NOVEL MULTICOMPONENT REACTIONS BASED ON ISOCYANIDES

THESIS SUBMITTED TO MAHATMA GANDHI UNIVERSITY IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY UNDER THE FACULTY OF SCIENCE

BY

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.....To My Grandmother

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DECLARATION

I hereby declare that the matter embodied in the thesis entitled "**Novel Multicomponent Reactions Based on Isocyanides**" is the result of the investigations carried out by me in the Organic Chemistry Division of Regional Research Laboratory (CSIR), Trivandrum, under the supervision of Dr. Vijay Nair and the same has not been submitted elsewhere for a degree.

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**Novel Multicomponent Reactions Based on Isocyanides**" has been carried out by Mr. A. U. Vinod under my supervision at the Organic Chemistry Division of the Regional Research Laboratory (CSIR), Trivandrum and the same has not been submitted elsewhere for any other degree.

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Words would be insufficient to express my feelings for my friends for all their support and association.

Last but not least, I thank all those whom I cannot mention, but who have helped me in various ways during the course of this work.

Vinod

Trivandrum
June, 2001

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PREFACE

Environmentally tolerable procedures, the preservation of resources and the increase in efficiency are the major goals of modern organic synthesis. The conventional preparative procedures for the synthesis of organic compounds are often tedious and involve many synthetic steps and expensive starting materials. An ideal synthesis, is one that leads to the target molecule in "one step and 100% yield from readily available starting materials." Many multicomponent reactions (MCRs), for instance display the aforementioned important characteristics. Reactions in which more than two starting compounds react to form a product in such a way that most of the atoms of the starting material are incorporated in the product are called multicomponent reactions. Contrary to the multistep sequential synthesis of a target molecule, MCRs offer the desired product in one pot from three or more starting materials. Thus in terms of efficiency, convergence, facile execution and versatility in products, MCRs are poised to revolutionize organic synthesis in general and heterocyclic synthesis in particular.

In the last decade, a conceptual change has occurred in the pharmaceutical industry with the introduction of combinatorial chemistry and high-throughput screening, which has led to the renaissance of MCRs. Today thousands of substances can be produced and characterized by means of automated research. MCRs are ideally suitable for building up such large compound libraries. By virtue of their ease of automation and the enormous number of possible products, they have moved to the forefront of contemporary endeavours to find new applications in shorter periods. There has been continuing interest in developing new MCRs. A large and important class of MCRs is the isocyanide based multicomponent reactions such as the Ugi and Passerini reactions. Isocyanides, due to their formally divalent carbon

atom, differ considerably from the rest of the organic species by their pronounced tendency to undergo multicomponent reactions. In the context of our general interest in the construction of heterocyclic systems and also in an attempt to devise novel multicomponent reactions, we have carried out a systematic investigation on the interception of *in situ* generated 1:1 zwitterionic intermediate between DMAD and isocyanides with a third component. The results validating the usefulness of the process are presented in the thesis entitled "**Novel Multicomponent Reactions Based on Isocyanides**."

The thesis is divided into four chapters. Relevant references are given at the end of each chapter.

A general introduction to the chemistry of isocyanides with special emphasis on multicomponent reactions is presented in chapter 1. A logical entrance to the present research problem is also incorporated.

The second chapter contains the results of our investigations of the reaction of 1:1 zwitterionic intermediate with various aromatic aldehydes. General information on the experimental procedure is given in this chapter.

The third chapter deals with the reaction of zwitterionic intermediate with various 1,2 and 1,4-quinones.

Chapter 4 describes the interception of the zwitterionic intermediate with the highly reactive C=N bond of the *N*-tosylimines.

It may be mentioned that each chapter of the thesis is presented as an independent unit and therefore the structural formulae, schemes and figures are numbered chapter wise.

A summary of the work is given towards the end of the thesis.

ABBREVIATIONS

br s	: broad singlet
Cy	: cyclohexyl
d	: doublet
dd	: double doublet
DEPT	: distortionless enhancement by polarization transfer
DMAD	: dimethyl acetylenedicarboxylate
DME	: dimethoxy ethane
DMSO	: dimethyl sulfoxide
EI	: electron impact
Et	: ethyl
HETCORE	: heterocosy
HOMO	: highest occupied molecular orbital
HRMS	: high-resolution mass spectrum
IR	: infrared
J	: coupling constant
LDA	: lithium diisopropylamide
LUMO	: lowest unoccupied molecular orbital
m	: multiplet
Me	: methyl
mg	: milligram
mL	: milliliter
mp	: melting point
NMR	: nuclear magnetic resonance
o	: ortho
p	: para
Ph	: phenyl
s	: singlet
t	: triplet
TCNE	: tetracyano ethylene
TosMIC	: tosylmethyl isocyanide
tert	: tertiary

Chapter 1

An Introduction to the Chemistry of Isocyanides

1.1 General

Isocyanides[1] **1** which are isoelectronic with carbon monoxide **2**, are part of a limited class of stable organic compounds of formally divalent carbon (Figure 1.1).

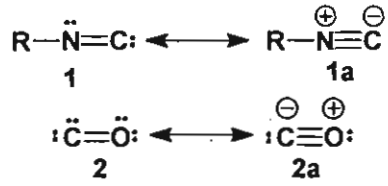


Figure 1.1

The unsurpassed versatility of the isocyanide group in chemical reactivity can be attributed to the facile transition to the tetravalent carbon by undergoing α-addition with suitable combination of reagents.

Isocyanides have been shown to be linear molecules by both electron diffraction[2] and microwave studies.[3] Like CO, isocyanides may be viewed as carbenoid in character.

In the molecular orbital model of isocyanides, the nitrogen is bonded to the terminal carbon atom by a σ bond and π_1 bond in much the same way as with cyanides. However, in contrast to cyanides, the isocyanide nitrogen donates two electrons to form a π_2 bond and a nonbonding pair of electrons resides at the carbon atom in an orbital of *sp* symmetry (Figure 1.2).[4]

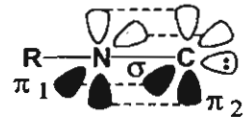


Figure 1.2

The presence of both nonbonding electrons and electron deficient π orbitals gives the isocyano carbon, a dual nature -a nucleophilic carbene, which is abundantly clear from the chemical properties of isocyanides.

