SOME RECENT ADVANCES IN THE CHEMISTRY OF IMINES, IN PARTICULAR CYCLOADDITION REACTIONS*

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Abstract - This articale summarizes recent advances in the chemistry of imines in general and cycloaddition reactions of 1-aza-1,3-butadienes, 2-aza-1,3-butadienes, 1,4-diaza-1,3-butadienes and 2,3-diaza-1,3-butadienes in particular.

CONTENTS :

1. Introduction

Imines, azomethines and Schiff bases are amongest the various names commonly used for the compounds bearing carbon-nitrogen double bond. Schiff bases nomenclature appears in the older literature and is in the name of the worker who prepared them for the first time in 1864. Later on, imine and azomethine names are frequently used in chemical abstracts and other chemical literature. Eversince the preparation of these compounds, the chemistry of this function

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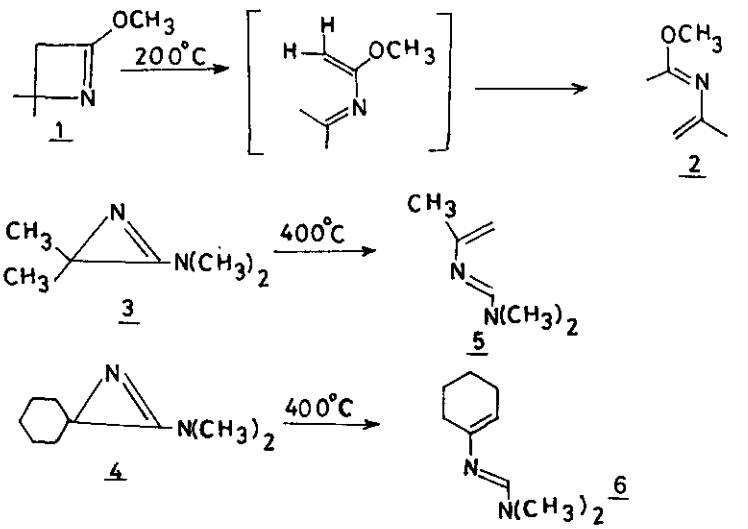
* Dedicated to Professor Tetsuji Kametani on the occasion of his 69th birthday (1st August, 1986).

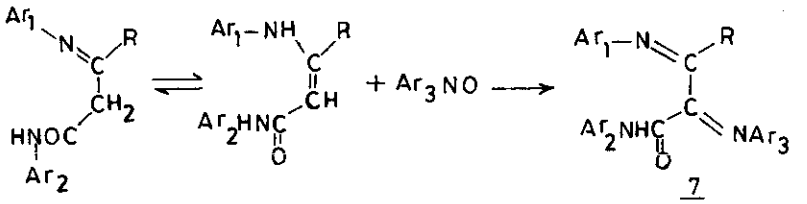
has been the focal point of investigations, in comparison to carbonyl compounds from which they were prepared. As the polarity of carbon-nitrogen double bond is comparatively much less than carbonyl function, therefore the reactivity of these compounds have also been investigated in comparision to carbon - carbon double bonds. Most of the earlier efforts have been reviewed by Layer[1] and Patai[2]. The developments in the chemical aspects of this group of compounds have been so fast and rigorous that one review has been written specially keeping in view the synthetic utility of these systems i.e. using these compounds easily available templates in the synthesis of novel heterocycles including the synthesis of complex natural products[3]. The object of the present review is to place before the readers some further interesting developments in this area and as far as possible attempt have been made to ommit the duplication of already reviewed work and in this respect only references are made to those monographs. To be more precise, the present review is aimed at covering the chemistry of conjugated imines : 1-aza-1,3-butadienes (C=C-C=N), 2-aza-1,3-butadienes (C=C-N=C), 1,4-diaza-1,3-butadienes (N=C-C=N) and 2,3-diaza-1,3-butadienes (C=N-N=C) exhaustively along with the some novel reactions of imines. The reactionsof azabutadienes where they formed part of heterocyclic rings and also when conjugated with C=O, C=S functions etc. are not included in this paper.

2. Methods of Preparation

The most common method for the preparation of imines is the reaction of aldehydes and ketones with amines[1,2]. 1-Aza-1,3-butadienes derived from unsaturated aromatic aldehydes e.g. cinnamaldehyde and crotonaldehyde are also similarly prepared. Aliphatic aldehydes in general, gave polymeric materials when reacted with amines and because of this difficulty the chemistry of this type of compounds is less developed. These imines can be conveniently prepared by adding an aldehyde to an aliphatic amine at $0^{o}C$ or below followed by addition of potassium hydroxide, separation of organic layer and distillation at reduced pressure[4]. 2-Aza-1,3-butadienes are generally prepared by thermolysis of azetines or azirines, for example, 2-methoxy-1-azetine 1 gave 2-azabutadien[5] 2 and 3-substituted 2-dimethylamino-1-azirines 3,4 gave 1-dimethylamino-2-azabutadienes 5 and 6 respectively[6].



1,4-Diazabutadienes 7 are prepared by base promoted condensation of β-anils of aceto and or benzoyl acetic acid anilide with nitrosoarenes[7].



R = Alkyl or aryl ; Ar_1, Ar_2, Ar_3 = Differently substituted phenyl groups.

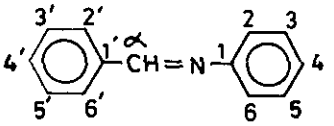
2,3-Diaza-1,3-butadienes commonly known as azines are readily prepared by the reaction of aldehydes or ketones with hydrazine hydrate or sulphate in alcoholic solution.

3. Spectroscopic Properties

Chemical properties are normally predictable from the physical measurements and for that reason spectroscopic properties of imines will be discussed briefly. Simple carbonyl compounds absorb weakly at about 280 mμ and more strongly at very small wavelength (below 190 mμ). The C=N- system is a weak chromphore, whose absorption lies in the ultraviolet region. Conjugation of both the systems with a phenyl group or a double bond shifts the absorption towards visible and α,β-unsaturated carbonyl or phenyl ketones show an intense absorption above 224 mμ. Anils of aromatic aldehydes and ketones, however, are usually yellow coloured. Kanda[8] measured the gas phase spectrum of benzalaniline and found two band systems at 294 - 283 mμ and at 248-235 mμ.

The infrared stretching vibrations of the C=C systems have been reported to fall at 1610 - 1635 cm^{-1}, and that of C=N at 1665 - 1690 cm^{-1}. The C=N stretching frequencies of the various substituted benzylidene-anilines have been rechecked by the Japanese workers[9,10] and they have assigned strong peak in the region 1618 - 1648 cm^{-1} in chloroform solution and 1613 - 1639 cm^{-1} in solid state (in KBr) to the C=N bond. These workers also reported that substituents in benzene ring of benzylidene group affected the frequency of C=N stretching absorption peak and that in the benzene ring of aniline did not. The effect of conjugation by a C=C bond on the stretching absorption peak of C=N bond in 1-aza-1,3-butadiene system was studied by the author by selective reduction of C=N bond with sodium borohydride[11,12] and comparing the infrared spectra of azadienes and dihydro products. The three bands which disappeared in the reduced compounds were 1575 cm^{-1} (medium intensity), 1600 and 1625 cm^{-1} (both the strong intensity) and in analogy with the previous reports, the absorption bands at 1600 and 1625 cm^{-1} were assigned to the C=N stretching absorption frequencies. Thus the effect of conjugation of C=C bond on C=N bond in diminishing the frequency of the later could be taken as very small in comparision with a similar decrease of 25 - 40 cm^{-1} in the case of conjugated enones.

The effect of substituents on NMR spectra of N-benzylidene-anilines have been reported by several groups[13-16]. Our studies[17,18] in this direction have indicated that in ^1H NMR spectra of substituted N-benzylidene-anilines 8 the transmission of the electronic effects from position 4 to α or 2' position is very weak contrary to earlier claim[14].



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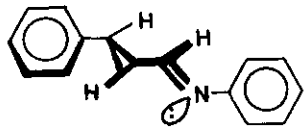
Systematical studies of the ^1H NMR spectra of 1-aza-1,3-butadienes derived from cinnamaldehyde and differently substituted amines[12] have also been reported. The azomethine proton signal showed almost, invariably at δ 8.20. While the 60 MHz NMR in $CDCl_3$ it showed either as a triplet or as a quartet, in C_6D_6 it showed up as a doublet at δ 7.9. The conformation 9 adopted by cinnamylideneaniline was concluded from the NMR spectra on the basis of INDOR assisted analysis of the complex spectrum patterns, further nuclear overhauser

experiments and solvent effect studies helped in the complete analysis. This appears to be the first report via NMR indicating that N-aryl part is twested out of the plane with respect to the rest of the molecule and some is true for 8 also.



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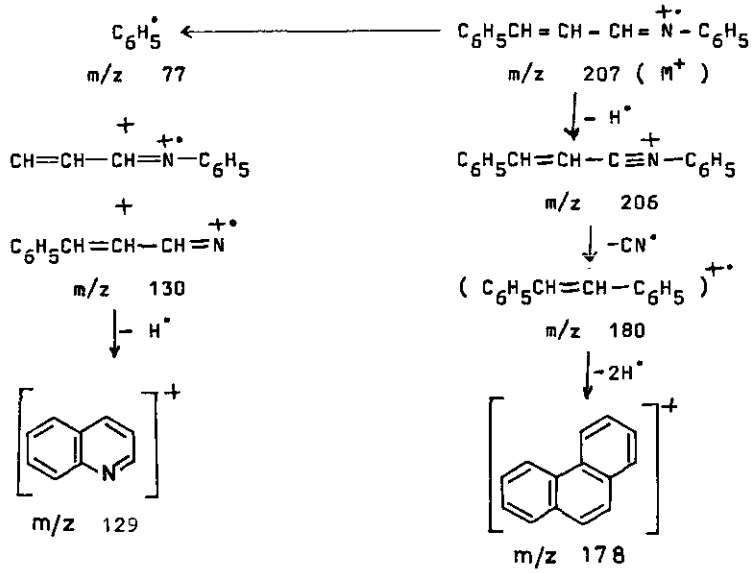
The mass spectra of Schiff bases have been reported to show strong M^+ and M^+-1 peaks[20-22]. The mass spectra of several 1-azadienes derived from cinnamaldehyde and substituted amines were recorded and the observed[23] general fragmentation pattern is shown below.



4. Chemical Reactions

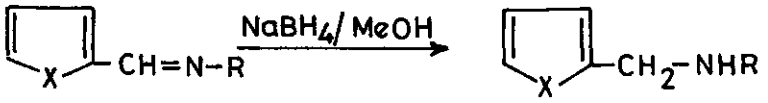
Imines mainly undergo two types of chemical reactions, namely addition reactions and cycloaddition reactions.

4.1 Addition Reactions

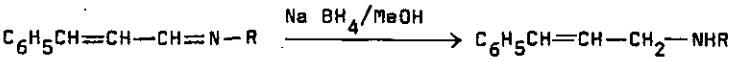
Like carbonyl group, C = N bond of imines contribute to the charge separated structure and can be represented as $>\overset{\delta+}{C}=\overset{\delta-}{N}-$. Therefore, variety of nucleophiles like cyanide, hydride, trihaloacetate ions and alkyl group of organometallic compounds attack the carbon atom of imines leading to the addition

across C = N bond. Similarly active methylene compounds, add across C = N bond followed by elimination. These reactions have been reviewed in two earlier reviews[1,2]. Addition reactions of conjugated imines along with some important recent reactions of imines shall only be discussed here.

Reduction of imines with sodium borohydride in methanol has been proved to be a very useful reaction for the synthesis of otherwise unaccessible heterocyclic and β,γ-unsaturated secondary amines[11,12].

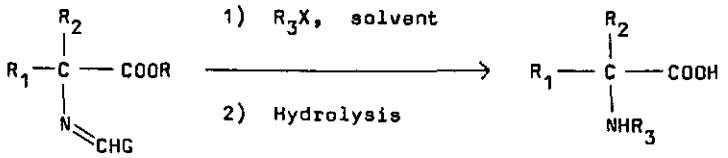


X = O, S ; R = Alkyl, aryl



R = Alkyl, aryl

Recently Botta and coworkers reported the synthesis of various secondary amines by reduction of ketimines with aluminium alkoxide in presence of Raney nickel[24]. Alkylation of Schiff bases has proved to be a very efficient method for the synthesis of optically active N-alkylamino acids[25] 10.



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In the generalised reaction presented by the authors R_1 groups have been varied from aliphatic to aromatic and in particular R_2 has been kept as hydrogen only.

4.2 Cycloaddition Reactions

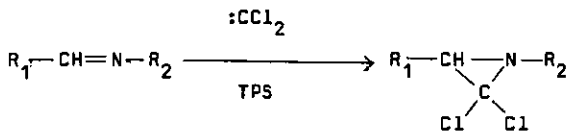
Imines are well known to undergo various types of cycloaddition reactions leading to the formation of three, four, five and six membered rings via 2+1, 2+2, 2+3, 3+2, 2+4 and 4+2 cycloadditions.

4.2.1 Three Membered Rings

Reaction with Carbenes

Reaction of imines with carbenes can be classified as 2+1→3 type cycloaddition to afford aziridines. Earlier work up to 1970 in this area has been included in the previous reviews[1,2].

