AZOMETHINE YLIDES FROM Δ^1-1,2,4-TRIAZOLINES AND ALLYLAMINOMALEATES FROM REACTIONS OF ALLYLAMINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

By

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AZOMETHINE YLIDES AND ALLYLAMINOMALEATES

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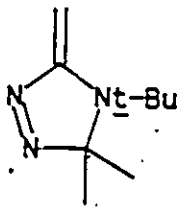
ABSTRACT

The major portion of this thesis deals with the chemistry of 5-t-butyl-3,3-dimethyl-5-methylene-Δ^1-1,2,4-triazoline (94) and its derivatives. Triazoline 94, formally also an enamine and an azo compound was treated with several substrates in attempts to synthesize new Δ^1-1,2,4-triazolines suitable for the generation of azomethine ylides.

When 94 was treated with heterocumulenes or simple Michael acceptors such as acrylonitrile, the products included highly substituted aziridines (e.g., 109), simple Michael addition products which contain the skeleton of 94, and in one instance, an azabicycloheptene. The reaction of 94 with more-substituted Michael acceptors, methacrylonitrile and methyl methacrylate, yielded 2-t-butyl-iminopyrrolidine derivatives.



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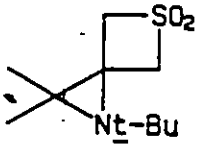

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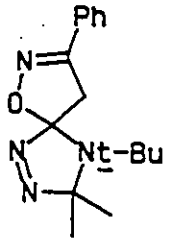
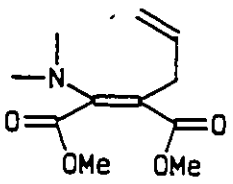


129a



177a

Spirotriazolines (e.g., 129a) were isolated from the reaction of 94 with benzonitrile oxide and diphenylnitrilimine. The thermal decomposition of these spiro species was found to follow the first order rate law. Treating 94 with phenyl azide and p-nitrophenyl azide provided spiro triazolines whose thermal decomposition involved the loss of two moles of molecular nitrogen.

An analog of 94, bearing a fumarato substituent on the exocyclic double bond was found to rearrange to a highly-substituted pyrrole when heated in MeOH. Another analog of 94, this species bearing an anilido substituent on the exocyclic double bond, was found to lose nitrogen with first order kinetics when heated in MeOH or C_6H_6.

In a separate study, allyldimethylaminomaleates (e.g., 177a) resulted from the reactions of allyldimethyl amines with dimethyl acetylenedicarboxylate. The maleates are believed to arise from initial zwitterion formation followed by intramolecular allyl transfer via a cyclic 6-membered transition state.

ACKNOWLEDGEMENTS

This thesis would be incomplete without thanking several of the people who helped me over the years.

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CHAPTER ONE

INTRODUCTION

Research in organic chemistry can be segregated into two major components. Physical organic chemistry is the study of how organic processes proceed while synthetic organic chemistry involves the preparation of interesting and/or useful compounds.

Synthetic organic chemistry too can be divided into two segments. There is the discovery of new reactions and methodology, divorced from specific synthetic goals. A result of this type of research is the extremely useful Wittig reaction.[1,2] The other element is the use of these reactions and methodologies in the synthesis of novel compounds and natural products. The landmark synthesis of vitamin B_{12} is a good example.[3]

Natural product syntheses are now being carried out by means of three principal types of key reactions. Ionic reactions are perhaps the most common and are also the oldest. Robinson's syntheses of tropinone[4] and ɣ-pelletierine[5] illustrate both the effectiveness and the age of this methodology. The work of Diels and Alder[6,7] and subsequently that of Huisgen[8] have brought the use of cycloaddition chemistry to light. One famous case is the first-step of the laboratory preparation of reserpine.[9] More recently, radicals[10] and in particular their intramolecular cyclizations have proven useful in synthesis.[11]

The work about which this thesis has been written was carried out in order to:

1. extend the knowledge regarding the reactivity of and synthetic routes to azomethine ylides,

2. learn more about heterocyclic ring transformations and the rules that govern them,

3. broaden the knowledge regarding the structures and reactivities of the zwitterionic intermediates proposed when nucleophiles add to Michael acceptors and heterocumulenes.

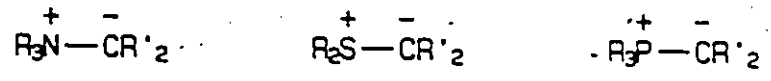
Each investigation was performed in order to make available more chemical knowledge for future synthetic pursuits by others.

The purpose of this introduction is to familiarize the reader with some of the research already published in these fields and to ensure that the reader has a suitable background in the chemistry utilized to carry out these studies. In the foregoing subdivisions, the aforementioned aspects and applications of 1,3-dipolar cycloadditions and the methods of generating azomethine ylides will be addressed.

1,3-Dipolar Cycloaddition Chemistry

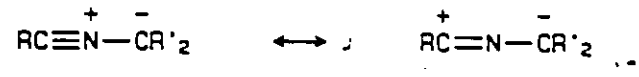
Morris defines ylides as "compounds in which a carbanionic centre is bonded to a heteroatom which carries a positive charge".[12] This strict definition has subsided somewhat, however, and the anion centred atom need not be restricted to carbon; nitrogen, sulfur, and oxygen can bear the negative charge also. The identity of the positively charged centre is not limited under Morris' definition.

Initially, ylides were generated by the deprotonation of a carbon atom adjacent to an "anion" site. Often the formation of ammonium (1), sulfonium (2) and phosphonium (3) ylides is a facile process. The heteroatom need not



1 2 3

always be sp^3 hybridized. Ylides 4 and 5 are examples where the heteroatom is unsaturated. Ylides of this type are also called 1,3-dipoles because they also bear charge at atoms situated in a 1,3-relationship (4b and 5b).



4a 4b

5a 5b

Numerous examples of 1,3-dipoles are known. Table 1 lists several of these.[8,13,14] Dipoles of this latter type can be divided into two types depending on the degree of substitution (Table 1). The propargyl-allenyl

type contains a π-bond perpendicular to the ylide molecular orbitals and is usually linear. The allyl type is lacking this additional π-bond and is therefore a bent species. Figure 1 provides representations of each of these dipoles.

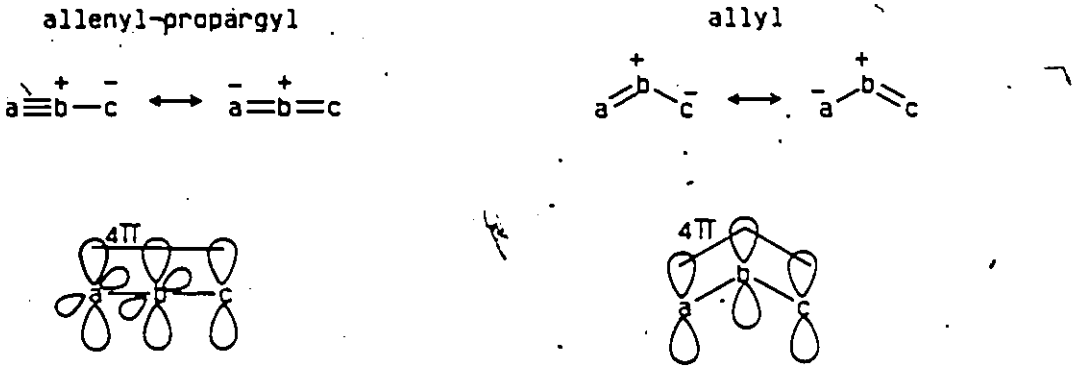


Figure 1. The Two Types of 1,3-Dipoles

The dipoles of the allyl type have more resonance contributors than indicated in Table 1 and Figure 1. Figure 2 illustrates how both termini may bear positive or negative charge. Thus, the dipole is capable of displaying electrophilic or nucleophilic character. Analysis of the propargyl-allenyl species shows that these ylides too may have ambivalent attributes.

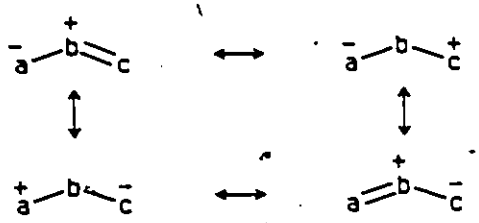
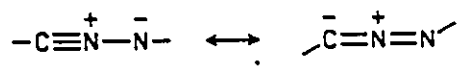
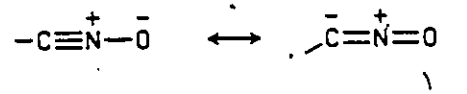
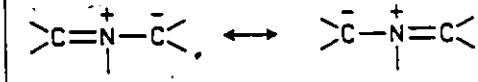
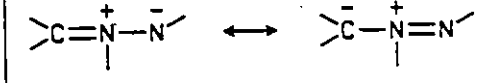
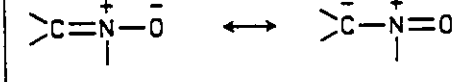
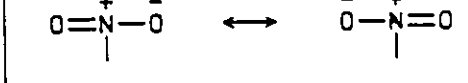
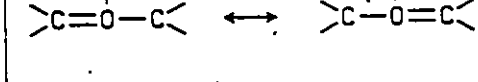
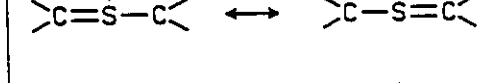
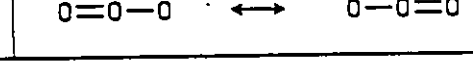
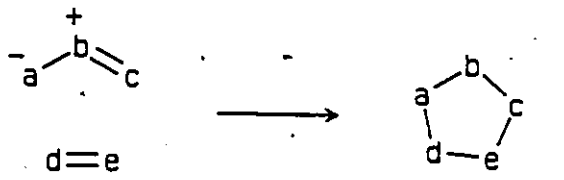


Figure 2. Resonance Structures of 1,3-Dipoles

The most powerful utility of 1,3-dipoles is heterocyclic synthesis via a 1,3-dipolar cycloaddition[13,15-17] (Scheme 1).

Table 1: Examples of 1,3-dipoles

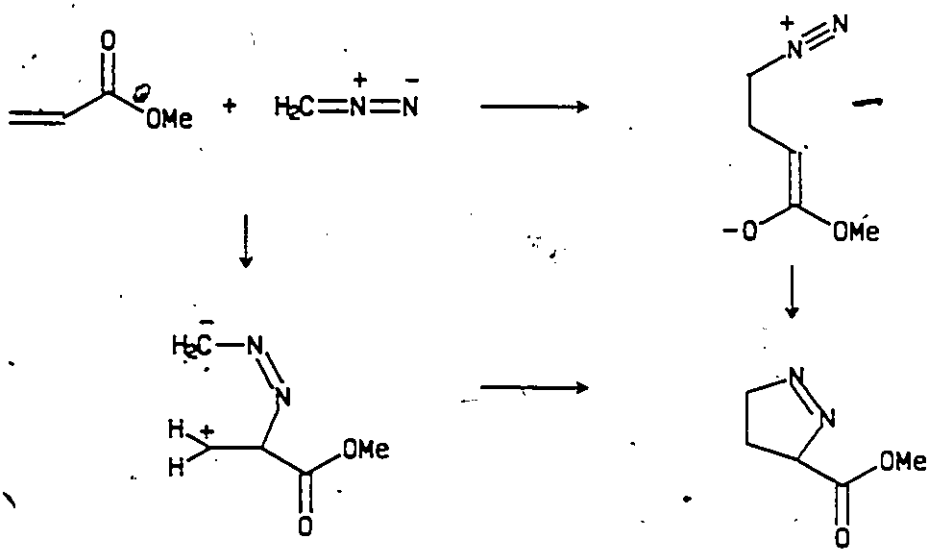
type of ylide	structure	common name
allenyl-propargyl		nitrile ylide
		nitrilimine
		nitrile oxide
		diazoalkane
		azide
allyl		azomethine ylide
		azomethine imine
		nitrone
		nitro compound
		carbonyl ylide
		thiocarbonyl ylide
		ozone



Scheme 1

The initial report of a 1,3-dipolar cycloaddition is thought[14] to be that by Buchner who in 1888[18] treated ethyl diazoacetate with α,β-unsaturated esters. The first review compiling these types of reactions was by L.I. Smith[19] in 1938. In that article, the "1,3-addition" chemistry of diazo compounds, azides, nitrones and nitrile oxides was updated.[19] The review did not provide the initiative for further research, though. Smith failed to recognize the difference between HX addition across a dipole and olefin addition to give a cyclic product.

Huisgen's review[20] in 1955 summarized diazoalkane chemistry and he readily accepted the notion that diazoalkanes add to olefins in a stepwise manner. Scheme 2 shows the two possible stepwise pathways.



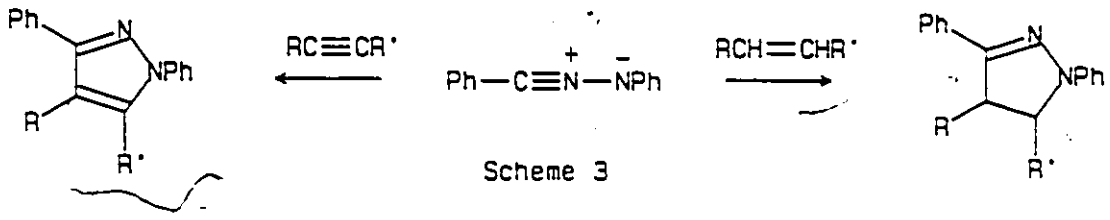
Scheme 2

When Huisgen's two further reviews appeared in 1963,[8] the chemistry world had a compilation of the utmost importance. The first paper summarized several examples of each type of ylide known to give 1,3-cycloadducts. The second article detailed the kinetics and mechanism of the cycloadditions. Observed reactivity ratios, regiochemistry and the effects of solvent and substituents were all explained. An encounter requiring molecular orbital overlap and the simultaneous formation of two σ-bonds was the mechanism that best accounted for the experimental data.[8]

Since then, research regarding azomethine ylides, azomethine imines, nitrile ylides, and diazoalkanes has been summarized in the two volume monograph edited by Padwa[13] and published in 1984. This compilation contains chapters on all ylides capable of undergoing 1,3-dipolar cycloadditions.

Amoung the many distinguishing characteristics of these cycloadditions is their early transition state. This is the strongest argument supporting the concerted nature of the reaction.[22] One would expect that a two step cycloaddition would have a later transition state, not unlike the structure of a diradical or dipolar intermediate.

Included in the experimental evidence for an early transition state is the addition of diphenylnitrilimine to olefins and acetylenes to give non-aromatic 2-pyrazolines and aromatic pyrazoles respectively (Scheme 3). Table 2 contains the rate constants for the cycloadditions indicated in



Scheme 3

Scheme 3. Addition to olefins is indeed faster than to the acetylenes. This must imply an early transition state.[23] There is insufficient development of aromatic character in the transition state for this to provide a driving force for the reaction. Any π-overlap is outweighed by other rate determining parameters. The Hammond postulate[24] states that the transition state is similar to starting materials in highly exothermic reactions such as these. There are other examples

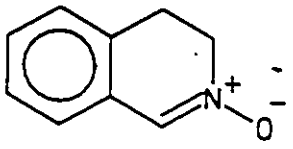
Table 2: Rate Constants for Diphenylnitrilimine Addition to Substituted Olefins and Acetylenes

R,R'	$10^6 k_{rel}$ (C_6H_6, 80°C)	
	RC≡CR'	RHC=CHR'
CO_2CH_3, CO_2CH_3	80	287
H, CO_3CH_3	5.8	48
H, Ph	0.12	1.6
Ph, CO_2CH_3	0.20	2.8

of ylides displaying similar reactivity tendencies.[25,26,27] The possibility that the aromaticity is a compensating effect making up for large inherent reactivity difference between acetylenes and olefins was precluded by the determination that similar relative rate constants are obtained when the aromatic transition state question is not applicable.[28]

More evidence supporting an early transition state is the relatively minor disruption of aromaticity during the cycloaddition reaction of an aromatic dipole. Cyclic nitrones 6 and 7 undergo cycloaddition with ethyl crotonate at different rates.[29] Isoquinoline N-oxide 7 reacts 36,000 times

more slowly than dihydroisoquinoline N-oxide 6. This is attributed to partial loss of aromaticity of 7 in the cycloaddition transition state. In similar examples benzonitrile oxide added to cyclopentadiene 930 times faster than to furan.[30] The authors suggest a 15-25% disruption of aromaticity at the transition state.[30]



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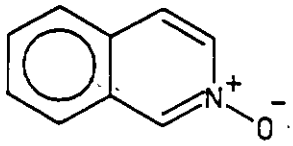

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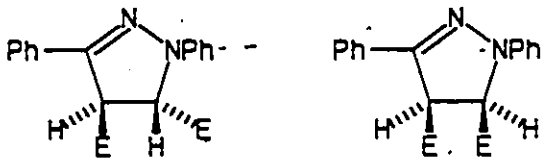
Another distinguishing feature of 1,3-dipolar cycloadditions is the small dependence of the reaction rate constants on the solvent. Cycloadditions of phenyldiazomethane to ethyl acrylate and to norbornene were carried out in twelve different solvents.[31] For ethyl acrylate the rate constants increase by a factor of six on going from CCl_4 to butanol and for norbornene the range is 1.8 with no correlation to solvent polarity.[31] This low solvent dependence is in keeping with the proposed early transition state for these cycloadditions.

The question of stepwise or concerted cycloadditions has been a major topic of discussion between Huisgen[8,22,33] and Firestone[33-36] over the last few decades. The fact that these reactions proceed with high stereospecificity is the major argument in favour of the concerted mechanism. Most cycloadditions proceed with stereospecificity to the extent of the detection limits.[32] Any stereochemical leakage in the cycloadditions has been attributed to artifacts of the experimental procedure. For example the

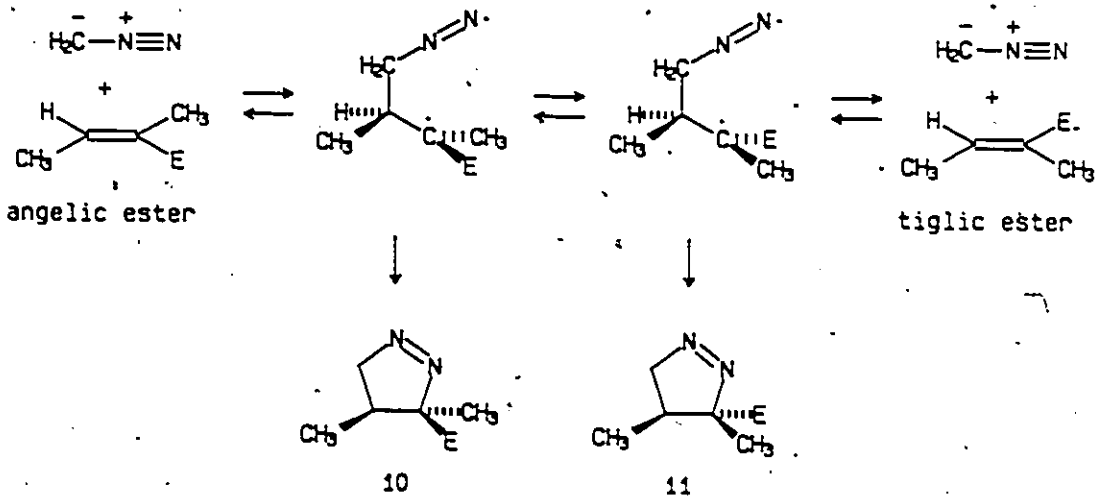
addition of diphenylnitrilimine to fumaric and maleic esters gave 99% and 93% of adducts 8 and 9 respectively.[37] It was subsequently determined that



8 9

the triethylamine employed to generate the ylide was isomerizing 9 to 8 when maleate was the dipolarophile. The use of dimethyl 2,3-dimethylfumarate and its isomeric maleate led to stereospecific cycloadditions.[37]

One experiment has been done to determine the degree of stereospecificity in these reactions. The addition of diazomethane to methyl tiglate and methyl angelate proceeds with 99.997% and 99.94% retention of dipolarophile configuration (Scheme 4).[38] Reaction mixture analysis by gas chromatography revealed one isomer. The subsequent addition of small



angelic ester tiglic ester

10 11

Scheme 4 (E=CO_2Me)

amounts of the other isomer revealed the detection limits of the instrument. The presence of 30 ppm of 10 in 11 gave rise to a noticeable signal. Therefore, the stereospecificity in formation of 11 must exceed 99.997%. Similarily, adduct 10 contains less than .06% of 11. The plausibility of rotation of biradical intermediates (Scheme 4) is discussed in terms of energetics and such rotation is considered unlikely.[38]

It should be noted that stereospecific cycloaddition does not verify a concerted mechanism. The absence of this specificity would rule out a concerted mechanism. In light of this the first example of a non-concerted 1,3-dipolar cycloaddition has recently appeared.[39] The reaction of two thiocarbonyl ylides with dimethyl 2,3-dicyanofumarate gave a mixture of cis and trans cycloadducts in each instance.[39] The authors assumed a zwitterionic intermediate. Such an intermediate has been intercepted when the dipolarophile was tetracyanoethylene.[40]

1,3-Dipolar cycloadditions have reasonably characteristic Eyring parameters. Values of $\Delta S^{\ddagger}$ range from -22 to -39 eu and its contribution to the free energy of activation is often quite significant.[14] These values are consistent with the expected ordering required for the approach of the two reactive species. Values of $\Delta H^{\ddagger}$ are usually 7 to 20 kcal mol^{-1}. These low values indicate that little rehybridization has taken place in the transition state, thus, providing more evidence in favour of its "early" nature.[14]

The last points to be addressed in this section are concerned with the regioselectivity and reactivity of the cycloaddends. Frontier Molecular Orbital (FMO) theory[41] splendidly explains the observed reactivities.[42-46]

The rates of reactions were found to be related to the energy difference between the highest occupied molecular orbital (HOMO) of one reacting species and the lowest unoccupied molecular orbital (LUMO) of the other. Sustmann[42,43] observed three types of cycloadditions (Figure 3). Those that are LUMO(dipolarophile)-HOMO(dipole) controlled are labelled Type I. Type III reactions occur when the LUMO(dipole)-HOMO(dipolarophile) is the dominant interaction and Type II is the designation assigned to those instances where the energy levels are similar and both HOMO(dipole)-LUMO (dipolarophile) and LUMO(dipole)-HOMO(dipolarophile) interactions may

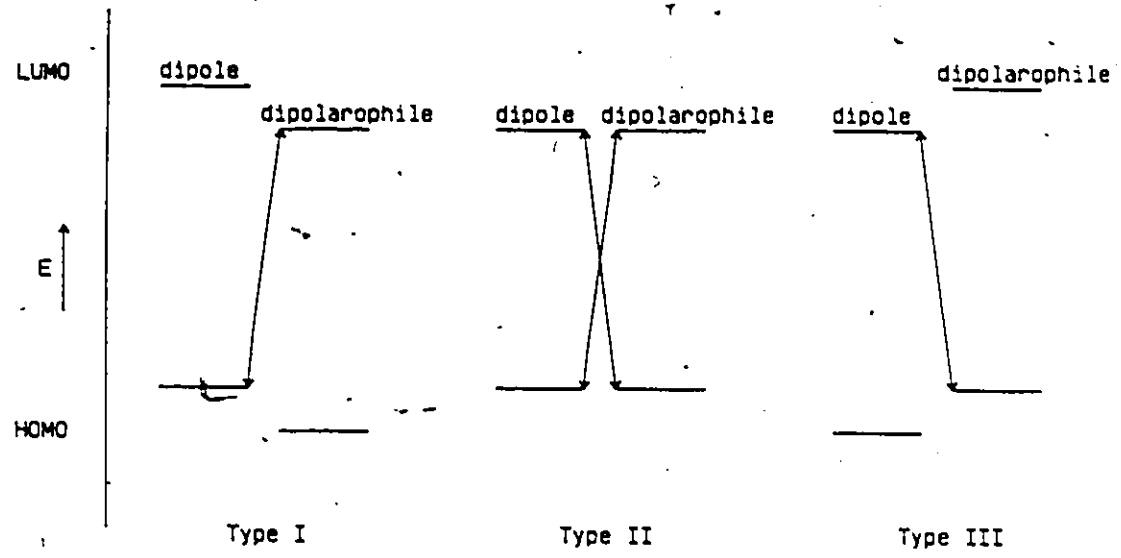


Figure 3. Sustmann's Classification of 1,3-Dipoles[42,43]

control reactivity. The dominant interaction is that which is the lowest energy pathway, as indicated by the arrows in Figure 3.

The relative HOMO/LUMO energy levels of a given species can be varied by changing substituents. The influence of substituents is similar for both

dipoles and dipolarophiles. Extra conjugation raises the HOMO energy and lowers the LUMO, electron-withdrawing groups lower the energy of both the HOMO and the LUMO and electron donating groups raise both HOMO and LUMO energy levels.

Once the HOMO-LUMO interaction controlling the reaction has been identified, then analysis of regiochemistry is simplified. The size of the lobes of the interacting frontier orbitals, as given by their coefficients, is employed to explain regiochemistry. The most efficient interaction is attained when two large lobes (large coefficients) overlap to make one bond and two smaller lobes (small coefficients) overlap to make the other bond. Representation a) of Figure 4 exemplifies a proper interaction of orbitals which will lead to a reaction. Representation b) demonstrates inefficient overlap which will not lead to a reaction. Again substituents have an influence on both dipole and dipolarophile; they prejudice the size of the orbital coefficients.

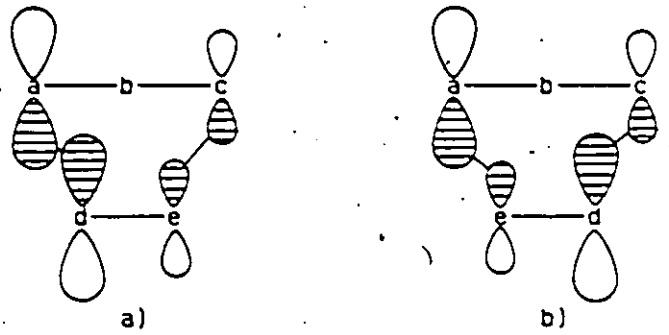


Figure 4. Modes of Orbital Overlap for 1,3-Dipolar Cycloadditions

Frontier molecular orbital characteristics are not the sole determinant for the course of these cycloadditions. Steric factors are also involved, although not as significantly as was once believed.[23] Examples of

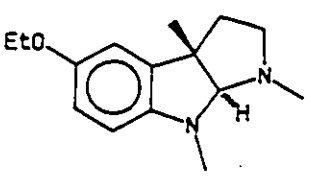
steric hindrance causing large changes in reaction rates[47,48] and regiochemistry[48-50] have been found and the steric factors involved in diazoalkane cycloadditions have been studied thoroughly.[48]

There are countless methods of generation of 1,3-dipoles and many reactions other than cycloadditions.[13] The preceeding summary is to demonstrate the more important aspects of 1,3-dipolar cycloaddition chemistry. A chapter illustrating the synthesis and uses of the very topical azomethine ylides follows.

Generation of Azomethine Ylides

The recent rise in value of azomethine ylides as synthetic precursors is evident by considering some natural products recently derived from them (e.g., 12[51], 13[52], 14[53]). Since the initial generation of an azomethine ylide of the type 15 by way of a pyridinium ion, several reviews have appeared describing the evolution of the different methods of synthesizing such ylides.[54-59]

Early work by Krohnke[60,61] led to the discovery of pyridinium ylides (eg, 15). They were prepared by deprotonation of a pyridinium ion or in general via deprotonation of an iminium salt.



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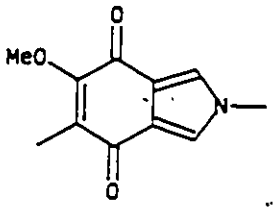

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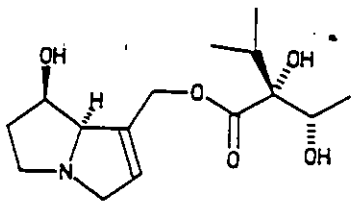

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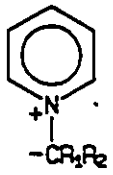

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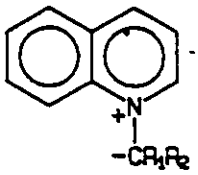

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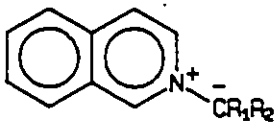

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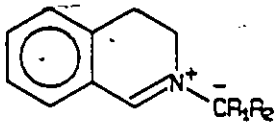

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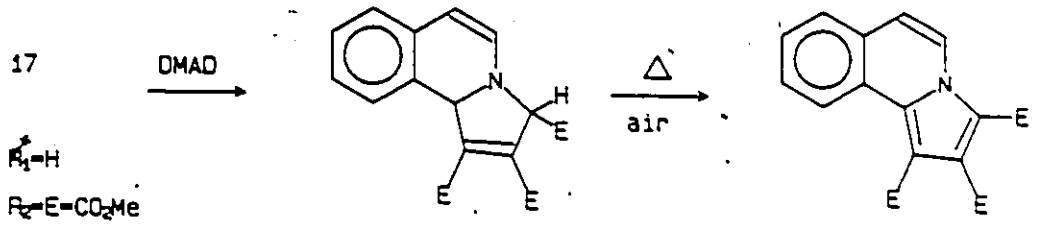
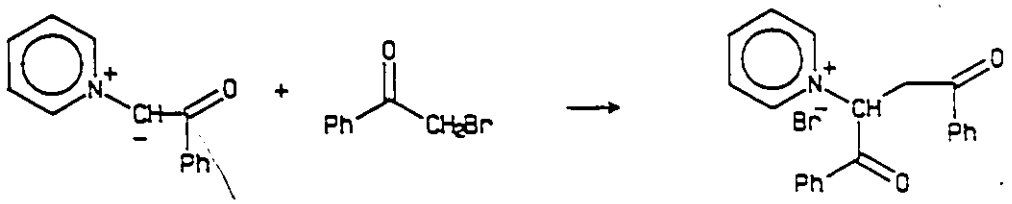


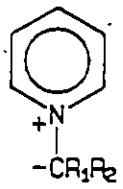
Scheme 5



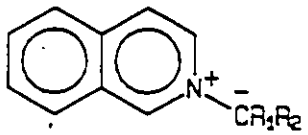
Scheme 6

Aromatic ylides 15, 16 and 17 and their dihydro analogues 18 undergo 1,3-dipolar cycloaddition with suitable dipolarophiles[60-64] (Scheme 5, DMAD = dimethyl acetylenedicarboxylate) and in some cases air oxidation is sufficient to re-aromatize the ring system. In other instances Pd/C, chloranil, or dicyanodichloroquinone are required to achieve the purpose.

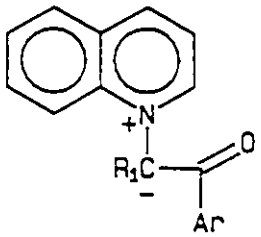
1,3-Dipolar cycloadditions are not the exclusive reaction of these ylides.[65-67] They have been shown to act as nucleophiles also[66] (Scheme 6). When ylides derived from heteroaromatic precursors undergo cycloaddition, the aromaticity must be disrupted. From the examples, this obviously occurs in some instances. Presumably, the exocyclic anionic portion of the ylide acts as a nucleophile in other cases because of the stability of the positive nitrogen in the heteroaromatic system. This stabilizing effect can be sufficiently significant to allow the isolation of some of these ylides (eg, 19,20,21).[68-70]



19 R_1=CN
R_2=CN, $CONH_2$, $COCH_3$



20 a) R_1=CN
R_2=CN, $CONH_2$, $COCH_3$
b) R_1=H, R_2=CO_2Et

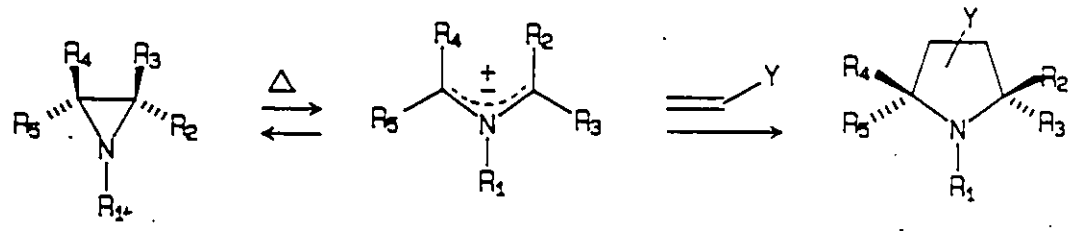


21 R_1=H
Ar=pBrC_6H_4, p$C_6H_5C_6H_4$

The iminium ion deprotonation procedure is not restricted to heterocyclic species. Deyrup and coworkers[71-73] have tried to develop the

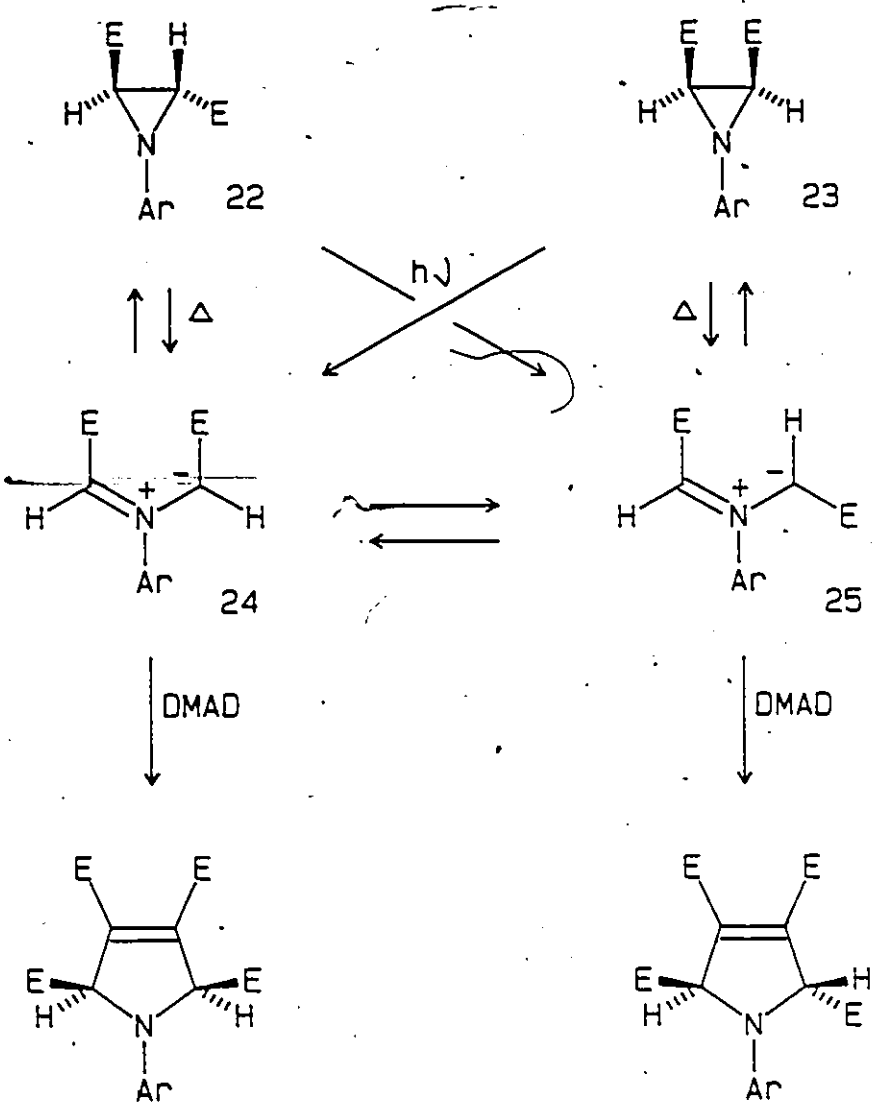
methodology for deprotonation of a simple iminium salt. This met with failure in terms of product formation by 1,3-dipolar cycloaddition. Recovered were aziridines from ring closure of ylides,[71] various dimers from the reaction of two ylides,[72,73] and products from the reaction of ylides with starting materials.[72,73] Although cycloadditions have been achieved,[74] the method is poor because of competing side reactions. Whereas a weak base such as triethylamine is sufficient to deprotonate a pyridinium salt, stronger bases are required for the task with non-heteroaromatic salts. These strong bases destroy dipolarophiles.[75] When a reaction does proceed with the iminium salt, the base may add to the iminium carbon or deprotonate from the wrong position to give an enamine, both in competition with ylide generation.

Obviously, the generality of the iminium deprotonation procedure is limited, so other methodology had to be found. One such mode of azomethine ylide generation, applicable to a greater number of systems, is the electrocyclic ring opening of aziridines, e.g., Scheme 7.



Scheme 7

Initially discovered independently by Padwa and Hamilton[76] (R_1,R_3,R_5=H; R_2=Ph; R_4=COPh) and Heine and Peavy[77,78] (R_1=pBrC_6H_4 or Ph; R_3,R_5=Ph; R_2,R_4=H), these reactions proceed in high yield (80-92%) when a



Ar=p-$CH_3C_6H_4$

E=CO_2Me

Scheme 8

dipolarophile and the aziridine are refluxed in benzene for 11-18 hours.[76-78] The reaction is extremely dependent upon the carbon substituents of the ring. Thus, at least two phenyl groups or one carbonyl derived substituent are required for sufficient activation toward ring opening.

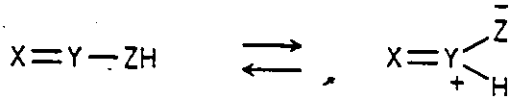
Huisgen rigorously determined[79-82] that the ring opening of cis and trans aziridines is in accord with predictions by Woodward and Hoffmann[83] (Scheme 8). Thus trans-aziridinedicarboxylic ester 22 undergoes thermal conrotatory ring opening to give 24 and photochemical disrotatory opening resulting in 25. Similarly the cis isomer aziridine 23, opens thermally to 25 and photochemically to 24.

