ESTER AZINES

FROM REACTIONS OF CARBENES WITH OXADIAZOLINES

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by

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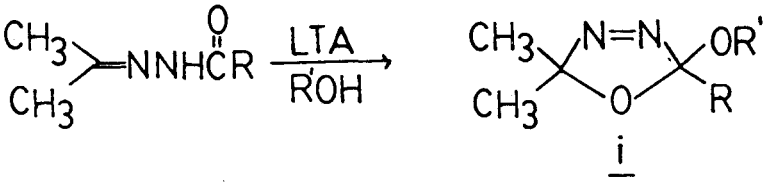
ABSTRACT

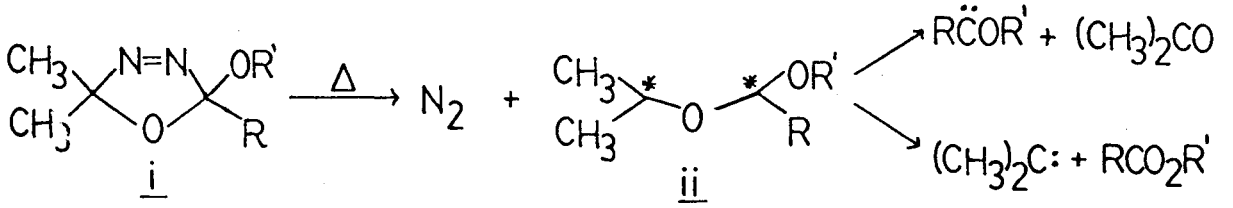
A series of 2-substituted Δ^3-1,3,4-oxadiazolines (i) were synthesized by oxidation of the corresponding hydrazones with lead-tetraacetate in alcohol, eq A.



R'=CH_3, CH_2CH_3
R=CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, and CH_2CX_3 X=Cl,F

[A]

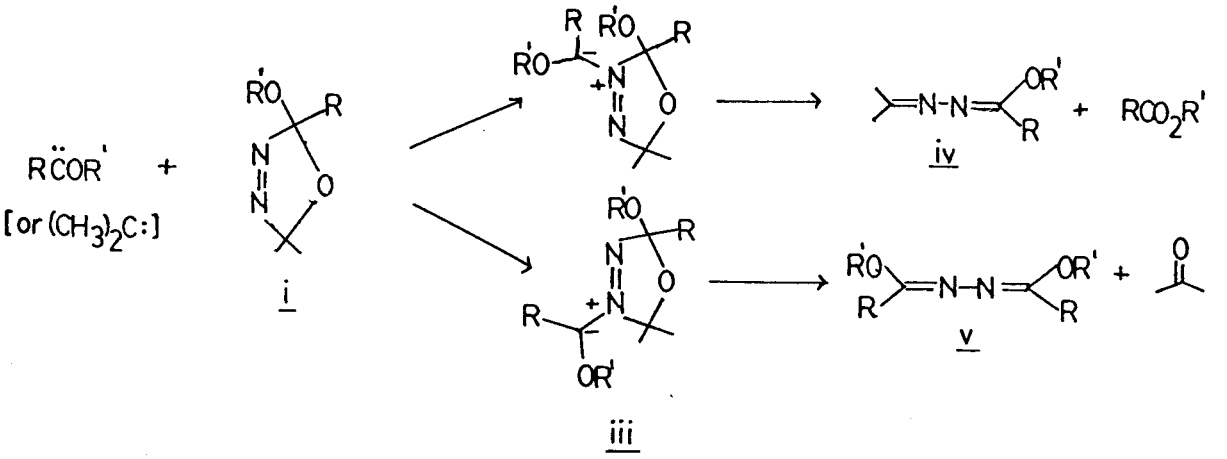
These oxadiazolines, upon thermolysis, generated carbonyl ylide intermediates (ii). These ylides are known to undergo fragmentation into carbenes and carbonyl compounds, eq B.



[B]

A new series of products were found from the thermolysis of these types of oxadiazolines, ester azines iv and v. A possible mechanism for the formation of these ester azines involves carbene attack on the oxadiazoline to give an azomethine imine intermediate (iii) which can subsequently

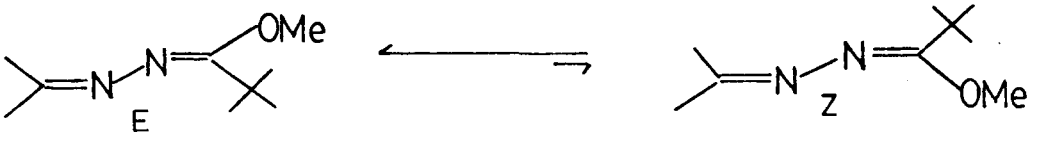
rearrange to give the azines and carbonyl compounds, eq C.



[C]

This mechanism is supported by the observation that the overall yields of ester azines rise with increasing initial concentration of oxadiazoline whereas the yield of propene, a rearrangement product of dimethyl carbene, falls with increasing initial concentration of oxadiazoline.

The ester azines (R=CH_3, CH_2CH_3 and $CH(CH_3)_2$) were found to be uniconfigurational and the E-configuration was assigned to ester azine iv and the E,E-configuration was assigned to ester azine v. Ester azines (R=$C(CH_3)_3$) were found to exist as configurational isomers. Equilibration studies were carried out on these ester azines and the thermodynamic parameters $\Delta G°$, $\Delta H°$ and $\Delta S°$ were found for equilibration shown in eq D.



[D]

Changing the R' substituent of i to OCH_2CCl_3 or OCH_2CF_3 did not stop fragmentation of the derived ylide. Ester azines were found from

the thermolysis of these oxadiazolines also. They were found to be uniconfigurational and were assigned the E-configuration.

ACKNOWLEDGEMENTS

I would like to thank Professor John Warkentin for his supervision and assistance while this project was in progress. His enthusiasm was an important factor in the success of this project.

I would also like to thank my co-workers in the lab, especially E. Osei-Twum, D. Jewell and D. McCallion for helping me get through this past year.

To my mother, father, and the rest of my family I can not express in words how much your support has meant to me.

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OVERVIEW

This thesis has one central theme and several peripheral themes. The central theme is the chemistry of reactive intermediates obtained by thermolysis of 2-alkoxy-Δ^3-1,3,4-oxadiazolines; namely, 1,3-dipoles and carbenes. The periphery of this structure includes the synthesis of the oxadiazolines, the kinetics of their thermal decompositions, and the ultimate products from the reactive intermediates. Most important among the products were ester azines which form a class of compounds that are relatively unexplored. Determination of the configurations of several new ester azines forms part of this thesis.

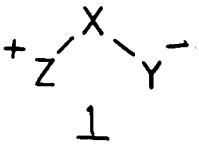
In order to provide background for the central and peripheral objectives, the Introduction contains material on 1,3-dipoles and carbenes, including the most relevant methods for their production and their most important reactions. It also includes some background material on the synthesis of azines and on the configurations of azines and related imidate systems.

It is hoped that this Overview will assist the reader by providing a rationale, in advance, for the many and diverse subjects discussed in the Introduction.

INTRODUCTION

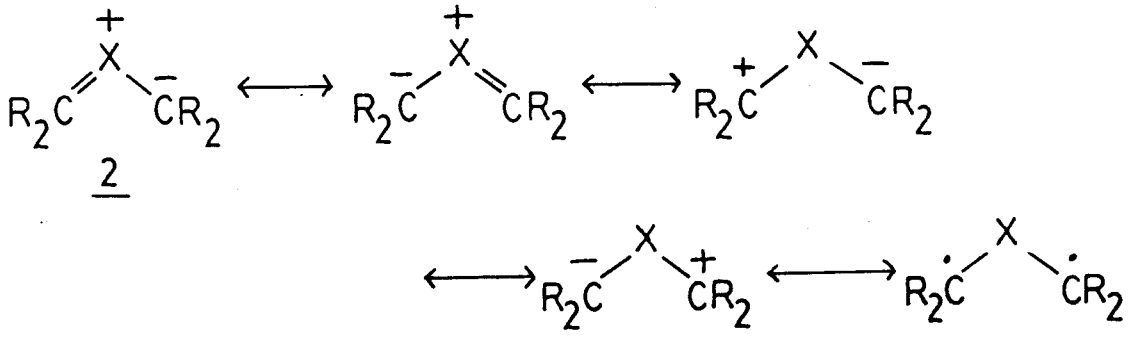
I.1 1,3-DIPOLES

A 1,3-dipole may be defined as an Z-X-Y system, where Z carries a formal positive charge and Y carries a formal negative charge (1).



1

Huisgen[2] recognized that molecules of the type R_2CXCR_2 (2), where X is a heteroatom, would exist and would be 1,3-dipolar species (X=NR,O,S).

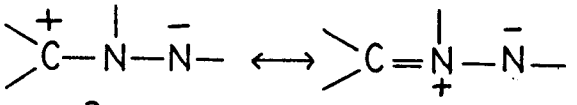


2

If X=NR, the molecule is an azomethine ylide, if X=O it is a carbonyl ylide and if X=S it is a thiocarbonyl ylide.[1]

If X has a lone pair of electrons, the system is stabilized through resonance, by forming a double bond. These compounds are called "betaines", and can be referred to as octet-stabilized 1,3-dipoles.

Another example of a 1,3-dipolar species is the azomethine imine (3).



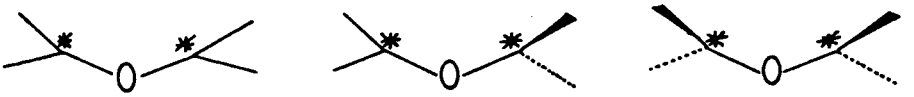
3

The following discussions will concentrate on carbonyl ylides and azomethine imines, their generation and reactions.

II.1 CARBONYL YLIDES

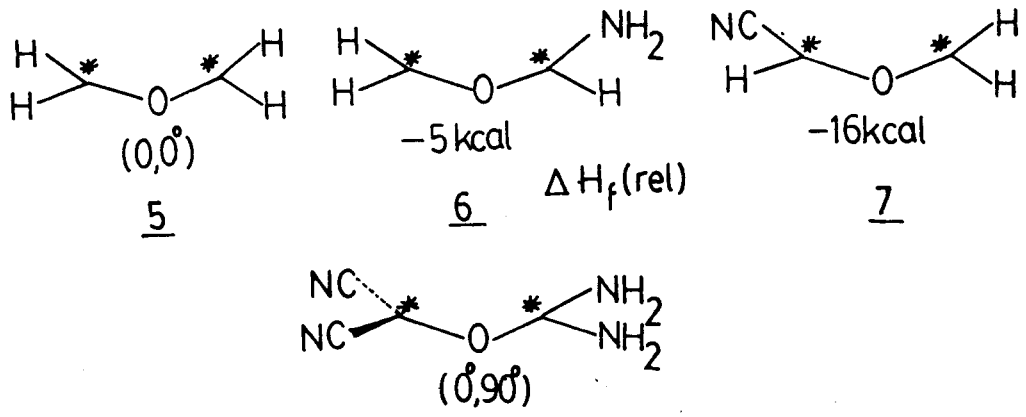
1. Structural Properties

Carbonyl ylides can adopt three different geometrical conformations[3]: a coplanar geometry, 0°, 0° (4a) and two nonplanar 0°, 90° (4b) and 90°, 90° (4c) geometries.



4a 4b 4c

The ground state of the carbonyl ylide is predicted[3] to be the coplanar 0°, 0° conformation (4a) which will rapidly invert about oxygen but can rotate only slowly about the partial CO double bonds. As donors (eg. NH_2, 6) or acceptors (eg. CN, 7) are added to the ylide (5), rotation about the CO bonds become easier.



5 6 7

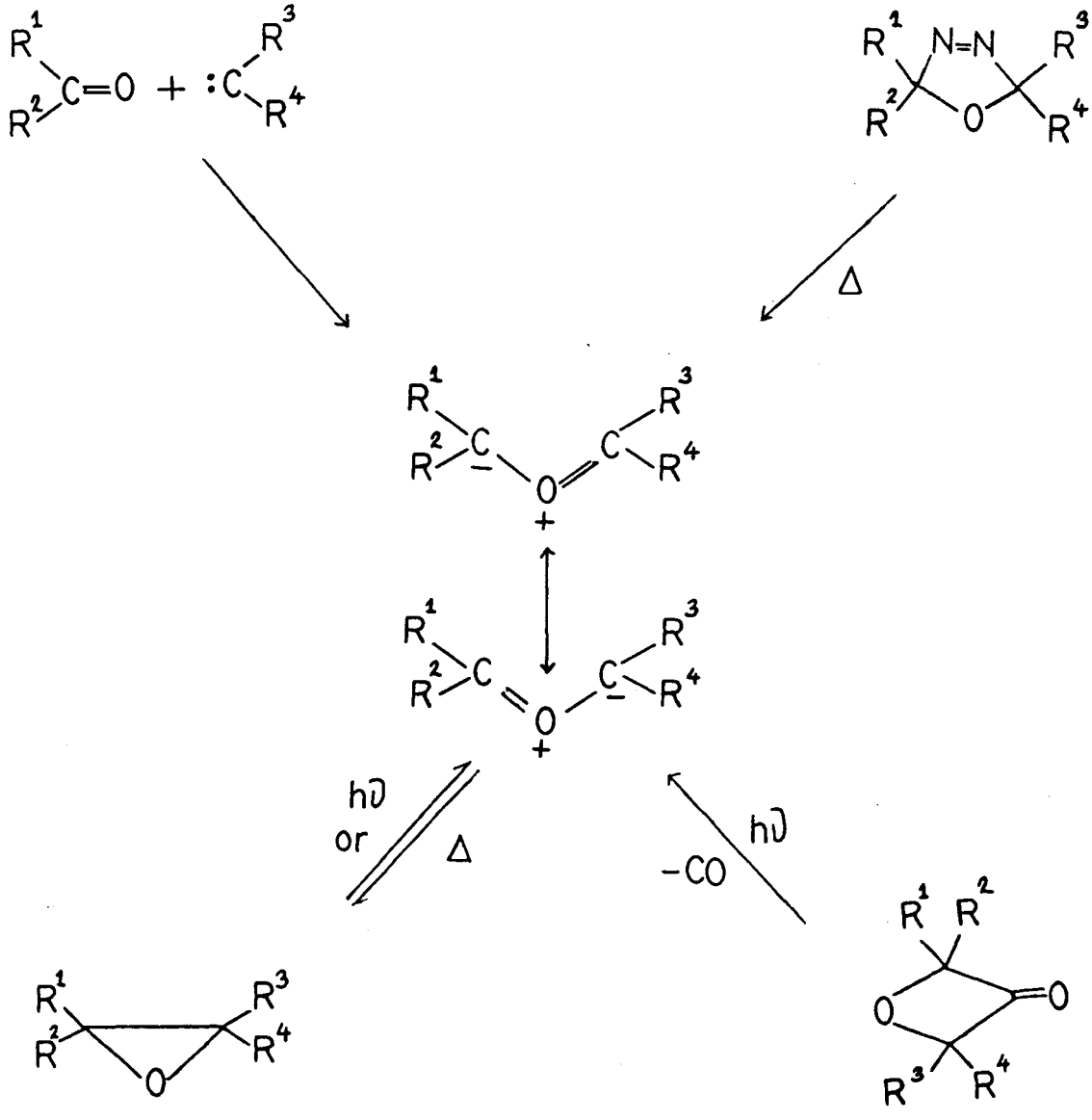
8

Electron donating substituents on one side and electron withdrawing substituents on the other side were found to stabilize the carbonyl ylide[3] (5). In the 1,1-diamino-3,3-dicyanocarbonyl ylide (8), stabilization is so great that the 0°,90° conformation is more stable than the planar conformation[3].

2. Generation of Carbonyl Ylides

There are several ways in which carbonyl ylides can be generated[4]: (i) by carbene addition to the carbonyl group of an aldehyde or ketone [5,6], (ii) through thermolysis or photolysis of monocyclic or polycyclic oxiranes[5,7,8], (iii) by chelotropic extrusion of carbon monoxide from oxetanes[8], and (iv) by the thermolysis of Δ^3-1,3,4-oxadiazolines[9,10]. (Scheme 1).

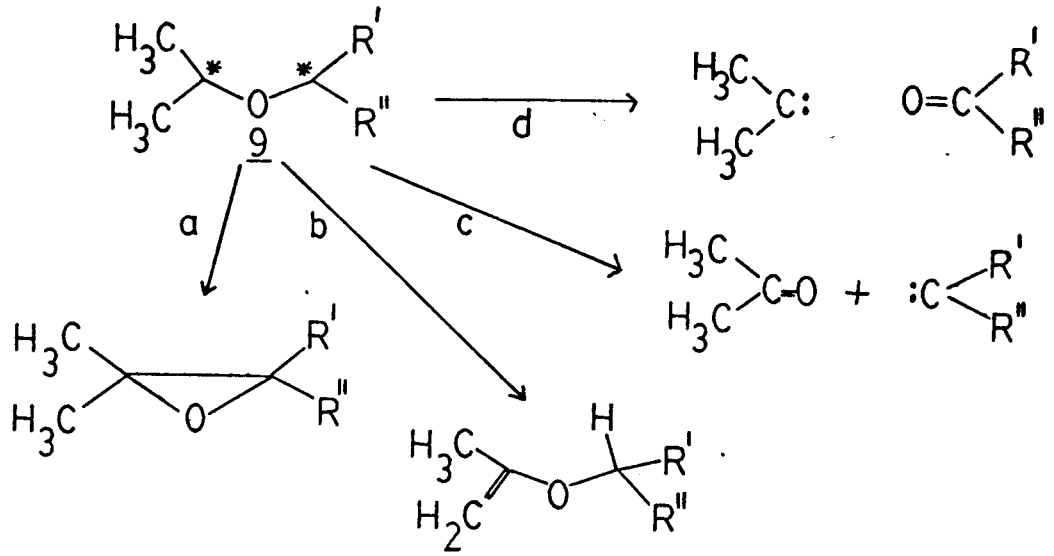
The next section will deal primarily with reactions of carbonyl ylides generated from the thermolysis of Δ^3-1,3,4-oxadiazolines.



Scheme 1

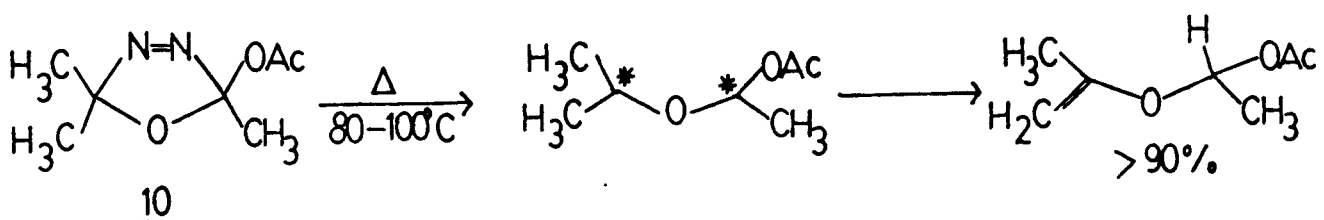
3. Reactions of Carbonyl Ylides

Carbonyl ylide (9) can undergo four different intramolecular reactions (Scheme 2). The ylide can a) cyclize to form an epoxide, b) undergo a 1,4-hydride shift to give an enol ether (when possible), and c) and d) fragment into carbonyl compounds and carbenes.



Scheme 2

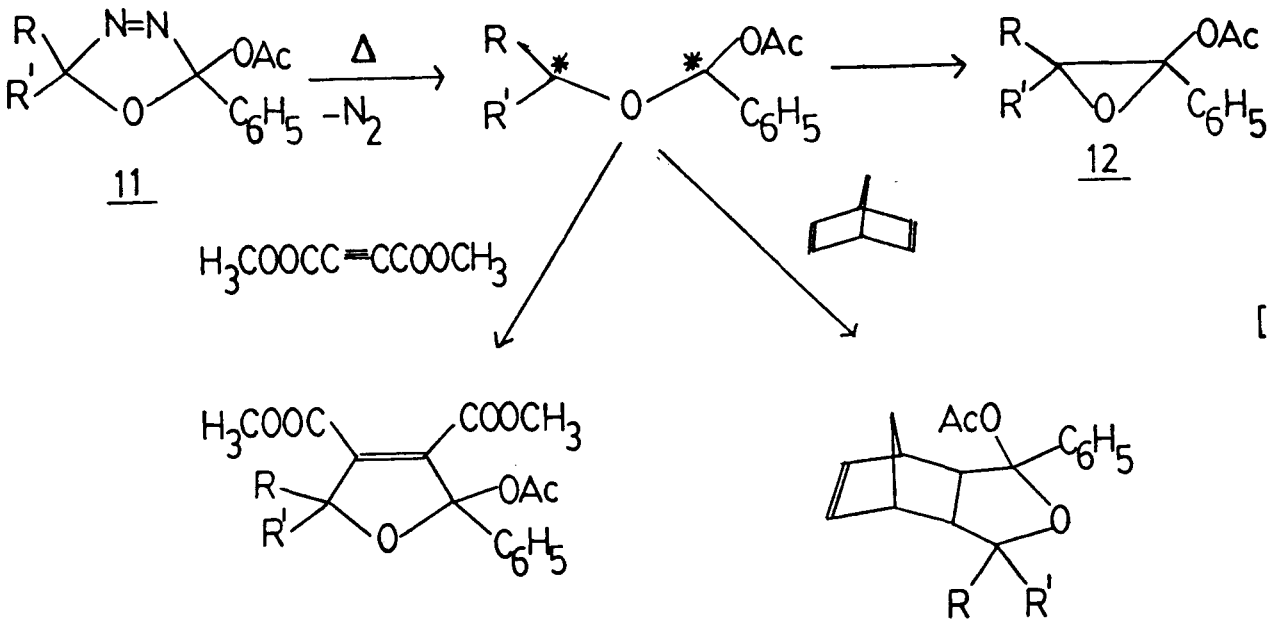
Substituents have a great influence on the reaction of a carbonyl ylide. For example, in the thermolysis of 2-acetoxy-oxadiazoline (10), the major product was that of a 1,4-hydrogen shift'', eq. 1.



10

[1]

However, Hoffmann[10] found that 2-acetoxyoxadiazoline (11) thermolyzed to give epoxy-acetates (12). A carbonyl ylide intermediate was proposed, and trapping experiments using norbornadiene and dimethylacetylene-dicarboxylate were successful, eq 2.

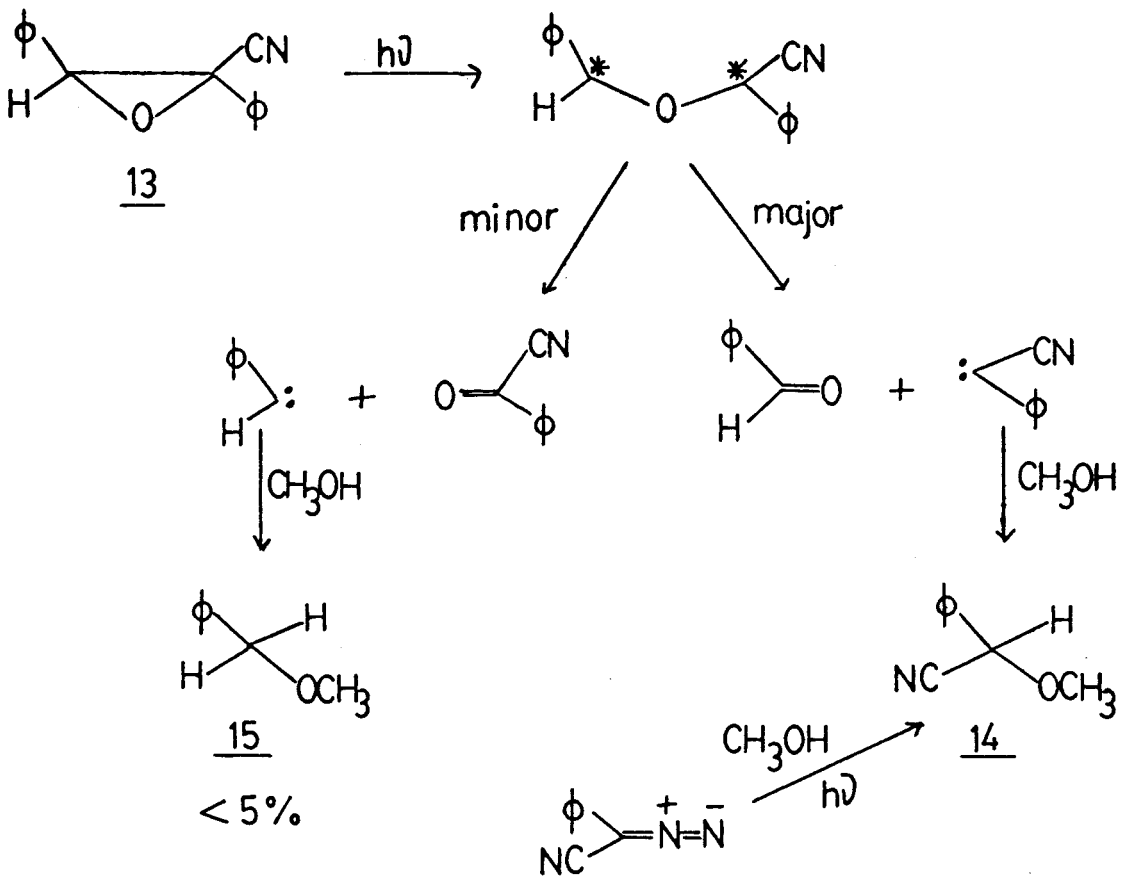


[2]

Photolysis or pyrolysis of three membered rings frequently yield products from fragmentations of 1,3-diradical or 1,3-dipolar intermediates[12-14]. Phenyl substituted oxiranes were found to be precursors to substituted arylcarbenes[15]. When irradiated in methanol, trans-2,3-diphenyl-2-cyano-oxirane (13) gave rise to α-methoxyphenylacetonitrile (14), benzaldehyde and other products (Scheme 3).

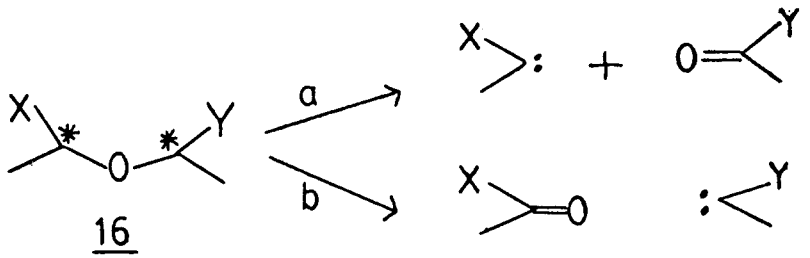
It was suspected that the cyanophenylmethylene was the precursor to ether 14. This was confirmed by carrying out a separate experiment involving irradiation of diazophenylacetonitrile in methanol. This also resulted in the formation of ether 14. The yield of benzylmethyl

ether (15) was less than 5%, showing that fragmentation of the ylide occurred in one preferred direction.



Scheme 3

Results of theoretical studies of reactions of substituted carbonyl ylides (16) were recently published by Houk, Griffin and co-workers[3]. They concluded that the thermal fragmentation of (16), eq 3, can occur in two different ways.



16

[3]

Their results[3] with regards to fragmentation are shown below.

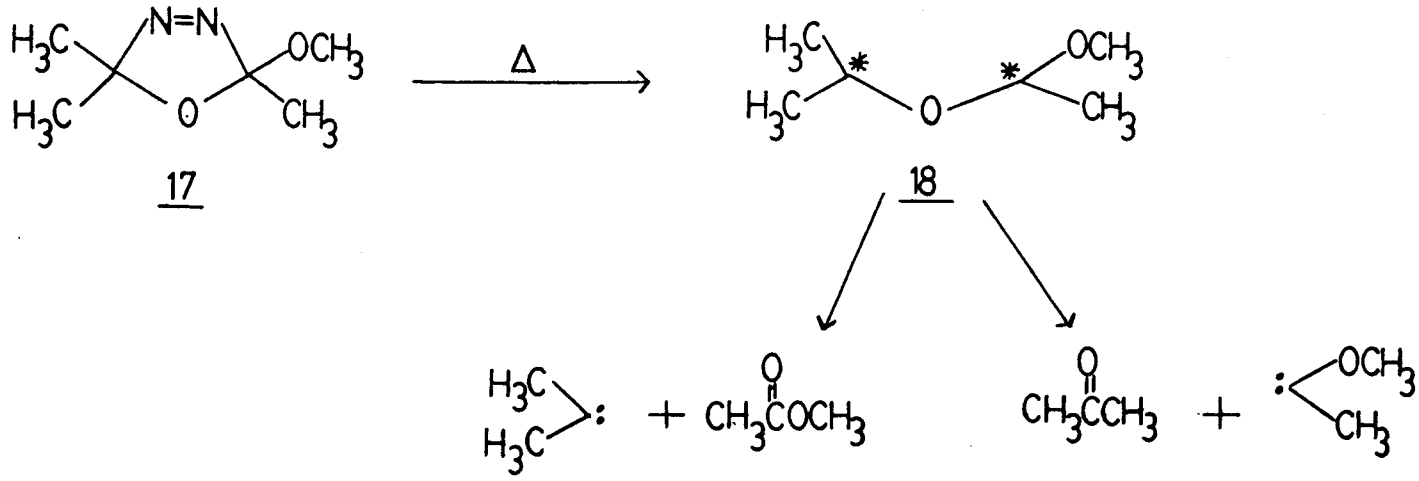
(i) Fragmentation of the carbonyl ylide (X=Y=H) is endothermic by about 39 kcal/mole.

(ii) One amino substituent ($Y=NH_2$) decreases the thermodynamic barrier of fragmentation in either sense and path a, leading to the amino carbene may actually be exothermic.

(iii) Thermal fragmentations of a carbonyl ylide from a coplanar ground state (0°,0°) is a disallowed process.

The first example of a thermal fragmentation of a carbonyl ylide was recently reported[16]. Carbonyl ylide (18) was generated from the thermolysis of oxadiazoline (17) and fragmented according to Scheme 4.

In order for ylide (18) to fragment thermally it must either have a nonplanar ground state or else have a nonplanar state which is readily accessible from a planar ground state. Calculations[3] indicate that a donor substituent reduces the barriers to rotation from a 0°,0° conformation to a 0°,90° conformation.



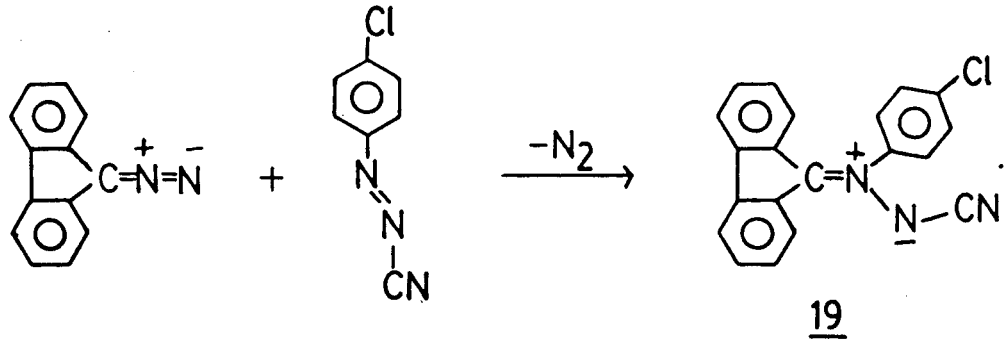
17 18

Scheme 4

I.1.2 AZOMETHINE IMINES

In the following section typical examples of the generation of azomethine imines and of their reactions will be discussed.

