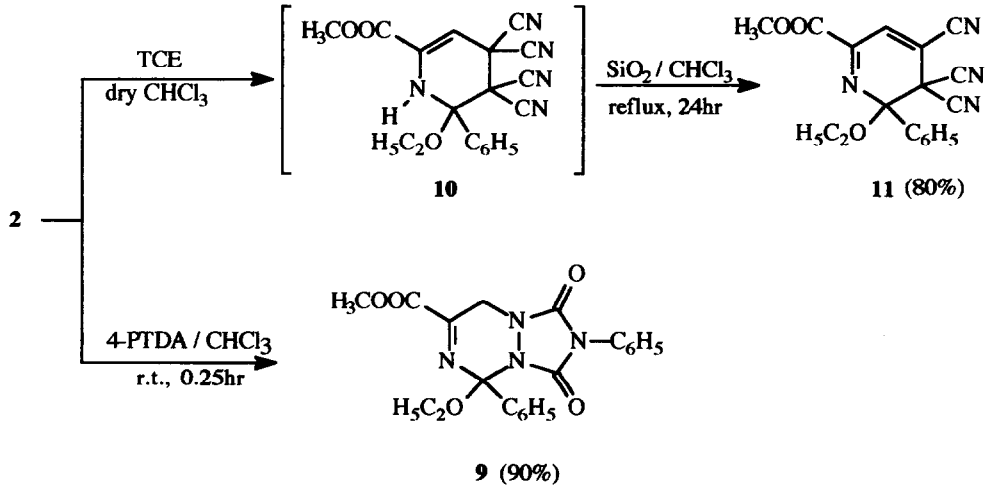
Following an approach with precedents in the literature on pyridine synthesis *via* azadienes,[16a-e] the 1-phenyl-1-ethoxy- 2-AD derivative **2** was prepared with the aim of obtaining 2-phenylpyridine derivatives by means of electrocyclic additions followed by a thermodynamically favoured elimination of ethanol.
Compound **2** was prepared as described in Scheme 5 and in the Experimental Section.



2

Scheme 5

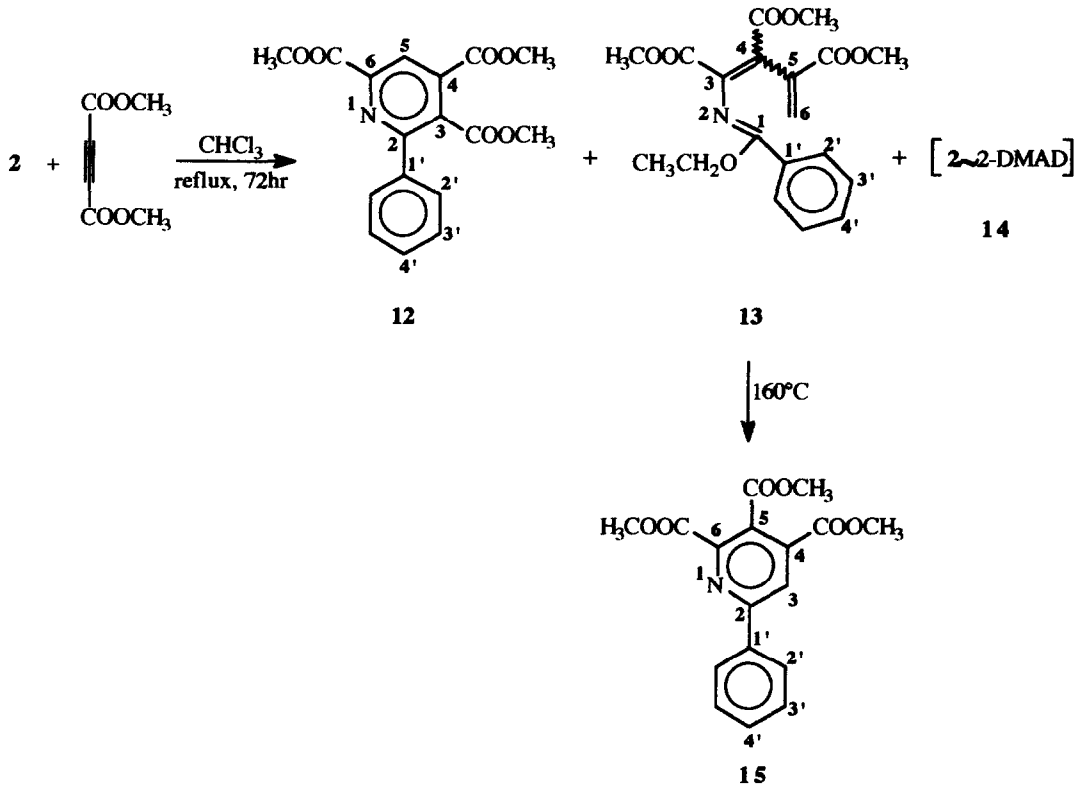
From **2** and 4-PTAD in $CHCl_3$ the cycloadduct **9** was isolated in 90% yield. In the reaction of **2** with TCE, the formation of cycloadduct **10** was suggested by IR and NMR data taken on the crude reaction mixture. When chromatographic purification was attempted, however, a mixture containing **10** and the tricyano substituted 1,2-dihydropyridine **11** (by loss of HCN) was obtained. Pure **11** was isolated in 80% overall yield by refluxing the crude Diels-Alder product **10** in $CHCl_3$ with silica gel as a catalyst (Scheme 6, Tables 3 and 5 of Exp. Sect.).