After initially determining that stereospecific cycloaddition took place,[79] Huisgen and coworkers obtained kinetic data for the 24/25 isomerism as well as for the thermal and photochemical ring opening. The activation energy required to open 22 and 23 is approximately 29 kcal/mol while for the 24 to 25 interconversion it is 22 kcal/mol. Closure of 24 and 25 to their respective aziridines has a barrier of 21 kcal/mol.[81]

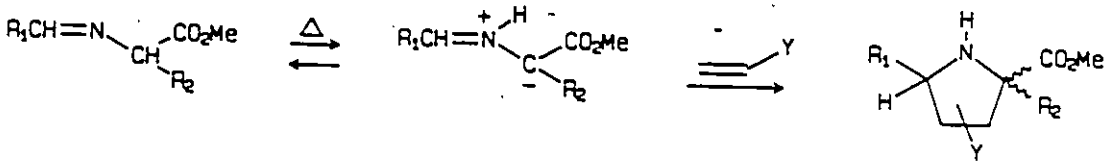
After a surge of papers regarding this aziridine ring opening method, fewer have appeared in recent years. Deyrup has tabulated many examples in a 1983 review.[84] The first intramolecular dipolar cycloaddition employing this methodology was reported by Padwa and Ku.[85] Recently, two groups have independently achieved intramolecular cycloaddition onto an unactivated olefinic side chain.[86,87]

Grigg and coworkers have shown that prototropic systems, such as the general case in Scheme 9,[88-90] could be utilized to generate transient

azomethine ylides suitable for trapping via 1,3-dipolar cycloaddition. Scheme 10 depicts how such a cycloaddition proceeds when an imine is heated in a non-polar solvent in the presence of a trap.[88,90,91] This chemistry has been successfully extended to intramolecular cycloadditions to give



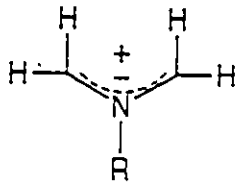
Scheme 9



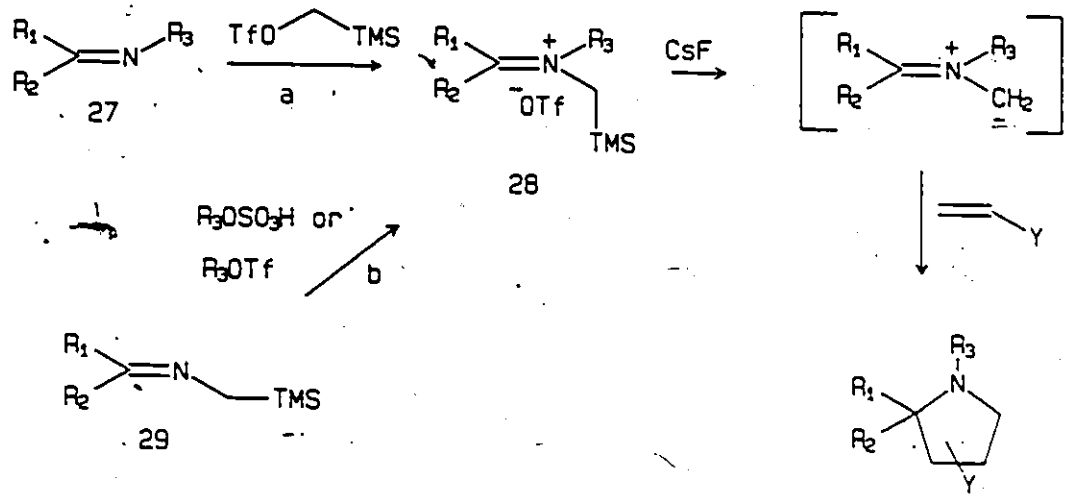
Scheme 10 (Y=CN, CO_2Et)

assorted heterocyclic ring systems.[92] This prototropy has also been found to exist with copper(II), zinc(II) and cadmium(II) complexes of imines.[93]

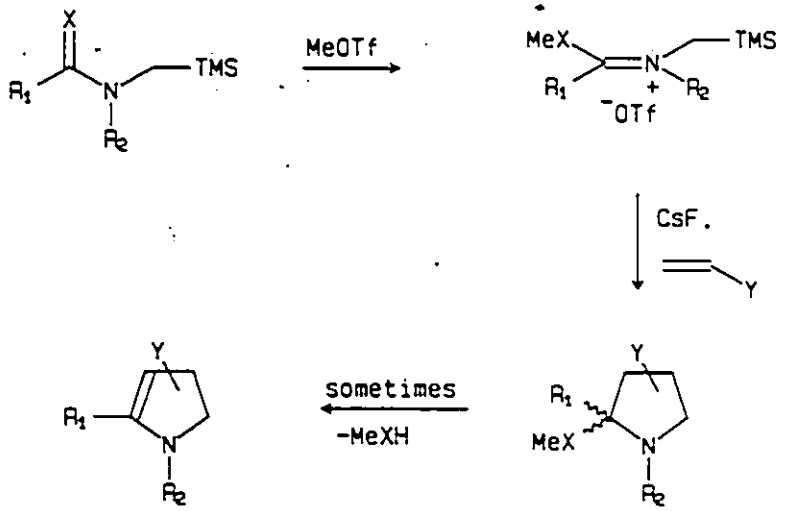
The use of aziridines and prototropic shifts for azomethine ylide generation is limited to systems having electron delocalizing substituents. Such methods are not applicable for a simple ylide such as 26. The use of silicon compounds and desilylating agents solves this problem rather effectively.[94,95] Thus, treatment of an imine (e.g., 27) with trimethylsilylmethyl triflate (Me_3SiCH_2OTf) leads to a silylated iminium salt (28; Scheme 11; path a)). Subsequent treatment of 28 with a desilylating



26

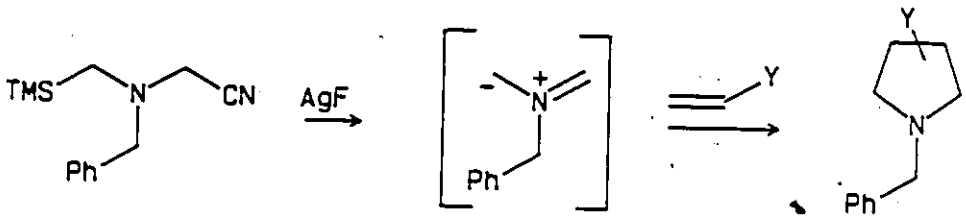


Scheme 11



Scheme 12 (X=O, S, NR_3)

agent containing F^- gives an ylide which is trapped in situ with a dipolarophile. Iminium salt 28 can also be generated by alkylation of iminosilane 29 with a triflate or fluorosulphonate alkylating agent.[51,53,94-97] These methods have been utilized extensively and variations have been developed. Thus, O-,S-, and N-alkylation of silylated amides, thioamides,[98] and amidines,[99] respectively, results in ions suitable for desilylation (Scheme 12). Vinylogous amides and thioamides are equally

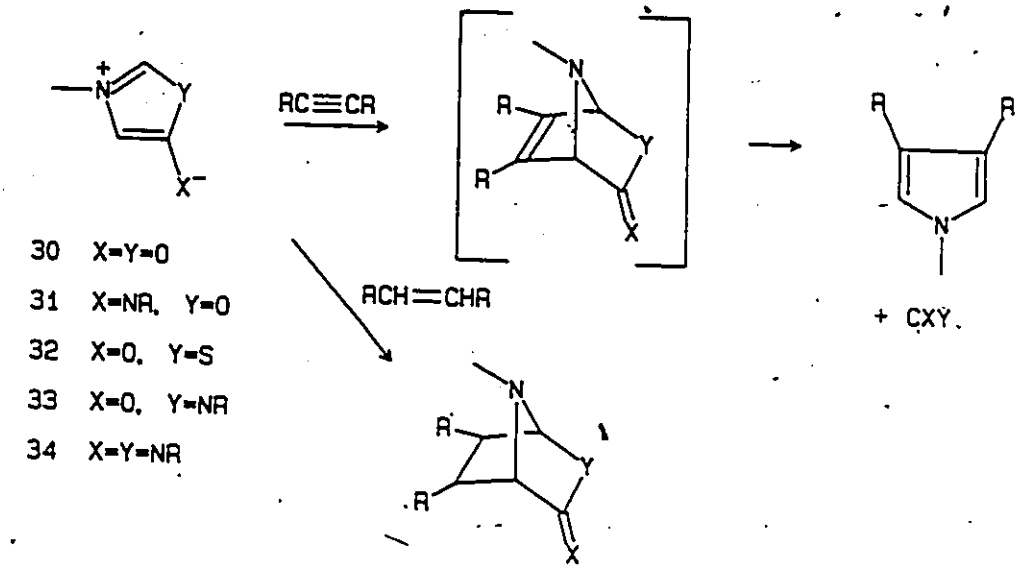


Scheme 13

suitable.[98] Alkylation of 29 (Scheme 11) with alkyl, acyl or aroyl halides and heating has been shown to be sufficient in order to generate the ylide,[100-102] even when R_1 or R_2 = NR'R" or SR.[103]

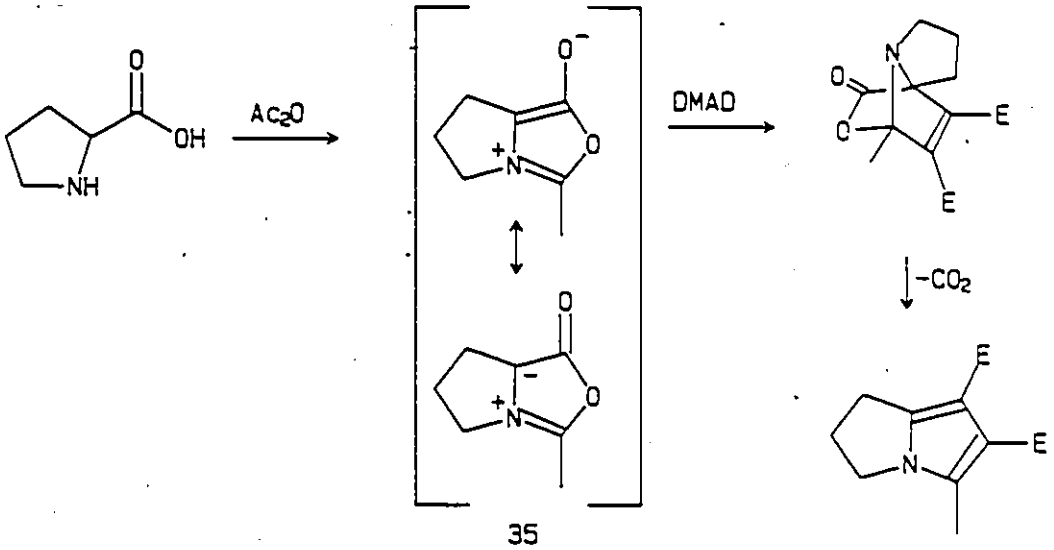
Padwa[52,58,104-106] has demonstrated how α-cyanosilylamines can produce azomethine ylides when treated with silver fluoride (Scheme 13). The Vedejs review[59] summarizes and tabulates the desilylation methods up to early 1986.

The final major azomethine ylide equivalents are mesoionic compounds.[107] Use of these as sources of various 1,3-dipoles for cycloaddition is extensive and is particularly common for azomethine ylides.[108,109] Thus, compounds 30[110,111], commonly referred to as munchnones, 31[112,113], 32[114,115], 33[116], and 34[117] (Scheme 14) have all been employed in cycloaddition chemistry. Scheme 14 depicts the general



30 X=Y=O
31 X=NR, Y=O
32 X=O, Y=S
33 X=O, Y=NR
34 X=Y=NR

Scheme 14

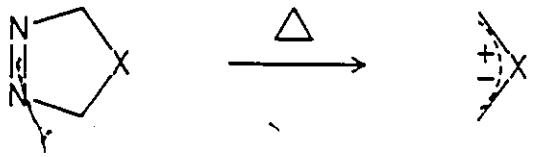


35

Scheme 15

methodology. The mesoionic species is often generated in situ with the trap, as shown in Scheme 15 with munchnone 35.

The variation in these methods for producing azomethine ylides is quite vast, yet one method is still lacking. The thermolysis of a heterocycle such as 36 gives a carbonyl ylide (X=O) and a thiocarbonyl ylide (X=S),[118] but the analogue where X=NR (Scheme 16) has yet to be reported.



36 X=O, S

X≠NR

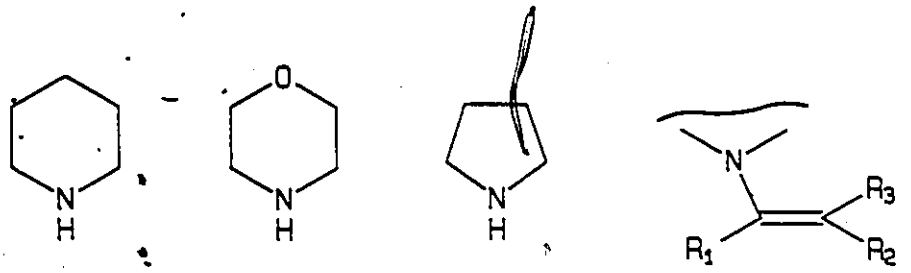
Scheme 16

The expectation is that 36 (X=NR), once made can lead to a synthetically useful azomethine ylide, in order to broaden the array of methods available for their synthesis.[118]

[2+2] Cycloaddition Chemistry of Enamines

Since the pioneering work of Stork and coworkers[119-121] concerning the synthetic applications of enamines, activity in this field has been neverending.[122-125]

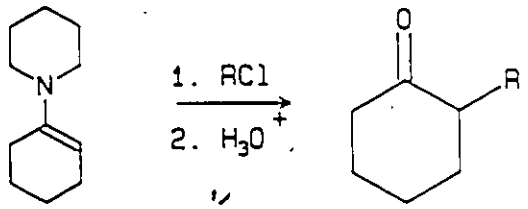
Simple C-alkylation or acylation of an enamine is now known as the Stork reaction (Scheme 17). The use of enamines has since been extended past derivatization of aldehydes or ketones and several more functionalized



37 38 39 40

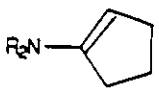
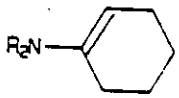
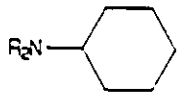
enamines have been shown to have synthetic utility. Thus reviews have appeared addressing the chemistry of enaminones,[126] β-enamino-esters,[127] cyanoenamines,[128] enamides,[129] and iminium salts.[130] As well, more general reviews discuss the synthesis of natural products using enamines,[131] acylation reactions,[132,133] and the overall chemistry of enamines.[122-125,134]

When a Stork alkylation product is desired, one of three amines is typically employed. The carbonyl compound is usually condensed with piperidine (37), morpholine (38), or pyrrolidine (39) to give a nucleophile of general structure 40. The reactivity of the enamines derived from these three amines has been determined and many structural data have been obtained, consistent with the observed reactivity. In various studies such as rates of alkylation,[135] rates of cycloaddition reactions,[27,136] and H-D exchange with hexadeuteroacetone,[137] the pyrrolidine derived enamines were found to react much faster than those



Scheme 17

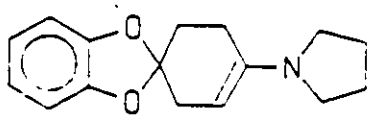
Table 3: Ionization Potentials (IP) of Enamines and Reference Compounds (eV)

	Amine		
R_2N			
pyrrolidino	7.10, 9.66[141]	7.14, 9.58[141] 7.10, 9.51[142] 7.15, 9.58[144]	7.96[143]
piperidino	7.4, 9.55[141]	7.50, 9.31[141] 7.42, 9.31[142] 7.44, 9.36[143] 7.54, 9.44[144]	7.93[143]
morpholino	7.60[141]	7.67, 9.40, 9.88[141] 7.66, 9.42, 9.91[142] 7.65, 9.40, 9.89[143]	8.18 9.50[143]
hydrogen	9.21[145]	9.14[145]	

from 37 or 38. Piperidine enamines tend to be slightly more nucleophilic than morpholine enamines.[135] This observed reactivity can be generally correlated to the ^{1}H NMR chemical shift of the hydrogen on the β-carbon of the enamines. As expected the chemical shift is furthest upfield due to shielding in the pyrrolidine case ($\Delta\delta \approx 0.20 - 0.30$ ppm upfield vs. morpholine and piperidine). A similar comparative correlation between piperidine and morpholine enamines is not observed.[135]

Crystal structure data have revealed that enamines derived from 39 tend to be closer to planarity throughout the nitrogen-olefin $p\pi$ systems than those for 37 and 38[138-140]. Enamine 41 contains a nearly planar nitrogen.[138]

Photoelectron spectroscopy (PES) has also proved to be informative with regard to relating reactivity and structure of enamines derived from these amines. Table 3 provides PES data for enamines derived from the condensation of 37, 38 and 40 with cyclopentanone and cyclohexanone as well as for some reference compounds.



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The shapes of the bands identified as the first and second IP's of these compounds are also informative. The first ionization potential (IP) is the broader one indicating that the nitrogen is pyramidal, as in a simple amine. This lineshape is due to large geometry differences in the pyramidal ground state vs. the planar radical cation. The sharper second IP band is predominantly alkene-like.

Figure 5 is an energy level diagram that depicts the mixing which takes place when an amine and an alkene are brought into interaction with one another. The highest occupied molecular orbital (HOMO), whose energy level is best estimated by the negative of the first ionization potential (IP_1), is given the [$\rho-\pi$] label while the second highest occupied MO (2nd IP, IP_2) is referred to as [$\rho+\pi$]. The difference in the IP_1 energy levels for a given enamine and its parent saturated amine is the amount of destabilization of the lone pair and is also a measure of the $\rho\pi$ interaction. It has been observed that the more destabilized enamines, those with greatest conjugation, do indeed react most rapidly. Thus the IP's for the pyrrolidine enamines are substantially lower than those for the other enamines, as expected from reactivity data.[135] Similarly, the small reactivity difference between piperidine and morpholine enamines predicts IP values for piperidine enamines to be the slightly lower of the two, as is the case.

The IP values for the different ring sizes tend to predict that aminocyclopentenes are more reactive than their cyclohexene counterparts, data consistent with the experimental findings.[135]

While the alkylation of enamines has found its niche in synthesis, enamines can undergo reactions with certain substrates to give [2+2] cycloaddition reaction products. Whereas alkylation forms one carbon-carbon bond in a reaction, this cycloaddition forms two C-C bonds in a single process.

Several reviews have appeared regarding polar [2+2] cycloaddition reactions of enamines.[146-150] These reactions were first discovered by

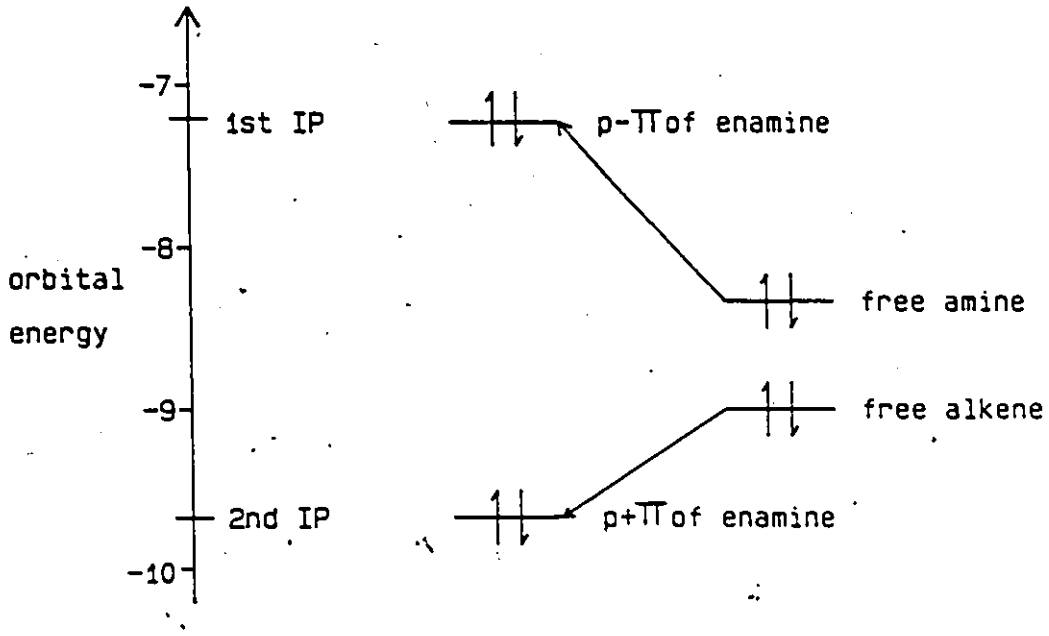
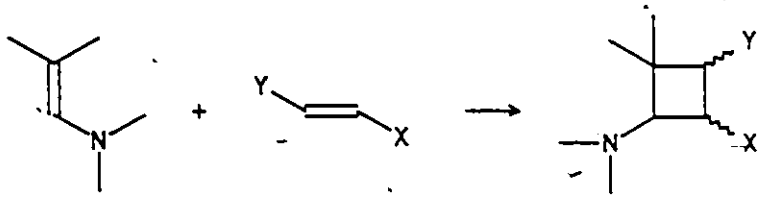


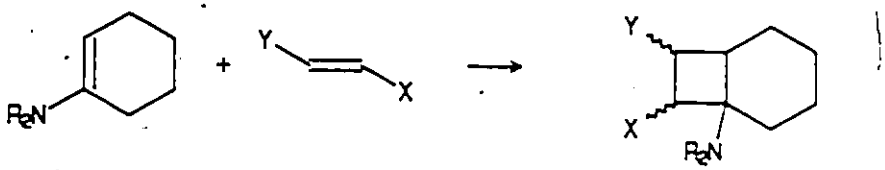
Figure 5. pπ-Conjugation in an Enamine



a) X=CN,CO_2Et: Y=H

b) X=Y=CO_2Me,CN

Scheme 18



a) X=SO_2Ph: Y=H

b) X=NO_2: Y=Ph,H

c) X=PO(OEt)$_2$: Y=H

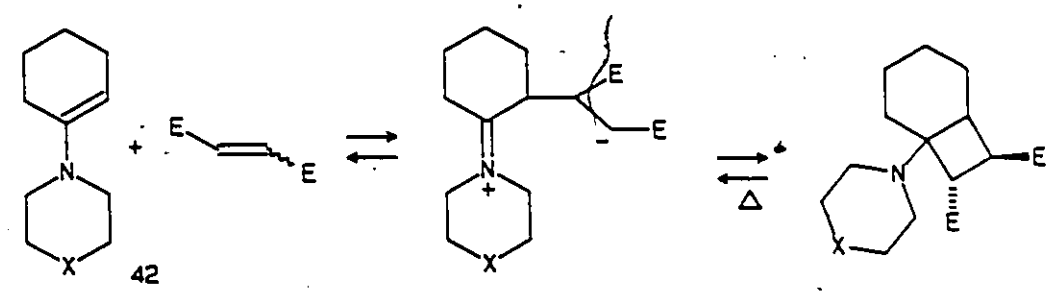
Scheme 19

Cook[151] and subsequently elaborated by Brannock and co-workers.[152,153] It was initially proposed that only enamines without β-hydrogens would give [2+2] cycloaddition products when treated with electron deficient olefins (Scheme 18).[151-153] Later work indicated that the β-hydrogen stipulation was not necessary that the [2+2]cycloadducts could be obtained when β-hydrogens were present on the enamine.[153,154] By isolating cyclobutanes at low temperatures, Fleming demonstrated that their formation was reversible and proposed their intermediacy in a typical Stork alkylation procedure.[155,156] The Brannock and Fleming research groups[153-156] reported that aldehyde-derived enamines gave the more stable cyclobutanes.

Cyclobutanes are also formed with olefins activated by groups other than carboxylate derivatives. Thus, vinyl sulfones,[153,159] vinyl phosphonates,[160] and nitroolefins[153,161] react with enamines to give [2+2] cycloadducts (Scheme 19.).

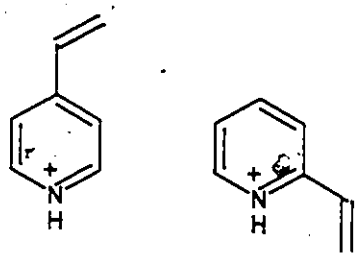
The cycloadditions are believed to be stepwise. The use of maleate and fumarate esters has provided evidence for this theory.[154,162,163] When amine 42 was treated with maleate or fumarate, one product (43), bearing ester groups trans to one another, was isolated. Adduct 43 was found to be thermolabile and reverted to only fumarate and 42 at high temperatures.[162,163] (Scheme 20).

Other substrates also give cyclobutane derived products when brought in contact with enamines. Among these are arynes,[164] ketenes,[132,165,166] 2- or 4-vinylpyridinium ions (44, 45),[167] diphenylcyclopropenone,[168,169] and



42 Scheme 20 43

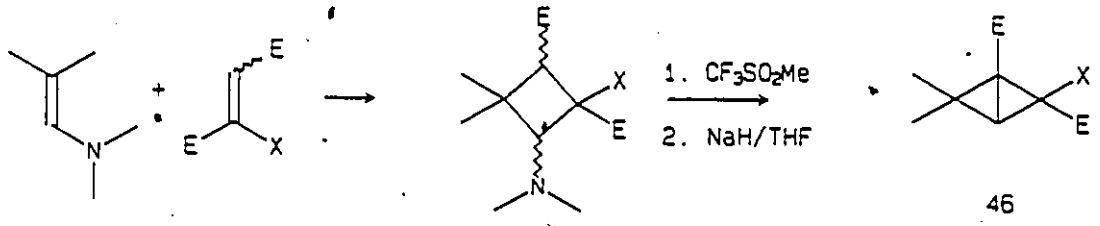
highly substituted ethylenes.[170] The cyclobutanes from this latter case have been transformed into bicyclo[1.1.0]butanes (46) (Scheme 21).[170]



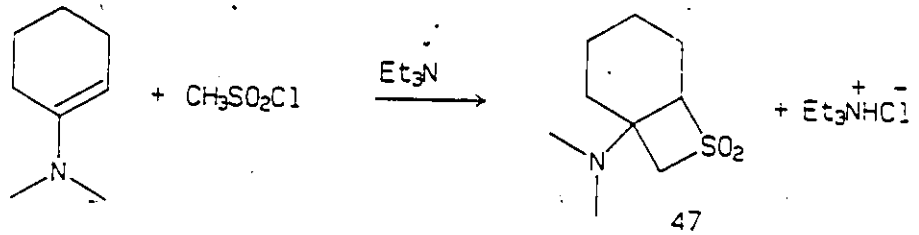
44 45

Enamines also undergo [2+2]cycloadditions with heterocumulenes, often giving rise to isolable heterocyclic products. Sulfene, which reacts as if it were [SO_2=CH_2], and its substituted analogs readily react with electron rich alkenes affording thietane-1, 1-dioxides (47).[171-173] Sulfene is usually produced by bringing a sulfonyl chloride into contact with a tertiary amine, often triethylamine. A less common method involves combining a diazomethane and sulfur dioxide.[174] This methodology precludes alkaline reaction conditions which may induce isomerism of products.

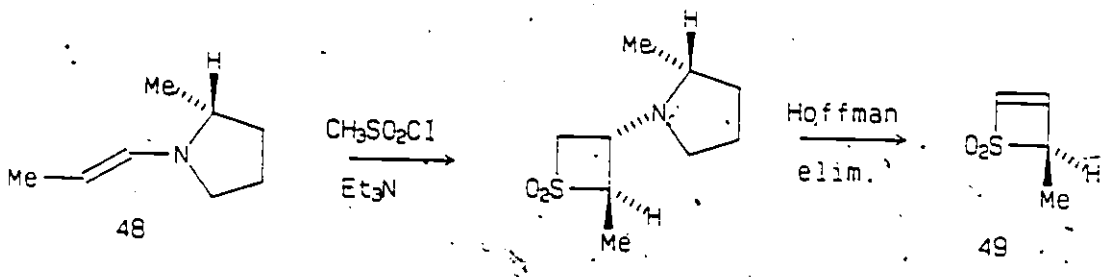
In order to determine whether the sulfene cycloadditions are concerted, Paquette and coworkers[175] synthesized thiete-1,1-dioxide 49 in 25% enantiomeric excess (ee), starting with optically active 48 (Scheme 23). The authors suggest that the sulfene approaches the underside of 48 in an orthogonal manner and undergoes a concerted $\pi_s^2 + \pi_a^2$ cycloaddition via a product-like transition state.[175] Stereoselectivity is also observed when



Scheme 21 (X=EWG)

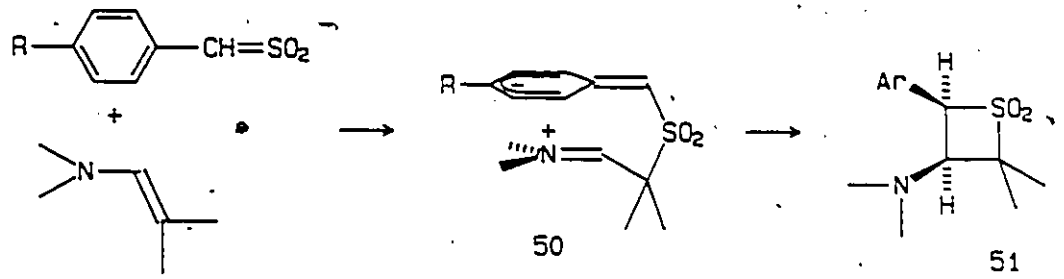


Scheme 22



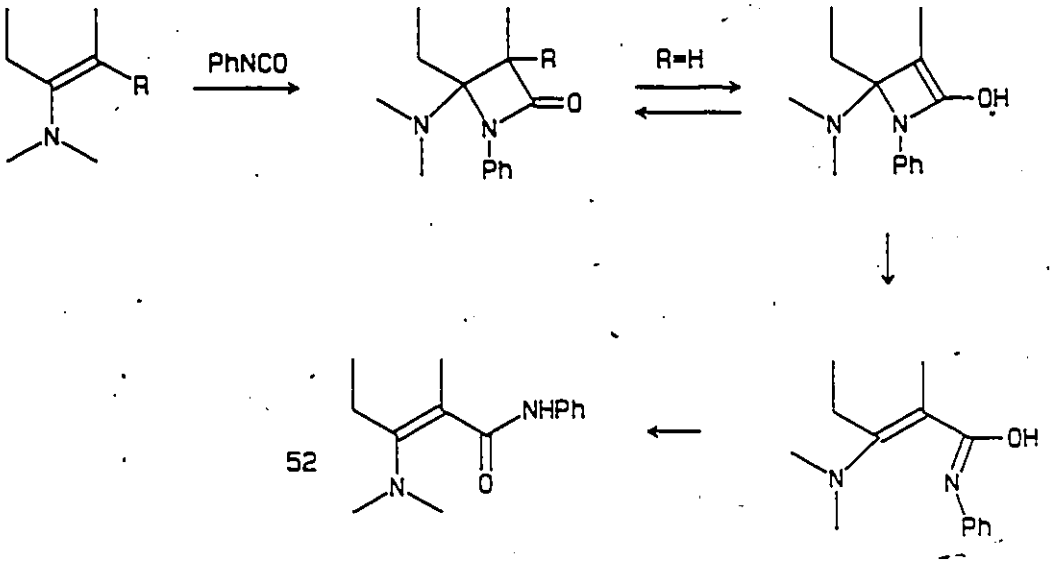
Scheme 23

aryl sulfenes react with enamines.[174,176] Thus the thermodynamically less stable cis isomer predominates when the aryl substituents are capable of stabilizing negative charge (Scheme 24). The formation of 51 is either due to a concerted reaction or can be explained in terms of electrostatic attraction causing alignment as shown by 50, followed by ring closure. If the aryl group bears an electron withdrawing group, 50 (R=EWG) has a sufficiently long lifetime to assume the conformation depicted by in Scheme 24; if R=H in 50, then the trans adduct is formed preferentially instead.[174,176]

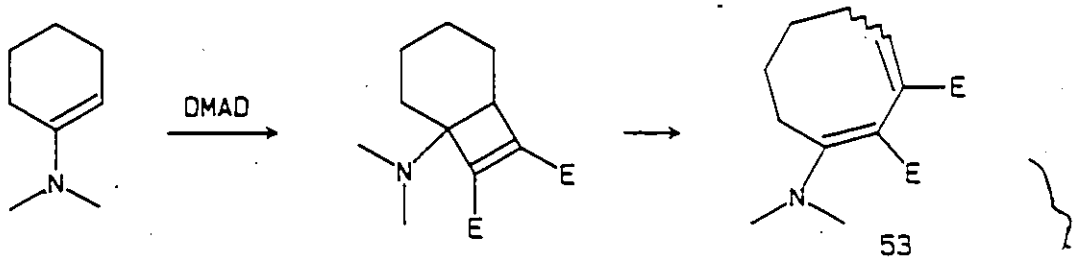


Scheme 24 (R=EWG)

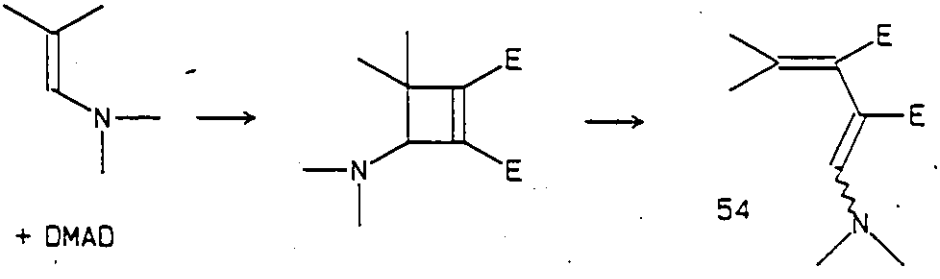
Thietane-1,1-dioxides can usually be isolated because their ring opening reactions are slow. The isolation of β-lactams, generated by the reaction of enamines with isocyanates, has proven to be a more formidable task. The reaction has been extensively studied.[122,177] Typically, a four-membered ring is formed initially and it can be isolated if the enamine precursor bears no β-hydrogens. If such hydrogens are present, the β-lactam is believed to decompose via amide enolization followed by electrocyclic ring-opening and finally by prototropic shift to give mono-vinylogous urea 52 (Scheme 25).[177] There is no mechanistic proof for this sequence. Also possible is a nucleophilic addition to the isocyanate to give a zwitterion



Scheme 25



Scheme 26



Scheme 27

which undergoes a series of proton transfers resulting in the formation of 52. When there are no β-hydrogens the zwitterion closes to the 4-membered ring. One would expect that some of these zwitterions could also be intercepted, however the high yield of β-lactam[177] precludes this possibility.

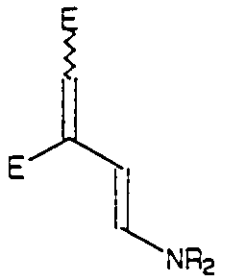
The cycloaddition chemistry of acyl isocyanates including the description of a synthesis of stable β-lactams bearing a β-hydrogen, has been reviewed.[178]

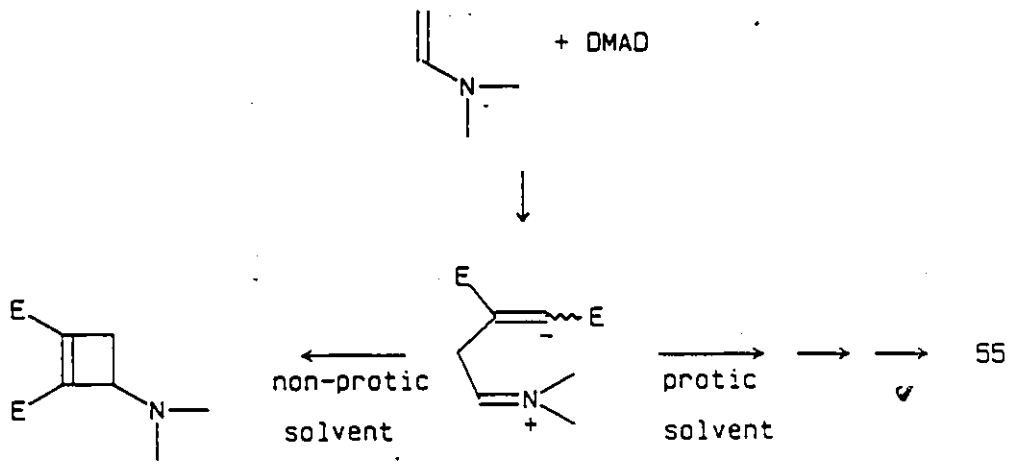
Enamines have been treated with dimethyl acetylenedicarboxylate (DMAD) more than with any other cycloaddend.[149,179-181] In non-polar solvents, the [2+2] adduct, an aminocyclobutene is formed which often undergoes facile electrocyclic ring expansions to give dienamines[182-184] (53, Scheme 26; 54, Scheme 27). The aminocyclobutenes can be isolated in some cases[182,184,185] including one instance where it could be reduced to the cyclobutane.[184]

The geometry about the enamine double bond of compounds such as 53 is Z, but about the other double bond it is either E or Z. The recent efforts by Reinhoudt et al[181] are attempts to end the controversy regarding the geometry.

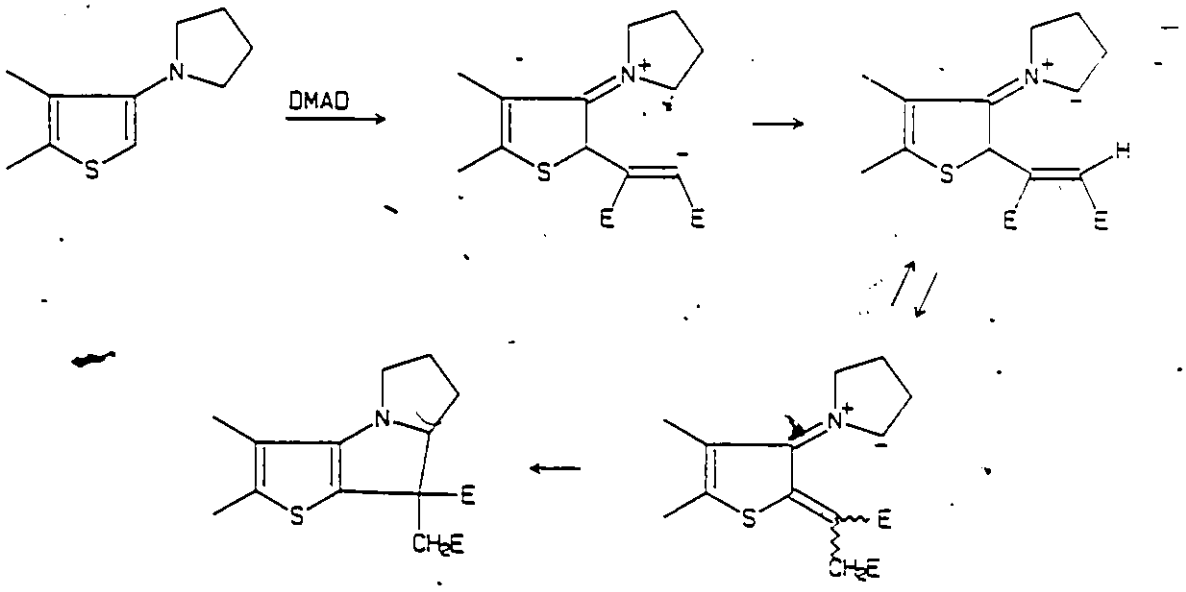
There is an amazing solvent dependence on the products of these reactions. The E (fumarate) and/or Z (maleate) Michael adducts (55) are often obtained in protic solvents.[186-188] With respect to the other double bond, the amine is usually trans to the fumarate/maleate moiety.

55





Scheme 28

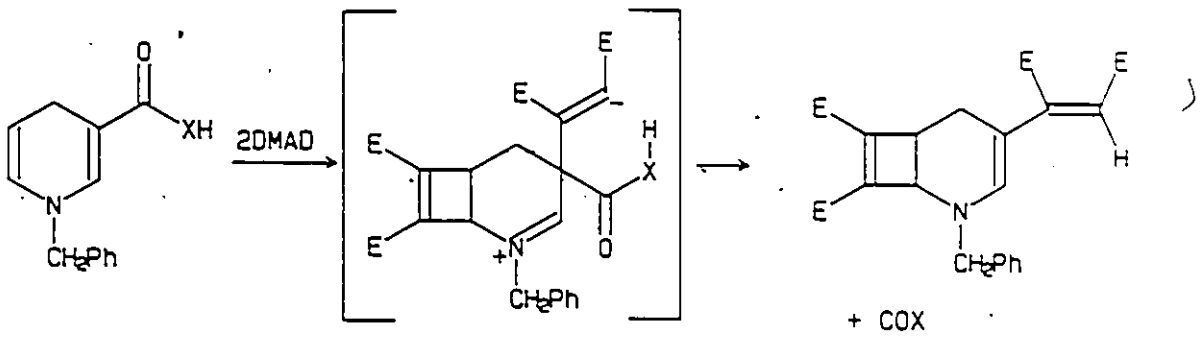


Scheme 29

To account for these results, the 1,4-dipolar zwitterionic intermediate depicted in Scheme 28 is proposed and it can close to give the four-membered ring or abstract a proton from solvent as the first step leading to Michael adducts (Scheme 28).