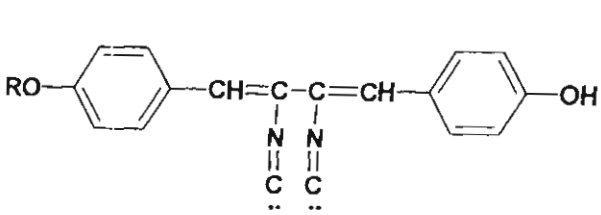
The reason why isocyanides did not attract much attention from researchers for a long time was neither the suspected toxicity, nor the vile smell, but rather it was the lack of accessibility to pure isocyanides. The classical isocyanide synthesis –the alkylation method by Gautier[5] and the carbylamine reaction of Hofmann[6] are of little use for the preparation of isocyanides in appreciable amounts.

Although most volatile isocyanides may be malodorous, they do not exhibit appreciable toxicity to mammals. However, 1,4-diisocyanobutane has been shown to be highly toxic and the toxicity is probably due to its ability to block haemoprotein and enzyme systems.[7]

In recent years, the chemistry of isocyanides has flourished vigorously. They are no longer an exotic class of compounds, but are versatile reagents routinely used by organic chemists. The isolation of naturally occurring isocyanides has invoked interest in their syntheses.

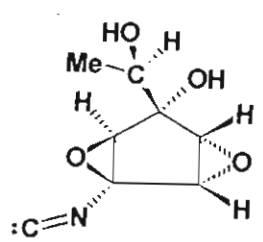
1.2 Naturally Occurring Isocyanides

A large number of naturally occurring compounds containing an isocyano group have been isolated. The antibiotics Xanthocillin **3** and Xanthocillin monomethyl ether **3a** are two such isocyanides.[8] Trichoviridine **4**, a fungal metabolite isolated from *Trichoderma* sp. was shown to contain a novel isocyano epoxide moiety (Figure 1.3).[9]



3 R = H, Xanthocillin

3a R = Me, Xanthocillin monomethyl ether



4 Trichoviridine

Figure 1.3

Two isocyano acids[10] have been isolated from cultures of the fungus *Trichoderma hamatum* as their corresponding methyl esters **5** and **6** (Figure 1.4).

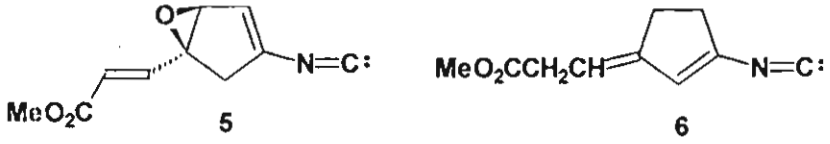


Figure 1.4

A number of sesquiterpenes and diterpene isocyanides possessing novel ring systems have been established as metabolites of marine sponges.[11] They constitute an intriguing class of natural products from both chemical and chemotaxonomic view points. These isocyanides have been reported to show a wide spectrum of antibiotic activity.

It is interesting to note that (±)-2-and (±)-9-isocyanopupukeanane **7** and **8** (Figure 1.5), a pair of sesquiterpenes produced by sponge *Hymeniacidon* sp. are used for defence purposes by nudibranch *Phyllidia varicosa.*

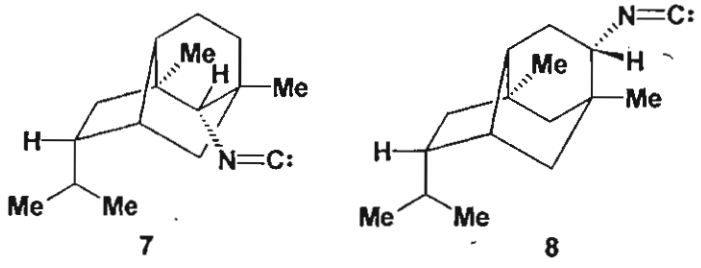


Figure 1.5

The (-) isomer of another naturally occurring isocyanide (+)-3-axisonitrile **9** (Figure 1.6) which was isolated from the marine sponge *Axinella cannabina* has been synthesized by Caine and Deutsch.[12]

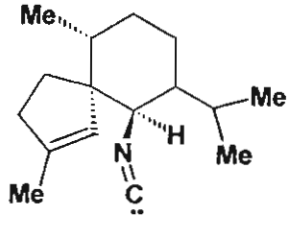
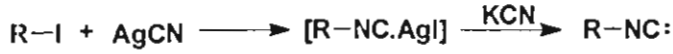


Figure 1.6

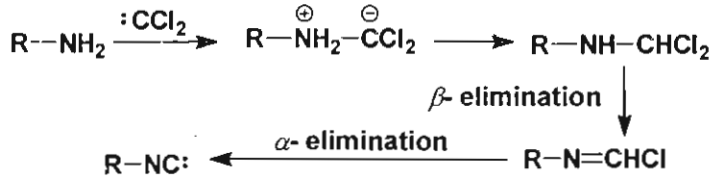
1.3 Synthesis of Isocyanides

Isocyanides were first prepared by Gautier by the reaction of silver cyanide with alkyl iodides; isocyanide-silver iodide complexes are formed from which it is liberated by KCN (Scheme 1.1).[5]



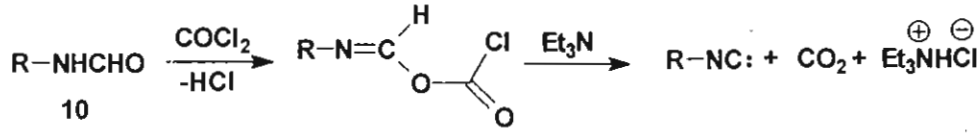
Scheme 1.1

Another early method for the synthesis of isocyanides is the carbylamine reaction by Hofmann. The reaction of primary amines with chloroform in the presence of strong bases such as ethanolic KOH has been recommended for the qualitative detection of primary amines (Scheme 1.2).[6]



Scheme 1.2

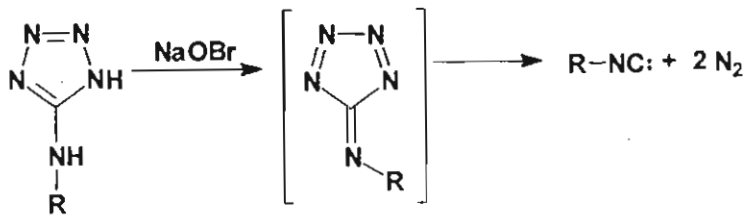
Generally, the above mentioned classical methods are not suitable for the preparation of appreciable quantities of pure isocyanides. Now most of the isocyanides have become readily available by the Ugi procedure involving the dehydration of the corresponding *N*-substituted formamides **10**.[13] The best dehydrating agents are phosgene and diphosgene in the presence of triethylamine or phosphorus oxychloride in the presence of diisopropylamine as illustrated in Scheme 1.3.