Scheme 6

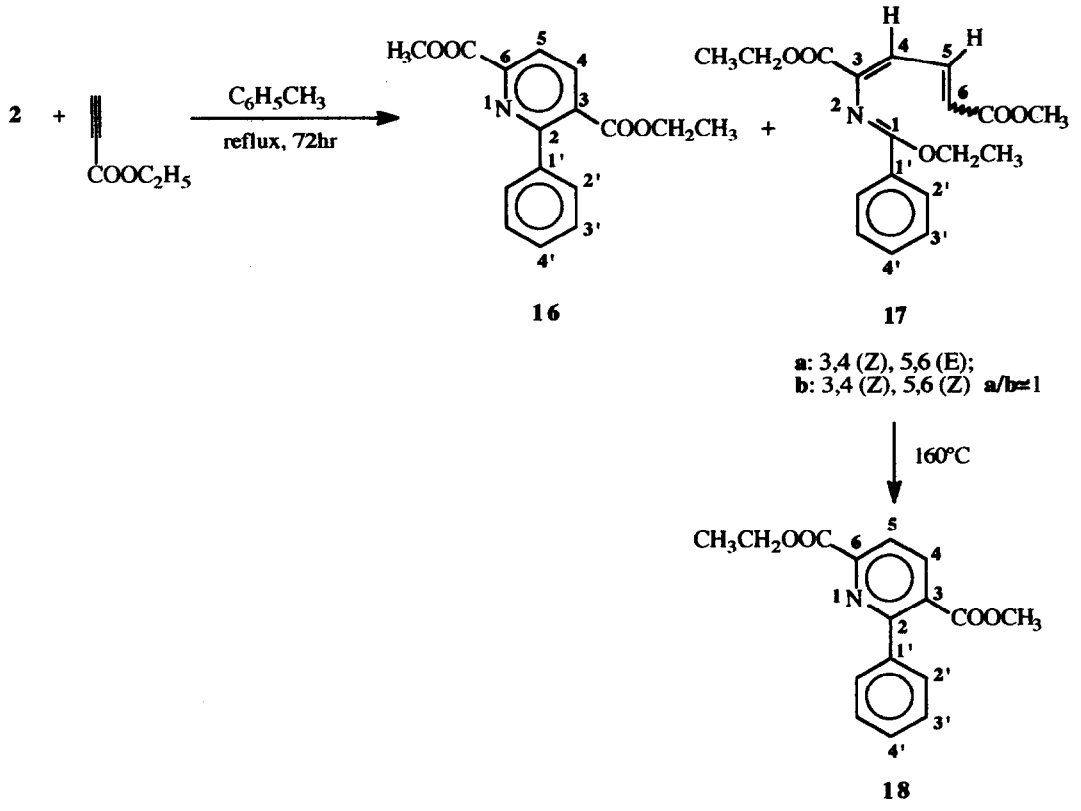
Reaction of **2** with two equivalents of DMAD in $CHCl_3$ for 72hr gave a mixture of three products: the desired 2-phenyl-3,4,6-tricarbomethoxypyridine **12** in 20% yield, the 1-phenyl-1-ethoxy-3,4,5-tricarbomethoxy-2-aza-1,3,5-triene **13** (20%)[17], and a compound **14** of undetermined structure, the MS and NMR of which suggest a derivation from the addition of one molecule of **2** and two molecules of DMAD. The reaction was repeated in dry toluene obtaining **12** (20%) and an equal weight of **14**.

The 2-phenyl-4,5,6-tricarbomethoxypyridine **15** formed in 58% yield when **13** (neat) was heated at 160°C for 20hr (Scheme 7).



Scheme 7

The reaction of **2** with ethyl propynoate (Scheme 8) yielded the 2-phenyl-3-carbethoxy-6-carbomethoxypyrydine **16** (20%) and unexpectedly the 2-azatriene **17**. The latter was then heated without solvent at 160°C obtaining 2-phenyl-3-carbomethoxy-6-carbethoxypyrydine **18** in 40% yield.



Scheme 8

product	dienophile	solvent	reaction time (hr)	Yield (%)	m.p.°C
9	4-PTDA	$CHCl_3$	0.25	90	118-9(dec)[a]
10	TCE	$CHCl_3$	0.5	-[d]	-[d]
11	TCE	$CHCl_3$	0.5+24	80[e]	91-2[b]
12	DMAD	$CHCl_3$	72	20	77-8[c]
13	DMAD	$CHCl_3$	72	20	oil
14	DMAD	$CHCl_3$	72	15	165[c]
16	ethyl propynoate	toluene	72	20	119[c]
17	ethyl propynoate	toluene	72	25	oil

Crystallization from a: CH_2Cl_2; b: Et_2O-light petroleum; c: Et_2O-hexane;
d: undeterminated; e: overall yield from **2** (see Scheme 6)

Table 3. Reactions of 2 with Dienophiles: Conditions, Yields and Physiochemical Data of Compounds 9-17.

Structural determinations

The structures of all the new compounds were deduced from suitable NMR, MS and IR experiments.

The IR data support the ^{1}H-NMR results determining the presence of NH in compounds **3a,b**, **5**, **8b-e** and **10** (weak absorbances in the range 3400-3250 cm^{-1}).

In many cases the structural assignments were established by the concerted use of DEPT, 2D COSY and CHCORR NMR experiments.

^{13}C-NMR provided substantial information on compound **4**, since only three signals were observed in the typical resonance fields (110-115ppm) of the cyano groups. The loss of one molecule of HCN following cycloaddition is further supported by the absence of NH assorbance in both ^{1}H-NMR and IR spectra and by the presence of the molecular ion m/z 366 in the MS.

The presence of resonances far downfield in the ^{13}C spectrum (about 212ppm) and the redoubling of all signals (except for OCH_3 peak) indicates that compound **7** is a cyclohexanone derivative with two chiral centers (diastereoisomeric mixture 3:2).

The electron impact (EI) mass spectrum of this compound exhibited a weak (≈1%) molecular ion signal at mass to charge ratio m/z 363. On the other hand, chemical ionization (CI) in isobutane showed the protonated molecule, m/z 364 as the base peak. Furthermore, the mass selected collision induced dissociation of this ion indicated $[MH^+-H_2O]$ as the first loss process. The measured exact mass of the same ion was found to be 364.18992 ± 0.6 Da, which is in good agreement with the calculated value of 364.19050 indicating the elemental composition $[C_{21}H_{24}N_4O_2]$.

With regard to enamines **8b-e**, the investigation of the stereochemistry of the 4,5 double bond is substantially correlated to the determination of the dehydroamino acids geometry, which is not a trivial matter as the sensitivity of spectroscopic pictures to environmental factors recommends the combined use of different techniques. Our case was somewhat complicated, because we had on hand only one of the isomers at C4-C5 of compounds **8b-e**. Nevertheless, the vicinal J_{CH} coupling constants resemble vicinal HH coupling constants and, like $^3J_{CC}$, $^3J_{CH}$ can give conclusive information concerning the relative configuration of C and H as coupled nuclei in alkenes.[18] In accordance with reports in the literature ,[10b,19] the magnitude of $^3J_{CH}$ between the C=O of carbomethoxy ester on C4 and H5, measured in the coupled nuclear enhanced ^{13}C spectra of **8d** and **8e**, supports the assignment of an E configuration to the 4, 5 double bond (Table 4).

product	δ (C=O) on C1 ($^3J_{C=O,H1}$,Hz)	δ (C=O) on C4 ($^3J_{C=O,H5}$,Hz)
8d (E,E)	164.42 (10.0)	164.07 (9.2)
8e (Z,E)	165.81 (4.4)	163.72 (9.2)

For a complete comparison even the values of $^3J_{C=O}$ of the C1-C2 double bonds are reported.

Table 4. Chemical Shifts and $^3J_{CH}$ Values for Alkenylic Moiety of Enamines 8d and 8e.

This assignment was comfirmed by adding a little amount of trifluoroacetic acid in the $CDCl_3$ solutions of both **8d** and **8e**. The isomerizations of the enamines were then monitored by ^{1}H-NMR; the isomerisation path observed after a few hours is depicted in Figure 1. The complete trend of ^{1}H chemical shifts of vinylic protons in all four isomers (see also Table 2) is in good agreement with the assigned E configuration at C4-C5.

Moreover, in our assignment the observed correlation between the C4-C5 configuration and the ^1H chemical shifts of H5 is correctly explicable on the basis of electronic effects, as in the model compounds dimethyl maleate and fumarate.