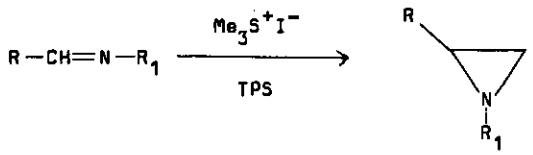
Addition of dichlorocarbene generated from chloroform and aqueous sodium hydroxide in two phase system (TPS) to aliphatic and aromatic imines has been reported to be a convenient method for the synthesis of aziridines 11[26].



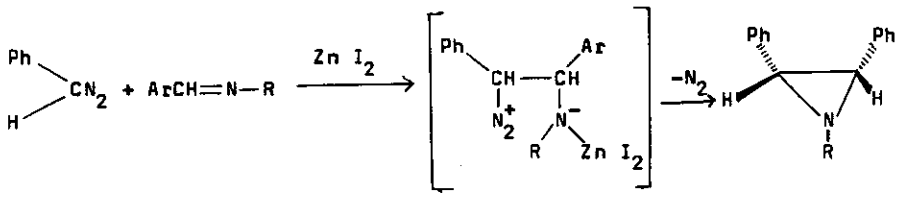
R_1, R_2 = Alkyl, aryl or heterocycles 11

Carbenes produced by thermal decomposition of diaryl diazomethane in the presence of bis(acetylacetonate)copper (II) reacted with imines to give insertion reaction instead of cycloaddition reactions[27].

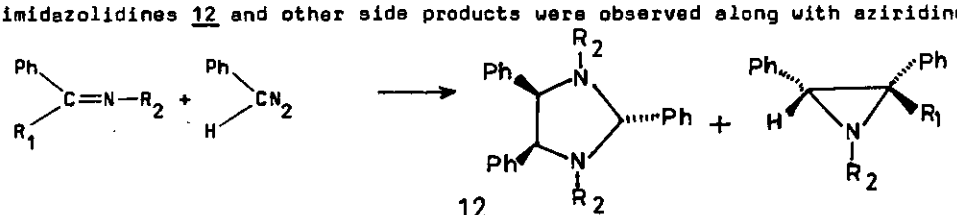
Tiwari et al.[28] reported the synthesis of 1,2-disubstituted aziridines from imines in two phase system (TPS) using methylene dimethyl sulfurane generated from $Me_3S^+I^-$ as methylene transfer agent.



Bartnik et al.[29] were successful in synthesizing 1,2,3-trisubstituted aziridines by treating aryl diazomethane with imines in presence of zinc iodide.



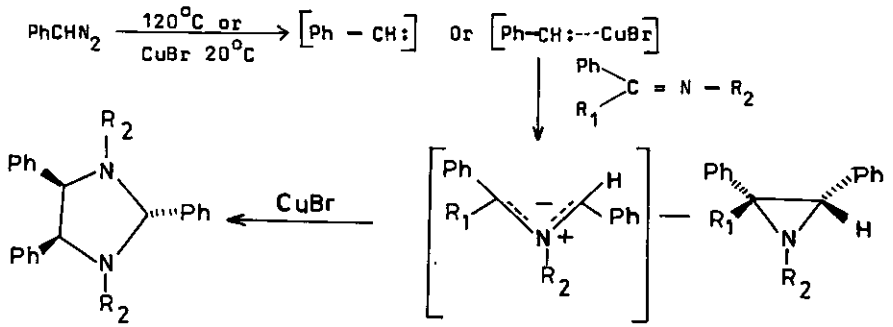
When these workers used cuprous bromide in place of zinc iodide formation of imidazolidines 12 and other side products were observed along with aziridines[30].



12 + by-products like stilbene and benzalazine

Compound	R_1	R_2
a	H	CH_3
b	H	C_2H_5
c	H	$CH(CH_3)_2$
d	H	$C(CH_3)_3$
e	CH_3	CH_3
f	CH_3	C_2H_5

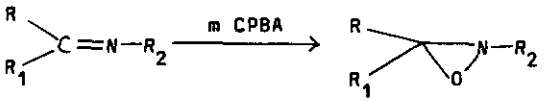
Formation of these products was explained by postulating an intermediate 1,3-dipole (azomethine ylide) with trans-configuration by the reaction of imine with phenylcarbenoid (PhCH---CuBr) or phenylmethylene formed by catalytic thermal decomposition of phenyldiazomethane. The conrotatory cyclization of the ylide will give cis-aziridine and if the ylide has sufficient life time it may undergo secondary 2+3 cycloaddition with C = N bond of imine to give imidazolidine derivative. The formation of by-product was explained via dimerization of carbenoid or free carbene and reaction with phenyldiazomethane.



Reaction of carbenes with conjugated imines does not seem to have been investigated.

Reaction with Peroxy Acid

Boyd et al.[31] reported the formation of oxaziridines 13 by oxidation of imines with m-chloroperbenzoic acid and the reaction was observed to be considerably influenced by steric and electronic effects.



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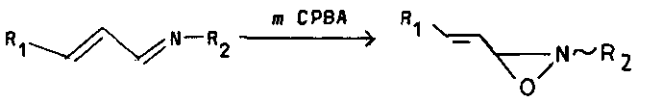
Oxidation of 1-azabutadienes with m-chloroperbenzoic acid yielded 3-alkenyl-oxaziridines in good yields with high stereoselectivity[32].

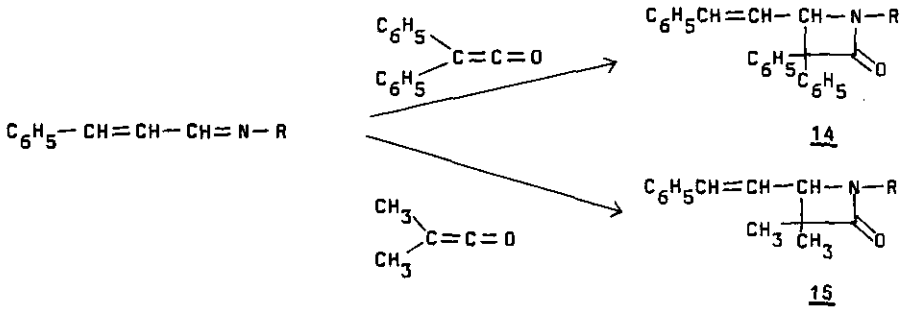


Compound	R_1	R_2	Compound	R_1	R_2
a	Ph	t-Bu	c	Ph	i-Pr
b	Me	t-Bu	d	Ph	Me

4.2.2 Four Membered Rings Synthesis of β-Lactams

The formation of β-lactams from imines and ketenes is the most systematically studied example of 2+2→4 type cycloaddition reaction. Although the first member was synthesized as early as in 1907 by Staudinger[33], the β-lactams as a class acquired importance only after the discovery of penicillin[34]. Cycloaddition reactions of imines with ketenes, acid chlorides in the presence of triethylamine have been widely used for the preparation of β-lactams and bulk of the literature on this subject up to 1976 has been reviewed[1,2,35], also some selected reactions have been recently reviewed[3]. Therefore, here we will discuss only the important reactions of imines affording β-lactams, which have not been included in the earlier reviews.

Staudinger[33] in 1907 reported the reactions of 1-aza-1,3-dienes with diphenyl and dimethyl ketenes to give 4-styryl-β-lactams 14, 15.



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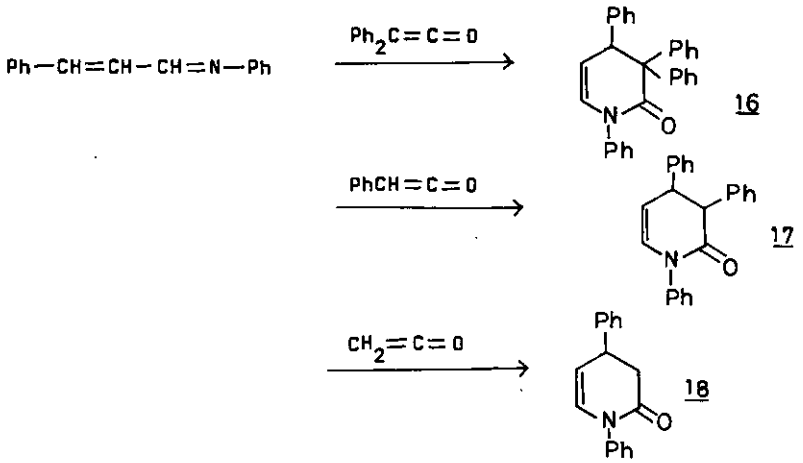
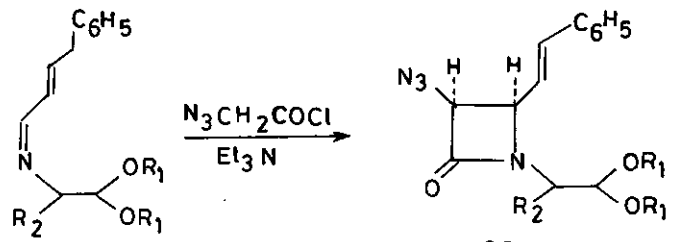
15

Later on in 1957 Pfleger and Jager[36] studied the reactions of cinnamylidene-aniline with diphenyl ketene, phenyl ketene and ketene and noted the formation of 3,4-dihydro-2-pyridones 16, 17 and 18 respectively.



Conjugated imines 19 when reacted with azidoacetylchloride in the presence of triethylamine gave cis-β-lactams 20 in good yields[37].

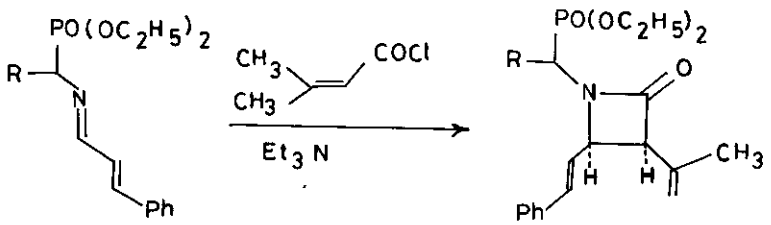


19

a, $R_1 = CH_3$, $R_2 = H$

b, $R_1 = C_2H_5$, $R_2 = COOC_2H_5$

Zamboni and Just[38] obtained cis-β-lactams 22 by treating cinnamaldehyde Schiff bases of diethylaminomethyl phosphonate 21 and its corresponding furyl derivatives with dimethylacryloyl chloride in presence of triethylamine.

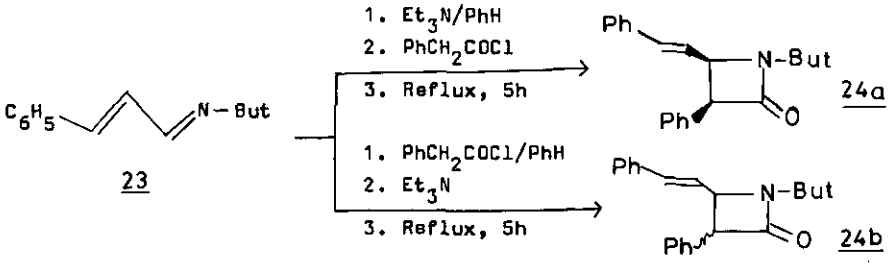


21 22

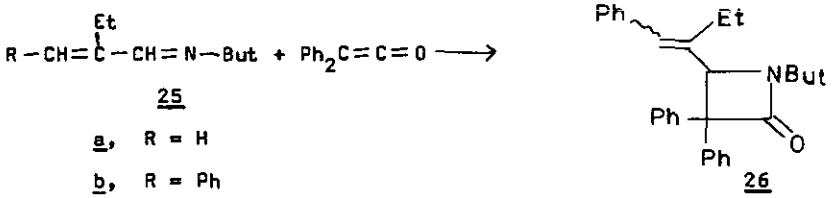
a, R = H

b, R = 

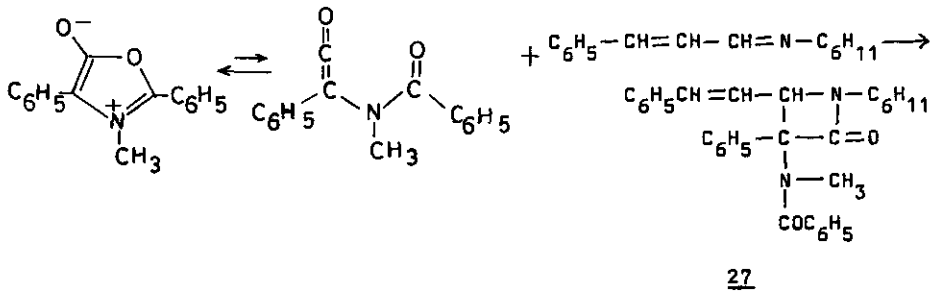
Ohshiro et al.[32] during their studies on the reactions of 1-azabutadiene 23 with phenylacetyl chloride and triethylamine observed that the order of addition of reagent effected the stereochemistry of the β-lactams formed. While addition of triethylamine to imine solution before adding phenylacetyl chloride yielded only cis-β-lactams 24a addition of triethylamine after phenylacetyl chloride yielded cis, trans mixture of β-lactams 24b. Doyle et al.[37] have also reported the effect of the order of addition of reagents on the stereochemistry of β-lactams formed.



Ohshiro et al.[32] also described the reaction of 1-azabutadienes 25 with diphenyl ketene to yield β-lactams 26.