Scheme 1.3

To circumvent the use of phosgene for large scale preparations, a variety of new dehydrating agents have been introduced. Walborsky and Niznik selected chlorodimethylformiminium chloride (Vilsmeier reagent) as the dehydrating agent.[14] Ziehn and co-workers have observed that isocyanides are formed very readily by the joint action of triphenylphosphine, CCl_4 and triethylamine on monosubstituted formamides.[15]

Höfle and Lange reported a novel approach for isocyanide synthesis starting from 5-alkyl(aryl)aminotetrazoles **11**. Oxidation of **11** leads to the liberation of two moles of nitrogen and one mole of isocyanide (Scheme 1.4).[16]

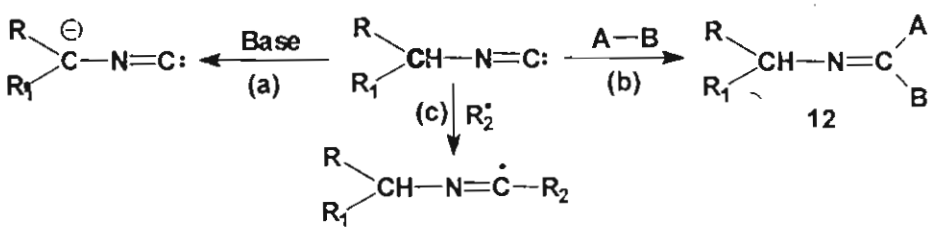


11 **Scheme 1.4**

Employing phase transfer catalysts, Ugi and co-workers have modified the classical carbylamine reaction. With this protocol, they have obtained isocyanides in yields around 60%.[17]

1.4 Chemistry of Isocyanides

The characteristics of isocyanide chemistry mainly depend on three basic properties: the α-acidity (**a**), the α-addition (**b**) and easy formation of radicals (**c**) (Scheme 1.5).



Scheme 1.5

The α-acidity is a striking feature and various heterocycles are synthesized based on α-metallated isocyanides, thanks mainly to the extensive work of Schöllkopf and van Leusen (*vide infra*). The radical reaction involving isocyanides is an emerging field and an elegant example is seen in the preparation of the key intermediate for the synthesis (±) camptothecin.[18]

The most important synthetic utility of isocyanides lies in the α-addition reactions. The dual capability of isocyanide carbon to react with electrophiles and nucleophiles leads to an α-adduct **12**. The majority of reactions including multicomponent reactions fall in this category.

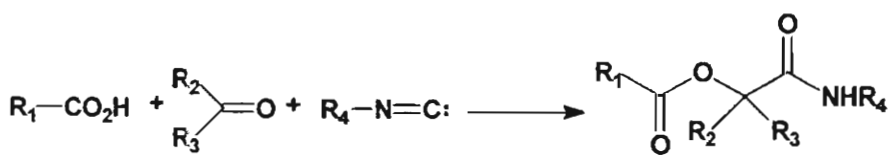
The following few sections will describe the chemistry and synthetic utility of reactions involving isocyanides.

1.4.1 Multicomponent Reactions

Most reactions in organic chemistry involve the use of either single or two starting materials. Reactions in which more than two starting compounds react to form a product in such a way that the majority of atoms of the starting materials incorporated in the product are called multicomponent reactions (MCRs). Although a number of multicomponent reactions have been known for sometime, no systematic effort has been made to exploit the synthetic potential of such reactions. Recently, with a paradigm shift in organic synthesis, the focus of attention has shifted to multicomponent reactions. These reactions by virtue of their convergence, productivity, facile execution and generally high yields of products are especially attractive from the vantage point of combinatorial chemistry.

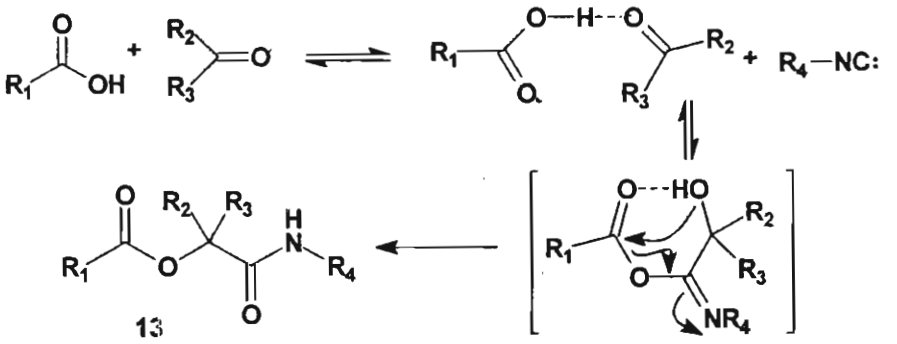
Of pivotal importance in this area are the isocyanide based MCRs like the Passerini[19] and Ugi[20] reactions. Isocyanides, due to their formally divalent carbon atom, differ considerably from the rest of the organic species by their pronounced tendency to undergo multicomponent reactions.

The formation of α-acyloxy carboxamides **13** by a three component reaction between isocyanides, carboxylic acids and carbonyl compounds (aldehydes, ketones, acylamides) is known as the Passerini (P-3CR) reaction (Scheme 1.6).



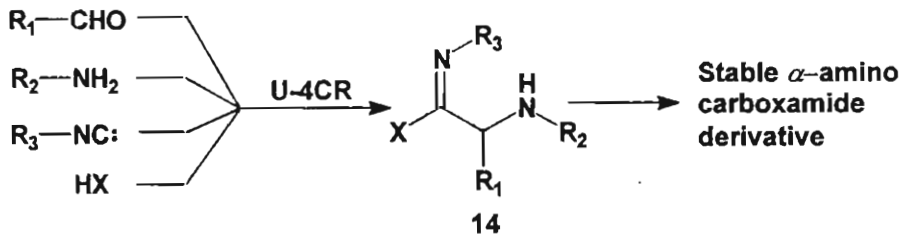
Scheme 1.6 13

A plausible mechanism, which agrees with the experimental data is given in Scheme 1.7.



