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DO OXAZOLES UNDERGO DIELS-ALDER REACTIONS WITH HETERODIENOPHILES ?[a]

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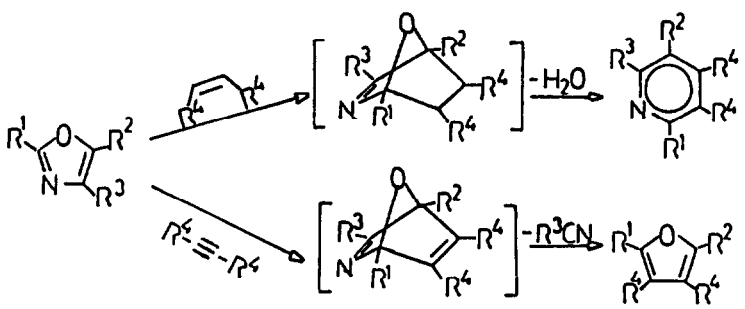
Abstract:

5-Alkoxy and 2-alkoxyoxazoles were shown to react with N=N, C=N or C=O dienophiles to form products that in most cases can be explained to result from a Diels-Alder addition, or by nucleophilic attack of the oxazole on the dienophile, followed by rearrangement. The products are triazolines, imidazolines or oxazolines respectively. Relative reactivities were established and mechanistic pathways discussed.

Introduction

Oxazoles have been a fertile ground for investigation as the 4-π component in Diels-Alder reactions.[2] Thus thermal reaction of oxazoles with acetylenes leads to furans while addition to olefins produces substituted pyridines (eq 1). In a few instances, the Diels-Alder adduct was isolated,[3] but in most cases the primary adduct was not isolable and instead underwent rearrangement. It is well known that the rate of a Diels-Alder reaction



equation 1

depends on the energy separation between the HOMO of the diene and the LUMO of the dienophile (or vice versa). Normally, heteroaromatic systems containing azadienes (electron poor dienes), are suitable for inverse demand Diels-Alder reactions (LUMO diene controlled) but substituting the azadiene with strong electron donating substituents helps in many cases to overcome the electron-poor nature of the azadiene and enables the use of electron poor dienophiles.[4]

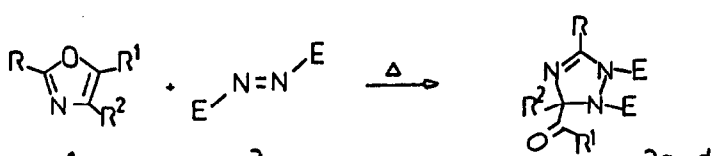
While the interaction of oxazoles with C-C multiple bonds has been

thoroughly investigated,[2] there are apparently only two reports[5] of oxazoles reacting with a heterodienophile. We decided to study the reaction of oxazoles with heterodienophiles containing the N=N, C=O, or C=N function with a view to determining 1) the reactivity scale of various substituted oxazoles, 2) which dienophiles are suitable partners, 3) what are the resulting products and 4) what is the regiochemistry and stereochemistry of such reactions.

Results and Structure Proof

Our first choice was diethyl azodicarboxyalte (DEAD, 2)[6] which because of its high reactivity as a dienophile could also serve as a baseline for reactivity of specific oxazoles as a diene partner. Since DEAD is an electron-poor dienophile the addition was expected to be HOMO-diene controlled and thus we first chose ethoxy and siloxy substituted oxazoles as electron-rich dienes.

When 2-phenyl-5-ethoxyoxazole (1a)[7] was heated with DEAD in benzene overnight a product was isolated in 99% yield. High resolution mass spectra (M-COOEt)[8] indicated a 1:1 adduct. Although the reaction product of a related oxazole with DEAD was assigned[5a] a Diels-Alder adduct structure of type 16, the spectral data of our product were consistent with the Δ^2-1,2,4-triazoline structure 3a (eq 2). Thus, IR showed NCO_2Et, CO_2Et, and C=N absorptions. ^{1}H-NMR indicated three carbethoxy groups and a CH singlet at 6.23 ppm. ^{13}C-NMR showed three ester carbonyls and a C=N, as well as a tertiary carbon (doublet) at 82.34 ppm correlated with the CH absorption. The C-H coupling of 166 Hz is consistent with a saturated carbon geminal to a carbethoxy group as well as to two nitrogens. Long range splitting (J_{CH} = 4 Hz) between the C=N carbon and the adjacent ortho aromatic hydrogens, is of the same order as the splitting (J_{CH} = 4 Hz) of the carbonyl group with the ortho hydrogens in benzoic acid. These data are inconsistent with a Diels-Alder adduct (see 16) or with other reasonable isomeric structures (e.g. a diazetidine, a diaziridine, or a 4-hydrazino oxazole) but fit well the 1,2,4-triazoline 3a.