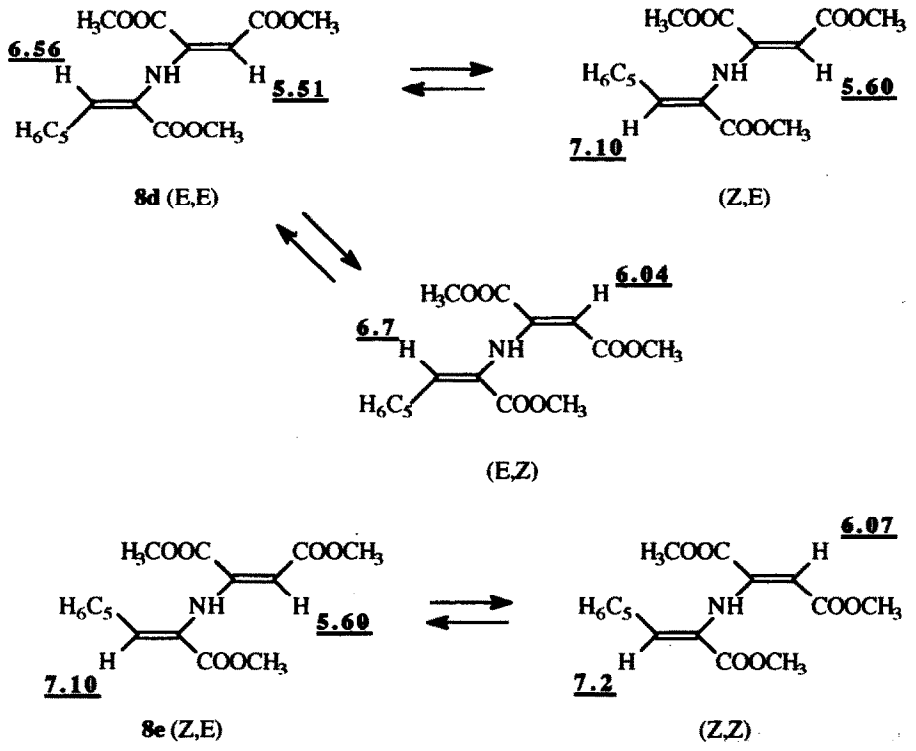


Figure 1. Isomerisation Path of **8a** and **8e** in the Presence of TFA.

The availability of both pyridine isomers of Scheme 7 (**12** and **15**) enabled us to establish unequivocally the positions of the three carboxymethyl groups, contrary to literature data.[16b] In both compounds the only pyridine carbon linked to a proton resonates at the characteristic frequence (about 122 ppm) of *meta* carbons. Thus, the positions of carbomethoxy groups were clarified by means of homonuclear NOEDS (Nuclear Overhauser Enhancement Difference Spectroscopy). These measurements established unequivocally the presence of a carbomethoxy on the C5 of **15** and on the C3 of **12** exploiting a through-space connection between the proton of pyridine and the suitable protons, the *ortho* ones of the 2-phenyl group.
The NOE experiments are reported in Figure 2.

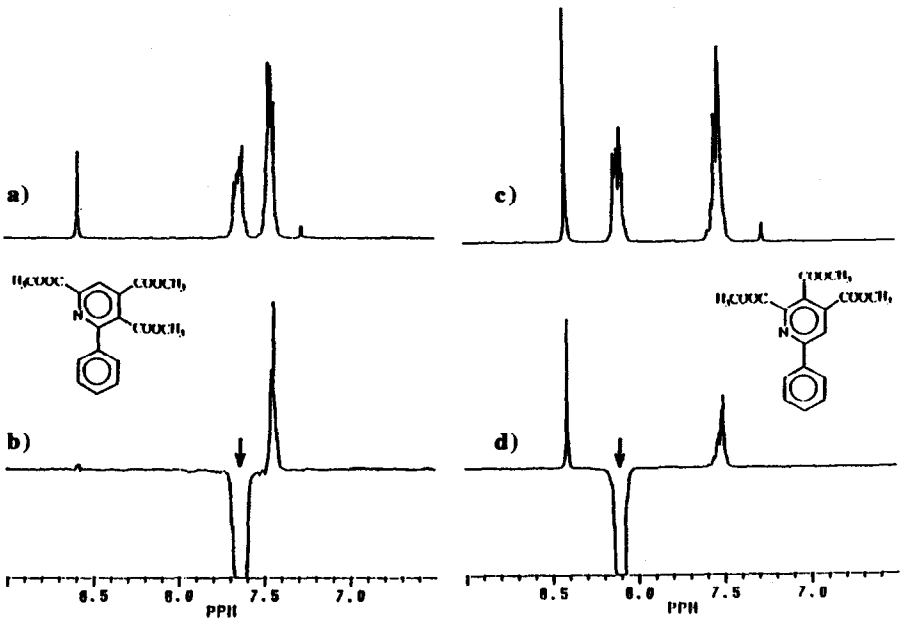


Figure 2: NOEDS Experiments. **a)** ^{1}H-NMR spectrum of **12** ($CDCl_3$) **b)** NOE difference spectrum of **12** resulting from irradiation of aromatic *ortho* protons. **c)** ^{1}H-NMR spectrum of **15** ($CDCl_3$) **d)** NOE difference spectrum of **15** resulting from irradiation of aromatic *ortho* protons.

Deductions based on the NMR data of compounds **12** and **15** were supported by the electron impact mass spectra which exhibited substantial differences indicating the presence of an abundant ion at m/z 314 in the mass spectrum of compound **12**. This ion is attributed to the loss process $[M-CH_3]^+$ resulting in the structure **12a** proposed in Figure 3. This loss process is likely to be associated with the adjacent phenyl and one of the carboxymethyl groups which may explain the absence of the ion m/z 314 from the mass spectrum of compound **15**. A similar reasoning can be advocated to explain the differences between the mass spectra of compounds **16** and **18**.

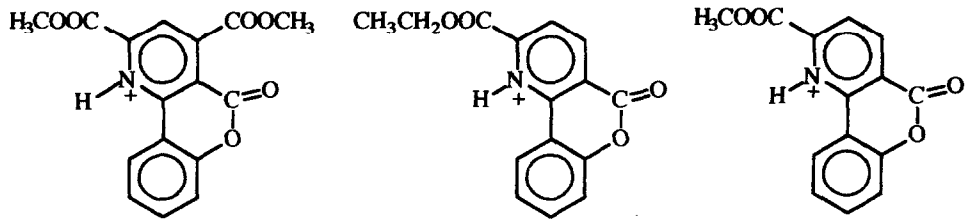


Figure 3

The spectrum of the first compound exhibits m/z 256 as the base peak and no signal at m/z 270, while the relative intensities of these two peaks in the mass spectrum of compound **18** were 28% and 30% respectively. The loss of CH_2CH_3 by compound **16** and of the CH_3 group by compound **18** are attributed to the presence of the phenyl in the vicinity of carboxyethyl group in the first case and carboxymethyl in the second.