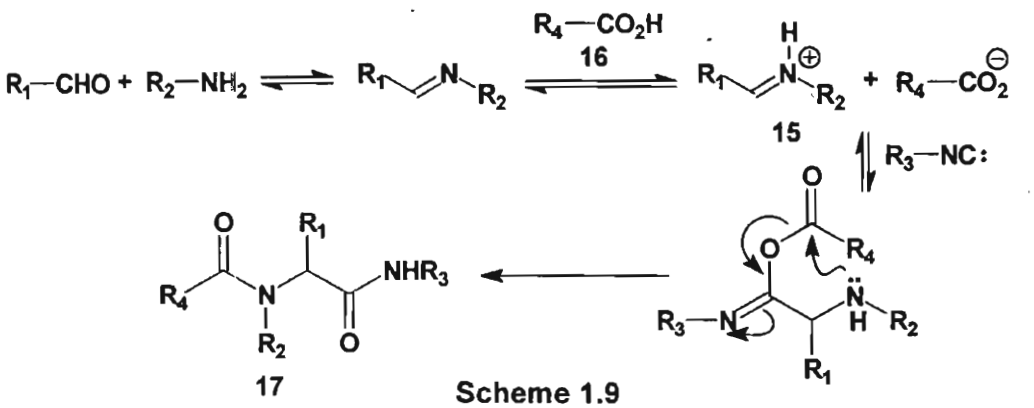
Scheme 1.7

In the Ugi four component (U-4CR) reaction, amines and carbonyl compounds react with isocyanides in the presence of suitable acid HX to form unstable α-adducts **14** which are transformed into stable α-aminocarboxamide derivatives (Scheme 1.8).



Scheme 1.8

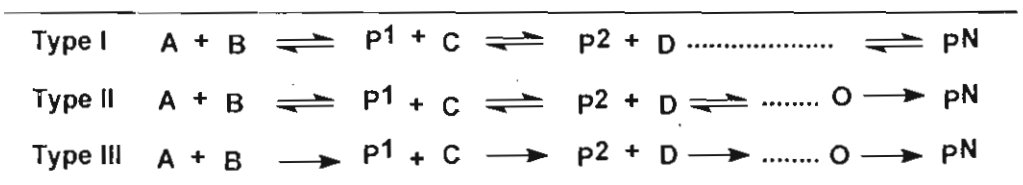
The characteristic feature of the Ugi reaction is the α-addition of an iminium ion **15** and anion X^- of an acid HX to isocyanide followed by the spontaneous rearrangement of the initially formed α-adduct to a stable product. The most commonly used acid components are carboxylic acids and if HX is considered as R_4-CO_2H **16** in the above scheme, the mechanism for the formation of stable α-amino carboxamide derivative can be rationalized as given below (Scheme 1.9).



Scheme 1.9

This reaction is found to be highly general and is applicable to the synthesis of a variety of organic compounds depending on the selection of each component. Any known type of C-isocyanides can be used as the isocyanide component and the only restriction for the acid components is that they must be able to rearrange irreversibly from the intermediate α-adduct of the isocyanide to a stable product. Except for sterically hindered diaryl ketones, most aldehydes and ketones can generally be used as carbonyl components. Ammonia, primary and secondary amines as well as hydrazine derivatives can be used as amine component. The U-4CR and related reactions can produce more different classes of chemical products than any other type of known reaction and is highly useful for the synthesis of peptide and β-lactam derivatives.[21]

As a theoretical background, and to understand specific characteristics and logic of these reactions, Ugi considers three idealized types of MCRs depending on the reversibility of reactions leading to intermediary products P^1, P^2.....and the final product P^N (Scheme 1.10).

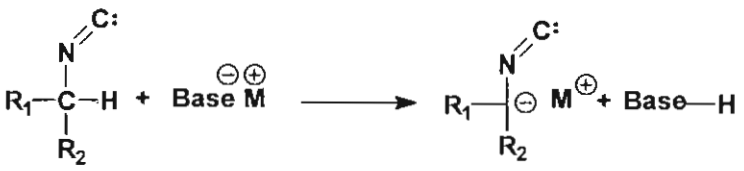


Scheme 1.10

In the Type I MCR, the starting compounds, intermediates and products are in a mobile equilibrium. As different states of balance can prevail yields ranging from 0-100% are possible. MCRs whose elementary reactions involve either equilibria or partial irreversible reactions and in which the last reaction step is irreversible belong to Type II. Reactions of this type are preparatively advantageous as the total equilibrium is shifted to the side of the products by the last irreversible step. Such irreversible steps for example, are the results of strongly exothermic reactions like the C(II)-C(IV) conversion of isocyanides, a ring closure reaction or an aromatization. MCRs of Type III are sequences of irreversible elementary reactions. They seldom occur in preparative chemistry. Type I can be virtually converted into Type II if the product is withdrawn from the equilibria.[22]

1.4.2 α-Metallated Isocyanides

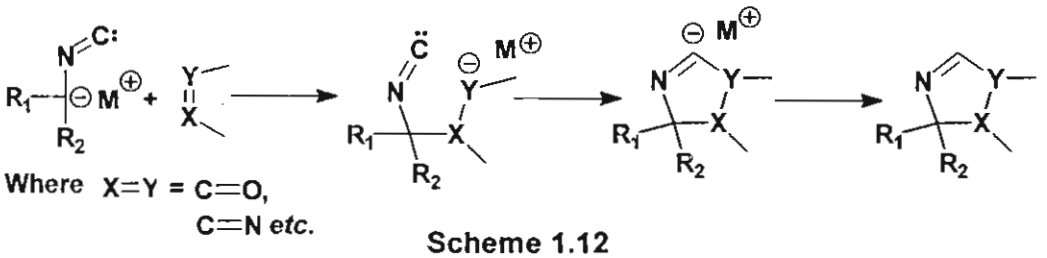
Schöllkopf and Gerhart have shown that alkyl isocyanides can be metallated in the α-position, albeit not quite so readily as alkyl cyanides (Scheme 1.11).[23]



18

Scheme 1.11

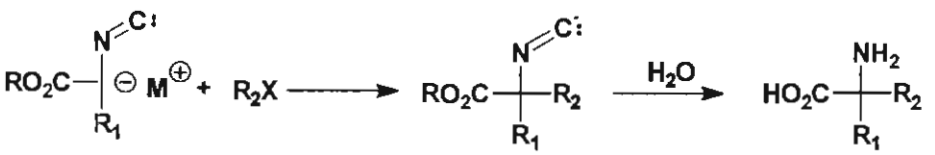
Being both nucleophilic and electrophilic, α-metallated isocyanides can add to polar double bonds such as carbonyls, imines *etc.* to form heterocycles (Scheme 1.12).[24] They are also synthons for α-metallated primary amines.