We studied the reaction of münchnone (3-methyl-2,4-diphenyloxazolium-5-oxide) which is known to react via its valence tautomer (N-benzoylmethylamino)-phenylketene[39,40] with cinnamylidene-N-cyclohexylimine and obtained β-lactam 27 in good yields[41].



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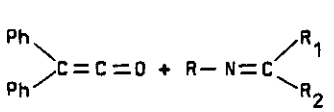
Reaction of conjugated imines with dichloroketene[42] and tert-butylcyanoketene[43] are known to yield 2-pyridones. There have been controversial claims regarding the formation of β-lactams or δ-lactams in the reaction of conjugated imines with ketenes[44] and a systematic study in this direction has been reported by Brady et al.[45], where the reaction of diphenyl ketene with conjugated imines 28 yielded β-lactams 29. However reaction of diphenyl ketene with 1-azabutadiene 30 yielded α-pyridone 31. Similarly reaction of dichloroketene with imines 32 yielded α-pyridones 33 but with β-phenylcinnamaldehyde-imine 34 gave β-lactam 35.



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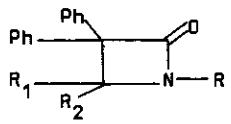
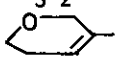
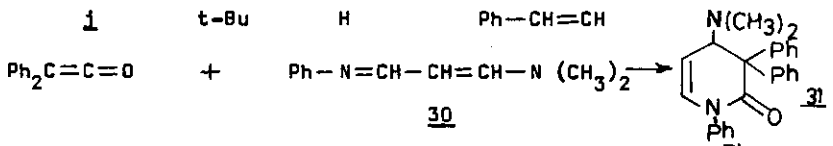


29

28	R	R_1	R_2
a	Ph	H	Ph−CH=CH
b	Ph	H	Ph−CH=C−CH_3
c	Ph	CH_3	Ph−CH=CH
d	Ph	H	
e	i-Pr	H	Ph−CH=CH
f	Ph	CH_3	$(CH_3)_2C$=CH
g	Ph	H	
h	C_6H_{11}	H	Ph−CH=CH
i	Ph	H	$(Ph)_2C$=CH
j	t-Bu	H	Ph−CH=CH



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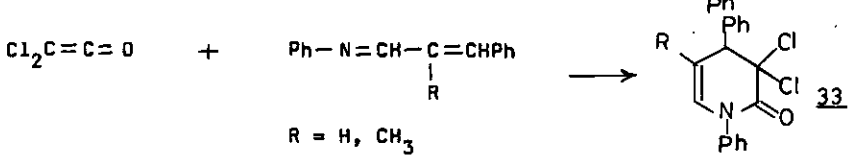

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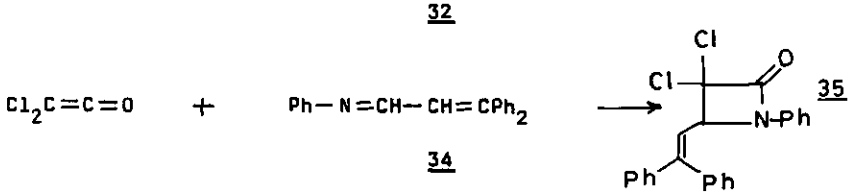
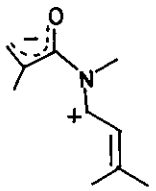
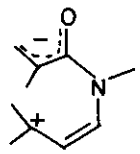


34 35

These results were interpreted on the basis of steric hindrance by assuming dipolar intermediates 36 and 37.

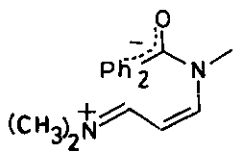


36



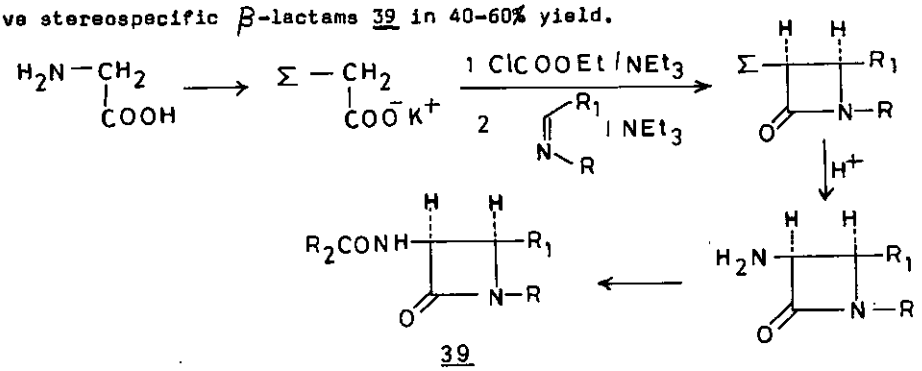
37

In the cycloaddition reactions of diphenyl ketene with α,β -unsaturated imines the bulky phenyl groups provide significant hindrance in 37 and cycloadditions occur from 36 leading to β -lactam. However, in dichloroketene chlorine atom does not present steric problem and generally 4+2 cycloadducts are obtained. In case of azadiene 30 the strong electron releasing ability of the dimethylamino group would be expected to cause the resonance structure 38 and thus yielding δ -lactam. Similarly bulky phenyl groups cause the formation of β -lactam 35.

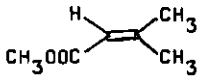


38

Preparation of stereospecific β-lactams from imines has been a very growing field. Bose et al.[46] reported a safe and convenient method for the synthesis of α-amido-β-lactams starting with glycine and azomethine. The amino group of glycine was protected with β -dicarbonyl compound and carboxylic group was activated through the formation of mixed anhydride or an active ester. The condensation between glycine derivatives and imine in presence of triethylamine gave stereospecific β-lactams 39 in 40-60% yield.

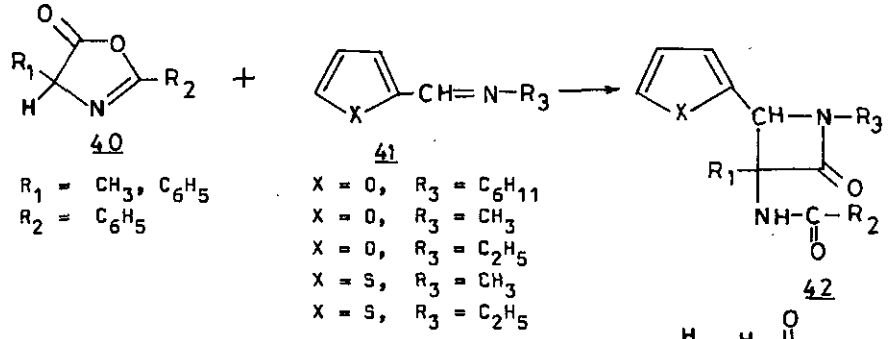


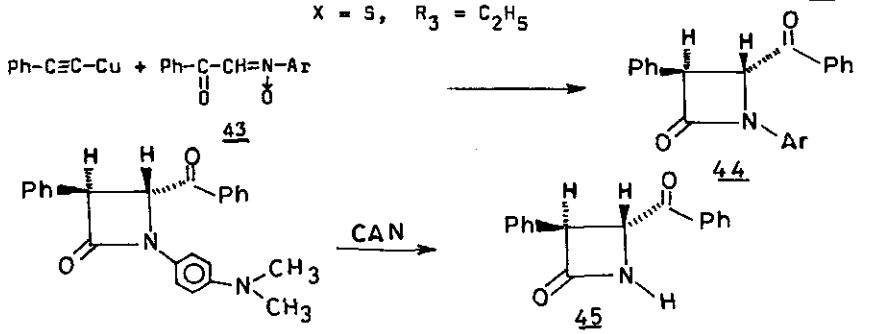
39

39	R_1	R	39	R_1	R
a	Ph	Ph	g		$CH_2C_6H_3(OCH_3)_2$-3,4
b	$C_6H_4N(CH_3)_2$(p)	Ph	h		$CH_2C_6H_3(OCH_3)_2$-2,4
c	$C_6H_4N(CH_3)_2$(p)	$C_6H_4SCH_3$(p)	i	CH=CH—Ph	$C_6H_4OCH_3$(p)
d		$C_6H_4OCH_3$(p)	j	Ph	$CH_2C_6H_3(OCH_3)_2$-3,4
e	$C_6H_4OCH_3$(p)	$C_6H_4CH_3$(p)	k	Ph	$CH_2C_6H_3(OCH_3)_2$-2,4
f	SCH_3				

Use of Reformatskii reaction[47,48] silyl ketene acetals[49], N-trimethylsilyl imines[50] p-toluenesulfinylacetic acid derivatives[51], p-nitrophenyl tosylacetate[52] allenes[53], lithioxy-2-phenylacetylene[54] and ketene bis(trimethylsilyl)acetals[55] for the preparation of β-lactams from imines have been reported in the recent years.

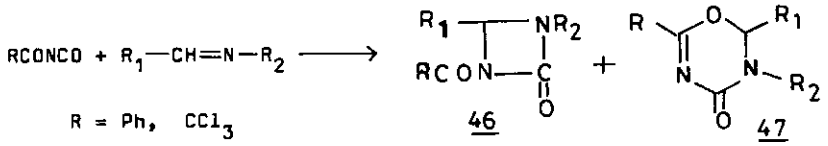
Our efforts in this area led to the novel synthesis of 3-amido-β-lactams 42[56,57] from azlactones 40, imines 41 and the synthesis of trans-β-lactams 44 from aroyl-N-arylnitrone 43 which could be converted to N-unsubstituted trans-β-lactams 45 by oxidative N-dearylation with cerric ammonium nitrite (CAN)[58].



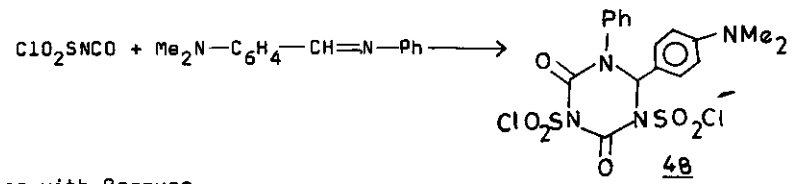


Reaction with Isocyanates and Isothiocyanates

Acyl isocyanates react with imines in (2+2) and (4+2) manner to yield 1,3-diazetidin-2-ones 46 and 1,3,5-oxidiazin-2-ones 47 respectively. The isomeric proportion was found to be controlled by temperature, duration of reaction and the electronic effect of the substituents[59].

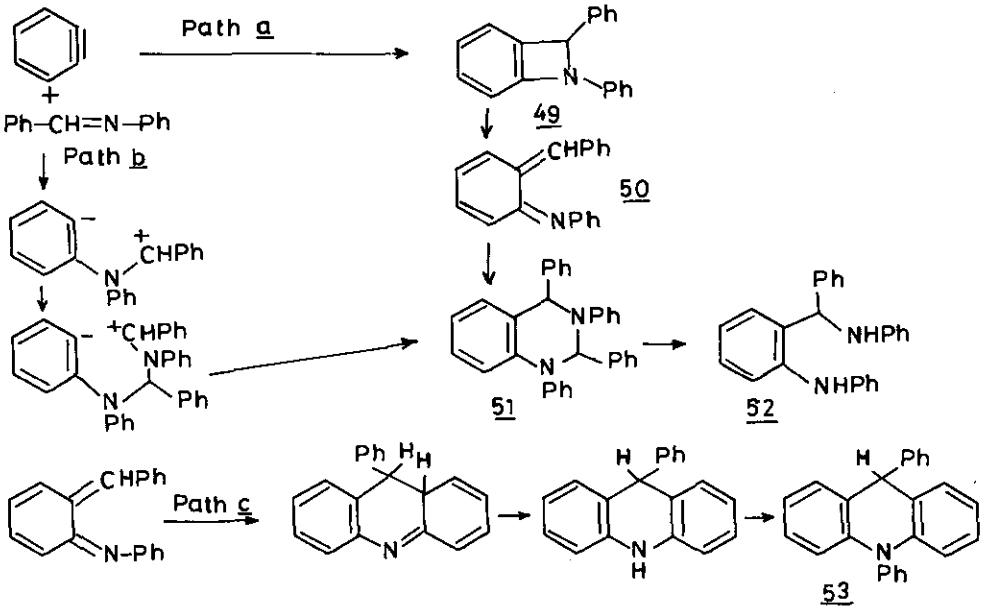


Chlorosulfonyl isocyanate[60] reacted with imines to give 2:1 adduct 48.



Reaction with Benzyne

Nakayama et al.[61] isolated N-[α-(O-anilinophenyl)benzyl] aniline 52 from thermal decomposition of benzene diazonium carboxylate in the presence of N-benzylideneaniline. These findings were interpreted in terms of (2+2) addition of benzyne with imine to give diphenyl-benzazetidine 49, which underwent spontaneous ring opening to an azaxylylene 50 and reacted with more N-benzylideneaniline to give the tetrahydroquinazolin derivative 51 which hydrolysed to give diamine 52 (Path a). Fishwick et al.[62] indicated that tetrahydroquinazoline derivative 51 could also be formed by stepwise 2+2+2 addition of imine to benzyne (Path b). However these workers were able to isolate 5,10-diphenyldihydroacridine 53 along with 51 during the reaction of benzyne with imine. The formation of 53 could be explained by electrocyclization involving the N-phenyl group of azaxylylene 50 followed by hydrogen tautomerization and phenylation with benzyne (Path c).