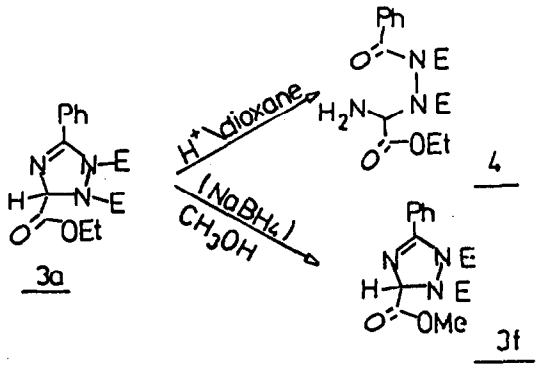


1 2 3a–d

a	R=Ph	R^1=OEt	R^2=H	E=CO_2Et
b	R=Ph	R^1=OSiMe$_3$	R^2=H	
c	R=Me	R^1=OEt	R^2=H	
d	R=OEt	R^1=Ph	R^2=H	
e	R=Ph	R=Me	R^2=Ph	

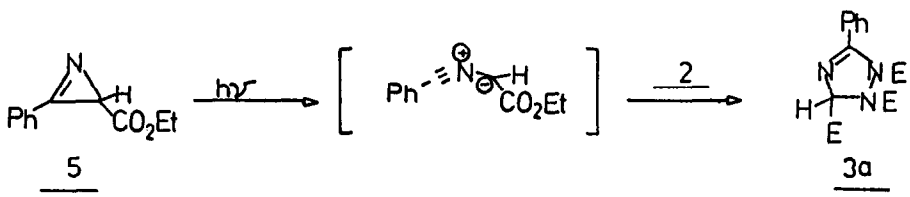
equation 2

Further structure proof was provided by chemical conversions. The presence of a carbethoxy group (in addition to the two carbamate ester functions) was indicated by treatment of 3a with $NaBH_4$ in methanol which left the molecule intact except for ester exchange to produce 3f (typical MeO absorption at 3.81 and 53 ppm in PMR and CMR). Hydrolysis with 5% HCl in dioxane produced 4 as indicated by NMR and mass spectra (eq 3).



equation 3

An independent synthesis of 3a was carried out by photolysis of 2-phenyl-3-carbethoxy-1-azirine (5) in the presence of DEAD (eq 4); it is known that under these conditions a nitrilium ylid is produced which can be trapped with a dienophile.[9] Furthermore, an analogous adduct of N-phenyl-1,3,4-triazolinedione (PTAD) to oxazole 1 (R=Ph, R'=OEt, R"=4-NO_2-Ph) was recently reported and its structure was proven by X-ray diffraction.[5b]

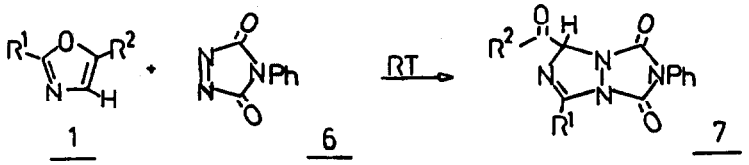


equation 4

Additional structure proof comes from the NMR spectra of the methyl analog 3c a product of the reaction of 2-methyl-5-ethoxy oxazole (1c) with DEAD. Here long range homoallylic coupling (J = 1.5 Hz) was observed between the CH and the Me group.

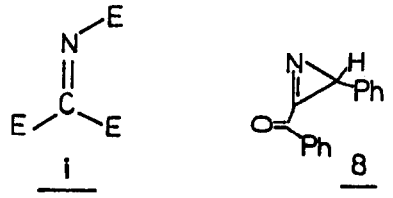
Analogous reactions using DEAD were achieved with 5-siloxyoxazole (1b)[10] to produce 3b in quantitative yield. Reaction with 2-ethoxy-5-phenyloxazole (1d)[11] led to 3d in 33% yield, although it proceeded at a much slower rate than the reaction of 1a-c with DEAD. With the more electrophilic N-phenyltriazolinedione (PTAD, 6), oxazole 1d reacted within 20 min in benzene

at room temperature, to produce in quantitative yield a bicyclic adduct 7 (eq 5). No reaction was observed between oxazole 1e and DEAD.

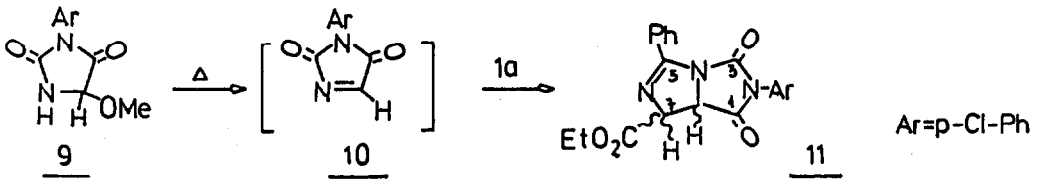


equation 5

Next we tried to extend the reaction of oxazoles with DEAD to other heterodienophiles. The C=N analog of DEAD (i), prepared from ethyl azidoformate with triphenylphosphine followed by reaction with diethyl ketomalonate 12,[12] did not react with oxazole 1b at 80°C but led to a mixture of unidentified products in refluxing toluene. Azirine 8 [13] also did not react with oxazole 1a at 80°C but decomposed instead to α-cyano-α-phenylacetophenone.[14]



Hydantoin 9[15] did react with oxazole 1a in refluxing xylene to produce a cis: trans (3:2) mixture of adducts 11, in 50% yield (eq 6). A regioisomeric product was not observed. This reaction was facilitated by the presence of BF_3.etherate (90% yield of 11 within 4 hr at 110°C vs 50% yield in 22 hr at 140°C).