Where X=Y = C=O, C=N *etc.*

Scheme 1.12

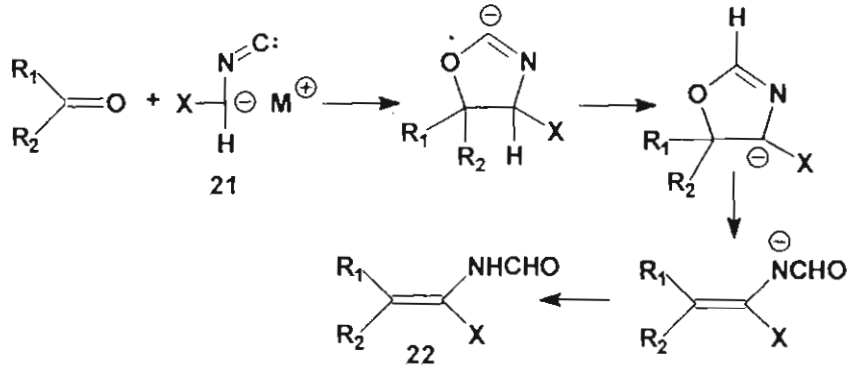
Alkylation of α-metallated α-isocyanoalkanoic esters **19** followed by hydrolysis leads to the formation of longer chain or α-branched amino acids **20** (Scheme 1.13).[25]



19 20

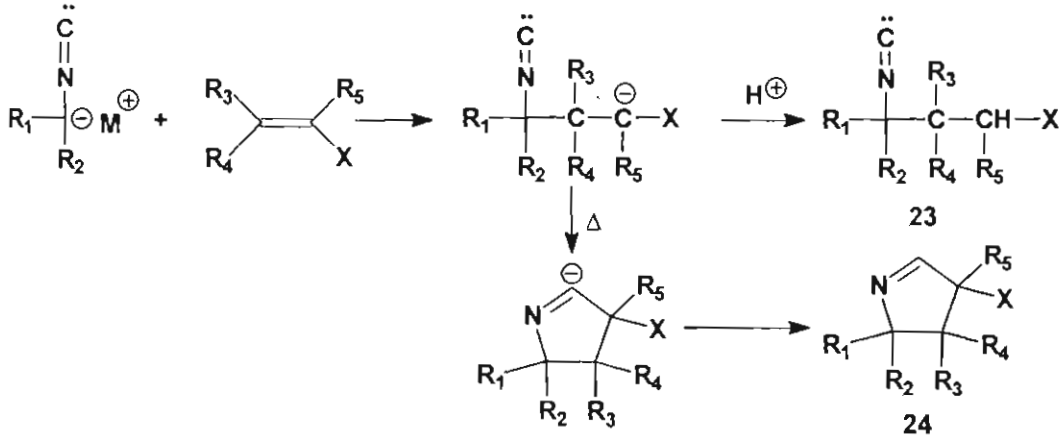
Scheme 1.13

α-Metallated isocyanides possessing a strongly activating group X besides a hydrogen atom **21** react with carbonyl compounds to give *N*-(1-alkenyl)formamides **22** (Scheme 1.14).[26]



Scheme 1.14

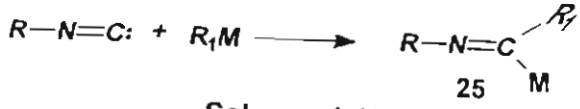
They also undergo Michael addition to a number of activated olefins such as α,β-unsaturated ketones, acrylic esters *etc.*[27] On protonation, the adducts gave isocyanides **23** with extended chain. When heated, the adducts cyclize to pyrrolinyl anion followed by protonation to afford pyrrolines **24** (Scheme 1.15).



Scheme 1.15

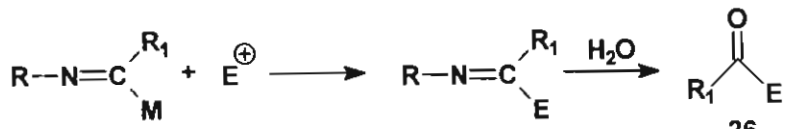
1.4.3 Reaction with Organometallic Reagents: Formation of Metalloaldimines

Isocyanides can undergo two types of reactions with the organometallic reagents depending on their structure. If the isocyanide possesses α-hydrogen atom, the organometallic reagent will abstract the acidic hydrogen to produce α-metallated isocyanides as shown above. However, when the isocyanide does not posses α-hydrogen atom then α-addition to the isocyanide occurs to yield the metalloaldimine **25** (Scheme 1.16).[28]



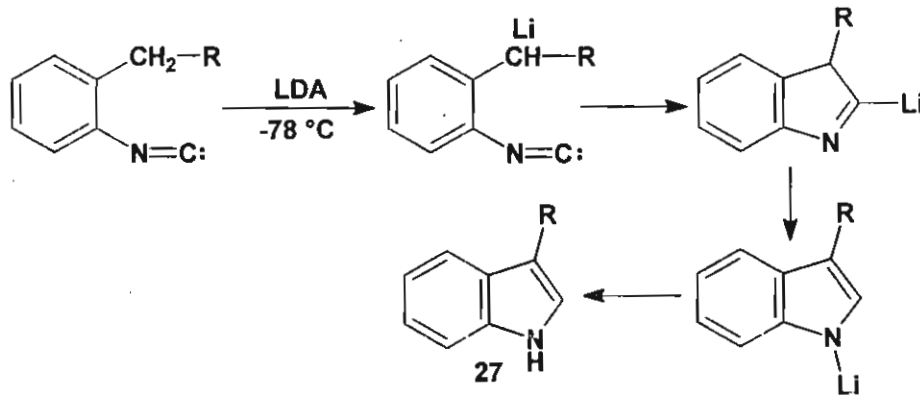
Scheme 1.16

Metalloaldimines may be viewed as masked acyl carbanions, the reaction of which with electrophilic reagents followed by hydrolysis of the imine, introduces the acyl moiety into the product (Scheme 1.17).[29]



Scheme 1.17

A unique and versatile synthesis of 3-substituted indoles **27** has been developed by Saegusa *et al.*[30] which involves the intramolecular α-addition of lithium reagent to an isocyanide (Scheme 1.18).