The above structural assignment was confirmed unambiguously by NMR experiments, from which it appeared immediately that the pyridine protons (AB system with J_{HH}=8.0 Hz) occupy the *para* and *meta* positions (relative to the nitrogen atom) in both compounds. This assignment is supported by the observation that the coupling constant between 4-H and 5 (or 3)-H is the largest (about 8 Hz) in ordinary pyridine derivatives.[20] These structural identifications are further confirmed by ^{13}C-NMR data (see Table 6). An unambiguous experiment put an end to the above question: NOE enhancements were observed between the carbethoxy and carbomethoxy resonances of pyridine substituents and the phenyl protons.

These effects clearly indicated that **18** and **16** are isomers in which the two ester groups ($COOCH_3$ and $COOCH_2CH_3$) are exchanged.

Their irradiation paths are reported in Figure 4.

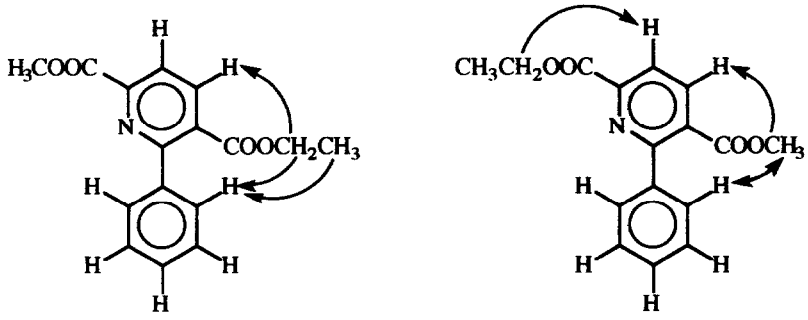
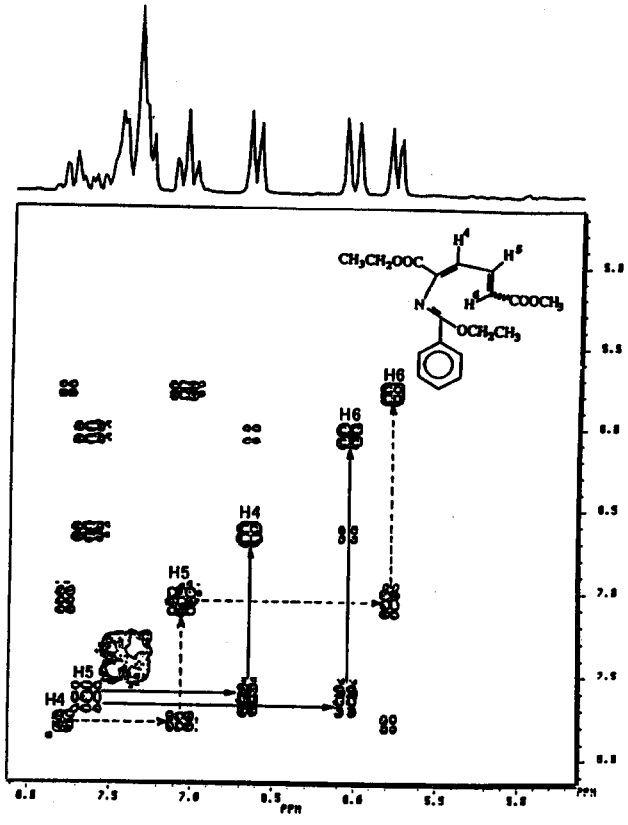


Figure 4. Irradiation Paths of Compounds 16 and 18.

The 1-ethoxy-1-phenyl-2-aza-3-carb***ethoxy***-6-carbo***methoxy***-1,3,5,-triene **17**, precursor of pyridine **18**, was obtained as a mixture of Z,Z and Z,E diastereoisomers. The structural determination also demonstrated that **17** comes from a rearrangement taking place by an unknown mechanism probably after the initial Michael addition of **2** to methyl propynoate. The ^{1}H-NMR showed three pairs of one-proton signals which are attached to different sp^2 carbons. The assignments were accomplished by 2D methods: the expanded vinylic region of the COSY spectrum in Figure 5 reports the checked correlation between the protons H4, H5 and H6 for both the isomers of compound **17**. Moreover, the combined 1D experiments (NOE effects, $^3J_{CH}$ and $^3J_{HH}$) defined the reported stereochemistry and the relative position of carbalkoxy groups. The stucture of the 1-ethoxy-1-phenyl-2-aza-3,4,5-tricarbomethoxy-1,3,5,-triene **13**, obtained as a single isomer and precursor of pyridine **15**, was also inferred from ^{1}H-NMR experiments (Tables 5 and 6). However, we were not able to obtain conclusive results in order to elucidate the stereochemistry of the C3-C4 double bond.



———17a (Z,E) isomer
- - - - - 17b (Z,Z) isomer

Figure 5. Vinylic Region of the COSY Spectrum of Compound 17.

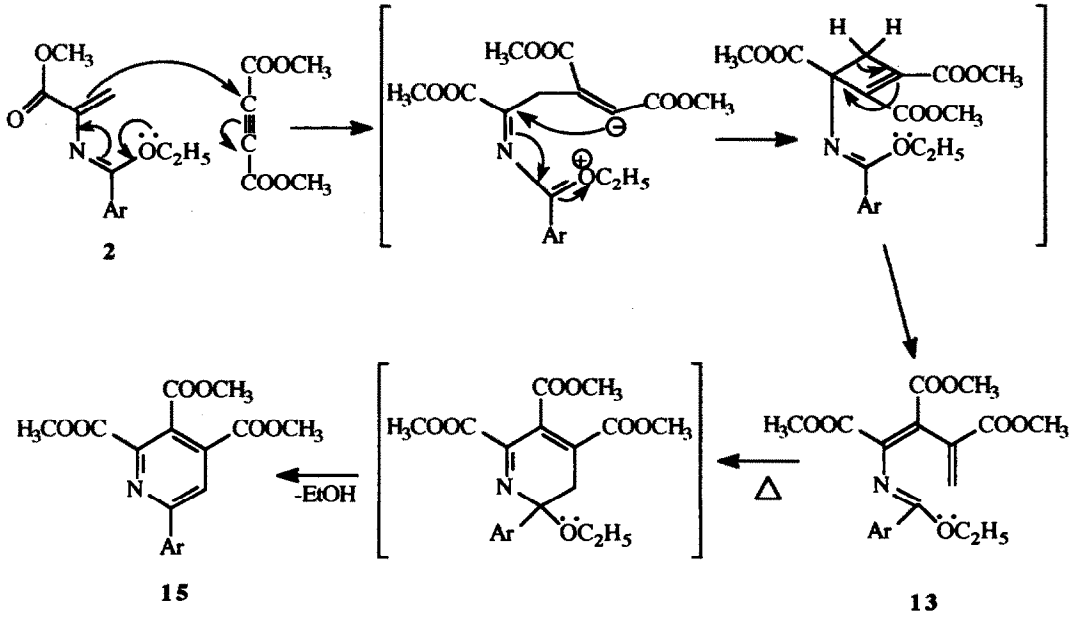
DISCUSSION

The reactions of **1a-e** with dienophiles were carried out with similar results in toluene, $CHCl_3$ and dioxane. The lack of influence of solvent polarity on the reaction rates is indicative of a concerted 6π electrocyclic mechanism. Unfortunately, and quite surprisingly, the successful reactions were limited to just a few of the most potent electron-poor dienophiles. Moreover, and despite the presence of the electron-withdrawing carboxymethyl substituent on C3, no Diels-Alder reactions were observed with electron-rich dienophiles. It has recently been reported[6] that the 1-phenyl-3-carboxymethyl-2-AD closely correlated to **1a** was able to give Diels-Alder cycloadducts, e.g. with ethyl propynoate and with the electron-rich 1-pyrrolidino-1-cyclohexene, but not with DMAD: the contrary of the result we obtained. We unsuccessfully attempted the reaction of **1a** with 1-pyrrolidino-1-cyclohexene in many solvents, and also under the conditions reported for 1-phenyl-3-