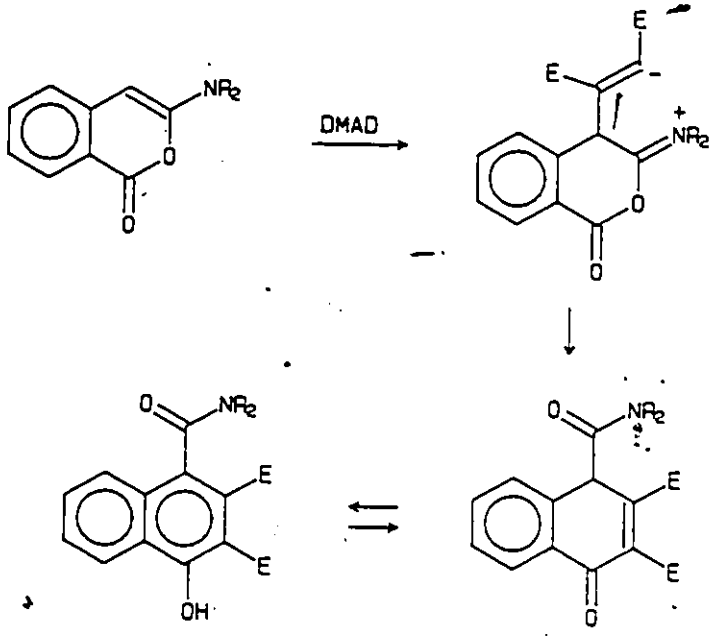
Considerable evidence is available to support the existence of a 1,4-dipolar zwitterionic intermediate. The products of reactions between DMAD and highly functionalized enamines provide much of this evidence. Reinhoudt and co-workers[181,189,190] have demonstrated several examples of intramolecular capture of the zwitterion. The chemistry of Scheme 29 is an indication of the type of work accomplished by these researchers.[189]

Scheme 30 depicts another example of intramolecular proton abstraction. In this instance, formation of a zwitterionic intermediate is thought to be followed by an intramolecular elimination of heterocumulene O=C=X via a six-membered cyclic transition state.[191]

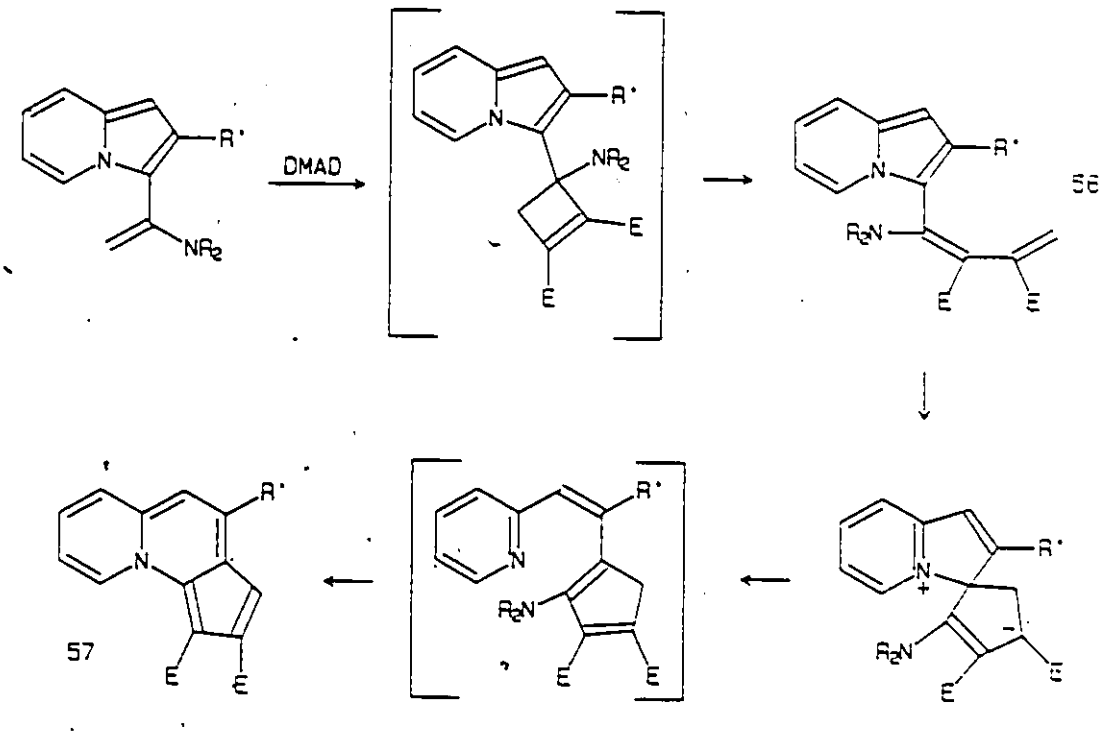


Scheme 30 (X=O, NH, NCH_2CH_2Ph)

In a third example, Boyd and co-workers[192] found that the nucleophilic end of the zwitterion attacked an appropriately situated carbonyl group rather than closing to a four-membered ring (Scheme 31).



Scheme 31



Scheme 32 (R'=Me, Ph: R=Me)

The indolizine in Scheme 32 was treated with DMAD and gave 56 which rearranged thermally to 57, a process involving the loss of a dimethylamine molecule[193] (Scheme 32).

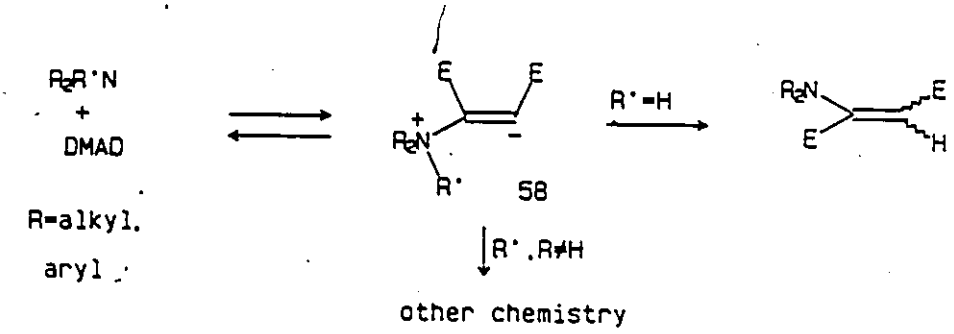
Reinhoudt et al in a recent report state that initial interaction does not involve a 1,4-zwitterionic intermediate. Rather, these reactions give the cyclobutene ring initially followed by reversible ring opening to the zwitterion, regardless of the reaction solvent.[181] The exact nature and geometry of the anionic end of these zwitterions will be discussed in a later section.

The reactions of methyl propiolate with enamines are essentially identical to those of DMAD.[180]

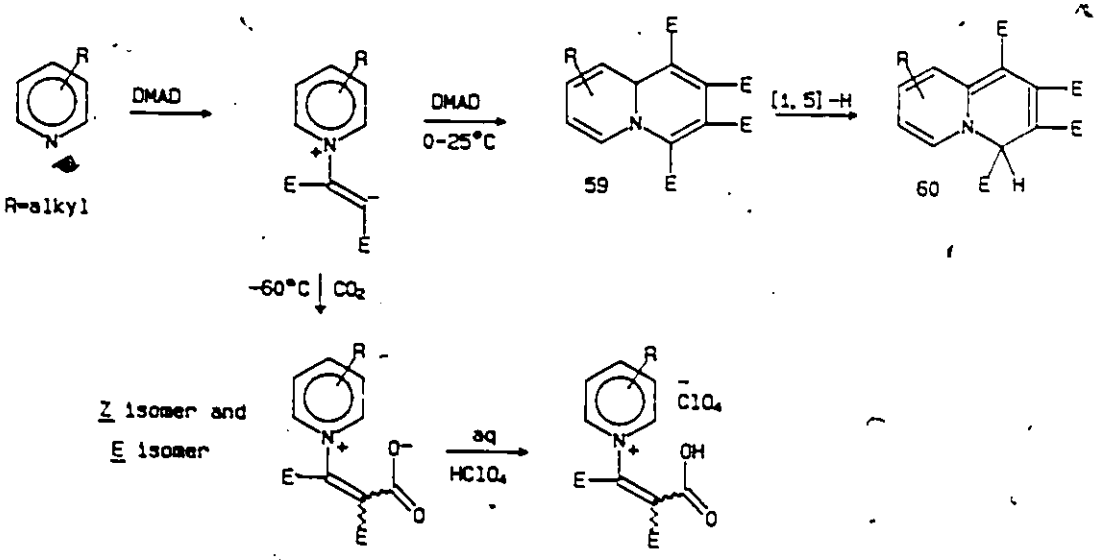
The Reactions of Amines with DMAD

Enamines are not the only nitrogen nucleophiles that can add to DMAD. Amines with various degrees of substitution also give rise to interesting products.[179,194,195] Many reviews have been written summarizing the reactions of DMAD with tertiary amines,[194] imines and azines,[196] and heterocycles of several types[179,197-199] including aromatic amines.[197,200] Two reviews concentrating on the physical aspects of the addition reactions have appeared.[201,202]

The reactions of tertiary amines are particularly interesting since there is no possibility of simple Michael adduct formation (Scheme 33). The intermediacy of a species such as 58 is best supported by the reaction of pyridine with DMAD. At 0-25°C, reactions of various pyridines with two equivalents of DMAD, typically lead to 4H-quinolizines (60).[203,204] The intermediate 9aH-quinolizine 59 can be observed by nmr spectroscopy[205] and



Scheme 33



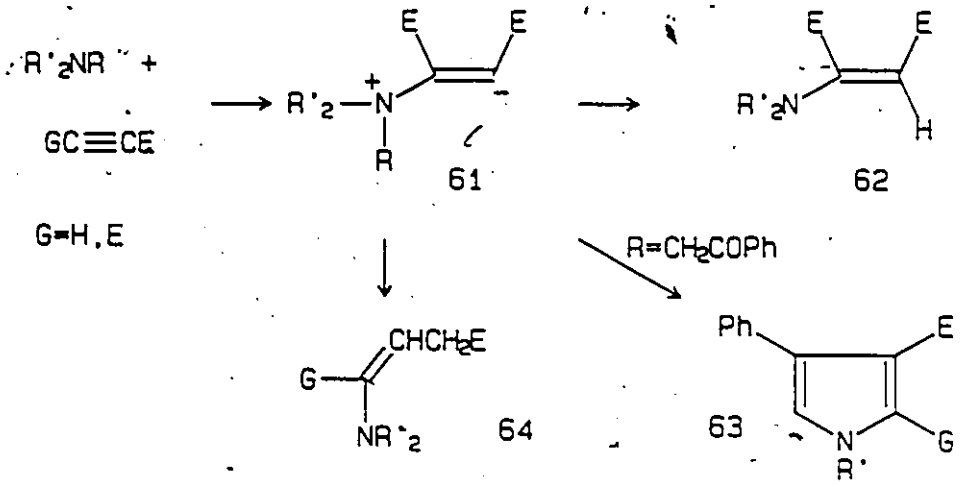
Scheme 34

has been isolated in one instance[206] (Scheme 34). At -60°C, the initial zwitterion can be trapped by carbon dioxide to give maleate and fumarate isomers. These are eventually isolated as their perchlorate salts[207] (Scheme 34). To date there has been no spectroscopic evidence for the intermediacy of a zwitterion such as 58 (Scheme 33).

There are numerous examples of products similar to 59 where two DMAD components have been incorporated before fusion to the original heterocycle.[197-200] This fusion is reasonable since the positive nitrogen of the heterocyclic intermediate increases the electrophilicity of the ring.[203,207] There are other instances where the anionic portion of 58 intramolecularly attacks an appropriately activated substituent of the amine.[179,194,208,209] In one instance, a secondary amine was employed and attack was so rapid that it precluded Michael adduct formation.[210] The number of these sorts of reactions is limited though. High yields are rare despite the suggested use of dilute solutions and low temperatures.[194]

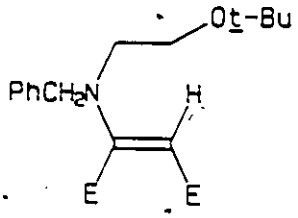
One of the early studies was by Winterfeldt who treated various β-amino-carbonyl compounds with methyl propiolate (MP) and DMAD.[208,211] Scheme 35 summarizes the principal reactions involved. Maleate 62 arises by Hoffman degradation of 61. Enamine 64 is formed by internal proton delivery to the anionic end of 61 followed by rearrangement. In DMSO, pyrrole 63 ultimately forms after initial attack by the anionic portion at the carbonyl group in R.

Tertiary alkyl amines, in the presence of their hydrochloride salts,

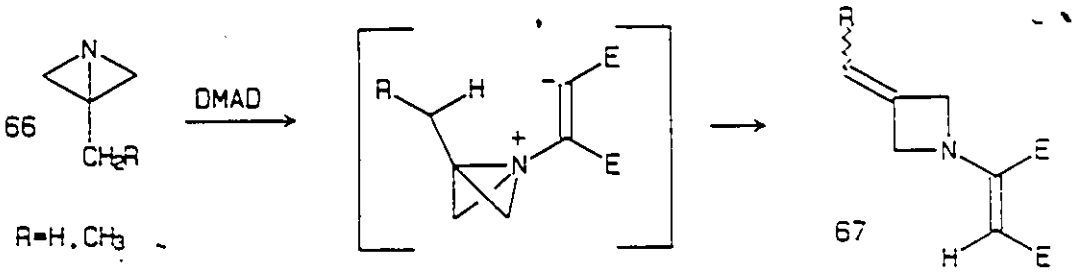


Scheme 35

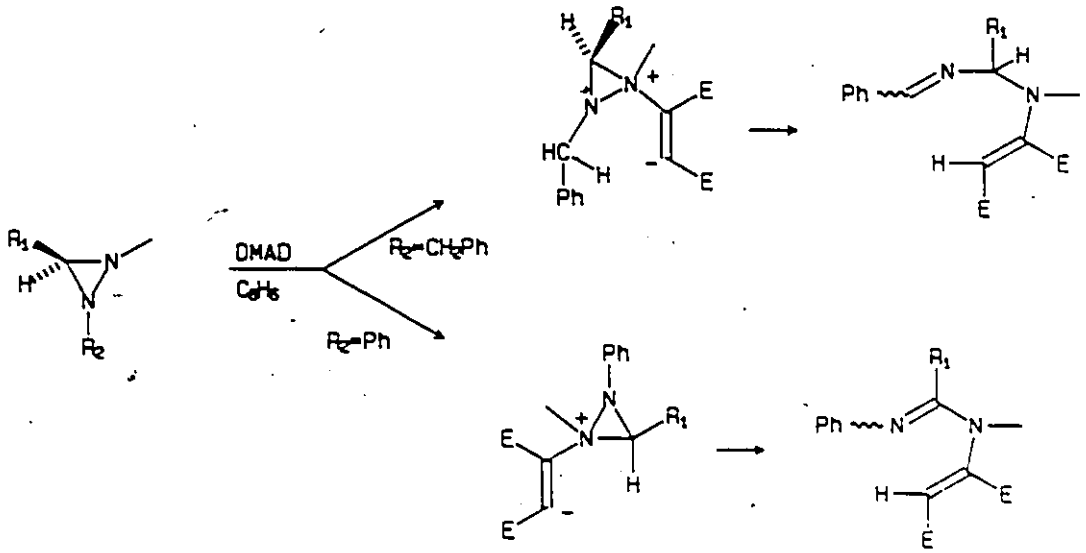
give the dialkylaminomaleate when treated with DMAD.[212] N-Benzylaziridine and DMAD give maleate 65 in the presence of t-butyl alcohol.[216] In a similar study, 1-azabicyclo[1.1.0] butane 66 and DMAD gave a ring-opened product 67, formed without the aid of solvent (Scheme 36).[209] Still another three membered ring opening reaction is achieved with DMAD and the diaziridines of Scheme 37.[213]



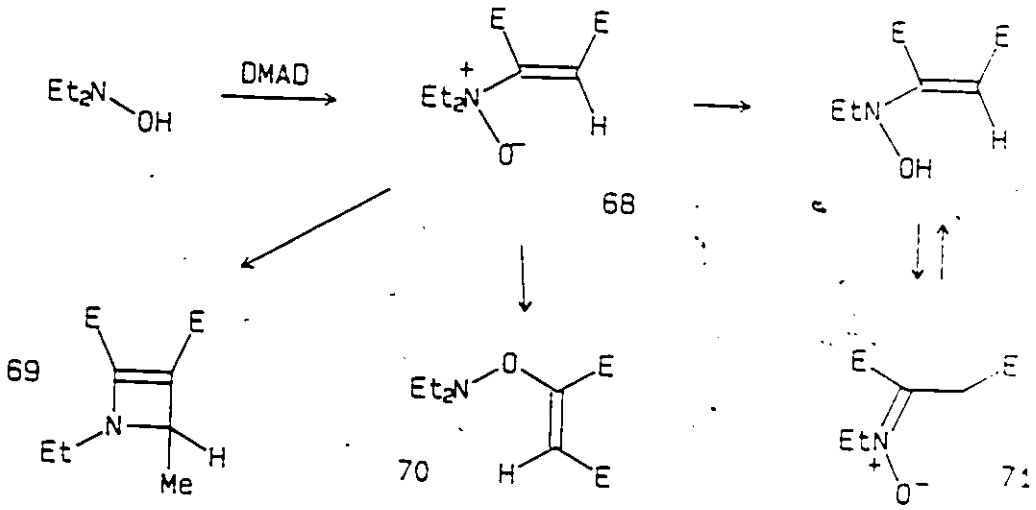
65



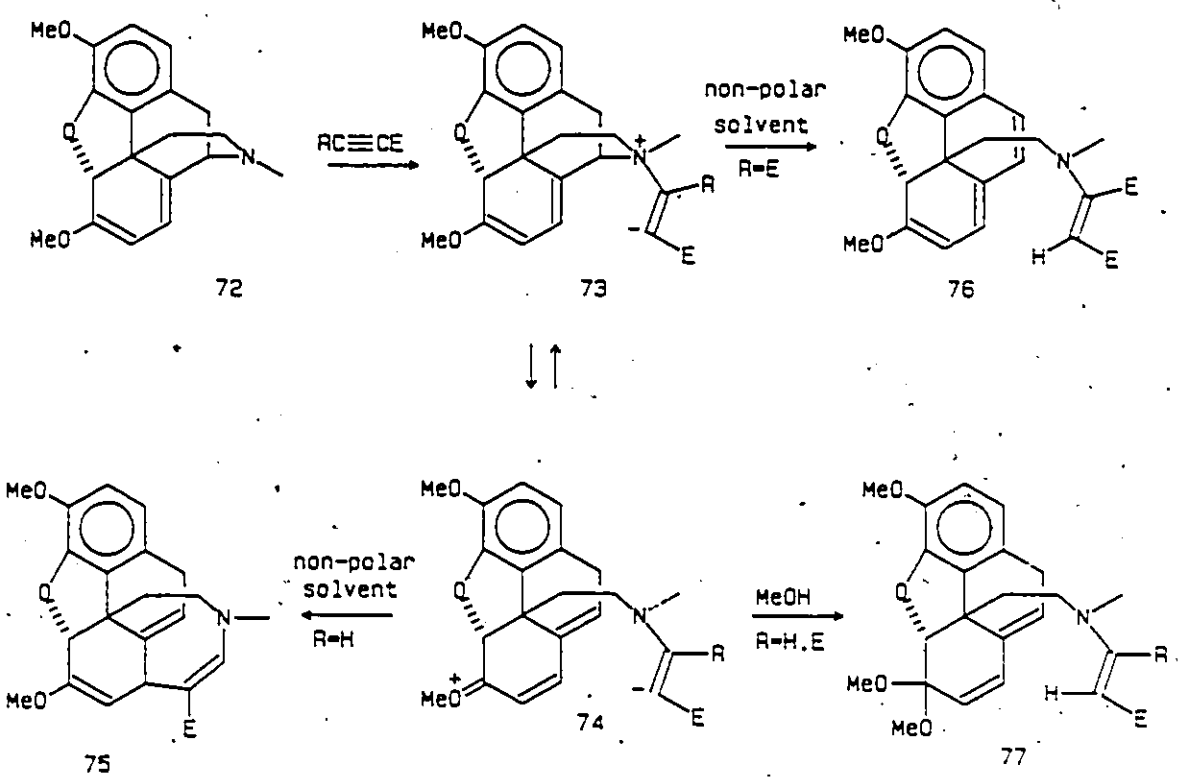
Scheme 36



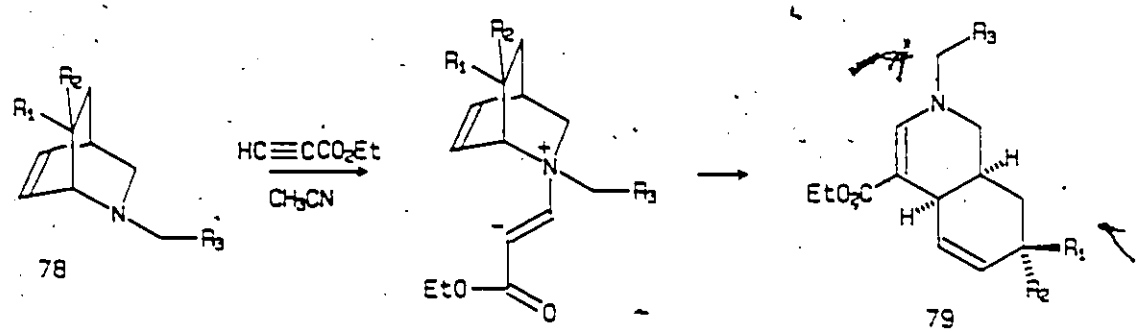
Scheme 37



Scheme 38



Scheme 39



Scheme 40

Diethyl hydroxylamine and DMAD gave nitrone 68 initially. Subsequent chemistry occurs and diesters 69, 70 and 71 are isolated[214] (Scheme 38).

More recently, successful applications of the zwitterion methodology to alkaloid chemistry have been reported. Two groups independently studied the reactivity of thebaine (72) with acetylenic esters.[215-217] With methyl or ethyl propiolate in a non-polar solvent, 73 (R=H) is initially formed (Scheme 39). It then closes onto the ring system after cleavage of the C-N bond to form 75.[215,216] In similar solvents, DMAD gives zwitterion 73 (R=E) which undergoes a Hoffman-like elimination to yield 76.[217] If MeOH is the solvent it adds to 74 after C-N bond cleavege to give 77, regardless of the acetylene employed (Scheme 39).[217]

In another instance, Mariano and co-workers have used a rearrangement similar to that required to form 75 in their synthesis of reserpine[218] and yohimbine[219] type alkaloids. Thus, the zwitterion resulting from the treatment of quinuclidinene 78 with ethyl propiolate undergoes a "zwitterionic amino-Claisen" rearrangement yielding alkaloid precursors of the type 79 (Scheme 40).

The use of tertiary amines precludes the formation of simple Michael adducts in these instances. There is a case, albeit specialized, where a secondary amine can be employed. The anionic portion of the zwitterion attacks an electrophilic end of the molecule before the proton transfers required for Michael adduct formation can occur.[210] Attack of the alkyl group with ring opening of the aziridine gives dihydroazepine 81 (Scheme 41). This transformation has also been achieved with some electron deficient olefins.[210]

A final interesting reaction is indicated by Scheme 42. Heteroatom substituted dimethylamines react with acetylenedicarboxylate esters to give the 1,2-disubstituted adducts 82.[220] The maleate isomer is formed initially in all cases except X=SPh. Where X=MMe_3,[220a] the authors believe that the metal transfer does not occur via the backside of the metal, rather transfer occurs without inversion at the metal centre.[220a]

The geometry about the diester double bond must be cis in all these cases since the electrophile is intramolecularly (internally) situated. This need not be the case when there is external electrophile delivery. Dickstein and Miller have attempted to create a working model for predicting the geometry of the products by considering parameters such as solvent polarity, electrophile availability and anion inversion barriers.[202]

In the previous schemes the vinyl anion end of the zwitterionic intermediate has been depicted as a vinyl anion for reasons of simplicity. Presently there is only speculation as to the exact nature of this anionic end.[215,217,221] Rarely has an effort been made to determine the geometry of the anion. The authors in one report prefer the geometry shown in Figure 6 because of the geometry assumed by its isoelectronic heteroanalog.[201]

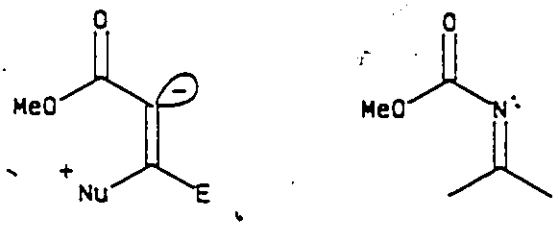
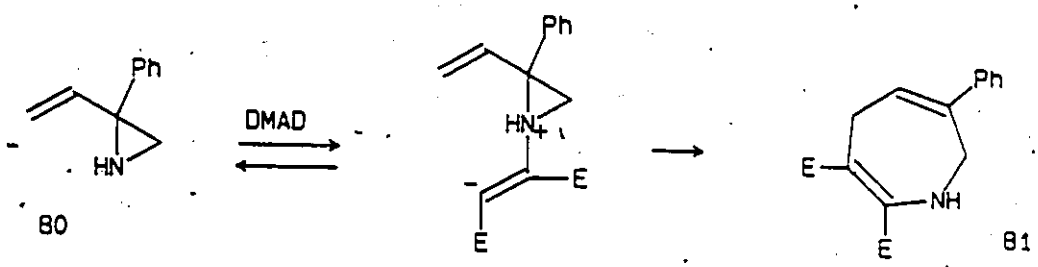


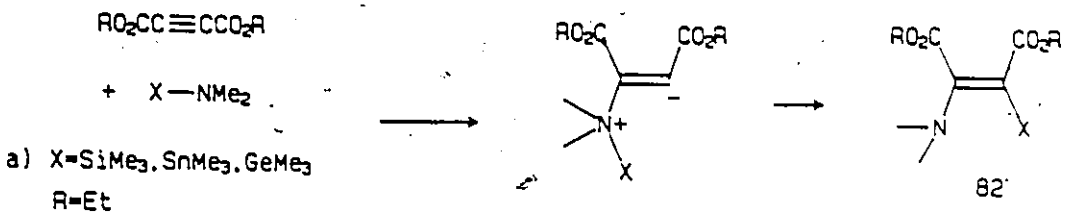
Figure 6. Structural Similarity Between Two Unsaturated Carbonyl Species

Houk and co-workers have performed calculations regarding the nature of such anions and their rates of inversion.[222,223] They noted that in most cases addition to the acetylene is initially anti (Figure 7). The resultant anion then readily protonates in a protic solvent. In non-protic



80 81

Scheme 41



82

Scheme 42

anti addition syn addition

Figure 7. Modes of Nucleophilic Addition to Acetylenic Esters

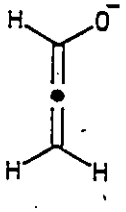
solvents anti addition is less favoured and the lack of readily accessible electrophiles prolongs the 'life' of the anion. This extended lifetime allows for inversion of the syn (or anti) addition isomer before subsequent chemistry.[222] With cyanoacetylene, it is believed that the anti isomer is favoured in polar solvents because of the small size of the cyano group.[222]

The structure/energy relationships of vinyl anions with various substituents have been determined using two basis sets (Table 4).[223] These data show that cyano- and carbomethoxy-substituted vinyl anions are bent but do have low inversion barriers.

Table 4: Energy Relationships Between Bent and Linear Vinyl Anions.

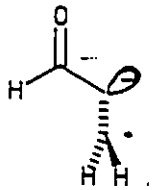
Stabilizing Substituent	E(linear)-E(bent) (kcal/mol)	
	STO-3G	4-31G
H	50.4	36.6
CN	16.7	9.4
CO_2Me	12.1	5.0
CHO	7.7	-5.7

More recently Grein and co-workers have determined the relative stabilities of four anions (83-86) using 4-31G geometry optimization.[224,225] It was concluded that with a formyl substituent the linear anion should be the only major isomer present.[224]



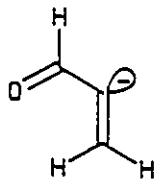
83

0 kcal/mol
(arbitrary standard)



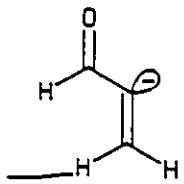
84

12.4 kcal/mol



85

17 kcal/mol



86

21 kcal/mol

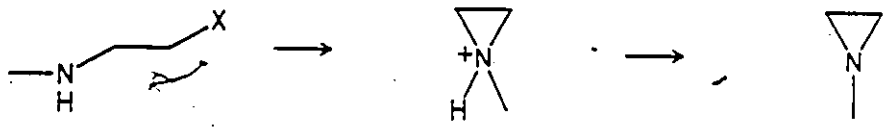
Heterocyclic Syntheses and Transformations

The utilities of heterocycles in chemistry and industry are endless. There are countless uses of these compounds now known both in nature and in society.[226,227]

One small but important component of this vast field is the chemistry of aziridines, saturated three-membered rings containing one nitrogen atom.[84,228] Their uses are plentiful and representative of the uses of heterocycles in general. Aziridines are employed throughout industry with applications ranging from pharmaceuticals to reprography and photography.[227] As well, aziridines have been shown to have significant biological activity.[229-231]

Several reviews have outlined the different synthetic methodologies for making aziridines.[84,147,228,229,232] There are four main methods for the ring synthesis. The most common method is outlined in Scheme 43. When $X=OSO_3^-$, the method is called the Wenker synthesis and if X=halogen it is the Gabriel synthesis.[84,229] Cyclization can be achieved when X=tosylate[233] or methanesulfonate[234] and amino alcohols have also been cyclized via a phosphine-halide mediated closure.[235,236]

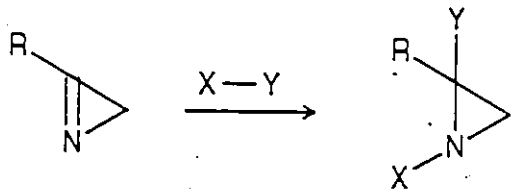
Azirines are also suitable precursors for aziridines. Addition of a substrate across the azirine double bond offers a simple route to the



X=Br.Cl.I.SO_3O^-.OTs

Scheme 43

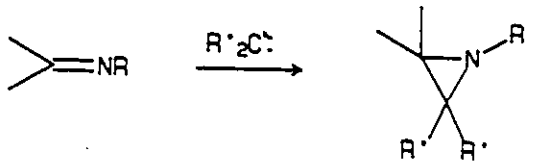
saturated form of the ring (Scheme 44). Formally X-Y can be H_2: reduction has been achieved catalytically[237] or with reducing agents such as $LiAlH_4$.[238] Both electrophiles such as acid chlorides,[239] or nucleophiles such as alkoxides[240] amines,[241,242] and organometallic reagents[243,244] are



Scheme 44

suitable substrates for addition across the double bond. The cycloaddition chemistry about this bond to give ring fused aziridines is also quite extensive.[245]

The third method of aziridine generation is carbene addition to an imine bond (Scheme 45). Halocarbenes give the best yields,[246,247] while non-halogenated carbenoid species add with limited success.[248]

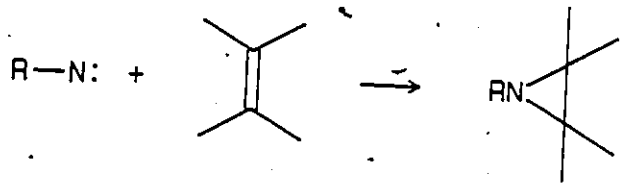


Scheme 45

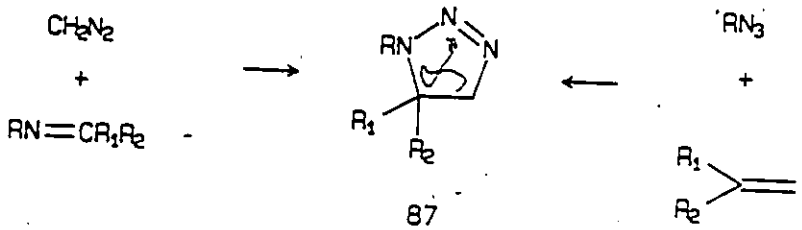
The cycloaddition of nitrogen compounds to alkenes also generates aziridines. The most simple cycloaddition is that between a nitrene and an alkene (Scheme 46). This chemistry has been extensively reviewed and proceeds with all types of nitrenes including carbonyl (R=R'CO) and amino ($R=R'_2N$) nitrenes.[249,250] The less obvious route is the cycloaddition of an azide to an alkene or of a diazoalkane to an imine to give a Δ^2-1,2,3-triazoline (87) (Scheme 47).[251-253] Subsequent decomposition of 87 thermally or, for a higher yield, photochemically leads to the formation of an aziridine (Scheme 48). A byproduct of the decomposition is imine 88 which is readily explained by proposing intermediate 89 which can close to the aziridine or transfer an alkyl group with displacement of N_2, to make the imine bond. This methodology has been well studied.[251,252]

Transformations and rearrangements exemplified here are commonplace in heterocyclic chemistry and are the subject of several reviews.[254-257]

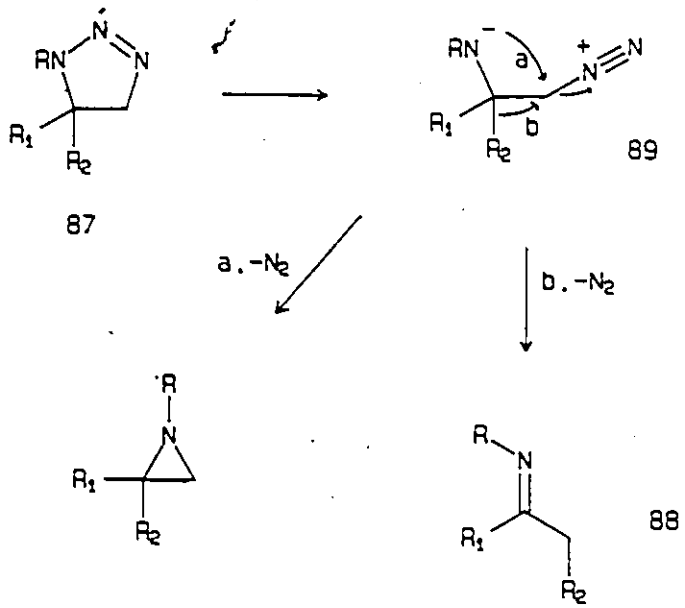
General reviews on heterocyclic chemistry are also available. Two series containing summaries of more specific heterocyclic topics are available.[258,259] A series of volumes is available to help in the structural assignment of heterocycles as well as aid in the determination of their physical properties.[260]



Scheme 46



Scheme 47



Scheme 48

Finally, a recent set of eight volumes has updated the evergrowing field of heterocyclic chemistry.[261] The first volume of this series contains a chapter listing all monographs and review articles available to the heterocyclic chemist.[227]

With a suitable background now provided the reader will be in a position to appreciate the efforts made here to follow up the thinking and pursuits of Kellogg, who tried to synthesize Δ^1-1,2,4-triazolines with the hope of employing them as azomethine ylide precursors.[118] To this end a series of Δ^1-1,2,4-triazolines, both isolable and transient, have been generated. These give rise to a number of different species including azomethine ylides, aromatic heterocycles, and aziridines all by novel pathways. As well, the background of amine–DMAD reactions has been outlined so that the mechanism of a new dimethylaminoallylation reaction across DMAD can be readily understood.

RESULTS AND DISCUSSION

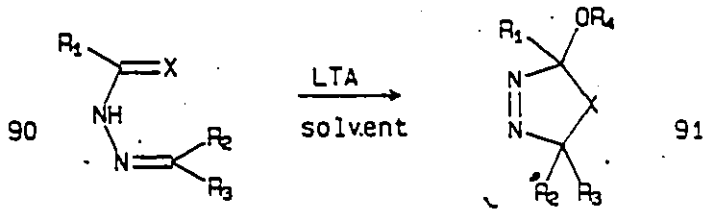
CHAPTER 2

Synthesis and Properties of 4-t-Butyl-3,3-dimethyl-5-methylene-Δ^1-1,2,4-triazoline

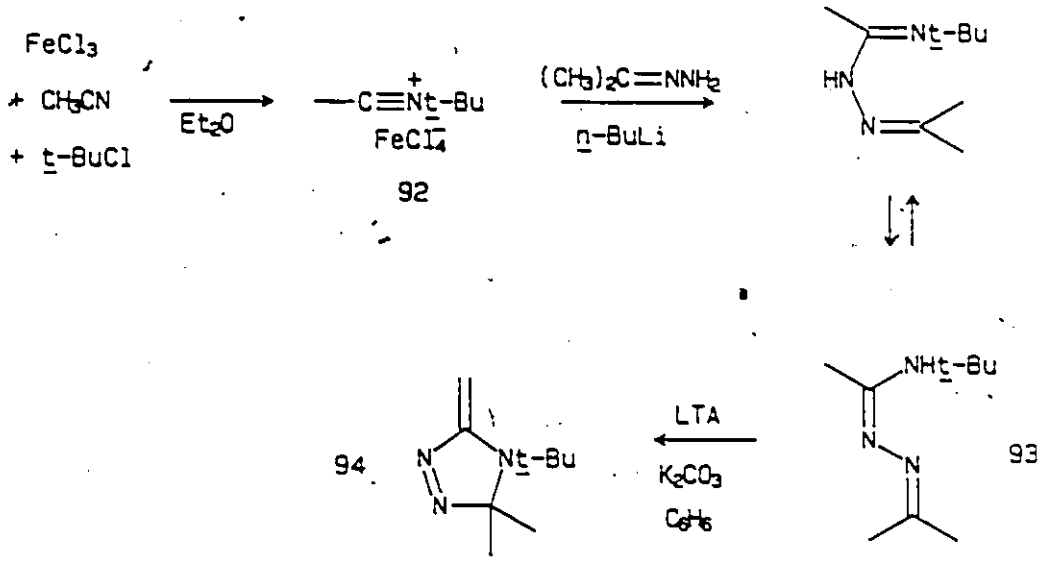
It was felt that the methodology successfully employed in the synthesis of Δ^3-1,3,4-oxadiazolines could be suitable for generating Δ^1-1,2,4-triazolines. The ketone hydrazones of hydrazides can be cyclized using lead tetraacetate (LTA) to give heteroatom-substituted oxadiazolines (Scheme 49, X=O).[262,263] When the solvent is a nucleophile, such as an alcohol, then R_4=alkyl whereas a non-nucleophilic solvent allows for acetate substitution onto the ring (R_4=acetyl).[262,263] Oxidation of 90 ($X=NR_5$) under similar conditions should give an analogous heterocycle (91, $X=NR_5$).

The appropriate oxidation precursor was prepared using the methodology of Fuks.[264] Anhydrous ferric chloride, acetonitrile, and t-butyl chloride were brought together to form nitrilium salt 92 (Scheme 50). Addition of this salt to a mixture of acetone hydrazone and n-BuLi affords N^3-t-butyl-N^1-isopropylideneacetamidrazone (93) in 51% yield. In solvents such as $CHCl_3$, 93 exists as two interconverting tautomers.

Oxidative cyclization of 93 did not yield a triazoline of the structure 91 ($X=N\underline{t}Bu$, $R_1=R_2=R_3=CH_3$). Rather, 4-t-butyl-3,3-dimethyl-5-methylene-Δ^1-1,2,4-triazoline (94) was the isolated product. Ideal conditions for this transformation were found. Addition of LTA (1.1 equiv.) to benzene followed by anhydrous K_2CO_3 and finally addition of 93 gave a reaction mixture which was stirred for 45 minutes at 0°C before workup (Scheme 50). Triazoline 94 was isolated in 45% yield.