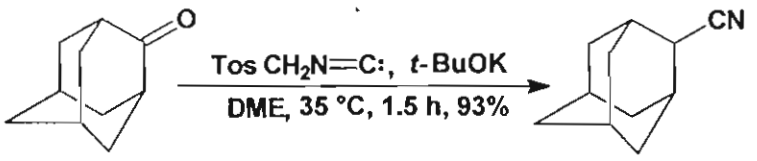


Scheme 1.18

1.4.4 Tosylmethyl Isocyanide (TosMIC)

p-Toluenesulphonylmethyl isocyanide ($TosCH_2N{=}C$), the best known compound of a series of (hetero-) substituted derivatives of methyl isocyanide, is a stable, odorless organic synthon. TosMIC undergoes a wide variety of reactions revealing its diverse applications in synthetic organic chemistry. The acidic α-hydrogens can be easily removed by treatment with a variety of bases. The reactions and synthetic utility of TosMIC have been extensively investigated by van Leusen's group.[31]

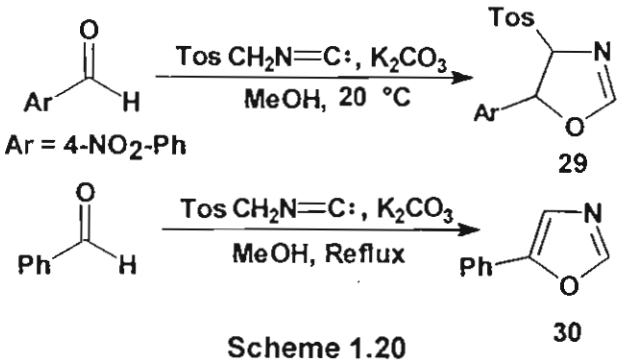
Most ketones are converted into cyanides with TosMIC and potassium *t*-butoxide in non protic solvents such as DME, DMSO *etc.* (Scheme 1.19).[32]



28

Scheme 1.19

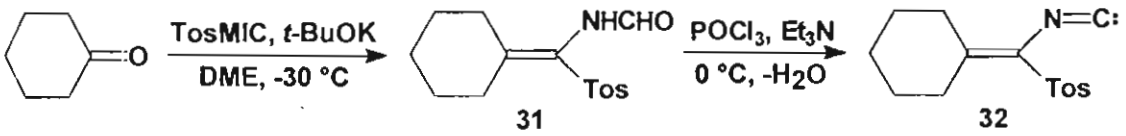
Oxazolines **29** are produced from the reaction of TosMIC with aldehydes in protic solvents[33] at 20 °C, whereas on refluxing, oxazoles **30** are formed by the elimination of *p*-toluene sulfinic acid (Scheme 1.20).[34]



Scheme 1.20

Similarly, imidazoles are obtained from imines, thiazoles from dithioesters or CS_2.

Reactions of TosMIC with aldehydes and ketones can be directed in such a way that formal Knoevenagel condensation products **32** are formed by the overall elimination of water by a two step process (Scheme 1.21).[35]

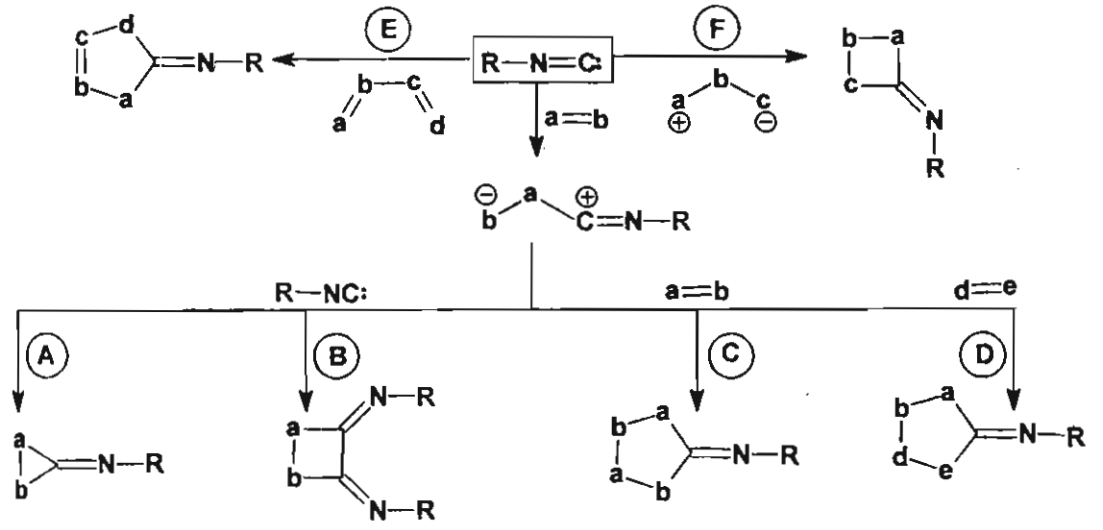


Scheme 1.21

1.4.5 Cyclization Reactions

Since isocyanide can act as both nucleophile and electrophile simultaneously, ring closure reactions that occur with incorporation of the isocyanide carbon atom have been established as an elegant approach to a large number of cyclic systems which are quite often inaccessible by other methods.

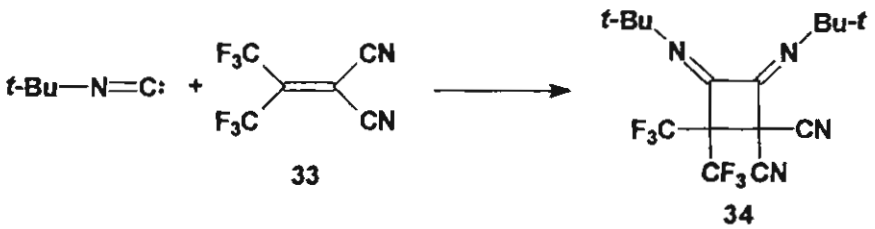
For practical purposes, the cyclization can be viewed as in Scheme 1.22.