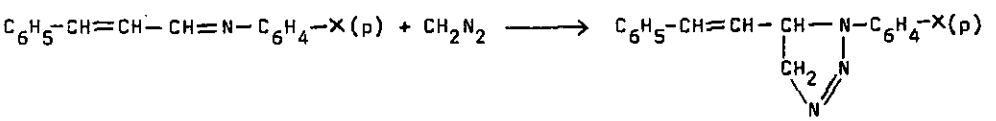


4.2.3 Five Membered Rings

1,3-Dipolar cycloaddition reactions of imines with dipoles like diazoalkanes, nitrilimines, azomethine ylides, azomethine imines, nitrile ylides, nitrile oxides and carbonyl ylides give stable five membered heterocycles and forms the examples of 2+3→5 type of cycloadditions. Imines derived from α-aminoacids act as azomethine ylides and their reactions with different dipolarophiles, reactions of 1,4-diaza-1,3-butadienes and 2,3-diaza-1,3-butadienes, where three atoms involved in the five membered ring formation are derived from imine can be catagorised as 3+2→5 type cycloadditions. Earlier literature on 1,3-dipolar cycloaddition reactions of imines has been well reviewed[1,2,3]. The recent literature on imines and conjugated imines which has not been reviewed[63,64,65] is discussed here..

Reaction with Diazoalkanes

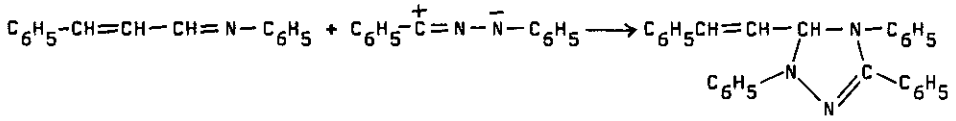
Cinnamylidene-anilines reacted with diazomethane in dioxane to give 1,2,3-triazolines 54 in moderate yields[12] and in all the cases investigated carbon-carbon double bond remained intact even when excess of diazomethane was used.



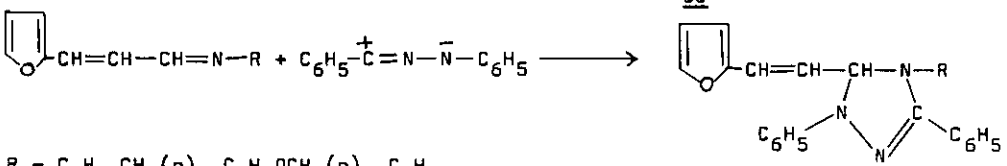
X = H, NO_2, Cl, Br, OCH_3, CH_3 54

Reaction with Nitrilimines

Diphenylnitrile imine generated in situ from corresponding hydrazinoyl chloride reacted with cinnamylidene-aniline[66] and furylacrolein anils[67] to give corresponding Δ^2-1,2,4-triazolines 55 and 56, respectively.



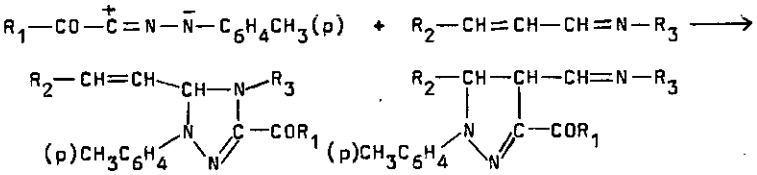
55



R = C_6H_4 CH_3(p), $C_6H_4OCH_3$(p), C_6H_5,
C_6H_4Br(p), $C_6H_4NO_2$(m).

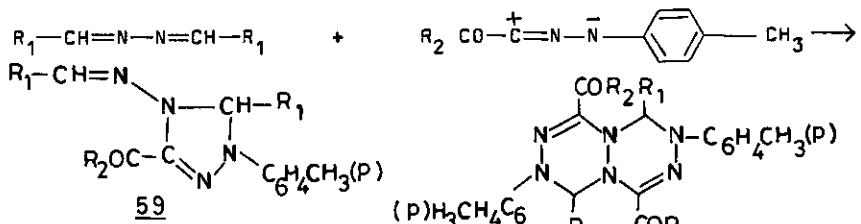
56

Similarly C-acetyl- and C-ethoxycarbonylnitrilimines generated in situ from the corresponding hydrazinoyl bromides reacted with several conjugated imines at C=N to give Δ^2-1,2,4-triazolines[68] 57 and there was no evidence for the formation of any other cycloadduct resulting from the reaction at carbon-carbon double bond 58.



57 58

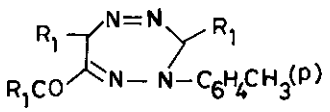
Cycloaddition reactions of C-acetyl- and C-ethoxycarbonylnitrilimines with various aldazines yielded Δ^2-1,2,4-triazolines[69-71] 59 without any evidence for the formation of 'criss-cross' addition products 60 or 1,4-dipolar cycloadducts 61.



59

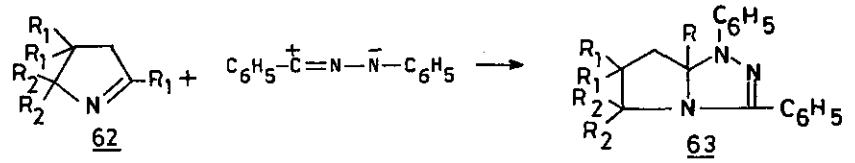
	a	b	c	d	e
R_1 =				C_6H_5	$C_6H_4CH_3$(p)
R_2 =	CH_3	OC_2H_5	CH_3	CH_3	CH_3

60



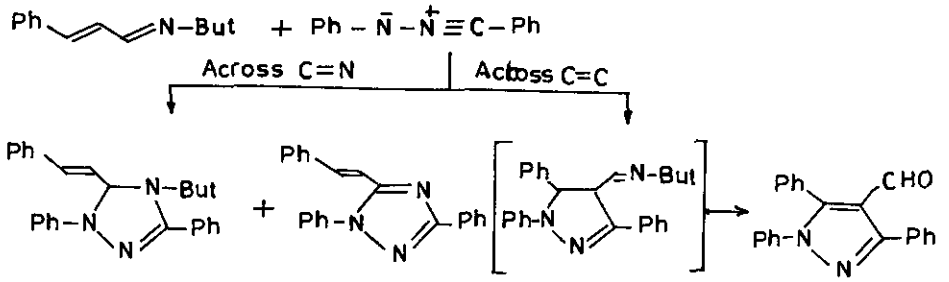
61

Dannhardt and Sommer[72] recently reported the synthesis of pyrrolo-triazoles 63 and other fused triazoles by reacting pyrrolines 62 with diphenyl nitrilimine.



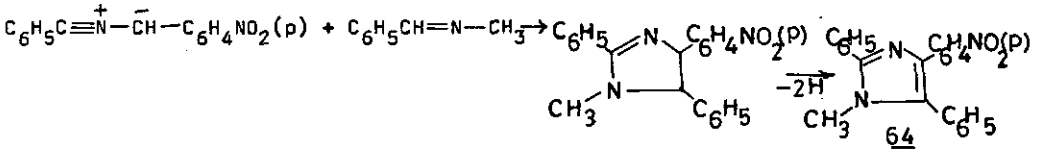
62 63

Ohshiro et al.[32] reported an interesting reaction of cinnamylidene-N-tert-butylamine with diphenylnitrilimine where addition occurred both across carbon-carbon double bond and carbon-nitrogen double bond.

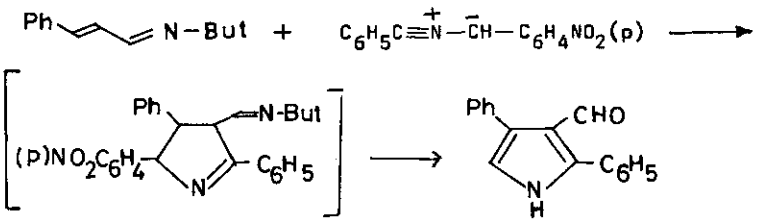


Reaction with Nitrile Ylides

Bunge et al.[73] have studied the reaction of benzonitrile-4-nitrobenzylide with benzylidenemethylamine and reported the formation of imidazole derivative 64



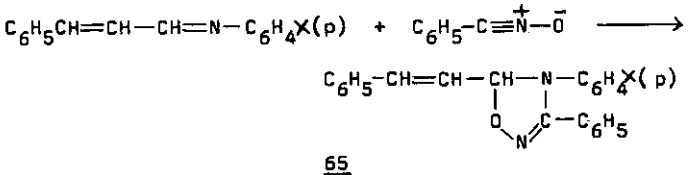
Benzonitrile-p-nitrobenzylide reacted with cinnamylidene-N-tert-butylamine to give formyl pyrrole which was formed by oxidative aromatization and hydrolysis of the cycloadduct formed by addition across carbon-carbon double bond[32].



Reaction with Nitrile Oxides

Singh et al.[74] studied the reaction of benzonitrile oxide with 1-aza-1,3-butadienes and reported the formation of Δ^2-1,2,4-oxadiazolines 65, formed by the

addition across carbon-nitrogen double bond. Use of drastic conditions and excess of nitrile oxides also did not yield any cycloadduct arising from the reaction at carbon-carbon double bond.

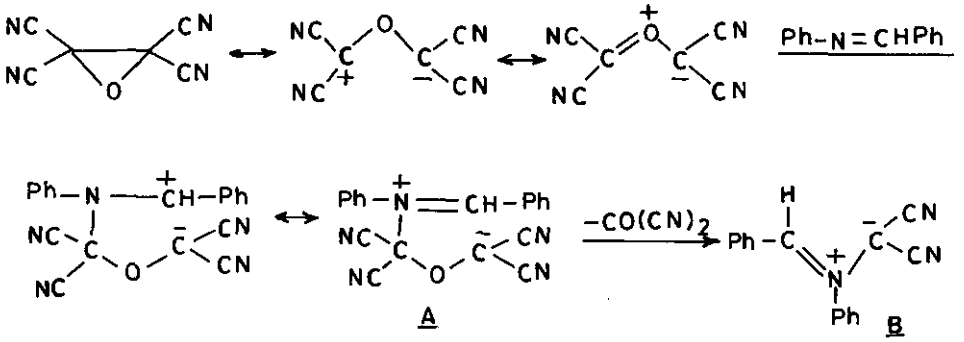


65

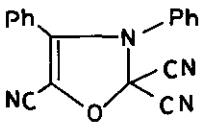
Subsequent studies by Rajanarendar et al.[75] on the addition of benzonitrile oxide to a system containing C = C and C = N also confirmed the addition preferentially taking place at C = N bond, even when there was no steric henderance to the dipole.

Reaction with Carbonyl Ylides

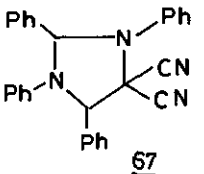
Carbonyl ylides have not been isolated but their existance has been proved by spectroscopic method and in situ reactions of oxiranes. Linn and Ciganek[76] found that tetracyanoethylene oxides reacts with N-benzylidene-aniline to give species A and B which are capable of reacting with dipolarophiles. In the absence of any dipolarophile the 4-oxazoline 66 is formed (by ring closure of A and elimination of one molecule of hydrogen cyanide) together with imidazolidine 67 (formed by 1,3-dipolar cycloaddition of benzylidene-aniline with azomethine ylide B).



A B

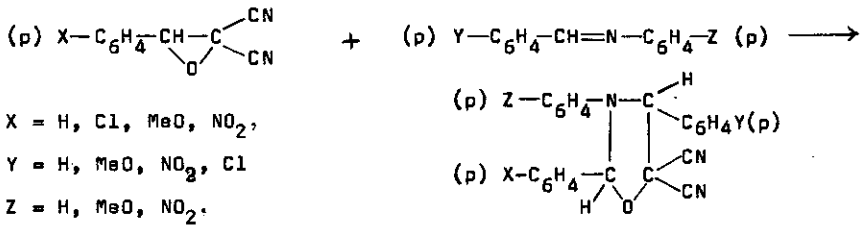


66



67

Similarly carbonyl ylides derived from gem dicyano epoxides[77] reacted with imines to yield oxazolidines[78] 68.

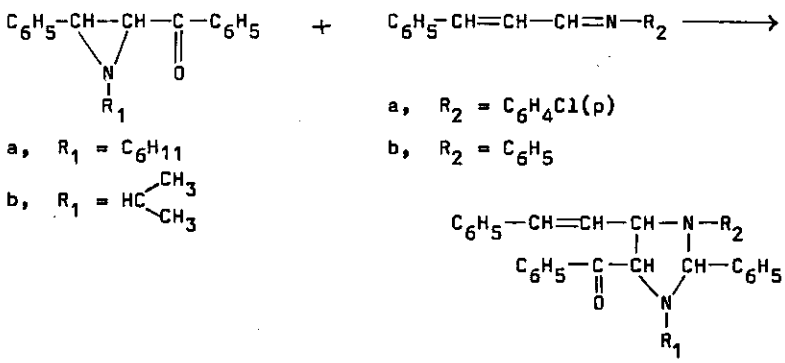


X = H, Cl, MeO, NO_2,
Y = H, MeO, NO_2, Cl
Z = H, MeO, NO_2.