Scheme 49



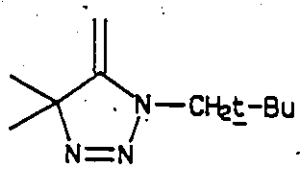
Scheme 50

The use of alcohol or methylene chloride solvents gave 94 in substantially lower yield and no heteroatom-substituted triazolines (e.g., 91, X=N<u>t</u>Bu) were detected. Deprotonation of 93 before treatment with LTA followed by reprotonation during the workup stage provided 94 in lower yields (~30%).

Triazoline 94 is the first Δ^1-1,2,4-triazoline without heteroatom substituents.[265] Ring skeletons identical to 94 have been generated previously, but these examples bear exocyclic carbonyl, thiocarbonyl or imine unsaturation.[265]

Triazoline 94 is a yellow oil which solidified upon storage below 0^0C. Its structure was established on the basis of its spectral data. An exact molecular mass (m/z=167.1432) consistent with the molecular formula $C_9H_{17}N_3$ was obtained. As well, an exact mass at m/z=139.1347 coincided with the molecular mass less $N_2(C_9H_{17}N)$. The infrared spectrum showed bands consistent with the unsaturation of the molecule (1636 and 1511 cm^{-1}). The geminate methyl groups resonate as a single peak in both the ^1H and ^{13}C nmr spectra. The ^1H nmr spectrum also showed a pair of doublets (J=2.2 Hz) having the highly shielded olefinic chemical shifts of 4.76 and 4.16 ppm ($CDCl_3$). Nuclear Overhauser enhancement (nOe) studies indicated that the proton <u>cis</u> to the N-<u>t</u>-Bu portion of the ring resonates at 4.16 ppm (Table 6, p 72).

The nmr data imply that the ring is planar or at least is inverting at a rate which is too fast for detection by the nmr instruments at ambient temperatures. This behaviour is much like that observed for interesting



95

azoenamine 95.[266] The planarity of 94, hinted at by the ^1H nmr spectrum is supported by the photoelectron spectrum (Figure 8). Triazoline 94 is an enamine. Its exocyclic double bond is substituted by two nitrogen atoms, one of which can readily attain the geometry required for conjugation of its lone pair with the carbon-carbon double bond. In the introduction the normal lineshapes of PES bands of enamines were outlined. On this basis, the lineshapes of the PES spectrum of 94 are atypical. Usually, the 1st IP is broader than the 2nd IP, for reasons introduced earlier.[125] With 94 though, the situation is reversed. One can conclude that since the 1st IP band of 94 is relatively sharp, then the normal geometry difference between the pyramidal ground state and the planar radical cation of an enamine must be substantially reduced. That is, there is minimal geometry change when an electron is removed from the HOMO of 94. This implies that the enamine nitrogen of 94 is near planarity in the ground state.

The 1st IP value is found at 7.6 eV. This compares favourably to that measured for morpholinocyclohexene and morpholinocyclopentene (Table 3). This may indicate that 94 is equivalent in reactivity to the morpholine derived enamines which would also imply that the pyrrolidine derived enamines are more reactive than 94.

The value of 9.0 eV for the 2nd IP of 94 is surprisingly low. The enamines of Table 3 have 2nd IP's (9.3-9.9 eV) that are greater than this value. The conjugation of the azo function of 94 with the exocyclic double bond may account for this finding.[146]

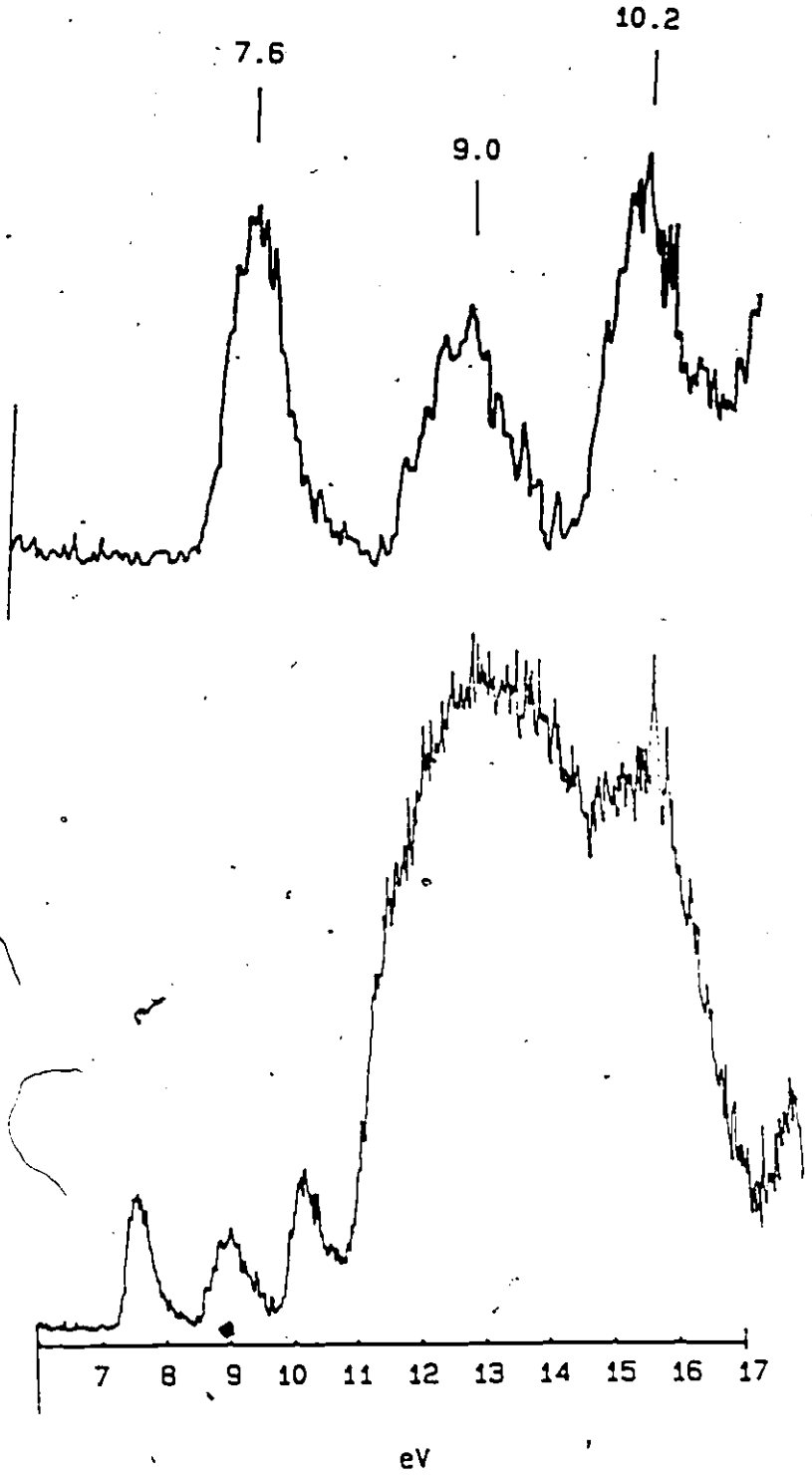
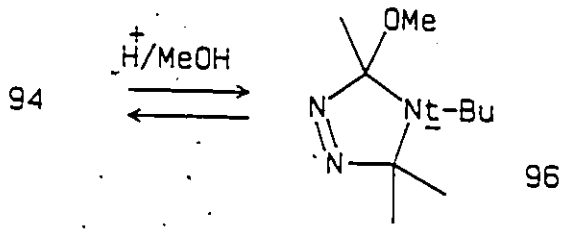


Figure 8. The Photoelectron Spectrum of 94[a]

[a] A MINDO calculation of 94 gave peak positions consistent with the observed spectrum.[267]

The other discernable band of Figure 8 is the 3rd IP of 94 which appears at 10.2 eV. This is due to an electron driven from a molecular orbital extending throughout the pπ system and including the quaternary t-Bu carbon.[267]

The nmr data and PES spectrum indicate that 94 should indeed have enamine-like reactivity. Chemical evidence for this is shown when 94 is dissolved in MeOH containing a catalytic amount of acid. An equilibrium between 94 and methoxytriazoline 96 is established (Scheme 51).[122,268]



Scheme 51

Proton and ^{13}C nmr spectra of the equilibrium solution were obtained. Using the spectral data of oxadiazoline 91 ($X=O, R_1=R_2=R_3=R_4=CH_3$) for comparison,[269] peaks consistent with structure 96 were observed. The ratio of 94:96 is 1.75.

The statement that 94 and 96 are in equilibrium is supported by the ^{13}C nmr spectrum of 94 when dissolved in acidic MeOD. Since broad-band proton decoupling enhances the signals of carbons bearing protons, and since the methylene carbon signal of 94 virtually disappears, the indication is that the site has become fully deuterated. This observation is best explained if 94 and 96 are in equilibrium.

Facile decomposition of 96 during manipulation and/or concentration of the mixture precludes its isolation.

The thermal stability of 94 is quite surprising. Refluxing 94 in $CHCl_3$ for several days gives only starting material. Similar treatment of

94 in neutral MeOH leads to the loss of 94 to give an unidentified dimer. Either way, the thermal chemistry of 94 is not useful. The exocyclic double bond tends to render 94 particularly stable with respect to loss of N_2 in inert solvents and the enamine and azo functionalities induce undesired transformations in a more chemically active solvent (MeOH).

The principal reason for the problem turned out to be the key to the solution. Use of the enamine functionality to quaternize the sp^2 ring carbon of 94, as was done to generate 96, led to triazolines with more favourable and useful thermolysis chemistry.

The initial attempts to generate more thermolabile triazolines were via [2+2] cycloaddition chemistry and a discussion of these efforts comprises the content of the following section.

The [2+2] Cycloaddition Chemistry of 4-t-Butyl-3,3-dimethyl-5-methylene-Δ^1-1,2,4-triazoline (94)

The initial substrates chosen for [2+2] cycloaddition with 94 were acrylic acid and methacrylic acid derivatives. Thus, diastereomeric spiroaziridines 97a (88%) and amidrazones 98b (70%) and 98c (~70%) were obtained when 94 was heated in neat acrylonitrile, methacrylonitrile, and methyl methacrylate respectively.

Aziridines 97a were obtained as a 50:50 mixture of diastereomers, partially separable by gas chromatography. The isomers were identified by way of their ^1H and ^{13}C nmr spectra. A 500 MHz ^1H nmr spectrum, although not fully resolved requires that the methylene and methine protons are attached to a rigid carbon framework. This observation is in keeping with the assignment of a 4-membered ring.

The proof that N_2 has been lost is found by inspecting the ^{13}C nmr data. By analogy with triazolines 94 and 96, if the product obtained still contained N_2, then the quaternary ring carbons would resonate at 100 110 ppm. This is not observed. All signals in the 41-55 ppm range are assigned to aziridine ring carbons, consistent with quaternary carbons bearing one nitrogen.

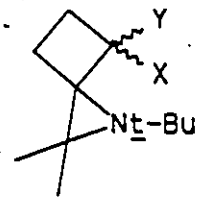
The ^1H nmr spectra of 98b and 98c each showed two methyl groups attached to an unsaturated carbon. This allows one to conclude that the triazoline ring has been opened. Also, the ^1H nmr spectra indicated four magnetically non-equivalent protons all coupling one another, in a rigid environment, thus providing evidence for the 5-membered ring. The infrared spectra of 98b and 98c gave broad bands near 1670 cm^{-1}, consistent with the presence of two similar C=N bonds.

It is believed that in these cases a 1,4-zwitterion is formed initially, by analogy with previous proposals.[149,154] The fate of zwitterion 100 can be depicted by three pathways, one of which leads to the spiroaziridine product (97a) (Scheme 52).

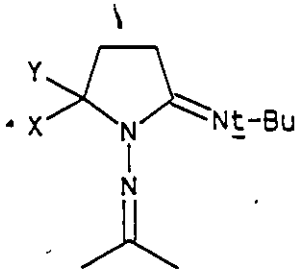
Aziridine 97a is ultimately formed after 100a closes in a 4-exo manner to yield spirotriazoline 101. At 80°C (reaction conditions), 101 extrudes N_2 and the ensuing ylide 102 then smoothly closes to 97a. Four diastereomers are possible but fast nitrogen inversion allows for the detection of only two.

Presumably 100b and 100c would have the identical pathway available except that the presence of the additional methyl groups (X=Me) increases the steric hindrance of the 4-exo closure. This increase is sufficiently large to prevent cyclobutane formation. The lifetimes of 100b and 100c are extended for this reason. The result is that other modes of decomposition of 100b and 100c are allowed to come to the forefront.

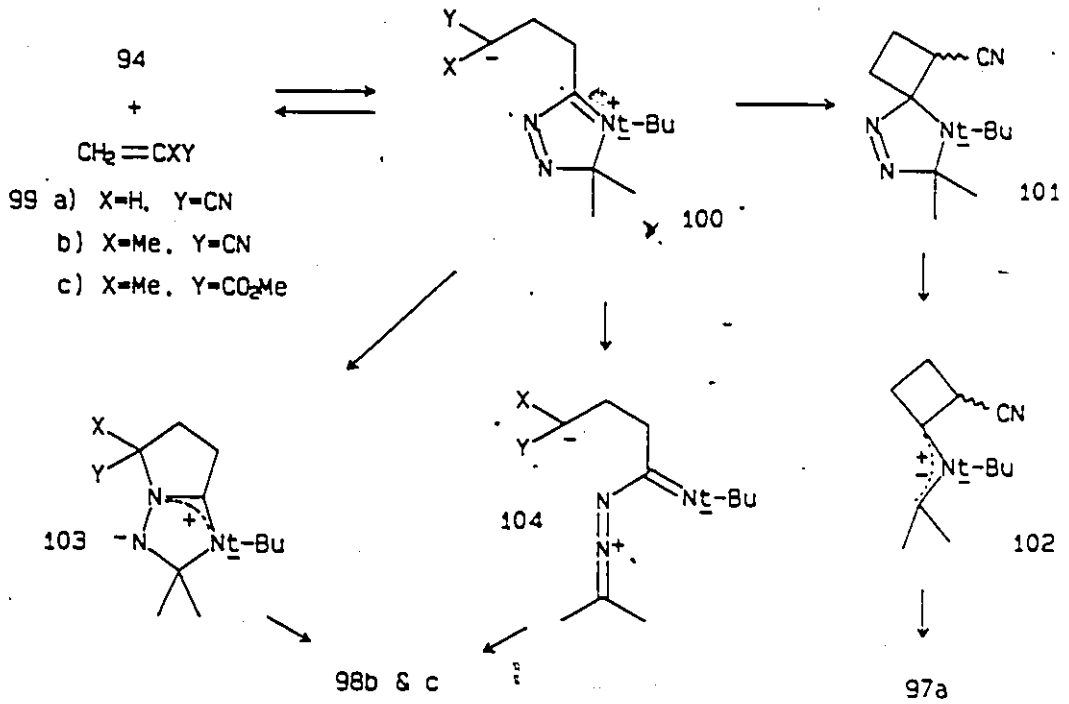
One such alternative route for zwitterion decay is by way of a less sterically encumbered 5-exo closure onto the azo group yielding azomethine imine 103. Subsequent ring opening of the original triazoline ring provides 98. This route has a drawback however. Although closure to 103 is a 5-exo-trig closure,[270] the near planarity of the cationic ring system of 100 adds structural restrictions to the approach of the carbanionic centre, giving the process a degree of difficulty more in line with that of a 5-endo-trig closure.[270] This difficulty is circumvented if the triazoline ring opening precedes the 5-exo closure. The stereoelectronic requirements for forming 104 are well provided for in 100 and there is precedent for such a transformation.[271] Acyclic zwitterions 104, species having greater flexibility than 100, then undergo the closure affording 98b and 98c.



97 a) Y=H, X=CN
b) Y=Me, X=CN
c) Y=Me, X=CO_2Me



98 b) Y=Me, X=CN
c) Y=Me, X=CO_2Me



Scheme 52

For mechanistic reasons both routes yield 98b and 98c having the same configuration about the C=N<u>t</u>Bu function. That geometry, as drawn, also minimizes non-bonding interactions.

The concept of a 1,4-zwitterion not closing to a [2+2] adduct, but rather decaying in another manner comes from the work of Boyd and coworkers.[192]

Treatment of 94 with acetone cyanohydrin in acrylonitrile, MeOH or methylene chloride gave arizidine 105 in 42-47% yield. Aziridine 105 was identified on the basis of its simple spectral data. The lack of a ^{13}C nmr resonance near 100-110 ppm provides evidence that the product does not have the azo functional group.

Presumably the acetone cyanohydrin acts as its own acid and protonates 94 at the β-carbon (Scheme 53). The resulting intermediate (106) then adds cyanide which was expelled during acetone formation. Triazoline 107 is not detected, nor is azomethine ylide 108 which is assumed to be formed after N_2 is extruded from 107. Rapid electrocyclic ring closure of 108 yields 105. Acrylonitrile and methanol are effective dipolarophiles,[13,272,273] yet 108 could not be intercepted even in neat trap.

When sulfene was generated in the presence of 94, spiroaziridine 109 was obtained in 40% yield. The distinctive ^{1}H and ^{13}C nmr chemical shifts[172] of the thietane ring protons and carbons are consistent with the assigned structure. Since the thietane ring proton signal appeared as an ab quartet, the molecule must have an effective plane of symmetry. This is attributed to facile aziridine ring inversion at room temperature. The

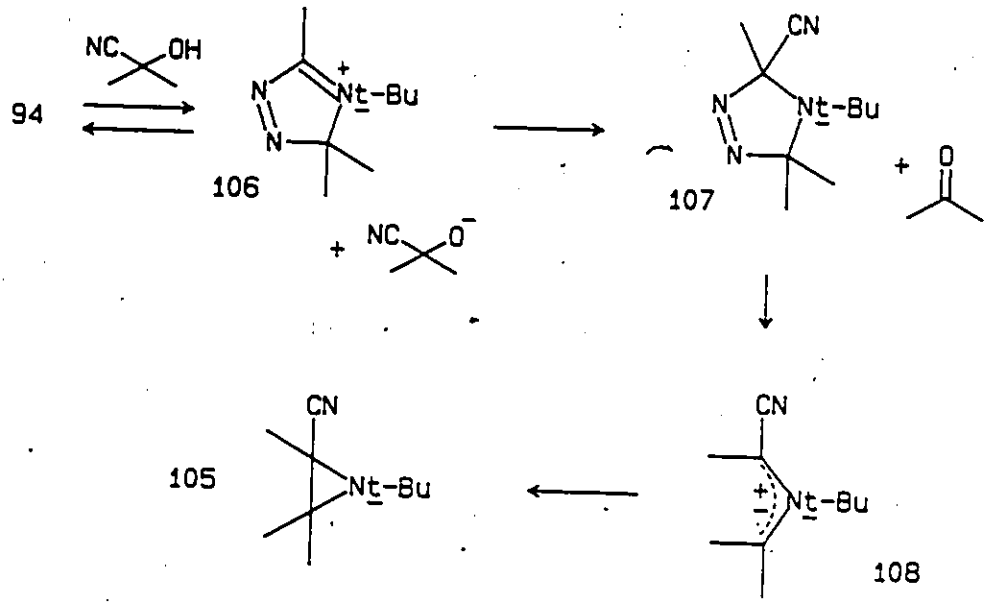
presence of three ^{13}C nmr resonances in the 41-55 ppm range indicated that the azo function has been lost.

The regiochemistry of the [2+2] cycloadduct is consistent with previous observations[171] and with FMO theory.[41] Once again no triazoline (i.e., 110) was detected in the reaction mixture. Loss of N_2 and closure of the resultant ylide must be rapid.

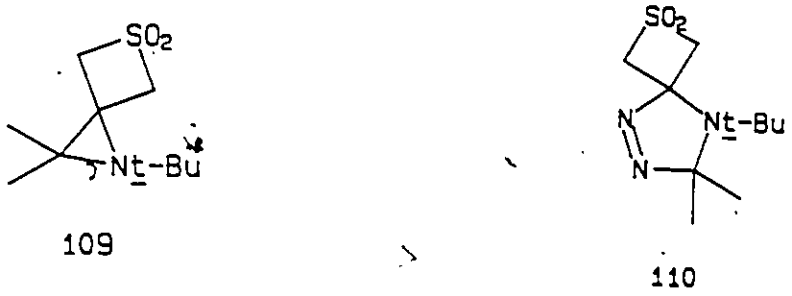
The failure of neat acrylonitrile to trap ylides 102 and 108 is somewhat surprising. The rate constants for 1,3-dipolar cycloadditions are generally quite high.[13] The ylides proposed (i.e., 102 and 108) as precursors to the aziridines obtained are highly substituted. The nitrogen bears a t-Bu group and the ylide termini each bear non-hydrogen substituents (Figure 9). Normally, 1,3-dipoles are at their energy minima when they are planar, a geometry which maximizes π-bonding.[81,274,275] From this configuration a high energy barrier often slows formation of a 3-membered ring.[13,81] However, with dipoles such as 102 and 108 the steric congestion may prevent the ylides from attaining a planar geometry and indeed the configuration taken by these ylides after loss of N_2 may be along the pathway for aziridine formation.

A different explanation incorporating similar principles says that the planar geometry is the energy minimum of the ylides. In the cases of sterically hindered ylides the minima would have to be at a high energy level, thereby substantially reducing the barrier to electrocyclic ring closure (Figure 10).

It should be realized that aziridine formation lessens steric congestion of the planar ylides in two ways. The elimination of π-overlap



Scheme 53



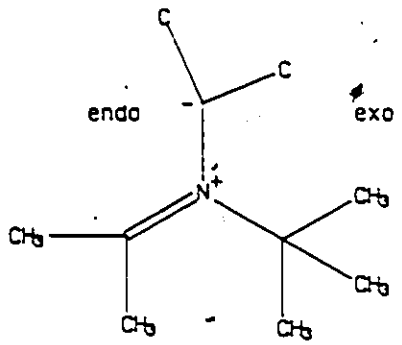


Figure 9. A Sterically Hindered Ylide

lengthens C-N bonds thereby extending the t-Bu group away from other aziridine substituents. As well, going from a planar geometry, where the t-Bu group eclipses the exo substituents of the ylide, to a rapidly

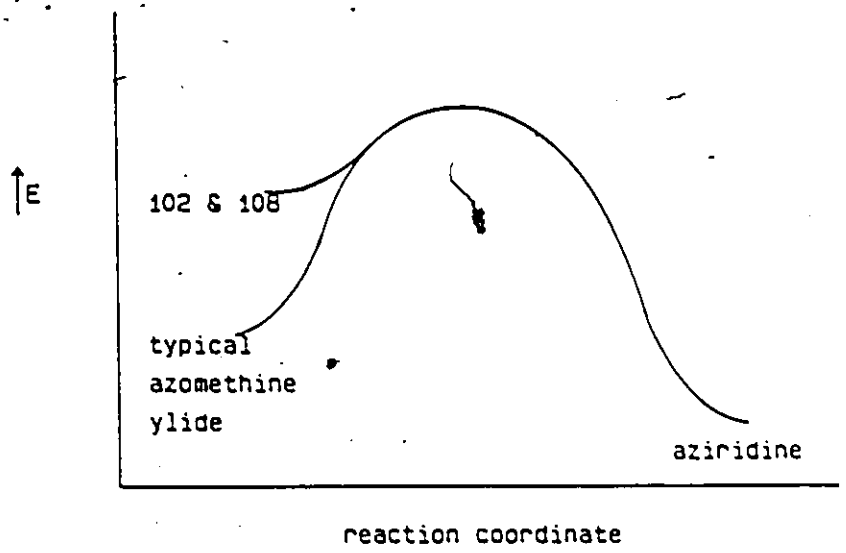


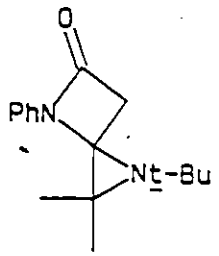
Figure 10. Energy Profile for Ylide Closure

inverting aziridine where the t-Bu group virtually bisects both pairs of aziridine substituents, is also a relief of steric encumbrance. High energy dipoles showing particularly large rate constants for ring closure have been noted previously.[71,276,277]

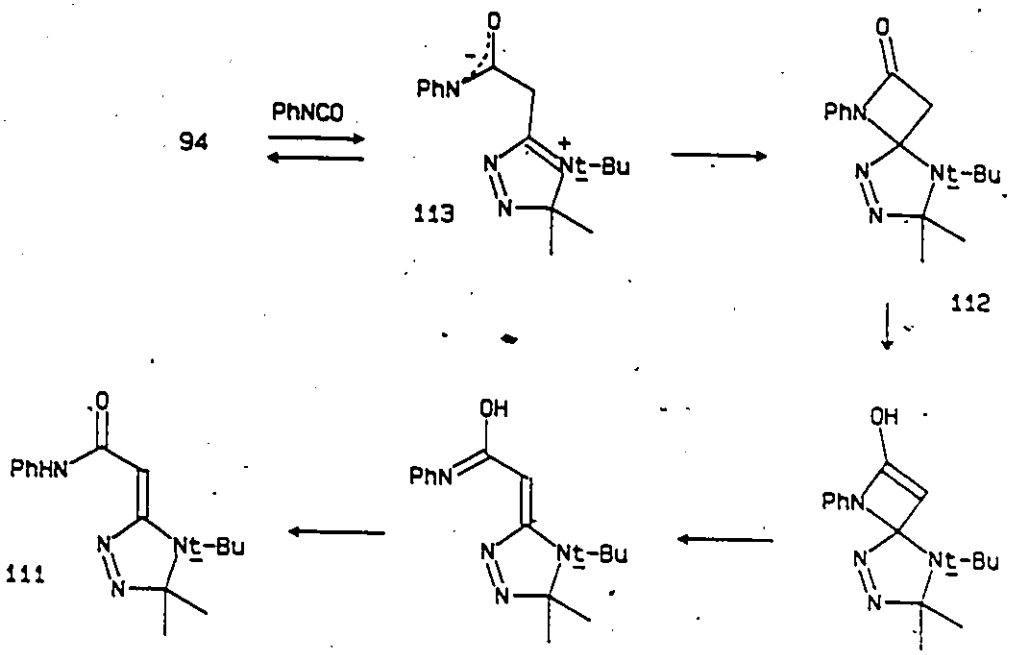
Treatment of 94 with phenyl isocyanate in chloroform, provided amidotriazoline 111 in 62% yield, rather than triazoline 112 or aziridine 114. The monovinylogous urea structure is consistent with that obtained from enamines with at least one β-hydrogen. The geometry about the exocyclic double bond of 111 was verified by nOe experimentation. Irradiation at the t-Bu frequency enhanced the ^{1}H nmr intensity of the vinyl hydrogen by 26% (see Table 6, page 72). Other ^{1}H and ^{13}C nmr spectral data are consistent with the structure indicated.

The mass spectral data of 111 deserves discussion. Under electron impact (ei) conditions the molecular ion peak was not observed, but there was a peak at m/z=258 corresponding to M^+-N_2. Chemical ionization (ci) mass spectra (NH_3 or CH_4), on the other hand, gave a signal at m/z=289 corresponding to $(M+3)^+$. In the ci(NH_3) mass spectrum the signal for m/z=289 was the most intense one, while in the case of ci(CH_4) the relative intensity for m/z=289 was 9% (base peak, m/z=110) and there were additional signals at m/z=288 (8%) and 287 (32%). This apparent reduction of 111 by NH_3 and CH_4 in the mass spectrometer was given credibility when it was determined that diethyl azodicarboxylate, an azocarbonyl compound known to have a low reduction potential,[278] also gave a significant m/z=$(M+3)^+$ signal under similar ci conditions.

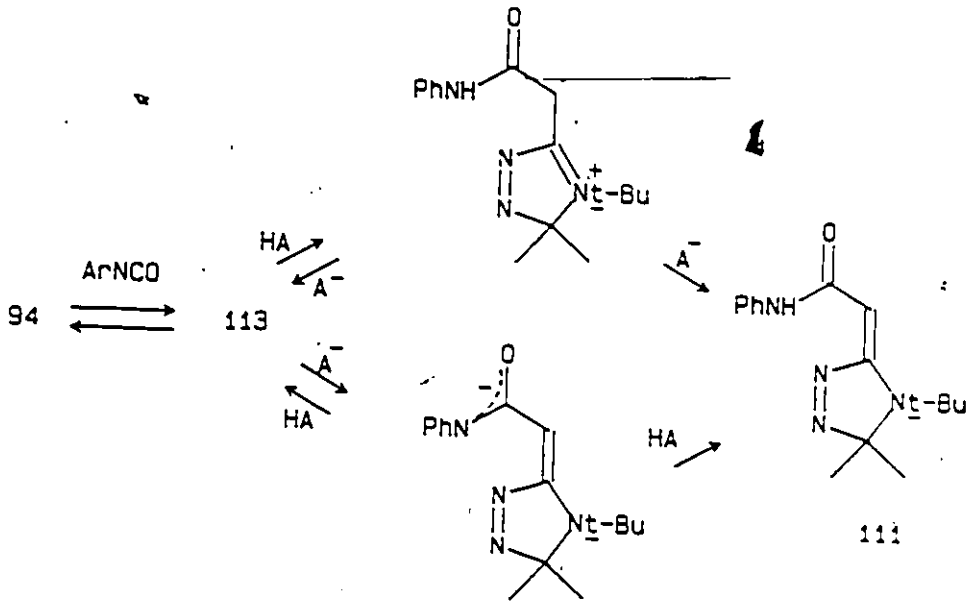
The mechanism of formation of 111 may well be analogous to that introduced in Scheme 25. Scheme 54 depicts this mechanism as it applies to the formation of 111. Since no mechanistic evidence has been forwarded to support this pathway (Schemes 25 and 54), the possibility of 111 forming by way of an initial zwitterionic intermediate (113) and subsequent proton transfers, must be considered (Scheme 55). The HA/A^- acid-base pair is unidentified but may be adventitious impurities or some of the ionic intermediates themselves. The set of transformations of Scheme 55 is preferred over the generally accepted mechanism (Schemes 25 and 54), since no intermediates were detected while the reaction was monitored by ^1H nmr. Species such as those depicted in Scheme 55 would be expected to be



114



Scheme 54



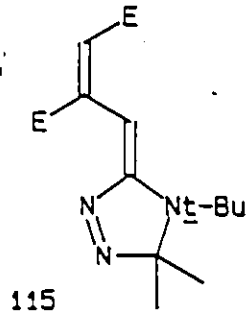
Scheme 55

short-lived, but 112 which is a necessary component in the alternative mechanism (Scheme 54) would be expected to lose the azo nitrogen or to accumulate. Since the azo nitrogen is still present in the product, 112 should be an intermediate observable by ^1H nmr spectroscopy.

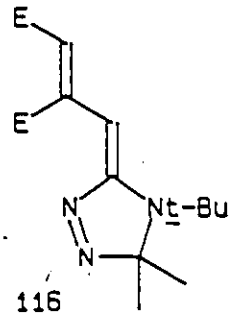
The reaction mixture from DMAD and 94 proved to be less trivial than those just described. Three products, 115, 116, and 117, were isolated from both CH_2Cl_2 and MeOH but in different amounts. An astounding solvent effect on the product yields was found for this reaction (Table 5).

Products 115 (E,E) and 116 (E,Z) were identified as Michael adducts on the basis of their spectroscopic data. Azobicycloheptene 117 was identified by means of single crystal X-ray crystallography.

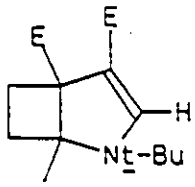
Geometric isomers 115 and 116 were assigned their respective geometries by way of the following criteria. One compound, the major



115



116



117

Table 5: Solvent Dependencies on Yields of 115, 116 and 117.

Solvent	115	116	117
MeOH	72	5	19
CH_2Cl_2	17	4	52

isomer was eluted more rapidly on both TLC plates and on a silica HPLC column. It is known that maleic esters are more polar than fumaric esters because of their additive ester dipole moments. The ester dipoles of fumarates are opposing and thus their net dipoles are somewhat reduced.[279,280]

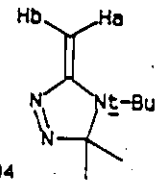
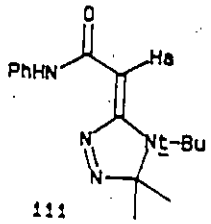
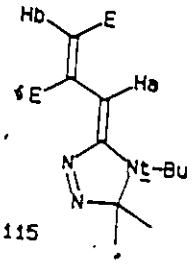
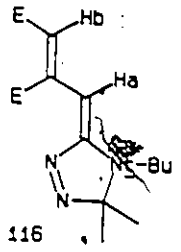
The ultraviolet absorption of the major isomer was found to be at longer wavelength and it had a greater transition probability, both consistent with fumaric esters which are allowed to lie flat and are not distorted from planarity. Maleates are twisted and therefore have a lesser transition probability and require more energy for excitation.[281]

Lastly, nOe measurements on the two geometric isomers provided still more evidence for their assignment. Irradiation at the t-butyl frequency and observation of the ^1H nmr signals of the vinyl protons gave significant enhancement of the exocyclic vinyl group protons of both 115 and 116, but only in the minor isomer was the terminal vinyl proton noticeably enhanced (Table 6). This is consistent with the terminal proton (H_b) being syn to the t-butyl group as it is in 116.

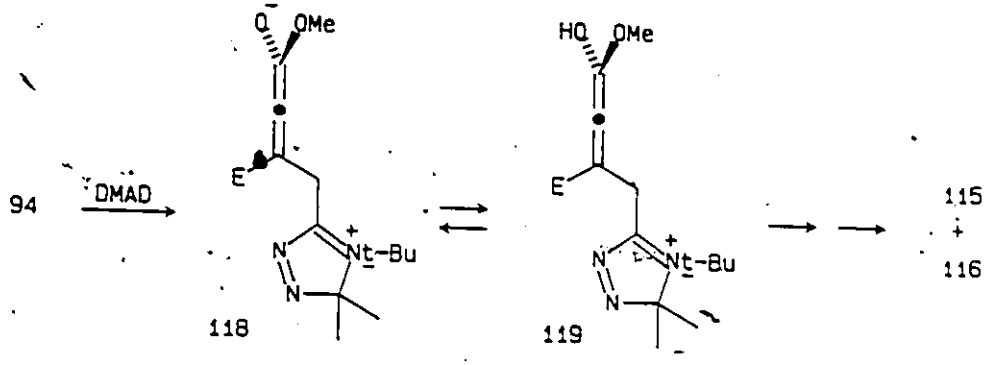
The above observations are consistent with 115 having the E,E geometry (fumarate) and 116 having the E,Z (maleate) configuration.

The nOe data also provide a basis for the assignment of the geometry about the exocyclic double bonds of 115 and 116. Using the enhancements of 94 as a guide (Table 6), then the exocyclic vinyl group hydrogen must be cis to the t-Bu group. Such a geometry is not unexpected in view of the steric interactions that would be present in the other isomers (Z,E and Z,Z). No products having the Z-configuration about the exocyclic double bond were detected.

Table 6: Noe Enhancements of Vinyl Hydrogens of Δ^1-1,2,4-Triazolines

Hydrogen	% Enhancement	
	Ha	Hb
 94	35	10
 111	26	-
 115	36	0
 116	45	9

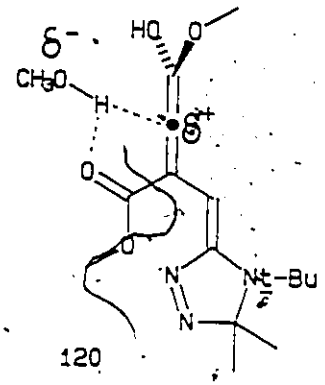
The finding that Michael adducts comprise the major portion of the MeOH reaction mixture is in keeping with previous results.[186-188] The mechanistic route to 115 and 116 begins with an encounter to form zwitterion 118. Rapid protonation at the oxygen of 118 provides an allenol which yields the observed products by way of several prototropic shifts (Scheme



Scheme 56

56; cf., Scheme 55). Each of these transfers is intermolecular because simple 1,3-H shifts must be antarafacial and are thus structurally unfeasible.[90] The intermolecularity of the proton transfers was confirmed when the reaction was performed in CH_3OD. The terminal vinyl positions of 115 and 116 were fully deuterated.

The preference for formation of 115 over 116 may be due to intramolecular influence during a reprotonation step. Intermediate 120,



120

which lies between 119 and the Michael adduct products in Scheme 56, provides a possible explanation for the product ratio. Internal hydrogen bonding to the ester function holds the hydrogen to be transferred in a position facilitating formation of isomer 115.

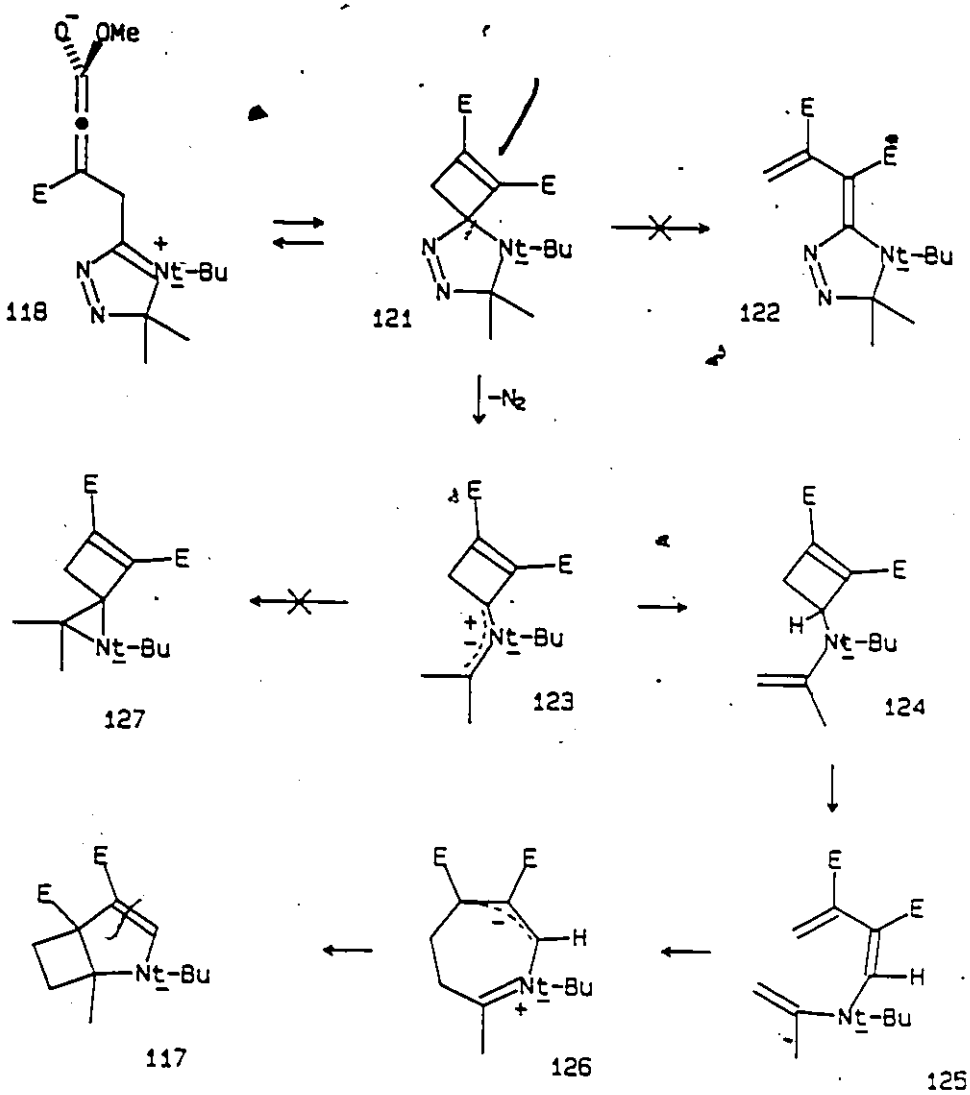
Independent experiments indicated that 115 and 116 are not interconvertible under conditions designed to mimic those of the reaction by which they were formed.