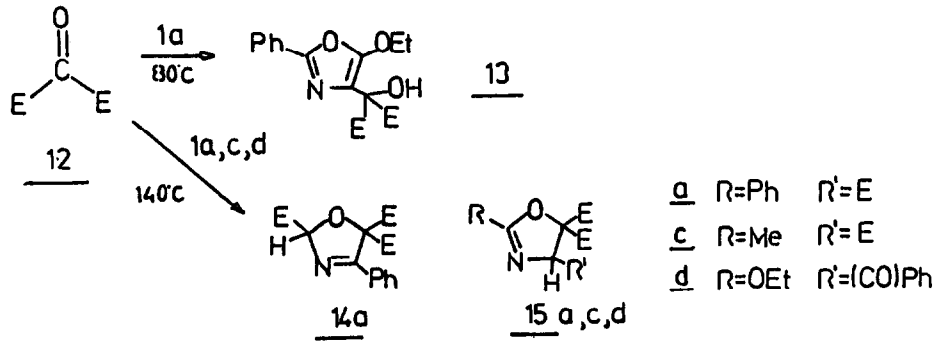


equation 6

Reaction of oxazole 1a with the C=O dienophile 12 at 80°C led to the alcohol adduct 13 in 24% yield together with starting material. At higher temperature (110°C) two new products, a 3-oxazoline 14 and a 2-oxazoline 15, were formed in 19% and 21% yields respectively. Heating of 1a with 12 to 140°C led to 14 and 56 (ratio of 1.2:1) in 96% yield. In both cases a small

amount (less than 3% yield) of oxazole 13 was also present. The Me analog 1c also reacted with 12 at 110°C to afford 2-oxazoline in 10% yield.

The 2-ethoxyoxazole 1d reacted with 12 only in the presence of BF_3 etherate to generate a 2-oxazoline 15d, in 43% yield (eq 7).



equation 7

PRODUCTS OF

REACTIONS OF OXAZOLES 1 WITH DIENOPHILES 6,2,12,10

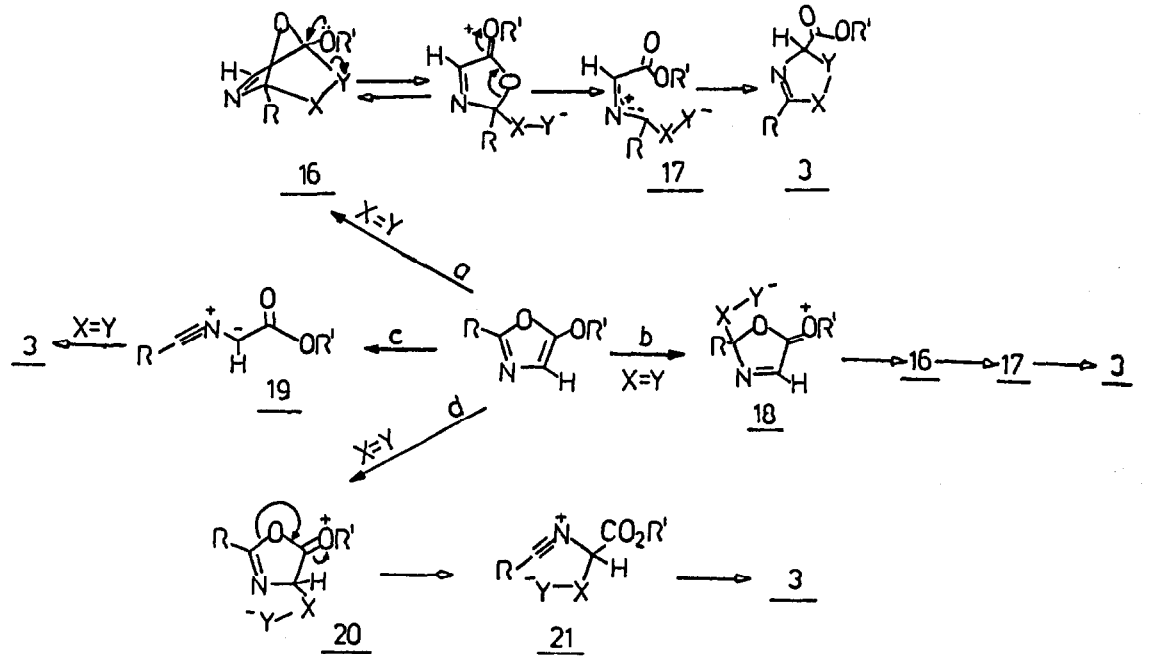
oxazole	Conditions (Yield) 7	Conditions (Yield) 3	Conditions (Yield) 13, 14+15	Conditions (Yield) 11
1a	20°C/12 min (100%)	80°C/17h (99%)	80°C/4d (24%) — 140°C/46h (~3%) (96%) [a]	140°C/23h (50%) [b] 110°C/4h/BF_3·ether (90%) [c]
1b		80°C/24h (100%)		
1c		80°C/17h (41%)	110°C/24h (10%)	140°C/3d (0)
1d	20°C/20min (100%)	80°C/4d (35%)	140°C/3d (0) 80°C/5h/BF_3·ether (43%) [d]	
1e		80°C/4d (0)		

(a) 14:15 = 1:1.2;
(b) cis:trans = 3:2;
(c) cis:trans = 3.1;
(d) only 15 was obtained.

Discussion

Though only two pathways (Diels-Alder and nucleophilic attack from C-4) were considered before[8] for reaction of oxazoles 1 with heterodienophiles, we feel that at least four reasonable mechanisms (see scheme 1) for formation of 3 need to be taken into account:

(a) The first is a Diels-Alder reaction of the oxazole with DEAD to produce 16, which undergoes a ring opening to 17 followed by reclosure to 3. (b) Alternatively, nucleophilic attack (Michael addition) unto DEAD by the 5-ethoxyoxazoles from C-2 (or by the 2-ethoxyoxazole from C-5) would lead to the same intermediates 16 or 17. (c) The third pathway involves thermal ring opening of the ethoxyoxazole 1 to a nitrilium ylid 19, a process analogous to the Cornforth rearrangement,[14] followed by a dipolar cycloaddition of DEAD to the 1,3-dipole. (d) The fourth possibility involves electrophilic attack from C-4 of 5-ethoxyoxazoles unto DEAD, followed by ring opening to a nitrilium ion 21 and ring closure to 3. The reaction of the symmetrical reagent DEAD with oxazoles 1 does not provide as good an opportunity to differentiate between the four pathways as do the unsymmetrical reagents 9 and 12.