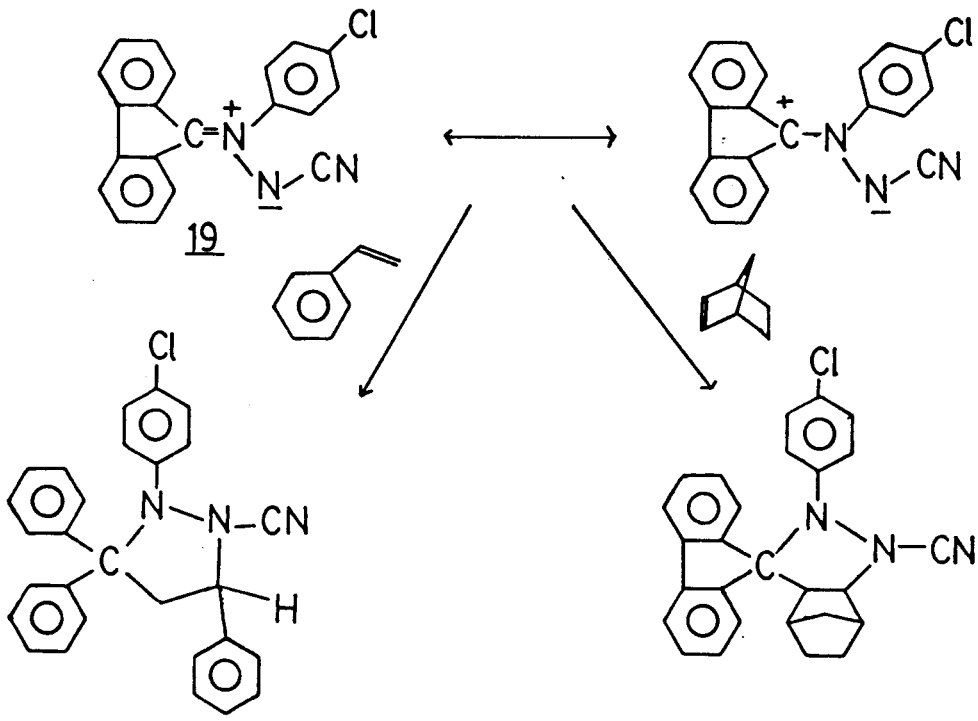
One class of isolable azomethine imines is the N-cyano azomethine imines, prepared from the reactions of aliphatic diazo compounds and diazocyanides. When equimolar amounts of diazofluorene and para-chlorophenyl-anti-diazocyanide are mixed, one equivalent of N_2 is evolved with slight spontaneous heating, and the orange-red needles of β-cyanoazomethine imine (19) are deposited from solution, eq 4. Diphenyl-diazomethane, instead of diazofluorene, gave the analogous result.



[4]

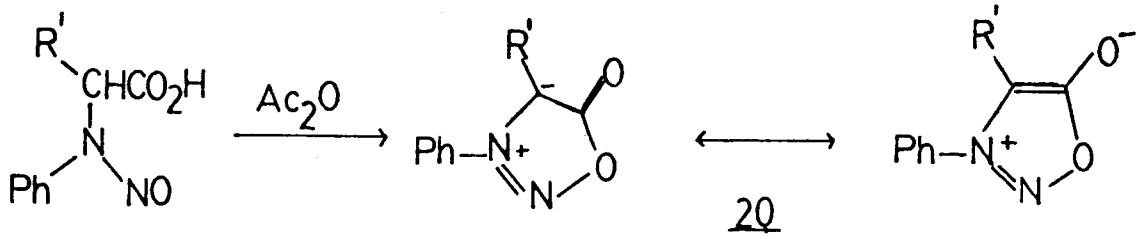
19

Ylide 19 was successfully trapped by both styrene and norbornene[18], Scheme 5.



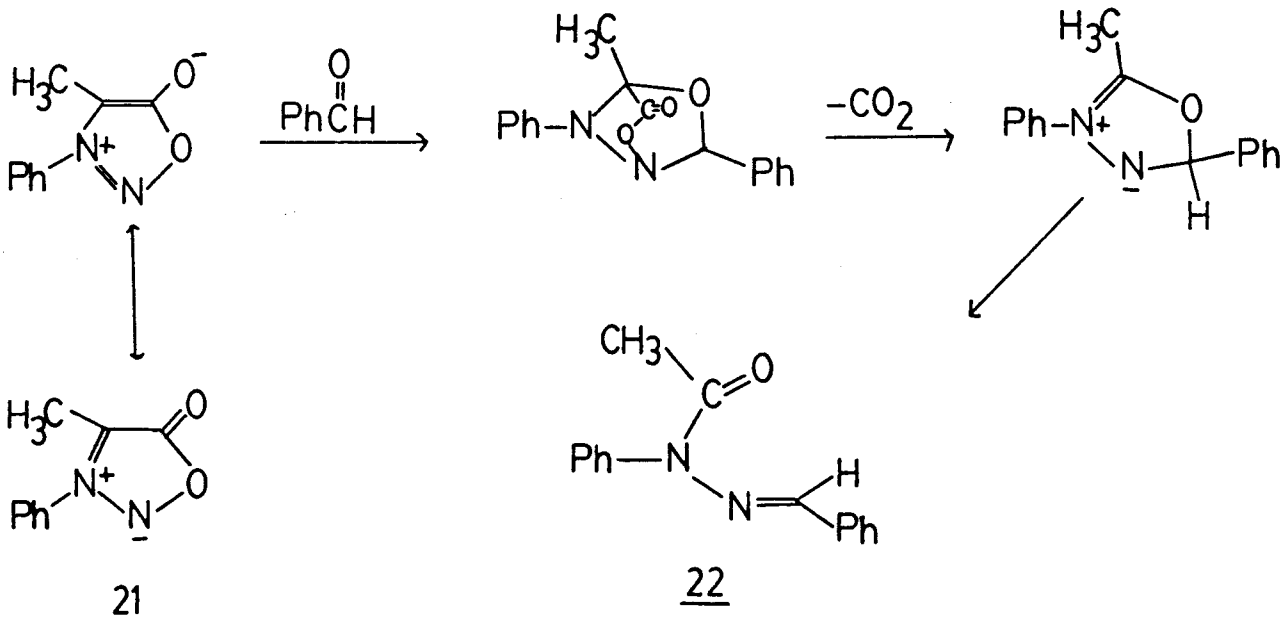
Scheme 5

Syndones (20), prepared through the cyclization of N-nitroso-α-amino acids, contain the cyclic azomethine imine system in an aromatic ring[5,19], eq 5.



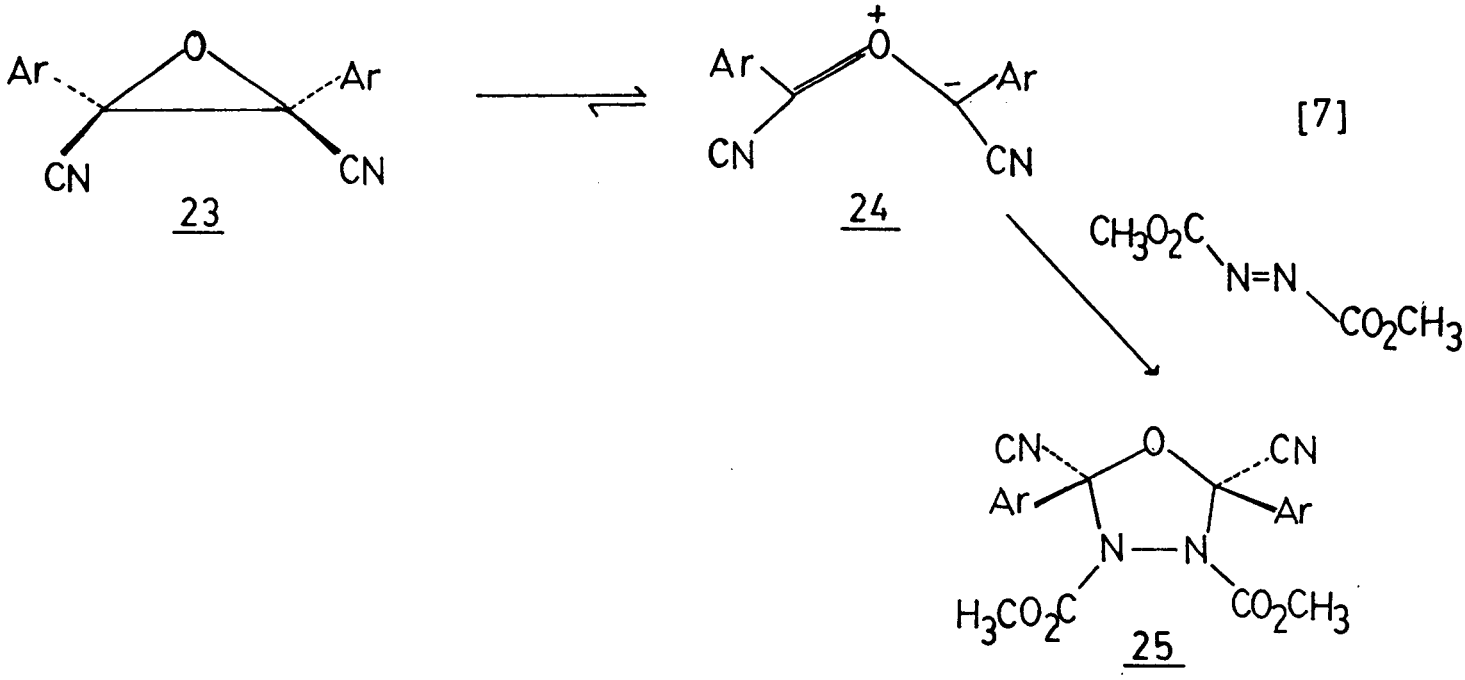
[5]

Huisgen et al.[20] have demonstrated that the mesoionic form, 20, reacts with dipolarophiles with elimination of carbon dioxide, thus behaving like an azomethine imine. The cycloadditions of 3-phenyl-4-methylsyndone (21) with aromatic aldehydes yield arylidene-N-acetyl-hydrazones (22), eq 6.



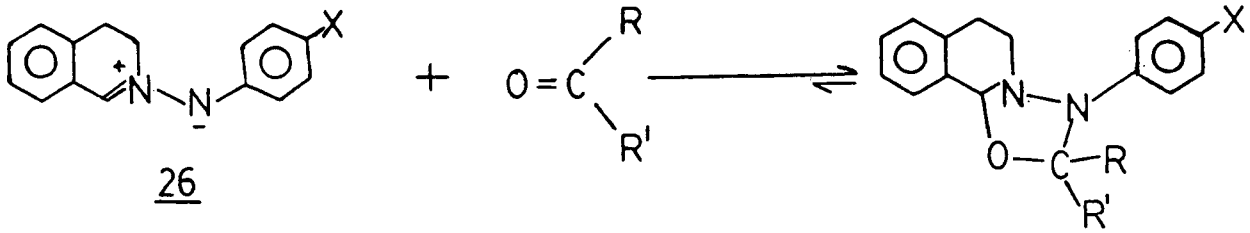
[6]

Substituted oxiranes (23) are in thermal equilibrium with small concentrations of the carbonyl ylides (24). Reactions of 23 with dimethyldiazodicarboxylate provide 1,3,4-oxadiazolidines of structure 25, eq 7.

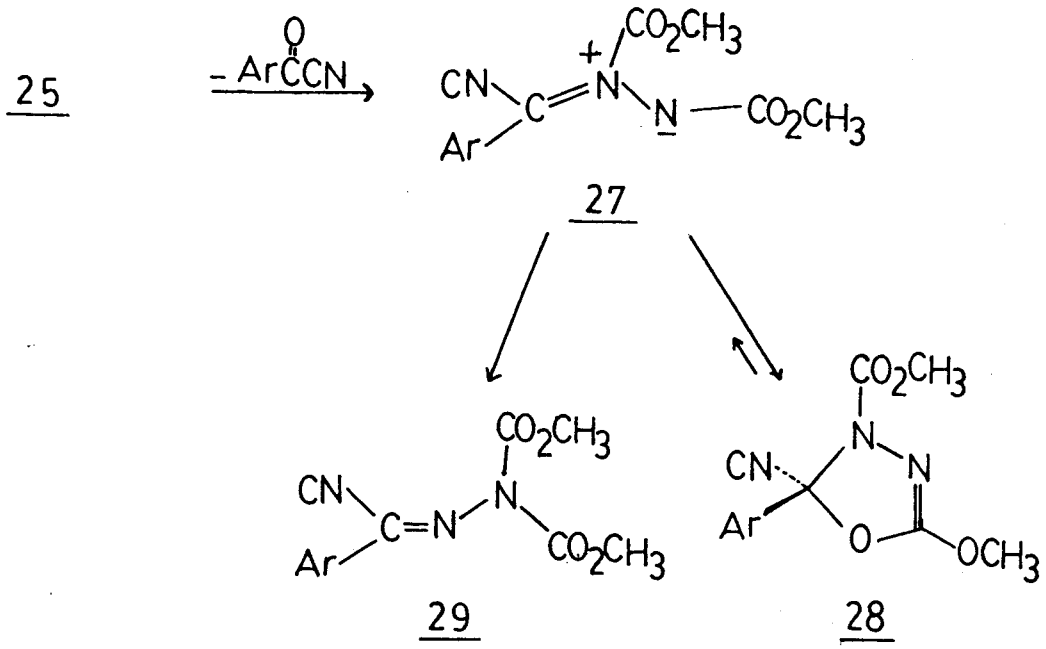


[7]

It has been shown that the cycloaddition of azomethine imines (26) to carbonyl compounds is reversible[21], eq 8. Thus, the 1,3-dipolar cycloreversion of 25 should yield azomethine imines (27) or their stabilization products, Scheme 6.



26 [8]



25 27 29 28

Scheme 6

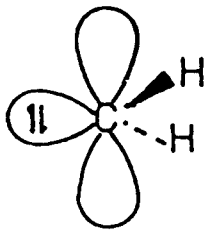
The azomethine imine N^{α},N^{β}-dicarboxylic esters (27), can undergo a reversible cyclization to 1,3,4-oxadiazolines (28) or an irreversible acyl shift to hydrazone-$N^{\alpha}N^{\beta}$-dicarboxylic esters (29).[22,23]

As already mentioned, one possible reaction pathway of the carbonyl ylide is fragmentation to yield carbonyl compounds and carbenes. The next section will deal with carbenes, their generation and reactions.

I.2 CARBENES

I.2.1 INTRODUCTION

Carbenes are neutral, divalent carbon intermediates in which a carbon atom has two covalent bonds, and two electrons in one or two non-bonding orbitals. The carbene is in a singlet state if the two electrons are spin-paired[24] (30). The carbon is sp^2 hybridized and due to a vacant p orbital, the carbene is highly electrophilic and therefore extremely reactive. Singlet carbenes are electron deficient like carbonium ions, while possessing a non-bonding pair like that of carbanions. The electrophilicity or nucleophilicity of singlet carbenes depends on the ability of the adjacent groups to withdraw electrons from or supply electrons to the carbene carbon[25]. The carbene is in a triplet state if the two electrons have spins that are parallel[24] (31). A triplet carbene is often diradical in character and since there are no empty p orbitals it is not as electrophilic in character as a singlet carbene.



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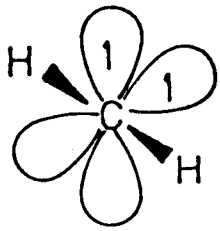

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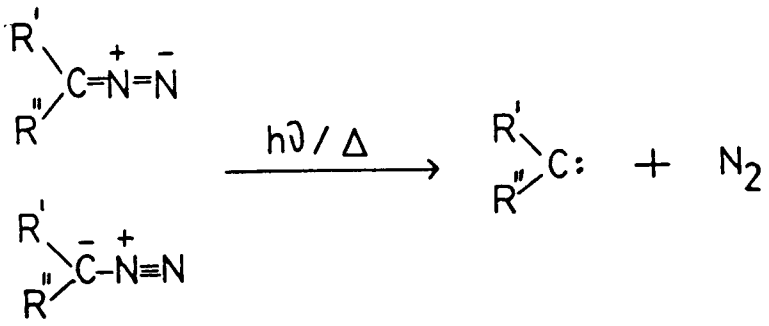
I.2.2 GENERATION OF CARBENES

There are various ways in which carbenes can be generated. Carbenes can be generated from diazoalkanes, hydrazones, diazirines, α-halo carbanions, ketenes, ylides and metal complexes as well as by other routes.

(i) Diazoalkanes

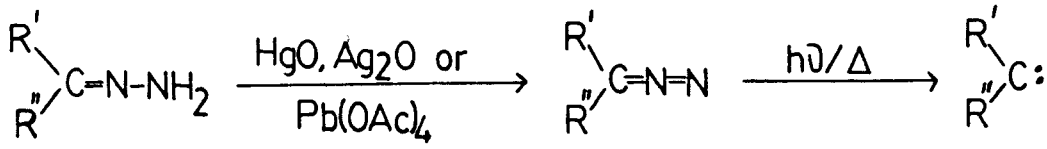
Carbenes can be generated by the photolysis or thermolysis of diazoalkanes[25], eq 9.



[9]

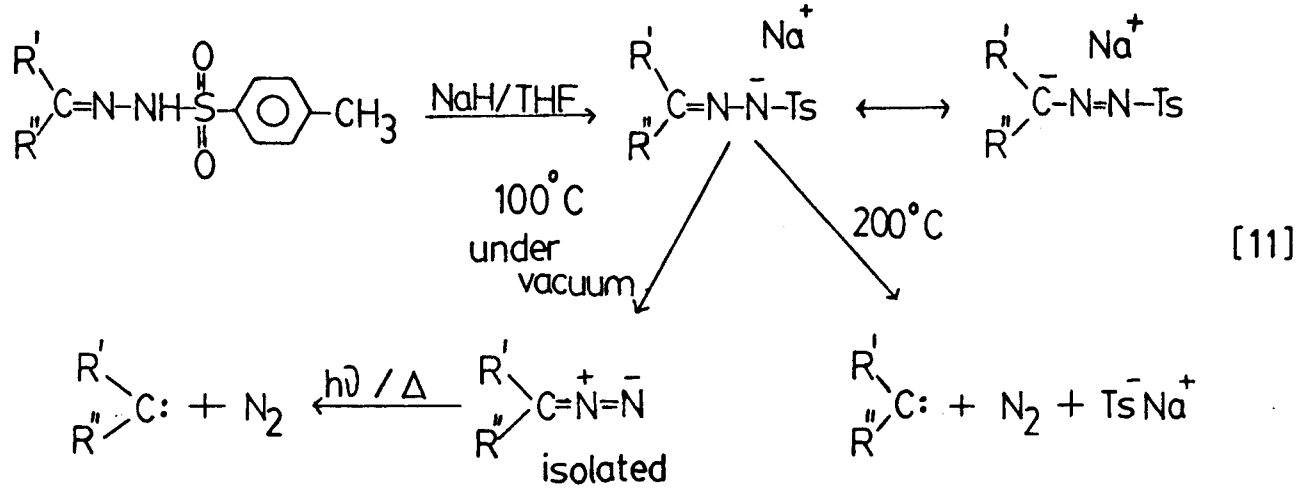
(ii) Hydrazones

Hydrazones can be oxidized to diazoalkanes[26], which then are photolytically or thermally converted to carbenes, eq 10.



[10]

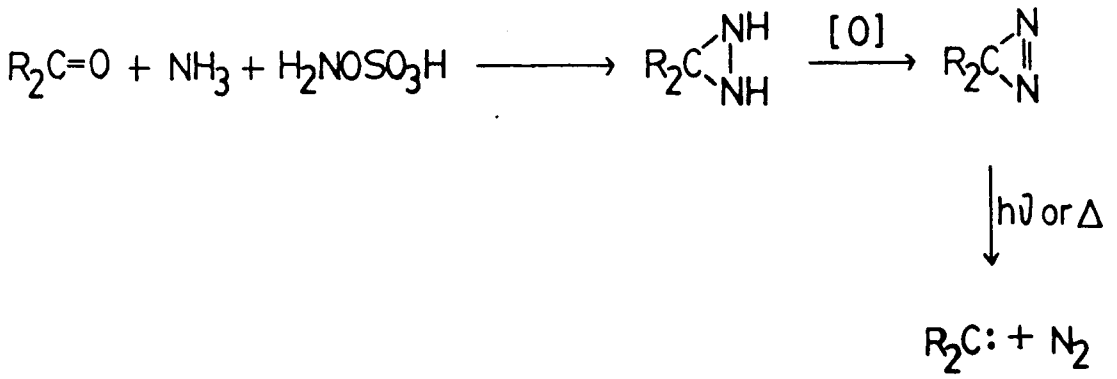
Carbenes can also be generated from the salts of tosylhydrazones[27,28], eq 11. At high enough temperatures, the salt may be directly converted to the carbene. At temperatures around 100°C under vacuum, the diazoalkane may be isolated.



[11]

(iii) Diazirines

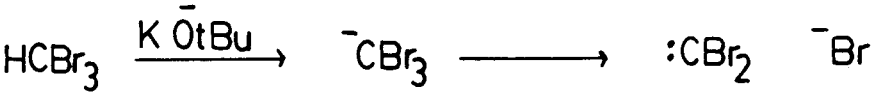
Photolysis or pyrolysis of diazirines also generates carbenes. Diazirines can be synthesized from ammonia, hydroxylamine-o-sulfonic acid and ketones [29], eq 12. There is evidence for diazoalkanes being intermediates in both the thermolysis and photolysis of diazirines[30-32].



[12]

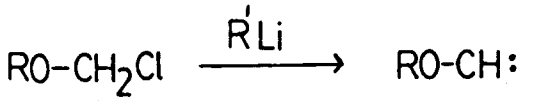
(iv) α-Elimination

Carbenes can also be generated by α-elimination of halide from carbanions[25], eq 13.



[13]

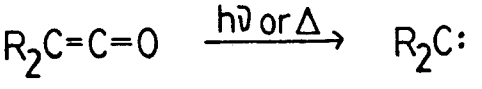
Phenoxy carbene and various alkoxycarbenes have been produced from the corresponding chloroethers by α-elimination of hydrogen chloride[33-36]. Because α-chloroethers undergo S_N2 displacement reactions readily, t-butyllithium was the only suitable base to effect the α-elimination in many cases, eq 14.



[14]

(v) Ketenes

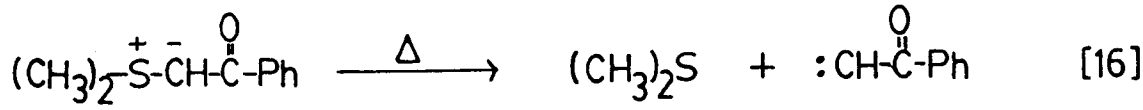
Substituted ketenes can generate carbenes by thermolysis or photolysis[25]. Carbon monoxide is lost in the carbene forming process, eq 15.



[15]

(vi) Ylides

Carbenes can be generated from the thermolysis or photolysis of sulphur[37], phosphorus[38] or nitrogen ylides[39], eq 16.

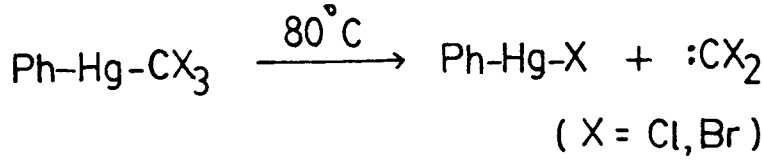


[16]

The carbene is generated by heterolytic cleavage of the sulphur-carbon bond.

(vii) Mercuric Compounds

Phenyl(trihalomethyl)mercury compounds have also been used as a dihalocarbene source[40]. The decomposition of tribromomethylphenylmercury at 80°C yields dibromocarbene. The trichloro-compound also decomposes at this temperature but needs prolonged heating, eq 17.



[17]

I.2.3 REACTIONS OF SINGLET CARBENES

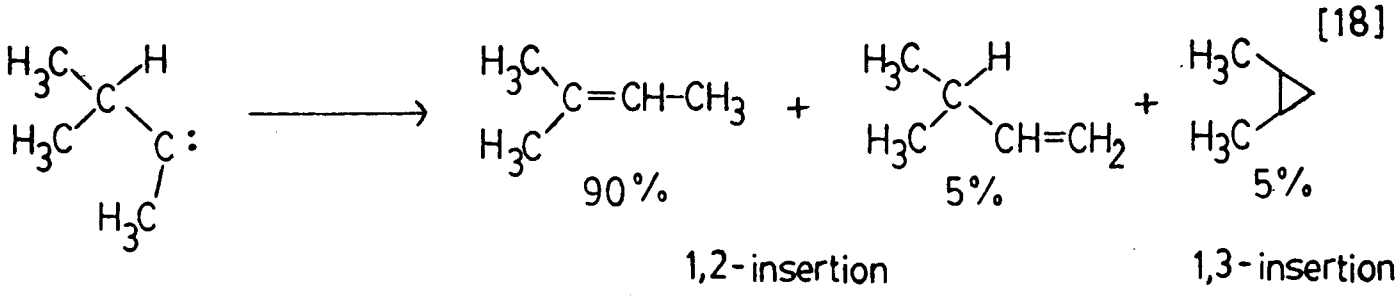
Singlet carbenes can undergo insertion and addition reactions, either intramolecularly or intermolecularly.

1. Insertion into C-H Bonds

Intramolecular

Alkyl and dialkyl carbenes react predominantly by insertion of

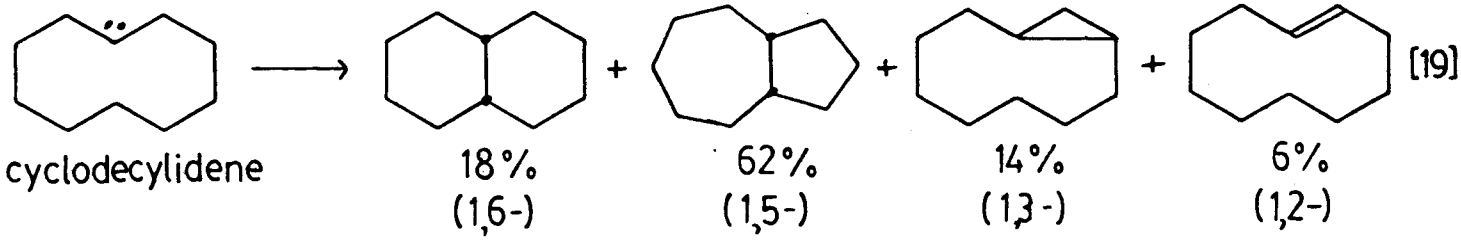
the divalent carbon into the β and γ C-H bonds (1,2- and 1,3-insertions respectively) yielding olefins and cyclopropanes, eq 18.



[18]

Aprotic solvents must be used to avoid protonation of the carbene and hence cationic behavior. The reaction leading to olefins is also termed a "hydride shift".

1,5- and 1,6- Insertions also occur. In the case of cyclodecylidene, 1,2-, 1,3-, 1,5- and 1,6- insertion products are obtained, eq 19. The formation of larger than 3-membered rings in transannular insertion reactions may be due to the proximity of the transannular hydrogen.



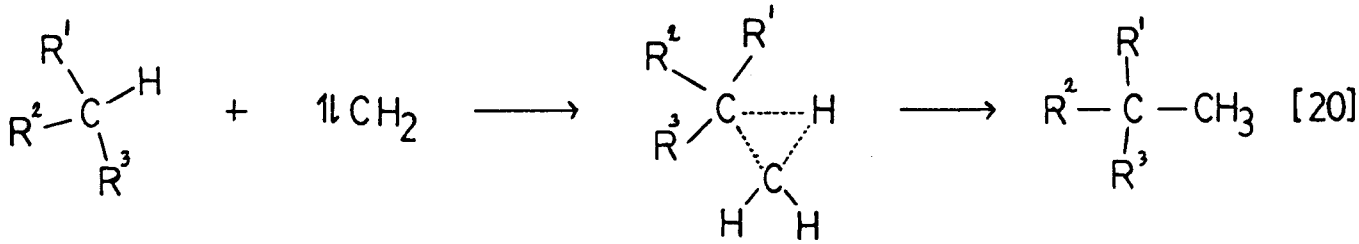
[19]

The 1,5- insertion product predominates since a 6-membered cyclic transition state is involved[41]. The exclusive formation of cis-bicyclic systems indicates the transfer to axial hydrogen and is consistent with the principle that insertions occur with retention of configuration.

Intermolecular

The ease of intramolecular stabilization leaves only a slight chance for intermolecular reactions of alkyl and dialkyl carbenes. Since primary hydrogen undergoes "hydride shift" less readily than secondary or tertiary hydrogen, a moderate stability of methylcarbene and dimethyl carbene can be expected.

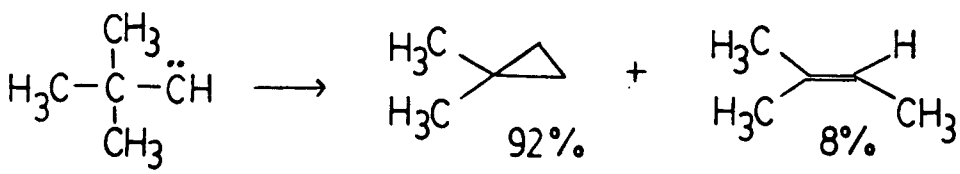
A concerted mechanism is proposed for the insertion of methylene into a C-H bond, eq 20.



[20]

2. Insertion into C-C Bonds

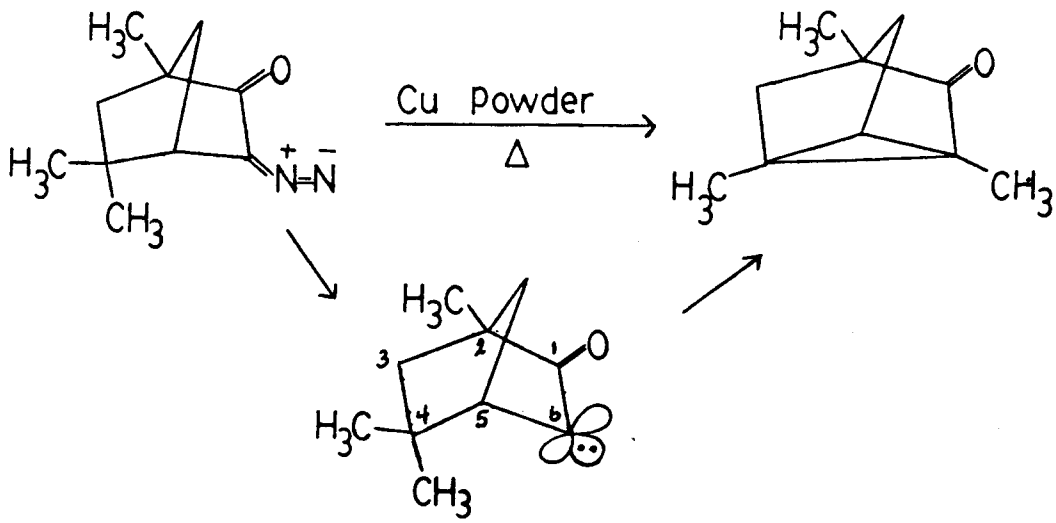
Intramolecular insertions into C-C bonds also occur, eq 21.