The formation of 115 and 116 in CH_2Cl_2 is less readily rationalized. This solvent cannot be readily deprotonated. Proton transfers must proceed with the aid of small amounts of impurities including water and/or by way of intermolecular reactions of intermediates such as 118, 119 and 120.

Reinhoudt's proposal[181] that cyclobutenes of the type 121 are the first formed species in a DMAD-enamine encounter is not favored in this instance. In MeOH a modest rate of reopening of 121 to 118 could be envisioned but in CH_2Cl_2 the activation energy can be expected to be substantially greater. As well, the availability of other facile modes of decomposition of 121 remove the need for the 121 → 118 process (Scheme 57).

A third competing pathway, the electrocyclic ring opening of cyclobutene 121 to give dienamine 122 is also possible, and is the reaction typically observed under non-protic conditions.[182-184] However, no products arising from 122 were detected, nor was 122 itself a detectable product.

The likely route chosen by 121 begins with the electrocyclic extrusion of N_2 yielding azomethine ylide 123. Ylide 123 could close to aziridine 127 by analogy with ylides 97a and 108, but this possibility can be excluded because 127 was not detected and the ring opening of 127 to regenerate 123 is a process that requires temperatures much greater than 25°C.[84] Instead that ylide (123) undergoes a known 1,4-hydrogen shift affording 124. At this stage, with the particularly facile reaction having taken place, the cyclobutene moiety ring-opens to trienamine 125. This process probably gives rise to two geometric isomers about the

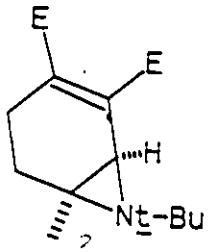


Scheme 57

non-terminal carbon-carbon double bond. The geometry indicated by 125 is that which is required for subsequent reactions on the way to 117. Since 117 is obtained in greater than 50% yield, then either 125 is formed preferentially or there must be some mechanism for its isomer to convert to the required geometry, i.e. that of 125. An uncharacterized species, having acidic properties could catalyze the transformation.

An 8-electron electrocyclic ring closure by 125 provides 126 which is another azomethine ylide. This step can also be perceived as an intramolecular Michael addition by an enamine.

The 125 → 126 pathway can be viewed in yet another way. An intramolecular Diels-Alder reaction by 125 would afford bicyclic aziridine 128. Subsequent ring opening of 128 would give 126. A 1,5-electrocyclization of 126 yields azobicycloheptene 117.



128

Acheson has suggested an equivalent mechanism, for conversion of an analog of 124 to a skeleton identical to that of 117.[199]

When the reaction of 94 with DMAD was followed by ^{1}H nmr spectroscopy the growth and decay of several intermediates could be observed. Thus, several transient species are present in the mixture, as is required for the postulated mechanism.

The 1,3-Dipolar Cycloaddition Chemistry of 4-t-Butyl-3,3-dimethyl-5-methylene-Δ^1-1,2,4-Triazoline (94)

In the preceding section, most of the triazolines proposed to account for the observed products are transients. There is one exception, though. Triazoline 96 has a prolonged lifetime and can be observed by ^1H and ^{13}C nmr spectroscopies.

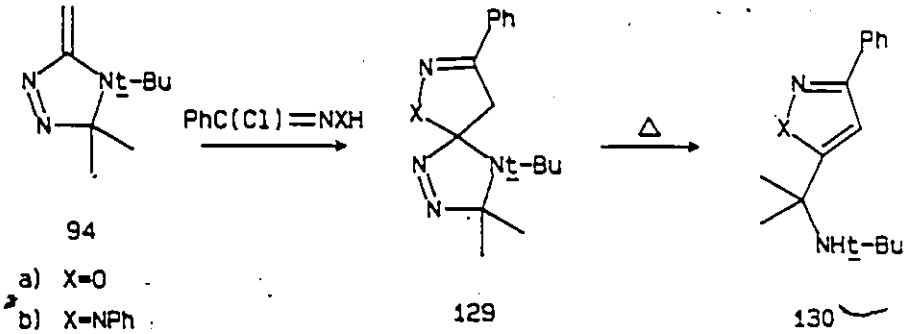
A second set of triazolines may also have significant lifetimes at room temperature. Triazoline 112 and its enol tautomer (Scheme 54) are part of a possible mechanism proposed to account for the formation of 111 and they do not lose nitrogen. Indeed, the azo group must remain present for 111 to form. Although Scheme 54 is not the preferred mechanism, the presence of 112 in the reaction mixture, which yields 111 is still a strong possibility. Interestingly, 112 and 96 have a similar quality. They each have a third heteroatom attached to one of their triazoline ring carbons.

This inherent stability is surprising. Intuition suggests that an added heteroatom would accelerate nitrogen extrusion from triazolines. Obviously, this is not the case and the persistence of triazolines such as 96 should be investigated further. One method of obtaining similar triazolines would be to treat 94 with 1,3-dipoles which bear a heteroatom at one of their termini.

The first two 1,3-dipoles chosen for reaction with 94 were benzonitrile oxide, Ph-C≡$\overset{+}{N}$-$\bar{O}$ and diphenylnitrile imine, Ph-C≡N^+-$\bar{N}$-Ph. These were chosen not only because they provided a heteroatom at the desired position but also because they are known to react with enamines at room temperature or lower.[14] Indeed such cycloadditions were achieved with 94

and both dipoles. Treating 94 with benzoyl chloride oxime[282] and triethylamine at -30°C for 15 minutes afforded 129a in 77% yield. Benzoyl chloride phenylhydrazone[283] together with triethylamine and 94 provided 129b in 84% yield after 40 hours at room temperature (Scheme 58).

Structures 129 were assigned as the triazolines resulting from 1,3-dipolar cycloaddition of the two substrates with 94 based on their spectral data. The ^{1}H nmr spectra of 129a and 129b each showed two magnetically non-equivalent methyl groups and the methylene protons appeared as ab quartets, demonstrating their non-equivalence. The ^{13}C nmr spectra support the suggestion that the cycloaddition proceeded with the expected regiochemistry[14] and that the azo function was still present in the products. The triazoline ring carbons resonated at 128.63 and 104.68 ppm for 129a and at 119.58 and 102.68 for 129b. These chemical shifts are in keeping with the values expected based on the number of adjacent heteroatoms (cf., the values for 97a, 105, and 109). Moreover, the presence of a strong band in the 1590-1600 cm^{-1} region of the Raman spectra of both 129a and



94

a) X=O

b) X=NPh

129

130

Scheme 58

and 129b is supportive of a cis azo function.[284]

The mass spectral data of 129, although less informative, are in keeping with the assignments. Molecular ions from 129a and 129b were not detected under electron impact conditions. Rather, weak m/z=$(M-N_2)^+$ and significant m/z=$(M-N_2-CH_3)^+$ fragments were observed. Under chemical ionization conditions the expected $(M+1)^+$ ions were observed.

Triazolines 129 are the first isolable Δ^1-1,2,4-triazolines with sp^3 ring carbons. With 129 in hand, the next step was to investigate their thermolysis chemistry, with the hope that they would be useful precursors to azomethine ylides.

Thermolysis of 129a and 129b in benzene afforded isoxazole 130a and pyrazole 130b respectively, in high yield (89% and 94%) (Scheme 58). Unfortunately these are also the products when the pyrolyses are carried out in methyl acrylate or DMAD, two efficient dipolarophiles.[14]

Heterocycles 130 were identified on the basis of the spectroscopic data which correspond well to those of other known similar heterocycles (Table 7). One significant aspect of the nmr data is that the gem-dimethyl groups appear as singlets indicating their magnetic equivalence. This provides strong evidence for the opening of the triazoline ring during the formation of 130 from 129.

The infrared spectra depicted NH stretching bands at 3355 cm^{-1} (130a) and 3378 cm^{-1} (130b). The mass spectra of 130 showed a weak m/z=M^+ signal under ei conditions. A signal at $(M-CH_3)^+$ was significant in both instances. Under ci conditions, the expected m/z=$(M+1)^+$ peaks were evident in both spectra. Finally, an interesting similarity was noted between the ei mass spectra of 129a and 129b and those of 130a and 130b. Among other

Table 7: NMR Chemical Shifts of Aromatic Heterocycles

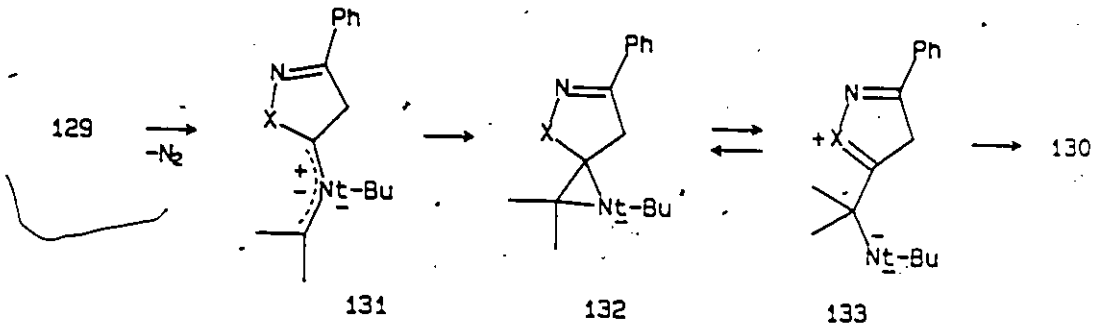
Heterocycle	Chemical Shift (ppm)[a]			
	^1H	^{13}C		
	4-H	3-C	4-C	5-C
isoxazole	6.41[285]	149.1[286]	103.7	157.9
3-phenyl-5-methylisoxazole	6.20[b,287]	169.6[288]	100.3	160.3
130a	6.37	162.36	98.10	181.20
1H-pyrazole	6.31[289]	134.6[c,290]	105.8	136.6
3-phenyl-1H-pyrazole	6.60[289]	150.2[c,290]	103.7	134.4
1-phenyl-1H-pyrazole	6.46[289]	140.98	107.1	126.2
130b	6.57	149.98	102.50	154.16
1-phenyl-1,2,3-triazole(141a)[292]	7.81	-	134.0	121.7
1-phenyl-5-(isopropylaminomethyl)-1,2,3-triazole (145)[293]	7.66	-	133.3	136.3
137a	7.64	-	132.04	138.58

[a] In $CDCl_3$ unless otherwise noted.

[b] In CCl_4. [c] In CD_2Cl_2

peaks, the background of 129a and 129b contained the characteristic spectrum of 130a and 130b, respectively. This is presumably due to some 129 being transformed into 130 during the heating process which is performed in order to volatilize 129 at the inlet of the mass spectrometer.

The mechanism of the transformation of 129 to 130 is not readily recognized. A possible pathway to 130 is outlined in Scheme 59. As has been observed with more thermolabile triazolines (e.g., 101, 121), N_2 is probably lost during pyrolysis. The resulting azomethine ylide (131) would be expected to close quickly to aziridine 132 due to the non-bonding interactions amoung the five ylide substituents. This is another case where sterically congested ylides form 3-membered rings with unimolecular rate constants large enough to prevent cycloaddition to a dipolarophile (cf. 97a, 108).[71,276,277] Thus, the failure of methyl acrylate and DMAD to



Scheme 59

trap 131 is not surprising.

The ring opening of 132 then follows via a mechanism which may be intramolecular as depicted in Scheme 59. Finally, deprotonation from the ring by the negatively-charged nitrogen allows for the aromatization of the heterocycle.

Other mechanisms may be possible but two features must be part of any proposal. The carbon bearing the gem-dimethyls must end up attached to the ring and the bond attaching the N-t-Bu to the ring must be broken. The conversion of 5-aminoisoxazolines to deaminated isoxazoles is commonplace[294-296] and serves as suitable precedent for the 132 to 130 transformation. Deamination of 5-aminopyrazolines to yield pyrazoles is also known to proceed readily.[297-299]

Since the spirotriazolines (129) decomposed fairly cleanly to azomethine ylides, the activation parameters for the decomposition of 129 could be obtained. Solutions of triazolines 129 and benzene were degassed and sealed into nmr tubes. The tubes were immersed in a constant temperature bath and were withdrawn periodically for integration of the ^1H nmr spectra. In the 40-80°C range, the decomposition was found to comply with the first order rate law. The rate constants obtained are listed in Table 8 and the activation parameters calculated from them are found in Table 9. The standard errors accompanying the activation parameters are calculated from the linear regression data which yielded the parameters[300] (see Experimental). The error values are quite small and since the nmr method that was used for acquiring the rate constants is rough, the expected error range is more likely to be ± 1.5 for $\Delta H^{\ddagger}$ and Ea, and ± 3.0 for $\Delta S^{\ddagger}$.[277,301]

The $\Delta S^{\ddagger}$ values (-1.7 and -0.3 eu) are in good agreement with values from the literature for nitrogen extrusion reactions.[301] The kinetic parameters are therefore supportive of the proposed mechanism (Scheme 59), with the first step irreversible and rate-limiting.

Table 8: Decomposition Rates of 129a and 129b in Benzene[a]

Temperature	129a $10^5 k/sec^{-1}$	129a $t_{1/2}$	129b $10^5 k/sec^{-1}$	129b $t_{1/2}$
40	.381	50.5 hr	.206	93.4 hr
50.5[b]	1.46	13.2 hr	.815	23.6 hr
60	4.71	4.1 hr	2.42	8.0 hr
69	1.37	84 min	7.94	145 min
80[c]	44.4	26 min	27.6	42 min
80	45.8	25 min	26.7	43 min

[a]Starting [129] = 0.069 M at room temperature unless otherwise indicated.
[b]51°C for 129b.
[c][129a] = .104 M; [129b] = .100 M.

Table 9: Activation Parameters for Decomposition of 129[a]

Parameter	129a	129b
$\Delta H^{\neq}$/kcal mol^{-1}	25.6 ± 0.1	26.4 ± 0.5
$\Delta S^{\neq}$/eu	-1.7 ± 0.4	-0.3 ± 1.5
Ea/kcal mol^{-1}	26.4 ± 0.1	27.1 ± 0.5
log A	13.0 ± 0.1	13.2 ± 0.4

[a]The method of calculation of standard error is described in experimental.

Two other dipoles were reacted with 94. Phenyl azide would not react with 94 at room temperature. Heating to 80°C in benzene for >24 hours was required and the chances of isolating spirotriazoline 134a were therefore reduced. Thus, only compounds believed to be derived from 134a were isolated. Triazoline 94 is an enamine and therefore the 1,3-dipolar cycloaddition with azides is predicted to be controlled by HOMO(olefin)-LUMO(dipole) interactions. Since substitution of a para-nitro group onto phenyl azide is known to lower the LUMO energy level of the azide and to render it more reactive toward π-excessive double bonds,[14] p-nitrophenyl azide was reacted with 94. An isolable triazoline (134b) was obtained in 65% yield.

The spectroscopic properties of 134b are similar to those of 129. In the ^{1}H nmr spectrum, the geminate methyl groups furnished two singlets and the methylene protons appeared as an ab quartet. The ^{13}C nmr spectrum was supportive of the assignment, with ring carbon signals (114.12 and 104.11 ppm) comparable to those of 129.

The ei mass spectrum of 134b provided a peak at m/z=$(M-N_4)^+$ while the ci spectrum gave the expected peak at m/z=$(M+1)^+$. The Raman spectrum of 134b showed a band at 1596 cm^{-1} along with intense nitro signals.

Cycloadduct 134b is a unique spiro species containing a Δ^2-1,2,3-triazoline ring and a Δ^1-1,2,4-triazoline ring. Whereas the background regarding the thermolysis chemistry of Δ^1-1,2,4-triazoline is limited to that which has been described in this thesis, very much is known about N_2 loss from Δ^2-1,2,3-triazolines.[251,252] These triazolines are believed to decompose via a zwitterion rather than an ylide to give

aziridines via ring closure and/or imino species by an alkyl shift as described previously (Scheme 48, page 52).

One would expect the Δ^1-1,2,4-triazoline ring of 134 to decay faster due to the conjugatively stabilized azomethine ylide that results from loss of molecular nitrogen. Breakdown of the 1,2,3-triazoline portion yields a non-stabilized zwitterion (Scheme 48). However, loss of N_2 from the 1,2,3-system may follow extrusion of N_2 from the 1,2,4-ring. If this is indeed the case, then various trends can be expected. For instance, it is known that aziridines rarely result from the breakdown of 5-amino-1,2,3-triazolines.[251,302,303] These 5-amino species often decompose to 1,2,3-triazoles via loss of amine. When the 1-position of the triazoline bears an electron withdrawing group, loss of N_2 leading to an amidine (Scheme 48, path b, R_1=N(R')$_2$) becomes significant and may compete with deamination to the triazole.[251] Finally, spiro-Δ^2-1,2,3-triazolines tend to give ring expanded imino compounds.

With these trends in mind, the thermal decomposition products of 134a and 134b could be readily identified and rationalized. Unfortunately, the decomposition of 134b did not proceed with the clean loss of one or two molecules of N_2. Cycloadduct 134b also cycloreverts to 94 and p-nitrophenyl azide. There is precedent for this reversion reaction and the equilibrium favours azide at higher temperatures.[304] This complication prevented the acquisition of a unimolecular decomposition rate constant for 134b.

For practical ease, the decomposition of 134b was carried out without its isolation. Thermolysis of 134a was also performed in this manner since it could not be isolated in pure form. Refluxing a solution of

phenyl azide and 94 in benzene followed by chromatographic separation provided products 137a, 139a, and 141a in the yields indicated in Table 10. When p-nitrophenyl azide was refluxed with 94 in benzene, compounds 139b (30%), 140b (21%), 143b (19%), 144b (4%) and p-nitroaniline (2%) were obtained.

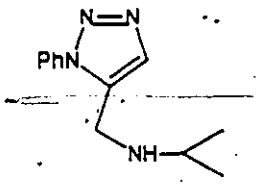
Triazole 137a was identified by comparison to similar heteroaromatic species including triazole 145[293] (Table 7). Triazole 141a is a known species and the spectral and physical data obtained for 141a were in keeping with those reported previously.[292,305]

Table 10: Yields of Products from Decomposition of 134a

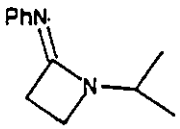
Solvent	% Yield of Product			
	137a	139a	141a	143a
C_6H_6	7%	16%	32%	-
C_6H_6[a]	3	14	14	5
CH_3CN	40	traces	-	-

[a]Initially in C_6H_6 followed by extended thermolysis in toluene.

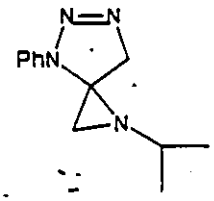
Amidines 139 were identified by comparison of their spectroscopic data to those of amidine 146.[293] The C=N stretch of 139a and 139b appeared at 1674 and 1652 cm^{-1} respectively. The ^1H nmr spectra showed singlets for the methylene groups of 139a and 139b and for their geminate methyl substituents.



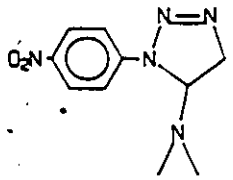
145



146



147



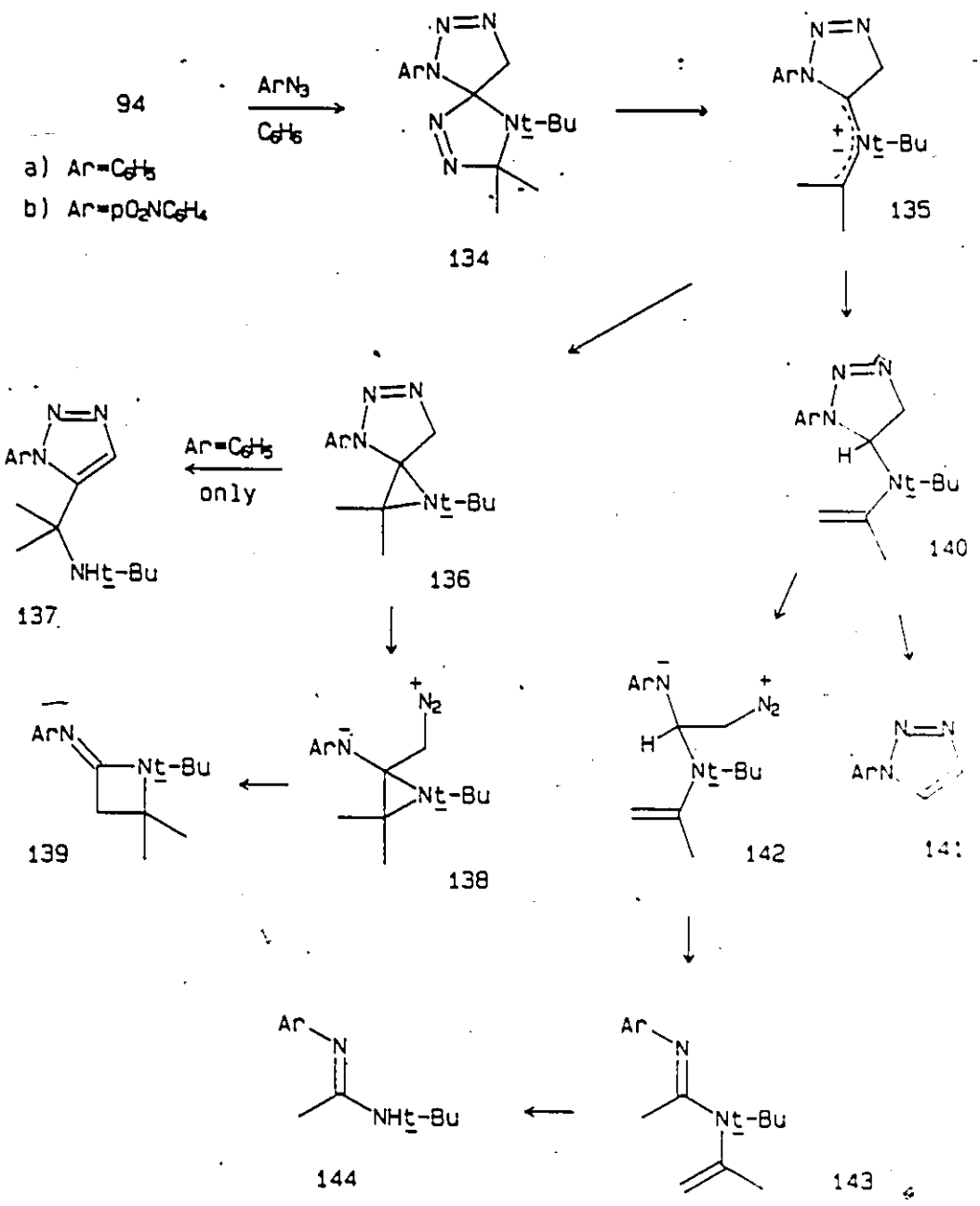
148

The ^{13}C nmr spectra showed signals at 156.66 (139a) and 157.49 ppm (139b) for the amidine carbons. Both values are in the range expected for amidines.[293,306] Although the geometry about the C=N cannot be determined from the spectroscopic data, amidines 139 are believed to possess the E-geometry since amidines with the Z-configuration are rare and are known to isomerize readily to the E-form.[306,307]

Amidines 143b and 144b demonstrate spectroscopic characteristics quite similar to those of 139 and 146. The ^{1}H nmr of 143b displayed a particularly distinctive trait. The methyl groups of 143b are found at 1.97 and 1.88 ppm. These signals are easily distinguished by their shape. The acetamidine methyl singlet is very sharp at 1.88 ppm while the isopropylidene methyl singlet is less intense and broader due to allylic coupling.

The nmr data and the mass spectrum of 144b suggested that the isopropenyl moiety was no longer present. Instead the group was replaced by a hydrogen as evidenced by the presence of an N-H bond at 3422 cm^{-1} in the ir spectrum.

Finally, Δ^2-1,2,3-triazoline 140b was identified by way of its ^{1}H nmr spectrum. The ABX pattern of the ring protons of 5-dialkylamino-Δ^2-1,2,3-triazolines is a readily recognizable feature (Table 11).[308] The other spectral data of 140b were totally consistent with the assignment.


94
a) Ar=C6H5
b) Ar=pO2NC6H4
ArN3
C6H6
Nt-Bu
134
135
140
136
137
Ar=C6H5
only
NHt-Bu
138
139
142
141
144
143

Scheme 60

Table 11: ^{1}H nmr Data of 5-Amino-1,2,3-triazolines

Triazoline	^{1}H chemical shifts(δ)			coupling constants (Hz)		
	H-4cis	H-4trans	H-5	J_{cis}	J_{trans}	J_{gem}
148[308,a]	4.00	4.49	5.32	9	2	17
140a[b]	4.08	4.58	5.47	10.5	3	17.4
140b[b]	4.19	4.72	5.50	10.0	2.9	17.7

[a]60 MHz, [b]500 MHz.

A ^{1}H nmr spectrum of the crude reaction mixture of phenyl-azide and 94 also showed a distinctive ABX pattern and this is ascribed to the presence of 140a in the crude mixture. Only small amounts of 141a could be detected in this crude mixture and because 141a is the ultimate major product it follows that 140a deaminates to 141a during chromatography. A 500 MHz ^{1}H nmr spectrum of the crude reaction mixture from decomposition of 134b showed very small peaks corresponding to 141b,[309] but this species was not recovered during chromatography.

Scheme 60 offers a series of pathways rationalizing the formation of the observed products. Cycloaddition between 94 and azide yields 134 which would be expected to break down with a rate constant similar to those for the decay of 129. This decomposition would generate azomethine ylide 135. Two reactions of 135 then lead to the series of products obtained. A [1,4]-hydrogen shift leads to Δ^2-1,2,3-triazoline 140. 1,2,3-Triazoline 140a deaminates to 141a upon chromatography. Analog 140b survives

chromatography at least to some extent but does decompose with prolonged manipulation. Presumably the nitro group of 140b renders the sp^3 nitrogen of the triazoline ring less nucleophilic and the breakdown of 140b is slowed.

Triazolines 140 however do break down thermally. Zwitterions 142 result from heterolytic cleavage of the triazoline ring. A hydride shift and loss of N_2 affords amidine 143b in the case of 142b. When the reaction mixture containing 140a was heated for longer periods of time a small amount of 143a was detected and identified by its ^1H nmr spectrum. The characteristic methyl group signals of 143b are also present in 143a. Other peaks which allowed the identification were the peaks at 4.91 and 5.20 ppm due to the protons of the terminal olefin of 143a. Only limited spectral data for 143a could be collected since it is a very sensitive species. Triazole 141a is the principal product of the thermolysis of 140a. Species 141a was detected in significant amounts in the crude thermolysis mixture indicating that 141a is not arising during chromatography. Amidine 144b is the product of enamine hydrolysis of 143b. p-Nitroaniline is the product of further hydrolysis of 143b and/or 144b and this process may be occurring, at least to some extent, during chromatography. The expected by-product of this hydrolysis, N-t-butylacetamide could not be found. Not surprisingly, extended refluxing of the mixture containing 140b led to greater yields of 143b, 144b, and p-nitroaniline at the expense of 140b (see Experimental).

The other unimolecular reaction of ylides 135 is the ring closure to 136. Crandall and co-workers[293] have proposed spiroaziridine 147 as an

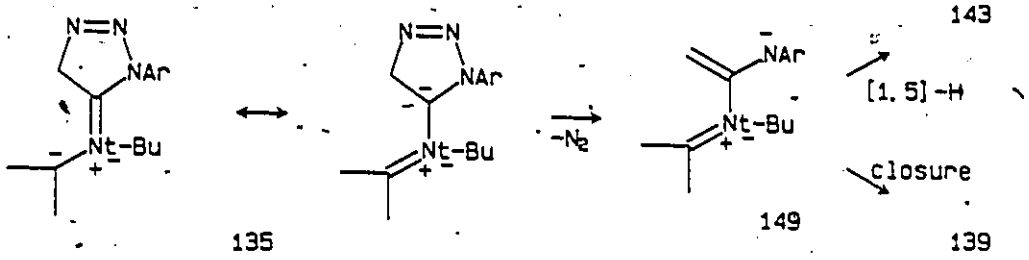
intermediate in the reaction of phenyl azide and N-isopropylmethylene-aziridine. Species 147 was not detected and rapidly decomposed to triazole 145 and amidine 146. The proposed decomposition pathway of 147 is analogous to that displayed in Scheme 60 for the breakdown of 136. Only 136a gives the deaminated triazole (137a). When 136a is generated in CH_3CN, 137a becomes the major product, most likely because the dipolar intermediate involved in the process is stabilized in that solvent. The mechanism suggested for the formation of heterocycles 130 is also a suitable pathway for rationalizing the presence of 137a (Scheme 59).

Amidines 139 are formed by cleavage of the 1,2,3-triazoline (136) to 138 which undergoes an alkyl shift that completes the expulsion of molecular nitrogen and affords the ring expanded species (139). In view of the known greater thermal stability of 1-phenyl-1,2,3-triazolines over their 1-p-nitrophenyl counterparts, it is not surprising that 136a decays to 137a as well as 139a whereas 136b does not lead to 137b.

When a pure sample of 134b was heated in methyl acrylate, no new products arising from 135b were detected.

On the whole, all of the products obtained from 94 and azide can be rationalized with the aid of ample precedent. The pathways of Scheme 60 are fairly secure since 140a can be detected and 140b can be isolated. As well, direct synthesis of 147 by another method lends credence to the proposal that 136 lies on the pathway from 134 to 137 and 139. Although the mechanism of Scheme 60 is sufficient, the possibility that there is another concurrent pathwaycannot be ruled out. Scheme 61 for example, depicts an alternative route for 135 to 139 and to 143. In this mechanism some of the

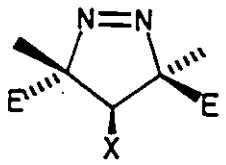
negative charge at one of the termini of ylide 135 can accelerate the loss of N_2 from the 1,2,3-triazoline moiety. The zwitterionic species resulting



Scheme 61

(149) can then close to 139 or deprotonate intramolecularly from a methyl group, affording 143. This latter step can also be perceived as a [1,5]-hydrogen transfer, assisted at least in part by the polarity of 149. Species 149b would be more stabilized than 149a due to the conjugative effects of the p-nitro group. The pathway in Scheme 61 may be more important for the decay of 135b than of 135a.

Unfortunately, there is no model system with which the reactivity of 135, with respect to loss of N_2, can be assessed. Deprotonation of Δ^2-1,2,3-triazolines that have been carried out have occurred from the 4-carbon.[310] Two examples are supportive of the proposal depicted in Scheme 61. Deprotonation from the 4-position of pyrazolines 150 enhances the rate of nitrogen loss by a factor of 10^{12} for X=CO_2Me[311] and 10^{29} for X=CN.[14,32] A closer analogy was suggested by Padwa et al[312] to account for the decomposition of heterocycle 151. Deprotonation from the 5-position of 151 yielded enolate 152 via anionic cycloreversion. The simplest case of anionic cycloreversion probably involves deprotonation from the 2-position of THF and the subsequent generation of ethylene and acetaldehyde enolate.[313]



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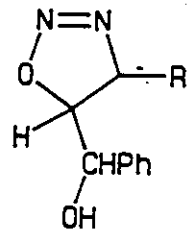

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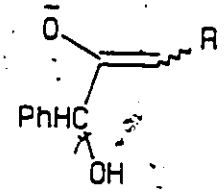


152

Based on these examples, some credibility can be given to the alternative mechanism for the formation of 139 and 143 as depicted in Scheme 61, even if there is not a full negative charge at the 4-position of the 1,2,3-triazoline ring of 135.

The fact that triazolines 129 and 134b can be isolated is truly surprising in light of the thermal instability of triazolines such as 105, 110 and 121. Intuitively one would expect the additional heteroatom to have a destabilizing effect. Analysis of all the examples presented in this thesis allows one to conclude that the size of the spiro ring, if present, has little effect on the stability of the triazoline.

There are three possible explanations for the observed stability of triazolines 129 and 134b. It could be due to the relative energies of the ground state triazolines or of the resulting ylides or both.

Considering the ylide energy levels, ylides 131 and 135b would have to be much more stabilized than those resulting from triazolines 105, 110 and 121. This is unlikely based on the calculated substituent effects on carbonyl ylides.[274] The corresponding stabilization is probably somewhat lower for azomethine ylides since they are considered to be more π-excessive than carbonyl ylides[14] and therefore have less to gain from the available

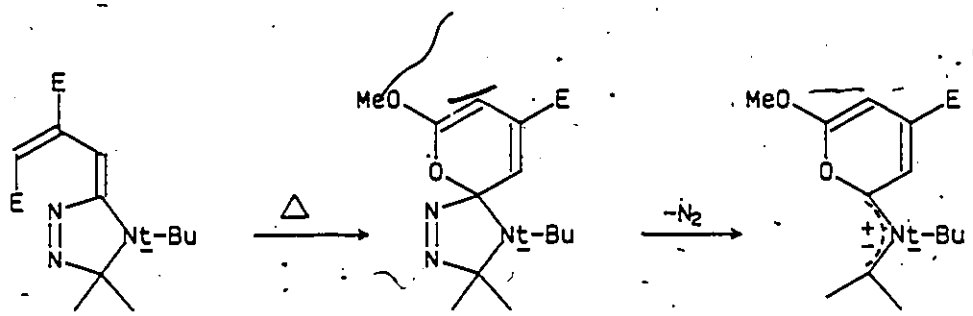
electrons of a nitrogen substituent. Moreover, the heteroatom substituent on ylides 131 and 135b is not simply amino or hydroxy. Rather, it is a heteroatom which can conjugate its electrons not only into the ylide but also into the adjacent unsaturation of the heterocycle. The effect of this is that the electrons of the heteroatom are not entirely utilized to stabilize the ylide. For these reasons, one would not expect ylides 131 and 135b to be much more stable than the all carbon substituted ylides (e.g., from 105).

By process of elimination it seems likely that a ground state effect is the reason for the observed stability of 129 and 134b. Unfortunately, there seems to be no readily recognizable reason why this should be so and therefore this question must remain unanswered.

The Thermal Intramolecular Chemistry of Δ^1-1,2,4-Triazolines 111 and 115

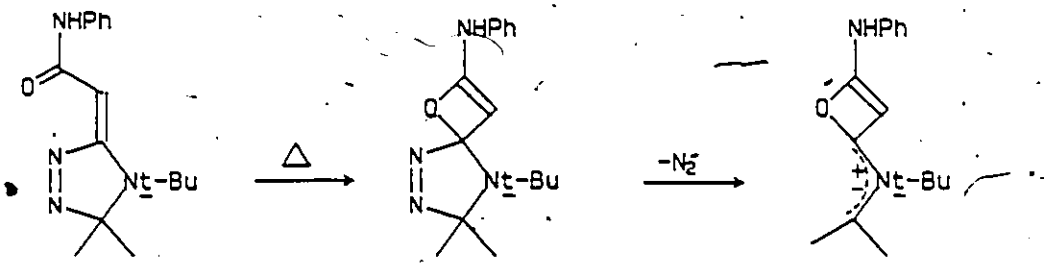
The syntheses of fumaratotriazoline 115 and amidotriazoline 111 have been described in an earlier section. As Δ^1-1,2,4-triazolines with extended conjugation, 115 and 111 held promise for the generation of azomethine ylides. Thus, 115 and 111 could conceivably lead to spirotriazolines 153 and 154 respectively by unimolecular cyclization. With quaternary carbons at C-3 and C-5 of the triazoline rings, 153 and 154 would be expected to serve as precursors to azomethine ylides 155 and 156, respectively (Schemes 62 and 63).

Refluxing a solution of fumaratotriazoline 115 in MeOH for 48 hours resulted in the complete consumption of 115. Careful separation via centrifugal chromatography afforded pyrroles 157 and 158 in 91% total yield.



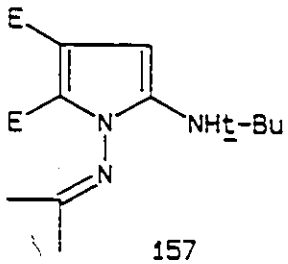
115 153 155

Scheme 62



111 154 156

Scheme 63



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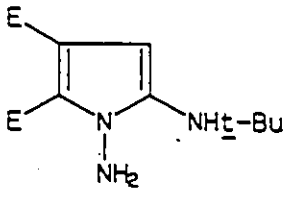

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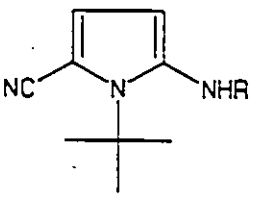


159 a) R=t-Bu

b) R=CH_2OCH_3

When 157 was allowed contact with air, hydrolysis of the hydrazone fragment occurred within 15 minutes yielding 158. It is therefore safe to assume that 157 is the thermolysis product and 158 results from hydrolysis of 157 in the reaction vessel and/or during its isolation. If the reaction mixture is allowed to stand before separation, the ratio 157:158 decreases.