68

Reaction with Aziridines

The thermal decyclization of aziridines gives corresponding azomethine ylides which add to different dipolarophiles to give five membered heterocycles[79]. Sain and Sandhu[80] reported the reactions of 3-benzoyl-1-cyclohexyl-2-phenylaziridine and 3-benzoyl-1-isopropyl-2-phenylaziridine with conjugated imines to yield corresponding imidazolidines 69 without any evidence for the formation of any addition product arising from the reaction with C = C bond.



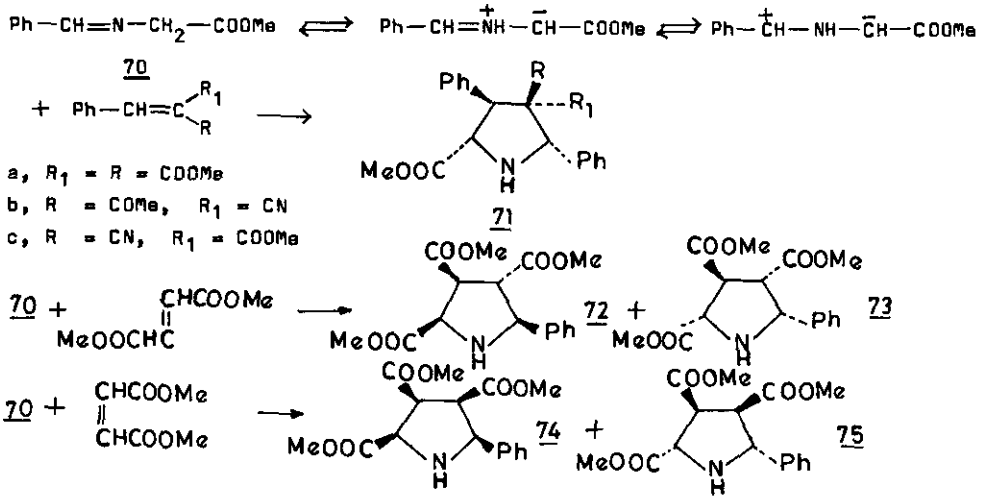
a, R_1 = C_6H_{11}
b, R_1 = $HC(CH_3)_2$

a, R_2 = C_6H_4Cl(p)
b, R_2 = C_6H_5

69

α-Amino Acid Ester Imines as dipoles

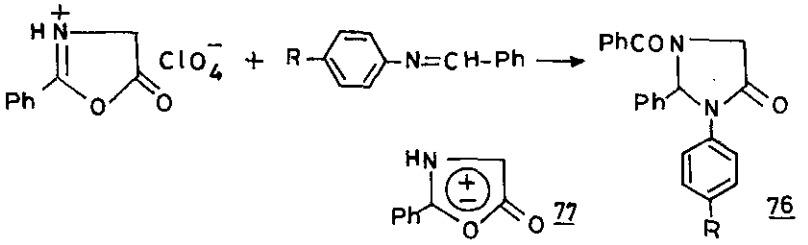
Imines derived from α-amino acid esters have been extensively used as dipoles for stereospecific cycloadditions to different dipolarophiles. Joucla et al.[81] reported the reactions of imines derived from glycine methylester and benzaldehyde 70 with number of dipolarophiles to yield stereoisomeric pyrrolidines 71 - 75.



Imines obtained from phenylglycine methyl ester and benzaldehyde underevent cycloaddition reactions with dimethyl fumarate and dimethyl maleate to yield stereoisomeric pyrrolidines[82]. Other studies in this direction include the use of pyridoxal α-amino acid ester aldimines[83] and diethyl aminomalonate imines[84] as dipoles.

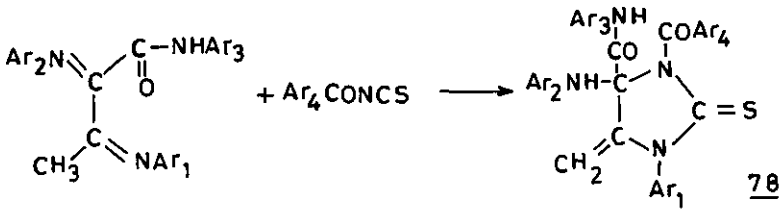
Reaction with 2-Phenyl-oxazolium Perchlorate

Boyd et al.[85] reported the reaction of imines with 2-phenyloxazolium perchlorate to give imidazolidin-4-one 76. Formation of imidazolidine was assumed through the mesoionic specie 77.



Reaction of 1,4-Diaza-1,3-butadienes

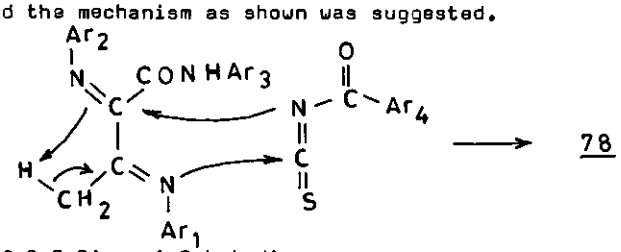
Moskal[86] reported an interesting reaction of 1,4-diazabutadienes with aroyl isothiocyanates to yield imidazolidine-2-thiones 78. The cycloadditions were found to be accompanied by 1,4-shift of hydrogen from a methyl group attached to C_2 of the 1,4-diazabutadienes.



78

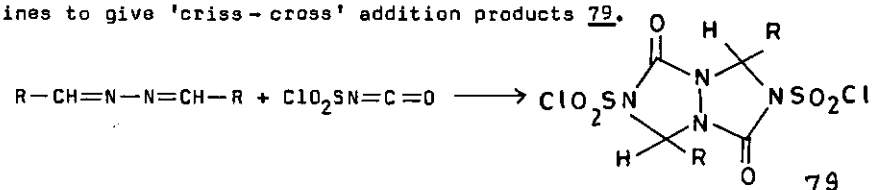
78	Ar_1	Ar_2	Ar_3	Ar_4
a	$C_6H_4OCH_3(p)$	C_6H_5	$C_6H_3Cl_2(2,4)$	C_6H_5
b	$C_6H_4CH_3(p)$	C_6H_5	$C_6H_3Cl_2(2,4)$	C_6H_5
c	$C_6H_4OC_2H_5(p)$	C_6H_5	C_6H_5	C_6H_5
d	$C_6H_4N(CH_3)_2(p)$	C_6H_5	C_6H_5	C_6H_5
e	$C_6H_4OCH_3(p)$	$C_6H_4Br(p)$	C_6H_5	C_6H_5
f	$C_6H_4OCH_3(p)$	C_6H_5	C_6H_5	$C_6H_4Cl(p)$
g	$C_6H_4N(CH_3)_2(p)$	C_6H_5	C_6H_5	$C_6H_4Cl(p)$

Mechanism for the formation of 2-imidazolidinethiones 78 was concluded on the basis of their earlier findings on the reaction of isocyanates with 1,4-diazabutadines[87-89] and that the reaction of aroyl isothiocyanate with 1,4-diazabutadiene containing phenyl group in place of methyl group at C-2, did not proceed. Thus N-1 and C-3 of the azadiene were taken as nucleophilic and electrophilic centres and the mechanism as shown was suggested.



Reaction of 2,3-Diaza-1,3-butadienes

2,3-Diaza-1,3-butadiene (azine) is a typical azadiene system and can undergo 3+2 cycloadditions where 'criss-cross' addition products are obtained[64]. Suschitzky et al.[90] reported the reactions of chlorosulphonyl isocyanate with aldazines to give 'criss-cross' addition products 79.



79

R = C_6H_5, $C_6H_4OCH_3(p)$, $C_6H_4CH_3(p)$, $C_6H_4NO_2(m)$, $C_6H_4Cl(p)$
$C_6H_4NO_2(p)$, $C_6H_4F(o)$, 2-furyl, 2-thienyl, 2-allyloxy,
$1\text{-}C_{10}H_7$, $C_6H_4NMe_2(o)$, $C_6H_4NMe_2(p)$, $C_6H_4NC_4H_8(o)$, $C_6H_4NC_6H_{12}(o)$

However, reactions of chlorosulfonyl isocyanate with aromatic ketone azines were not successful.

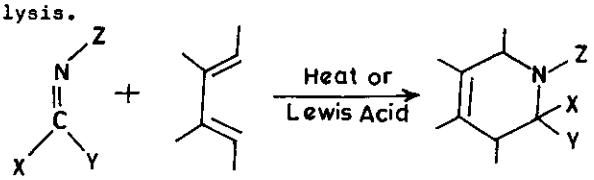
Reaction of azines with maleic anhydride[91,92] N-phenylmaleimide[93] and phenyl isocyanate[64] are also known to afford 'criss-cross' products.

4.2.4 Six Membered Rings

Cycloaddition reactions of imines with dienes such as benzoyl sulfene, diketene, dimethyl acetylenedicarboxylate yield six membered ring heterocycles and can be classified as 2+4→6 type cycloadditions. Reactions of imines with enamines, vinyl ether and Diels-Alder type reactions of conjugated imines including intramolecular cycloadditions and reactions with mesoionic oxazolones which lead to the formation of six membered ring can be classified as 4+2→6 type cycloadditions. Earlier literature including some recent reports which have been included in the reviews[1,2,3] and the literature on photochemical cycloaddition reaction of imines which has been thoroughly reviewed[94-96,3] are not discussed here.

Reaction with Dienes

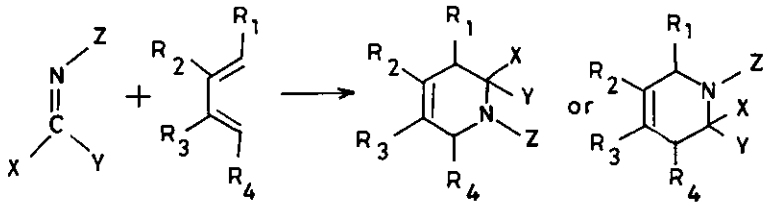
The use of imines as dienophilic component in (4+2) cycloaddition reactions was thoroughly reviewed[97] in 1967, and was updated by Weinreb and Levin[98] in 1979. All the imino compounds are not effective dienophiles and simple Schiff bases thus have proved to be unreactive in 4+2 cycloadditions unless exceptionally reactive dienes such as o-quinodimethane are employed[99]. Electron deficient dienes however provided more reliable reaction partners. In particular N-sulphenylimine and N-acylimines add to 1,3-dienes affording tetrahydropyridines in good yields. Such cycloadditions can be effected either thermally or under lewis acid catalysis.



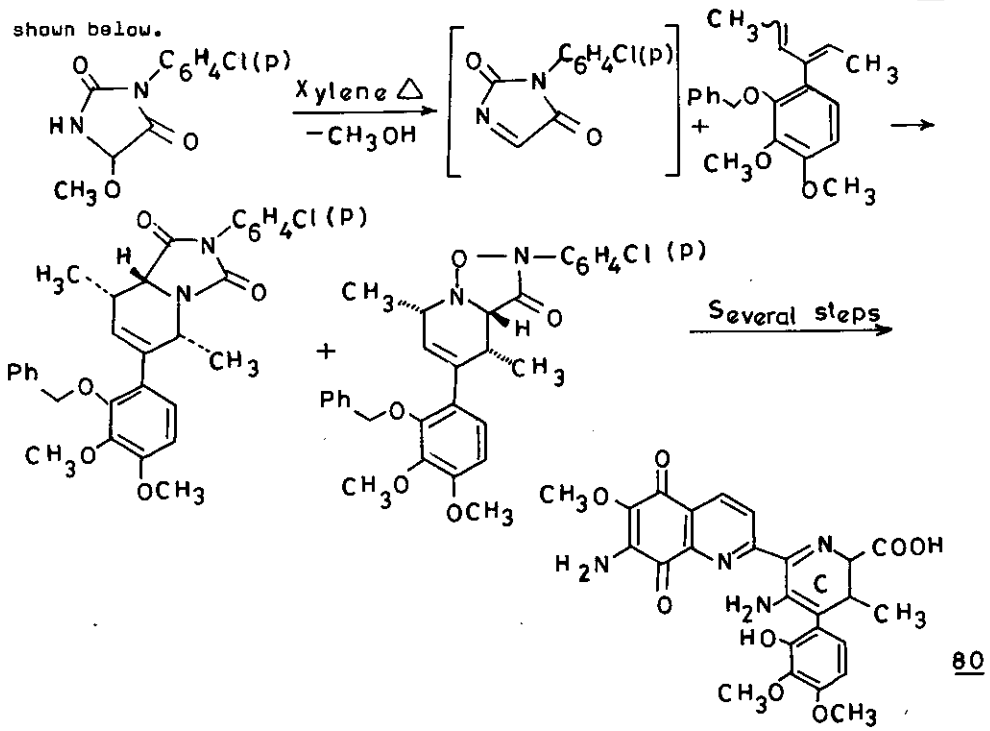
Z = SO_2Ar, COR

X, Y = H, COOR, Ar, CCl_3

Addition of an imine to an assymetrical diene can in principle give two regioisomeric adducts. In fact imino- Diels-Alder reactions show an excellent regioselectivity comparable to all carbon systems.