Scheme 1.22

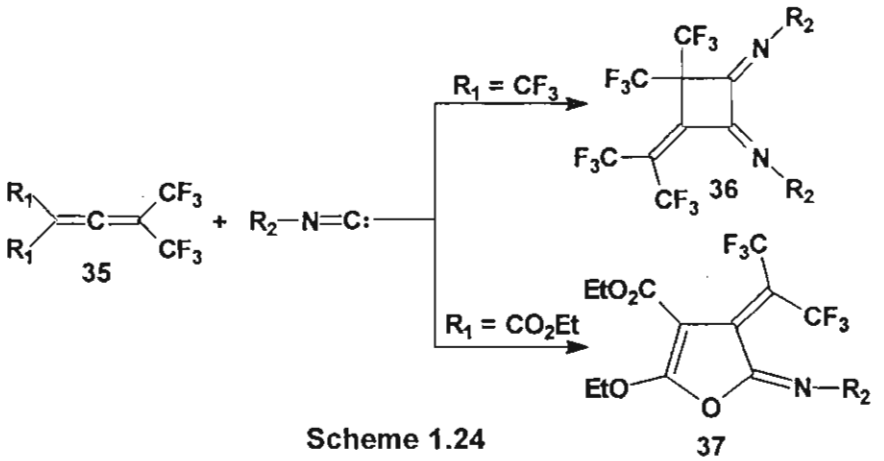
Frequently in these reactions, a dipolar compound a=b which is in equilibrium with a^{+}–b^{-} is involved. The electrophilic part of the dipole forms a bond with the lone pair of the isocyanide carbon atom; this carbon then becomes electrophilic and closes the ring with the electron rich part of the dipole. Although three membered rings have been postulated for (**A**) as intermediates, they have never been isolated. Instead, a further molecule of either one of the two partners isocyanide (**B**) or a=b (**C**) or even a third reactant d=e (**D**) is inserted into the initially formed 1,3-dipolar intermediate so that ultimately a ring of at least four members is formed. Compounds having double bond in conjugation to another π system in general do not follow this cyclization pattern; such molecules by virtue of their 1,4-dipolar character, give rise to five membered rings (**E**). Reactions of 1,3-dipolar species with isocyanides give four membered ring systems (**F**).

The activated double bond of 1,1-bistrifluoromethyl 2,2-dicyanoethylene **33** reacts with two equivalents of isocyanide even below 0 °C to afford the cyclobutane derivative **34** (Scheme 1.23).[36]



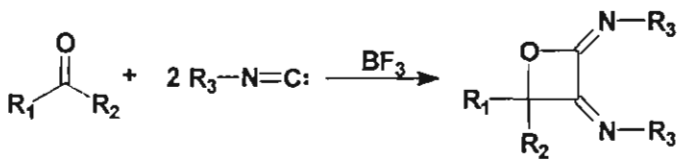
Scheme 1.23

Allenes **35** have been found to react with alkyl isocyanides under mild conditions to form adducts **36** and **37**, depending on the substituent R_1 as shown in Scheme 1.24.[37]



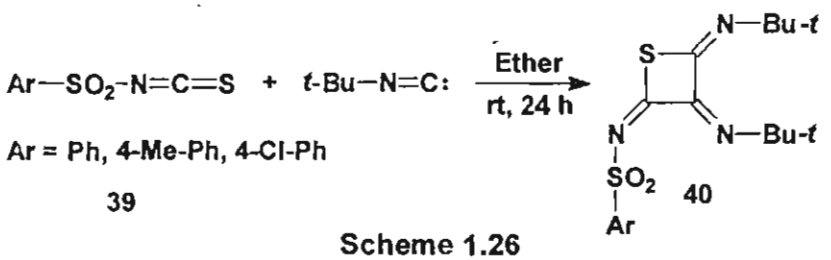
Scheme 1.24

When catalytic amounts of Lewis acids such as boron trifluoride are present, a variety of aldehydes and ketones are known to cyclize with alkyl isocyanides in a [1+1+2] manner to produce 2,3-bis(alkylimino)oxetanes **38** (Scheme 1.25).[38]



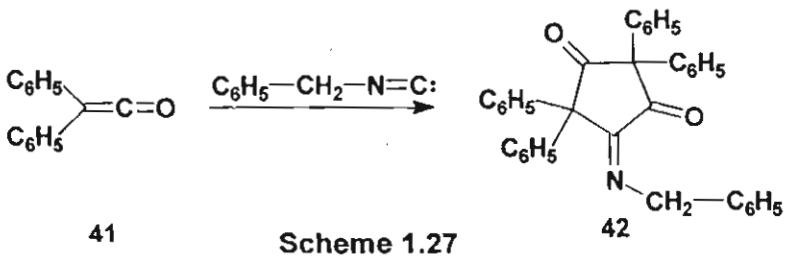
Scheme 1.25

Triiminothietanes **40** are formed from the reaction of arenesulfonyl isothiocyanates **39** and *t*-butyl isocyanide (Scheme 1.26).[39]



Scheme 1.26

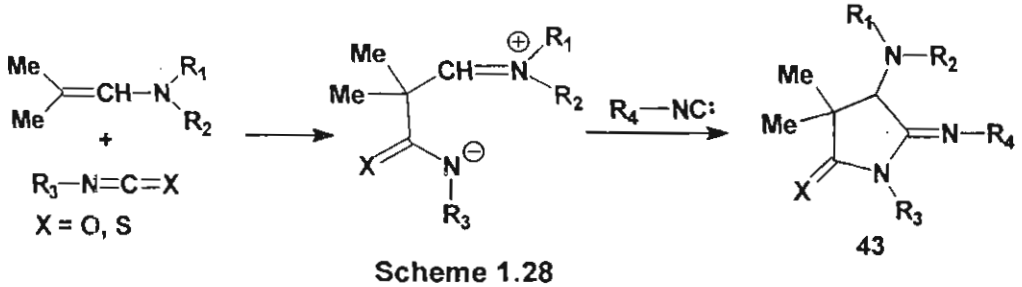
Ugi and Rosendhal found that diphenyl ketene **41** reacts with benzyl isocyanide in a 2:1 ratio to form 1-imino-2,4-cyclopentane dione **42** as illustrated in Scheme 1.27.[40]