carboxymethyl-2-AD. In light of these results it is difficult to rationalize the effects of carbomethoxy substituents in these reactions. On the other hand, the diminished rates found in the reaction of C4 substituted substrates **1b-e** in relation to those of **1a** could be correlated to the normal stereoelectronic effects of this type of substitution on the Diels-Alder reaction rates. The effects of the geometry at C4 of substrates **1b-e** could not be rationalised: in fact, the highest yields were observed in reactions of the E-isomers with TCE and 4-PTAD and in the reactions of Z ones with DMAD.

A Michael addition of 1-pyrrolidino-1-cyclohexene to **1a** in the presence of water is reported in Scheme 3. This reaction falls in the range of the normal reactivity of compounds **1** with nucleophiles.[10a] The role of water could be tracked back in the proton transfer to the carbanionic intermediate and in the subsequent hydrolisis of the cyclohexanone iminium intermediate. Disappointingly, this reaction appears to be limited to the C4 unsubstituted term **1a**. The reactivity of the 1-phenyl-1-ethoxy-3-carbethoxy-2-AD **2** is connected with the dual character (nucleophilic and enophilic) of this reagent, as the reactions reported in Schemes 6-8 demonstrated.

In the reactions with TCE and 4-PTAD, **2** appears to react as an enophile in normal electron demand Diels-Alder reactions: actually, stable 2-phenyl -2-ethoxy substituted cycloadducts were formed almost quantitatively within a few minutes. The reactions of **2** with DMAD and ethyl propynoate are more complex : in fact, it is reasonable to suppose that pyridine **12** could derive from a Diels-Alder cycloaddition followed by the elimination of a molecule of ethanol, and that 2-azatriene **13** was formed by the ionic mechanism described in Scheme 9. In this case, the Michael-type addition of **2** to DMAD is followed by rearrangement *via* a cyclobutene intermediate. The nucleophilicity of the C4 of **2** is due to the electron-donating mesomeric effect of the ethoxy group.
The 1-phenyl-4,5,6-tricarbomethoxypyridine **15** was then formed at 160°C by thermal intramolecular Diels-Alder and subsequent elimination of ethanol (Scheme 9).



Scheme 9

A mechanism similar to that described in Scheme 9 was formulated by Worley and co-workers[21] to explain the results of the reaction of 1-phenyl-1-dimethylamino-4-methyl-2-AD with DMAD. Differently, a [2+2] electrocyclic reaction was conceived as a first step in this reaction by Nomura[22] and, in relation to an analogous rearrangement occurring in a carbocyclic Diels-Alder, by Padwa.[23] It is worth noting that pyridine derivative **15** had been previously obtained by Gompper and Heinemann[16b] from the reaction of 1-phenyl-3-carboxymethyl-4-dimethylamino-2-AD with DMAD but described erroneously as the Diels-Alder derived pyridine **12**. We repeated Gompper's experiment obtaining a compound (**15**) identical to that we had obtained from **13**, the structure of which has now been unambigously determined (see Structural Determination section). The above discussed mechanism should rule out the reaction obtained by Gompper as well.

The reaction of **2** with ethyl propynoate (Scheme 8) again gave both 1-phenyl-3-carboxyethyl-6-carboxymethylpyridine **16**, a compound probably derived from a Diels-Alder followed by loss of ethanol, and the 1-phenyl-1-ethoxy-3-carbethoxy-6-carbomethoxy-2-aza-1,3,5-triene **17** probably derived from a Michael addition. Heating at 160°C of **17** gave rise to pyridine derivative **18**, in which the carboxyalkyl groups are inverted with respect to **16**. The structure of **17** was deduced from NMR experiments indicating the presence of a mixture of two diastereoisomers and the positions of the estereal alkyl groups. Although we have not formulated any hypotheses regarding the mechanism of the formation of **17**, some considerations could be made: the lack of stereoselectivity of the cycloaddition giving **17**, together with the results of the reaction of **2** with DMAD, suggests that an ionic rather than a concerted mechanism should be admitted; the rearrangement responsible for the formation of **17** should be different from those assumed for the formation of **13** or, if the mechanisms leading to **13** and **15** were the same, (the inversion of the carbalkoxy groups is not detectable in the case of **13** as it was in the formation of the azatriene **17**, where the two ester alkyl groups were different), those depicted in Scheme 9 may be incorrect or incomplete.

In conclusion, it has been shown that the chemistry of 2-AD **1a-e** and **2** could lead to new syntheses of six-membered azaheterocycles. However, the synthetic applications appear limited by the number of reactive dienophiles and suffer from low yields in some instances.

Notwithstanding the presence of an electron-withdrawing carboxymethyl substituent in position 3, **1a-e** and **2** smoothly afford normal electron-demand Diels-Alder, but only with the most powerful electron-poor dienophiles. This work confirms the results on Michael additions previously reported (at times inadvertently) in the cases of nucleophilic 2-AD and, although it was not addressed to the mechanistic aspects of the reaction described, it gives critical support to the mechanisms previously proposed for the rearrangements observed in such reactions.

Finally analogies have been found between the cyclodimerizations of 1-phenyl-3-carboxymethyl-2-AD[6] and 1,1-diphenyl (**1a**) 2-AD derivatives: however, in spite of the structural similarity of these compounds, the patterns of their Diels-Alder reactions are not superimposable. This clearly indicates that many factors may affect the reactions of 2-AD with dienophiles, and that much work is still necessary for a satisfactory understanding of the chemistry of these reactions.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi SPM-510 open capillary apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer 257 spectrometer. NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 spectrometer and are reported in δ using TMS as internal standard. In NOED experiments the following parameters were used: D1 (relaxation time) 3s, D2 (irradiation time) 4s and S3 (decoupler power) 50L, according to the method of Kinns and Sanders[24] (NOEMULT); coupling constants were measured in Hertz. MS spectra (EI, 70 eV) were obtained on a GC-MS HP5995 instrument and the exact mass measurements were performed on a trisector instrument (V.G.Autospec, Fisons Instruments, U.K.). Microanalyses for C, H and N were performed on a Perkin-Elmer CHN 240 C analyzer and were within ± 0.4 % of theoretical values (see Table 7). Dichloromethane, toluene and chloroform were distilled over calcium hydride; all the other solvents and reagents were of the highest grade commercially available (Aldrich) and were used without additional purification. Evaporations *in vacuo* were conducted on a Büchi rotavapor at water aspirator pressure. Column chromatography purifications were performed under flash conditions using Merck 230-400 Mesh silica gel. Analytical thin layer chromatography was performed using pre-coated plates (Merck Kieselgel 60 F_{254}) visualized by UV lamp at 254 nm. Compounds **1a-e** were prepared as previously described.[10b]

1-Phenyl-1-ethoxy-3-carbomethoxy-2-aza-1,3-butadiene (2).