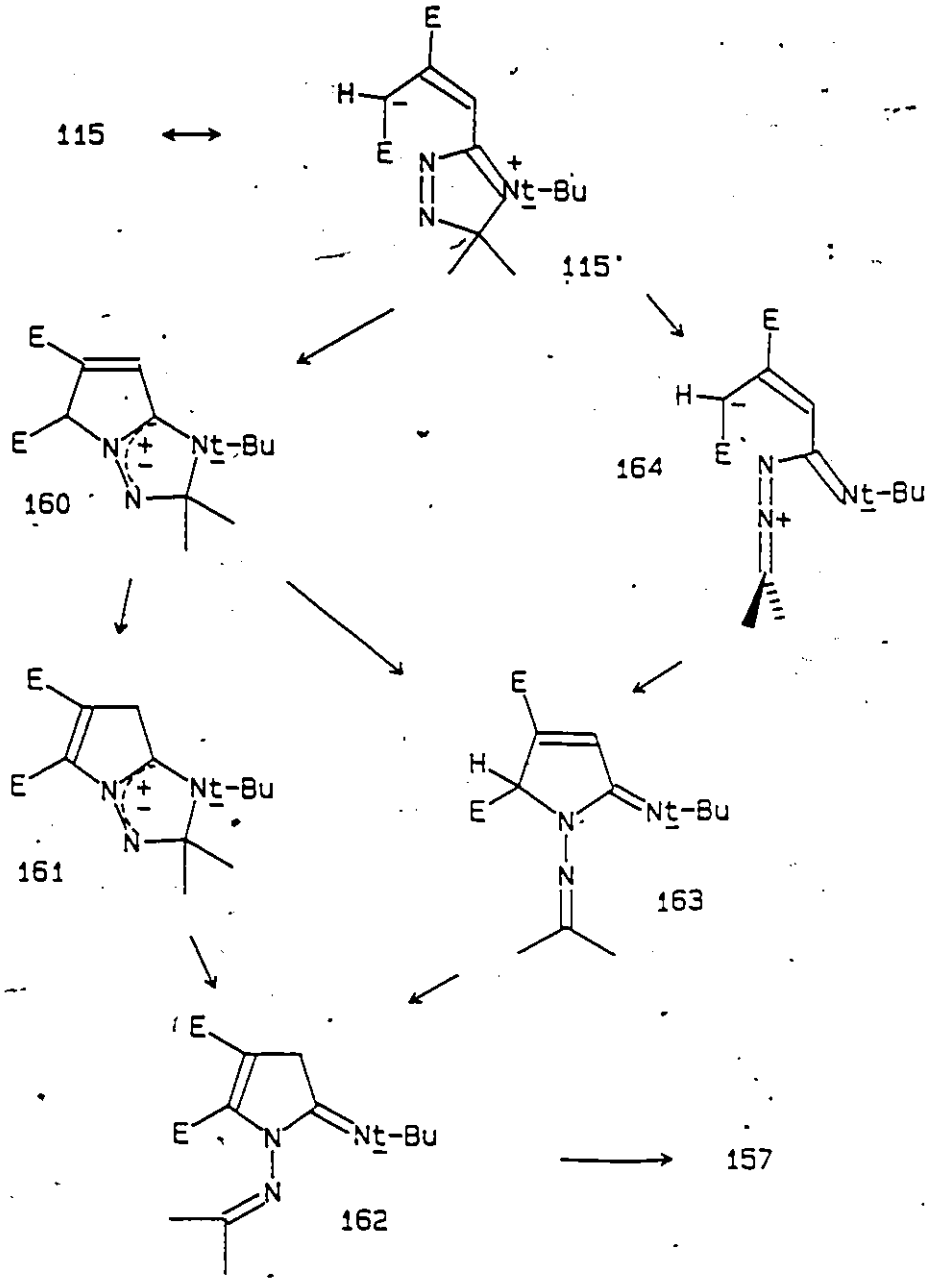
The assignment of 157 and 158 as pyrroles is based on their spectroscopic data. Their infrared spectra are similar to those of highly substituted pyrroles.[314-316] Both ^{1}H and ^{13}C nmr spectra support the structural assignments (Table 12).[317]

Scheme 64 offers three similar themes for the mechanism for the formation of 157. Resonance contributor 115' suggests incipient polar

Table 12: ^{1}H and ^{13}C nmr Data of Pyrroles

Compound	^{1}H nmr	^{13}C nmr (ring carbon)			
	δ of 3-H	C-2	C-3	C-4	C-5
159a[317]	5.50				
159b[317]	5.69				
157	5.71	137	93	112(119)	119(112)
158	5.54	142	91	113(121)	121(113)
pyrrole	6.30	117	108	108	117

factors that can induce the initiation of the rearrangement of 115. The anionic terminus can close onto the azo functionality to give azomethine



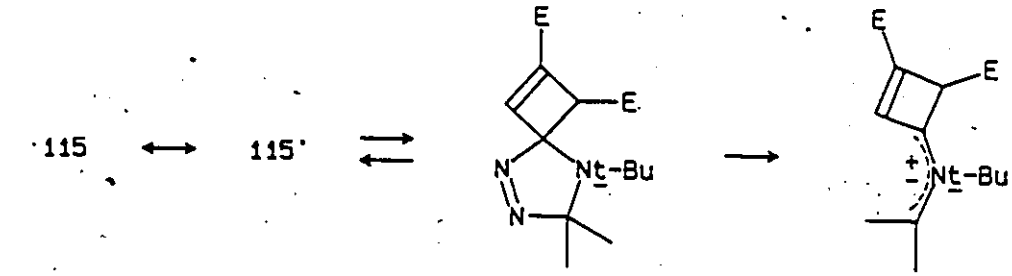
Scheme 64

imine 160, whose newly formed ring is cyclopentadiene-like. This quality allows for two rapid 1,5-hydrogen shifts yielding 161. Intermediate 161 may then break open the original triazoline ring affording 162, a tautomer of 157. A slightly different version of this mechanism involves triazoline ring opening at the 160 stage. The result is 163 which is one prototropic shift from 162.

These mechanisms which invoke the intermediacy of 160 are analogous to the mechanism for the formation of 98, which was spurned, and indeed these pathways suffer from the same drawback. The closure of the anionic end of 115' onto the planar ring of 160 has unfavourable 5-endo-trig qualities although it is formally a 5-exo-trig closure.[270]

Fortunately in this instance as with the previous example, this problem can be by-passed. The ring opening of 160 yielding acyclic zwitterion 164 is a more plausible mechanistic offering.[271] Closure of the anionic end of this flexible intermediate (164) onto the cumulated double bond system affords 163. Two prototropic shifts through 162 yields pyrrole 157. It has been shown that pyrroles are thermodynamically favoured over their iminopyrroline tautomers (e.g., 162).[318]

Although 165 or derivatives of it were not detected, it may still be forming but the step yielding 165 must be reversible due to the high yield of pyrrole and because the unidentified compound which comprises the remaining 9% of the reaction mixture is a species which contains three nitrogen atoms (see Experimental).



165 166

Scheme 65

Closure of 115' to give significant amounts of 165 (Scheme 65) can be ruled out. The chemistry of 121 is an indication that 165 should lose N_2 very rapidly at 65°C to give a product derived from 166. No such product was detected.

Although 4,5-dicarboalkoxypyrroles are much less common than their 3,4-substituted counterparts, methods are available for their synthesis.[315,316,319-321] These methods are unsuitable for 2-(alkylamino)-4,5-dicarboalkoxypyrroles such as 157 and 158 which seem to be the first members of their family.

Reductive removal of the 1-amino substituent of 158 should be facile as it is for other 1-aminopyrroles.[322,323]

Thermolysis of 111 in various solvents led to the isolation of dienamine 167. In MeOH the yield was 53% but in benzene and methyl acrylate the yield reached 85%. The E configuration about the internal double bond of 167 was assigned on the basis of the 12 Hz coupling constant between the vinyl hydrogens.

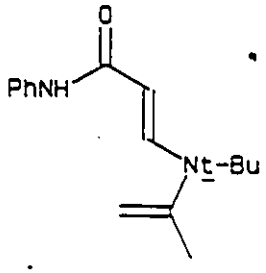
A mechanism for the 111 to 167 transformation must accomodate the following experimental observations. First, the decomposition of 111 follows first order kinetics in both MeOH and benzene (Table 13). Activation

Table 13: Kinetics of Decomposition of 111

Solvent	[111][a]	T(°C)	$10^5 k\ (s^{-1})$
CH_3OH	0.055	58.5	0.143
CH_3OH	0.055	73.0	0.874
CH_3OH	0.103	80.0	2.09
CH_3OH	0.055	87.5	4.34
CH_3OH	0.055	102.0	27.2
C_6H_6	0.072	80.0	4.90

[a]Initial concentration at room temperature

parameters were obtained for the decomposition in MeOH (log A = 13.7 ± 0.6; Ea=29.7 ± 0.9 kcal/mol). These values are comparable to the activation parameters measured for the decomposition of spriotriazolines 129 and they



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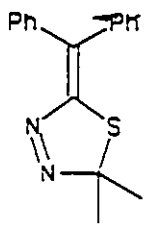

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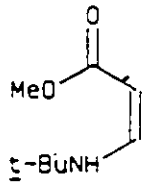


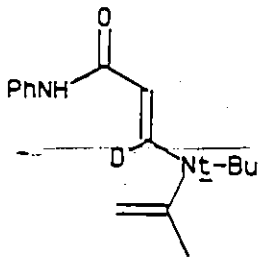
169

represent low barriers compared to thiadiazoline 168 which is a suitable parallel to 111 due to the presence of a third heteroatom and the exocyclic double bond. Thiadiazoline 168 was found to lose molecular nitrogen within 60 minutes at 165°C.[324] Using the experimental activation parameters measured for the transformation of 111 to 167, breakdown of 111 would be complete (>98%) in less than one minute at 165°C.

Secondly, 111 was found to decompose 2.3 times faster in benzene than in MeOH at 80°C. In either solvent there was no accumulation of intermediates detectable by ^{1}H nmr spectroscopy. Additional products were obtained in the methanol reaction mixture. Aniline and enaminoester 169[280] are significant co-products (≈15% each).

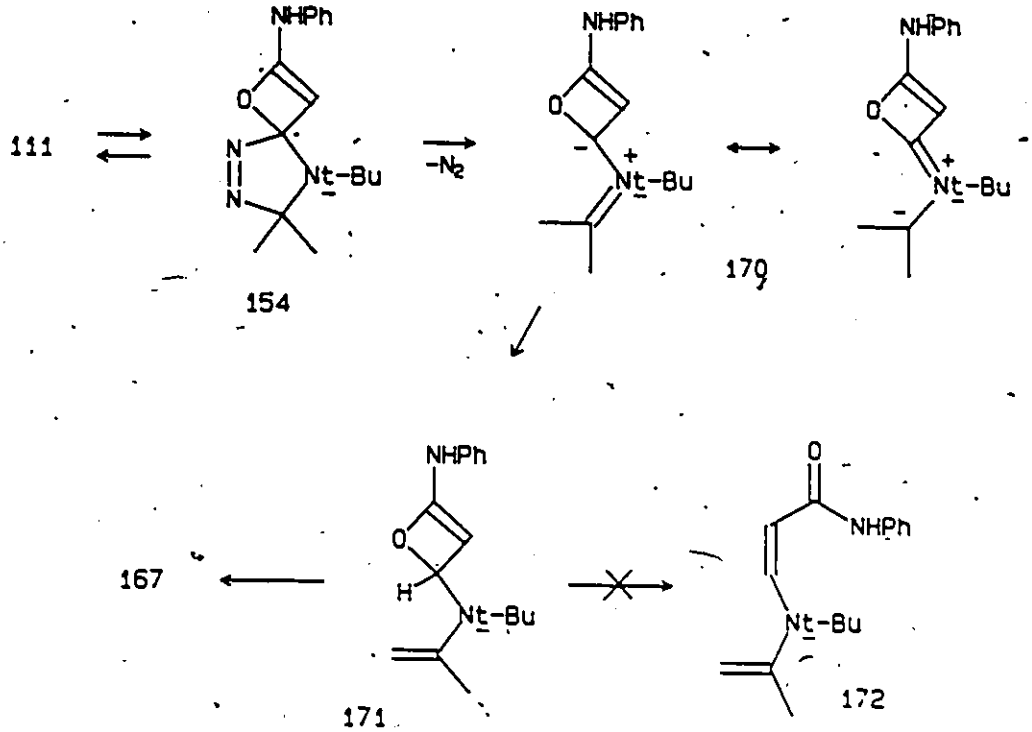
Finally, when the thermolysis of 111 was carried out in MeOD, 167 was found to be fully deuterated at the site adjacent to the amino nitrogen as indicated (167-d_1).

The mechanism depicted in Scheme 66 shows the pathway that best fits the experimental findings. The activation parameters suggest decomposition of a triazoline having two sp^3 ring carbons (e.g., 129) rather than a triazoline with exocyclic unsaturation (e.g., 94, 115). The electrocyclic ring closure to give 154 circumvents the need for direct decomposition of 111. Moreover, this proposal provides a triazoline (154) with two sp^3 ring carbons.



167-d_1

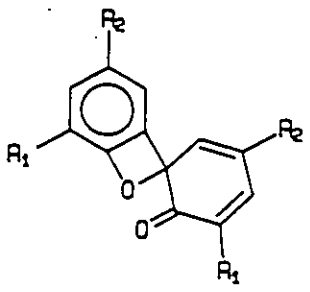
Although oxete formation is not common, the 4-electron cyclization is thermally allowed and the theoretical work of Epiotis[325] suggests that transformations of diene components that are "push-pull" polarized should be



Scheme 66

facilitated. The β-amido enamine structure of 111 seems ideally polarized for the ring closure. Some oxetes, albeit suitably substituted, can be isolated. Benzoxete 173, for example, results from the oxidation of 2,4-disubstituted phenols.[326]

The observed rate constants for decomposition of 111 (Table 13) are a combination of the 111/154 equilibrium constant and the unimolecular rate constant for decomposition of 154. In general, solvent dependencies on pericyclic reactions are small,[327] and one would expect that the solvent effect measured in this instance manifests itself on both components of the observed rate constant due to the nature of the transformations and since both are isopolar reactions. One would also expect the entropy of activation ($\Delta S^{\neq}$=1.5 ± 0.2 eu, MeOH, see page 82) originates from both



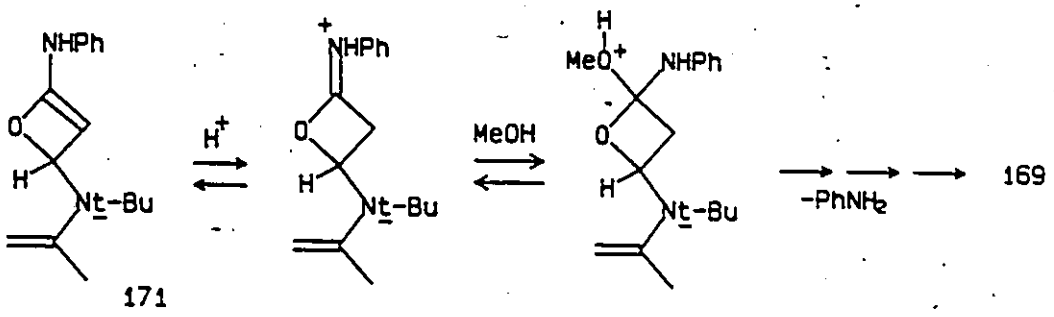
173

components of the overall transformation. The value of $\Delta S^{\neq}$ is reasonable for a process involving a combination of decreased solvent ordering and increased substrate ordering as the oxete ring of 154 develops and the value is typical for a nitrogen extrusion reaction.[301]

After loss of N_2 from 154, azomethine ylide 170 then undergoes a [1,4]-hydrogen shift yielding 171. The fact that 167 is recovered in high yield in methyl acrylate suggests that 1,3-dipolar cycloaddition reactions involving 170 are slow (cf., 102, 108 and 131) and the ylide therefore decays by another route. This other pathway is unimolecular in benzene and methyl acrylate but in methanol, solvent intervention is necessary to account for the formation of 167-d_1. Presumably, the more negative end of ylide 170 is protonated by MeOH and then the solvent deprotonates from the gem-dimethyl terminus to yield the isopropenyl moiety of 171.

Ring opening of the oxete yields 167. Conrotatory ring opening could go in two directions yielding cis and trans isomers in a structurally unrestricted system. However, bearing in mind the sterically hindered geometry of 172, it is not surprising that the oxete ring opening proceeds with unidirectionality.

Finally, the formation of aniline and 169 in methanol can be explained best if it is assumed that an enaminooxete such as 171 can add methanol across its double bond (Scheme 67). Such a transformation would require initial protonation at the sp^2 carbon β to the oxygen and to the nitrogen with subsequent addition of MeOH. Protonation of aminooxetes should be preferred over protonation of 111 or 167 due to their relative basicities. Indeed 167 was found to withstand refluxing MeOH, an experiment proving the inertness of 167 and similar structures (i.e., 111) to the



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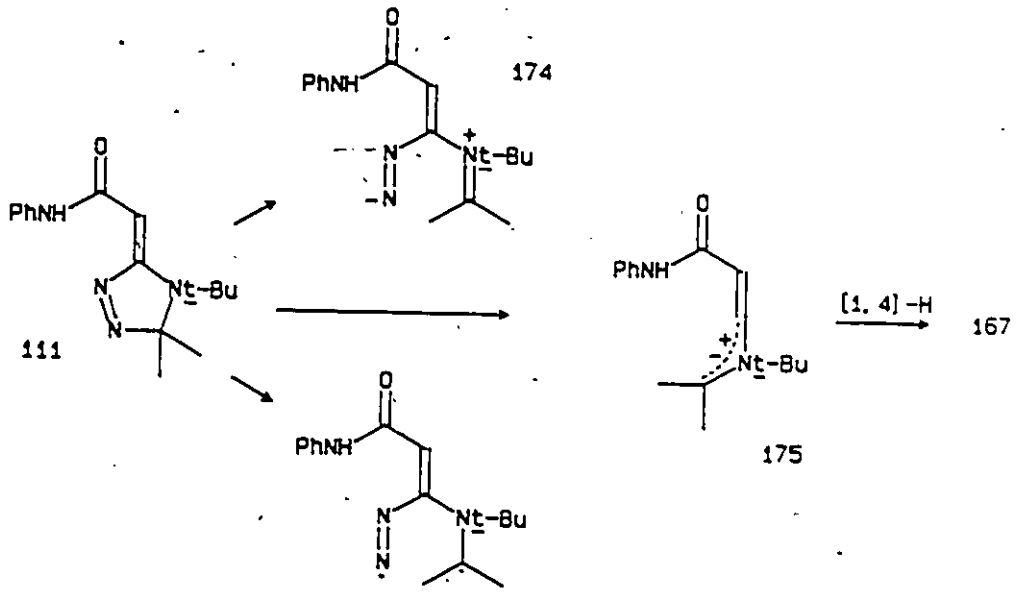
Scheme 67



Scheme 68

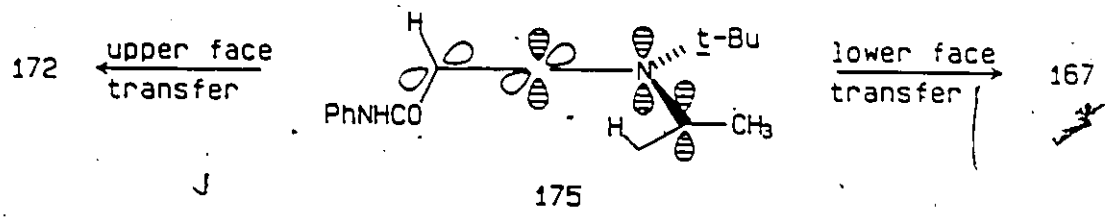
reaction conditions. After addition of methanol, subsequent elimination of aniline constitutes formal anilide methanolysis and thus provides a mechanism rationalizing the presence of aniline and 171 in the methanol reaction mixture.

Other mechanisms are possible and Scheme 68 outlines several slightly different versions of direct decomposition of 111.

One key argument against any of the pathways in Scheme 68 is the fact that methylenetriazolines 94 and 115 do not lose N_2 under similar treatment and that the thiadiazoline analog (168) requires much higher temperatures for N_2 extrusion.[324]

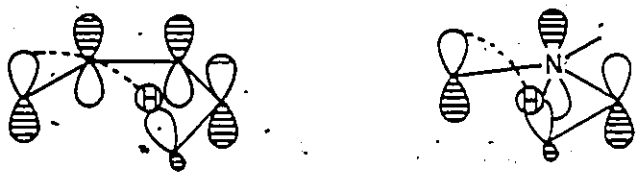
One bond heterolysis of 111 to give 174 can be ruled out, since formation of a dipolar intermediate should be facilitated, not retarded in a polar solvent. Thirdly, regardless of the route for its generation, one end of ylide 175 is allenic in nature having an sp carbon for one of its termini. In benzene, where the [1,4]-hydrogen shift proceeds with no solvent intervention, it would have to do so on the upper face and the lower face of 175 to give both 167 and its geometric isomer 172, possibly with 172 predominating due to the steric influence provided by the anilide substituent (Figure 11).

For the above reasons the mechanism depicted in Scheme 66 is favoured to account for the transformation of 111 to 167.



175

Figure 11. The Modes of [1,4]-H Transfer in Azomethine Ylide 175



a) [1,5]-H shift b) [1,4]-H shift

Figure 12. Comparison of two [1,x]-Hydrogen Shifts

At this point, a rationalization of the behavior of the various azomethine ylides proposed in this thesis is due. Two modes of decay were observed. All ylides underwent either closure to aziridines or a [1,4]-hydrogen transfer except 135 which succumbed to both transformations.

Aziridine formation is an electrocyclic reaction, proceeding by conrotatory ring closure. The [1,4]-hydrogen shift is a sigmatropic rearrangement much like the [1,5]-hydrogen shift of diene systems (Figure 12). Both ylide transformations are controlled principally by HOMO-LUMO interactions and by steric effects. The behavior of the ylides generated from 94 is also governed by these effects.

All of the ylides are sterically hindered due primarily to the t-butyl and gem-dimethyl substituents and all should have a large rate constant for closure. The extreme example would be ylide 108 (Scheme 53, page 66) which did not originate from a spirotriazoline and thus does not have the substituents on one of its termini tied back as a ring. Thus the CH_3-C-CN bond angle of 108 is probably close to 120^0 since the internal carbon is sp^2 hybridized.

The two ylides which do not close but undergo the [1,4]-shift instead do not have the same electronic structure as the other ylides. At one of their termini, there is strong delocalization of negative charge. Ylide 170 has a 6 electron oxete ring and should possess some aromatic character while 123 can stabilize negative charge by conjugation with a double bond and with a carbomethoxy group. The negative charge can also be stabilized inductively by the other carbomethoxy group. It is known that electron releasing groups attached to the H-bearing carbon acccelerate the [1,5]-shift in diene systems,[328] so it would follow that electron withdrawing groups at the receptor carbon would facilitate a [1,4]-hydrogen shift in ylides. This is indeed what appears to occur in the cases of ylides 123 and 170. Ylide 108 also has a strong electron withdrawing group but the steric effects in this particular instance are at an extreme and as a result only aziridine formation is observed.

These electron conjugating groups would also tend to decelerate ring closure for the following reason. Aziridine ring opening is accelerated by electron withdrawing substituents and indeed there are examples of ylide - aziridine equilibria that are close to 1:1 at room temperature.[329] Thus just as substituents allow facile ring opening, they stabilize the incipient ylide enough and create a significant barrier to ring closure.

Frontier molecular orbital theory explains the phenomenon well. The HOMO(ylide) closes by way of conrotation to give the aziridine (Figure 13). This process would be most efficient when the coefficient of the interacting lobes are of the same magnitude. An unsubstituted ylide is a suitable example in this instance. When electron withdrawing groups are substituted

on the ylide, the lobe sizes become different in the sense that the magnitude at one terminus increases while the magnitude at the other terminus decreases. This leads to less efficient overlap for the conrotatory closure process and thus it creates a greater energy barrier.

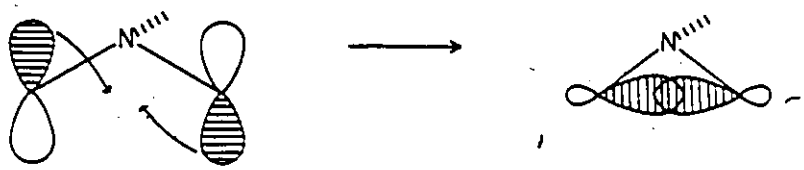


Figure 13. FMO Representation of Electrocyclic Ylide Closure

In light of this rationalization, the reason for the bidirectional reactivity of ylides 135 is more difficult to pinpoint. Perhaps the substituent nitrogens in ylides 135 conjugate with their contiguous phenyl and azo groups more than the heteroatoms (X) of ylides 131 conjugate with their adjacent unsaturation. This would create more positive charge on the substituent nitrogen which could then accommodate negative charge at the neighbouring ylide terminus. The negative charge stabilization would not be to the same extent as with ylides 123 and 170. Therefore, the reactivity of ylides 134 does not reach the same extreme of selectivity.

This completes the description and discussion of the triazoline chemistry that was investigated. The key conclusion to be made here is that these heterocycles are indeed suitable precursors for azomethine ylides. By way of these ylides, the thermolysis of Δ^1-1,2,4-triazolines can lead to highly substituted aziridines. As well, 5-membered aromatic heterocycles with various substitution patterns were also generated from triazolines, sometimes via azomethine ylides.

Unfortunately, no bimolecular cycloadditions could be achieved, so further study should be by the mechanistic chemist, at least for the time being. The reasons for the behaviour of the ylides generated from triazolines can only be fully understood once more examples have been investigated. With time, the synthetic chemist will make use of triazolines and these compounds will inevitably become known as synthons for azomethine ylides and for the subsequent generation of nitrogen heterocycles.

CHAPTER 3

The Reactions of DMAD with Allyldimethylamines.

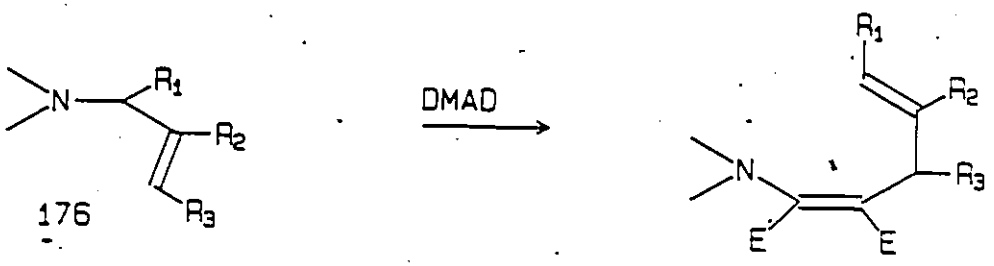
The reactions of tertiary amines with acetylenedicarboxylic acid diesters has been outlines in the introduction. The intramolecular behavior of the intermediate zwitterion provides interesting chemistry for study by both mechanistic and synthetic chemists.

Particularly interesting are the double bond migrations, exemplified by Schemes 39, 40 and 41 (pp.44 and 46). Each of these is accompanied by a second, presumably simultaneous transformation rendering the overall rearrangement energetically feasible[210,215-219]. In some cases there is a release of ring strain accompanying the double bond migration[210,218,219], while in other instances a suitably disposed methoxy group aids in the migration of the double bond and overall neutralization of the quaternary nitrogen[216-218].

The question as to whether these structurally specialized systems are necessary for the success of the reaction was not answered by the authors[210,215-219]. The reactions of DMAD with several simple allyldimethylamines could answer the question.

Several amines of the general structure 176 were synthesized. Refluxing these amines with one equivalent of DMAD in CH_3CN yielded a series of 1-dimethylamino-2-allyl maleates 177 in all but two cases (177e,f) (Scheme 69). These products were identified from their ^1H and ^{13}C nmr data as well as from infrared and mass spectra (Tables 16, 17 and 18). The maleate geometry was assigned with the aid of mechanistic arguments (see below).

The geometry of the 2-butenyl moiety of 177b could not be readily assigned by measuring the ^{1}H nmr coupling constants of the vinyl protons because a 500 MHz nmr instrument was incapable of separating the vinyl proton signals. Therefore a different criterion had to be employed. The ^{13}C nmr chemical shift of the methyl group of the 2-butenyl side chain was found to be 18.6 ppm. This correlates well with trans-2-butene and trans-2-octene whose vinyl methyl groups resonate at 17.3 and 19 ppm respectively.[330] The methyl signals of the cis analogs appear at 10.6 ppm (cis-2-butene) and 13 ppm (cis-2-octene).[330] Comparison to these data allow the assignment of the geometry of the 2-butenyl portion of 177b as trans.



a) $R_1=R_2=R_3=H$
b) $R_1=CH_3$, $R_2=R_3=H$
c) $R_1=R_3=H$, $R_2=CH_3$
d) $R_1=R_3=H$, $R_2=Ph$
e) $R_1=R_3=H$, $R_2=Cl$
f) $R_1=R_3=H$, $R_2=Br$
g) $R_1=R_2=H$, $R_3=Me$

Scheme 69

Product 177g was obtained as an inseparable mixture of fumarate and maleate isomers. Proton nmr spectroscopy indicated that the ratio was 3:1. The major isomer was assigned the fumarate geometry on the following basis.

Dimethylamino groups have been shown to shield protons on substituents cis to them. That is, in instances where geometric isomers have been obtained and their ^1H nmr spectra have been recorded, the protons on substituents cis to the dimethylamino moiety resonated at higher field than those trans to the dimethylamino group.[331,332] The methine proton of the major isomer of the mixture 177g resonated at 3.47 ppm while the signal from the analogous proton of the minor isomer was found at 2.92 ppm. This is consistent with the dimethylamino group being cis to the butenyl function of the minor isomer of 177g.

The other criterion for distinguishing between the two isomers is the chemical shifts of the methoxyl protons of butenedioic esters. The shifts of the methoxyl protons of maleic esters are found slightly downfield from those of the fumarates.[189,280,333] The methoxy peaks of the minor isomer of 177g were found at 3.61 and 3.72 ppm while those of the major isomer appeared at 3.56 and 3.69 ppm. These two points allow confident assignments to be made regarding the geometry of the components of the mixture 177g.

A product common to all the reaction mixtures is the previously synthesized dimethylaminomaleate 178.[280] Facile separation of reaction components was achieved by column chromatography. Table 14 shows the yields of products 177 and 178 in each reaction. The aminoallylation products are all new compounds and were obtained as oils. A significant amount of coloured by-products remained at the top of the chromatography columns.

Benzyldimethylamine (179) was treated with DMAD in CH_3CN but only dimethylaminomaleate 178 and starting amine 179 were among the non-polar products recovered.

Some of the amines were also treated with one equivalent of DMAD in $CHCl_3$ at room temperature. Reaction times extended from one day to six weeks. Reaction products in this case were very dependent upon initial concentrations. More concentrated solutions gave increased yields of 178, in most cases, and poorer yields of 177 (Table 15).

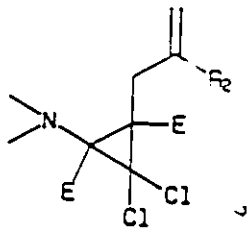
Table 14: Allyl Transfer Product Yields in Refluxing CH_3CN

Amine 176	Initial conc. of each reactant	Duration of reaction[a]	Yield of 177	Yield of 178
a	0.200 M	14 hours	37%	22%
a	0.914 M	1.5 hours	8	43
a	0.008 M	20.5 hours	54	21
b	0.217 M	11.5 hours	51	16
c	0.217 M	9.5 hours	44	30
d	0.202 M	12 hours	64	14
e	0.201 M	34 hours	0	31
f	0.201 M	42 hours	0	28
g	0.212 M	5.5 hours	43[b]	32

[a]Reactions may have been completed in a shorter period of time.

[b]Obtained as a 3:1 = fumarate maleate mixture.

Amines 176a and 176c reacted with DMAD in $CHCl_3$ to afford 180a and 180c respectively, as additional non-polar products. Both were isolated in low yields. In both solvents, DMAD was usually the limiting reagent and yields were therefore based on the amount of amine consumed.



180 a) R_2=H
c) R_2=CH_3

Table 15: Allyl Transfer Product Yields in $CHCl_3$

Amine 176	Starting conc. of each reactant	Duration of reaction[a]	Yield of 177	Yield of 178	Yield of 180 + 177
a	0.164 M	14 days	16%	40%	34%
a	0.165 M[b]	6 days	13	37[c]	17
b	0.585 M	1 day	28	15	28
b	0.069 M	4 days	52	28	52
c	0.464 M	40 days	22	31	32
d	0.434 M	21 days	46	34	46

[a]Reactions may have been completed in a shorter time period.

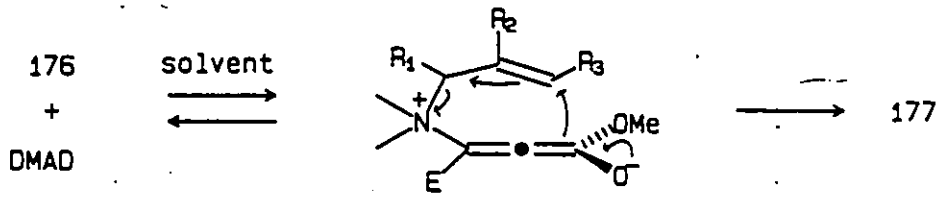
[b]In $CDCl_3$

[c]Vinyl position was 85-90% deuterated as estimated from the ^1H nmr spectrum of the crude reaction mixture.

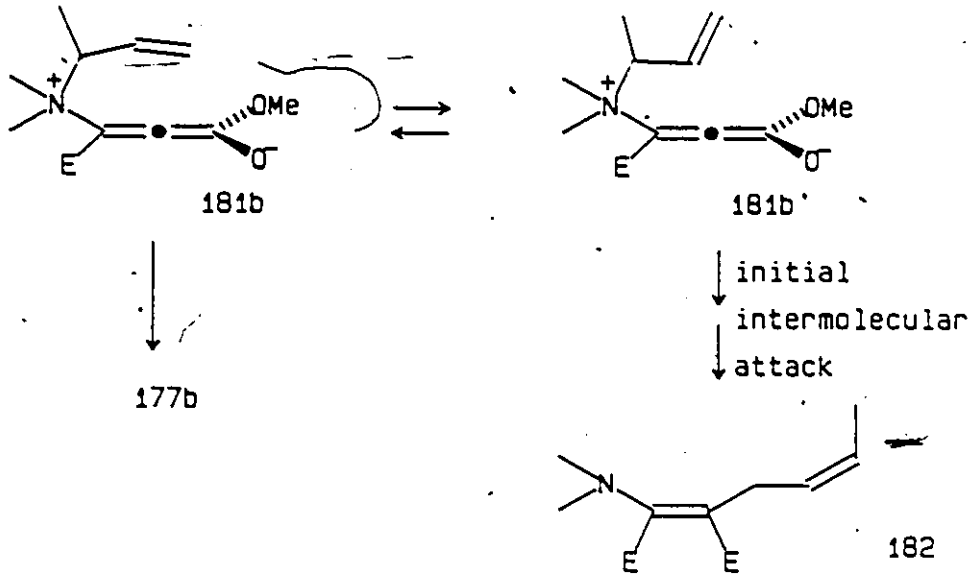
Amines 176a and 176d were also treated with DMAD in CH_2Cl_2 but lower yields of 177 were obtained in these cases (15% 177c, 10% 177d).

The double bond migration, or allyl transfer, presumably proceeds via a zwitterionic intermediate (eg, 181) as proposed by several other authors[179,194,210,215-219]. In keeping with the recent findings of Grein and coworkers[224,225], 181 has been depicted as an allenolate anion rather than a bent vinyl anion (Scheme 70).

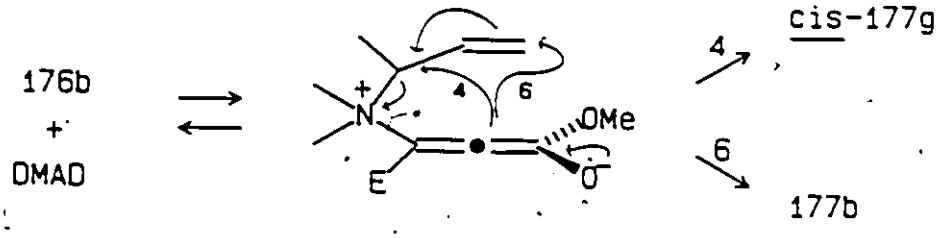
Strong evidence for the intramolecularity of this reaction lies in the fact that more dilute chloroform solutions led to cleaner reaction mixtures (Table 14). If 181 were to lead to 177 via an intermolecular route (i.e., bimolecular in 181), then the yield of 177 would be expected to be lower in more dilute solutions due to the likelihood of competitive side reactions becoming more prevalent, i.e., formation of polar, colored byproducts.



Scheme 70



Scheme 71



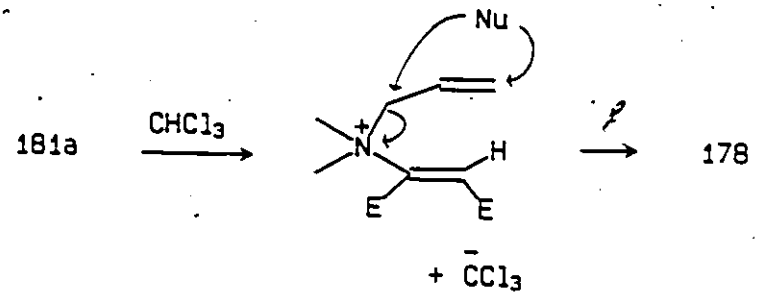
Scheme 72

Amine 176b gave solely allyl transfer product 177b and none of its cis isomer 182. This result also lends credence to the proposed intramolecular mechanism. Scheme 71 shows two of many possible one-bond rotamers of 181b. Intermolecular or intramolecular reaction of 181b would result in the formation of 177b because the geometry of the alkenyl side chain required for 177b is already present. Rotamer 181b' is susceptible to intermolecular attack only and perhaps more so than 181b because a more open entry is available to the nucleophile. Moreover, 181b' would lead to 182 because the geometry is conducive to the formation of 182 with the cis-2-butenyl geometry. Since 182 is not formed, and since intermolecular attack on 181b' should be at least as favored as that on 181b the only remaining possibility is intramolecular rearrangement via 181b, to give 177b.

The question of whether there is a six-membered transition state or a four-membered transition state (Scheme 72) during allyl transfer is also answered by analysis of the reaction products of amine 176b and DMAD. Maleate 177b was isolated whereas maleate 177g should have been the product of the allyl transfer if a four-membered transition state were involved. Consistent with the proposed mechanism is the fact that 177g rather than 177b is the product when 176g is treated with DMAD.

Isomers 177g are the only allyl transfer products obtained as a mixture of maleate and fumarate isomers. Presumably the steric bulk of the sec-butenyl side chain of 177g aids in the facile isomerism of the initial maleate product. The 3:1 ratio was consistently present after workup whether the reaction was carried out in CH_3CN for 1, 2, or 5.5 hours or in $CHCl_3$. The 3:1 ratio is probably the equilibrium composition for the two geometric configurations.

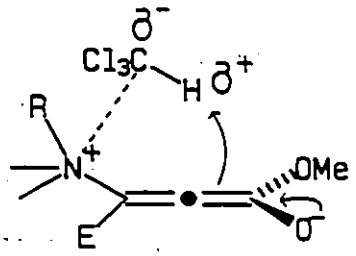
The reaction proceeds more readily in CH_3CN than in $CHCl_3$. The best conditions that were found for the allyl transfer in $CHCl_3$ are dilute solution and low temperature. Consumption of starting materials may therefore take extended periods of time. A competing reaction in this solvent is deprotonation of $CHCl_3$ by the anionic end of the zwitterion (Scheme 73). The cation may then lose its allyl group to a nucleophile in solution, such as starting amine, via an Sn2 or Sn2' substitution with the aminomaleate as the leaving group. This would account for the significant amounts of 178 observed.



Scheme 73

The observation that the product resulting from deprotonation of the solvent (178) is the maleate rather than the fumarate deserves discussion. The maleate is more often obtained in non-protic than in protic solvents.[201,202,222] Despite early recognition of this phenomenon, a suitable explanation is still unavailable. One theory is that the fumarate anion is formed initially and if there is no proton transfer agent available (e.g., alcohol), then it inverts to the maleate anion which undergoes subsequent reaction perhaps including deprotonation from $CHCl_3$ or CH_3CN.[222,334]

An alternative explanation that is preferred in this case, says that the anionic end is allenic and has the option of adding an electrophile at either face to give the maleate or the fumarate. In $CHCl_3$ a structure such as 183 depicts why maleate formation might be preferred. If the molecule of $CHCl_3$ to be deprotonated is situated "inside" the zwitterion, then it is between the ammonium and the allenyl moieties. This proximity to the ammonium nitrogen allows for a favourable coulombic interaction which lowers the energy of the proton transfer transition state. The maleate configuration is a necessary result from alignment as in 183. Formation of the fumarate has no such intramolecular stabilizing effect available. A similar explanation can be invoked for deprotonation from CH_3CN. This explanation for maleate formation is similar to that proposed when the two addends deposited across the acetylene originate from one molecule.[202]

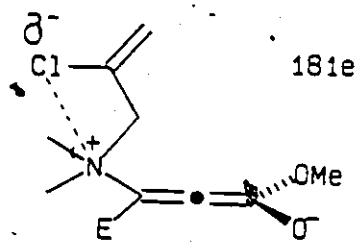


183

In alcohol solvents, the deprotonation is very fast and presumably the allenolate oxygen is initially protonated. Subsequent formation of the two geometric isomers, usually predominantly fumarate, is then governed at least in part by thermodynamics. Any requirement for charge or partial charge stabilization during proton transfers can be accommodated in large measure by the polar solvent, without a significant stabilizing component from coulombic interactions depicted by 183.

The presence of trichloromethyl anions accounts for the formation of cyclopropenes 180a and 180c. The anions lose chloride ion to generate dichlorocarbene which adds to the more nucleophilic double bond of maleates 177a and 177c.[335] The stereochemistry of amines 180a and 180c is assigned as cis (diester) based on the geometry of the starting allyl transfer products. It is uncertain as to why cyclopropanes derived from 177b and 177d are not formed. The greater efficiency of allyl transfer in the phenyl substituted case and the lower amount of 178 formed in the case of 176b, may have significant bearing on any explanation.