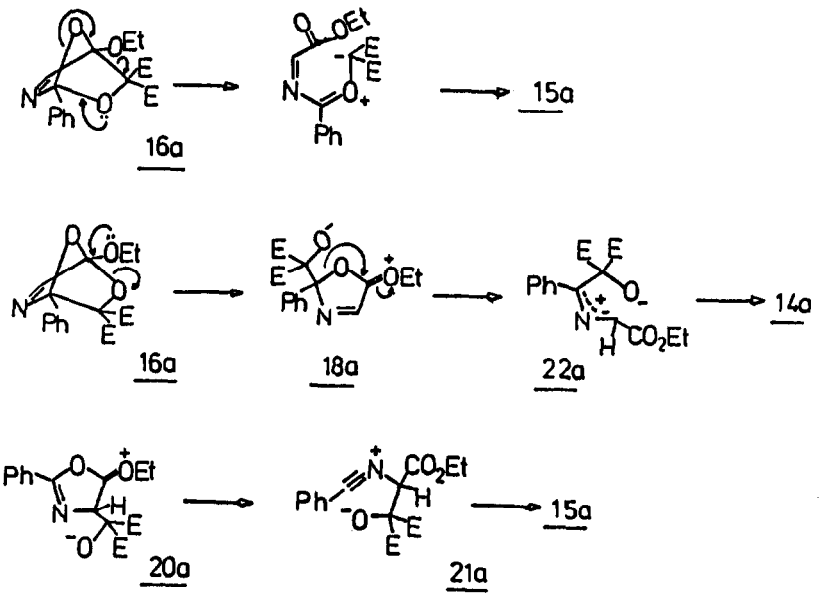


Scheme 1

The nitrilium ylid mechanism (c) fits Ibata's results,[8] namely that, in the reaction of oxazoles 1 with PTAD, the presence of electron withdrawing groups at C-4 leads to better yields of adducts. However, this pathway seems

unlikely for the reaction of 1 with ketomalonate 12, on the following grounds. Trapping of authentic nitrilium ylid 19, obtained by photolysis of azirine 5, was possible with DEAD, but no trapping occurred with 12. Though 1a had reacted with ketomalonate 12, heating it with chloral or benzaldehyde (known dipolarophiles for nitrilium ylids) was unproductive. Furthermore, the fact that 1a reacted with 6 at room temperature whereas formation of nitrlium ions 19 from oxazoles generally require heat, means that opening of 1 to 19 cannot be the rate determining step in the reaction.

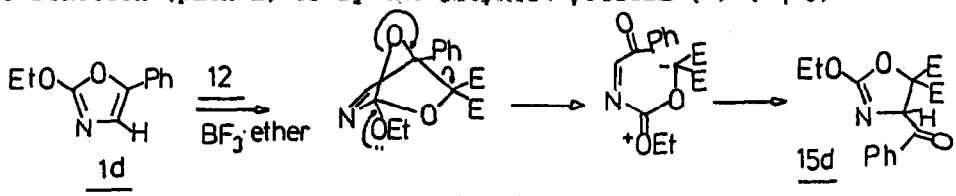
The formation of alcohol adduct 13 (at 80°C) is best explained by the pathway (d), namely nucleophilic attack of the oxazole from C-4 unto the keto group of 12 followed by proton transfer. 2-Oxazolines 15 can result from a Diels-Alder adduct (path a) or via C-4 attack (path d), whereas 3-oxazolines 14 can only be explained via path (a) or (b) (scheme 2). So far it is not possible to distinguish between a Diels-Alder process (a) via 16 or a stepwise reaction (b) since they involve the same intermediate 18 . Thus it appears that there are two separate temperature dependent pathways leading at 80°C to 13 (by nucleophilic attack at C-4, path (d)) and at higher temperature (110 - 140°C) to 14 and 15 (possibly via two regioisomeric Diels-Alder adducts, see 16a --> 15a). Alternatively 15 could be formed via path (d), while 14 could be the result of a Diels-Alder addition (path a).



Scheme 2

Regiospecific generation of 11 from hydantoin 10 can be explained as derived from opening of a primarily formed adduct 16, which was formed in a

regiospecific sense either in a Diels-Alder reaction or via C-4 attack, but catalysis by BF_3 may be better accounted for by a Diels-Alder addition. The reaction of 2-ethoxyoxazole 1d with DEAD to produce 3d or with 12 in the presence of BF_3 to form 15d can of course only be accounted for by a Diels-Alder reaction (path a) or by the stepwise process (b) (eq 8).



equation 8

Though the Diels Alder mechanism seems reasonable, monitoring the reaction of 1a with 2 by NMR showed only product 3a and starting material and no intermediate Diels-Alder adduct was detected.

In conclusion, we have shown that oxazoles can react with heterodienophiles to produce adducts that usually can be explained by a Diels Alder reaction followed by ring opening and rearrangement. In the case of keto malonate a separate lower temperature pathway proceeds via C-4 attack on the keto function to form 13. Nucleophilic attack of C-4 unto the dienophile (path d), still can explain formation of 15a-c and 11.

The order of decreasing reactivity with DEAD (2) is 5-ethoxy-(or siloxy)oxazoles 1a-c, followed by 2-ethoxyoxazole 1d; 2-methyl-4,5-diphenyl oxazole was unreactive. The most reactive dienophiles are the N=N species PTAD or DEAD, followed by keto malonate 12, and hydantoin 9. Other C=N or C=O species such as i, azirines 8 or chloral are not reactive.