[21]

From the product ratios, there is still a preference for 1,3-CH bond insertions even though it results in making a highly strained cyclopropyl ring.

C-C bond insertions also occur in bicyclic systems[25], eq 22.

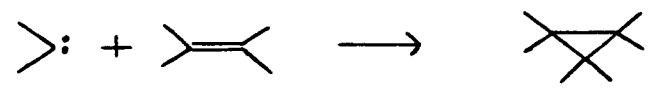


[22]

C-C Bond insertion occurs between C_4 and the C of the endo methyl group at C_4 because of orbital alignment requirements. C-C bond insertions do not occur as readily as C-H insertions.

3. Addition to C=C Bonds

Singlet carbenes add to olefins in a concerted process, eq 23.



(1ℓ)

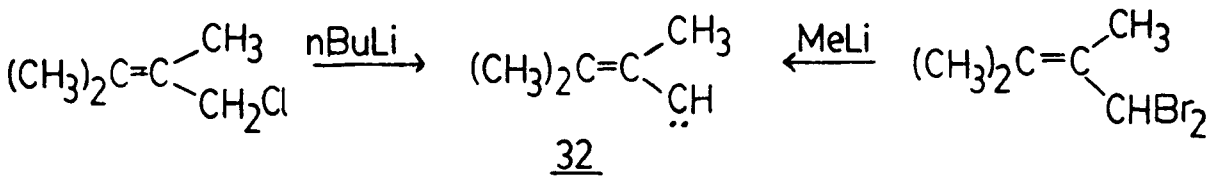
[23]

The reactivity of olefins towards singlet carbenes increases with increased substitution of the double bond with alkyl groups[25].

Intramolecular

α-Elimination of hydrogen chloride from 2,3,3-trimethylallyl-chloride has been brought about in low yields by lithium alkyls[42,43].

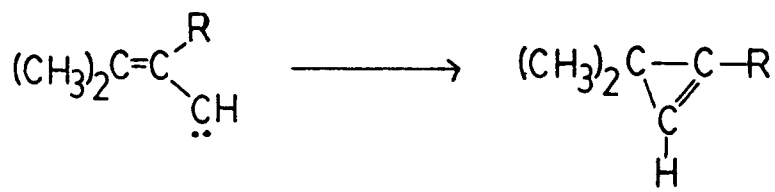
Halogen-metal interchange on 1,1-dibromo-2,3-dimethyl-2-butene proved to be a more effective route to the carbene intermediate[43] (32), eq 24.



[24]

32

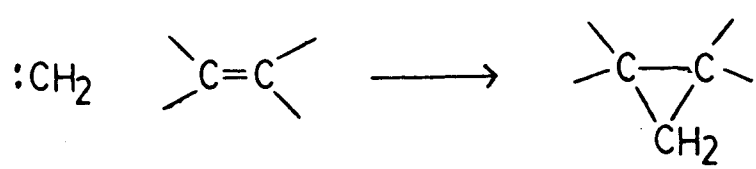
The only products from these alkenyl carbenes are substituted cyclopropenes, formed from intramolecular addition[42-44], eq 25.



[25]

Intermolecular

Carbon-carbon single bonds are inert toward methylene even in highly strained small ring compounds such as spiropentane[25]. Carbon-carbon double bonds add methylene easily to form cyclopropanes, eq 26.

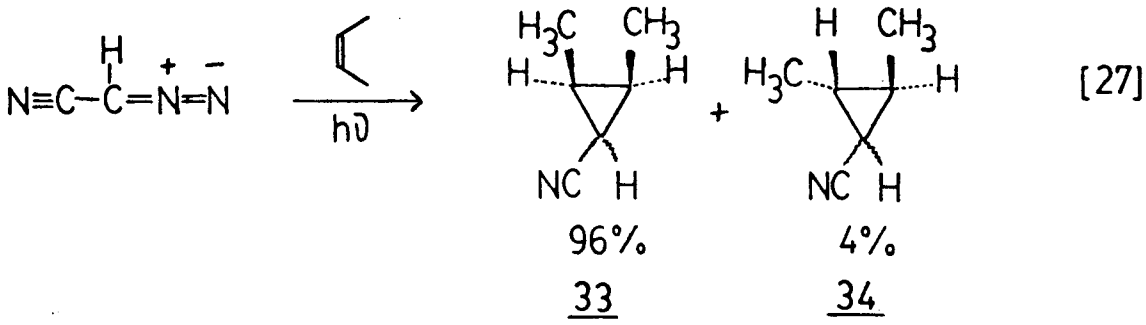


[26]

Most addition reactions of methylene are stereospecific cis additions. For example, cis-1,2-disubstituted cyclopropanes are obtained from cis-olefins and trans-1,2-disubstituted cyclopropanes from trans-olefins. The stereochemistry is thought[25] to reflect the

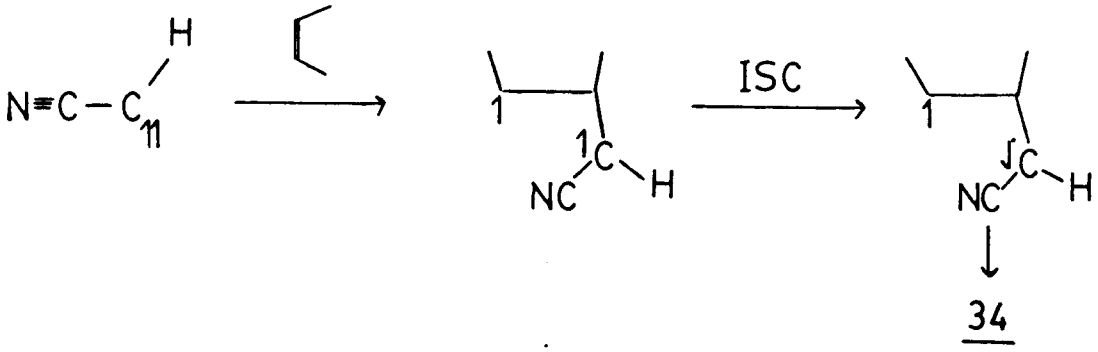
singlet state of the reacting methylene. The addition process itself can be nonstereospecific whenever methylene reacts in its triplet state. In the gas phase, under high pressures of inert gas, the methylene carbenes may collide many times and may be converted to the triplet state before they react with the olefin. Nonstereospecific addition of methylene to cis- and trans-2-butene has been observed[25] under these conditions.

Singlet ground state carbenes undergo insertion reactions into C=C bonds in a concerted fashion. When cyanomethylene is photolytically generated from the diazoprecursor in the presence of cis-2-butene, two insertion products are formed, 33 and 34, eq 27.



[27]

Compound 33 is formed by a direct concerted insertion into the olefin by the singlet carbene. Compound 34, however, is formed by the intervention of the carbene in its triplet state. The carbene in its triplet state will add to the double bond to form a 1,3-diradical with spins unpaired. Before this 1,3-diradical can close to form a cyclopropane, one of the electrons of the diradical must undergo intersystem crossing, eq 28.



[28]

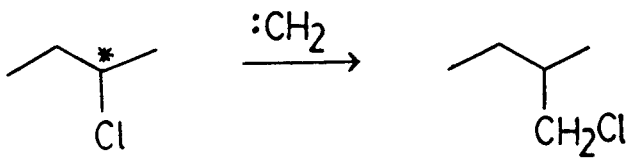
If a radical trap, such as 1,1-diphenylethene, is added, the yield of 34 decreases. This is supporting evidence for the formation of 34 by the triplet carbene.

4. Insertion into C-X Bonds

X=halogen

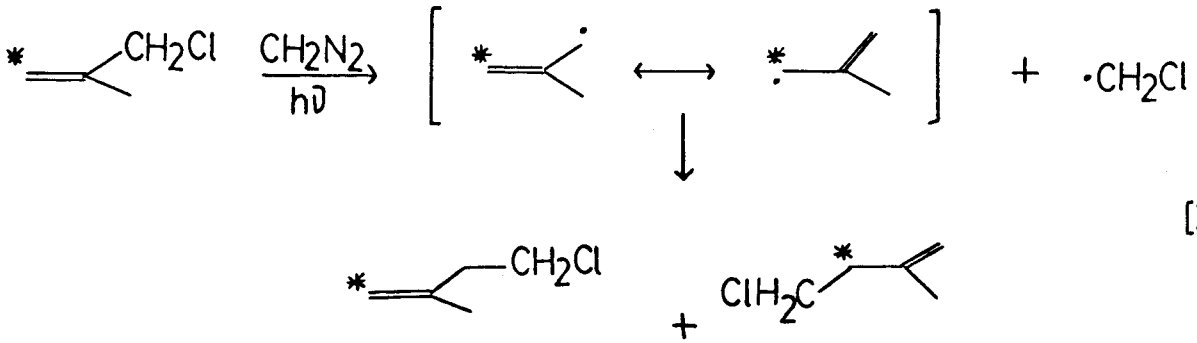
Carbon-halogen bonds are quite labile toward methylene. With both isopropyl chloride and isopropyl bromide, insertion into the carbon-halogen bond is the main process[45].

Doering and Sampson[46] showed that the reaction with optically active sec-butylchloride gave insertion product which was 90% racemic, eq 29.



90% racemic [29]

A radical reaction is thus implicated. This was confirmed[47] by observation of a large amount of rearrangement in the reaction of methylene with labelled methallyl chloride, eq 30.



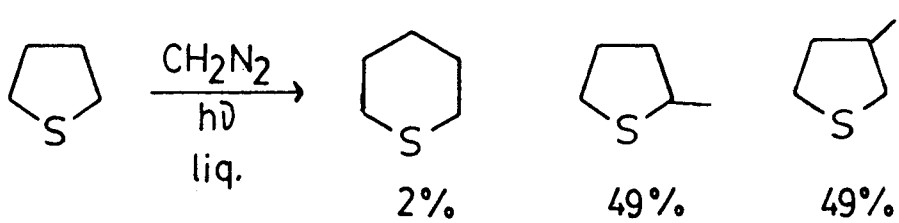
[30]

It seems clear that carbon-chlorine insertion is a two-step process and does not occur by a direct process found for the carbon-hydrogen bond.

The use of both ClDNP[48,49] and CO[50] as a triplet scavenger have implicated the singlet state in chlorine abstraction and the triplet state in hydrogen abstraction.

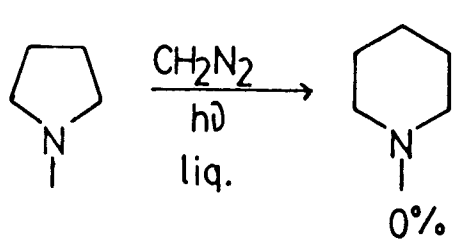
X=S,N

Insertion into a carbon-sulphur bond does take place but it is not a major process[51], eq 31.



[31]

Insertion is not observed in N-methylpyrolidine[52], eq 32.

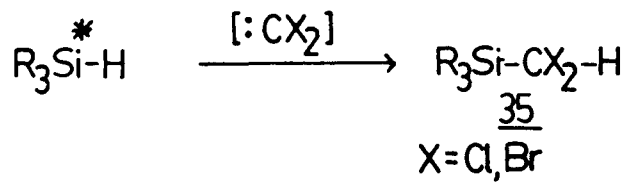


[32]

X=Si

The carbon-silicon bond is not attacked[53] by methylene, but the silicon-hydrogen bond is[54]. Silicon-hydrogen insertion occuring in solution was found to be at least 100 times as fast as carbon-hydrogen insertion. In the gas phase a Si-H/C-H insertion ratio of 8.9 was found for singlet methylene, using oxygen as a radical scavenger. Abstraction to give radicals accompanies insertion and accounts for at least 27% of the primary reaction[55,56].

Dihalocarbene underwent insertion into the Si-H bond of optically active α-naphthylphenylmethylsilanes[57], eq 33.



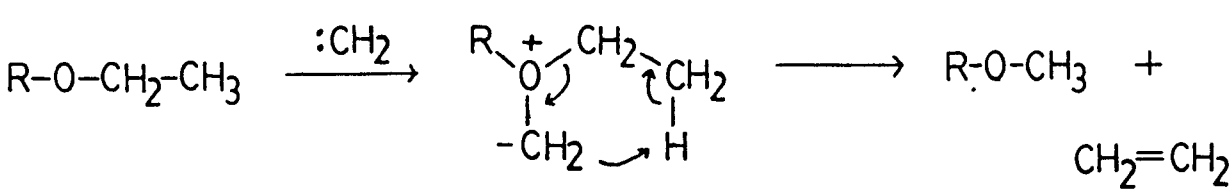
[33]

Product 35 was formed with retention of configuration implying a concerted insertion.

5. Ylide Formation

Oxygen Ylides

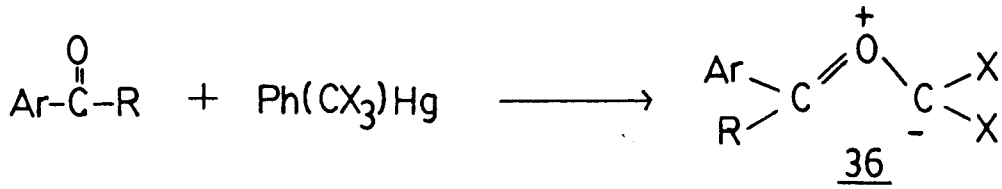
Methyl ethers often are obtained in decompositions of ethereal solutions of diazomethane[58], eq 34.



[34]

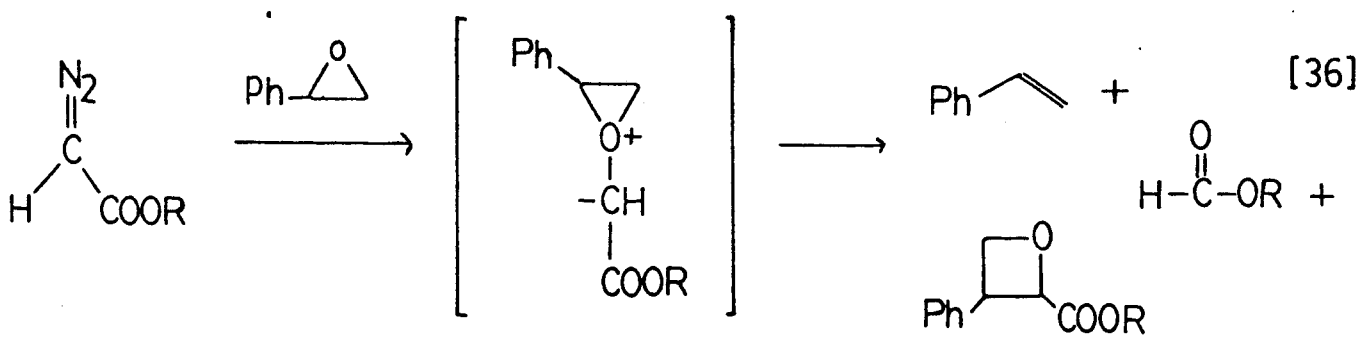
The presence of methyl ether was explained in terms of the β-hydrogen transfer mechanism.

Experimental observations in the reactions of phenyl(trihalomethyl) mercury with benzophenone[59,60] and several benzaldehydes[61,62] support the initial formation of a dihalocarbonyl ylide (36), eq 35.



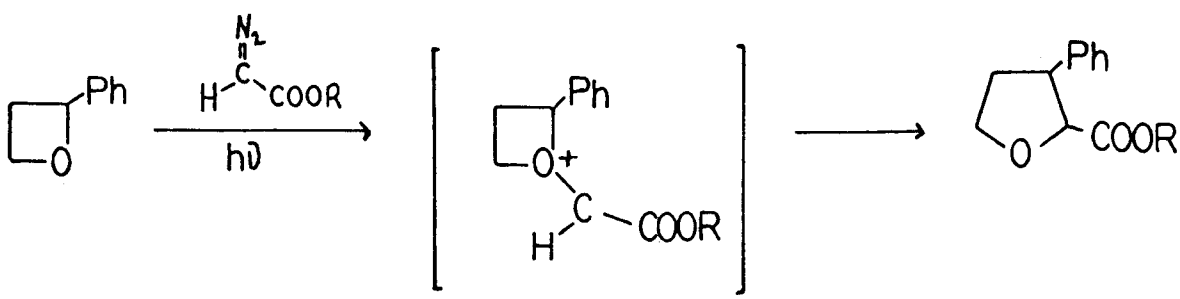
[35]

Decomposition of ethyldiazoacetate by either thermal or photochemical means in styrene oxide gave products of ring expansion and fragmentation of the ylide[63,64] (37), eq 36.



[36]

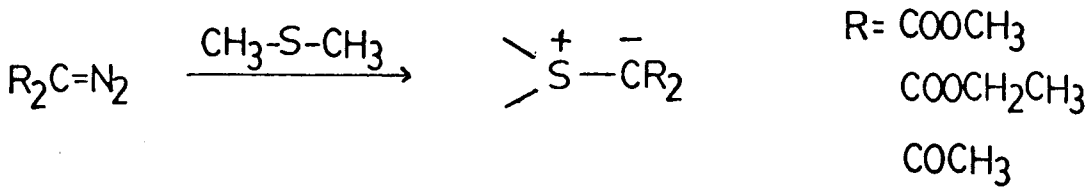
2-Phenyloxetane gave ring expansion but no deoxygenation[64], eq 37.



[37]

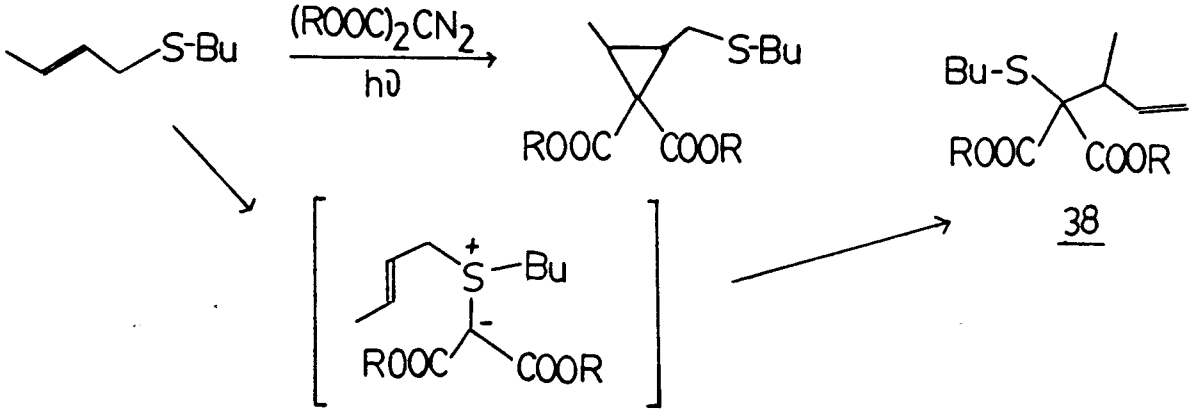
Sulphur Ylides

Stable ylides are formed from the reaction of carbenes with alkyl sulfides[65], eq 38.



[38]

A sulphur ylide is also proposed as the intermediate in the following reaction, in which one group bound to the sulphur is unsaturated, eq 39.

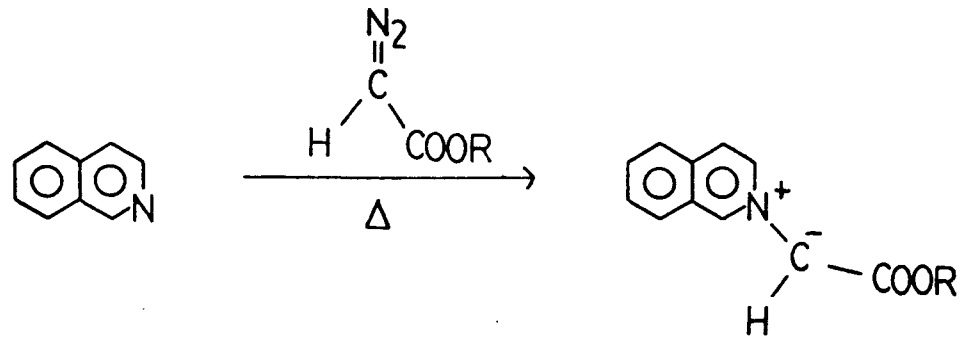


[39]

Product 38 is thought to be a rearrangement product of the unisolable ylide intermediate[66].

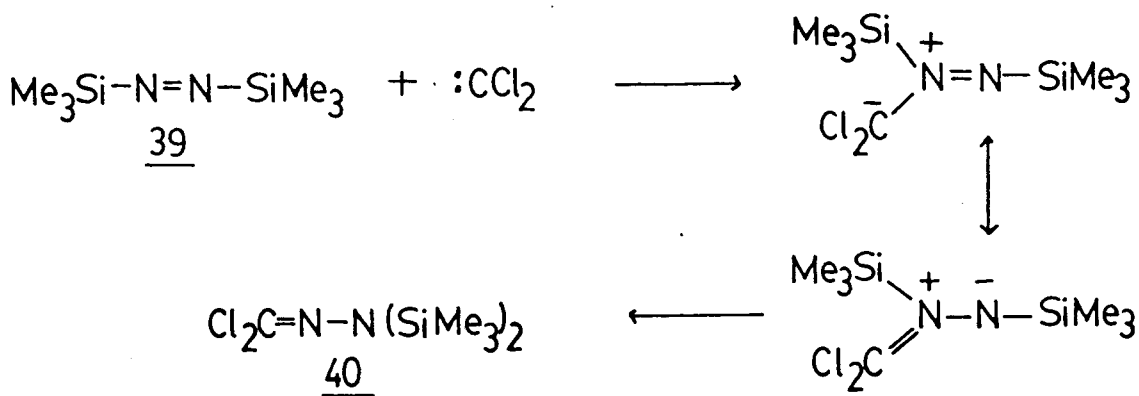
Nitrogen Ylides

Stable ylides are formed from isoquinoline and carboethoxycarbene[25], eq 40.



[40]

A phosphene hydrazone product was obtained in the reaction of dichlorocarbene with diazocompound 39, eq 41.



[41]

Product 40 was apparently derived from rearrangement of an ylide intermediate[67].

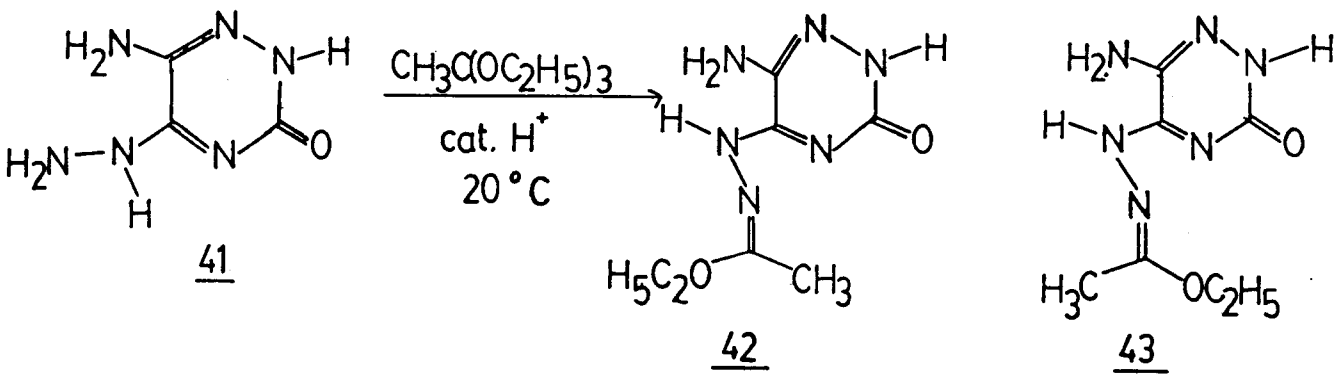
I.3 REACTIONS OF ORTHOESTERS WITH SUBSTITUTED HYDRAZINES AND AMINES

I.3.1 AMINES

The reaction of ethylorthoformate with various organic nitrogen compounds has been studied in great detail[68]. Particular attention has been focused on the reaction of ethylorthoformate with primary aromatic amines. The fundamental equations of this reversible reaction are shown in equation 42.

$$ArNH_2 + CH(OC_2H_5)_3 \rightleftharpoons ArN{=}CH(OC_2H_5) + 2\,C_2H_5OH$$
$$ArN{=}CH(OC_2H_5) + ArNH_2 \rightleftharpoons ArN{=}CH{-}NHAr + C_2H_5OH \qquad [42]$$

When 6-amino-5-hydrazino[1,2,4]triazin-3(2H)-one (41) was treated with ethylorthoformate and a catalytic amount of hydrochloric acid, the reaction followed a pathway shown in equation 43.

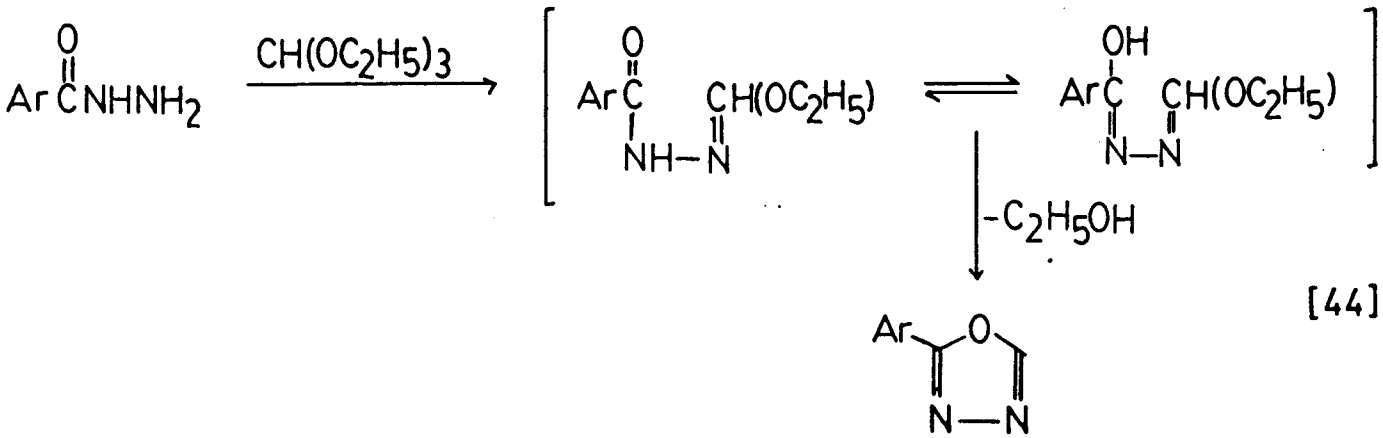


41 42 43 [43]

Stereoisomers, 42 and 43, in a ratio of 2:1 were obtained. The significant resonances from the proton spectrum, used in making these assignments, were the methyl singlets at δ1.85 and δ1.95 ppm, with the isomer possessing the more deshielded methyl predominating[69].

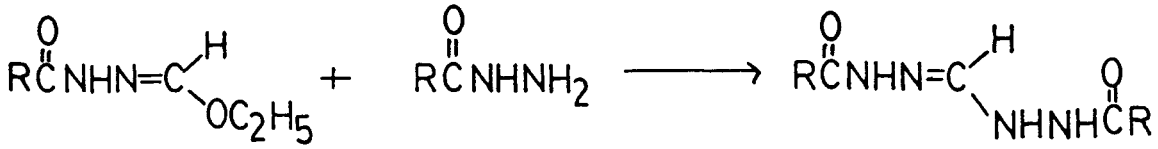
I.3.2 SUBSTITUTED HYDRAZINES

Aromatic hydrazides react with ethylorthoformate to form 1,3,4-oxadiazoles[70], eq 44.



[44]

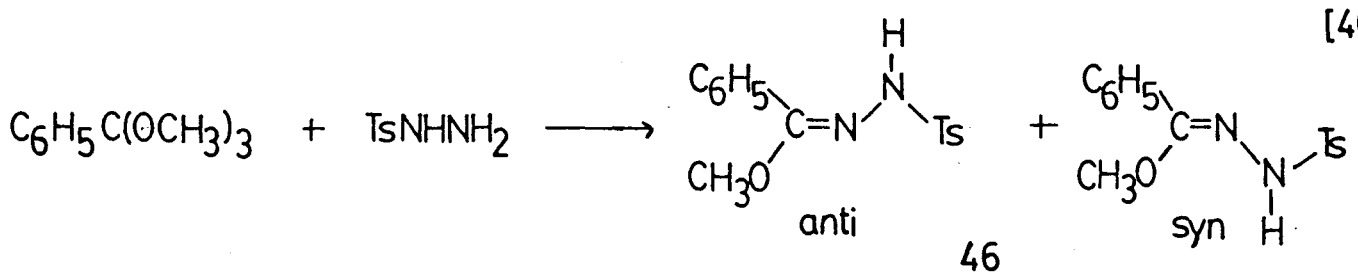
It was found during the reaction of ethylorthoformate and carboxylic acid hydrazides, that the ethoxymethylene intermediate (44) and the carboxylic acid hydrazide react further to form the bis compound (45)[71], eq 45.



[45]

44 45

Orthoesters have been used in the preparation of ester hydrazones. Methyl benzoate (p-tolylsulfonyl) hydrazone (46) was prepared from the reaction between (p-tolylsulfonyl) hydrazide and methylorthobenzoate in a 72% yield, eq 46. The product consisted of a mixture of both syn and anti isomers[72].



[46]

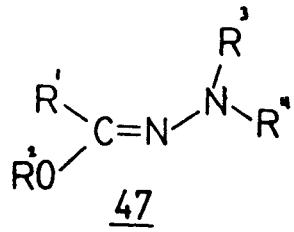
anti syn

46

The next section will deal with ester hydrazones and their preparation.

I.4 ESTER HYDRAZONES

Ester hydrazones or hydrazonates, have the general formula 47.



47

Hydrazonates have been very little studied and hence not a great deal can be found in the literature concerning them[73,74].