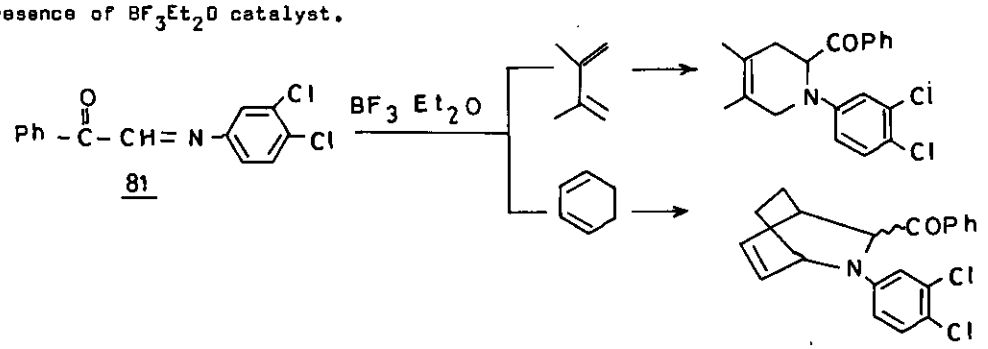


Although the mechanistic data concerning these cycloadditions are spordic at present but however, Weinreb et al.[100] have outlined a scheme of the stereochemical consequences of addition of an acyclic imine to a substituted diene. Weinreb and coworkers[101,102] further used the imino- Diels-Alder reaction in the synthesis of C/D ring system of the antitumor antibiotic streptonigrin 80 as shown below.



80

Mckay and Proctor[103] reported the reaction of imines 81 with several dienes in presence of BF_3Et_2O catalyst.

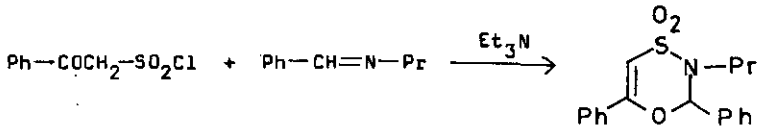


81

Lewis acid catalysed condensation of siloxy dienes with imines to yield six membered heterocycles are also reported[104,105].

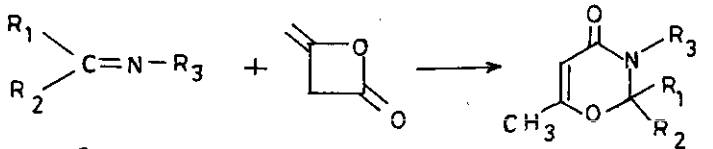
Reaction with Benzoylsulfene

Benzoylsulfene generated from benzoylmethanesulphonyl chloride and triethylamine reacted with benzylidine-N-propylamine to give (4+2) cycloadduct[106]. This reaction appears to have further considerable potential.



Reaction with Diketenes

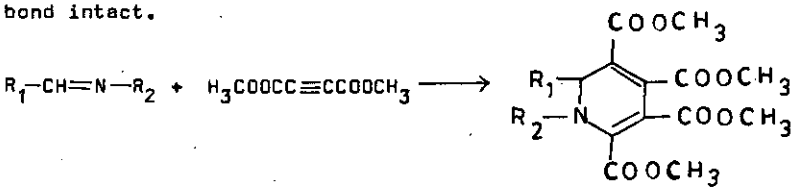
Reaction of imines with acid chlorides in the presence of tertiary base generally yields β-lactams. Maujean and Chuche[107] reported an interesting reaction of acetyl chloride with imines in presence of triethylamine to obtain dihydrooxazinones 82. Same products could also be obtained by reacting ketene dimer with imines.



a, R_1 = Ph, R_2 = H, R_3 = Ph, CH_2Ph 82
b, R_1 = R_2 = Me, R_3 = Ph

Reaction with Dimethyl Acetylenedicarboxylate

Imines reacted with dimethyl acetylenedicarboxylate to yield dihydropyridines[108-110] 83. Cinnamaldehyde anils also reacted in a similar manner leaving C=C bond intact.

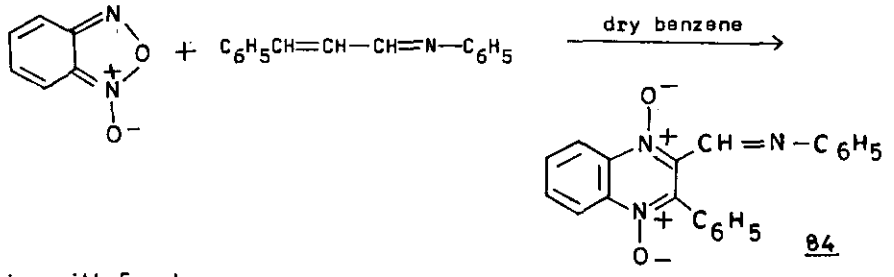


83

Reaction with Benzofurazan N-Oxide

Our investigations coupled with the literature reports on the reactions of 1-aza-1,3-butadienes revealed that dipoles as well as nucleophiles, generally react at carbon-nitrogen double bond leaving carbon-carbon double bond intact.

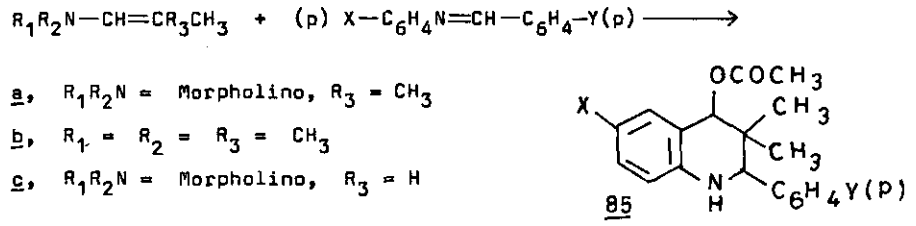
In 1984 an interesting reaction of cinnamylidene-aniline with benzofurazan N-oxide was reported, where the reaction occurred at C=C bond of azadiene to yield a novel class of quinoxaline N,N'-dioxide imine[111] 84. The clear mechanism of this reactions is still obscure.



84

Reaction with Enamines

Enamines having α-hydrogen, reacted with a variety of benzylidene-anilines to give 1,2,3,4-tetrahydroquinolines[112] 85.



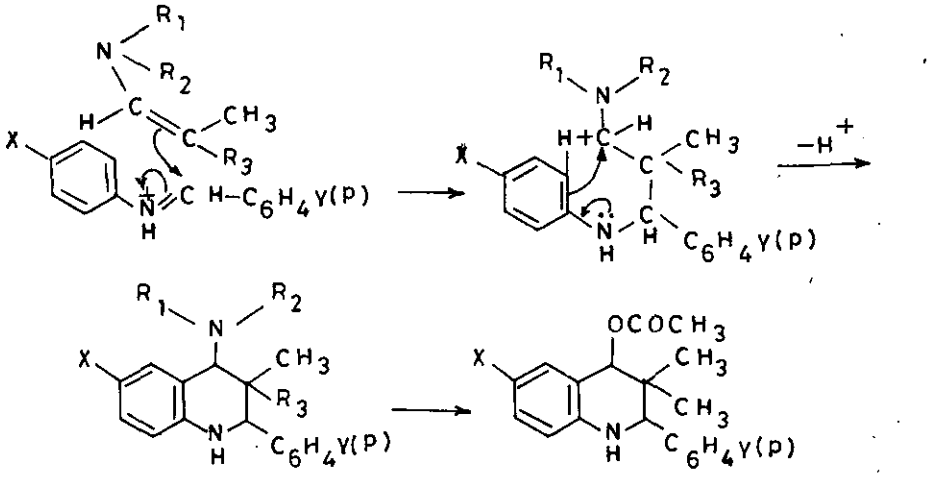
a, R_1R_2N = Morpholino, R_3 = CH_3

b, R_1 = R_2 = R_3 = CH_3

c, R_1R_2N = Morpholino, R_3 = H

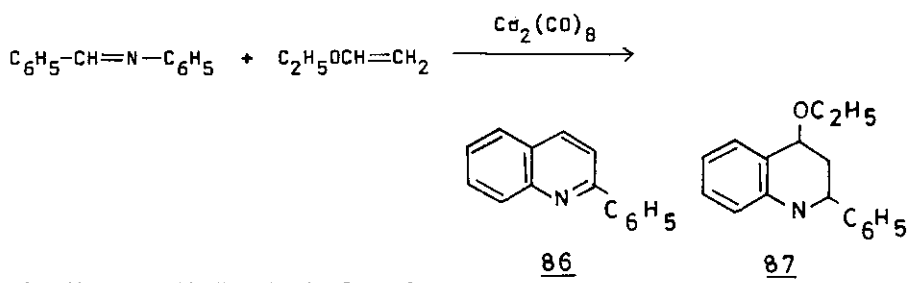
85

The mechanistic route for this reaction has been proposed as :



Reaction with Vinyl Ethers

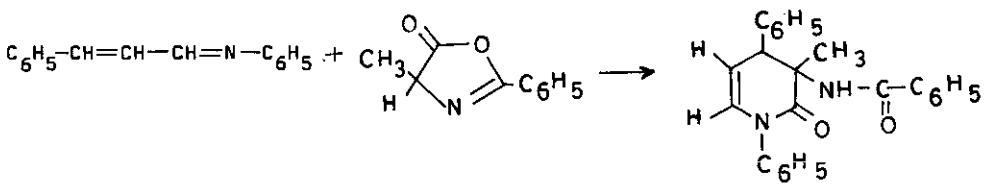
Reaction of imine with vinyl ether in the presence of dicobaltoctacarbonyl is known to yield 2-phenylquinoline 86 and 2-phenyl-4-ethoxy-1,2,3,4-tetrahydroquinoline[113] 87.



86 87

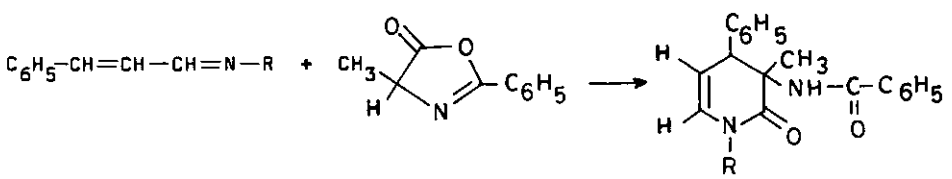
Reaction of Azadienes with Mesoionic Oxazolones

As early as in 1971 we[114] reported the reaction of cinnamylidene-aniline with 4-methyl-2-phenyl-2-oxazolin-5-one to yield dihydro-α-pyridone 88.



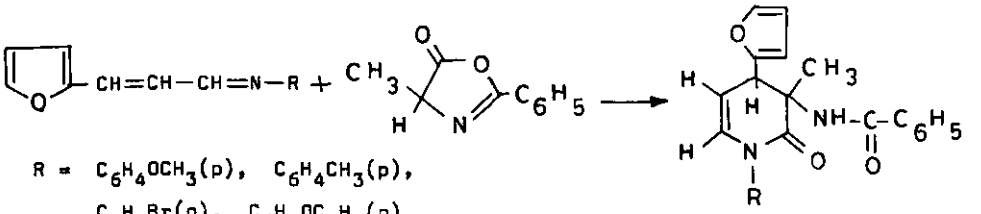
88

To generalize this reaction and study the effect of different substituents in azadiene we reacted a series of cinnamylidene-anilines with 4-methyl-2-phenyl-2-oxazolin-5-one[115]. Although dihydro-α-pyridones were the only product isolated from these reactions, the reactions with N-aliphatic azadienes were found to be fast and exothermic in comparison with N-aromatic counterparts.



R = $C_6H_4OCH_3$(p), C_6H_4Br(p), C_6H_4Cl(p), $C_6H_4Cl_2$(2,4), $C_6H_4CH_3$(p), CH_3, C_6H_{11}

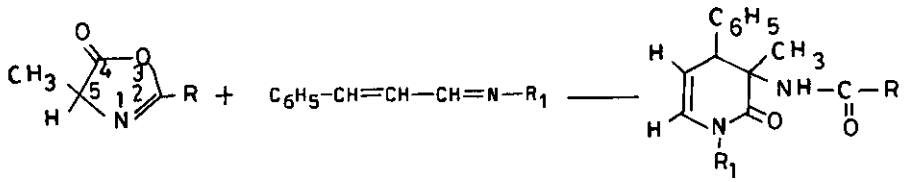
To further generalize this reaction and study the effect of substituents on azadiene, reactions of 4-methyl-2-phenyl-2-oxazolin-5-one with furanacrolein-anils were studied. Again we obtained corresponding dihydro-α-pyridones and their was no evidence for the furan ring taking part in the reactions[116]. The structures were fully confirmed by x-ray analyses.



R = $C_6H_4OCH_3(p)$, $C_6H_4CH_3(p)$, $C_6H_4Br(p)$, $C_6H_4OC_2H_5(p)$, C_6H_5

Reaction of 1-aza-3-bromo-1,3-butadienes with 4-methyl-2-phenyl-2-oxazolin-5-one also yielded α-pyridones[117].