Acknowledgement: We are grateful to Dr. H. Gottlieb for his help with NMR spectra. This research was supported by a grant from the US-Israel Binational Science Foundation.

EXPERIMENTAL

General. The NMR spectra were recorded on a Bruker AM 300 FT NMR instrument. ^1H at 300 MHz and ^{13}C at 75.5 MHz in $CDCl_3$ using TMS as an internal standard. Mass spectra were obtained on a Finnigan 4021 instrument. IR spectra were recorded on a Perkin-Elmer model 457. The following abbreviations for NMR spectra were used: o=ortho, p=para, me=meta, i=ipso. Benzene, toluene and xylene were dried over sodium. The cycloaddition reactions were carried out in a flame dried system under Ar. Silica gel (Merck Art.9385) was used for chromatography. Oxazoles 1a-d were prepared according to literature procedures.

1,2,5-Tricarbethoxy-3-phenyl-Δ^3-1,2,4-triazoline (3a): A benzene solution of 1a (1 g, 5.3 mmol) and DEAD (0.83 ml, 5.3 mmol) was heated under reflux for 17 h to give adduct 3a as a colorless oil (1.91 g, 99%). ^1H NMR δ: 7.87 (m, 2H,

o), 7.52 (m, 1H, p), 7.43 (m, 2H, me), 6.23 (s, 1H, H-5), 4.40-4.15 (m, 6H, CH_2), 1.35, 1.30 and 1.16 (t, 3H, CH_3); ^{13}C NMR δ: 166.31 (CO_2Et), 160.97 (C=N), 156.66 and 153.05 (NCO_2Et), 132.01 (p), 129.76 (o), 128.61 (i), 127.90 (m), 82.34 (d, CH), 63.56 and 62.09 (t, CH_2), 14.37 and 13.92 (q, CH_3); IR (neat) ν_{max}: 1740 (CO_2Et), 1725, 1715 (NCO_2Et), 1620 (C=N) cm^{-1}. MS m\e 364 (M+1), 320 (M-OEt), 292 (M-HCO_2Et) ; HRMS: 290.1129 ($C_{17}H_{21}N_3O_6$- CO_2Et) cald. for $C_{14}H_{16}N_3O_4$ 290.1141.

1,2,5-Tricarbethoxy-3-phenyl-Δ^3-1,2,4-triazoline (3a) (from azirine 5): A benzene solution of 2-phenyl-3-carbethoxyazirine (5) (0.0125 g, 0.066 mmol) and DEAD(0.0115 g, 0.066 mmol) in a pyrex NMR tube was irradiated for 6h by a Mercury high pressure immersion lamp (400W). After evaporation of the solvent the NMR spectrum showed the presence of azirine 5 and triazoline 3a in a 3:1 ratio.

1,2-Dicarbethoxy-3-phenyl-5-trimethylsililoxy-Δ^3-1,2,4-triazoline (3b) :A benzene solution of 1b (2.8 g,12 mmol) and DEAD (1.9 ml, 12 mmol) was heated under reflux for 24 h ,to give adduct 3b (4.88 g, 100%) as a yellow oil. ^1H-NMR δ: 7.86(m, 2H, o), 7.6-7.4 (m, 3H, me+p), 6.19 (s, 1H, H-5), 4.34 (tq, 2H, CH_2), 4.20 (q, 2H, CH_2), 1.36 and 1.26 (t, 3H, CH_3), 0.32 (s, 9H, $SiMe_3$) ; ^{13}C-NMR δ: 165.81 (CO_2TMS), 160.84 (C=N), 156.71 and 152.86 (NCO_2Et), 132.02 (p), 129.67 (o), 127.91 (me), 83.26 (d, CH), 63.59 and 63.51 (t, CH_2), 14.36 and 13.88 (q, CH_3), -0.49 (OTMS) ;IR(neat) ν_{max}: 1745 (CO_2TMS), 1715 (NCO_2Et), 1620 (C=N) cm^{-1} ;MS m\e 408 (M+1), 336 (MH^+-OTMS) ;HRMS: 218.0966 ($C_{10}H_{22}N_3O_4Si$-CO_2Et-CO_2SiMe_3) cald. for $C_{11}H_{12}N_3O_2$ 218.0930

1,2,5-Tricarbethoxy-3-methyl-Δ^3-1,2,4-triazoline (3c): A benzene solution of 1c (0.5 g, 3.9 mmol) and DEAD (0.71 ml, 3.9 mmol) was heated under reflux for 17 h. Chromatography using chloroform:ethyl acetate 9:1 as an eluent gave 3c as a colorless oil 0.48 g, 41%. ^1H-NMR δ: 5.98 (q, J=1.5 Hz, 1H, CH), 4.4-4.2 (m, 6H, CH_2), 2.49 (d, J=1.5 Hz, 3H, CH_3), 1.34, 1.32, 1.30 (t, 3H, CH_3); ^{13}C NMR δ: 166.64 (CO_2Et), 158.61 (C=N), 156.82, 151.61 (NCO_2Et), 82.40 (d, CH), 63.67, 63.54 and 62.11 (t, CH_2), 14.34, 14.27 and 13.98 (q, CH_3). IR(neat) ν_{max}: 1750 (CO_2Et), 1730, 1725 (NCO_2Et), 1645 (C=N) cm^{-1}; MS m\e 302 (M+1), 257 (M-OEt), 230 (M-HCO_2Et); HRMS: 228.1039 ($C_{12}H_{13}N_3O_4$-CO_2Et) cald. for $C_9H_{14}N_3O_4$ 228.0984.