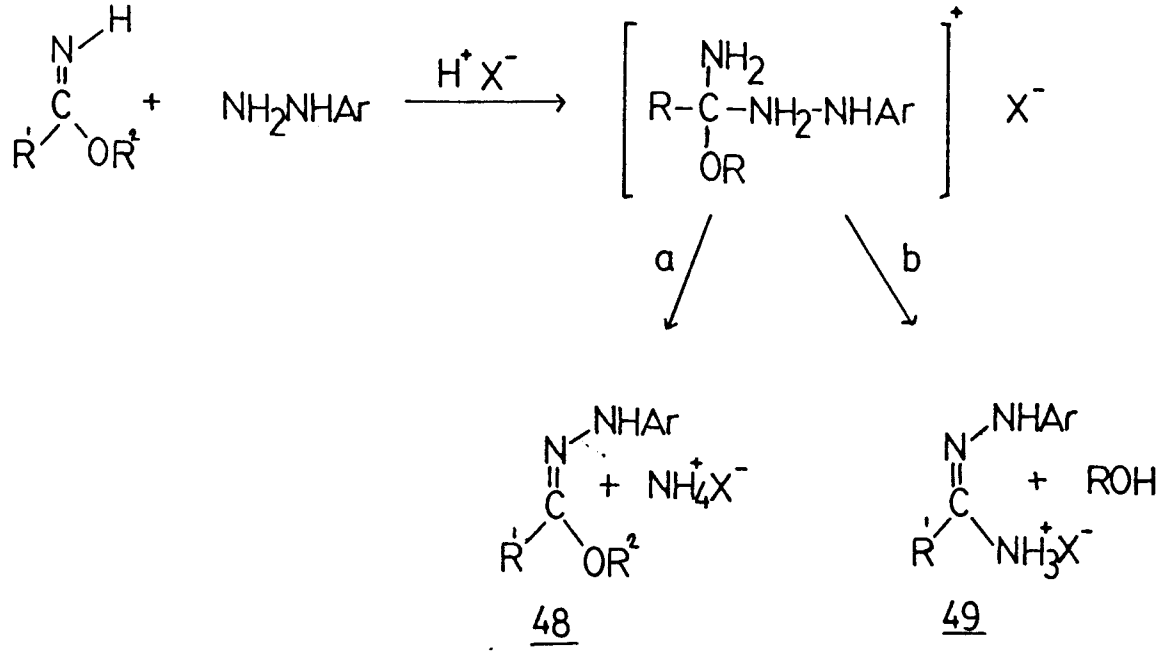
I.4.1 PREPARATION

In 1978, Chihaoui and Baccar[75], proposed two methods for the preparation of hydrazonates:

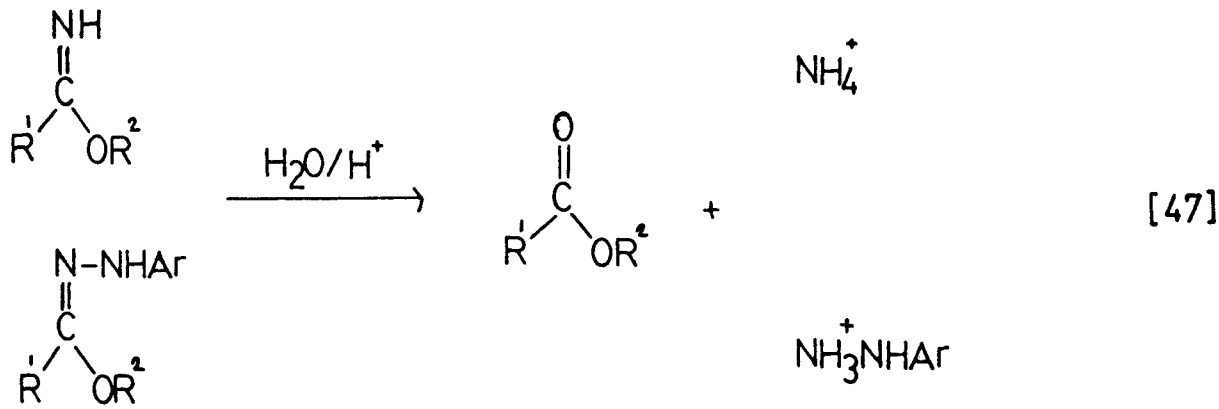
1. Reaction of Hydrazine with Imidates

Like amines and hydroxylamines, the reaction of hydrazines with imidates leads to substitution products, Scheme 7.

If a polar solvent, such as H_2O or MeOH, is used the exclusive product is that of substitution on the alkoxy group, 49. When the reaction is carried out in a water-nonpolar solvent mixture (benzene, CCl_4 etc.) one obtains in the organic phase the hydrazonate (48). The yield, however, rarely exceeds 60% due to hydrolysis reactions of the imidate and hydrazonate, eq 47.


NH2NHAr
H+ X-
NH2
R-C-NH2-NHAr
OR
X-
a
b
NHAr
+ NH4X-
OR2
48
NHAr
+ ROH
NH3X-
49

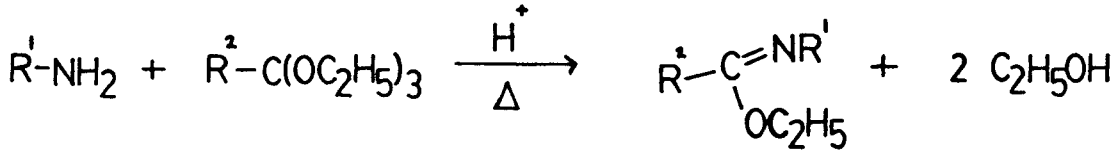
Scheme 7


NH
OR2
N-NHAr
OR2
H2O/H+
O
OR2
NH4+
NH3NHAr

[47]

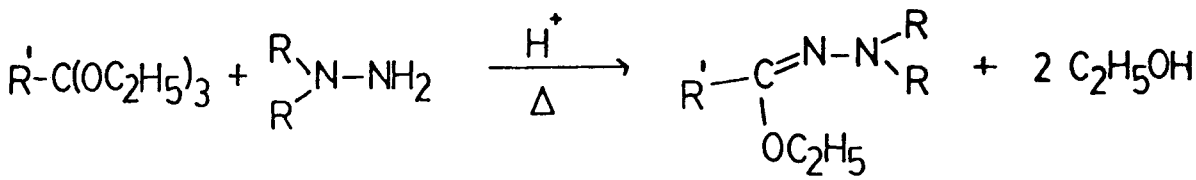
2. Reactions of Orthoesters and Hydrazines

The reaction of amines on orthoesters is well known[76], eq 48.

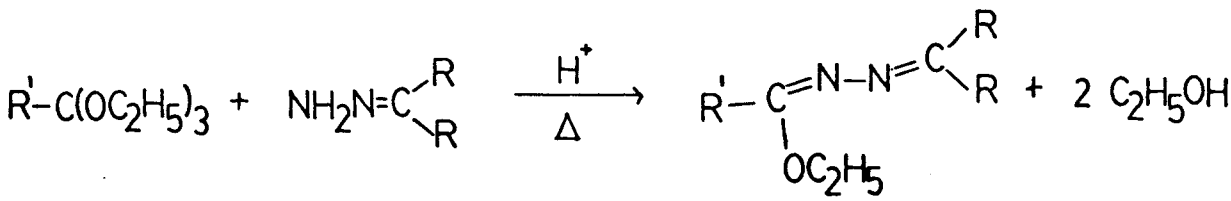


[48]

When amines are replaced by hydrazines or by hydrazones, under identical conditions, hydrazonates are obtained, eq 49.



[49]



Ester hydrazones have also been prepared from alkylselenone esters and from tosylhydrazones.

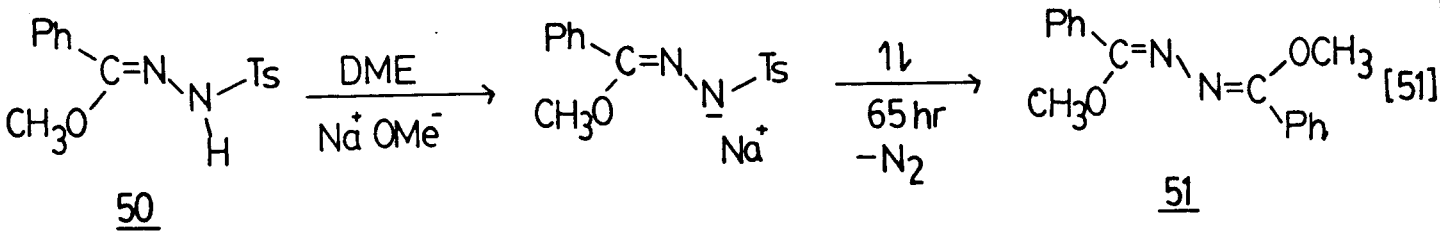
3. Reaction of Alkylselenone Esters with Hydrazine

Ester hydrazones have been prepared by the reaction of alkylselenone esters with hydrazine[77], eq 50.

[50]

4. Tosyl Hydrazones

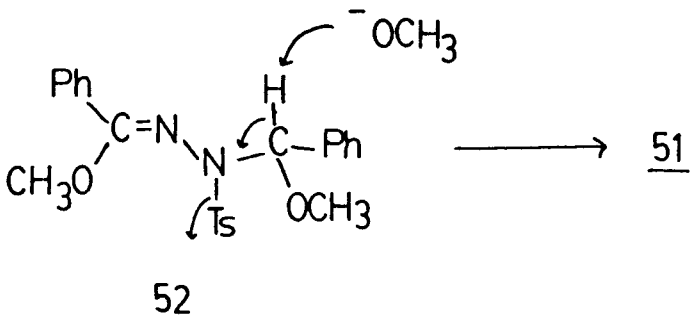
Another reported case in which an ester hydrazone was formed was in the following reaction[78], eq 51.



[51]

50 51

The ester hydrazone (51) was formed as a major product and its structure was confirmed by preparation of an authentic sample, eq 52.



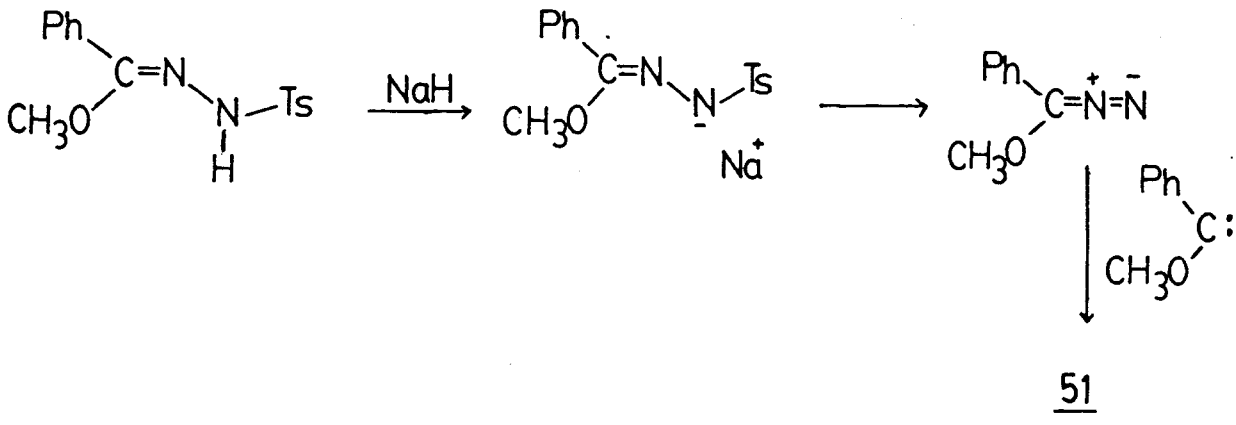
[52]

52

Product 51 was prepared from methylbenzoate (α-methoxybenzyl)-(p-tolylsulfonyl) hydrazone (52) by refluxing with sodium methoxide in DME.

When an equimolar mixture of 50 and its potassium salt, was heated in diglyme at 180°C, 51 was obtained in a 36% yield[78]. This type of product has recently been isolated by Nozaki et al.[79] in an investigation of the reaction of phenylcarbene formed from benzaldehyde (p-tolylsulfonyl) hydrazone in various solvents.

The major product, α-methoxybenzalazine (51) is believed to result from the trapping of α-methylphenylcarbene by its diazoprecursor, eq 53.

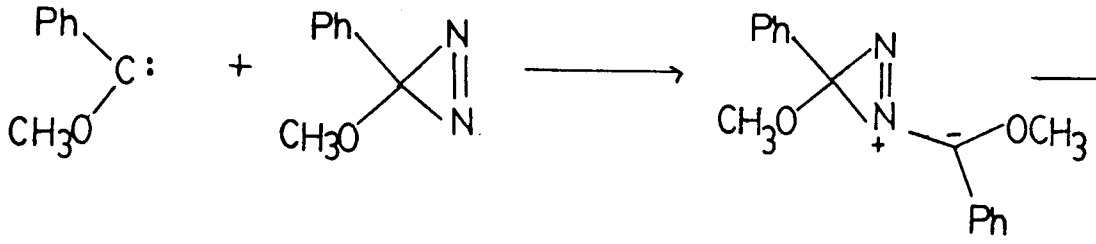


[53]

51

This is by analogy with a report[80] that a number of carbenes react with diphenyldiazomethane to yield the corresponding azines. It was also shown that the thermal decomposition of diphenyldiazomethane is first order in the diazo compound.

Methoxybenzalazine (51) was also reported, as a minor product (∿ 1%), in the photolysis of methoxyphenyldiazirine to produce methoxyphenylcarbene, which yielded cyclopropanes in the presence of alkanes. A probable mechanism for the formation of 51 is carbene attack on the precursor diazirine to form an ylide intermediate[81], eq 54.



51 [54]

Very little is known about the stereochemistry of ester hydrazones of type 51. Azines, however, have been studied in great detail and the stereochemistry of alkyl substituted azines is known. The next section will deal with azines, their preparation and their stereochemistry.

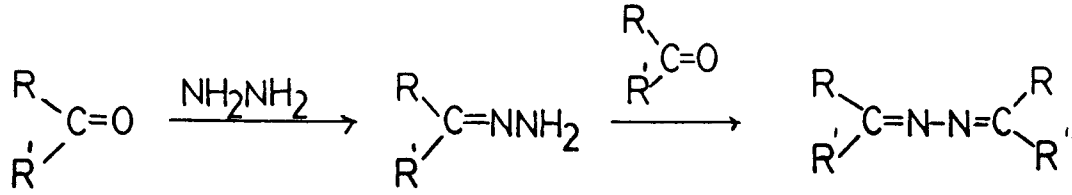
I.5 AZINES

I.5.1 INTRODUCTION

The study of azines began in 1888 by Curtius[82-85]. They have received some practical applications in that they can be used as initiators for olefin polymerizations[86], stabilizers for soaps[87], alkanes, and aliphatic alkenes[88]. Furthermore, aromatic azines are used as UV absorption filters[89,90].

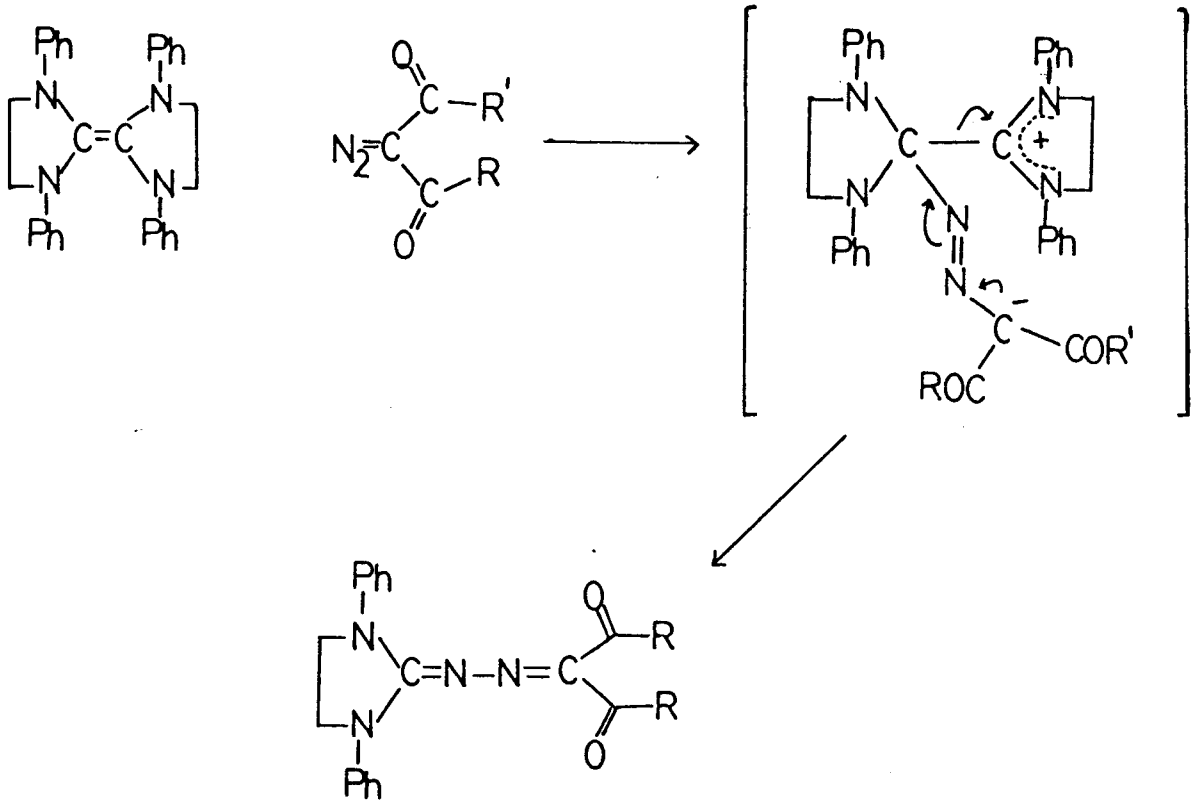
I.5.2 PREPARATION

Azines are generally prepared from the condensation of two moles of carbonyl compounds and one mole of hydrazine, eq 55. The intermediate hydrazone cannot generally be isolated except in the case where R and R' are aryl groups[91]. Mixed azines can be prepared by the reaction of different carbonyl compounds on hydrazine.



[55]

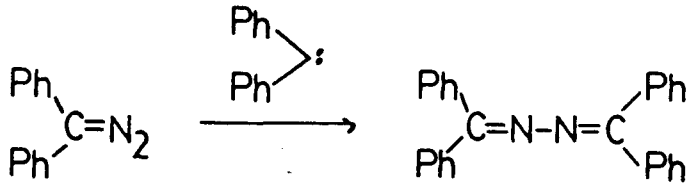
Azines can also be prepared from the reaction between olefins and α-dicarbonyl diazoalkanes, eq 56.



[56]

Reactions of carbenes with diazoalkanes also yield azines[4]. The reaction involves electrophilic attack of carbene on the terminal

nitrogen of the diazoalkane, eq 57.



[57]

The formation of azines in the thermal decomposition of diazoalkanes does not necessarily involve the prior formation of a carbene, but attack of one diazoalkane on another with the loss of N_2.

I.5.3 STEREOCHEMISTRY OF AZINES

1. Structural Studies

Azines exhibit two types of isomerism: (i) conformational isomerization about the N-N bond and (ii) configurational isomerization around the C=N bond.

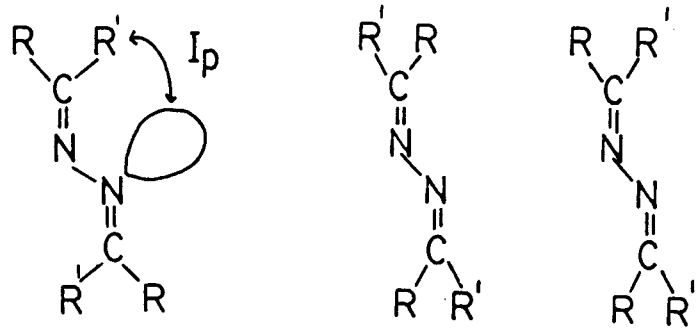
(i) Isomerization Around N-N Bond

Isomerization of this sort was studied by Audrieth, et al.[92] in 1933 using dipole moment measurements. From the low dipole value of benzalazine in benzene, μ=1.0D, it was deduced that the C_6H_5-CH=N group preferentially rotates in a trans position. The X-ray structure[93] of cinnamaldazine showed that in a solid state, the skeleton of the molecules (C=N-N=C) is entirely planar. The non zero values found for the dipole moments could correspond to a low percentage of the cis structure[94].

(ii) Isomerization Around C=N Bond

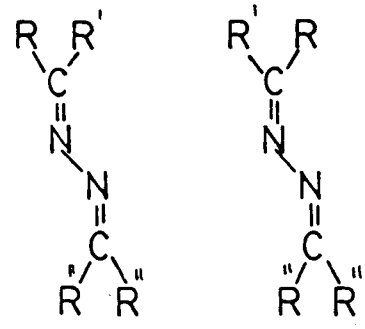
One can predict for azines in the s- trans orientation the existence of three isomers with respect to R; E-E, Z-Z and E-Z

(Z-E being identical in this case because the azine is symmetrical), shown as structures 53, 54 and 55, respectively.



53 54 55

Mixed azines can only exist in two isomeric forms which are E and Z with respect to R, shown as structures 56 and 57 respectively.



56 57

For all azines, the interaction between the substituent R' and the nitrogen lone pair seen in 53 must be considered. This interaction has been referred to[91] as the principal interaction, Ip. Also to be taken into account is the interaction between substituents R and R' which influence the value of Ip. This interaction has been referred to[91] as the secondary interaction, Is.

2. NMR Studies of Symmetric Azines

In the case where R ≠ R' there are three possible isomers. In order to assign the signals to these isomers, an hypothesis of Karabatsos[95] for the case of hydrazones, was used: the most abundant isomer will be that which is least crowded; in this case isomer 53 (E-E) if R represents the most bulky substituent. The results of NMR studies on various azines are shown in Tables 1 and 2.[91]

Table 1: NMR Spectra of Ketazines with R=R'

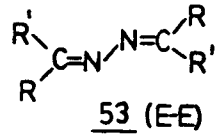
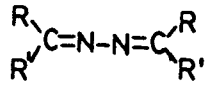
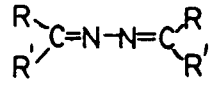
 53 (E-E)		^{1}H NMR ($CDCl_3$, δppm)	
R	R'	R(E)	R'(Z)
CH_3	CH_3	2.00	1.83
CH_2CH_3	CH_2CH_3	1.14(t,3H) 2.29(q,2H) J=7.8Hz	1.00(t,3H) 2.31(q,2H) J=7.8Hz

TABLE 2: NMR Spectra Of Ketazines With R≠R'

		Isomer 53(E-E)		Isomer 54(Z-Z)			Isomer 55(E-Z)		
R	R'	R(E)	R'	R(Z)	R'	R(E)	R(Z)	R'(E)	R'(Z)
CH_2CH_3	CH_3	1.14(t,3H) 2.30(q,2H) J = 7.8Hz	1.78(s,3H)	1.01	1.97	1.13 2.27	.99 2.28	1.79	1.98
$CH(CH_3)_2$	CH_3	1.14(d,6H) 2.55(m,1H J = 6.5Hz	1.73(s,3H)			1.14 2.58	0.97 3.18 J=7.0Hz	1.77	1.92
$C(CH_3)_3$	CH_3	1.09(s,9H)	1.72(s,3H)						

The yields of the various isomers for the azines in Table 2 are shown below.

		ISOMER		
R	R'	E-E	Z-Z	E-Z
CH_2CH_3	CH_3	53%	6%	41%
$CH(CH_3)_2$	CH_3	90%		10%
$C(CH_3)_3$	CH_3	100%		

From the study of these three azines, it can be noted that the least hindered isomer is the most abundant. An increase in the yield of the E-E isomer (53) is seen as the substituent R becomes larger. When combining the results, it is possible to note the effect of the substituents in the Z position on the E-methyl of isomer (53) in the NMR spectra:

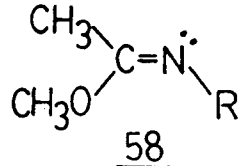
R	CH_3	CH_2CH_3	$CH(CH_3)_2$	$C(CH_3)_3$
R'(E)	1.83ppm	1.78	1.73	1.72

I.6 CONFIGURATION OF IMIDATE SYSTEMS

Configurational studies have been done on some imidate systems. Some results will be discussed in this section since these systems are closely related to ester hydrazones.

I.6.1 O-METHYL IMIDATES

Moriarty, et al.[96] have done configuration studies on O-methyl imidates (58). They have concluded from NMR studies that these types of imidates tend to exist in the Z-form.



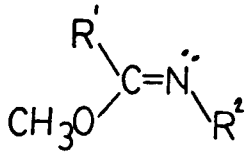
58

(Z)

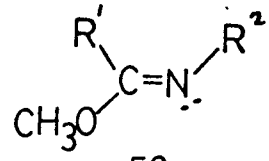
R= CH_3, Ph, C_2H_5, n-C_4H_9

It was suggested that the Z-form was more stable due to the electron repulsion in the E-form between oxygen non-bonding electrons and a lone pair localized in an sp^2 orbital on the nitrogen.

This E/Z stereoisomerism in imidates was reinvestigated by Meese, et al.[97]. Their determination of configuration was based on long-range coupling. The five-bond coupling of the C-methyl protons to the N-methyl groups directly attached to the C=N bond is much greater when the configuration of the coupling nuclei is "trans" than "cis"[98-100]. They have reported the homoallylic coupling between hydrogens in R' and R^2 separated by five bonds in the acetimidates 59a and 59b, leading to the opposite signal assignments than that reported by Moriarty[96].



59
(Z)



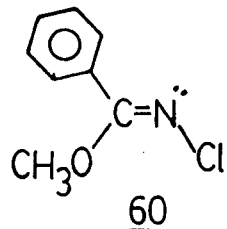
59
(E)

59a, $R' = R^2 = CH_3$
59b, $R' = CH_3$, $R^2 = CH_2CH_3$

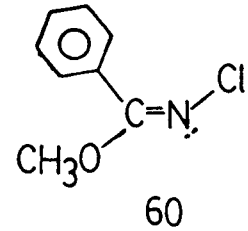
From these results, it seems that there is some controversy over the configuration of these imidates.

I.6.2 N-HALO-IMIDATES

N-halo-imidates (60) have also been found[101] to exist in E and Z forms. The N-chloro compound was shown by NMR spectroscopy to be a mixture of isomers in which the OCH_3 and Cl groups on an imine double bond are in E and Z configuration.



60
(Z)



60
(E)

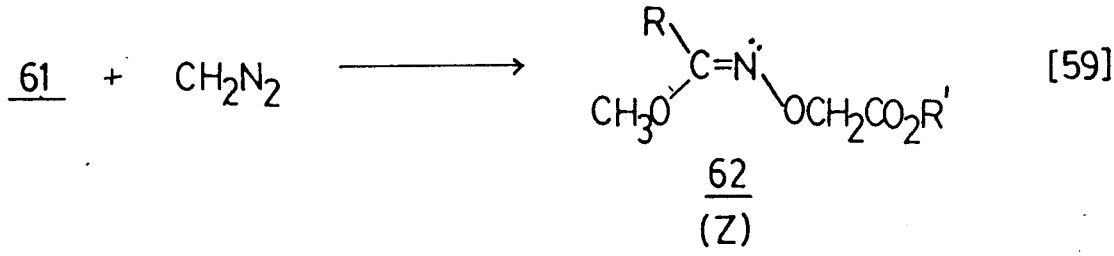
The assignments however were only based on extension of the generalization for ethylenes (C=C) where it is known that protons cis to an electronegative group absorb further downfield than trans protons. Compound 60 was found to be a 9:1 mixture of Z and E isomers. Heating 60 at 100°C produced an equilibrium mixture at 3:1 of Z to E isomers, respectively.

I.6.3 N-ALKOXY IMIDATES

Systems that are more closely related to ester hydrazones are the derivatives of hydroxamic acids. Hydroxamic acids can be alkylated with halides such as $BrCH_2CO_2R'$,[102] eq 58.

$$RC(=O)NHOH + BrCH_2CO_2R' \longrightarrow \underset{\underline{61}}{RC(=O)NHOCH_2CO_2R'} \qquad [58]$$

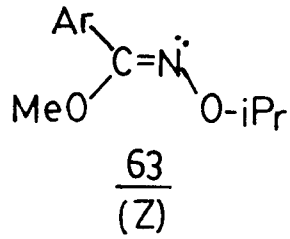
The product (61) is acidic enough to be methylated with diazomethane and the product (62) has the Z configuration, shown in eq 59.



[59]

The basis of the configurational assignment of these hydroximic esters is from dipole moments[103,104]. The steric interaction in this product (R=Ar) is relieved through deviation from coplanarity.

Dipole studies[104] have also supported the Z structure for imidates of the N-alkoxy type, 63, and in addition it has been suggested that the methoxy group is twisted in the opposite sense by 30°.

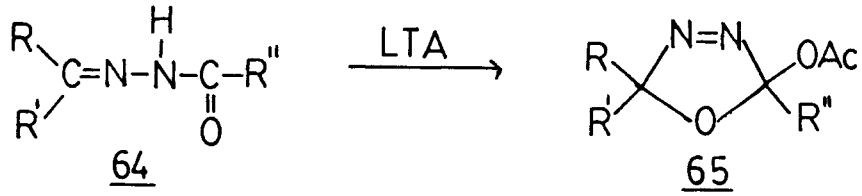


Very little is mentioned on the relative stabilities of the Z and E configurations but it is claimed that the Z configuration is less stable. Whenever a reaction involves a change of configuration as in acylation or saponification of the acyl derivative (62), it is always the Z compound which isomerizes to the E, never the reverse[105].

I.7 OXIDATION OF HYDRAZONES USING LTA

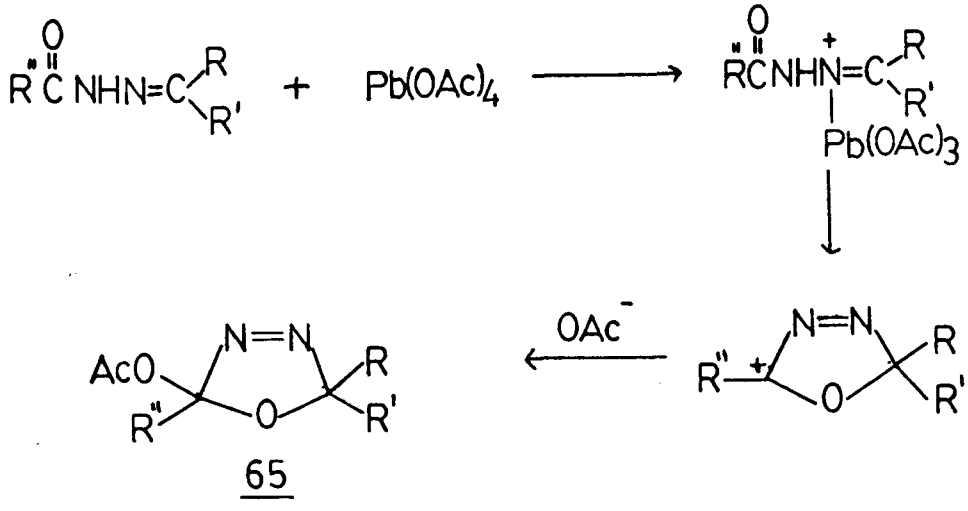
Ketone carbonyl hydrazones of type 64 readily cyclize with lead tetraacetate (LTA) to form 2-acetoxy-Δ^3-1,3,4-oxadiazolines 65[10,106,107],

eq 60.



64 65 [60]

The formation of 65 was thought to involve an ionic mechanism in which there was loss of acetate ion from azoacetate, followed by attack on the resulting carbocation by the carbonyl carbon. This cyclization was also reported by Norman[108], who proposed a polar mechanism not involving the azoacetate intermediate, eq 61.