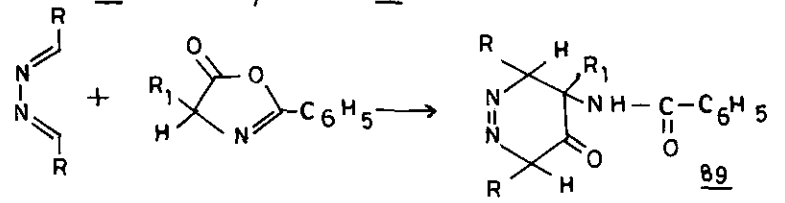
Having been studied the reactions of 1-aza-1,3-butadienes with different substituents, we directed our studies on this reaction, towards changing the substituents in mesoionic oxazolones. Thus we studied the reactions of 2-oxazolin-5-ones having different substituents in position 2 with cinnamylidene-anilines. Although dihydro-α-pyridones were the only reaction products without any evidence of the formation of β-lactam or 1,3-dipolar cycloadduct, it was observed that when an aryl group in position 2 of the oxazolone contains an electron withdrawing group in para position the reaction is slower and in case of electron donating group, it is faster than the unsubstituted aryl group being present[118].



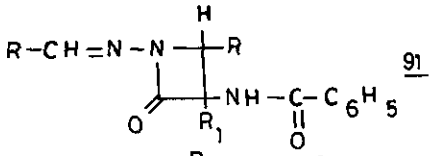
R = $C_6H_4Cl(p)$, $C_6H_4OCH_3(p)$, $C_6H_4NO_2(p)$, $CH_2C_6H_5$

R_1 = C_6H_5, $C_6H_4Cl(p)$, $C_6H_4CH_3(p)$, $C_6H_4OCH_3(p)$

Reaction of 2,3-diaza-1,3-butadienes with 2-oxazolin-5-ones yielded pyridazinones[119-120] 89 without any evidence for the formation of 'criss-cross' product 90 or amido-β-lactam 91.

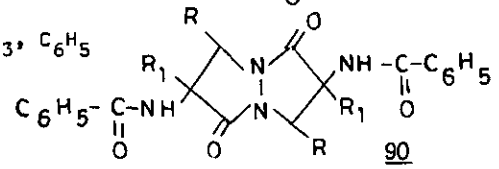


89



91

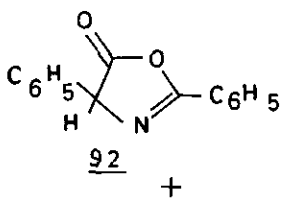
R = C_6H_5, C_4H_3S, C_4H_3O, $C_6H_4OCH_3(p)$, $C_6H_4Cl(p)$, $C_6H_4NMe_2(p)$ $\quad R_1 = CH_3, C_6H_5$



90

Reaction of 2,4-Diphenyl-2-oxazolin-5-one with 1-Azabuta-1,3-dienes

Our studies on the reaction of 2,4-diphenyl-2-oxazolin-5-one 92 with 1-azabuta-1,3-dienes 93 yielded interesting results and we obtained two sets of products ; α-pyridones 94 when azadienes with N-alkyl groups were used and acetylated adducts 95 when their N-aryl analogues were used[121].

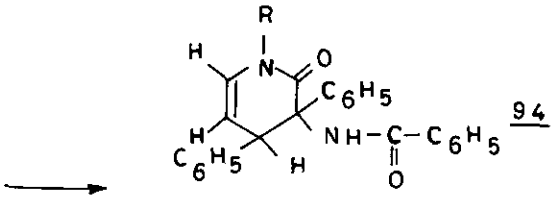


92

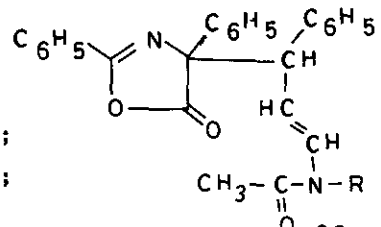
+

$C_6H_5-CH=CH-CH=NR$

93



94



95

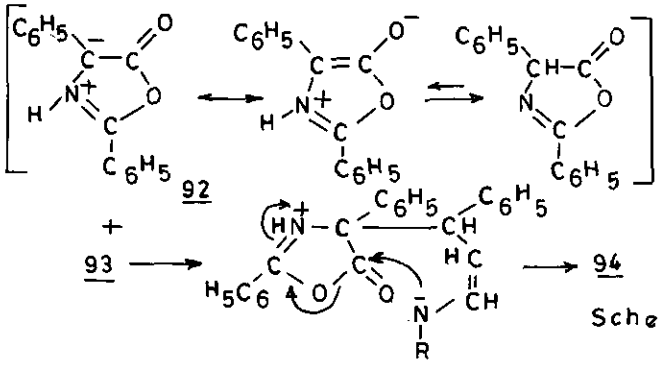
a, R = CH_3 ; b, R = C_6H_{11} ; c, R = C_6H_5 ;
d, R = $C_6H_4OCH_3(p)$; e, R = $C_6H_4CH_3(p)$;
f, R = $C_6H_4Cl(p)$; g, R = $C_6H_4Br(p)$

The azlactone 92, mp 90-92°C (lit.[122], mp 103.5-105.5°C), was prepared following the method reported by Huisgen[122]. Repeated crystallization from light petroleum ether did not raise the melting point. The ^1H NMR spectra of this compound showed the presence of acetic anhydride presumbly in the crystal lattice. This azlactone 92 containing acetic anhydride, when reacted with azadienes 93a,b

yielded ∝-pyridones 94a and 94b in 60% yields. However its reactions with azadienes 93c - g yielded acetylated adducts 95c - g in 46-52% yields. Also we were able to prepare the azlactone 92 free of acetic anhydride by passing the benzene solution of azlactone 92 through a short column of active basic alumina where all the acetic anhydride was trapped. The azlactone 92 thus obtained showed mp 103.5-105.5°C (the same as that reported by Huisgen) and the ^{1}H NMR spectra indicated the absence of any acetic anhydride. Acetic anhydride free azlactone 92 reacted with N-arylimines 93c-e affording the ∝-pyridones 94c - e in 14, 20 and 15% yields respectively. However, its reaction with N-alkylimines 93a and 93b yielded the ∝-pyridones 94a and 94b in comparable yields.

Mechanism for the Dihydro- ∝-pyridone Formation

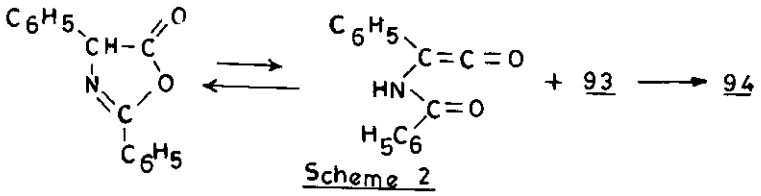
The isolation of acetylated adducts of the type 95c - g clearly indicated that the reaction is initiated by attack of oxazolone at C= C bond of azadiene followed by N-acetylation. In the case of compounds 93a and 93b the cyclized products (∝-pyridones) were obtained ; the most logical explanation probably could be that the addition of oxazolone in its carbanion form to the C = C bond and attack of nucleophilic nitrogen is a completely concerted process (Scheme-1), leaving no time available for the attack of acetyl group, the source of which appears to be the acetic anhydride in the crystal lattice of 92, at nitrogen. In case of compounds 95c - g the anion formed at the nitrogen atom is more stable and has a longer lifetime because of its delocalisation into the aromatic ring, and the competing acetylation reaction is much faster than the intramolecular attack on the azlactone carbonyl carbon, giving the acetylated adducts as the sole isolable products.



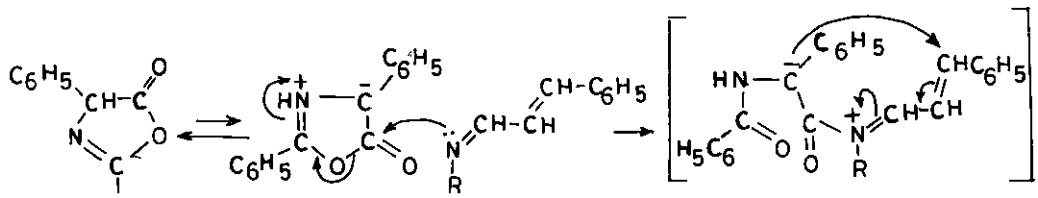
Scheme-1

The other two plausible mechanistic pathways for the formation of ∝-pyridone from conjugated imines and azlactones could be (1) the azlactones are known to

undergo (4 + 2) cycloadditions involving the valence tautomeric ketene intermediate[123] and ∝-pyridones may be formed analogously by a ketene imine reaction (Scheme-2). (2) The reaction may be initiated by attack of the imine at the carbonyl group of the azlactone and subsequent cyclization may yield ∝-pyridone as shown in Scheme - 3. This has analogy to the mechanism proposed by Knowles et al.[85] for the reaction between oxazolium perchlorate and Schiff bases.



Scheme 2

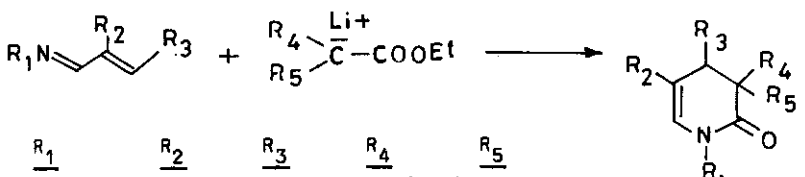


Scheme 3

The isolation of the acetylated adducts 95c - g indicated that the probable mechanism for this type of reaction is that shown in Scheme - 1. This trace amount of acetic anhydride playing a typical role is particularly important in context with Pott's method of in situ generation[124]. A critical report to this method has recently been published[125].

Reaction of 1-Azabutadienes with Enolates of Substituted Acetates

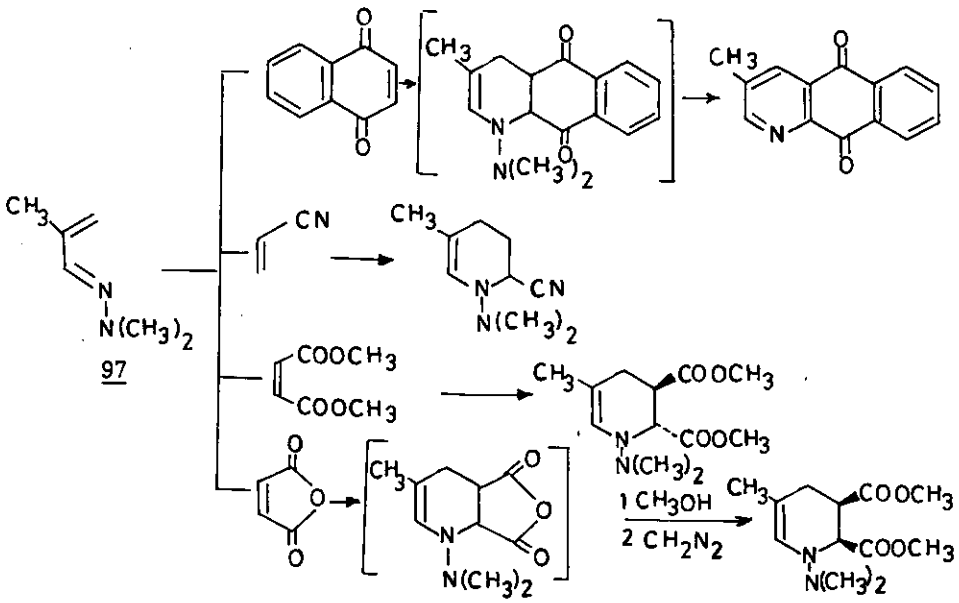
Komatsu et al.[126] reported the reaction of 1-azabutadienes with enolates of substituted acetates to yield 3,4-dihydro-2-pyridones 96.



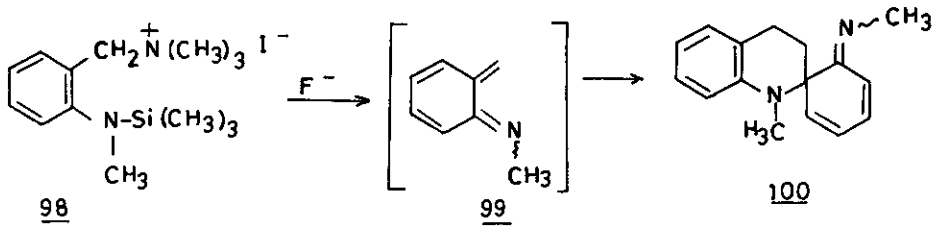
96	R_1	R_2	R_3	R_4	R_5
a	CH_3	H	C_6H_5	- $(CH_2)_5$ -	
b	CH_3	H	C_6H_5	CH_3	CH_3
c	$HC(CH_3)_2$	H	CH_3	CH_3	CH_3
d	$C(CH_3)_3$	H	C_6H_5	CH_3	CH_3
e	CH_3	CH_3	C_6H_5	CH_3	CH_3
f	$C(CH_3)_3$	C_2H_5	H	CH_3	CH_3

Intermolecular and Intramolecular Diels-Alder Cycloaddition Reactions of Conjugated Imines

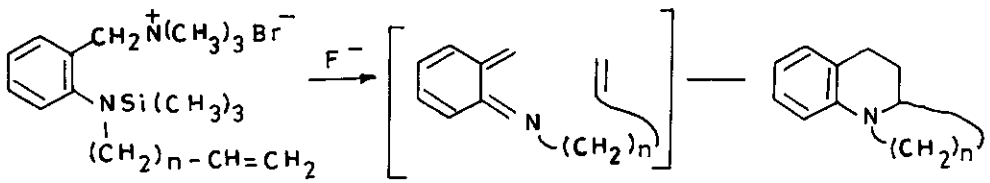
Ghosez et al.[127] reported that α,β-unsaturated hydrazones 97 react regioselectively with a wide range of dienophiles to give the corresponding (4 + 2) cycloadducts. Reductive cleavage of the N - N bond of these adducts gave tetrahydropyridines.