1,2-Dicarbethoxy-3-ethoxy-5-benzoyl-Δ^3-1,2,4-triazoline (3d): A benzene solution of 1d (0.3 g, 1.6 mmol) and DEAD (0.25 ml, 1.6 mmol) was heated under reflux for 4 days. Chromatography using ethyl acetate:hexane 1:2.5 gave 3d as a yellowish oil (0.2 g, 35%). ^1H- NMR δ: 8.16 (m, 2H, o), 7.62 (m, 1H, p), 7.51 (m, 2H, me), 6.73 (s, 1H, CH), 4.6-4.2 (m, 6H, CH_2), 1.48-1.3 (m, 9H, CH_3). ^{13}C- NMR δ: 191.57 (PhC=O), 157.48 (C=N), 151.66 (NCO_2Et), 131.96 (p), 129.27 (o), 128.70 (m), 80.55 (d, CH), 66.33, 63.65 and 63.57 (t, CH_2), 14.32, 14.19 and 14.11 (q, CH_3) ;IR(neat) ν_{max}: 1725 (NCO_2Et), 1695 (PhC=O), 1650 (C=N) cm^{-1}; MS m\e 364 (M+1), 290 (M-CO_2Et) ; HRMS: 258.1134 ($C_{17}H_{21}N_3O_4$-PhCO) cald. for $C_{10}H_{16}N_3O_5$ 258.1090.

1,2-Dicarbethoxy-3-phenyl-5-carbmethoxy-Δ^3-1,2,4-triazoline (3f): A methanolic solution of $NaBH_4$ (6 mg, 0.65 mmol) was added dropwise to a methanolic solution of 3a (0.118 g, 0.325 mmol) at -18°C and the temperature was raised to 20°C. The methanol was evaporated and the residue was dissolved in CH_2Cl_2 and washed with water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent,the product was purified by flash chromatography (ethyl acetate:hexane 1:1) to give 3f as a colorless oil (0.07 g, 62%). ^1H NMR δ: 7.87 (m, 2H, o), 7.54 (m, 1H, p), 7.44 (m, 2H, me), 4.40-4.17 (m, 4H, CH_2), 3.81(s, 3H, CO_2Me), 1.35 and 1.16 (t, 3H, CH_3); ^{13}C NMR δ: 166.91 (CO_2Me), 161.07 (C=N), 156.68 and 153.06 (NCO_2Et), 132.11 (p), 129.85 (o), 128.58(i), 127.96 (me), 82.17 (d, CH), 63.69 and 60.36 (NCO_2Et), 52.94 (q, CO_2Et), 14.42 and 13.99 (NCO_2Et); IR (neat) ν_{max}: 1755 (CO_2Et), 1740 (NCO_2Me), 1625 (C=N)

cm^{-1}; MS m\e: 350 (M+1), 278 (MH^+-CO_2Et); HRMS: 290.1211 ($C_{16}H_{19}N_3O_6-CO_2Me$) cald. for $C_{14}H_{14}N_3O_4$ 290.1141.

Ethyl-α-(1,2-dicarbethoxy-2-benzoylhydrazino)glycinate (4):An aqueous solution of 5% HCl (2.5 ml) was added to a dioxane solution of 3a (0.103 g, 0.28 mmol).The solution was stirred at 20°C for 3 days, neutralized and extracted with CH_2Cl_2. Separation by flash chromatography (ethyl acetate:hexane 1:1) gave 4 as a colorless oil which solidified m.p.82c (0.022 g, 21%). ^{1}H-NMR δ: 7.85(m, 2H, o), 7.54 (m, 1H, p), 7.45 (m, 2H, me), 7.04, 6.84, 6.56 and 6.25 (br.lines, 1H, CH), 4.31 (q, 2H, CH_2), 4.20 (br.m, 4H, CH_2), 1.33 (t, 3H, CH_3), 1.27 (br.t, 6H, CH_3) .^{13}C-NMR δ: 171.0 (N(CO)Ph), 166.82 (CO_2Et), 154.78 (NCO_2Et), 133.15 (i), 131.97 (p), 128.53 (me), 127.26 (o), 67.02 (d, CH), 62.64 and 60.31 (t, CH_2), 14.15 and 14.03 (q, CH_3); IR (neat)ν_{max}: 3290 (NH_2), 1744 (CO_2Et), 1730 (NCO_2Et), 1662 (PhCO) cm^{-1} ; MS m\e: 382 (M+1).

2-Phenyl-5-carbethoxy-7-phenyl- 2,4,6,8 tetraaza-[3.3.1]bicyclooct-5-ene-1,3-dione (7d): A benzene solution of 1d (0.137 g, 0.726 mmol) and PTAD (0.127 g, 0.726 mmol) was stirred at 20°C for 20 min.The solvent was evaporated to give adduct 7d as a yellow oil (0.25, 94%). ^{1}H-NMR δ: 8.17 (m, 2H, o), 7.66 (m, 1H, p), 7.55-7.39 (m, 7H, me+N-Ph), 6.82 (s, 1H, H-5), 4.48 (q, 2H, CH_2), 1.44 (t, 3H, CH_3) ;^{13}C-NMR δ: 189.80 (PhCO), 155.20 and 153.20 (N(CO)N), 149.43 (C=N), 134.35 (p), 133.69 (i), 130.68 (i'), 129.36 (o), 129.24 (m), 128.81 (m'+p'), 125.86 (o'), 81.56 (d, CH), 68.97 (t, CH_2), 13.91 (q, CH_3) ; IR(neat)ν_{max}: 1741 (N(CO)N), 1702 (PhCO), 1659 (C=N) cm^{-1} ;MS m\e: 365 (M+1), 294 (MH^+-EtOCN), 260 (MH^+-PhCO).