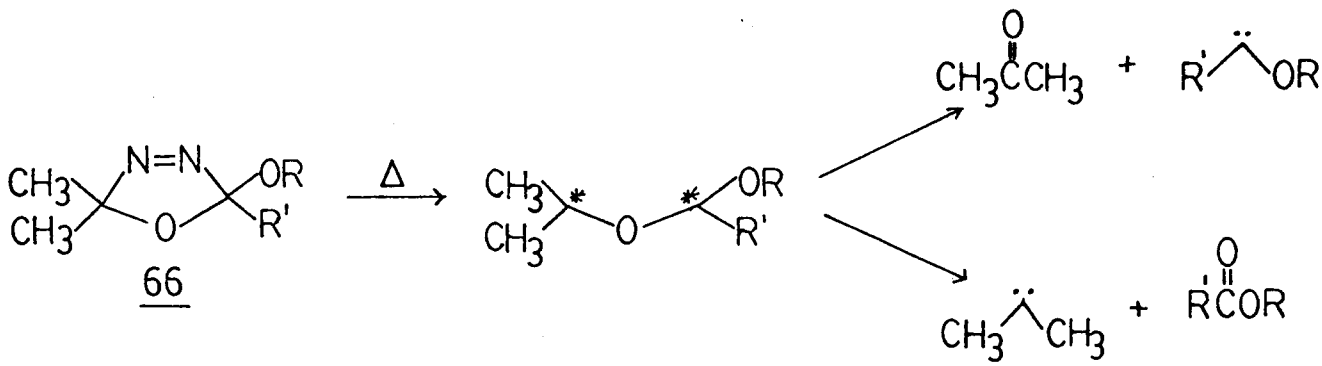


65 [61]

RESULTS AND DISCUSSION

R.D. 1 OVERVIEW

Carbonyl ylides can be generated from the thermolysis of Δ^3-1,3,4-oxadiazolines. Once generated the ylides of oxadiazolines 66 can fragment into carbenes and carbonyl compounds, eq 62.



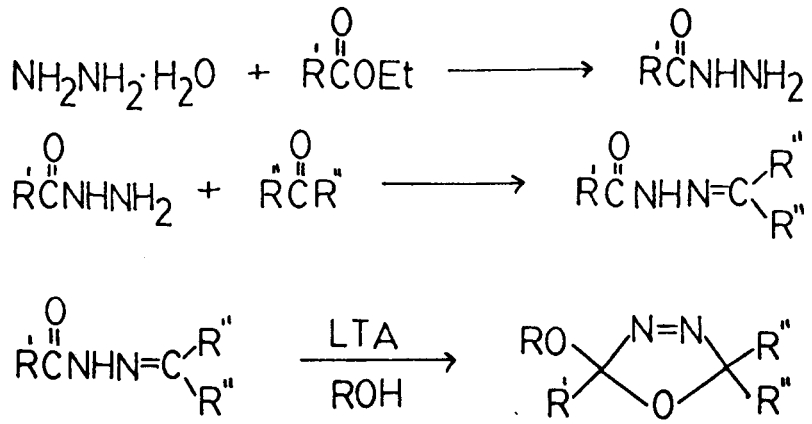
[62]

In the thermolysis of oxadiazolines of type 66, ester azines were found as products. One of our objectives was to probe for the mechanism of formation of these ester azines. Also substituent R' of oxadiazolines 66 was changed in order to see of configurational isomers of these ester azines could be obtained.

R.D. 2 SYNTHESIS OF OXADIAZOLINES

The synthesis of the oxadiazolines involves a three step reaction pathway. Hydrazine hydrate was reacted with the appropriate esters to give the corresponding hydrazides. The hydrazides were then reacted with acetone to give the acetone hydrazones which were oxidized

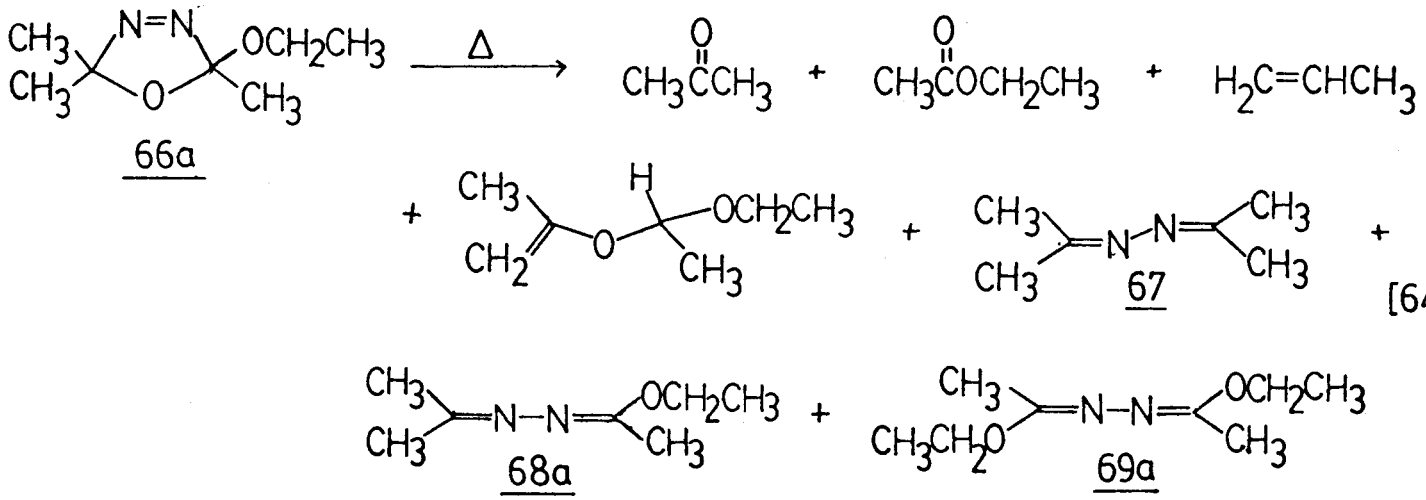
using LTA in an alcohol solvent to the corresponding oxadiazolines, eq 63.



[63]

R.D. 3 THERMAL DECOMPOSITION OF 2-ETHOXY-2,5,5-TRIMETHYL-Δ^3-1,3,4-OXADIAZOLINE (66a)

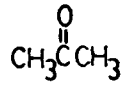
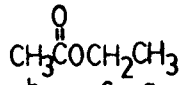
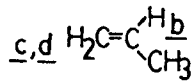
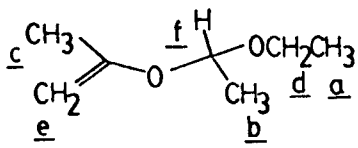
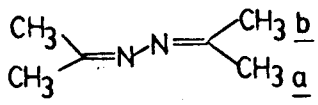
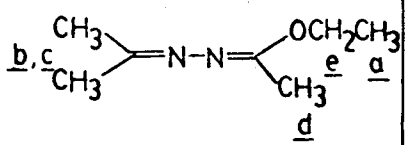
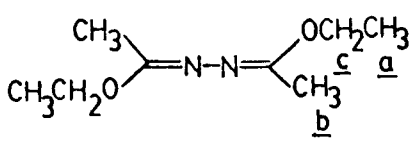
A solution of oxadiazoline 66a in benzene was thermolyzed at 80°C for five days. The major products of this reaction included acetone, ethyl acetate, propene, an acetal, acetone azine (67), and two types of ester azines, 68a and 69a, eq 64.



[64]

Support for the structures of the products came from ^{1}H NMR and mass spectral data. The results are shown in Table 3.

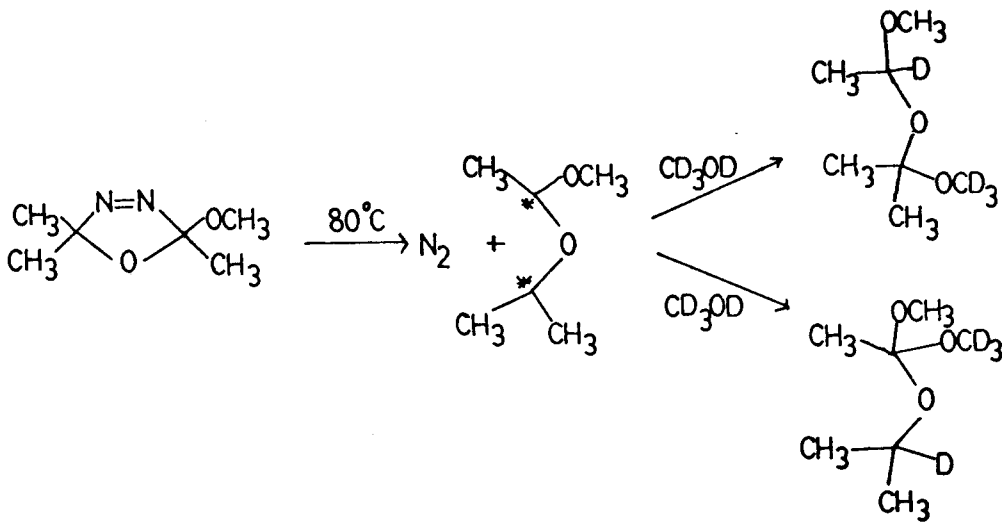
Table 3: Products From Thermolysis of 66a

Product	^{1}H NMR (δ $CDCl_3$ = 7.27 ppm)	M.S. (fragment +, m/z)
	2.17 (s)	C_3H_6O 58 C_2H_3O 43
	H_a, 1.25 (t,3H,J=7.0Hz) H_b, 2.03 (s,3H) H_c, 4.12 (q,2H,J=7.0Hz)	$C_4H_8O_2$ 88 C_3H_3O 43 C_3H_5O 73 C_2H_5O 45
	H_a, 1.69 (m,3H) H_b, 4.91 (m,1H) H_c, 4.99 (m,1H) H_d, 5.78 (m,1H)	C_3H_6 42
	H_a, 1.22 (t,2H,J=7.0Hz) H_b, 1.40 (d,3H,J=5.2Hz) H_c, 1.83 (s,3H) H_d, 3.61 (q,AB,2H) H_e, 3.93 (s,2H) H_f, 5.17 (q,1H,J=5.2Hz)	$C_7H_{13}O_2$ 130 $C_4H_9O_2$ 89 C_5H_9O 85 C_4H_9O 73 C_3H_6O 58
	H_a, 1.85 (s,6H) H_b, 2.02 (s,6H)	$C_6H_{12}N_2$ 112 $C_3H_6N_2$ 70 $C_5H_9N_2$ 97 C_3H_6N 56
	H_a, 1.31 (t,3H,J=7.0Hz) H_b, 1.95 (s,3H) H_c, 2.01 (s,3H) H_d, 2.03 (s,3H) H_e, 4.18 (q,2H,J=7.0Hz)	$C_7H_{14}N_2O$ 142 C_3H_6N 56 $C_6H_{11}N_2O$ 127 $C_4H_7N_2O$ 99 C_3H_5NO 86 $C_3H_6N_2$ 70
	H_a, 1.30 (t,6H,J=7.0Hz) H_b, 2.03 (s,6H) H_c, 4.16 (q,4H,J=7.0Hz)	$C_8H_{16}N_2O_2$ 172 $C_6H_{11}N_2O$ 127 $C_7H_{13}N_2O_2$ 157 $C_4H_8N_2O_2$ 116 $C_6H_{12}N_2O_2$ 144 C_4H_8NO 86

Compounds 67 and 69a have been reported in the literature.[77,91] Both ^{1}H NMR spectra and mass spectra are consistent with the literature

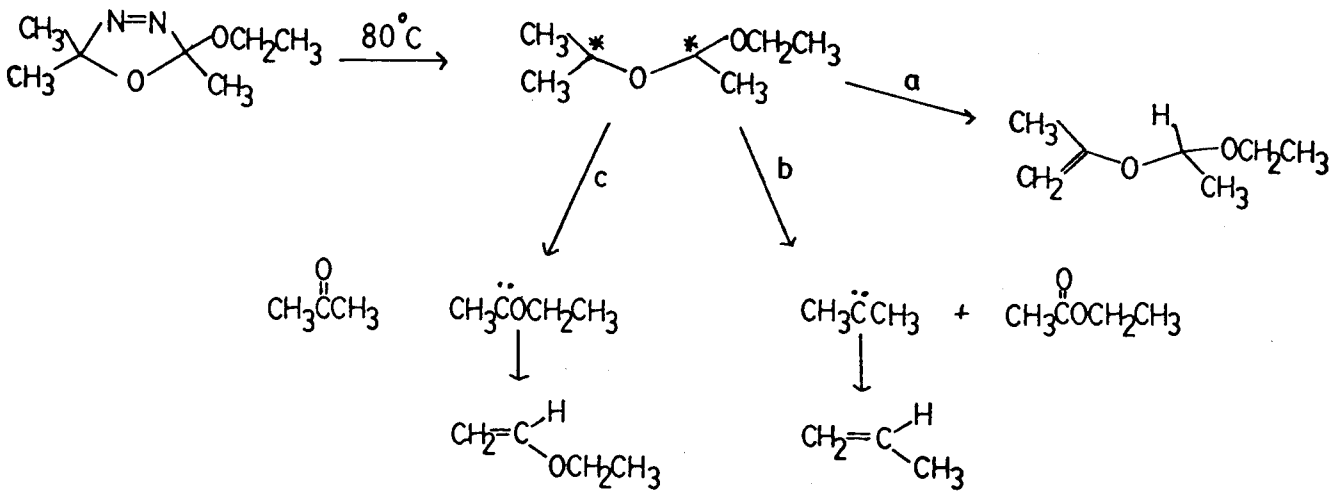
spectra.

Alkoxysubstituted oxadiazolines of type 66 are known to decompose thermally to generate a carbonyl ylide intermediate. Trapping experiments of the carbonyl ylide from 66 ($R'=R=CH_3$) in the presence of CD_3OD[16] and substituted olefins[109] were successful, eq 65.



[65]

The mechanism proposed to rationalize the products obtained from the thermolysis of 66a in benzene is shown below as Scheme 8.



Scheme 8

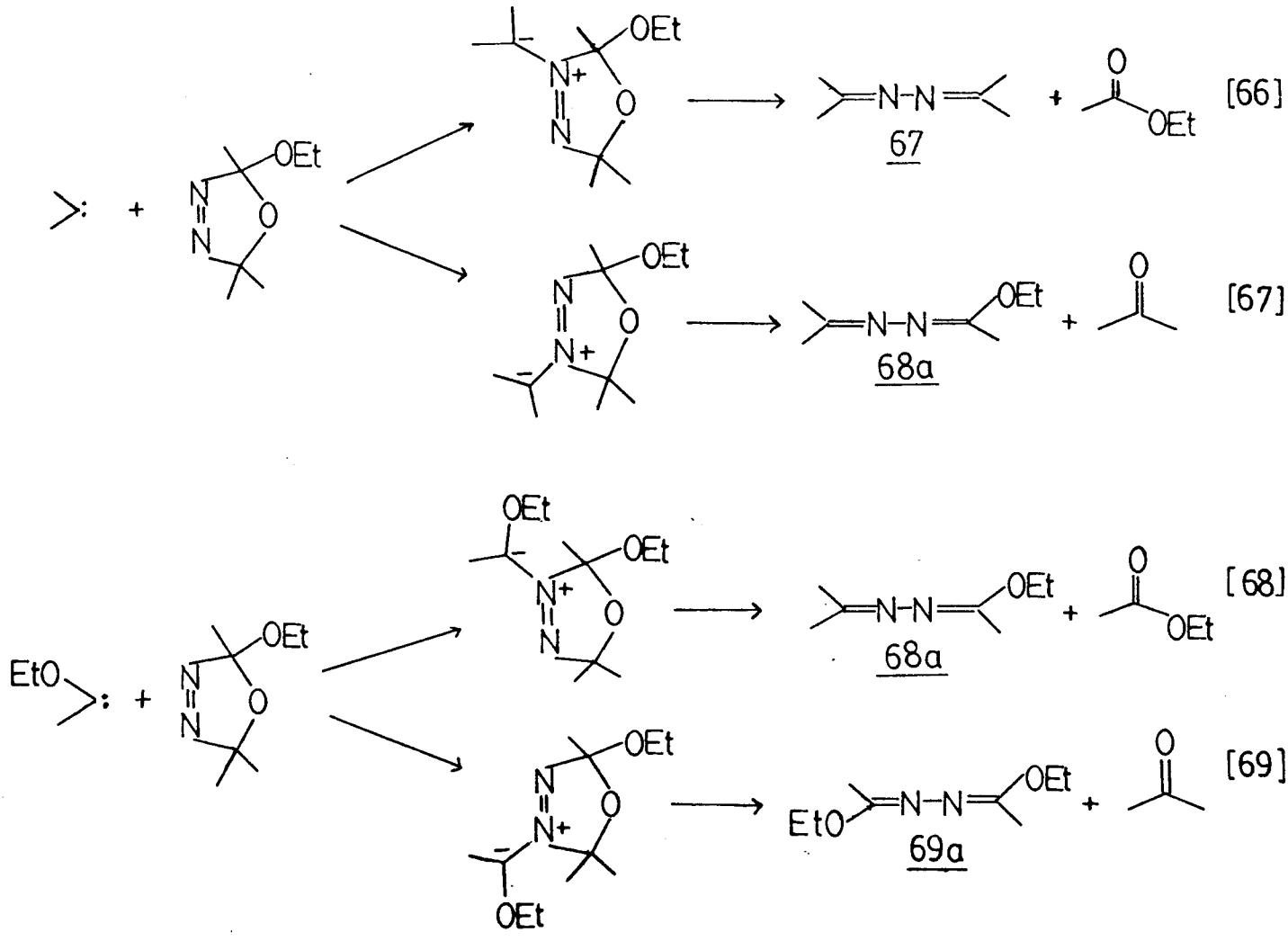
As shown in Scheme 8, once generated the carbonyl ylide can undergo an intramolecular 1,4-hydrogen shift to yield an enol-ether (path a). Fragmentation of the ylide produced dimethyl carbene and ethylacetate through path b and ethoxymethyl carbene and acetone through path c. Dimethyl carbene can undergo a 1,2-hydride shift to give propene. The ethoxymethyl carbene can also undergo a 1,2-hydride shift but this rearrangement product is formed in low yields. The fact that the products of intramolecular rearrangement of the carbenes are found in low yield implies that these carbenes are involved in intermolecular reactions. The next section will deal with the probable mechanism for the formation of the azines.

R.D.4 FORMATION OF ESTER AZINES

R.D.4.1 Proposed Mechanism

The proposed mechanism for the formation of azines 67, 68a and 69a involves attack by the carbenes, formed from the fragmentation of the carbonyl ylide, on the oxadiazoline (66a) to form azomethine imine intermediates, eq 66-69.

Once formed, the azomethine imine intermediates can fragment to yield carbonyl compounds and azines as products. Precedent for such a fragmentation of an azomethine imine was shown in equation 6 of the Introduction.



R.D.4.2 Experimental Evidence

If the carbenes generated from the carbonyl ylide were attacking the oxadiazoline to form the azine products in competition with unimolecular carbene reactions, then the yield of azines formed from the decomposition of oxadiazoline should be dependent on the concentration of the starting material. Such a concentration dependance was found, as shown in Table 4.

The total product yields from the thermal decomposition of oxadiazolines 66 are expected to be over 100% since fragmentation of 1 mole of ylide leads to 2 moles of product (1 mole of carbonyl compound and 1 mole of carbene). Since fragmentation is not the only pathway of

Table 4: Concentration Dependance on the Yields of Azines in C_6D_6 at 80°C

Product	Initial Concentration of 66a				
	1.6 M	2.1 M	2.6 M	3.1 M	3.7 M
propene	18%	17%	13%	9%	7%
acetone	6	7	9	13	15
ethyl acetate	44	48	48	51	53
acetal	39	37	36	35	35
67	10	11	11	12	14
68a	19	22	23	26	27
69a	4	4	4	4	5
TOTAL YIELD %	140	144	144	150	156

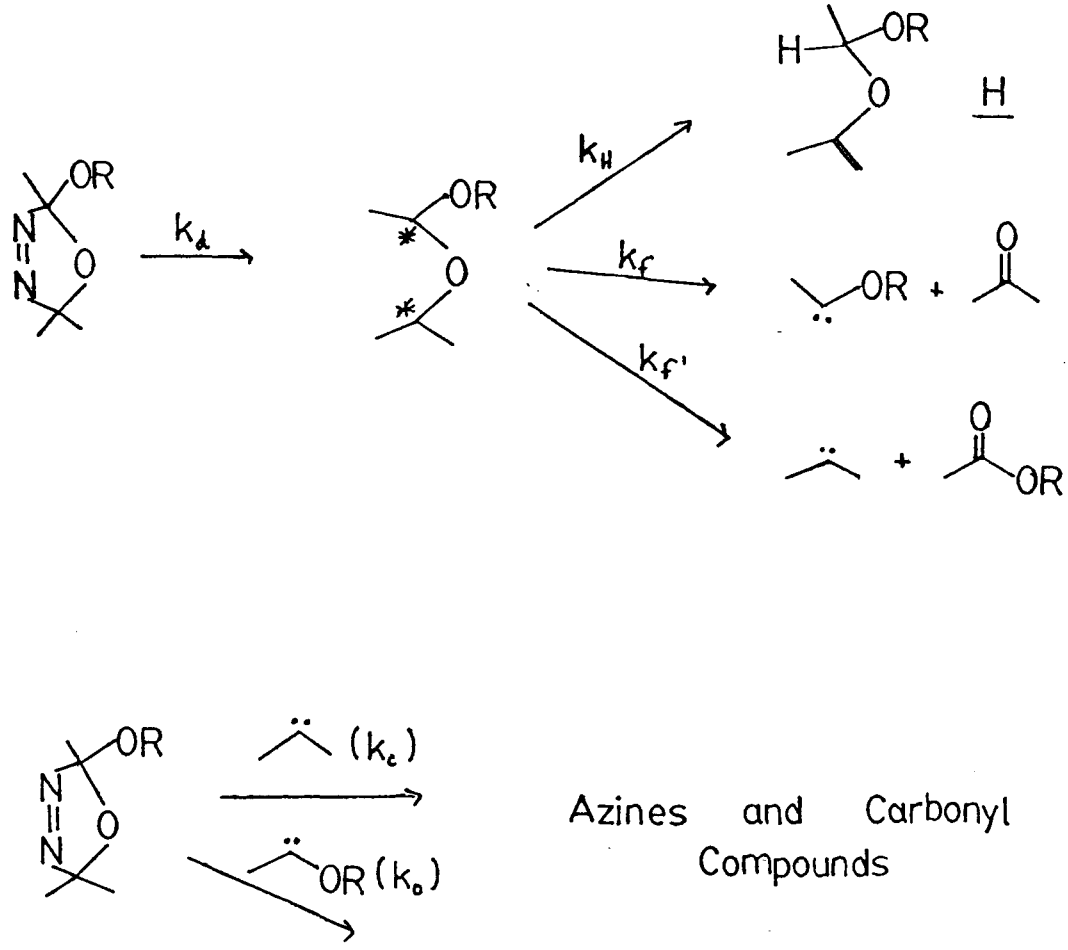
the ylide, the total yield of the products will be less than 200%. The yields were calculated as: $\frac{\text{\# moles product}}{\text{\# moles starting material}} \times 100$.

From the results shown in Table 4, the yield of azines increases as the initial concentration of the oxadiazoline increases. The yield of propene decreases in accordance with the proposed mechanism. The dimethyl carbene, being very reactive, can quickly undergo a 1,2-hydride shift to give propene, but in the presence of high concentrations of 66a, can attack the nitrogens of the azo function.

The yields of 67, 68a, and 69a also indicate the efficiency with which dimethylcarbene rearranges intramolecularly. The yield of 67, coming only from the pathway shown in equation 66 is less than the yield of

68a. Ester azine 68a, however can be produced by two different pathways, involving the dimethyl carbene or the ethoxymethyl carbene, and hence is expected to be the most abundant of the azines. Propene was found in appreciable amounts but no rearrangement products of the ethoxymethyl carbene could be separated from the reaction mixture. This implied that this carbene was involved in the major pathway for the formation of azine 68a, shown in eq 68. Hence dimethyl carbene is mainly involved in the formation of propene and acetone azine 67. The propene yield indicates that rearrangement is faster than addition at initial concentrations of 66a up to about 2.6M. At 1.6M, for example, the yield of propene is 18% while the yield of acetone azine is 10%.

The yields of acetone and ethyl acetate would also be expected to increase, and are found to, with an increase in the yields of the azines since they are formed as biproducts in the proposed mechanism. Assuming that all the oxadiazoline has decomposed to the carbonyl ylide, the absolute yield of the acetal should remain constant throughout changes in the concentration of 66a if it reflects the ratio of two unimolecular pathways of the carbonyl ylide; intramolecular rearrangement versus fragmentation. However, a slight decrease is seen in the yield of acetal as the initial concentration of 66a increases. This implies that less than 100% carbonyl ylide is being generated from the thermolysis of 66a and that 66a is involved in another reaction pathway, namely the interception of carbenes (Scheme 9) as already postulated from product identity alone. If the processes shown in Scheme 9 are the only processes involved in the decomposition of 66a, then the yield of acetal product H can be represented as follows:


OR
N
N
O
k_d
OR
O
k_H
k_f
$k_{f'}$
H
OR
O
H
OR
+
O
+
O
OR
OR
N
N
O
(k_c)
OR (k_o)
Azines and Carbonyl Compounds

Scheme 9

$$\%(H) = \left(\frac{k_d}{k_d+k_c[\ddot{\wedge}]+k_o[\ddot{\wedge}OR]}\right)\left(\frac{k_H}{k_H+k_f+k_{f'}}\right) \times 100.$$

fraction going to ylide — fraction of ylide going to H

At low oxadiazoline concentrations, the carbene concentration (steady state) will be low, the first term in the equation will be larger and therefore the % H will be higher.

Table 4 shows the results of the dependance of azine formation on the initial concentration of the starting material (66a). The yields given are those of azines obtained from 66a, as the concentration changes from its initial value to zero, hence the results do not reflect the dependence at any given concentration of 66a. The experiments were repeated with various initial concentrations of 66a, but only allowing approximately 10% completion of the thermal decomposition of 66a. This was done in order to see if the yields of azines were in fact more dependent on the concentration of 66a than seen in Table 4. The results are shown in Table 5. The product yields were determined from the 250 MHz ^{1}H NMR spectra by comparison of resonance signals and their integrals to those of a reference standard of known concentration, 1-bromo-4-chlorobenzene.

Table 5: Yields of Azines at Average Concentrations of 66a

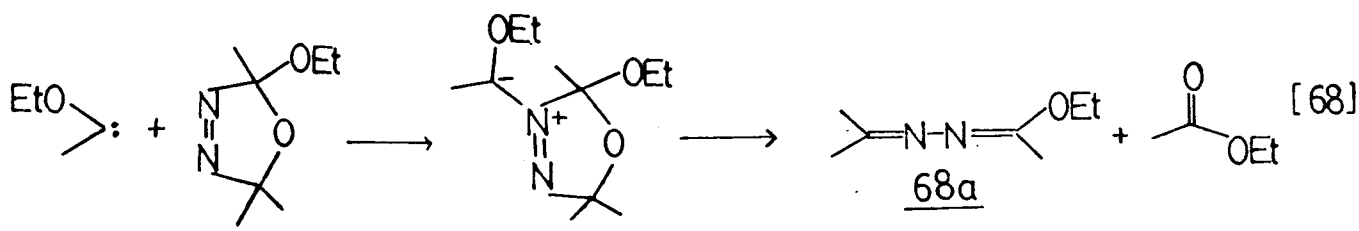
Concentration of 66a			% Product Distribution						
Initial	Final	Average	propene	acetone	ethyl acetate	acetal	67	68a	69a
2.93	2.60	2.76	18	22	63	27	10	25	3
.99	.87	.93	22	28	55	32	7	19	2
.54	.48	.51	28	33	48	36	4	12	2

The results from Table 5 show large changes in yields of product as compared to the results from Table 4. Comparison of the results from 2.7M (average) 66a with those from 2.76M (initial) 66a shows that the yield of acetone is different by a factor of 2 (9 vs 22%). The results from Table 4 are useful nevertheless because they reflect preparative conditions whereas those from Table 5 have greater mechanistic significance.

In order to determine the preference for the formation of 68a, whether from attack by dimethyl carbene (eq 67) or by ethoxymethyl carbene (eq 68), it was necessary to determine which of these carbenes is generated in higher yield. Since the carbenes are generated from fragmentation of the carbonyl ylide, their yields can be obtained from the amounts of biproducts, ethyl acetate and acetone, which are generated. However, since acetone and ethyl acetate are also biproducts in the formation of the azines, the fragmentation pattern of the carbonyl ylide must be obtained under conditions where no azines are formed. We have already shown that the yield of azines is dependent on the initial concentration of 66a. As the initial concentration of 66a is decreased the yield of azines decreases. A .1M solution of 66a in benzene was decomposed thermally. The carbonyl ylide was found to fragment in nearly 1:1 ratio to form dimethylcarbene and ethoxymethyl carbene as implied by the yields of acetone (37%) and ethyl acetate (33%). At this initial concentration of 66a, the combined yield of the azines was approximately 3%.

However, in high concentration of 66a, where relatively high yields of azines are formed, the yield of ethyl acetate is substantially greater than that of acetone. As shown in Table 5, the thermolysis of 66a at average concentration of 2.8M yielded 63% ethyl acetate and 22% acetone. This indicates that the preferred reaction pathway leading to

the formation of 68a is that shown in eq 68, where the ethoxymethyl carbene preferentially attacks N-3. Attack at N-4 must be a minor pathway, as it would lead to product 69a which is formed in only 3% yield.



[68]

R.D.4.3 Synthesis of 69a

In the Introduction, the reactions of orthoesters with amines and substituted hydrazines was discussed (I.3). The major products from these reactions are those of condensation. An attempt was made to synthesize azine 69a using orthoesters.

An authentic sample of ethyl acetate azine (69a) was prepared from the reaction of orthoester with hydrazine. Triethylorthoacetate (20 g, .123 mole), hydrazine (2.0 g, .062 mole) and glacial acetic acid (5 drops) were refluxed in a round-bottomed flask for about 6 hours. The desired product was found in low yield (15%). The product was distilled out of the reaction mixture (63°C @ 10 mm). The ^{1}H NMR and mass spectral data agree with those reported in the literature.[91]

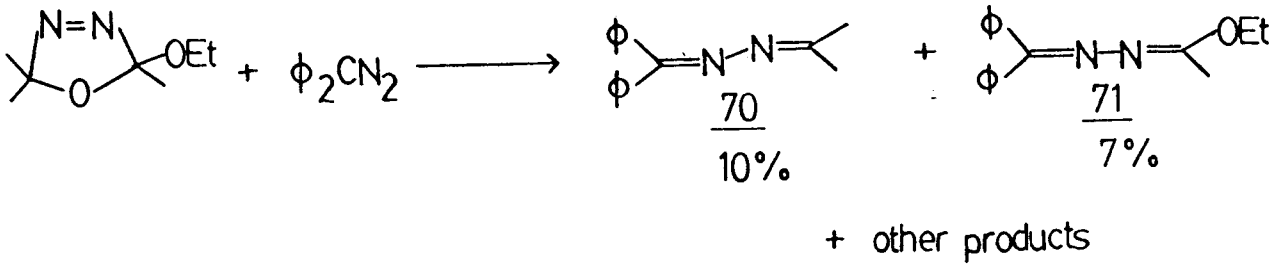
R.D.5 GENERATION OF AZINES USING DIPHENYLDIAZOMETHANE

One possible approach to determining if the proposed mechanism is correct is to generate carbenes from an external source in the presence of the oxadiazoline and to probe for azine formation. Diphenylcarbene can be generated by the thermolysis or photolysis of diphenyldiazomethane.

This carbene was used as our external source but the results from these experiments were inconclusive with regard to mechanism.