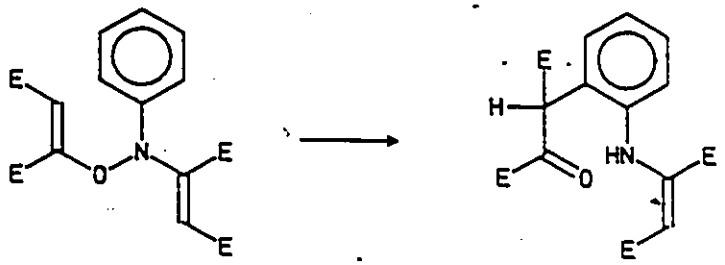
Amines 176e and 176f do not undergo the allyl transfer reaction. A possible explanation for this may be that the geometry assumed by zwitterions 181e and 181f prevents allyl transfer. It is possible that the electronegative halogen is attracted toward the positive nitrogen by dipole interactions. This explanation has drawbacks however. The ring size of the interaction is four and there is one sp^2 centre to spread out an internal bond angle. This would indicate that any dipolar interaction may be weak and that the other conformations should remain significantly populated. It should be emphasized, though, that 181e and 181f having the geometry and interaction as shown for 181e need only be ~1.5 kcal mol^{-1} lower in energy than their freely rotating counterparts. Such an energy difference would reduce the yield of 181e and 181f below the limits of detection.



181e

The allyl transfer is formally a 3,3-sigmatropic rearrangement. Some heteroatomic species which have demonstrated the capabilities to undergo this rearrangement include zwitterions,[210,215-219] ammonium ions,[336] and neutral maleates (Scheme 74).[337,338]

Regarding the chemistry already described in this chapter, since the solvent was already being deprotonated and dichlorocarbene was being formed,

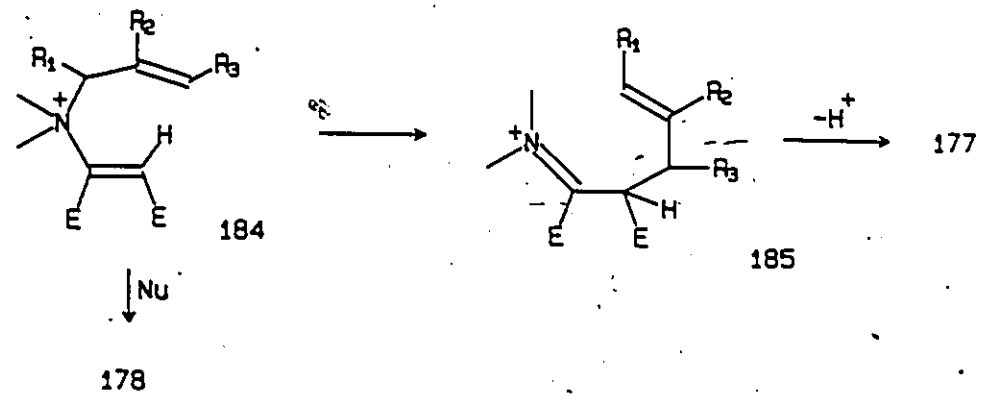


Scheme 74

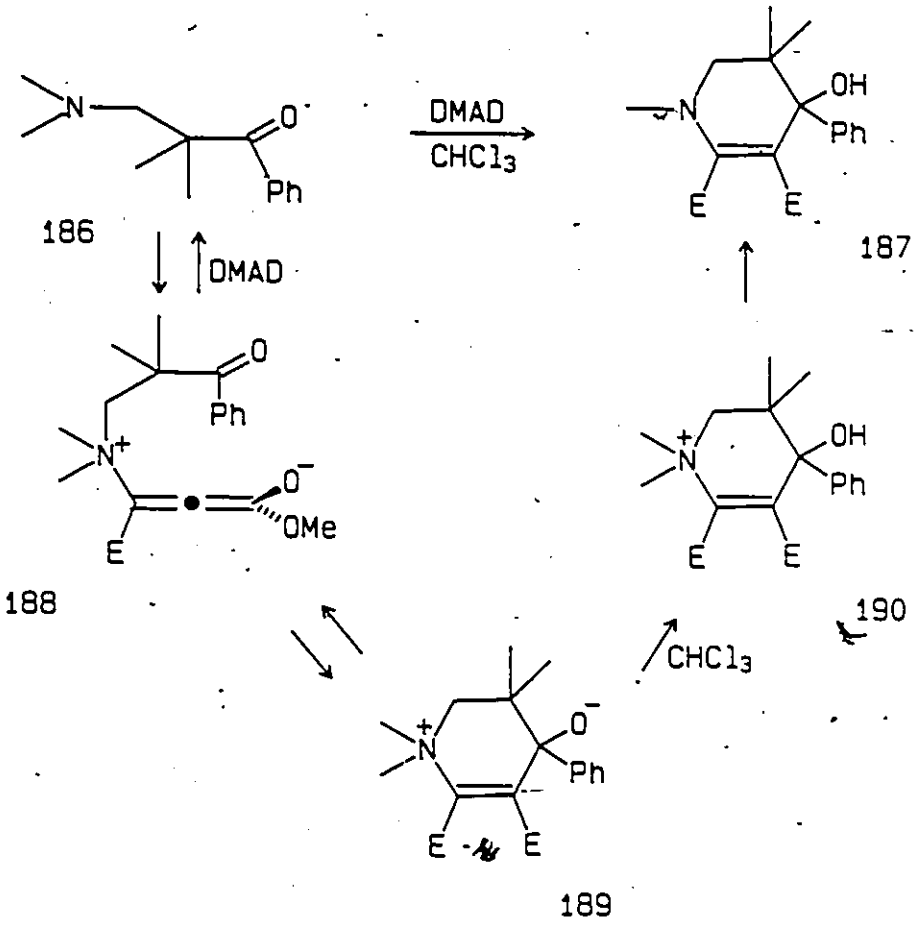
the reaction environment is probably of an alkaline nature. This does not however, eliminate the possibility that a species such as 184 (formed by deprotonation of $CHCl_3$) is doing the rearrangement (Scheme 75). Deprotonation of 185 would then yield 177. It would follow then that the addition of benzoic acid to the reaction mixture would serve as a probe for the cation rearrangement (Scheme 75), since it should facilitate formation of 184 and reduce by-product formation to give an overall increased yield of allyl transfer product. The inclusion of benzoic acid (8% of [176a]) with 176a and DMAD in $CHCl_3$ gave a reduced rather than an enhanced yield of 177a. Had the benzoic acid experiment lent credence to the postulate that 184 was the rearranging species, then an explanation for why the reaction does not proceed as efficiently in CH_2Cl_2 would also have been provided. Deprotonation from CH_2Cl_2 is much more difficult and thus the rate of formation of 184 in CH_2Cl_2 would have been significantly less. As it is, there is no explanation for the $CHCl_3$-CH_2Cl_2 solvent dependence.

Amine 179 did not undergo the rearrangement. Presumably the disruption of aromaticity requires too much energy, although maleates have been shown to overcome this barrier and to undergo 3,3-sigmatropic rearrangements (Scheme 74).[337,338]

Another tertiary amine was found to give an interesting product when treated with DMAD in $CHCl_3$. α-(Dimethylaminomethyl)-isobutyrophenone (186) gave heterocyclic alcohol 187 in 42% yield. Scheme 76 indicates that this is another example demonstrating the nucleophilicity of the anionic portion of zwitterions such as 58. Scheme 76 complies with the mechanistic evidence acquired. As in other cases, formation of zwitterion 188 should be reversible. Elimination of amine, and return to 186 in this case, should be a facile process. The next step to give 189 must also be reversible for the following reason. It was found that in deuteriochloroform, the alcohol hydrogen was replaced with a deuterium. The rate of formation of the hydroxylated product in $CHCl_3$ was 1.9 times the rate of formation of the deuterated analog in $CDCl_3$. At first glance this could be construed as a kinetic isotope effect (kie) of 1.9. However, if formation of 189 is not reversible, then the preceding steps have no solvent dependence and protonation or deuteration of the alkoxide should proceed regardless of their relative rate constants. Since some selectivity is observed, there must be a competing pathway, which is 189 going to 188. There is probably some protonation of 188 to form maleate derivatives, much like the first step on the way to forming 178. This should serve to lower the yield of 187 in $CHCl_3$ (compared to $CDCl_3$) because a kie at the maleate formation stage should manifest itself, although the reverse seems to be true for zwitterion 181a (Table 15). It does so presumably to some extent and the value of 1.9 is therefore some sort of weighted average of the kie for maleate formation and the kie for alcohol formation.



Scheme 75



Scheme 76

Once ammonium ion 190 is formed, it can either be demethylated to give 187 or remain as a polar by-product. Trichloromethyl anions are not the demethylating agents since CH_3CCl_3 was not found in the reaction mixture. It is expected that chloride ion is not the demethylating agent either since ammonium chloride salts remain as such at room temperature rather than equilibrating with alkyl chlorides and amines. Therefore the demethylating agent is probably starting amine and this would help to account for the low yield of non-polar product 187.

In this last chapter, it has been shown that a reaction that was previously applied to specialized systems can also be achieved in simple systems. The new products have considerable potential in synthesis as highly functionalized dienophiles and dipolarophiles, either directly or after facile conversion to their respective N-phenylmaleimides.[339]

The formation of 187 indicates the potential of the procedure for the synthesis of interesting heterocycles.

CHAPTER 4

EXPERIMENTAL

Melting points (mp) were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra, obtained with a Perkin-Elmer model 283 instrument, are reported in wavenumbers calibrated against the 1601.4 cm^{-1} band of polystyrene. Only major and diagnostic bands are reported.

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on either a Bruker AM-500, a Bruker WH-250, or a Varian EM-390 spectrometer. $CDCl_3$ was the solvent in all cases, with TMS serving as the internal standard. Chemical shifts are reported in δ values (ppm), followed in brackets by the multiplicity symbol (s=singlet, d=doublet, t-triplet, q=quartet, m-multiplet), the relative proton integral, and the coupling constant where appropriate. The deuterium nuclear magnetic resonance (^{2}H nmr) spectrum was recorded on the Bruker AM-500 instrument at 75.76 MHz. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were obtained with either the Bruker AM-500 (125.76 MHz), the Bruker WH-250 (62.90 MHz) or a Bruker WP-80/90 (22.62 MHz) spectrometer. The solvent was $CDCl_3$ unless otherwise noted and the peaks are calibrated against the 77.20 ppm peak of $CDCl_3$.

Ultraviolet (uv) spectra were obtained with a Hewlett-Packard model 8451A diode array spectrophotometer. Mass spectra (ms) were recorded on a VG 70-70F double focussing or a VG ZAB-E triple focussing mass spectrometer. Samples were introduced via a direct insertion probe system. The energy of the ionizing electrons was 70 eV.

For Raman spectra, a Coherent Model Innova 90 argon laser giving up to 3.5 W at 5145Å was used for excitation. The spectrometer was a Spex Industries Model 14018 double monochromator equipped with 1800 groves/mm holographic gratings. Slit widths were set at 100 or 200 μm. The power setting was 50 or 100 mW. The scan rate was set at 1 or 2 $cm^{-1}s^{-1}$. Raman shifts quoted are believed to be accurate to ±2 cm^{-1}.

The He(I) photoelectron spectrum (PES) of 94 was obtained with a non-commercial instrument based on a 10 cm diameter aluminum hemispherical electrostatic energy analyzer. The photoelectrons were retarded and focussed onto a rectangular entrance slit (0.5 x 2 mm) by a suitable lens. He(I) photons were generated by an air-cooled DC discharge lamp operated at 1.3 kV. With this lamp the typical count rate on Ar $^2P_{\frac{3}{2}}$ is 100,000 Hz with a 40-meV fwhm.

Centrifugal chromatography was carried out on silica (Merck, Kieselgel 60 PF_{254}) coated glass plates (coating 2mm thick) spinning in a Chromatotron model 7924T apparatus. Plastic-backed, Merck Kieselgel 60 F_{254}, 0.2 mm silica plates or plastic-backed Polygram ALOX, N/UV_{254}, 0.2 mm neutral alumina plates were used for analytical thin layer chromatography (tlc).

The chemicals used were purchased from Aldrich, Baker, Fisher, or BDH unless otherwise indicated. Chemicals were purified prior to use where appropriate. The reaction solvents were dried by distillation from P_2O_5 before use. $CHCl_3$ was washed with conc. H_2SO_4 prior to distillation. Ether supplied by Allied was used without further drying.

Nuclear Overhauser enhancement (nOe) measurements

The substrate (10-20 mg) in ca. 0.4 mL of $CDCl_3$ containing a trace of CH_2Cl_2 was sealed into a medium-walled nmr tube after three cycles of freeze-pump-thaw degassing at 0.03 Torr. Eight normal scans on the WH-250 spectrometer were followed by eight scans taken during irradiation at the frequency of the substrate's tert-butyl signal. Each spectrum was integrated against the signal from internal CH_2Cl_2. No correction was made for enhancement, if any, of the reference signal during double irradiation. For the analysis of 111, MeOH was employed as the internal standard.

Synthesis of N^1-isopropylidene-N^3-tert-butylacetamidrazone (93)

The procedure for preparation of 93 is based on that of Fuks.[264] A two-necked flask, fitted with an efficient mechanical stirrer and a pressure equalizing dropping funnel, was charged with anhydrous ferric chloride (30g, 0.1 mol). During constant stirring and cooling with ice were added, dropwise and in succession, anhydrous ether (40 mL), anhydrous acetonitrile (7.6 g, 0.19 mol) in ether (10 mL), and tert-butyl chloride (17.1 g 0.1:8 mol) in 20 mL of dry ether. The mixture was stirred for 30 minutes at ice temperature, during which time an orange-red suspension was formed. The suspension was added quickly, at -78°C, to a solution of the lithium salt of acetone hydrazone, prepared as follows. n-Butyllithium in hexane (0.31 mol of BuLi) was added to 200 mL of ether at -78°C. Acetone hydrazone (20.4 g, 0.28 mol) in ether (80 mL) was then added, dropwise with stirring, to the cold solution.

When addition of the suspension was complete the resulting mixture was allowed to reach 0°C, approximately, during one hour of stirring, after which aqueous sodium hydroxide solution (0.64 mol of NaOH in 50 mL) was added. The subsequent workup according to the procedure of Fuks[264] gave crude amidrazone which was distilled. After an initial fraction of acetone azine, 93 and N-tert-butyl acetamide distilled together at 120-130°C (30 Torr). That fraction was chromatographed on Al_2O_3(II) to afford 93 (10.6 g, 35% based on acetonitrile) as a low melting solid. A sample of 93 collected by preparative gc had mp 49-50.5°C. Spectral data for 93, 2:1 mixture of tautomers; ^{1}H nmr, δ: 1.35 (s, 3H), 1.40 (s, 6H), 2.00 (s, 7H), 2.03 (s, 1H), 2.16 (s, 1H); ^{13}C nmr (22.62 MHz) δ: 16.62, 17.56, 18.00, 19.71, 24.87, 25.30 (Me's), 28.82, 31.09 (t-Bu's), 50.31, 51.04 ($\underline{C}Me_3$'s) 157.06, 157.24, 157.72, 159.29 (C=N's); ms(ei), m/z(%): 169(52), 98(100), 72(37), 69(21), 57(42), 56(41), uv (hexanes), λ_{max}(log ϵ): 248 nm (3.87); ir ($CDCl_3$), cm^{-1}: 3464, 3335, 1636, 1590, 1505, 1412, 1370, 1360, 1250.

Synthesis of 4-tert-butyl-3,3-dimethyl-5-methylene-Δ^1-1,2,4-triazoline 94

In a typical oxidation, amidrazone 93 (1.0 g, 5.9 mmol) in 10 mL of benzene was added all at once to lead tetraacetate (2.9 g, 6.5 mmol) in 30 mL of benzene over 16 g of anhydrous potassium carbonate. The reaction mixture was stirred and cooled with ice-water during the addition and for 45 minutes after. Aqueous sodium bicarbonate solution (5%) was then added, the mixture was filtered through Celite, and the organic phase was separated. It was washed with brine and dried over magnesium sulfate. The dried benzene solution was concentrated and the residue was chromatographed on

Al_2O_3(II) using ether (10%) in light petroleum for elution. After pure 94 had been collected, the solvent was changed to 50% ether in petroleum to elute unreacted 93. Addition of solid NaOH to the aqueous phase (above), extraction with dichloromethane, washing the organic phase with brine, drying over $MgSO_4$, and evaporation of the dichloromethane and distillation afforded additional 93 (25-35% recovery overall) of the same quality as that initially used for oxidation. The yield of 94 based on 93 consumed, was 45%. It is an oil at room temperature but it freezes during storage at ca. -20°C. Spectral data for 94: ^{1}H nmr (90 MHz), δ: 1.41 (s, 9H), 1.58 (s, 6H), 4.16 (d, 1H, J=2.2 Hz), 4.76 (d, 1H, J=2.2 Hz); ^{13}C nmr (22.62 MHz), δ: 26.02 (di-Me), 28.12 (t-Bu), 52.82 (CMe_3), 83.70 (CH_2), 104.23 (sp^3 ring C), 163.13 (sp^2 ring C); ms (ei, high resolution) m/z: calc'd for $C_9H_{17}N_3$ 167.1432; found 167.1427; calc'd for $C_9H_{17}N$ [M^+-N_2] 139.1347; found 139.1354; uv (CH_3OH), λ_{max} (log ϵ): 216 nm (3.68), 364 nm (3.49); ir (neat), cm^{-1}: 1636, 1511.

Methylenetriazoline (94)-methoxytriazoline (96) equilibrium

Triazoline 94 (0.20 g) in methanol (2 mL) containing a few crystals of toluenesulfonic acid hydrate was kept at room temperature for 5h. Analysis of the solution by ^{1}H nmr and ^{13}C nmr spectroscopy showed the presence of unreacted 94 and 4-(t-butyl)-3,5,5-trimethyl-3-methoxy-Δ^1-1,2,4-triazoline (96). The ratio 96:94 = 0.6, estimated by integration of the ^{1}H nmr spectrum, remained constant with time for several weeks.

Spectral data for 96; ^{1}H nmr (90 MHz), δ: 1.34 (s, 9H), 1.49 (s, 3H), 1.64 (s, 3H), 1.72 (s, 3H), 2.97 (s, 3H); ^{13}C nmr (22.62 MHz, MeOH at 49.9 ppm), δ: 25.6, 28.2, 28.4 (Me's), 31.0 (t-Bu), 47.9 (OMe), 51.7 (CMe_3), 104.0; 126.2 or 128.8 (ring C's).

Reactions of 94 with acrylonitrile, methacrylonitrile, and methyl methacrylate

Triazoline 94 (0.120 g) in 10 mL of acrylonitrile was sealed into a tube which had been evacuated at 0.1 torr. The tube and contents were heated with an oil bath at 80°C (8 hr) or at 50°C (14.5 hr). After cooling, the tube was opened and the excess acrylonitrile was removed under reduced pressure (aspirator). The residue, in ether, was applied to a neutral Al_2O_3(II) column from which it was eluted with 40% ether in light petroleum. The first fraction collected contained the diastereomeric 2-aza-2-(t-butyl)-4-cyano-3,3-dimethyl- spiro[2.3]hexanes, (97a), (r_f = 0.61, Al_2O_3, ether) isolated as an oil, 139 mg (88%). Spectral data for 97a, 1:1 mixture of diastereomers; ^{1}H nmr (500 MHz), δ: 1.13 (s, 3H), 1.14 (s, 9H), 1.19 (s, 9H), 1.21 (s, 3H), 1.24 (s, 3H), 1.45 (s, 3H), 2.14 (m, 3H), 2.31 (m, 3H), 2.52 (m, 1H), 2.94 (q, 1H, J=12.9 Hz), 3.07 (m, 1H), 3.33 (t, 1H, J=9.5 Hz); ^{13}C nmr (22.62 MHz), δ: 17.93, 20.26, 21.08, 24.67, 25.81, 27.69, 30.87, 31.14, 32.15, 40.12, 41.62, 48.56, 49.31, 54.80, 52.26, 120.43, 122.06; ms(ei), m/z(%): 192(10), 177(8), 135(46), 121 (20), 109(20), 82(48), 81(37), 57(100); ms (ei, high resolution), m/z: calc'd for $C_{12}H_{20}N_2$ 192.1626; found 192.1627; uv (hexane), λ_{max}(log ϵ): 212 nm (3.01); ir (CCl_4), cm^{-1}: 2221, 1450, 1396, 1384, 1366, 1355.

Similar heating of 94 (0.127 g) in methacrylonitrile (9 mL) at 80°C for 26 hr, and analogous workup except for elution with ethyl acetate (10%) in light petroleum, afforded amidrazone 98b (0.128 g, 70%), r_f = 0.08 (Al_2O_3, ether). Recrystallization from light petroleum gave 98b as a colourless solid, mp 60-61.5°C. Spectral data for 98b: ^{1}H nmr (500 MHz), δ: 1.19 (s, 9H), 1.52 (s, 3H), 1.83 (s, 3H), 1.93 (m, 1H), 2.11 (s, 3H),

2.47 (m, 1H), 2.60 (m, 2H); ^{13}C nmr (22.62 MHz), δ: 21.59, 24.69, 25.09 (Me's), 25.43, 32.89 (CH_2's), 31.05 (t-Bu), 53.33 (CMe_3), 58.89 (C-CN), 120.97 (CN), 150.61, 172.83 (C=N's); ms(ei), m/z(%): 234(2), 219(24), 163(67), 95(24), 57(100), 56(19); ms (ei, high resolution), m/z: calc'd for $C_{13}H_{22}N_4$ 234.1844; found 234.1848; uv (MeOH), λ_{max} (log ϵ): 234 nm (3.52); ir(film), cm^{-1}: 2225(vw), 1674(br), 1449, 1371, 1358, 1254, 1217, 1166, 853, 736.

Analogous treatment of 94 (0.260 g) with methyl methacrylate (10 mL) at 80°C for 26 hr led to significant polymer formation. The contents of the tube were added to dry methanol (20 mL), the precipitate was filtered off, and the residue was concentrated to afford crude 98c, which is very easily hydrolyzed. The ^{13}C nmr spectrum was obtained directly with the crude sample. For other spectra pure samples were collected by preparative glpc (6'x1/4" column packed with OV-17, 10% on Chromosorb W) at 172°C. With a helium flow rate of 18 mL min^{-1}, the retention time for 98c was 7 min. Spectral data for 98c; ^1H nmr (500 MHz), δ: 1.21 (s, 9H), 1.42 (s, 3H), 1.85 (s, 3H), 2.05 (s, 3H), 2.17 (m, 1H), 2.41 (m, 1H), 2.54 (m, 1H), 2.66 (m, 1H), 3.71 (s, 3H); ^{13}C nmr (22.62 MHz), δ: 21.21, 21.53, 24.96 (Me's), 28.53, 29.46 (CH_2's), 30.79 (t-Bu), 51.86 (OMe), 53.33 (CMe_3), 66.34 (CC=O), 154.16, 174.49 (C=N's), 177.60 (C=O); ms(ei), m/z(%): 267(3), 252(28), 197(49), 196(100), 152(29), 112(45), 87(37), 57(77); ms (ei, high resolution), m/z: calc'd for $C_{14}H_{25}N_3O_2$ 267.1949; found 267.1949; uv ($CHCl_3$), λ_{max}(log ϵ): 240 nm (3.87); ir (film), cm^{-1}: 1739, 1670(br), 1459, 1372, 1359, 1258, 1220, 1192, 1095.

Reaction of 94 with acetone cyanohydrin

A solution of triazoline 94 (210 mg) in 2.5 mL of a solvent (see below) and 0.25 mL of acetone cyanohydrin was stirred at room temperature until the triazoline was consumed (5 hr for CH_2Cl_2 solvent, 3 hr for methanol or acrylonitrile). Once the reaction was complete, CH_2Cl_2 (10 mL) and dilute aqueous base (20 mL) were added. After five minutes more of stirring, the layers were separated. The aqueous portion was extracted (3 x 10 mL) with CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$.

After filtration and concentration (aspirator) the residue was applied to a column of 10 g of Al_2O_3(II) and eluted with 50% ether in light petroleum. The first fraction (r_f=.57, ether) was 1-(t-butyl)-2-cyano-2,3,3-trimethylaziridine (105) obtained as an oil (88-99 mg, 42-47%). Spectral data for 105; ^{1}H nmr (90 MHz), δ: 1.13 (s, 3H), 1.18 (s, 9H), 1.36 (s, 3H), 1.45 (s, 3H): ^{13}C nmr (22.62 MHz), δ: 19.67, 20.19, 23.68 (Me's), 29.34 (t-Bu), 46.08, 52.18, 55.89 (4re C's), 122.19 (CN); ms(ei), m/z(%): 151(9), 110(25), 109(25), 83(53), 57(100): ms (ci, NH_3), m/z(%): 167(100), 111(31); ms (ei, high resolution), m/z: calc'd for $C_9H_{15}N_2$ [M^+-CH_3] 151.1235; found 151.1243; uv: no λ_{max} > 200 nm; ir (CCl_4), cm^{-1}: 2210, 1455, 1386, 1378, 1364.

Reaction of 94 with sulfene

A 50 mL round bottom flask was charged with 94 (0.280 g, 1.7 mmol), triethylamine (0.350 g, 3.5 mmol) and 10 mL of anhydrous ether. The solution was stirred and cooled with ice while methanesulfonyl chloride (0.379 g, 3.3 mmol) was added dropwise over 20 min. The ice bath was

removed and stirring was continued for 4 hr. Dichloromethane (10 mL) was added, the precipitated amine salt was filtered off and the filtrate was concentrated. The residue was applied to a column of Al_2O_3 (II) from which the product was eluted with ether (50%) in light petroleum (rf = 0.17, ether). Further chromatographic purification of the product from the first column gave 2-aza-2-(t-butyl)-3, 3-dimethyl-5-thiaspiro[2.3]hexane-5,5-dioxide (109) (0.084 g, 40% based on 0.20 g of triazoline consumed), mp 78.5-80°C (from petroleum). Spectral data for 109; ^{1}H nmr (90 MHz), δ: 1.16 (s, 9H), 1.25 (s, 6H), 4.22 (ab q, 4H, J=12.8 Hz); ^{13}C nmr (22.62 MHz), δ: 22.04 (di-Me), 30.26 (t-Bu), 41.35, 53.46, 55.68 (4re C's), 68.55 (CH_2); ms(ei), m/z(%): 217(4), 216(4), 202(22), 160(30), 97(43), 96(97), 57(100); ms (ei, high resolution), m/z: calc'd for $C_9H_{16}NO_2S$ [M^+-CH_3] 202.0902; found 202.0898; uv: no λ_{max} > 200 nm; ir ($CDCl_3$), cm^{-1}: 1450, 1385, 1377, 1368, 1358, 1325, 1200.

Reaction of 94 with phenyl isocyanate

A solution of triazoline 94 (0.158 g) in 6 mL of dry chloroform containing 0.25 mL of phenyl isocyanate was stirred at room temperature for 48 hr. More isocyanate (0.25 mL) was added and stirring was continued for a further 48 hr. Dry chloroform (20 mL) was added and the resulting solution was washed twice with aqueous NaOH (20 mL, 0.5 M). The organic layer was dried over $MgSO_4$. Concentration and chromatography of the residue on a silica column (ether) led to separation of an orange compound with r_f=0.22 (ether). Fractions containing the orange material were concentrated and the residues were subjected to centrifugal chromatography with ethyl acetate

(25%) in light petroleum. The viscous orange product would not crystallize. The yield of triazoline 111 was 168 mg (62%). Spectral data for 111; ^{1}H nmr (90 MHz), δ: 1.50 (s, 9H), 1.69 (s, 6H), 5.17 (s, 1H), 7.01-7.82 (m, 5H), 10.45 (s, br, 1H); ^{13}C nmr (22.62 MHz), δ: 25.31 (di-Me), 28.06 (t-Bu), 54.43 ($\underline{C}Me_3$), 94.03 (vinyl CH), 105.15 (sp^3 ring C), 120.00, 123.21, 128.89, 139.37 (Ph C's), 159.07 (sp^2 ring C), 164.91 (C=O); ms(ei), m/z(%); 258(11), 129(18), 166(12), 110(100), 93(30), 71(21), 70(20), 57(78), 55(26); ms (ci, CH_4), m/z(%): 289(9), 288(8), 287(32); ms (ei, NH_3), m/z(%): 289(100); ms (ei, high resolution), m/z: calc'd for $C_{16}H_{22}N_2O$ [M^+-N_2] 258.1732; found 258.1748; uv (ethanol), λ_{max} (log ϵ): 226 nm (3.85), 256 nm (4.32), 310 nm (3.53), 392 nm (3.83); ir ($CHCl_3$), cm^{-1}: 3345, 3017, 1632, 1617, 1594, 1540, 1499, 1442, 1373, 1317, 1296, 1263, 1202, 1159.

Reaction of 94 with DMAD

A solution of 94 (200 mg, 1.2 mmol) and DMAD (200 mg, 1.4 mmol) in 20 mL of solvent (methanol or dichloromethane, see text) was stirred at room temperature for 2 hours. The solution was concentrated with a rotary evaporator and the residue was chromatographed on Al_2O_3(II). The column was developed initially with 10% ether in light petroleum and the polarity was increased gradually after each component was eluted. The component to be eluted first was 115 (r_f=0.65, ether) which was recrystallized from petroleum to give mp 115-116°C. Compound 117 (r_f=0.50) was obtained second, mp 90-91°C (from petroleum) and 116 (r_f=.36) was eluted last.

Analyses by high performance liquid chromatography (hplc) were carried out with a Varian 5000 instrument equipped with a Varian Vista 402 processor

and with a uv detector set at 310 nm. A Varian SI-5 silica column (4x150 mm) was used with the following elution program: 0-10 min (10% CH_2Cl_2 in hexane changing to 9% CH_2Cl_2, 1% isopropyl alcohol in hexane); 10-35 min (no change); 35-40 min (return to initial composition). With that program and a pumping rate of one mL min^{-1}, the retention times were 19 min (115), 23 min (117), and 27 min (116). Spectral data for 115; ^1H nmr (90 MHz), δ: 1.55 (s, 9H), 1.66 (s, 6H), 3.70 (s, 3H), 3.81 (s, 3H), 5.52 (s, 1H), 7.01 (s, 1H); ^{13}C nmr (22.62 MHz), δ: 25.45 (di-Me), 28.44 (t-Bu), 51.71, 51.28 (OMe's), 54.56 ($\underline{C}Me_3$), 93.37 (vinyl C), 106.09 (sp^3 ring C), 110.56 (terminal CH=), 148.16 (sp^2 ring C), 158.57 (inner CH=), 167.62, 170.67 (C=O's); ms(ei), m/z(%): 309(25), 294(17), 238(23), 224(28), 197(51), 166(31), 57(100); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{23}N_3O_4$ 309.1687; found 309.1686; uv (MeOH), λ_{max} (log ϵ): 216 nm (3.87), 268 nm (3.60), 318 nm (3.87), 420 nm (4.13); ir (CCl_4), cm^{-1}: 1741, 1705, 1611, 1568, 1432.

Spectral data for 116: ^1H nmr (90 MHz), δ: 1.42 (s, 9H), 1.58 (s, 6H), 3.68 (s, 3H), 3.86 (s, 3H), 5.30 (s, 1H), 5.67 (s, 1H); ms(ei), m/z(%): 281(8), 205(21), 166(31), 139(33), 108(34), 57(100); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{23}NO_4^{\cdot}$ [M^+-N_2] 281.1627; found 281.1609; uv (MeOH), λ_{max}(log ϵ): 200-275 nm (3.27-3.33, continuum), 308 nm (3.67), 414 nm (3.55); ir (CCl_4), cm^{-1}: 1734, 1713, 1671, 1615, 1565, 1439.

Spectral data for 117: ^1H nmr (250 MHz), δ: 1.28 (s, 9H), 1.52 (s, 3H), 1.94 (ddd, 1H, J=3.6, 10.2 and 11.7 Hz), 2.14 (ddd, 1H, J=3.6, 9.9 and 11.9 Hz), 2.46 (m, 1H), 2.79 (ddd, 1H, J=9.4, 10.2 and 11.9 Hz), 3.58 (s, 3H), 3.65 (s, 3H), 7.56 (s, 1H); ^{13}C nmr (22.62 MHz), δ: 22.14 (Me), 31.09

(t-Bu), 26.61, 34.93 (CH_2's), 50.38, 51.91 (OMe's), 55.65, 59.78, 73.97 (4^{re}, C's), 101.70 (vinyl C), 151.34 (=CH), 166.43, 172.67 (C=O's); ms(ei), m/z(%): 281(8), 280(24), 253(11), 250(6), 221(26), 193(19), 165(100), 134(13), 107(10), 57(30); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{23}NO_4$ 281.1627; found 281.1603; uv (MeOH), λ_{max}(log ϵ): 206 nm (4.58), 310 nm (4.18); ir(CCl_4), cm^{-1}: 1736, 1690 (br).

Reaction of 94 with benzonitrile oxide

A flask containing 4 mL of dry CH_2Cl_2 and benzoyl chloride oxime[282] (162 mg, 1.14 mmol) was stirred at -30°C (alcohol-dry ice). A solution of 94 (162 mg, 0.97 mmol) and Et_3N (150 mg, 1.49 mmol) in 4 ml CH_2Cl_2 was added all at once. After 15 minutes, 4 volumes of ether were added and the solution was filtered. The filtrate was concentrated (aspirator) and applied to a basic Al_2O_3(II) column. Elution was with 40% ether in light petroleum. The fraction eluting with r_f=0.28 (40% ether) contained 129a (193 mg, 0.75 mmol) 77%. Recrystallization from light petroleum provided white crystals, mp 120-122°C decomp. Spectral data for 129a; ^1H nmr (90 MHz), δ: 1.36 (s, 9H), 1.58 (s, 3H), 1.67 (s, 3H), 3.59 (s, 2H, (ab q, J=18 Hz in C_6H_5)), 7.38-7.58 (m, 3H), 7.67-7.82 (m, 2H); ^{13}C nmr (62.90 MHz), δ: 26.85, 27.88 (Me's), 31.99 (t-Bu), 42.63 (CH_2), 53.08 (CMe_3), 104.68 (ring C), 128.63 (spiro C), 126.61, 128.95, 129.99, 130.47 (Ph C's), 157.59 (C=N); ms(ei), m/z(%): 258(5), 257(4), 244(18), 243(89), 187(58), 186(62), 159(31), 103(30), 77(27), 58(100), 57(47); ms (ci, CH_3), m/z(%): 287(19), 259(22), 243(48), 203(29), 201(30), 186(31), 159(56), 118(70), 114(100), 104(86), 99(50), 84(36); ms (ei, high resolution), m/z: calc'd for $C_{16}H_{22}N_2O$ [M^+-N_2]

258.1732; found 258.1748; calc'd for $C_{15}H_{19}N_2O$ [$M^+-N_2-CH_3$] 243.1497; found 243.1503; uv ($CHCl_3$), λ_{max} (log ϵ): 264 nm (3.88), 317 nm (2.95); ir (film), cm^{-1}: 1596 (vw), 1580 (vw), 1450, 1420, 1399, 1366, 1310, 1258, 1208; Raman, cm^{-1}: 1600, 1592 (N=N), 1564.

Reaction of 94 with diphenylnitrilimine

A flask containing 94 (236 mg, 1.41 mmol), benzoyl chloride phenylhydrazone[283] (326 mg, 1.41 mmol), Et_3N (300 mg, 2.87 mmol) and 5 mL of dry CH_2Cl_2 was stirred at room temperature for 44 hours. At this time, 4 volumes of ether were added and the solution was filtered. After concentration of the filtrate, the residue was applied to a basic Al_2O_3 (II) column. Development with 10% ether in light petroleum afforded 129b (425 mg, 1.18 mmol) 84%, as a solid, mp 110°C decomp., r_f=0.10 (10% ether). Spectral data for 129b; ^1H nmr (90 MHz), δ: 1.28 (s, 9H), 1.49 (s, 3H), 1.70 (s, 3H), 3.42 (ab q, 2H, J=18.3 Hz), 6.83-7.86 (m, 10H); ^{13}C nmr (125.76 MHz), δ: 26.85, 27.16 (Me's), 31.00 (t-Bu), 43.30 (CH_2), 52.72 (CMe_3), 102.68 (ring C), 119.58 (spiro C), 117.80, 121.80, 125.61, 128.17, 128.75, 128.93, 132.88, 143.15 (Ph C's), 146.51 (C=N); ms(ei), m/z(%): 333(1), 318(26), 262(32), 261(31), 143(26), 117(21), 77(100), 58(45); ms (ci, NH_3), m/z(%): 362(85), 334(100), 261(92), 74(46); ms (ei, high resolution), m/z: calc'd for $C_{21}H_{24}N_3$ [$M^+-N_2-CH_3$] 318.1970; found 318.1974; uv (hexanes), λ_{max} (logϵ): 240 nm (4.14), 298 nm (3.93), 326 nm (4.18), 352 nm (4.10); ir (film), cm^{-1}: 1599, 1581(w), 1493; 1445(w), 1384, 1378, 1365, 1313, 1273, 1232, 1218; Raman, cm^{-1}: 1595 (N=N), 1562.

Conversion of 129a to 130a

Triazoline 129a (104 mg, 0.36 mmol) was heated in 5 mL of benzene at 80°C for 3 hours. After cooling and concentration, centrifugal chromatography of the residue (10% ethyl acetate in light petroleum) afforded 130a (83 mg, 0.32 mmol) 89%, as a solid, mp 56-58°C (light petroleum), r_f=0.65 (25% EtOAc in petroleum, Al_2O_3). Spectral data for 130a; ^1H nmr (90 MHz), δ: 1.08 (s, 9H), 1.60 (s, 6H), 1.85 (s, br, 1H), 6.37 (s, 1H), 7.43-7.55 (m, 3H), 7.79-7.92 (m, 2H); ^{13}C nmr (125.76 MHz), δ: 30.64 (di-Me), 31.77 (t-Bu), 52.05, 52.76 (4^{re} C's), 98.10 (C-4), 126.63, 129.04, 129.57, 130.02 (Ph C's), 162.36 (C-3), 181.20 (C-5); ms(ei), m/z(%): 258(1), 243(79), 187(36), 186(38), 77(13), 58(100); ms (ci, CH_4), m/z(%): 259(8), 243(43), 186(26), 114(100), 74(9); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{19}N_2O$ [M^+-CH_3] 243.1497; found 243.1503; uv (MeOH), λ_{max} (log ϵ): 240 nm (4.04); ir (film), cm^{-1}: 3352(br), 3121, 1597, 1576, 1508, 1467, 1438, 1405, 1391, 1379, 1362, 1214(br).

Conversion of 129b to 130b

Triazoline 129b (95 mg, 0.26 mmol) was heated in benzene at 80°C for 3 hours. After cooling and concentration, centrifugal chromatography (10% EtOAc in petroleum) afforded 130b (82 mg, 0.25 mmol) 94%, as a solid, mp 104-105°C (petroleum), r_f=0.63 (25% EtOAc in petroleum, Al_2O_3). Spectral data for 130b; ^1H nmr (90 MHz), δ: 0.99 (s, 9H), 1.47 (s, 6H), 1.92 (s, br, 1H), 6.57 (s, 1H), 7.20-7.76 (m, 8H), 7.81-7.98 (m, 2H); ^{13}C nmr (125.76 MHz), δ: 31.71 (t-Bu), 32.28 (di-Me), 51.70, 52.80 (4^{re} C's), 102.50 (C-4), 125.57, 126.51, 128.49 (br), 128.54, 128.65, 133.28, 142.33 (Ph C's), 149.98

(C-3), 154.16 (C-5); ms(ei), m/z(%): 333(2), 318(61), 262(80), 261(100), 77(18), 58(26); ms (ei, high resolution), m/z: calc'd for $C_{22}H_{27}N_3$ 333.2205; found 333.2210; uv (hexane), λ_{max} (log ϵ): 258 nm (4.24); ir (film), cm^{-1}: 3378 (br), 3063, 1599, 1538(w), 1498, 1460, 1421(w), 1389, 1377, 1363, 1213(br).