2-Phenyl-5-phenyl-7-carbethoxy-2,4,6,8-tetraaza [3.3.1]bicyclooct-5-ene-1,3-dione (7a): A benzene solution of 1a (0.189 g,1 mmol) and PTAD (0.175 g,1 mmol) was stirred at 20c for 12 min. The solvent was evaporated to give adduct 7a as a yellow oil (0.364 g, 100%). ^{1}H-NMR δ: 8.10 (m, 2H, o), 7.61 (m, 1H, p), 7.52-7.37 (m, 7H, me+N-Ph), 6.23 (s, 1H, H-5), 4.41-4.30 (m, 2H, CH_2), 1.37 (t, 3H, CH_3) ;^{13}C-NMR δ: 165.51 (CO_2Et), 155.64 and 154.11 (N(CO)N), 149.30 (C=N), 133.19 (p), 130.41 (i), 130.25 (o), 129.05 (me), 128.73 (p'), 128.14 (me'), 125.65 (o'), 124.75 (i), 82.24 (d, CH), 62.96 (t, CH_2), 13.86 (q, CH_3) ;IR(neat)ν_{max}: 1740 (N(CO)N+CO_2Et), 1627 (C=N) cm^{-1} ; MS m\e: 365 (M+1), 291 (MH^+-$EtCO_2H$), 262 (MH^+-PhCN).

2-Phenyl-4-(dicarbethoxyhydroxymethyl)-5-ethoxy-oxazole (13): A benzene solution of 1a (0.8 g, 4.2 mmol) and diethyl ketomalonate (0.64 ml, 4.2 mmol) was heated under reflux for 4 days. Product 13 was obtained ,after flash chromatography using ethyl acetate:hexane 1:2.5 as the eluent,as a colorless oil (0.37 g, 24%). ^{1}H-NMR δ: 7.90 (m, 2H, o), 7.42-7.37 (m, 3H, me+p),4.355, 4.35 and 4.31 (q, 2H, CH_2), 1.41 (t, 3H, CH_3), 1.34 (t,6H,CH_3); ^{13}C-NMR δ: 168.48 (CO_2Et), 154.85 (C-2), 151.96 (C-5), 129.78 (p), 128.52 (me), 127.28 (i), 125.64 (o), 114.77 (C-4), 76.09 (E_2COH), 70.50 and 62.96 (t, CH_2), 14.94 and 13.98 (CH_3) ;IR(neat)ν_{max}: 3460 (OH), 1750 (CO_2Et), 1645 (C=N) cm^{-1} ;MS m\e 364 (M+1), 346 (M-H_2O) ;HRMS: 363.1092 cald. for $C_{16}H_{21}NO_7$ 363.1318.

2-(p-Chloro-phenyl)-5-phenyl-7-carbethoxy-2,4,6 triaza-[3.3.1] bicyclooct-5-ene-1,3-dione (11): Reaction of 1a with 10. a. Without catalyst.
A xylene solution of 1a (0.188 g, 1 mmol) and hydantoin 10 (0.56 g, 2.3 mmol) was heated under reflux for 23 h. After filtration of the excess hydantoin 10 and evaporation of the solvent, the residue was separated by flash chromatography (ethyl acetate:hexane 1:2.5). the product was a colorless oil containing both isomers of 11, combined weight: 0.2 g, 50%. The ratio of isomers: cis:trans=3:2.

b. with BF_3.etherate catalysis: To a toluene solution of 1a (0.107 g, 0.56 mmol) and hydantoin 10 (0.135 g, 0.56 mmol) in a flame dried system under Ar, an equivalent amount of BF_3.ether was added (0.063 ml, 0.56 mmol).The solution

was heated under reflux for 4h. After cooling,the toluene solution was removed from the oily residue that stuck to the flask. The oily residue was dissolved in $CHCl_3$ and purified by chromatography (ethyl acetate:hexane 1:2.5). The $CHCl_3$ fraction contained 11 (cis:trans 3:1) which was obtained as a yellow oil (0.198 g, 90%).
11(cis): ^{1}H-NMR δ: 8.06 (m, 2H, o), 7.57 (m, 1H, p), 7.46 (m, 2H, me), 7.44, 7.36 (ABq, p-Cl-Ph), 5.44 (d, J=8.8 Hz, 1H, CH), 5.03 (d, J=8.8 Hz, 1H, CH), 4.39 (m, 2H, CH_2), 1.40 (t, 3H, CH_3); ^{13}C-NMR δ: 169.38 (NC=O), 168.82 (CO_2Et), 160.05 (C=N), 153.78 (N(CO)N), 134.64(i), 132.82 (p), 130.59 (o), 129.36 (p-Cl-Ph), 129.08 (i), 128.18 (me), 127.56 (i), 127.17 (p-Cl-Ph), 70.66 (d, CH), 64.17 (d, CH), 62.98 (t, CH_2), 14.13 (q, CH_3) ; IR(neat)ν_{max}: 1730 (N(CO)N, CO_2Et), 1615 (C=N) cm^{-1}; MS m\e: 398 (M+1), 324 (M-CO_2Et).HRMS: 397.0745 ($C_{20}H_{16}N_3O_4Cl$) cald. 397.0829 (399.0799).