A large number of nitrogen bearing unsaturated heterocycles are known to participate in (4+2) cycloadditions but these examples are not discussed here. O-Quinone methide imines generated in situ are also known to react with a variety of dienophiles[128-130]. Ito et al.[131] observed the formation of spirotetrahydroquinoline derivative 100 by treating [o-[(trimethylsilyl)methylamino]-benzyl] trimethylammonium iodide 98 with cesium fluoride or tetrabutylammonium fluoride in acetonitrile at room temperature.

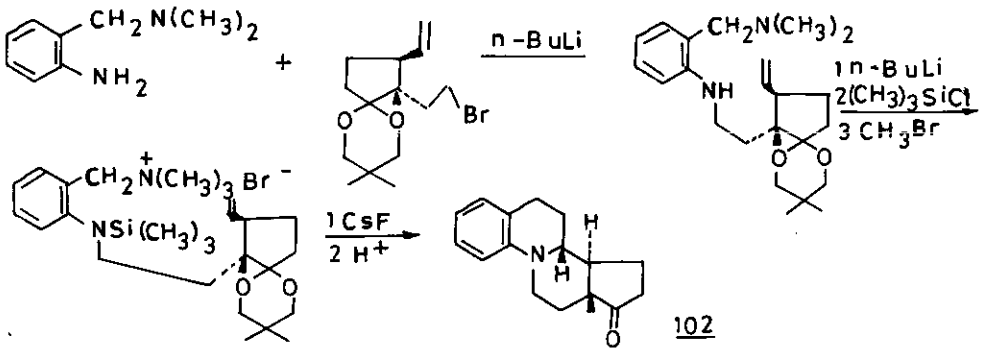


The spirotetrahydroquinoline derivative 100 may be derived from (4+2) cycloaddition of the o-quinonemethide imine 99. Attempts to trap the imine 99 with dienophiles like acrylate, fumurate, acetylenedicarboxylate and N-phenylmaleimide failed and resulted in the formation of 100 only. However, intramolecular Diels-Alder reaction of o-quinonemethide N-alkenylimine intermediate 101 provided a useful synthetic method for construction of nitrogen containing polycycles.

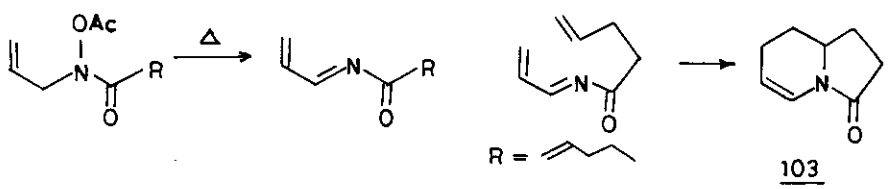


101 n = 3,4

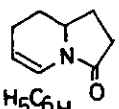
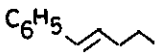
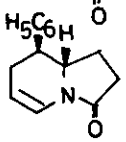
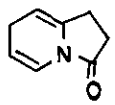
Finally this procedure was extended for the stereoselective synthesis of 9-azaestra-1,3,5(10)-trien-17-one 102.



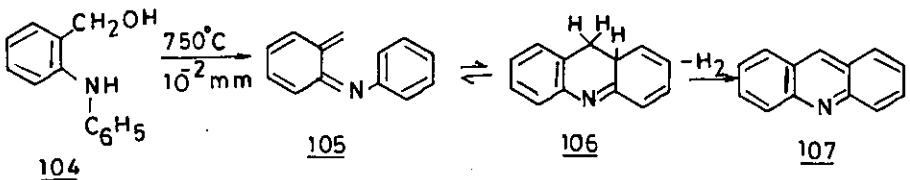
Fowler et al.[132,133] reported the preparation of N-acyl-1-azadienes by thermal elimination of acetic acid from O-acetyl hydroxylamine derivatives. These reactive imines underwent intramolecular Diels-Alder reactions to give indolizidine derivatives 103. The reaction has been reported to follow predominantly an exo stereochemical pathway.



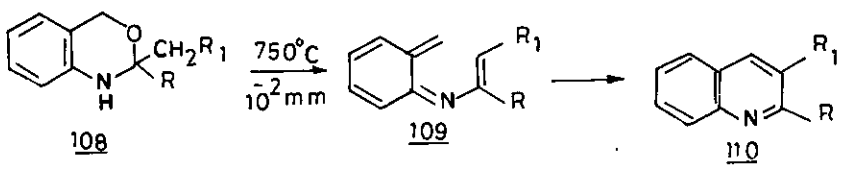
Thus by employing different substituents R a number of indolizidines were synthesized.

R	Product	Yield
		75%
		74%
		90%

Mao et al.[134] reported gas phase pyrolysis of N-phenyl-o-(hydroxymethyl)aniline 104 at 750°C to give acridine 107. As a rationalization for the formation of acridines 107 it was assumed that 104 undergoes water elimination to give imine 105, which then undergoes cyclization to 106 followed by elimination of hydrogen to give 107.

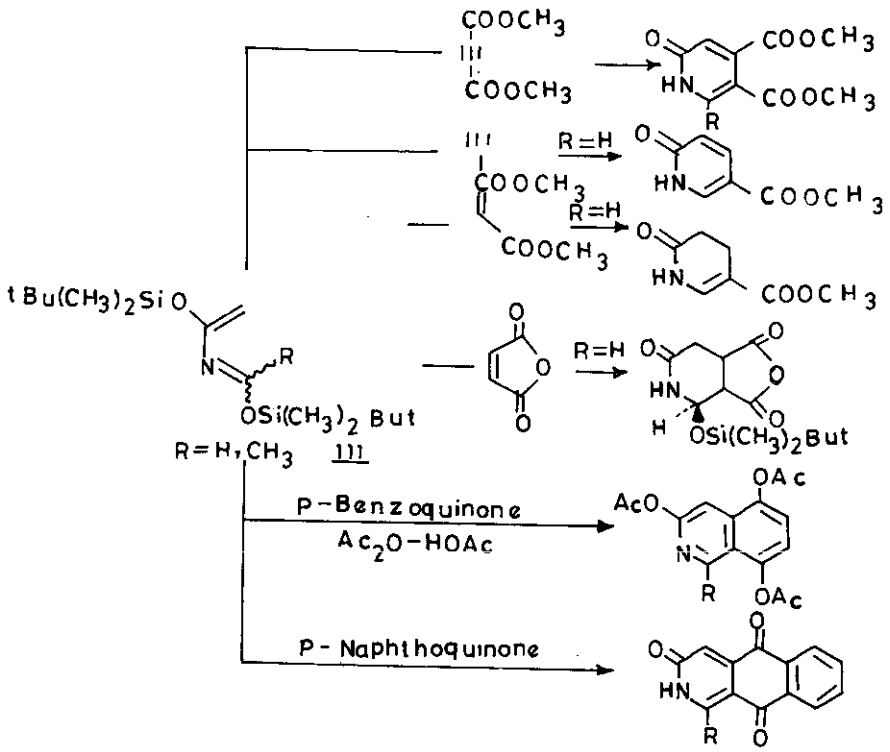


Further these workers[134] carried out gas phase pyrolysis of spiro-oxazines 108, which presumbly involves first ring opening with the loss of water to give corresponding o-xylylene derivatives 109, which on cyclization and thermal elimination of hydrogen yields quinoline derivatives 110.

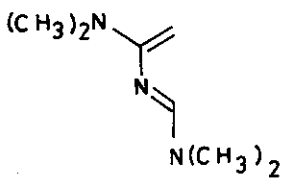


108	R	R_1	108	R	R_1
a,	- $(CH_2)_3$ -		c,	CH_3	H
b,	- $(CH_2)_4$ -		d,	H	CH_3

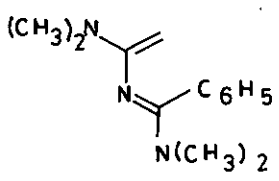
There are a number of reports on (4+2) cycloaddition reactions of 2-azabutadienes. However these dienes are generally substituted with electron donating groups which make them capable of extending their reactivity towards electron deficient dienophiles. Ghosez et al.[135] reported the reactions of 1,3-bis(t-butyldimethylsilyloxy)-2-azabutadienes 111 with a range of typical dienophiles.



Gompper and Heineman[136] reported the preparation of reactive 1,3-bis(dimethylamino)-2-azabutadienes 112, 113 which readily reacted with a series of electron deficient dienophiles.

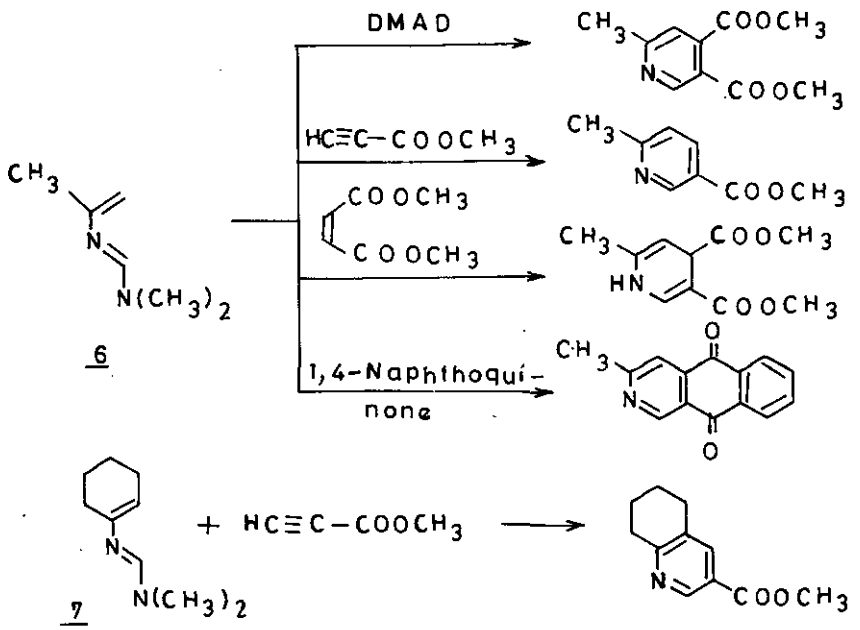


112



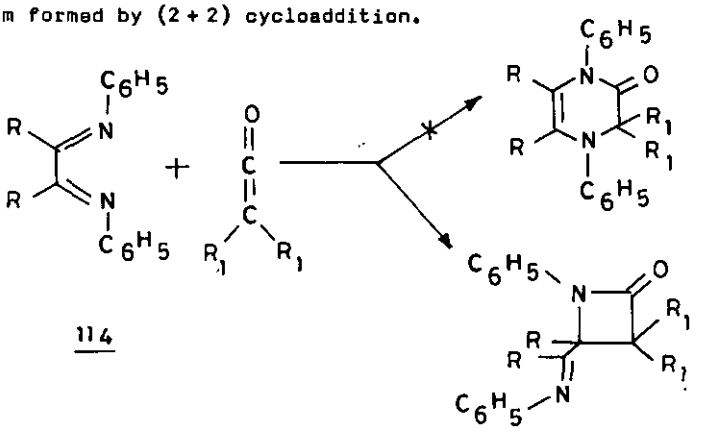
113

In fact Ghosez et al.[6] were the first to report that 2-azadienes 6, 7 bearing electron donating group are capable of reacting with dienophiles.



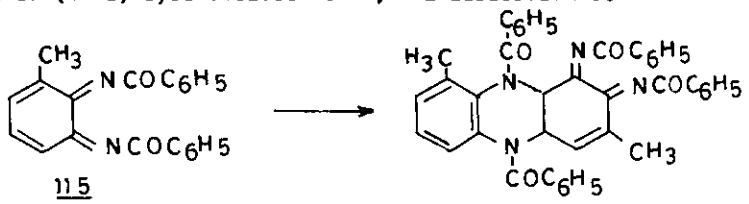
Other interesting example of cycloaddition reactions of 2-azabutadienes with electron deficient dienophiles are by Gompper[137], Normura[138], Jung et al.[139] Daniels et al.[140] and Steglich et al.[141].

There are very few examples of 1,4-diazabutadienes participating in (4+2) cycloaddition reactions. Pfleger and Jager[36] reported that dimethyl and diphenyl ketene react with α-diimines 114 to give (4+2) cycloaddition product. However reinvestigation of this reaction by Sakamoto et al.[142] revealed the product to be β-lactam formed by (2+2) cycloaddition.

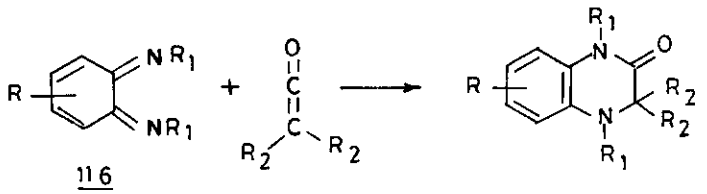


114

The dimerization[143] of substituted o-benzoquinonediimines 115 and reaction of o-benzoquinonediimines 116 with diaryl ketenes[144] can be taken as the example of (4 + 2) cycloaddition of 1,4-diazabutadienes.



115



116

Diels-Alder reactions of 2,3-diazabutadiene system with dienophiles does not appear to have been reported in the literature.

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Received, 16th June, 1986