R.D.5.1 Thermolysis of $\emptyset_2CN_2$

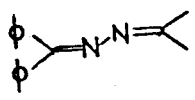
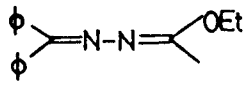
A solution of 66a (1.0M) and $\emptyset_2CN_2$ (0.3M) in benzene was thermolyzed at 80°C. Both azines expected from diphenylcarbene were found, 70 and 71, eq 70.



[70]

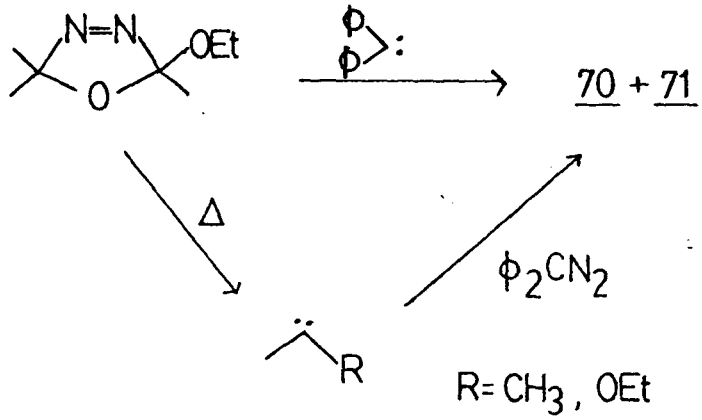
The structures of 70 and 71 were determined from ^1H NMR and mass spectral data, Table 6.

Table 6: Structure Determination of Azines Formed from $\emptyset_2CN_2$

Product	^1H NMR (δ $CDCl_3$=7.27ppm)	M.S. (m/z^+)
	H_a, 1.93 (s,3H) H_b, 2.01 (s,3H) H_c, 7.20-7.60 (m,10H)	$C_{16}H_{16}N_2$ 236 $C_{13}H_{19}$ 165 $C_{16}H_{15}N_2$ 235 $C_{10}H_{11}N_2$ 159 $C_{15}H_{13}N_2$ 221 C_6H_5 77 $C_{13}H_{10}N$ 180 C_3H_6N 56
	H_a, 1.17 (t,2H,J=6.9Hz) H_b, 2.03 (s,3H) H_c, 4.00 (q,2H,J=6.9Hz) H_d, 7.20-7.60 (m,10H)	$C_{17}H_{18}N_2O$ 266 $C_{13}H_9$ 165 $C_{15}H_{14}N_2O$ 238 C_6H_5 77 $C_{15}H_{13}N_2O$ 221 $C_{13}H_{10}N$ 180

The question still remains at this point as to how azines 70 and 71 were formed. At 80°C in benzene, $\emptyset_2CN_2$ decomposes to diphenyl-

carbene slowly with rate constant k = 6.10×10^{-5} s^{-1} while 66a decomposes with rate constant k = 1.09×10^{-5} s^{-1}. The rates are similar suggesting that while $\emptyset_2C$: is being produced so are the carbenes from 66a. Two possibilities for the formation of 70 and 71 are shown in Scheme 10.

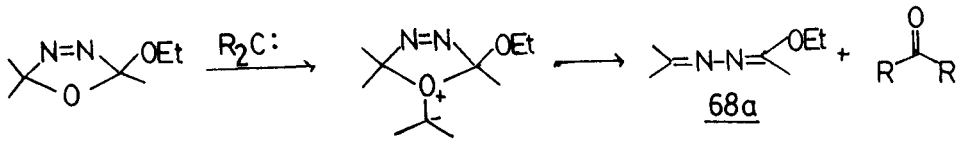


Scheme 10

Azines 70 and 71 can be formed from the attack of diphenylcarbene, generated from thermolysis of diphenyldiazomethane, on 66a (path a) in the same manner as has been proposed for the formation of azines 67, 68a and 69a, eq 66-69. The azines (70, 71) could also be formed from attack of the carbenes generated from 66a on diphenyldiazomethane.

The possibility of attack of a carbene on the oxygen atom of the oxadiazoline to yield azines has not yet been discussed. In the thermolysis of 66a, another possible mechanism for the formation of 68a involves attack of a carbene on oxygen, shown in eq 71.

The ylide intermediate can then fragment to give 68a and a carbonyl compound. This mechanism was ruled out as the only possible mechanism, since only azine 68a (and not 67 or 69a) can be formed from

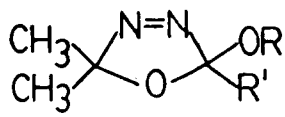


[71]

its operation. There was no way of disregarding its possibility however since the biproducts acetone or ethyl acetate, depending on the carbene used in eq 71, are the same as the products of fragmentation of the carbonyl ylide. In the formation of 71, this mechanism can be disregarded since no benzophenone was found in the reaction mixture.

R.D.6 THERMOLYSIS OF VARIOUS SUBSTITUTED Δ^3-1,3,4-OXADIAZOLINES

The thermolyses of oxadiazolines of type 66 were carried out.



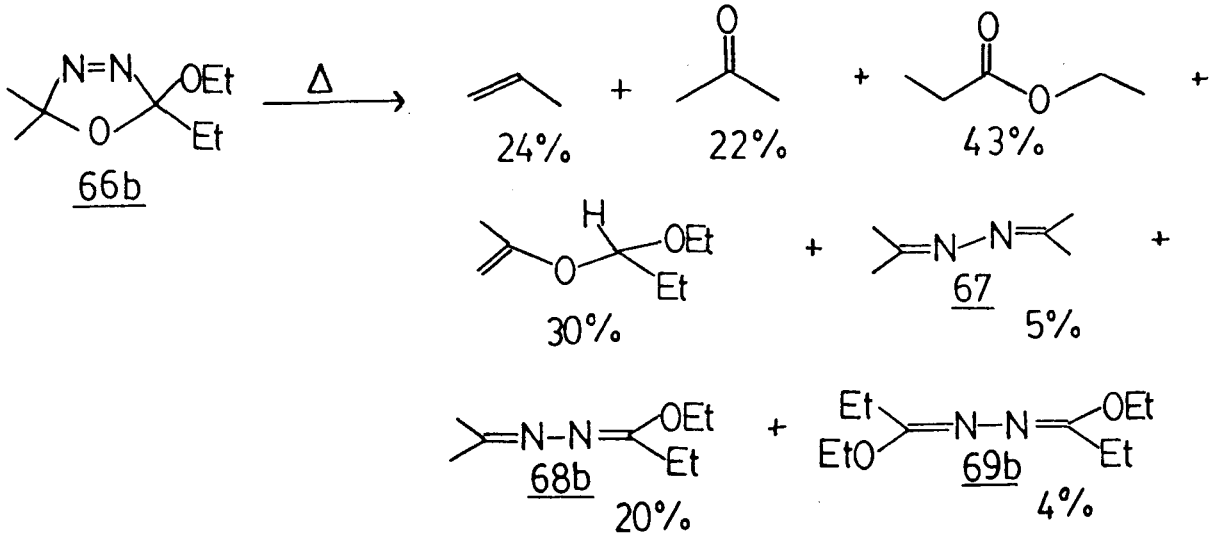
66

66a R = CH_2CH_3, R' = CH_3
66b R = CH_2CH_3, R' = CH_2CH_3
66c R = CH_2CH_3, R' = $CH(CH_3)_2$
66d R = CH_3, R' = $CH(CH_3)_2$

This section will deal with the chemistry of the thermolyses of oxadiazolines 66b - 66d.

R.D.6.1 Thermolysis of 66b

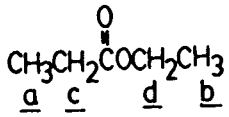
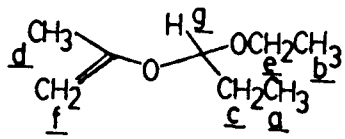
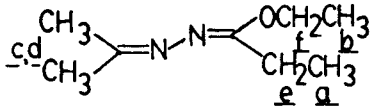
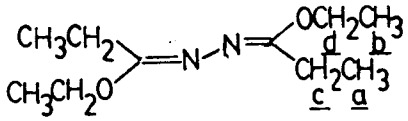
Thermolysis of a 1M solution of 66b in benzene at 80°C gave products similar to those from 66a, eq 72.



[72]

The structures of the products were confirmed from ^{1}H NMR and mass spectral data, Table 7.

Table 7: Products From Thermal Decomposition of 66b

Product	^{1}H NMR (δ $CDCl_3$=7.27ppm)	M.S. (fragment$^+$, m/z)
	H_a, 1.13 (t,3H,J=6.9Hz) H_b, 1.27 (t,3H,J=7.0Hz) H_c, 2.33 (q,2H,J=6.9Hz) H_d, 4.14 (q,2H,J=7.0Hz)	M^+ 102 C_2H_5O 45 $C_4H_7O_2$ 87 C_3H_6O 74 C_3H_5O 57
	H_a, 0.95 (t,3H,J=7.1Hz) H_b, 1.22 (t,3H,J=7.0Hz) H_c, 1.53-1.86 (m,2H) H_d, 1.84 (s,3H) H_e, 3.03-3.86 (m,2H) H_f, 3.97 (s,2H) H_g, 4.96 (t,1H,J=7.0Hz)	$C_6H_{11}O_2$ 115 C_3H_7O 59 $C_5H_{11}O_2$ 103 C_3H_6O 58 $C_6H_{10}O$ 99 C_2H_5O 45 $C_5H_{11}O$ 87 $C_3H_7O_2$ 75
	H_a, 1.08 (t,3H,J=7.1Hz) H_b, 1.10 (t,3H,J=7.0Hz) H_c, 1.94 (s,3H) H_d, 2.00 (s,3H) H_e, 2.48 (q,2H,J=7.1Hz) H_f, 4.16 (q,2H,J=7.0Hz)	M^+ 156 $C_5H_{10}O$ 86 $C_7H_{13}N_2O$ 141 C_3H_6NO 72 $C_6H_{12}N_2O$ 128 C_3H_6N 56 $C_6H_{11}N_2$ 111 C_3H_6 42 $C_5H_{10}NO$ 100
	H_a, 1.20 (t,6H,J=7.0Hz) H_b, 1.21 (t,6H,J=7.0Hz) H_c, 2.46 (q,4H,J=7.0Hz) H_d, 4.15 (q,4H,J=7.0Hz)	M^+ 200 $C_8H_{15}N_2O$ 155 $C_9H_{17}N_2O_2$ 185 $C_5H_{10}NO$ 100 $C_8H_{16}N_2O_2$ 172 C_3H_6NO 72 $C_8H_{15}N_2O_2$ 171 $CHON_2$ 57

R.D.6.2 Thermolysis of 66c

The thermolysis of a 1M solution of 66c in benzene gave products shown in eq 73. The structure of the products were confirmed from ^{1}H NMR and mass spectral data, Table 8.

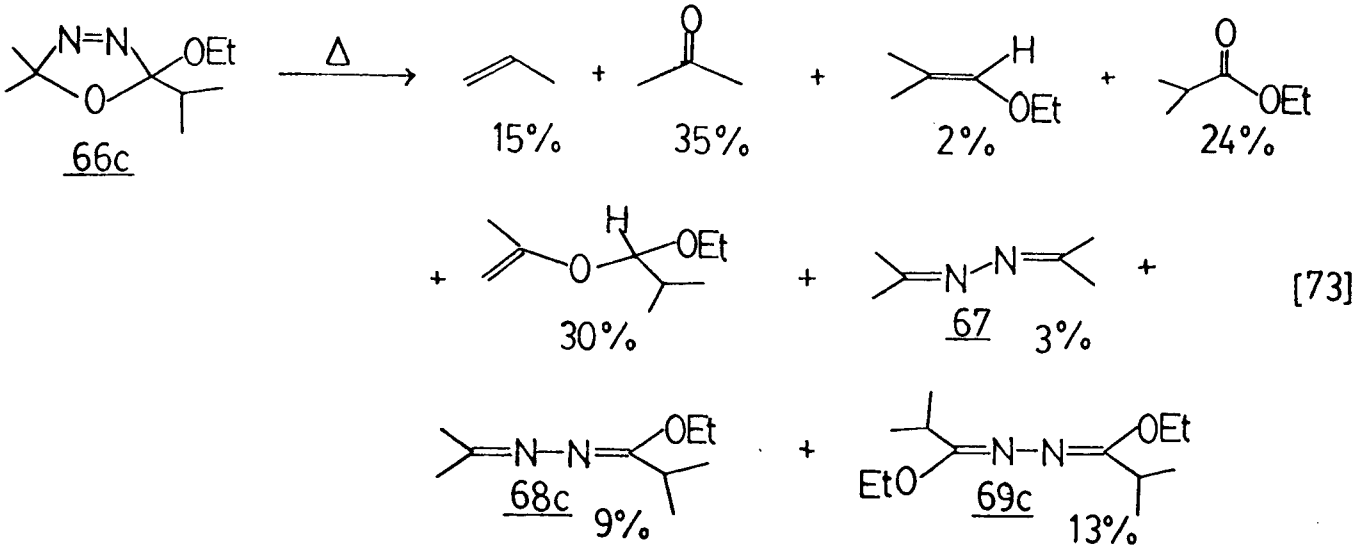
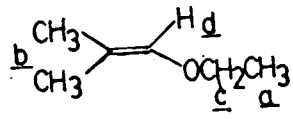
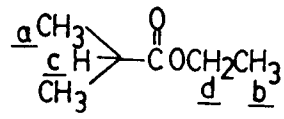
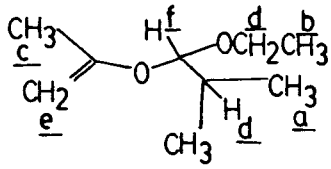
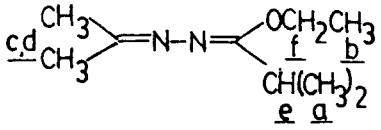
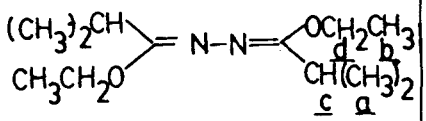


Table 8: Products From Thermal Decomposition of 66c

Product	^{1}H NMR (δ $CDCl_3$=7.27ppm)	M.S. (fragment$^+$, m/z)
	H_a, 1.23 (t,3H,J=7.1Hz) H_b, 1.53 (m,6H) H_c, 3.71 (q,2H,J=7.1Hz) H_d, 5.82-6.12 (m,1H)	M^+ 100 C_4H_8O 72 C_5H_9O 75 C_3H_5O 57
	H_a, 1.18 (d,6H,J=6.9Hz) H_b, 1.26 (t,3H,J=7.1Hz) H_c, 2.54 (septet,1H, J=6.9Hz) H_d, 4.14 (q,2H,J=7.1Hz)	M^+ 116 C_4H_7O 71 $C_5H_9O_2$ 101 C_2H_5O 45 $C_4H_8O_2$ 88 C_3H_7 43 $C_3H_5O_2$ 73
	H_a, 0.95 (d,6H,J=6.7Hz) H_b, 1.21 (t,3H,J=7.0Hz) H_c, 1.85 (s,3H) H_d, 3.11-3.97 (m,3H) H_e, 3.99 (dd,2H,J=3.0Hz) H_f, 4.76 (d,1H,J=5.4Hz)	$C_6H_{11}O_2$ 115 $C_6H_{13}O$ 101 C_4H_9O 73 C_4H_9 55 C_3H_7 43
	H_a, 1.0M (d,6H,J=6.9Hz) H_b, 1.29 (t,3H,J=7.1Hz) H_c, 1.94 (s,3H)	M^+ 170 C_4H_8NO 86 $C_8H_{15}N_2O$ 155 $C_3H_6N_2$ 70 $C_6H_{11}N_2O$ 127 C_3H_6N 56

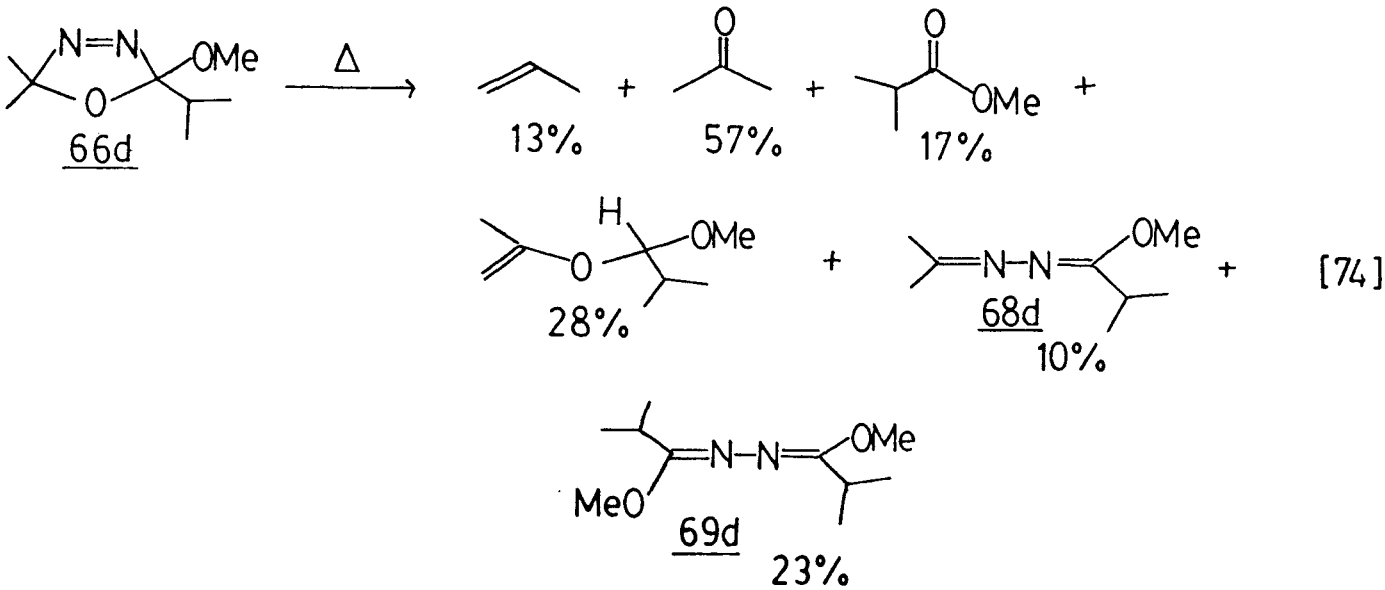
..... continued

Table 8: Products From Thermal Decomposition of 66c (continued)

Product	^{1}H NMR (δ $CDCl_3$=7.27ppm)	M.S. (fragment$^+$, m/z)
68c continued	H_d, 2.00 (s,3H) H_e, 3.39 (septet,1H, J=6.9Hz) H_f, 4.14 (q,2H,J=7.1Hz)	$C_6H_{12}NO$ 114 C_3H_7 43 $C_4H_7N_2O$ 99
	H_a, 1.11 (d,12H,J=6.9Hz) H_b, 1.28 (t,6H,J=7.1Hz) H_c, 3.48 (septet,2H; J=6.9Hz) H_d, 4.12 (q,4H,J=7.1Hz)	M^+ 228 $C_{10}H_{19}N_2O$ 183 $C_{11}H_{21}N_2O_2$ 213 $C_{10}H_{18}N_2O$ 182 $C_{10}H_{20}N_2O_2$ 200 $C_7H_{13}N_2O$ 157 $C_{10}H_{17}N_2O_2$ 185 $C_5H_{12}NO$ 114

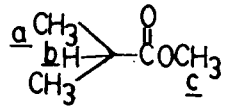
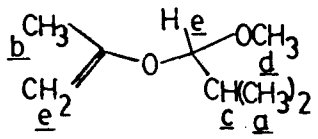
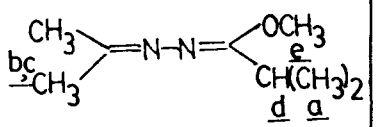
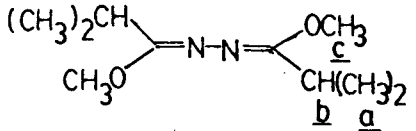
R.D.6.3 Thermolysis of 66d

The thermolysis of a 3.1M solution of 66d in benzene gave products shown in eq 74.



The structures were determined from ^{1}H NMR and mass spectral data, Table 9.

Table 9: Products From Decomposition of 66d

Product	^{1}H NMR (δ $CDCl_3$=7.27ppm)	M.S. (m/z^+)			
	H_a, .95 (d,6H,J=6.7Hz) H_b, 2.22-28.4 (m,1H) H_c, 3.35 (s,3H)	M^+ $C_4H_7O_2$ C_4H_7O	102 87 71	$C_2H_3O_2$ C_3H_7	59 43
	H_a, .95 (d,6H,J=6.7Hz) H_b, 1.86 (s,3H) H_c, 2.18-1.86 (m,1H) H_d, 3.35 (s,3H) H_e, 4.02-3.99 (m,2H) H_f, 4.69 (d,2H,J=5.5Hz)	$C_5H_9O_2$ $C_4H_6O_2$ C_4H_7 C_4H_5O C_3H_7 C_3H_5O	101 86 71 69 43 57		
	H_a, 1.07 (d,6H,J=6.7Hz) H_b, 1.96 (s,3H) H_c, 2.01 (s,3H) H_d, 3.50 (septet,1H, J=6.7Hz)	M^+ $C_7H_{13}N_2$ $C_5H_9N_2O$ C_4H_6NO	156 125 113 84	$C_3H_6N_2$ C_4H_6N C_3H_6N C_3H_7	70 68 56 43
	H_a, 1.09 (d,12H,J=7.0Hz) H_b, 3.51 (septet,2H, J=7.0Hz) H_c, 3.72 (s,6H)	M^+ $C_7H_{13}N_2O$ $C_5H_{10}NO$	200 157 100	$C_5H_{10}O$ C_4H_6NO C_4H_6N C_3H_7	86 84 68 43

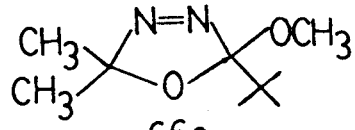
R.D.6.4 Summary

Upon thermolysis, oxadiazolines 66b - 66d gave azine products similar to those seen in the thermal decomposition of 66a. The relative yields of the azines differ however according to the oxadiazoline precursor. In the thermolysis of 66b, the most abundant azine was 68b, the monoethoxysubstituted azine. In the thermolysis of 66c and 66d, the most abundant azine was the diethoxysubstituted azine, 69c and 69d.

These results further support the proposed mechanism and will be explained in the next section.

R.D.7 THERMAL DECOMPOSITION OF 2-t-BUTYL-2-METHOXY-5,5-DIMETHYL-Δ^3-1,3,4-OXADIAZOLINE

So far we have discussed the thermolysis of oxadiazolines 66 where the alkyl substituent at C-2 has been changed. All these oxadiazolines yielded azines but no configurational isomerism of these azines was seen. The reason for changing the alkyl substituent at C-2 was to change the steric requirements in the azine products with the hope that configurational isomerism would be observable. Changing this substituent from methyl to isopropyl, was insufficient to cause a change in the configuration of the azine. In this section, we will discuss the results of the thermolysis of an oxadiazoline in which the substituent has been changed to t-butyl, 66e.

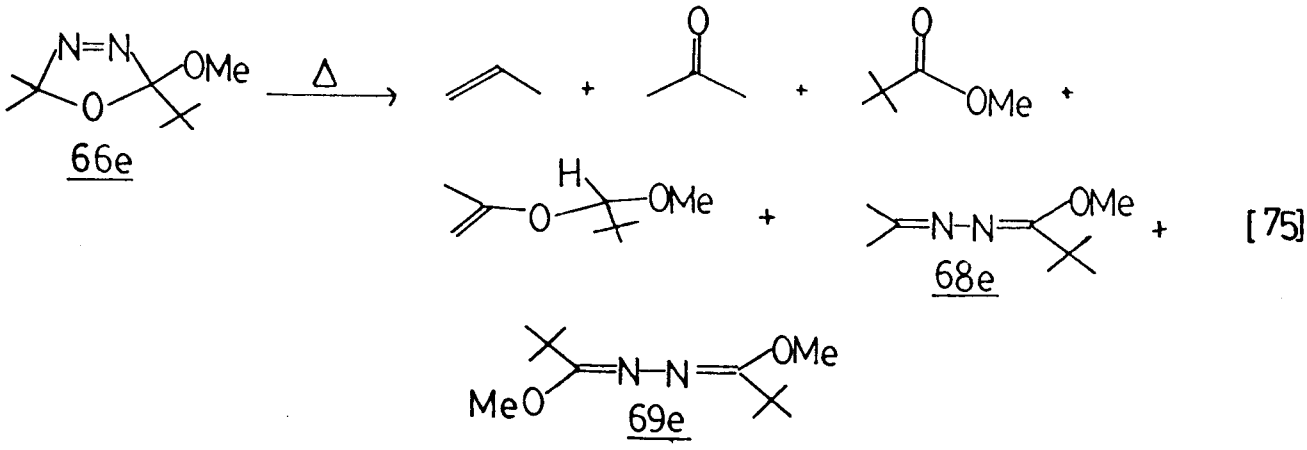


66e

R.D.7.1 Results

The major products obtained from the thermolysis of a solution of 66e in benzene at 80°C are shown in eq 75.

As was seen in the thermolysis of the isopropyl oxadiazolines (66c and 66d), the dialkoxysubstituted azine is the most abundant (Table 10). The low yield of propene and the absence of acetone azine (67) imply that dimethylcarbene was being generated in low yield. A



[75]

Table 10: Product Distribution From Thermolysis of 66e at Different Concentrations

Product	Initial Concentration of 66e	
	.18 M	2.76 M
propene	3%	1%
acetone	60	63
methyl acetate	11	15
acetal	20	15
68e	2	8
69e	7	32

dilute solution (0.18M) of 66e was thermolyzed to determine the preferred pathway for fragmentation of the derived ylide, Table 10.

As seen from the results shown in Table 10, the preferred direction for fragmentation of the carbonyl ylide is that giving acetone

and t-butylmethoxycarbene. The fact that the relative yield of 69e is greater than the yield of 68e and that little propene and no acetone azine (67) is found when the yield of ester is very low further supports the proposed mechanism for azine formation involving carbene attack on the starting material.

A trend is seen in the relative yields of azines as the size of the alkyl group at C-2 increases in the ethoxy- or methoxy-oxadiazolines. By changing the group from Me to Et to iPr to tBu the fragmentation pattern of the carbonyl ylide begins to favour the formation of acetone and alkoxyalkylcarbene. This leads to an increase in the yield of azine 69 and a decrease in the yield of acetone azine 67, Table 11.

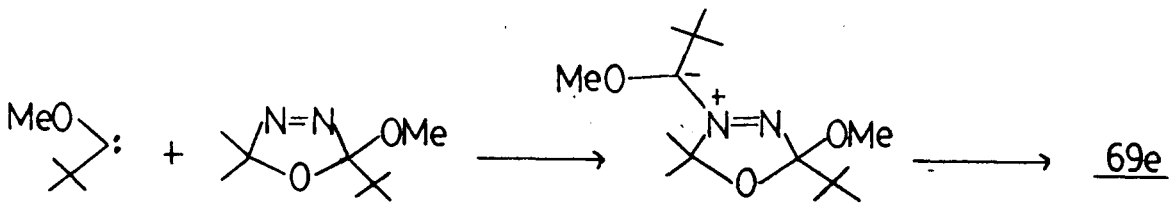
Table 11: Relative Yields of Azines From Thermolysis of 66a - 66e (%)

Oxadiazoline 66	Initial Conc. of 66	67	68	69
66a R'=CH_2CH_3, R=CH_3	3.1	12	26	4
66b R'=CH_2CH_3, R=CH_2CH_3	1.0	5	20	4
66c R'=CH_2CH_3, R=$CH(CH_3)_2$	1.0	3	9	13
66d R'=CH_3, R=$CH(CH_3)_2$	3.1	-	10	23
66e R'=CH_3, R=$C(CH_3)_3$	2.8	-	8	32

In the case where the alkyl group at C-2 in 66 is t-butyl (66e), fragmentation occurs almost exclusively to give acetone and t-butylmethoxy carbene as indicated by the absence of acetone azine 67 and the extremely low yields of propene. It can be safely assumed that azines 68e and 69e

are found from attack of the t-butylmethoxy carbene on oxadiazoline 66e. From the yields of azines 68e and 69e, the nitrogen of the oxadiazoline at which the carbene preferentially attacks can now be determined.

Azine 69e is the most abundant implying that the carbene is preferentially attacking the oxadiazoline at N-4 according to eq 76.



[76]

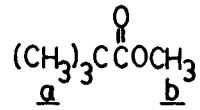
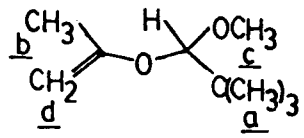
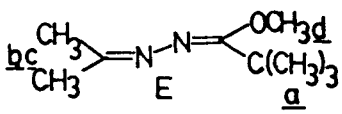
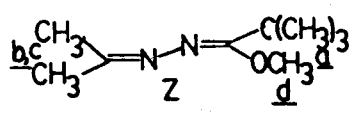
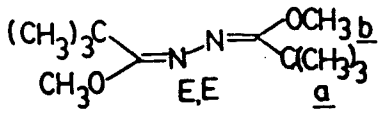
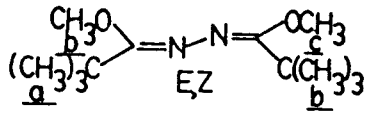
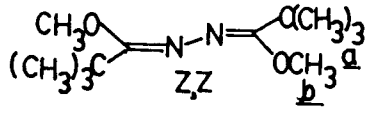
In the thermal decomposition of 66a, azine 68a was found in higher yield and we concluded that the favoured site for attack by $CH_3\ddot{C}OCH_2CH_3$ was N-3. The inherent preference is presumably still there for $(CH_3)_3C\ddot{C}OCH_3$ but is overshadowed by the steric factor. As the alkyl group of the alkylalkoxy carbene increases in size, we find that the yield of azine 69 increases. The formation of 68e would involve attack of the t-butylmethoxy carbene at N-3, which would be less preferred because a more hindered azomethine imine intermediate is formed.

R.D.7.2 Structure Determination

The structures of the products from the thermolysis of 66e were determined from ^1H NMR and mass spectral data, Table 12.

As seen from the results shown in Table 12, both azines 68e and 69e were found existing in configurationally isomeric forms. The next section of the discussion will deal with the stereochemistry of the azines.