11(trans):^{1}H-NMR δ: 8.06 (m, 2H, o), 7.58 (m, 1H, p), 7.48 (m, 2H, me), 7.44, 7.36 (ABq,p-Cl-Ph), 5.20 and 5.10 (d, J=9.6 Hz, 1H, CH), 4.31 (m, 2H, CH_2), 1.32 (t, 3H, CH_3) ;^{13}C- NMR δ: 169.28 (NC=O), 161.68 (C=N), 153.97 (N(CO)N), 134.68 (i), 132.90 (p), 130.62 (o), 129.39 (p-Cl-Ph), 128.22 (me), 127.75 (p-Cl-Ph), 70.16 and 64.46 (d, CH), 62.63 (t, CH_2), 14.07 (q, CH_3) ;MS m\e: 398 (M+1), 324 (M-CO_2Et).

2,5,5-Tricarbethoxy-4-phenyl-3-oxazoline (14a) and 2-Phenyl-4,5,5-tricarbethoxy-2-oxazoline (15a): A xylene solution of 1a (0.35 g, 1.85 mmol) and diethyl ketomalonate (0.3 ml, 1.96 mmol) was heated under reflux for 46 h.The product was isolated as a yellowish oil (0.65 g, 96%). Ratio of 14a: 15a = 1:1.2. 3-Oxazoline (14a): ^{1}H-NMR δ: 8.02 (m, 2H, o), 7.49 (m, 1H, p), 7.40 (m, 2H, me), 6.38 (s, 1H, H-2), 4.35-4.20 (m, 6H, CH_2), 1.31, 1.28 and 1.22 (t, 3H, CH_3) ;^{13}C-NMR δ: 166.49 (CO_2Et), 165.84 and 165.74 (CO_2Et), 165.35 (C-2), 131.85 (p), 129.82 (o), 128.73 (me), 102.97 (d, C-2), 93.80 (C-5), 62.85 , 62.72 and 61.63 (t, CH_2), 13.96, 13.84 and 13.73 (q, CH_3); IR(neat)ν_{max}: 1750 (CO_2Et), 1612 (C=N) cm^{-1} ;MS m\e 364 (M+1), 292 (M-CO_2Et) ;HRMS 290.0978 ($C_{16}H_{21}NO_7$-CO_2Et) cald. for $C_{15}H_{16}NO_5$ 290.1028.
2-Oxazoline (15a): ^{1}H-NMR δ: 8.02 (m, 2H, o), 7.5 (m, 1H, p), 7.39 (m, 2H, me), 5.52 (s, 1H, H-5), 4.38-4.25 (m, 6H, CH_2), 1.30, 1.28 and 1.27 (t, 3H, CH_3) ;^{13}C- NMR δ: 168.24 (CO_2Et), 165.94 and 165.23 (CO_2Et), 164.53 (C-2), 134.24 (p), 128.83 (o), 128.32 (me), 125.91 (i), 87.87 (C-5), 75.35 (d, C-4), 63.19, 62.67 and 61.91 (t, CH_2), 13.94, 13.84 and 13.97 (q, CH_3) ;IR(neat)ν_{max}: 1750 (CO_2Et), 1655 (C=N) cm^{-1} ;MS m\e 364 (M+1).

4,5,5-Tricarbethoxy-4-methyl-2-oxazoline (15c): A toluene solution of 1c (0.25 g, 1.34 mmol) and diethyl ketomalonate (0.2 ml, 2.68 mmol) was heated under reflux for 24 h. After evaporation of the solvent and separation on a coloumn (ethyl acetate:hexane 2:1), product 15c was obtained as a yellow oil (0.04 g, 10%). ^{1}H-NMR δ: 6.13 (q, J=2 Hz, 1H, CH), 4.4-4.2 (m, 6H, CH_2), 2.34 (d, J=2 Hz, 3H, CH_3), 1.32, 1.31 and 1.28 (t, 3H, CH_3); ^{13}C-NMR δ: 167.55 and 164.86 (CO_2Et), 164.99 (C=N), 102.82 (d, C-4), 90.0 (C-5), 62.90, 62.60 and 62.02 (t, CH_2), 16.41 (q, CH_3), 13.89 (q, CH_3); MS m\e: 302 (M+1), 228 (M-CO_2Et).

2-Ethoxy-4-benzoyl-5,5-dicarbethoxy-2-oxazoline (15d): To a toluene solution of 1d (0.09 g,0.477 mmol) and diethyl keto malonate (0.073 ml,0.477 mmol) in a flame dried system under Ar, an equivalent amount of BF_3.ether (0.059 ml, 0.477 mmol) was added at 20c. After heating at 80c for 5.5 h,the solvent was evaporated and the residue was chromatographed (ethyl acetate:hexane 1:1).The product was obtained as a yellow oil (0.073, 43%). ^{1}H-NMR δ: 8.06 (m, 2H, o), 7.65 (m, 1H, p), 7.51 (m, 2H, me), 6.05 (s, 1H, H-4), 4.37+4.44 (ABq split into a q J=11,7 Hz) and 4.34 (q, J=7 Hz)(4H, CH_2), 3.83+3.71 (ABq split into a q J=11,7 Hz, 2H, CH_2), 1.36 and 1.32 and 0.96 (t, 9H, CH_3); ^{13}C-NMR δ: 193.17 (PhCO), 165.85 and 163.72 (CO_2Et), 156.29 (C=N), 134.50 (p), 134.30 (i), 124.83 (o+me), 84.10 (C-5), 63.84 and 63.87 and 63.23 (t, CH_2), 59.93 (d, CH),

13.78 and 13.21 (q, CH_3); IR (neat)ν_{max}: 1750 (CO_2Et), 1694 (PhCO), 1652 (C=N) cm-1 ;MS m\e 364 (M+1) ,308 (M-OEtCN), 290 (M-CO_2Et).

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