To a suspension of benzimino ethyl ether hydrochloride[25] (36 mmol) in dry CH_2Cl_2 (40 mL) a 6M aqueous solution of K_2CO_3 (10 mL) was added and the mixture was stirred for 15 minutes at room temperature. The organic layer was separated, dried (Na_2SO_4) and treated with a solution of methyl 2-amino-3-chloro-propionate hydrochloride[26] (24 mmol) in dry CH_2Cl_2 (100 mL). The mixture was then stirred for 24hr at room temperature with moisture exclusion. After cooling the suspension was filtered on celite, the filtrate washed with water, dried (Na_2SO_4), and evaporated to give a yellowish crude oil. The excess of benzimino ethyl ether and ethyl benzoate was separated by distillation (60-65°C, 0.7 mmHg). DBU (2 equiv) was added to a solution of the residue in dry $CHCl_3$ (40 mL) and the reaction mixture was stirred 1.5hr at room temperature, then washed first with a saturated solution of NH_4Cl and then with water, dried (Na_2SO_4) and evaporated to dryness. The crude oil was purified by column flash-chromatography on silica gel (cyclohexane-ethyl acetate 95-5) to give the desired compound **2** (3.2g).

2: Oil; IR (film) 1710, 1685, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.40 (t, 3H, $C\underline{H}_3CH_2O$, J_{HH}=7.1 Hz), 3.63 (s, 3H, $COOCH_3$), 4.35 (q, 2H, $OC\underline{H}_2CH_3$, J_{HH}=7.1 Hz), 4.88 (s, 1H, =CH), 5.57 (s, 1H, =CH), 7.33-7.47 (m, 5HArom).

^{13}C-NMR 14.10 (q, $OCH_2\underline{C}H_3$), 51.81 (q, OCH_3), 62.65 (t, OCH_2), 109.69 (t, $=CH_2$, C-4), 128.02 (d, Arom), 128.24 (d, Arom), 129.98 (d, Arom), 132.66 (s, Arom), 143.75 (s, C-3), 161.30 (s, C-1), 165.09 (s, C=O, $^3J_{CH}$=4.6, 8.6).

[4+2] Cycloadditions of dienophiles with 2-azadienes derivatives 1a-e and 2.

A solution of 2-aza-1,3-butadiene **1a-e** or **2** (5 mmol) and of the appropriate dienophiles (10 mmol) in 15 mL of toluene or $CHCl_3$ was refluxed (room temperature for 4-PTDA). After cooling, the solvent was evaporated under reduced pressure and the crude oils were purified by column flash-chromatography on silica gel (cyclohexane-ethyl acetate 8-2) and crystallization. Reaction conditions, yields and physiochemical data are reported in Tables 1, 3, 5 and 6.

Reaction of 1-pyrrolidino-1-cyclohexene with 1a (7).

To a solution of **1a** (1 mmol) in toluene (6 mL) 302 mg (2 mmol) of 1-pyrrolidino-1-cyclohexene were added. The reaction mixture was refluxed 15hr, the solvent evaporated under reduced pressure and the crude material purified by column flash-chromatography (cyclohexane-ethyl acetate 8-2). Yield=70%

7: Oil; IR (film) 1745, 1720 cm^{-1}. Major isomer: ^{1}H-NMR ($CDCl_3$) 1.2-2.5 (m, 11H; H2,H3,H4,H5,H6,H1'), 3.70 (s, 3H, OCH_3), 4.16 (dd, 1H; H2', J_{HH}=5.4, 8.3 Hz), 7.0-7.7 (m, 10HArom); ^{13}C-NMR 24.25, 27.95, 33.50, 33.85, 41.90 (t, C-3, C-4, C-5, C-6, C-1'), 47.18 (d, C-2), 51.90 (q, OCH_3), 62.93 (d, C-2'), 127.7-139.5 (Arom), 170.53 (s, C=N), 172.75 (s, $\underline{C}OOCH_3$), 211.89 (s, C-1).

Minor isomer ^{1}H-NMR ($CDCl_3$) 1.2-2.5 (m, 11H; H2,H3,H4,H5,H6,H1'), 3.70 (s, 3H, OCH_3), 4.26 (dd, 1H; H2', J_{HH}=4.7, 8.5 Hz), 7.0-7.7 (m, 10HArom); ^{13}C-NMR 25.26, 28.18, 33.32, 35.04, 42.08 (t, C-3, C-4, C-5, C-6, C-1'), 47.05 (d, C-2), 51.90 (q, OCH_3), 63.22 (d, C-2'), 127.7-139.5 (Arom), 170.76 (s, C=N), 172.60 (s, $\underline{C}OOCH_3$), 211.70 (s, C-1).

MS: m/z 363 (M^+), 105 (100).

Reaction of DMAD with 1b-e, $EtAlCl_2$ catalyzed (8b-e).

A solution of 1M $EtAlCl_2$ in hexane (10 mL, 10 mmol) was added to a solution of the appropriate 2-aza-1,3-butadiene **1b-e** (5 mmol) and DMAD (15 mmol) in dry CH_2Cl_2 (20 mL) cooled to 0°C. The reaction mixture was stirred at room temperature for 1hr, then poured into an ice-cold saturated solution of $NaHCO_3$ (40 mmol). The mixture was filtered on celite, the two layers separated and the aqueous one extracted twice with CH_2Cl_2. The organic fractions were combined and washed with water, dried (Na_2SO_4) and evaporated to dryness. The crude material was purified by column flash-chromatography on silica gel (cyclohexane-ethyl acetate 8-2). Reaction conditions, yields and physiochemical data are reported in Tables 2 and 6.

Thermal intramolecular rearrangement (15 or 17).