Table 12: Products From Thermolysis of 66e

Product	^{1}H NMR (δ $CDCl_3$=7.27ppm)	M.S. (m/z$^+$)
	H_a, 1.16 (s,9H) H_b, 3.63 (s,3H)	$C_6H_{12}O_2$ 116 $C_4H_8O_2$ 73 C_5H_9O 101 $C_2H_3O_2$ 59 C_4H_9O 85 C_4H_9 57
	H_a, 0.90 (s,9H) H_b, 1.83 (s,3H) H_c, 3.48 (s,3H) H_d, 4.00 (dd,2H,J=6.0Hz) H_e, 4.62 (s,1H)	$C_5H_9O_2$ 131 $C_8H_{12}O$ 127 $C_5H_{11}O$ 87 C_5H_9O 85 $C_2H_4O_2$ 59
	H_a, 1.26 (s,9H) H_b, 1.90 (s,3H) H_c, 2.00 (s,3H) H_d, 3.68 (s,3H)	$C_9H_{18}N_2O$ 170 $C_8H_{15}N_2O$ 155 $C_8H_{15}N_2$ 139 $C_5H_9N_2O$ 113
	H_a, 1.19 (s,9H) H_b, 1.90 (s,3H) H_c, 2.00 (s,3H) H_d, 3.91 (s,3H)	$C_4H_7N_2O$ 99 $C_3H_6N_2$ 70 C_4H_9 57 C_3H_6 56
	H_a, 1.63 (s,18H) H_b, 3.77 (s,6H)	$C_{12}H_{24}O_2$ 228 $C_{11}H_{21}N_2O$ 213
	H_a, 1.36 (s,9H) H_b, 1.64 (s,9H) H_c, 3.60 (s,3H) H_d, 4.07 (s,3H)	$C_{11}H_{21}N_2$ 197 $C_8H_{10}N_2O_2$ 171 $C_6H_{12}N_2O$ 128 $C_6H_{12}NO$ 114
	H_a, 1.30 (s,18H) H_b, 4.09 (s,6H)	$C_6H_{12}O$ 100 C_4H_9 57

R.D.8 STEREOCHEMISTRY OF ESTER AZINES

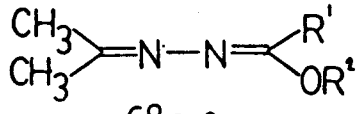
There have been no reports in the literature on the stereochemistry of ester azines (hydrazonates). The stereochemical preferences for compounds that are related to these azines have already been discussed

in the Introduction.

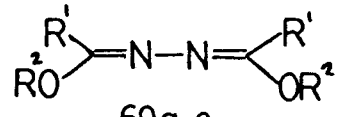
A steric factor determines which of the two configurations about the C=N group is more stable in systems such as oximes, azines, imines, and hydrazones. The most stable configuration is usually that in which the larger of the two alkyl substituents at sp^2-carbon is anti.

Compounds with a second heteroatom substituent (X) at sp^2-carbon (i.e. $\begin{matrix} R \\ X \end{matrix}$>C=N-Y, X=N,O,S,hal.) have configurations that will be determined by repulsions between electron pairs at X, N and Y as well as substituent sizes. In the case of ester azines, both these factors must be taken into consideration when determining the configurational preference. The configurational preference for azines of type 68 and 69 will now be discussed.

R.D.8.1 Configuration of Ester Azines



68a-e



69a-e

a) $R^1 = CH_3$, $R^2 = CH_2CH_3$
b) $R^1 = CH_2CH_3$, $R^2 = CH_2CH_3$
c) $R^1 = CH(CH_3)_2$, $R^2 = CH_2CH_3$
d) $R^1 = CH(CH_3)_2$, $R^2 = CH_3$
e) $R^1 = C(CH_3)_3$, $R^2 = CH_3$

The ^1H NMR spectra showed that azines 68a-d and 69a-d existed as one isomeric form while only the t-butyl systems 68e and 69e were not configurationally pure.

The E-configuration was assigned to azines 68a - 68d and the

E,E-configuration to azines 69a - 69d on the basis of the fact that the larger of the two substituents at sp^2-C of an azine is preferentially located at the anti site, the least hindered site. If these uniconfigurational compounds were Z-isomers, where the alkyl group is anti, then the t-butyl systems should also be uniconfigurational since the t-butyl group would then be in the least hindered site. There is no reason for an anti alkyl group to wish to go syn as the size increases. Since a change in configuration is seen in the t-butyl systems we are led to the conclusion that the preferred configuration of compounds like 68 and 69 is that with the alkoxy groups anti; the E-configuration. By placing the alkoxy substituent in the anti position, the 1,4-electron pair repulsion between the alkoxy oxygen and nitrogen can be kept to a minimum. Similarities are seen when comparing ^1H NMR chemical shift differences between the resonances of the isomers of 68e and 69e and the isomers of azines. For example, in the case of methylethylketazine (53, R=CH_2CH_3, R'=CH_3), the methyl signal for the E,E-isomer is at δ 1.78 ppm, while for the Z,Z-isomer it is at δ 1.97 ppm. A downfield shift is seen when the methyl group is placed syn. In the case of the isomeric mixture of 68e we find the same shift in the δ values for the individual isomers. The E-isomer has the t-butyl resonance at 1.26 ppm and the methoxy resonance at δ 3.68 ppm while the z-isomer has the t-butyl resonance at 1.19 ppm and the methoxy resonance at δ 3.91 ppm. Again, the methoxy resonance or the t-butyl resonance is shifted downfield when that particular substituent is placed in the syn position. The same occurrences are found for the isomeric mixture of 69e.

No direct comparison could be made (for the extent of these shifts

in the resonance signals) between 69e and azine 53 ($R=C(CH_3)_3$, $R'=CH_3$) since these azines are found only in the E,E configuration.

R.D.8.2 Assignment of Configuration

The individual configurations of the t-butyl azines (68e and 69e) were assigned on the basis of their ^1H NMR spectra. On the basis of the methoxy signal at δ 3.73 in the spectrum of 68d, the isomer of 68e which had the δ 3.68 methoxy signal in the ^1H NMR spectra was labelled E. The Z-isomer was then assigned the δ 3.91 methoxy signal and the t-butyl signals were assigned on the basis of integration ratios. The methyl signals of 68e were not resolved for the two isomers.

From the ^1H NMR spectrum of the mixture of isomers 69e, the easiest isomer to assign signals to was the unsymmetric (E,Z) isomer. The spectra of the (E,E) and (Z,Z) isomers were assigned on the basis of the chemical shifts of the methoxy signals, which are upfield for E-isomers, and on the basis of isomer populations (E,E > Z,Z). The methoxy signal for the (E,E) isomer was not resolved from one of the two methoxy signals from the (E,Z) isomer, hence the relative concentration of the (E,E) isomer was obtained by correcting the composite integral for the contribution from the (E,Z) isomer.

R.D.9 EQUILIBRATION STUDIES OF AZINES 68 AND 69

Equilibration studies at different temperatures were attempted on azines 68b-e and 69c-e. Samples of these isomeric azines were heated at the various temperatures and the ^1H NMR spectra were taken to see if the relative ratios of the isomers changed. Results are shown in Table 13.

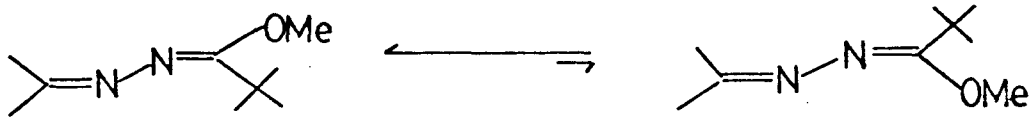
Table 13: Equilibration of Configurational Isomers of 68 and 69

Compound	T(K)[a]	Equilibration Composition (%)				
		E	Z	E,E	E,Z	Z,Z
68b - 68d	305	100	0			
	353	100	0			
	393	100	0			
68e	305	89	11			
	353	82	18			
	393	75	25			
69c - 69d	305			100	0	0
	353			100	0	0
	393			100	0	0
69e	305			62	33	5
	353			53	40	7
	393			43	49	8

[a]Probe Temperatures, ± 1°K

The spectra were run using DMSO-d_6 as solvent. The azines with ethyl or isopropyl alkyl groups were not affected by heating to 120°C. However, the composition of the t-butyl azines (68e and 69e) did change with temperature. The barrier to isomerization is not very large since the t-butyl systems reached equilibria in less than 0.5 hr at 80°C. For the systems with less bulky alkyl groups, no equilibration changes occurred even at 120° for 2 hours. The conclusion reached is that the methyl, ethyl and isopropyl systems were already equilibrated. The equilibrium concentrations of the Z-isomers (for 68 a-d) and E,Z- and Z,Z-isomers (for 69 a-d) are less than the detection limit which is about 1% at 120°C.

The thermodynamic parameters for the isomerization of 68e were calculated from the temperature dependence of K_{eq}, eq 77.



(E) (Z) [77]

ΔG° = 1.3 kcal/mole (25°C)

ΔH° = 2.7 kcal/mole

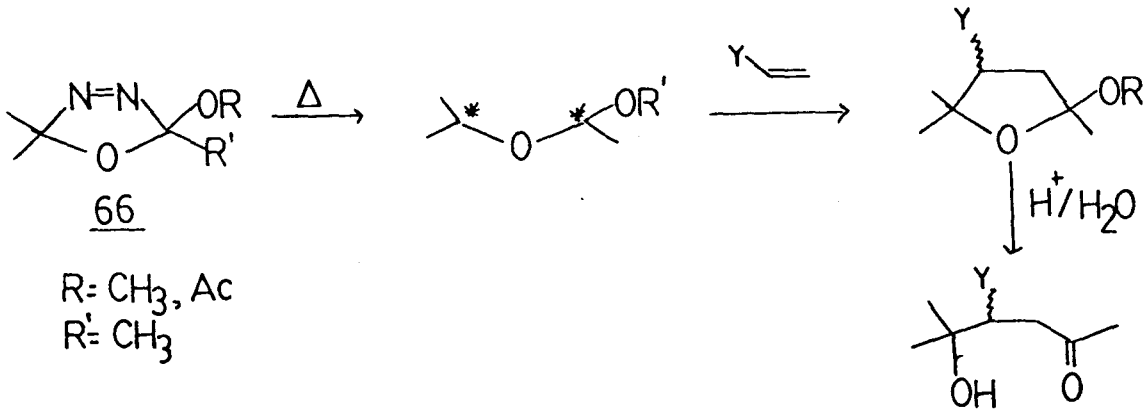
ΔS° = 4.7 cal/deg

The parameters were calculated in the sense Z minus E. The entropy difference indicates that the Z-isomer has the higher entropy which may partly be attributed to more freedom on motion of the t-butyl group in that isomer.

Similar calculations were done on the equilibration of azine 69e. The results are not reported since the errors in the equilibration constants are too large.

R.D.10 THE THERMOLYSIS OF 2-[2,2,2-TRIHALOETHOXY]-2,5,5-TRIMETHYL-Δ^3-1,3,4-OXADIAZOLINES

The generation of compounds derived from trapping the carbonyl ylide intermediate from oxadiazoline 66 (R=CH_3 or R=AC) constitutes a potential route to γ-hydroxy ketones, eq 78. The ylide derived from 66 (R=CH_3), however, fragments quickly reducing the probability of trapping and the ylide derived from 66 (R=AC) readily undergoes a 1,4-shift, leaving it essentially useless also as a trappable 1,3-dipole.



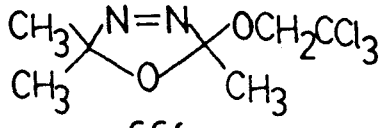
66

R= CH_3, Ac
R'= CH_3

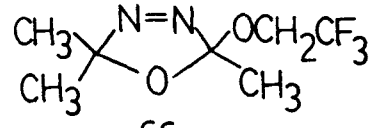
[78]

From theoretical calculations[3], the presence of electron donors in the ylide decreases the barrier to rotation (0°,0° - 0°,90°) making fragmentation from the 0°,90° conformation possible. One approach of preventing fragmentation while retaining the envisioned potential route to γ-hydroxy ketones, would be to reduce the electron donating ability of the alkoxy group in oxadiazoline (66), by introducing a group such as OCH_2CCl_3 or OCH_2CF_3. Such substituents may raise the barrier to ylide fragmentation significantly, thus improving the chances of cycloaddition to dipolarophiles during the ylide's lifetime.

Oxadiazolines 66e and 66f were synthesized to test the above hypothesis and their reaction pathway in various solvents was observed.



66f



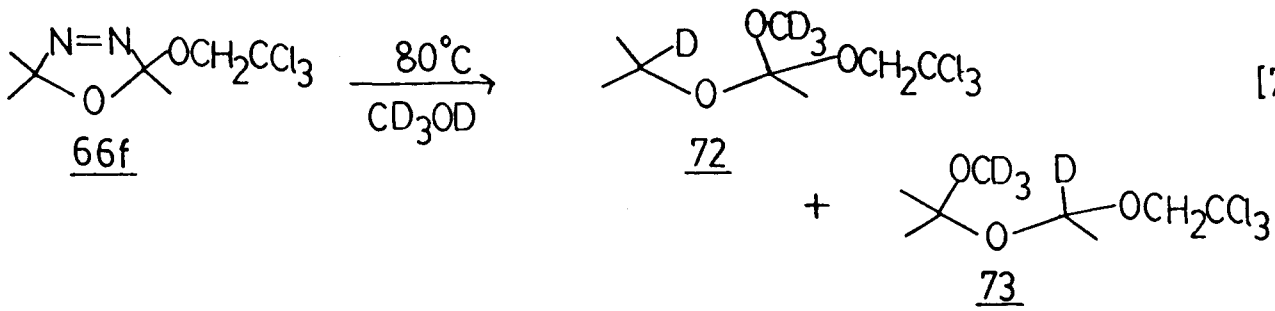
66g

R.D.10.1 EFFECT OF SOLVENT CHANGES ON THE THERMAL DECOMPOSITION OF 2-[2,2,2-TRICHLOROETHOXY]-2,5,5-TRIMETHYL-Δ^3-1,2,4-OXADIAZOLINE

1. THERMOLYSIS OF 66e IN CD_3OD

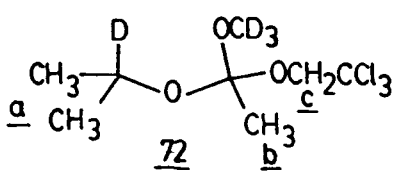
The thermolysis of 66f in CD_3OD at 80.0°C, afforded ketals 72

and 73, eq 79.



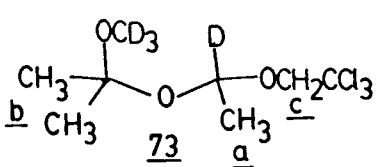
[79]

Products 72 and 73 were not separated, but their structures could be inferred from the ^{1}H NMR spectrum of the mixture.



^{1}H NMR (CD_3OD, δ TMS=0.0):

H_a, 1.40 (s,6H)
H_b, 2.34 (s,3H)
H_c, 4.25 (s,2H)



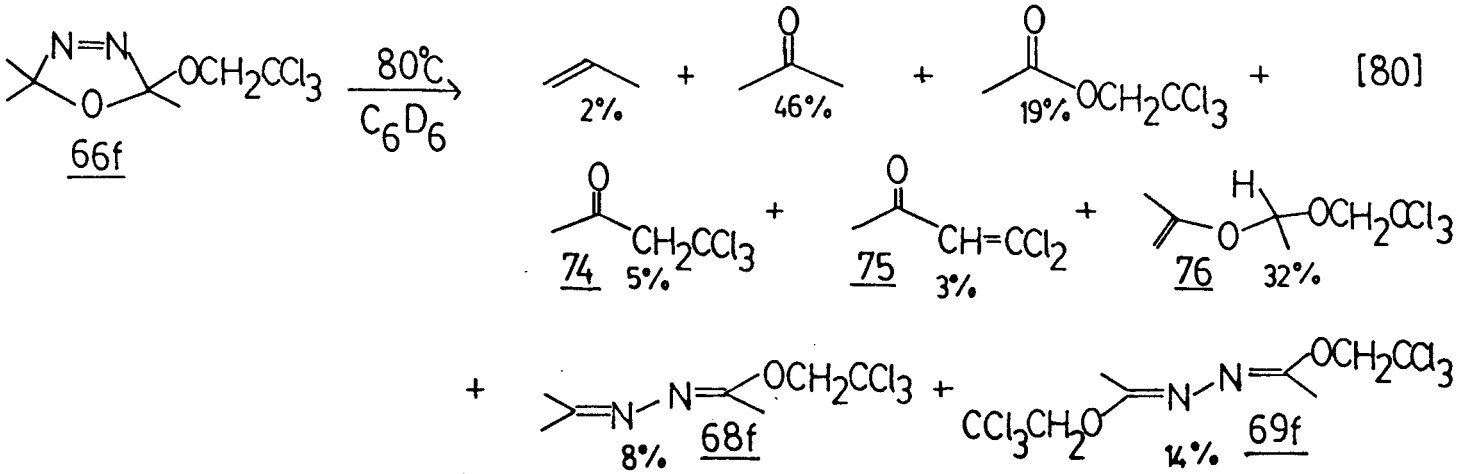
^{1}H NMR (CD_3OD, δ TMS=0.0)

H_a, 1.30 (s,6H)
H_b, 2.15 (s,3H)
H_c, 4.25 (s,2H)

The yields of 72 and 73 were found to be approximately in the ratio of 2:1. These results indicate that the oxadiazoline (66f) is decomposing to give a carbonyl ylide intermediate. That is, the first step of the oxadiazoline thermolysis is unaffected by the trihaloalkoxy-substituent.

2. THERMOLYSIS OF 66f in C_6D_6

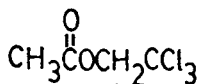
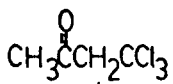
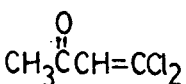
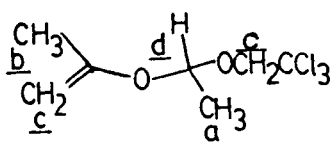
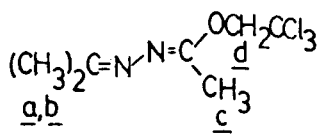
The main products of the thermolysis of a 1.0M solution of oxadiazoline 66f in C_6D_6, at 80.0°C, are shown in eq 80.



The products were separated by preparative GC. Their structures were deduced from their respective ^1H NMR and mass spectral data which are shown in Table 14.

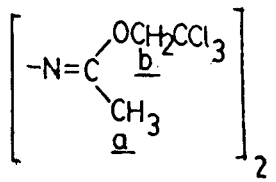
The mechanism proposed for the formation of these products is the same as that described for 66a except for products 74 and 75. Their derivation will be described in the next section.

Table 14: Products From Thermolysis of 66f in C_6D_6

Product	^1H NMR (δ $CDCl_3$=7.27ppm)	M.S. (fragment$^+$, m/z)	
	H_a, 2.18 (s,3H) H_b, 4.65 (s,2H)	$C_4H_5Cl_2O_2$ $C_2H_2Cl_3$ C_2HCl_2 CCl_3 $C_3H_5O_2$ C_2H_3O	155,157,159 (9:6:1) 131,133,135 (3:3:1) 95,97,99 (9:6:1) 117,119,121 (3:3:1) 73 43
	H_a, 2.07 (s,3H) H_b, 2.97 (s,2H)	$C_4H_5Cl_3$ CCl_3 C_2HCl_2 C_3H_5O C_2H_3O	131,133,135 (3:3:1) 117,119,121 (3:3:1) 95,97,99 (9:6:1) 57 43
	H_a, 2.07 (s,3H) H_b, 6.48 (s,1H)	$C_4H_4Cl_2O$ $C_3H_1Cl_2O$ C_2HCl_2 C_2H_3O	134,136,138 (9:6:1) 123,125,127 (9:6:1) 95,97,99 (9:6:1) 43
	H_a, 1.88 (d,3H,J=6.0Hz) H_b, 2.07 (s,3H) H_c, 4.02-4.50 (m,4H) H_d, 5.85 (q,1H,J=6.0Hz)	$C_4H_6Cl_3O$ $C_2H_2Cl_3$ CCl_3 C_3H_5O CHO_2	175,177,179 (3:3:1) 131,133,135 (3:3:1) 117,119,121 (3:3:1) 57 45
	H_a, 1.94 (s,3H) H_b, 2.01 (s,3H) H_c, 2.10 (s,3H) H_d, 4.74 (s,2H)	$C_7H_{11}Cl_2N_2O$ $C_2H_2Cl_3$ $C_4H_7N_2O$ C_2H_6N	209,211,213 (9:6:1) 131,133,135 (3:3:1) 99 56

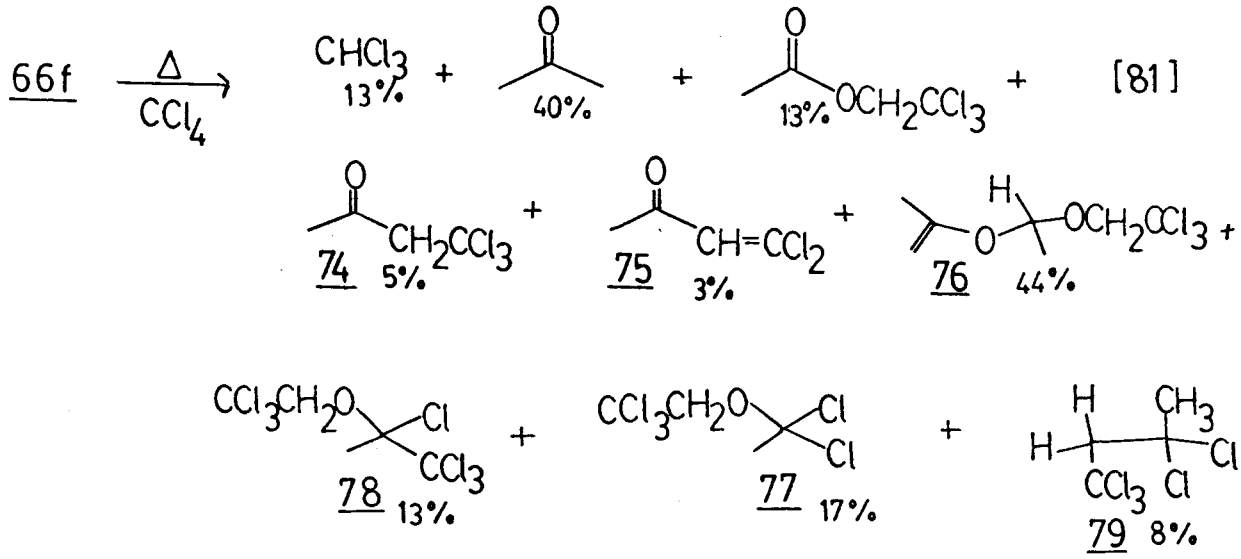
..... continued

Table 14: (continued)

Product	^{1}H NMR (δ $CDCl_3$=7.27ppm)	M.S. (fragment$^+$, m/z)
	H_a, 2.12 (s,6H) H_b, 4.75 (s,4H)	$C_8H_{10}Cl_5N_2O_2$ 341,343,345,347 (243:507:90:15) $C_6H_9Cl_3N_2O_2$ 246,248,250,252 (27:27:4:1) $C_6H_9Cl_2N_2O_2$ 211,213,215 (9:6:1) $C_2H_2Cl_3$ 131,133,135 (3:3:1) $C_4H_8N_2O_2$ 116 $C_4H_7N_2O$ 99

3. THERMOLYSIS OF 66f IN CCl_4

The major products of thermolysis of oxadiazoline 66f in CCl_4, at 80°C, are shown in eq 81.

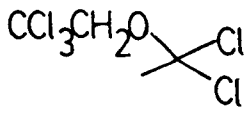
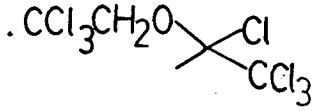
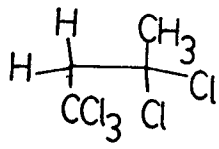


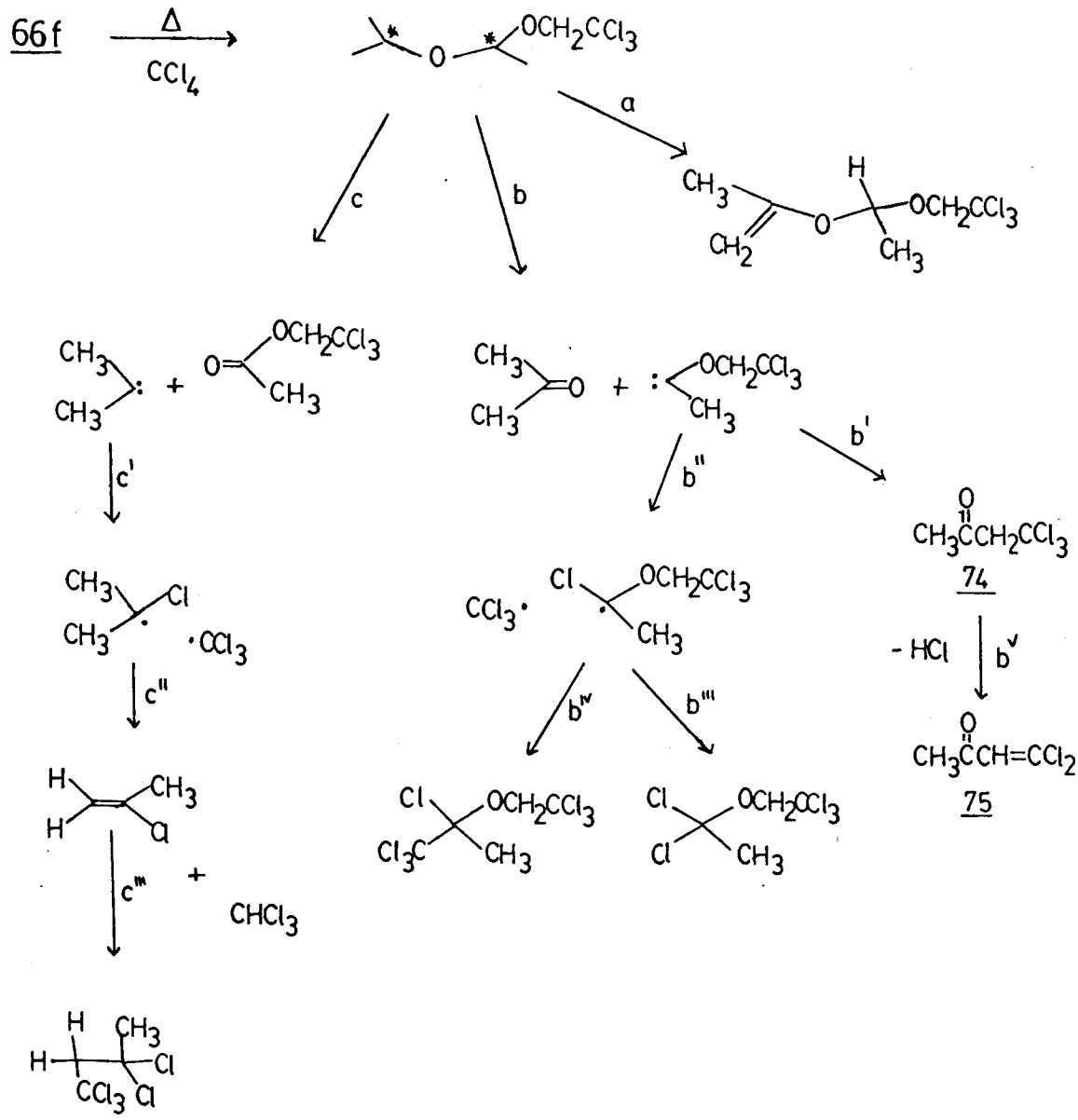
The products were separated by preparative GC and their structures were deduced from their respective ^1H NMR and mass spectral data, Table 15.

Acetone and chloroform were identified by comparing their ^1H NMR spectra and GC retention times to those of authentic samples (acetone (δ 2.17(s)), chloroform (δ 7.27(s)). Products 78 and 79 were tentatively assigned from the mass spectral data.

The probable mechanism for the thermolysis of oxadiazoline 66f is shown in Scheme 11. The carbonyl ylide can undergo a 1,4-hydrogen shift to yield enol-ether 76 (path a). Fragmentation of the ylide produced 2,2,2-trichloroethoxymethyl carbene and acetone (path b) and dimethyl carbene and ester (path c).

Table 15: Products From Thermolysis of 66f in CCl_4

Product	^1H NMR (δ CDCl =7.27ppm)	M.S. (fragment$^+$, m/z)
	H_a, 2.48 (s,3H) H_b, 4.43 (s,2H)	$C_4H_5Cl_4O$ 209,211,213,215 (91:108:54:12) $C_2H_2Cl_3$ 131,133,135,137 (27:27:9:1) C_2HCl_2 97,99,101 (9:6:1) C_2H_3O 43
		$C_5H_5Cl_5O$ 256,258,260,262 (243:405:270:90) $C_2H_2Cl_3$ 131,133,135,137 (27:27:9:1) $C_3H_3Cl_2O$ 125,127,129 (4:6:1) $CHCl_2$ 83,85,87 (9:6:1) C_2H_2Cl 61,63 (3:1) C_2H_3O 43
		$C_4H_5Cl_4$ 193,195,197,199 (91:108:54:12) $C_2H_2Cl_3$ 131,133,135 (3:3:1) CCl_3 117,119,121 (3:3:1) $C_2H_3Cl_2$ 97,99,101 (9:6:1) $C_2H_2Cl_4$ 61,63 (3:1)



Scheme 11

Trichloromethoxymethyl carbene can undergo an alkyl shift (path b') to give 74, or it can abstract a chlorine from CCl_4 (path b") to form a radical pair, which can either abstract another chlorine from CCl_4 (path b'") to form 77 or couple with CCl_3 (path b^V) to form 78.

Abstraction of chlorine by dimethyl carbene (path c') followed by disproportionation of 2-chloro-2-propyl radical (path c") leads to 2-chloropropene and $CHCl_3$. Addition of CCl_4 to the alkene gives 79.

4. CONCLUSIONS

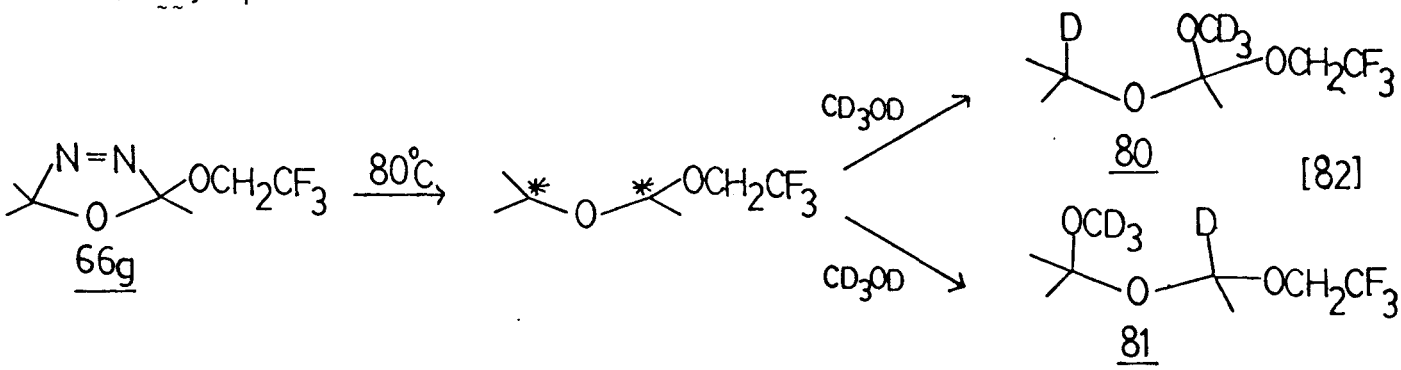
Oxadiazoline 66f decomposes to give a carbonyl ylide intermediate which was trapped by CD_3OD to give ketal products. Thermolysis of 66f in C_6D_6 again gave azine products. From the low yield of propene and the absence of acetone azine (67), we can say that the preferred fragmentation pathway is that which yields acetone and the 2,2,2-trichloroethoxymethyl carbene. The major azine formed is 69f which is formed from attack of the 2,2,2-trichloroethoxymethyl carbene on the starting material.