Decomposition kinetics of triazolines 129

Medium-walled nmr tubes were charged with 129 and with sufficient benzene to give solutions with the concentrations indicated in Table 8. The solutions were degassed by means of three "freeze-pump-thaw" cycles before the tubes were sealed and immersed in constant temperature baths controlled to ±0.1°C.

Progress of the decomposition was monitored by ^1H nmr spectroscopy. Integration of the t-butyl and gem-dimethyl signals of all components provided the normalizing integrals. Decompositions were followed to at least 85% conversion. Good fits of the data to the first order rate law were obtained. The activation parameters listed in Table 9 were calculated using the Arrhenius equation (A and Ea) and the Eyring equation ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$).

The uncertainty in the slope of the plots was calculated using equation [1] where n is the number of pairs of data points, x are the individual x-values, and $(\sigma y)^2$ is given by eq. [2].[300] Parameter r in eq. [2] is the correlation coefficient and y represents the individual y-values. The uncertainty in the intercept is given by equation [3].[300]

$$\text{uncertainty in slope} = \sqrt{\frac{n(\sigma y)^2}{n\Sigma x^2-(\Sigma x)^2}} \qquad [1]$$

$$(\sigma y)^2 = \frac{(1-r^2)[n\Sigma y^2-(\Sigma y)^2]}{n(n-2)} \qquad [2]$$

$$\text{uncertainty in intercept} = \sqrt{\frac{(\sigma y)^2}{n}\left(1+\frac{(\Sigma x)^2}{n\Sigma x^2-(\sigma\Sigma x)^2}\right)} \qquad [3]$$

Synthesis of triazoline 134b

A flask was charged with 94 (171 mg, 1.03 mmol), p-nitrophenyl-azide[340] (169 mg, 1.02 mmol) and 5 mL of dry CH_3CN. The contents were stirred at room temperature for five days. At this time the contents were concentrated (aspirator) and applied to a basic Al_2O_3 (II) column. Elution was with 33% ether in light petroleum. The fraction with r_f=0.20 (33% ether) was collected and concentration afforded 134b (220 mg, 0.66 mmol) 65% as a yellow solid, mp 80°C decomp. (light petroleum). Spectral data for 134b; ^{1}H nmr (90 MHz), δ: 1.12 (s, 9H), 1.64 (s, 3H), 1.88 (s, 3H), 4.63 (ab q, 2H, J=18.6 Hz), 7.40 (d, 2H, J=9.3 Hz), 8.30 (d, 2H, J=9.3 Hz); ^{13}C nmr (125.76 MHz), δ: 26.82, 27.05 (Me's), 31.60 (t-Bu), 53.04 ($\underline{C}Me_3$), 73.03 (CH_2), 104.11 (sp^3 ring C), 114.12 (spiro C), 116.62, 125.13, 143.64, 144.48 (Ph C's); ms(ei), m/z(%): 275(16), 218(24), 163(50), 138(42), 117(21), 98(38), 82(73), 58(44), 57(100); ms (ci, NH_3), m/z(%): 332(8), 276(48), 246(47), 168(100), 140(38), 113(75), 111(40), 109(81); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{21}N_3O_2$ [M^+-N_4] 275.1634; found 275.1633; uv

($CHCl_3$), λ_{max} (log ϵ): 280 nm (3.75), 332 nm (4.19); ir (film), cm^{-1}: 1604, 1524, 1502, 1400(w), 1382(w), 1370, 1341, 1328, 1300(w), 1290, 1272, 1172; Raman, cm^{-1}: 1596 (C-N=N-C), 1589, 1329, 1290, 1113.

Reaction of 94 and phenyl azide in benzene.

Triazoline 94 (384 mg, 2.30 mmol) and phenyl azide[341] (375 mg, 3.15 mmol) were heated together in 30 mL of benzene at 80°C for 43 hours. After cooling, the benzene was removed (aspirator) followed by the excess phenyl azide (vacuum line). The residue was applied to a neutral Al_2O_3 (II) column. Development with 2% ether in petroleum afforded 139a (85 mg, 0.37 mmol) 16% as a white solid, mp 52-54°C (light petroleum), r_f=0.28 (2% ether). Increasing the solvent polarity to 20% ether gave 137a and 141a as a mixture (r_f=0.10, 20% ether). Centrifugal chromatography of this mixture (5% EtOAc in petroleum) gave pure 141a (107 mg, 0.74 mmol) 32%, obtained as a solid, mp 52-53.5°C (light petroleum), lit[305] mp 55-56°C. Product 137a could not be recovered. The yield of 137a (7%) was estimated from the ^1H nmr spectrum of the crude reaction mixture. Spectral data for 139a: ^1H nmr (90 MHz), δ: 1.41 (s, 9H), 1.42 (s, 6H), 2.52 (s, 2H), 6.78-7.28 (m, 5H); ^{13}C nmr (125.76 MHz), δ: 28.27 (di-Me), 28.39 (t-Bu), 44.14 (CH_2), 55.30 ($\underline{C}Me_3$), 61.01 (sp^3 ring C), 121.65, 122.71, 128.79, 150.66 (Ph C's) 156.42 (C=N); ms(ei), m/z(%): 230(38), 173(18), 139(28), 118(100), 98(25), 89(60), 57(77); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{22}N_2$ 230.1783; found 230.1780; uv (MeOH), λ_{max} (log ϵ): 246 nm (4.01); ir (film), cm^{-1}: 1674(vs), 1594, 1489, 1368, 1271, 1251, 1230, 1131.

Partial ^{1}H nmr data for 140a; from ^{1}H nmr spectrum of crude reaction mixture (500 MHz), δ: 1.24 (s, 9H), 1.53 (s, 3H), 4.08 (dd, 1H, J=10.5 and 17.4 Hz), 4.54 (s, br, 1H), 4.58 (dd, 1H, J=3.2 and 17.4 Hz), 4.83 (s, br, 1H), 5.47 (dd, 1H, J=3.2 and 10.5 Hz).

Extended heating of 94 and phenyl azide

Triazoline 94 (354 mg, 2.12 mmol) and phenyl azide (140 mg, 3.48 mmol) were heated in 30 mL of benzene at 80°C for 30 hours. After removal of the benzene and the phenyl azide as described above, 20 mL of toluene were added. This solution was refluxed for 22 hours before cooling and removal of the toluene by vacuum distillation. The residue was applied to a neutral Al_2O_3 (II) column. Elution was with 1% ether in petroleum and afforded 143a (24 mg, 0.10 mmol) 5%, r_f=0.18 (1% ether) followed by 139a (68 mg, 0.30 mmol) 14%. Increasing the solvent polarity provided 137a and 141a as a mixture. Centrifugal chromatography of this mixture provided 141a (43 mg, 0.30 mmol) 14%. The yield of 137a was estimated to be 3%. Spectral data for 143a: ^{1}H nmr (90 MHz), δ: 1.53 (s, 9H), 1.79 (s, 3H), 1.93 (s, br, 3H), 4.91 (s, br, 1H) 5.20 (s, br, 1H), 6.61-7.17 (m, 5H); uv (hexanes), λ_{max} (log ϵ): 236 nm (4.23); ir (film), cm^{-1}: 3061, 1610(vs), 1592, 1482, 1370, 1345, 1267, 1223.

Reaction of 94 and phenyl azide in CH_3CN

Triazoline 94 (176 mg, 1.05 mmol) and phenyl azide (317 mg, 2.66 mol) were heated in 5 mL of CH_3CN at 65°C for 3 days. After cooling the CH_3CN was removed (aspirator) followed by the phenyl azide (vacuum line).

Centrifugal chromatography (10% EtOAc in petroleum) of the residue provided pure 137a (109 mg, 0.42 mmol) 40%, obtained as a solid, mp 55-56°C (light petroleum), r_f=0.17 (Al_2O_3), 10% EtOAc). Product 139a was detected by analytical GC in < 1% yield. Spectral data for 137a; ^{1}H nmr (90 MHz), δ: 1.02 (s, 9H), 1.50 (s, 6H), 7.57-7.63 (m, 5H), 7.64 (s, 1H); ^{13}C nmr (125.76 MHz), δ: 32.01 (di-Me), 32.15 (t-Bu), 51.91, 52.01 (sp^3 C's), 127.99, 128.71, 129.85, 147.21 (Ph C's), 132.04 (4-C), 138.58 (5-C); ms(ei), m/z(%): 258(2), 243(25), 186(21), 158(16), 114(24), 77(20), 58(100); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{22}N_4$ 258.1844; found: 258.1839; uv (MeOH), λ_{max} (log ϵ): 262 nm (3.43); ir (film), cm^{-1}: 3340 (br), 3158, 1600, 1537(w), 1581, 1471(w), 1452, 1413(w), 1390, 1380, 1363, 1311, 1230, 1220, 1201, 1180, 1169, 1164, 1127.

Reaction of 94 and p-nitrophenyl azide in benzene

Triazoline 94 (260 mg, 1.56 mmol) and p-nitrophenyl azide (260 mg, 1.58 mmol) were heated together in 15 mL of benzene at 80°C for 20 hours. After cooling, the benzene was removed (aspirator) and the residue was triturated with 3 x 30 mL of hot 30-60°C petroleum ether. The petroleum extracts were combined and put in a freezer at -20°C for 12 hours. After removal, the liquid was decanted from the solid film which fell from solution. The liquid was concentrated and applied to a neutral Al_2O_3 (II column. Development with 2% ether in light petroleum provided p-nitrophenyl azide (r_f=0.39, 2% ether) followed by amidine 143b (82 mg, 0.30 mmol) 19%, as a yellow solid, mp 90-92°C (light petroleum), r_f=0.57 (10% ether). Gradual increase of the polarity to 10% ether afforded amidine 139b (128 mg,

0.47 mol) 30%, mp 93-94°C (petroleum), r_f=0.32 (10% ether) followed by 144b (15 mg, 0.06 mmol) 4%, as a yellow solid, mp 137-138°C (from $CHCl_3$ in light petroleum), r_f=0.12 (10% ether).

The solid which fell from the cold petroleum ether solution was taken up in a small amount of solvent and applied to a neutral Al_2O_3 (II) column. Development with 33% ether in light petroleum provided 1,2,3-triazoline 140b (99 mg, 0.33 mmol) 21%, mp 120-122°C, r_f=0.61 (33% ether) followed by p-nitroaniline (4 mg, 0.03 mmol) 2%, r_f=0.09 (33% ether). Spectral data for 139b: ^{1}H nmr (90 MHz), δ: 1.51 (s, 9H), 1.57 (s, 6H), 2.66 (s, 2H); 6.91 (d, 2H, J=9.3 Hz), 8.13 (d, 2H, J=9.3 Hz); ^{13}C nmr (22.62 MHz), δ: 27.94 (di-Me), 28.21 (t-Bu), 44.39 (CH_2), 55.97 ($\underline{C}Me_3$), 62.18 (sp^3 ring C), 122.48, 125.10, 141.96, 157.62 (Ph C's), 157.49 (C=N); ms(ei), m/z(%): 275(32), 218(26), 204(17), 163(41), 139(49), 98(30), 82(67), 58(38), 57(100); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{21}N_3O_2$ 275.1634; found 275.1633; uv ($CHCl_3$), λ_{max} (log ϵ): 372 nm (4.52); ir (film), cm^{-1}: 1652(br), 1578(br), 1502, 1381, 1369, 1327, 1260, 1219, 1168, 1131, 1104, 1073.

Spectral data for 140b: ^{1}H nmr (500 MHz), δ: 1.31 (s, 9H), 1.53 (s, 3H), 4.19 (dd, 1H, J=10.0 and 17.7 Hz), 4.53 (s, br, 1H), 4.72 (dd, 1H, J=2.9 and 17.7 Hz), 4.85 (s, br, 1H), 5.50 (dd, 1H, J=2.9 and 10.0 Hz), 7.56 (d, 2H, J=9.2 Hz), 8.23 (d, 2H, J=9.2 Hz); ^{13}C nmr (125.76 MHz), δ: 25.12 (Me), 29.78 (t-Bu), 55.17 ($\underline{C}Me_3$), 66.90 (CH), 71.71 (CH_2), 116.82 ($=CH_2$), 114.87, 125.57, 140.75, 146.02 (Ph C's), 145.96 (vinyl C); ms(ei), m/z(%): 275(7), 204(11), 177(33), 121(87), 82(60), 57(100), 41(72); uv (hexanes), λ_{max} (log ϵ): 220 nm (3.66), 3.38 nm (3.79); ir (film), cm^{-1}: 3042, 1578(br), 1502, 1383, 1370, 1329, 1208.

Spectral data for 143b; ^{1}H nmr (90 MHz), δ: 1.56 (s, 9H), 1.88 (s, 3H), 1.97 (s, br, 3H), 4.92 (s, br, 1H), 5.23 (s, br, 1H), 7.16 (d, 2H, J=9.3 Hz), 8.29 (d, 2H, J=9.3 Hz); ^{13}C nmr (22.62 MHz), δ: 18.30 (N=C-Me), 25.12 (C=C-Me), 28.72 (t-Bu), 57.61 ($\underline{C}Me_3$), 118.02 ($=CH_2$), 121.62, 125.25, 141.64, 158.65 (Ph C's), 145.86 (vinyl C), 153.75 (C=N); ms(ei), m/z(%): 275(11), 219(38), 218(100), 163(92), 117(52), 82(92), 57(67); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{21}N_3O_2$ 275.1634; found 275.1636; uv (hexanes), λ_{max} (log ϵ): 222 nm (4.11), 333 nm (4.23); ir (film), δ: 3100, 1617(br), 1582(br), 1499, 1372, 1360, 1325, 1285, 1239, 1191, 1165, 1105.

Spectral data for 144b; ^{1}H nmr (90 MHz), δ: 1.46 (s, 9H), 1.79 (s, 3H), 4.38 (s, br, 1H), 6.78 (d, 2H, J=9.0 Hz), 8.16 (d, 2H, J=9.0 Hz); ^{13}C nmr (22.62 MHz), δ: 18.81 (Me), 28.74 (t-Bu), 51.84 ($\underline{C}Me_3$), 122.21, 125.09, 142.03, 159.08, (Ph C's), 153.21 (C=N); ms(ei), m/z(%): 235(44), 179(21), 178(100), 163(38), 138(100) 108(38), 76(36), 57(57); ms (ei, high resolution), m/z: calc'd for $C_{12}H_{17}N_3O_2$ 235.1320; found 235.1324; uv ($CHCl_3$), λ_{max} (log ϵ): 350 nm (3.90); ir (film), cm^{-1}: 3422(br), 1644, 1584, 1526, 1487, 1323, 1261, 1202, 1611, 1102.

^{1}H nmr data for 137b: obtained from crude reaction mixture[309] (500 MHz), δ: 7.92 (s, 1H), 8.00 (d, 2H, J=9.1 Hz), 8.13 (s, 1H), 8.43 (d, 2H, J=9.1 Hz).

Extended heating of 94 and p-nitrophenyl azide

Triazoline 94 (219 mg, 1.31 mmol) and p-nitrophenyl azide (220 mg, 1.34 mmol) were heated in benzene at 80°C for 24 hours. After cooling, concentration, and trituration of the mixture into 3 x 30 mL of hot 30-60°C

petroleum, the petroleum was concentrated (aspirator) and the residue was taken up in 10 mL of toluene. This solution was heated for 12 hours at 110°C. After cooling and removal of the toluene by vacuum distillation, the residue was triturated with 3 x 30 mL of hot petroleum ether. The combined petroleum ether extracts were put in a freezer for 12 hours.

Chromatography of the components remaining in solution was done as described above and afforded 143b (94 mg, 0.34 mmol) 26%, 139b (115 mg, 0.42 mmol) 32% and 144b (15 mg, 0.07 mmol) 5%.

Chromatography of the solid that fell from the cold petroleum solution afforded p-nitroaniline (27 mg, 0.20 mmol) 15%.

Partial decomposition of 134b in benzene

20 mg of 134b were heated in 3 mL of benzene for 2 hours. After cooling tlc indicated the presence of 139b, 140b, 143b, 144b and p-nitroaniline as well as starting material 134b, p-nitrophenyl azide and triazoline 94.

Thermolysis of 115 in methanol

Fumaratotriazoline 115 (369 mg, 1.2 mmol) was added to a flask containing methanol (100 mL). Dissolution of 115 occurred during heating to reflux temperature. Periodic withdrawal of aliquots of the boiling solution, and analysis by tlc, showed that no more 115 remained after 48 hr. Cooling and evaporation of the solvent with a rotary evaporator was followed by centrifugal chromatography of the residue in two portions. Elution with ethyl acetate (15%) in light petroleum afforded pyrroles 158 and 157, in

that order, combined yields (from both portions) of 13% and 78%, respectively. On silica tlc plates, developed with 50% ethyl acetate in light petroleum, 158 and 157 had r_f values of 0.40 and 0.22, respectively. Both were oils at room temperature. Spectral data for 157: ^{1}H nmr (90 MHz), δ: 1.22 (s, 9H), 1.27 (s, br, 1H), 1.80 (s, 3H), 2.21 (s, 3H), 3.68 (s, 3H), 3.77 (s, 3H), 5.71 (s, 1H); ^{13}C nmr (22.62 MHz), δ: 20.29, 24.93 (Me's), 29.53 (t-Bu), 51.28 (OMe), 51.74 ($\underline{C}Me_3$ and OMe), 92.71 (C-3), 112.17, 119.90 (C-4 and C-5), 137.34 (C-2), 160.35, 165.83 (C=O's), 183.91 (C=N); ms(ei), m/z(%): 309(54), 253(25), 197(100), 169(28), 164(23), 137(20), 57(100), 56(86); ms (ei, high resolution), m/z: calc'd for $C_{15}H_{23}N_3O_4$ 309.1689; found 309.1687; uv ($CHCl_3$), λ_{max} (log ϵ): 240 nm (4.07), 328 nm (4.01); ir ($CDCl_3$), cm^{-1}: 3378(br), 1730, 1688, 1571, 1518, 1498, 1465, 1436, 1388, 1358, 1264, 1209, 1130, 1061.

Spectral data for 158: ^{1}H nmr (90 MHz), δ: 1.26 (s, 9H), 3.72 (s, 3H), 3.74 (s, 3H), 4.90 (s, br, 1H), 5.54 (s, 1H); ^{13}C nmr (22.62 MHz), δ: 29.63 (t-Bu), 50.96 ($\underline{C}Me_3$ and OMe), 52.20 (OMe), 90.86 (C-3), 113.34, 120.80 (C-4 and C-5), 142.31 (C-2), 161.70, 165.88 (C=O's); ms(ei), m/z(%): 269(83), 238(22), 213(83), 197(100), 181(62), 165(30), 137(35), 122(43); ms (ei, high resolution), m/z: calc'd for $C_{12}H_{19}N_3O_4$ 269.1376; found 269.1379; uv ($CHCl_3$), λ_{max} (log ϵ): 242 nm (3.96), 332 nm (4.03); ir ($CDCl_3$), cm^{-1}: 3384, 3353, 1730, 1678, 1640(br), 1567, 1530, 1497, 1435, 1399, 1352, 1253, 1222, 1210, 1134, 1065.

Spectral data for unidentified component (9%): ^{1}H nmr (90 MHz), δ: 1.53 (s, 9H), 2.69 (s, 3H), 3.72 (s, 3H), 6.37 (d, 1H, J=3.0 Hz), 6.66 (d, 1H, J=3.0 Hz); ms(ei), m/z(%): 269(8), 195(50), 149(26), 139(65), 124(32), 108(100), 107(46), 69(41); ir ($CDCl_3$), cm^{-1}: 1701(v br), 1547, 1440, 1370, 1329, 1240, 1215(br), 1134, 1060.

Hydrolysis of 157

Pyrrole 157 (10 mg) was dissolved in ether (0.5 mL) and the solution was transferred to a watch glass from which the ether was evaporated in ca. 5 min. Ten minutes after the ether had evaporated, analysis of the residue by ir revealed that little, if any, 157 remained and that 158 was the major product.

Thermolysis of 111 in methanol

Amidotriazoline 111 (120 mg, 0.42 mmol) in methanol (5 mL) was heated at the reflux temperature for six days. Cooling, concentration, and centrifugal chromatography (15% ethyl acetate in light petroleum) afforded 167 (47 mg, 0.18 mmol) 43%, as a white solid, mp 163-164.5°C (from acetone in petroleum ether), rf = 0.58 (ethyl acetate).

Direct analysis by gc of a similar thermolysate from 111 in methanol showed that both aniline and 169 were present in ~15% yield. An authentic sample of 169 prepared from methylpropiolate and t-butyl amine,[280] had r_f=0.21 (10% ethyl acetate in petroleum) and gave the published ^{1}H nmr data.[280] Crude 169 isolated from the thermolysate, gave the ^{1}H nmr spectrum of authentic 169.

Spectral data for 167; ^{1}H nmr (90 MHz), δ: 1.32 (s, 9H), 1.88 (s, 3H), 4.75 (d, 1H, J=12.4 Hz), 4.83 (s, br, 1H), 5.18 (s, br, 1H), 6.80 (s, br, NH), 6.94-7.71 (m, 5H), 7.92 (d, 1H, J=12.4 Hz); ^{13}C nmr (22.62 MHz), δ: 21.12 (Me), 30.05 (t-Bu), 57.52 ($\underline{C}Me_3$), 90.10 ($=CH_2$), 116.73 (O=C-$\underline{C}$H), 119.50, 122.76, 128.95, 139.89 (Ph C's), 144.29 (=$\underline{C}$-Me), 145.64 (=$\underline{C}$H-N), 167.70 (C=O); ms(ei), m/z(%): 258(12), 182(18), 166(30), 112(19), 110(100),

105(18), 93(46), 82(17), 77(21), 70(22), 57(67); ms (ei, high resolution), m/z: calc'd for $C_{16}H_{22}N_2O$ 258.1732; found 258.1734; uv ($CHCl_3$), λ_{max} (log ϵ): 200-270 nm (3.69, continuum), 302 nm (4.48); ir (film), cm^{-1}: 3288, 3247, 3130, 3058, 1654, 1598, 1574, 1535, 1497, 1438, 1379, 1332, 1289, 1242, 1261, 1038, 1003.

Spectral data for 169: ^1H nmr (90 MHz), δ: 1.27 (s, 9H), 3.65 (s, 3H), 4.42 (d, 1H, J=8.0 Hz), 6.80 (dd, 1H, J=8.0 and 14.0 Hz), 8.12 (s, v br, NH); ^{13}C nmr (22.62 MHz), δ: 30.21 (t-Bu), 50.14 ($\underline{C}Me_3$), 52.01 (OMe), 81.42 (O=C-$\underline{C}$H), 148.19 (=CH-N), 165.50 (C=O); uv (CCl_4), λ_{max} (log ϵ): 280 nm (3.79); ir (film), cm^{-1}: 3334, 1668, 1618, 1480, 1461, 1371, 1307, 1196, 1140.

Thermolysis of 111 in benzene

Heating of 111 (120 mg) in benzene (5 mL) at the reflux temperature for three days afforded 167 in 85% yield, estimated by integration of the ^1H nmr spectrum.

Kinetics of thermolysis of 111

Medium-walled nmr tubes were charged with 111 and with enough solvent to give solutions at the concentrations given in Table 13. The solutions were degassed by means of three "freeze-pump-thaw" cycles before the tubes were sealed and immersed in constant temperature baths controlled to $\pm 0.1^0C$.

Progress of the decomposition was monitored by ^1H nmr spectroscopy. For samples in methanol the internal standard, for normalizing integrals of all methyl signals of remaining 111, was the sum of integrals from all

t-butyl and methyl signals except for the propenyl methyl group signal of 167, which was doubled before entry into the summation. For samples in benzene the methyl group signal from added toluene was used as internal standard. Decompositions were followed to at least 80% and usually to more than 85% conversion. Good fits of the data to the first order rate law were obtained. From the temperature dependence of the rate constant in methanol (Table 13) the activation parameters calculated were: Arrhenius equation log A = 13.6 ± 0.6, Ea = 29.6 ± 0.9 kcal/mol: Eyring equation, $\Delta H^{\neq}$=28.9 ± 0.1 kcal/mol, $\Delta S^{\neq}$ = 1.5 ± 0.2 eu.

Preparation of some starting amines

Amines 176a[342] and 176[343] were prepared according to published procedures. Amines 176c (bp 81-83°C, lit[344] by 82-83.5°C) and 179 (bp 85°C (27 mm)), lit[344] bp 72-78°C (8 mm) were prepared from methallylamine and benzylamine, respectively, by using the Eschweiler-Clarke methodology employed for 176a.[342]

1-Amino-2-butene and 3-amino-1-butene were prepared from their respective chlorides via the Gabriel synthesis.[345] Amine 176b was then synthesized from 3-amino-1-butene via the Eschweiler-Clarke method[342] (bp 87-88°C, lit[346] bp 91°C). Similarly, 176g (90-95% pure) was prepared from 1-amino-2-butene (bp 95-98°C lit[347] bp 93°C). The impurity was found to be inert to DMAD.

Synthesis of amine 176e

A 100 mL flask was charged with 2,3-dichloropropene (8.92 g, 0.080 mol), 30mL of 40% Me_2NH/H_2O and 20 mL of MeOH. The solution was warmed at

60°C for 15 hours. After cooling, 50 mL of 50% aq. KOH were added and the solution was extracted with 2 x 40 mL of ether. The organic phases were combined and dried over KOH. After concentration (aspirator), the residue was dried once more over KOH and then distilled from KOH. The yield of 176c was 3.56 g, (37%), bp 113-114°C, lit[348] bp 119-120°C (755 mm).

Synthesis of amine 176d

A 250 mL flask was charged with 100 mL of α-methylstyrene and t-butylhypochloride (13.6 g, 0.11 mol)(Frinton). AIBN (0.25 g, 1.8 mmol) was added and the contents were warmed to 80°C for 4 hours. After cooling, the contents were distilled under reduced pressure. The fractions collected above 70°C (6.5 mm) were combined (≈20 mL) and dissolved in 170 mL of MeOH. The solution was stirred with ice cooling while 70 mL of 40% Me_2NH/H_2O were added dropwise over a period of 20 minutes. The ice bath was then removed and the contents were allowed to stir at room temperature for 16 hours. The solution was then carefully added to 200 mL of ice-cooled aqueous HCl (6%). The aqueous solution was washed (3 x 70 mL) with ether and was then added dropwise to ice-cooled aqueous Na_2CO_3 (5%). After addition was complete, the solution was saturated with Na_2CO_3 and extracted (3 x 100 mL) with ether. The combined organic extracts were washed with brine and dried over $MgSO_4$.

After filtration and concentration, the residue was applied to a neutral Al_2O_3 (II) column and eluted with 10% ether in light petroleum. The only compound that was eluted was amine 176d (4.60 g, 27% yield overall). Spectral data for 176d; ^1H nmr (90 MHz), δ: 2.24 (s, 6H, 3.27 (s, br, 2H), 5.19 (s, br, 1H), 5.42 (s, br, 1H), 7.24-7.60 (m, 5H); ^{13}C nmr (22.62 MHz,

δ: 45.28, 64.52, 115.18, 126.27, 127.55, 128.27, 140.21, 145.35; ms(ei), m/z(%): 161(30), 118(16), 115(15), 59(13), 58(100).

Reactions of DMAD with amines 176

In the general procedure, the appropriate amine and one equivalent of DMAD were mixed together in a volume of solvent chosen to give the concentrations indicated in Tables 14 and 15. Air above the chloroform solutions was displaced with N_2 and the solutions were allowed to stand protected from light. The CH_3CN solutions were refluxed with a $CaCl_2$ drying tube attached to the condensor. When periodic ^1H nmr spectra of the mixtures indicated complete consumption of either reactant, mixtures were worked up. Mixtures were separated as described below. Spectral data for products 177 and 178 are found in Tables 16, 17 and 18.

Amine 176a and DMAD.

After removal of solvent (aspirator), the residue was applied to a column containing basic Al_2O_3(II). Elution with 50% ether in light petroleum provided three components from reaction in $CHCl_3$ and two components from reaction with CH_3CN as solvent. Product 180a was eluted first (r_f=0.79, 50% ether), followed by 177a (r_f=0.41) and 178 (r_f=0.26, mp 80-80.5°C) (petroleum ether-acetone) lit[280] mp 83-84.5°C). Spectral data for 180a; ^1H nmr (500 MHz), δ: 2.33 (s, 6H), 2.81 (dd, 1H, J=8.0 and 13.8 Hz), 2.98 (dd, 1H, J=6.2 and 13.8 Hz), 3.75 (s, 3H), 3.81 (s, 3H), 5.13 (dd, 1H, J=10.3 and 1.3 Hz), 5.19 (dd, 1H, J=17.1 and 1.3 H), 5.94 (m, 1H); ^{13}C nmr (62.90 MHz), δ: 39.90, 40.87, 51.71, 52.76, 73.78, 118.94, 125.83,

133.06, 135.18, 166.18, 167.84; ms (ci, CH_4), m/z(%): 314(6), 312(23), 310(52), 308(18), 270(52), 268(78), 254(8), 252(41), 250(63), 56(100); ms(ei), m/z(%): 272(14), 270(66), 268(100), 156(35), 150(32); ms (ei, high resolution), m/z: calc'd for $C_9H_{12}NO_4{}^{35}Cl^{37}Cl$ [$M^+-C_3H_5$], 270.0114; found 270.0116; calc'd for $C_9H_{12}NO_4{}^{35}Cl_2$ 268.0143; found 268.0139; uv ($CHCl_3$), λ_{max} (log ϵ): 240 nm (3.13); ir (film), cm^{-1}: 1732(v br), 1639, 1595(br)

Amine 176b and DMAD

After removal of solvent, the residue was applied to a column containing basic Al_2O_3(II). Elution with 20% ether in petroleum provided first 177b (r_f=0.53, 50% ether) followed by 178.

Amine 176c and DMAD

After removal of solvent and application of the residue to a basic Al_2O_3(II) column, elution with 20% ether in petroleum yielded 180c (from reaction in $CHCl_3$ solution only) (r_f=0.31, 20% ether). Increasing the ether component to 50% gave 177c (r_f=0.44, 50%) followed by 178. Elution of the product mixture from reaction in CH_3CN was begun with 50% ether in light petroleum. Spectral data for 180c: ^1H nmr (90 MHz), δ: 1.81 (s, 3H), 2.42 (s, 6H), 2.91 (ab q, 2H, J=13.5 Hz), 3.76 (s, 3H), 3.82 (s, 3H), 4.96 (s, br, 2H); ^{13}C nmr (62.90 MHz), δ: 24.26, 40.67, 41.26, 51.41, 52.61, 117.32, 126.63, 135.40, 140.84, 166.44, 167.31; ms (ci, CH_4), m/z(%): 328(4), 326(10), 324(22), 322(12), 272(12), 270(60), 268(100), 266(28), 264(38), 170(58); ms(ei), m/z(%): 272(10), 270(65), 268(100), 266(40), 264(65), 170(18), 150(23); ms (ei, high resolution), m/z: calc'd for $C_9H_{12}NO_4{}^{35}Cl^{37}Cl$

$[M^+-C_4H_7]$ 270.0114; found 270.0113; calc'd for $C_9H_{12}NO_4{}^{35}Cl_2$ 268.0143; found 268.0132; uv ($CHCl_3$), λ_{max} (log ϵ): 240 nm (3.14); ir (film), cm^{-1} 1741, 1735, 1646, 1603.

Amine 176d and DMAD

After removal of solvent and application of the residue to a basic Al_2O_3(II) column, elution with 40% ether in light petroleum gave 177d (r_f=0.43, 50% ether) followed by 178.

Amines 177e and 17f and DMAD

Chromatography of the residue after concentration of the reaction mixture gave only 178.

Amine 177g and DMAD

After concentration of the solution and application of the residue on to Al_2O_3(II), elution with 33% ether in light petroleum provided cis and trans 177g as an inseparable mixture (r_f=0.40, 33%) followed by 178.

Amine 179 and DMAD

After ^1H nmr spectroscopy revealed complete consumption of DMAD, chromatography yielded only 178 and starting amine 179.

Reaction of 186 with DMAD

A reaction vessel was charged with 5 mL of dry $CHCl_3$, amine 186[349] (341 mg, 1.66 mmol) and DMAD (235 mg, 1.65 mmol). Air was displaced by passing N_2 briefly over the solution which was allowed to stand in the dark.

After 21 days at room temperature, the solution was concentrated and applied to a basic Al_2O_3(II) column. Elution with 10% ether in petroleum afforded unreacted amine 186 (41 mg). By increasing the polarity gradually, 187 (mp 126-127°C, petroleum) was eluted (r_f = 0.24, 25% EtOAc in petroleum). The yield was 42% based on the amount of 186 consumed. Spectral data for 187; ^{1}H nmr (90 MHz), δ: 0.67 (s, 3H), 1.20 (s, 3H), 2.93 (ab q, 2H, J 13 Hz), 2.99 (s, 3H), 3.53 (s, 3H), 3.94 (s, 3H), 4.81 (s, br, 1H), 7.26-7.58 (m, 5H); ^{13}C nmr (22.62 MHz), δ: 21.88, 22.77, 36.22, 40.27, 51.93, 52.75, 59.51, 77.37, 98.46, 127.31, 146.21, 149.78, 166.02, 167.74; ms(ei), m/z(%): 333(12), 302(14), 300(14), 276(25), 244(32), 218(22), 198(49), 186(46), 105(100), 77(23); ms (ei, high resolution), m/z: calc'd for $C_{18}H_{23}NO_5$ 333.1576; found 333.1576; uv (MeOH), λ_{max} (log ϵ): 208 nm (3.89), 292 nm (4.18); ir (film), cm^{-1}: 3402 (vbr), 1746, 1696, 1652.

Relative rates of reactions of 186 with DMAD in $CHCl_3$ and in $CDCl_3$

Solutions of DMAD and 186 (each 0.33 M) in $CHCl_3$ ($CDCl_3$) were degassed by means of three freeze-pump-thaw cycles at 0.05 Torr and sealed into nmr tubes. The tubes were kept at room temperature for six days, during which time changes were monitored by ^{1}H nmr spectroscopy. Product 187 was formed 1.9 times faster in $CHCl_3$ than in $CDCl_3$. Examination of the contents of the $CDCl_3$-containing tube by ^{2}H nmr spectroscopy (76.75 MHz) revealed a strong broad signal at δ 4.81, as well as the ^{2}H signal from the solvent. Addition of CH_3CCl_3 to the $CHCl_3$-containing tube led to a new peak in the ^{1}H nmr spectrum.

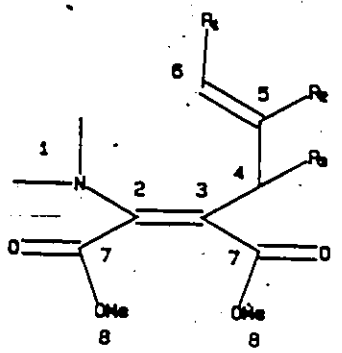
Table 16: ^{1}H nmr Data of Allyl Transfer Products[a]

Product	Protons		
	NMe_2	OMe	Other
177a	2.92	3.69 3.87	3.16 (dd, 2H, J=7 and 1.5 Hz) 4.96 (m, 1H); 5.12 (m, 1H) 5.71-6.22 (m, 1H)
177b	2.86	3.66 3.82	1.65 (dd, 3H, J=6 and 1.5 Hz) 3.07 (m, 2H) 5.47 (m, 2H)
177c	2.86	3.64 3.83	1.66 (s, 3H); 3.05 (s, 2H) 4.66 (s, br, 1H) 4.78 (s, br, 1H)
177d	2.89	3.64 3.88	3.54 (t, 2H, J=1.5 Hz) 5.07 (s, br, 1H) 5.47 (s, br, 1H) 7.26-7.60 (m, 5H)
177g[b] (major)	2.65	3.56 3.69	1.21 (d, 3H, J=7 Hz) 3.47 (p, 1H, J=7 Hz) 4.87 (dt, 1H, J=10.4 and 1.5 Hz) 4.92 (dt, 1H, J=17.2 and 1.5 Hz) 5.92 (ddd, 1H, J=17.2, 10.4 and 6.3 Hz)
177g[b] (minor)	2.60	3.61 3.72	1.13 (d, 3H, J=7 Hz) 2.92 (p, 1H, J=7 Hz) 4.83 (dt, 1H, J=10.3 and 1.5 Hz) 4.86 (dt, 1H, J=17.2 and 1.5 Hz) 5.86 (ddd, 1H, J=17.2 10.3 and 6.1 Hz)
178	2.90	3.64 3.94	4.60 (s, 1H)

[a] 90 MHz unless otherwise indicated.

[b] 500 MHz, obtained as a mixture of isomers.

Table 17: ^{13}C nmr Data of Allyl Transfer Products[a]



Product	Carbon								
	1	2	3	4	5	6	7	8	Other
177a	42.63	153.99	102.90	31.91	137.17	115.10	169.80 167.43	52.49 51.57	
177b	42.72	153.59	104.88	30.89	129.44	125.80	169.64 167.51	52.44 51.59	18.01
177c	42.36	154.28	102.97	35.80	145.52	110.48	169.72 167.84	52.74 52.30	23.81
177d	41.94	154.25	101.52	33.34	147.43	112.53	169.62 167.35	52.40 51.53	141.46 128.15 125.69
177g[b] (major)	43.34	151.02	119.94	37.16	141.41	113.51	168.51 166.82	51.98 51.15	19.09
177g[b] (minor)	42.35	147.36	113.06	39.29	141.96	112.40	167.98 167.10	52.03 50.82	19.09
178	39.65	155.23	84.35	-	-	-	168.11 166.06	52.79 50.62	

[a] 22.62 MHz, unless otherwise indicated

[b] 125.76 MHz, obtained as a mixture of isomers

Table 18: Other Spectral Data for Allyl Transfer Products

Product	uv($CHCl_3$) λ_{max}(log ϵ) (nm)	Mass Spectrum m/z(%)	High res. Mass Spectrum	ir(film) cm^{-1}	
177a	304(3.88)	227(34) 108(58) 195(16) 72(19) 168(100) 152(25)	obs. 227.1159 calc. for $C_{11}H_{17}NO_4$ 227.1158	3060 3045 1735 1692 1595	1429 1385 1302 1248 1222
177b	306(3.85)	241(38) 72(12) 209(22) 182(100) 166(29) 122(55)	obs 241.1315 calc. for $C_{12}H_{19}NO_4$ 241.1315	3022 1740 1696 1575 1432	1388 1302 1246 1226
177c	304(3.84)	241(81) 150(40) 210(40) 123(51) 200(46) 122(100) 182(93) 108(50) 166(38) 96(46)	obs. 241.1317 calc. for $C_{12}H_{19}NO_4$ 241.1315	3078 1739 1693 1575 1432	1385 1307 1248 1221
177d	302(3.81)	303(40) 96(28) 244(35) 200(100) 184(29) 118(26)	obs. 303.1469 calc. for $C_{17}H_{21}NO_4$ 303.1471	3049 3020 1741 1695 1578	1433 1387 1309 1251
177g[a]	312(2.79)	241(18) 150(32) 226(36) 122(52) 209(20) 108(35) 182(100) 72(21) 166(40)	obs. 241.1314 calc. for $C_{12}H_{19}NO_4$ 241.1315	3080 1740(br) 1701(br) 1572(br) 1452	1433 1390 1325 1241(br)
178	280(4.22)	187(38) 82(22) 156(40) 72(37) 155(43) 68(24) 128(100)		3090 1742 1684 1584	1434 1412 1371 1245

[a] 3:1 mixture of isomers.

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