The oily compound **13** (or **17**) was heated without solvent at 160°C for 20hr (36hr for **17**). The crude material was purified by column flash-chromatography on silica gel (cyclohexane-ethyl acetate 8-2) and then by crystallization (Et_2O-hexane). Physiochemical data are reported in Tables 3, 5 and 6

15 m.p. =127-8°C Yield=58%

17 m.p. =52-3°C Yield=40%

product	IR cm^{-1}	MS (m/z) M^+; 100%	^{1}H-NMR($CDCl_3$)
3a	3380,1740, 1720,1710[a]	407, 330	3.55, 3.65, 3.80 (3s, 9H, OCH_3), 5.86 (br s, 1H, NH), 7.20-7.50 (m, 10HArom), 7.80 (s, 1H, =CH).
3b	3400,1740, 1725,1710[a]	421, 344	2.34 (s, 3H, CH_3), 3.29, 3.67, 3.91 (3s, 9H, OCH_3), 4.18 (br s, 1H, NH), 7.24-7.48 (m, 10HArom)
4	1728,1628[a]	366, 69	3.75 (s, 3H, OCH_3), 6.82 (s, 1H, =CH), 7.44-7.62 (m, 10HArom)
5	3390,1740, 1715[a]	407, 379	2.35 (s, 3H, CH_3), 4.01 (s, 3H, OCH_3), 5.49 (s, 1H, NH), 7.44-7.47 (m, 10HArom)
6a	1775,1720, 1655[b]	440	3.95 (s, 3H,OCH_3), 4.70 (s, 2H, CH_2), 7.35-7.42 (m, 15HArom)
6b	1765,1720, 1660[b]	454	1.65 (d, 3H, CH_3), 3.93 (s, 3H, OCH_3), 5.28 (q, 1H, CH), 7.30-7.54 (m, 15HArom)
6e	1770,1720, 1650[b]	516, 165	3.61 (s, 3H, OCH_3), 6.3 (s, 1H, CH), 7.27-7.47 (m, 20HArom)
9	1720,1420[a]	408	1.43 (t, 3H, $CH_2C\underline{H}_3$), 3.8 (q, 2H, $C\underline{H}_2CH_3$), 4.0 (s, 3H, $COOCH_3$), 4.43,5.0 (2d, 2H, CH_2), 7.23-7.7 (m, 10HArom)
10	3380,1730, 1655[a]	____	1.4 (t, 3H, $CH_2C\underline{H}_3$), 3.36 (q, 2H, $C\underline{H}_2CH_3$), 3.95 (s, 3H, $COOCH_3$), 5.76 (d, 1H, CH=), 6.1 (br s, 1H, NH), 7.4-7.8 (m, 5HArom)
11	1730,1630[a]	334, 105	1.43 (t, 3H, $CH_2C\underline{H}_3$), 3.58 (s, 3H, $COOCH_3$), 4.56 (q, 2H, $C\underline{H}_2CH_3$), 6.83 (s, 1H, CH=), 7.26-7.63 (m, 5HArom)
12	1720,1650[a]	329, 271	3.76 (s, 3H, $COOCH_3$), 3.98 (s, 3H, $COOCH_3$), 4.03 (s, 3H, $COOCH_3$), 7.43 (m, 3H, H3', H4'), 7.63 (m, 2H, H2'), 8.56 (s, 1H, H5).
13	1720,1650[c]	375, 105	1.44 (t, 3H, $OCH_2C\underline{H}_3$,J=7.1 Hz), 3.57 (s, 3H, $COOCH_3$), 3.59 (s, 3H, $COOCH_3$), 3.73 (s, 3H, $COOCH_3$), 4.43 (q, 2H, $OC\underline{H}_2CH_3$, J=7.1 Hz), 5.55 (d, 1H, H6, ^{2}J=1.3 Hz), 6.30 (d, 1H, H3 ^{2}J=1.3 Hz), 7.35-7.40 (m,3HArom), 7.72 (m, 2HArom).
15	1738[a]	329, 155	4.00 (s, 3H, $COOCH_3$), 4.03 (s, 6H, $COOCH_3$), 7.53 (m, 3H, H3', H4'), 8.11 (m, 2H, H2'), 8.41 (s, 1H, H3).
16	1720,1690[a]	285, 256	1.04 (t, 3H, $OCH_2C\underline{H}_3$, J=7.1 Hz), 4.01 (s, 3H, $COOCH_3$), 4.17 (q, 2H, $OC\underline{H}_2CH_3$, J=7.1 Hz), 7.44 (m, 3H, H3', H4'), 7.56 (m, 2H, H2'), 8.14 (AB system, 1H, H5, J=8.0 Hz), 8.22 (AB system, 1H, H4, J=8.0 Hz)
17	1720,1650[c]	331, 105	**a** (**Z**,**E**): 1.05 (t, 3H, $COOCH_2C\underline{H}_3$, J=7.0 Hz), 1.46 (t, 3H, $OCH_2C\underline{H}_3$ J=7.0 Hz), 3.76 (s, 3H, OCH_3), 3.98 (q, 2H, $COOC\underline{H}_2CH_3$ J=7.0 Hz),4.45 (q, 2H, $OC\underline{H}_2CH_3$ J=7.0 Hz), 6.04 (dd, 1H, H6, J=15.6, ^{4}J=1.0 Hz), 6.64 (dd, 1H, H4, J=11.8, ^{4}J=1.0 Hz), 7.32-7.36 (m, 3HArom), 7.44-7.49 (m, 2HArom), 7.63 (dd, 1H, H5, J=11.8, J=15.6 Hz). **b** (**Z**,**Z**): 1.06 (t, 3H, $COOCH_2C\underline{H}_3$, J=7.0 Hz), 1.44 (t, 3H, $OCH_2C\underline{H}_3$ J=7.0 Hz), 3.76 (s, 3H, OCH_3), 4.00 (q, 2H, $COOC\underline{H}_2CH_3$ J=7.0 Hz),4.42 (q, 2H, $OC\underline{H}_2CH_3$ J=7.0 Hz), 5.78 (dd, 1H, H6, J=11.4, ^{4}J=1.3 Hz), 7.06 (dd, 1H, H5, J=11.4, J=12.1 Hz), 7.32-7.36 (m, 3HArom), 7.44-7.49 (m, 2HArom), 7.76 (dd, 1H, H4, J=12.1, ^{4}J=1.3 Hz).
18	1720,1690[a]	285, 213	1.45 (t, 3H, $OCH_2C\underline{H}_3$, J=7.1 Hz), 3.72 (s, 3H, $COOCH_3$), 4.49 (q, 2H, $OC\underline{H}_2CH_3$, J=7.1 Hz), 7.45 (m, 3H, H3', H4'), 7.59 (m, 2H, H2'), 8.11 (AB system, 1H, H5, J=8.0 Hz), 8.18 (AB system, 1H, H4, J=8.0 Hz).