The absence of azine products in the thermolysis of 66f in CCl_4 again implies this formation via a carbene mechanism since products of chlorine abstraction by the carbene are found. Also, when 66f is thermally decomposed in CCl_4, not only are no azines formed, but the yield of the 1,4-hydrogen shift product of the ylide increased. Since no azines were found, it can be assumed that the oxadiazoline is decomposing to give 100% ylide and hence an increase in the yield of intramolecular rearrangement products of the ylide is expected.

R.D.10.2 EFFECT OF SOLVENT CHANGES ON THE THERMAL DECOMPOSITION OF 2-[2,2,2-TRIFLUOROETHOXY]-2,5,5-TRIMETHYL-Δ^3-1,3,4-OXADIAZOLINE

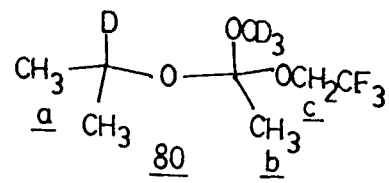
1. THERMOLYSIS OF 66g IN CD_3OD

The thermolysis of 66g in CD_3OD at 80.0°C, afforded ketals 80 and 81, eq. 82.

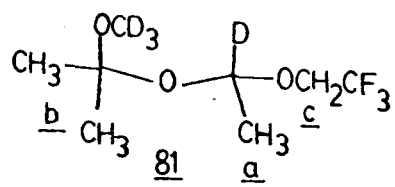


[82]

The structures of 80 and 81 were inferred from the ^1H NMR spectrum of the mixture. Products 80 and 81 were found in a 1:1 ratio.



^1H NMR (δ CD_3OD = 3.26ppm)
H_a, 1.22 (s,6H)
H_b, 1.93 (s,3H)
H_c, 3.60-4.00 (m,2H)



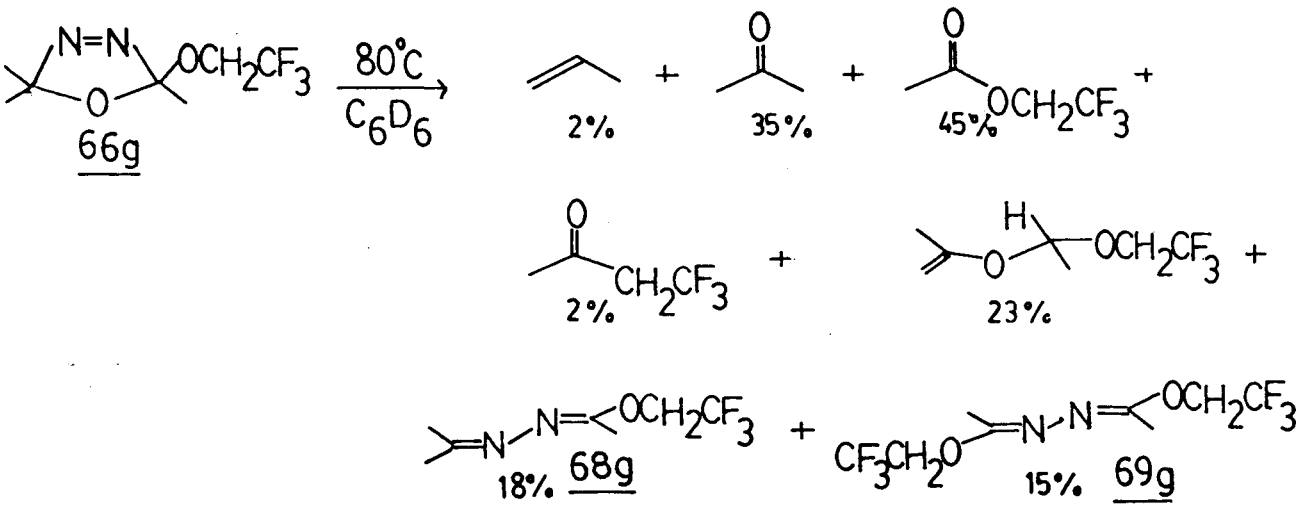
^1H NMR (δ CD_3OD = 3.26ppm)
H_a, 1.07 (s,3H)
H_b, 2.07 (s,6H)
H_c, 3.60-4.00 (m,2H)

The products are those of trapping of the carbonyl ylide intermediate, from the thermolysis of 66g by the CD_3OD solvent.

2. THERMOLYSIS OF 66g in C_6D_6

The main products from the thermolysis of 66g in C_6D_6 at 80.0°C

are shown in eq 83.



[83]

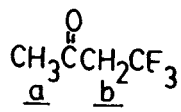
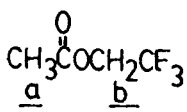
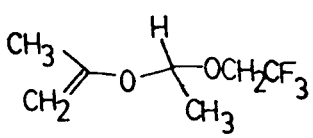
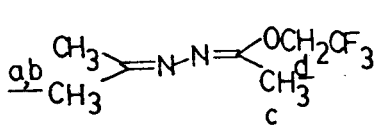
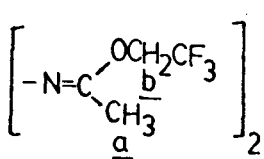
The structures of the products were determined from ^{1}H NMR and mass spectral data, Table 16.

3. CONCLUSIONS

From the yields of azines 68g and 69g it can be said that the preferred fragmentation pathway is that to give acetone and 2,2,2-trifluoroethoxy carbene. Again a low yield of propene and no acetone azine (67) was found. The 2,2,2-trifluorethoxy carbene was found to undergo a C-O insertion to give a ketone product.

The azine products from the thermolysis of oxadiazolines 66f and 66g were uni-configurational. By changing the alkoxy substituent of oxadiazoline 66 (R'=CH_3) to OCH_2CCl_3 or OCH_2CF_3, ylide fragmentation has not been stopped. The prospects for trapping the ylides with dipolarophiles are not good. Trapping of the carbonyl ylide derived from 66f and 66g using dimethylacetylenedicarboxylate as a dipolarophile was unsuccessful.

Table 16: Products From Thermolysis of 66g in C_6D_6

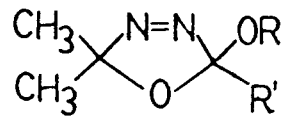
Product	^1H NMR (δ CDCl =7.27ppm)	M.S. (fragment$^+$, m/e)			
	H_a, 2.07 (s,3H) H_b, 2.85 (s,2H)	$C_4H_5F_3O$ $C_3H_2F_3O$ $C_2H_2F_3$	126 111 83	CF_3 C_2H_3O	69 43
	H_a, 2.17 (s,3H) H_b, 4.23 (s,2H)	$C_4H_5F_3O_2$ $C_3H_2F_3O_2$	142 127	$C_2H_2F_3O$ CF_3 C_2H_3O	99 69 43
	H_a, 1.86 (d,3H,J=6.0Hz) H_b, 2.07 (s,3H) H_c, 4.02-4.50 (m,4H) H_d, 5.83 (q,1H,J=6.0Hz)	$C_7H_{11}F_3O_2$ $C_4H_6F_3O_2$ $C_4H_6F_3O$ C_5H_9O	184 143 127 85	C_5H_8O C_3H_6O C_2H_3O	84 58 43
	H_a, 1.95 (s,3H) H_b, 2.03 (s,3H) H_c, 2.12 (s,3H) H_d, 4.55 (m,2H)	$C_7H_{11}N_2OF_3$ $C_6H_8N_2OF_3$ $C_4H_5NOF_3$	196 181 140	$C_5H_9N_2$ $C_2H_2F_3$ C_3H_6N	97 83 56
	H_a, 2.12 (s,6H) H_b, 4.50 (m,4H)	$C_8H_{10}N_2O_2F_6$ $C_8H_{10}N_2O_2F_5$ $C_7H_{10}N_2O_2F_3$ $C_6H_7N_2OF_3$ $C_4H_5NOF_3$ $C_2H_2F_3$	280 261 211 181 140 83		

R.D.11 KINETICS OF THERMOLYSIS OF VARIOUS OXADIAZOLINES

The rates of thermal decomposition of the various oxadiazolines in benzene at 80°C were followed by ^{1}H NMR spectroscopy using dichloromethane as an internal standard for peak height measurements. The ^{1}H NMR spectra were taken every 4 - 5 hours during the first half-life of the reaction and then every 5 - 10 hours. The reaction was followed to 75% completion. In order to take a reading the reaction was stopped by cooling the ^{1}H NMR tube in liquid nitrogen and the time outside the bath was not included. The rate constant was calculated by plotting the natural logarithm of the ratio of the peak area of the starting material to the peak area of the internal standard, versus time. The line which best fitted the data was found by the method of least squares. Evaluation of the slope of that line then gave the rate constant for the reaction. The reactions were found to obey first order kinetics. The results are shown in Table 17.

The rate constants for oxadiazoline 66 (R=CH_2CH_3) decrease as the R' substituent increases in size. It is known that steric strain is an important factor in the thermolysis of cis azo compounds. Heating these oxadiazolines leads to nitrogen and carbonyl ylides. The ground state conformation of the carbonyl ylide is the 0°,0° conformation. Hence, during the loss of nitrogen, the substituents must undergo conrotatory motion. Therefore, a sterically hindered system will decompose more slowly since large substituents will be forced closer together at the transition state. The rate of thermal decomposition of 66g is faster than that of 66f since the OCH_2CF_3 group is smaller than the OCH_2CCl_3 group.

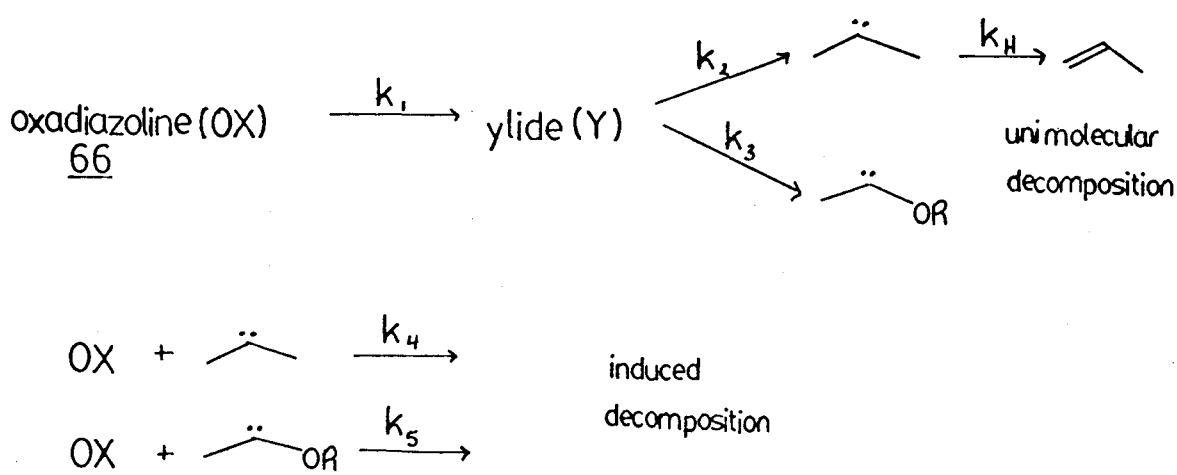
Table 17: Rate Constants For Thermolysis of Oxadiazoline 66 in C_6D_6 at 80°C



66

Oxadiazoline	Rate Constant (k)	$t_{1/2}$ (hrs)	Correlation Coeff.
66a, R=CH_2CH_3, R'=CH_3	$1.09\pm.03\times10^{-5}$ s^{-1}	21.1	.9991
66c, R=CH_2CH_3, R'=$CH(CH_3)_2$	$8.19\pm.03\times10^{-6}$ s^{-1}	23.5	.9966
66e, R=CH_3, R'=$C(CH_3)_3$	$3.62\pm.03\times10^{-6}s^{-1}$	53.1	.9998
66f, R=OCH_2CCl_3, R'=CH_3	$8.47\pm.03\times10^{-6}$ s^{-1}	22.7	.9969
66g, R=OCH_2CF_3, R'=CH_3	$1.12\pm.03\times10^{-5}$ s^{-1}	17.2	.9988

The oxadiazoline decomposes via two mechanisms, one involving unimolecular decomposition to the carbonyl ylide and the other involving carbene-induced decomposition, Scheme 12.



Scheme 12

A general rate equation for the decomposition of oxadiazoline 66 according to Scheme 12 can be written:

$$\frac{-d[OX]}{dt} = k_1[OX] + k_4[\ddot{\Lambda}][OX] + k_5[\ddot{\Lambda}OR][OX]$$

Steady state conditions for the ylide and for the carbenes must be assumed. That is the rate of disappearance of reactive intermediates must be equal to the rate of formation. The rate determining step must be the generation of the ylide (Y) from the oxadiazoline.

Steady-state equations:

$$\frac{d[\ddot{\Lambda}]}{dt} = k_2[y] - k_H[\ddot{\Lambda}] - k_4[\ddot{\Lambda}][OX] = 0$$

$$[\ddot{\Lambda}] = \frac{k_2[Y]}{k_H + k_4[OX]}$$

$$\frac{d[\ddot{\Lambda}OR]}{dt} = k_3[Y] - k_5[\ddot{\Lambda}_{OR}][OX] = 0$$

$$[\ddot{\Lambda}_{OR}] = \frac{k_3[Y]}{k_5[OX]}$$

$$\frac{d[Y]}{dt} = k_1[OX] - k_2[Y] - k_3[Y] = 0$$

$$[Y] = \frac{k_1[OX]}{k_2 + k_3}$$

Substitution of $[\ddot{\Lambda}]$, $[\ddot{\Lambda}_{OR}]$ and $[Y]$ into $\frac{-d[OX]}{dt}$ leads to:

$$\frac{-d[OX]}{dt} = k_1[OX] + k_4\left(\frac{k_2[Y]}{k_H + k_4[OX]}\right)[OX] + k_3[Y]$$

$$= k_1[OX] + \frac{k_4k_2k_1[OX]^2}{(k_H+k_4[OX])(k_2+k_3)} + \frac{k_3k_1[OX]}{k_2 + k_3}$$

$$= k_1(1 + \frac{k_3}{k_2+k_3+k_6})[OX] + \frac{k_4k_2k_1[OX]^2}{(k_H+k_4[OX])(k_2+k_3+k_6)}$$

Hence, the general rate equation for the thermal decomposition of oxadiazoline is shown in eq 84.

$$\frac{-d[OX]}{dt} = k_1[OX](1 + \frac{k_3}{k_2+k_3+k_6} + \frac{k_4k_2[OX]}{(k_H+k_4[OX])(k_2+k_3+k_6)}) \qquad [84]$$

Thermolysis of low concentrations of oxadiazoline will lead to kinetics that are first order in oxadiazoline, the second term in eq 84 will be negligible since the terms $[OX]^2$ and $k_4[OX]$ will be small. The rate constant observed will not be k_1, the rate of decomposition of the oxadiazoline to the ylide, but will be a composite of rate constants:

$$k_{obs} = k_1(1 + \frac{k_3}{k_2+k_3+k_6}).$$

That is, the decomposition of the oxadiazoline will be dependent on k_1, the rates of fragmentation of the ylide to give the carbenes, k_2 and k_3 and the rate of intramolecular rearrangement of the ylide, k_6.

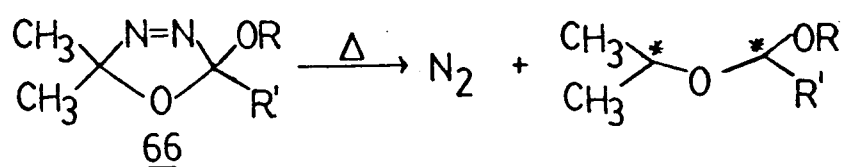
When looking at the rate of thermal decomposition for the series of oxadiazolines 66a - 66e, the fragmentation pattern of the carbon ylide must be considered. For example, the rate for 66e will be first order in oxadiazoline. Since fragmentation gives almost exclusively acetone and t-butylmethoxy carbene, the second term of eq 84 can be ignored since the pathways leading to the dimethyl carbene (k_2 and hence k_4) and the induced decomposition of 66e by dimethyl carbene (k_4) will not need to be considered (Scheme 12).

Since the kinetics of the thermal decomposition of the oxadiazolines in Table 17 were measured with dilute solutions of oxadiazolines

in benzene, the observed fit to first order kinetics is not surprising. In order to best determine the rate of decomposition of the oxadiazoline to the ylide, k_1, and to avoid interference from the carbene induced decomposition, the thermolysis should be carried out in a solvent such as CCl_4, where the carbenes will be scavenged before attacking oxadiazoline, as seen in R.D.10.1.3.

R.D.12 SUMMARY

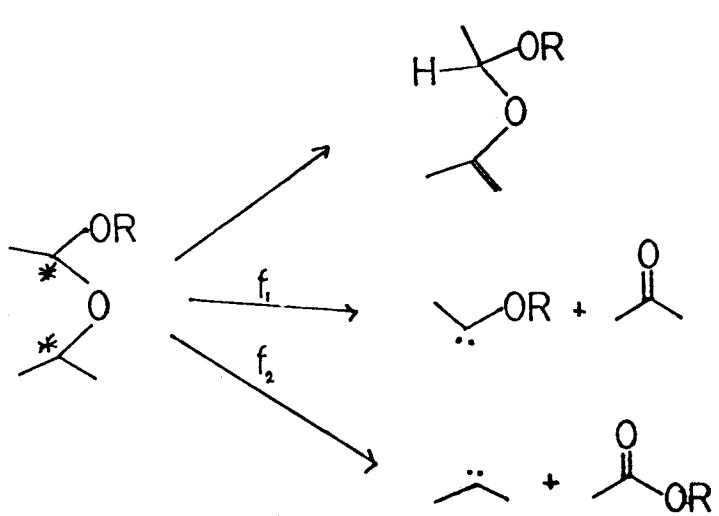
The thermolysis of an oxadiazoline of type 66 yields a carbonyl ylide intermediate, eq 85.



66

[85]

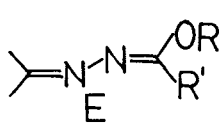
The carbonyl ylide intermediate can then undergo an intramolecular 1,4-hydrogen shift to yield an acetal product or it can fragment to form carbenes and carbonyl compounds, eq 86.



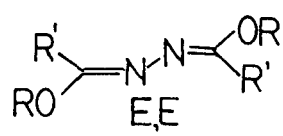
[86]

The fragmentation pattern was found to change when the substituent R' was changed. When R' was CH_3, the fragmentation pathways f_1 and f_2 occurred in approximately 1:1 ratio. As the size of R' increased, the fragmentation began to favour the f_1 pathway, until at R'=t-butyl the fragmentation occurred with almost exclusive formation of acetone and t-butylalkyl carbene (path f_1).

A new series of products, ester azines, were found in the thermolysis of these oxadiazolines (66). A carbene mechanism is proposed for the formation of these ester azines. The mechanism is supported by evidence that the formation of these azines is dependent on the initial concentration of starting material and on the availability of the carbenes. That is, as the fragmentation pattern of the carbonyl ylide changes to favour the formation of one carbene, the azines formed from that particular carbene are generated in higher yields.



68



69

The most stable configuration assigned to these azines was the E-configuration for 68 and the E,E-configuration for 69. Azines 68 and 69, where R'=Me, Et or iPr, were found to be uniconfigurational (E) while those with R'=tBu were found to be configurationally isomeric.

Changing R to OCH_2CCl_3 or OCH_2CF_3 in compound 66 does not stop the fragmentation of the ylide generated. The azines formed were also found to be uniconfigurational (E).

EXPERIMENTAL

E.1 INSTRUMENTAL

Proton magnetic resonance (^{1}H NMR) spectra were obtained from Varian's T-60 and EM-390, and Bruker's WP-80 and WH-250 instruments. Tetramethylsilane (TMS) was used as an internal standard. The chemical shifts are reported in δ values (ppm), followed by the multiplicity symbol in brackets (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

Mass spectra (MS) were recorded on a VG 7070 mass spectrometer (VG Micromass, Altricham, UK.). Samples were introduced via a direct insertion probe system or through a Varian model 3700 GC via a jet separator. The spectra were acquired and processed with the VG 2035 data system.

Preparative gas chromatography (GC) was performed on a Varian Aerograph instrument, model 920. Analytical GC was performed on a Varian, model 3700, instrument.

Melting points were determined on a Thomas Hoover capillary melting point apparatus, and are not corrected.

Bulb-to-bulb distillations were performed using a "T" joint attached to the vacuum line, a round-bottomed flask and a receiver flask.

The yields of the products of thermolysis of the oxadiazolines were calculated from ^{1}H NMR peak heights and from GC peak areas.

E.2 SYNTHESIS

E.2.1 Synthesis of Lead Tetraacetate (LTA)

The method used for the synthesis of lead tetraacetate was that of Fieser[111]. Acetic acid (400 ml) and acetic anhydride (267 ml) were mixed in a one litre, three-necked, round-bottomed flask, fitted with a mechanical stirrer and a thermometer. The mixture was heated to 55°C and stirred vigorously. Red lead oxide (467 g) was added in portions of 15-20 g over a period of 5 hours. A new portion was added only after the orange colour due to the preceeding portion had almost disappeared. The temperature of the reaction mixture was maintained between 55-60°C during these additions of red lead oxide. At the end of the additions, the reaction mixture was cooled to room temperature and then filtered. The lead tetraacetate collected was washed with cold acetic acid and then recrystallized from hot acetic acid (245 g, 81% yield). Lead tetraacetate was stored in a nitrogen-filled glove bag.

E.2.2 Synthesis of Hydrazones

a. Acetone-N-Acetyl Hydrazone

Hydrazine hydrate (200 g, 4 moles) was added dropwise to a solution of ethylacetate (300 ml) in ethanol (300 ml, 95%) in a three-necked, round-bottomed flask. The solution was refluxed for 48 hours, after which the ethanol was evaporated with a rotary evaporator ($\sim$ 20 Torr). The hydrazide was obtained from vacuum distillation of the residue (10 Torr, fraction collected between 140 and 150°C). Recrystallization from ethanol gave acethydrazide

of satisfactory purity; mp 65-66°C (literature [112]: 66-67°C), yield 72%. Spectral data: ^{1}H NMR ($CDCl_3$), δ1.90(s).

Acethydrazide (72 g, 1.0 mole) was dissolved in acetone (116 g, 2.0 moles), and the solution left stirring for 2 hours. Evaporation of the unreacted acetone with a rotary evaporator afforded crude hydrazone which was recrystallized from ethanol, (96 g, 87% yield) of satisfactory purity; mp 137.5-139°C. Spectral data are reported in Table 18.

b. Other Hydrazones

Acetone-N-ethyl hydrazone, acetone-N-isopropyl hydrazone and acetone-N-t-butyl hydrazone were synthesized by the same procedure as in (a). Recrystallization of the crude products from ethanol gave materials with the spectral data listed in Table 18.

Table 18: Acyl Hydrazones of Acetone $R'\overset{O}{\overset{\|}{C}}NHN=C(CH_3)_2$ a,b

Sample	Yield (%)	M.P. °C (lit.)	^{1}H NMR,δ ($CDCl_3$-TMS)
R'-CH_3 c	87	137.5-139 (139-140)[113]	Ha,1.87 (s,3H) Hb,1.97 (s,3H) Hc,2.20 (s,3H)
R'=CH_2CH_3 c a'	80	99-101 (105-106)[114] (101)[115]	Ha',1.15 (t,3H,J=7.2Hz) Ha,1.94 (s,3H) Hb,2.00 (s,3H) Hc,2.65 (q,2H,J=7.2Hz)
R'=$CH(CH_3)_2$ c a'	82	91-93 (92-96)[116]	Ha',1.13 (d,6H,J=6.2Hz) Ha,1.87 (s,3H) Hb,1.97 (s,3H) Hc,3.34 (septet,1H,J=6.2Hz)
R'=$C(CH_3)_3$ a'	55	69-70	Ha',1.20 (s,9H) Ha,1.85 (s,3H) Hb,1.97 (s,3H)

E.2.3 Synthesis of Alkoxyoxadiazolines

a. 2-Ethoxy-2.5.5-Trimethyl-Δ^3-1,3,4-Oxadiazoline (66a)

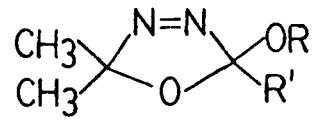
Lead tetraacetate (48.7 g, 0.11 mole) was dissolved in absolute ethanol (200 ml), giving a yellow coloured solution. Acetone-N-acetyl hydrazone (11.4 g, 0.10 mole) was added to the stirred solution while the temperature was maintained at 0°C. The discharge of colour was taken as evidence for the completion of the oxidation. At the end of the reaction, the lead diacetate biproduct was filtered off, and KOH pellets (10 g) were added to the filtrate to hydrolyze the acetoxyoxadiazoline biproduct. The solution was left stirring for 2 hours at 0°C. The solvent was then evaporated with a rotary evaporator and water was added. The aqueous solution was extracted with CH_2Cl_2. The organic layer was washed several times with H_2O, and then dried over Mg_2SO_4 (anhydrous). Evaporation of the solvent followed by a bulb-to-bulb distillation (10^{-2} Torr, room temperature) afforded pure ethoxyoxadiazoline (9.1 g, 58% yield). Spectral data are in Table 19.

b. Other Oxadiazolines

Oxadiazolines 66b, 66c, 66d and 66e were synthesized and purified by the procedure described above. Spectral data are in Table 19.

2-[2,2,2-Trichloroethoxy]-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (66f) and 2-[2,2,2-trifluoroethoxy]-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (66g) were also synthesized by the method described above. The crude products were purified using a packed basic alumina column, which was eluted with a 50% ethyl acetate in petroleum ether solution. The oxadiazolines eluted first. Spectral data are also in Table 19.

Table 19: ALKOXYOXADIAZOLINES (66)



66

SAMPLE	YIELD (%)	^{1}H NMR (δ, $CDCl_3$/TMS, ppm)
66a R=CH_2CH_3 R'=CH_3	58	1.17 (t,3H, J-6.0 Hz); 1.40 (s,3H); 1.60 (s,6H); 3.20 (m,2H, J-6.0 Hz)*
66b R=CH_2CH_3 R'=CH_2CH_3	58	1.00 (t,3H,J=6.0Hz);1.17(t,3H,J=7.0Hz) 1.41 (s,3H); 1.51 (s,3H); 1.60-2.06 (m,2H)*;2.93-3.54(m,2H)*
66c R'=CH_2CH_3 R'=$CH(CH_3)_2$	57	1.20 (t,3H,J=6.8Hz);1.20(dd,6H);1.55(s,3H) 1.65 (s,3H);2.12(m,1H);3.32(m,2H,J=6.8Hz)*
66d R'=CH_3 R'=$CH(CH_3)_2$	53	1.09(d,3H,J=6.9Hz);1.13(d,3H,J=6.9Hz); 1.50(s,3H) 1.69*s,3H);2.03(m,1H);3.13(s,3H)
66e R=CH_3	50	1.02(s,9H);1.54(s,3H);1.60(s,3H);3.01(s,3H)
66f R=CH_2CCl_3 R'=CH_3	49	1.50(s,3H);1.60(s,3H);1.73(s,3H); 3.87(dd,AB,2H,J-9.0Hz)
66g R=CH_2CF_3 R'=CH_3	52	1.56(s,3H);1.69(s,3H);1.76(s,3H); 3.64(m,2H)**

* complex coupling due to diastereotopism

** coupling to ^{19}F (I = 1/2)

E.3 THERMOLYSIS OF OXADIAZOLINES

E.3.1 Thermolysis in C_6D_6

A solution of the appropriate oxadiazoline in benzene (1-3M, .3 ml) and CH_2Cl_2 (1 drop) were mixed together in a medium-walled ^1H NMR tube. After three cycles of degassing, at liquid nitrogen temperature, and thawing at room temperature, the tube was sealed under vacuum (10^{-2} Torr). The thermolysis was carried out in a constant temperature oil bath, maintained at 80.0°C ± 0.2°C, for at least six half-lives. A half-life ranged from 7×10^4 s for oxadiazoline 66a to 2×10^5 s for oxadiazoline 66c. At the end of the thermolysis, the tube was opened and the contents were separated by preparative gas chromatography. The reaction mixture was injected into an 10% OV-17 column (6', .25" OD, flowrate 30ml/min) using a temperature program that increased the column temperature from 40°C to 200°C at a rate of 5°C per minute. The different products were collected and ^1H FT-NMR spectra were obtained. The major products eluted in the following order: propene, acetone, benzene, ester, acetal, acetone azine (67), 68 and 69. Mass spectra of each eluent were obtained (GC-MS). The yields were calculated from the integrals of the ^1H NMR peaks, by normalizing the integrals with respect to that of internal standard, CH_2Cl_2.

E.3.2 Thermolysis in CD_3OD

The thermolysis of oxadiazolines 66f and 66g were carried out in methanol. Oxadiazoline (25 mg), methanol-d_4(.3ml) and benzene (1 drop) were mixed together in a medium-walled ^1H NMR tube. After

three cycles of degassing at liquid nitrogen temperature, and thawing at room temperature, the tube was sealed under vacuum (10^{-2} Torr). The thermolysis was carried out in a constant temperature oil bath, maintained at 80.0°C, for 8 days. At the end of the reaction, the products were not separated, but their structures were deduced from the ^1H NMR spectrum of the mixture. The yields were calculated from integration of the ^1H NMR peaks, normalizing the integrals, using C_6H_6 as internal standard.

E.4 EQUILIBRATION STUDIES OF ESTER AZINES

Samples of 68 and 69 were collected from the gas chromatograph, dissolved in DMSO-d_6 and sealed into ^1H NMR tubes. The ^1H NMR spectrum was recorded at three different temperatures, first at the ambient probe temperature (305K) of a Bruker WP-80 spectrometer and then at 353K and 393K. Samples were left at a given temperature until after the composition had become constant. If the composition of the sample did not change, it was left for at least two hours at 393K. Chemical shifts in DMSO-d_6, relative to the solvent lock signal at δ2.55 ppm, are listed for 68e and 69e.

68e (E), 1.27(s,9H), 1.91(s,3H, 1.99(s,3H), 3.67(s,3H);

68e (Z), 1.19(s,9H), 1.86(s,3H), 1.99(s,3H), 3.90(s,3H);

69e (E,E), 1.35(s,18H), 3.71(s,6H);

69e (E,Z), 1.21(s,9H), 1.33(s,9H), 3.71(s,3H), 4.06(s,3H);

69e (Z,Z), 1.21(s,18H), 4.04(s,6H).

The isomer ratios for 68e and 69e were found from the integration ratios of the methoxy signals.

E.5 KINETIC STUDIES

The oxadiazolines (25 mg) and CH_2Cl_2 (1 drop) were dissolved in the solvent (0.3 ml, C_6D_6 or CD_3OD). The solutions were transferred to NMR tubes which were put through three freeze-pump-thaw cycles (vacuum line pressure 10^{-2} Torr) prior to sealing.

The thermolysis was performed in a controlled temperature oil bath, at 80.0 ± 0.2°C. The reactions were monitored by following the decrease in the integrals of the methyl signals (at C-5) in the ^1H NMR spectrum which was obtained from Varian's EM-390. The time outside the bath was not counted and the reactions were followed to, at least, 75% of completion.

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