[a]$CHCl_3$ [b]nujol [c]film

Table 5. Spectroscopic Data of Compounds **3a-b, 4, 5, 6a-e, 9-18.**

product	^{13}C-NMR$_{(CDCl_3)}$
8d	51.18 (q, OCH_3), 51.77 (q, OCH_3), 52.60 (q, OCH_3), 94.80 (d, C-5), 125.72 (d, C-1), 127.88 (d, Arom), 127.92 (d, Arom), 129.01 (d, Arom), 129.62 (s, C-4), 134.83 (s, Arom), 146.77 (s, C-2), 164.07 (s, C=O on C-4), 164.42 (s, C=O on C-2), 169.67 (s, C=O on C-5).
8e	51.12 (q, OCH_3), 52.29 (q, OCH_3), 52.46 (q, OCH_3), 92.73 (d, C-5), 125.79 (d, C-1), 128.27 (s, C-4), 128.78 (d, Arom), 129.00 (d, Arom), 129.63 (d, Arom), 133.79 (s, Arom), 147.62 (s, C-2), 163.72 (s, C=O on C-4), 165.81 (s, C=O on C-2), 170.03 (s, C=O on C-5).
12	52.87 (q, OCH_3), 53.20 (q, OCH_3), 53.30 (q, OCH_3), 122.57 (d, C-5), 128.47 (d, Arom), 128.63 (d, Arom), 129.46 (d, Arom), 131.25 (s, C-3), 137.56 (s, C-4), 137.88 (s, Arom), 148.87 (s, C-6), 157.91 (s, C-2), 164.16 (s, C=O), 164.54 (s, C=O), 167.53 (s, C=O).
13	14.17 (q, $OCH_2\underline{C}H_3$), 51.69 (q, OCH_3), 52.09 (q, OCH_3), 52.36 (q, OCH_3), 63.87 (t, $O\underline{C}H_2CH_3$), 114.73 (s, C-4), 128.00 (d, Arom), 128.06 (t, C6), 128.50 (d, Arom), 130.93 (d, Arom), 136.86 (s, C-5), 146.59 (s, C-3), 161.68 (s, C-1), 165.51 (s, C=O), 165.77 (s, C=O), 166.34 (s, C=O).
15	53.11 (q, CH_3), 53.30 (q, OCH_3), 53.30 (q, OCH_3), 122.39 (d, C-3), 127.38 (d, Arom), 128.64 (s, C-5), 129.07 (d, Arom), 130.48 (d, Arom), 136.62 (s, Arom), 137.98 (s, C-4), 146.7 (s, C-6), 158.77 (s, C-2), 164.24 (s, C=O), 164.81 (s, C=O), 167.07 (s, C=O).
16	13.57 (q, CH_3), 53.10 (q, OCH_3), 61.82 (t, $O\underline{C}H_2CH_3$), 122.73 (d, C-5), 128.23 (d, Arom), 128.75 (s, C-5), 128.99 (d, Arom), 130.37 (s, C-3), 138.69 (d, C-4), 139.33 (s, Arom), 148.99 (s, C-6), 158.79 (s, C-2), 165.16 (s, $\underline{C}OOCH_3$), 167.57 (s, $\underline{C}OOCH_2CH_3$).
17	**a (Z,E)**: 13.68 (q, $COOCH_2\underline{C}H_3$), 14.17 (q, $OCH_2\underline{C}H_3$), 51.57 (q, OCH_3), 61.27 (t, $COO\underline{C}H_2CH_3$), 63.31 (t, $O\underline{C}H_2CH_3$), 119.22 (d, C-4), 122.83 (d, C-6), 128.06 (d, Arom), 128.26 (d, Arom), 130.63 (d, Arom), 132.58 (s, Arom), 139.10 (d, C-5), 142.00 (s, C-3), 161.66 (s, C-1), 163.81 (s, $\underline{C}OOC_2H_5$), 167.23 (s, $\underline{C}OOCH_3$). **b (Z,Z)**: 13.92 (q, $COOCH_2\underline{C}H_3$), 14.27 (q, $OCH_2\underline{C}H_3$), 51.26 (q, OCH_3), 61.19 (t, $COO\underline{C}H_2CH_3$), 63.15 (t, $O\underline{C}H_2CH_3$), 117.28 (d, C-4), 119.16 (d, C-6), 128.06 (d, Arom), 128.26 (d, Arom), 130.63 (d, Arom), 132.58 (s, Arom), 138.53 (d, C-5), 142.23 (s, C-3), 161.48 (s, C-1), 163.95 (s, $\underline{C}OOC_2H_5$), 166.73 (s, $\underline{C}OOCH_3$).
18	14.26 (q, CH_3), 52.57 (q, OCH_3), 62.19 (t, $O\underline{C}H_2CH_3$), 122.56 (d, C-5), 128.26 (d, Arom), 128.78 (d, Arom), 129.10 (d, Arom), 129.76 (s, C-3), 138.71 (d, C-4), 139.16 (s, Arom), 149.52 (s, C-6), 158.64 (s, C-2), 164.61 (s, $\underline{C}OOCH_2CH_3$), 168.16 (s, $\underline{C}OOCH_3$).

Table 6. ^{13}C-NMR Spectra of Compounds **8d-e, 12-18.**

Comp.					MW	requires %			found %		
	C	H	N	O		C	H	N	C	H	N
2	13	15	1	3	233.27	66.94	6.48	6.00	67.16	6.27	5.81
3a	23	21	1	6	407.42	67.80	5.20	3.44	67.97	4.86	3.81
3b	24	23	1	6	421.45	68.40	5.50	3.32	68.39	5.55	3.16
4	22	14	4	2	366.38	72.12	3.85	15.29	72.17	3.79	15.22
5	24	17	5	2	407.43	70.75	4.21	17.19	70.51	4.55	17.07
6a	25	20	4	4	440.46	68.17	4.58	12.72	68.10	4.52	12.91
6b	26	22	4	4	454.49	68.71	4.88	12.33	68.82	4.96	12.41
6e	31	24	4	4	516.56	72.08	4.68	10.85	71.88	4.29	10.71
7	23	25	1	3	363.46	76.01	6.93	3.85	75.89	7.23	4.06
8b	11	15	1	6	257.24	51.36	5.88	5.44	51.09	5.82	5.79
8c	11	15	1	6	257.24	51.36	5.88	5.44	51.28	6.01	5.55
8d	16	17	1	6	319.31	60.18	5.37	4.39	60.46	5.45	4.75
8e	16	17	1	6	319.31	60.18	5.37	4.39	60.20	5.53	4.07
9	21	20	4	5	408.41	61.76	4.94	13.72	62.03	5.33	13.97
11	18	14	4	3	334.33	64.67	4.22	16.76	65.02	4.31	16.72
12	17	15	1	6	329.31	62.00	4.59	4.25	62.00	4.74	3.86
13	19	21	1	7	375.38	60.79	5.64	3.73	61.01	5.95	3.42
15	17	15	1	6	329.31	62.00	4.59	4.25	62.31	4.71	4.24
16	16	15	1	4	285.30	67.36	5.30	4.91	66.99	5.34	4.86
17	18	21	1	5	331.37	65.24	6.39	4.23	65.15	6.31	4.12
18	16	15	1	4	285.30	67.36	5.30	4.91	66.98	4.96	4.97

Table 7. Microanalyses of the new compounds described.

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17. The correct names of compounds **13** and **17** are 2-(ethoxy-phenyl-methyleneamino)-3-methoxycarbonyl-4-methylene-pent-2-enedioic acid dimethylester and 2-(ethoxy-phenyl-methyleneamino)-hexo-2,4-dienedioic acid 1-ethylester-6-methylester, respectively. In this paper, they have been named 2-aza-trienes for the sake of clarity.

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It seems reasonable to suggest even for the enamines **8b** and **8c** the E configuration at the C4-C5 double bond since the 1H resonance for proton H5 falls in the same range (5.33-5.60ppm) in the all four compounds **8b-e**.

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