41 Scheme 1.27 42

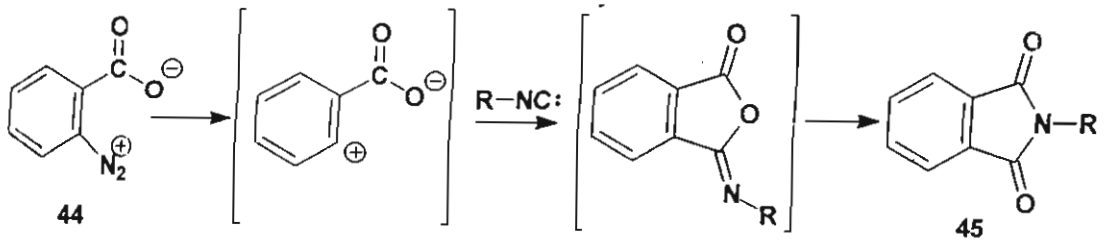
The reaction of *t*-butyl cyanoketene follows a unique reaction pathway in which the cycloaddition takes place across the carbonyl bond of the ketene component, contrary to all other examples which give the products arising from the reactions involving addition to the alkene bond of the cumulene.[41]

A three component condensation involving enamines, isocyanides and isocyanates/isothiocynates is known to afford succinimide derivative **43** (Scheme 1.28).[42]



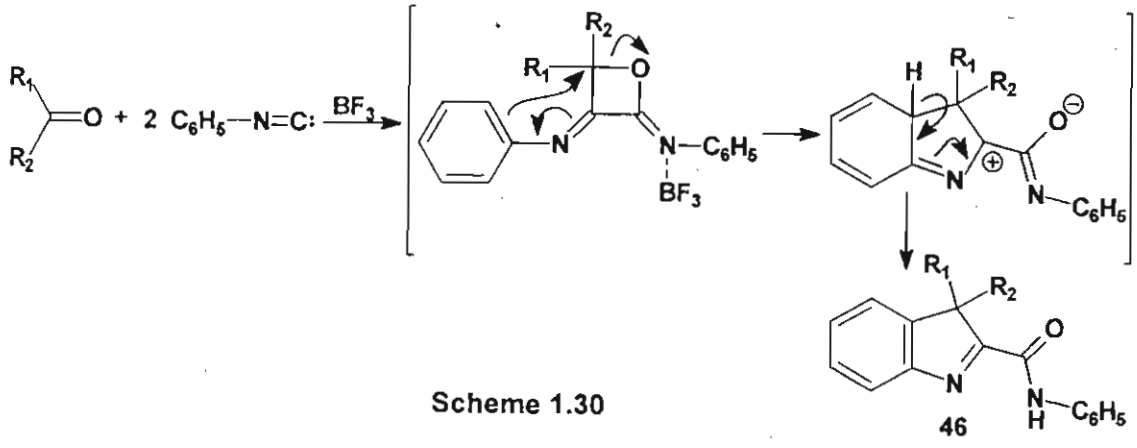
Scheme 1.28 43

Yaroslavsky[43] and Knorr[44] independently investigated the reaction of benzenediazonium carboxylate **44** and isocyanides. The primary product rearranges to give phthalimide **45** (Scheme 1.29).



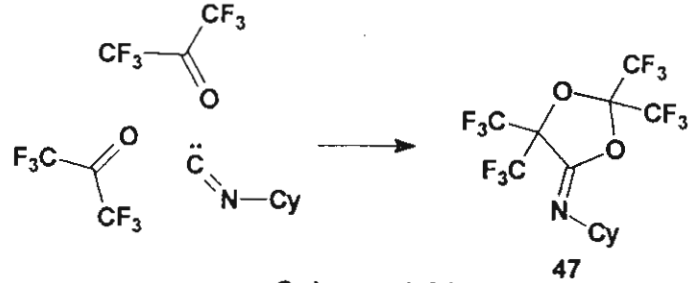
44 Scheme 1.29 45

Zeeh has reported the cyclization of aromatic isocyanides with ketones in the presence of catalytic amounts of BF_3 to form indolenins **46** (Scheme 1.30).[45]



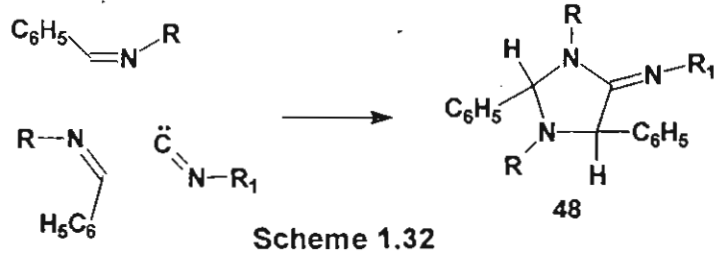
Scheme 1.30

Reaction of hexafluoroacetone with cyclohexyl isocyanide represents another type of isocyanide-ketone cyclization reaction. *N*-cyclohexylimino dioxolane **47** is formed in high yield (Scheme 1.31).[46]



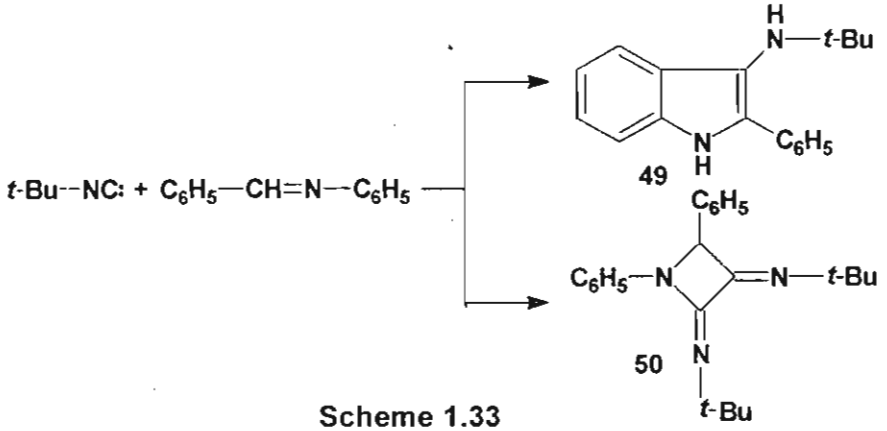
Scheme 1.31

Similarly, it was shown by Saegusa *et al.* that reaction of aliphatic isocyanides with Schiff bases gives 2,5-diphenylimidazolidine **48** (Scheme 1.32).[47]



Scheme 1.32

t-Butyl isocyanide and *N*-arylimines react at 120 °C in CCl_4 to afford both 1:1 and 2:1 adducts (**49** and **50**) in fair yields (Scheme 1.33).[48]

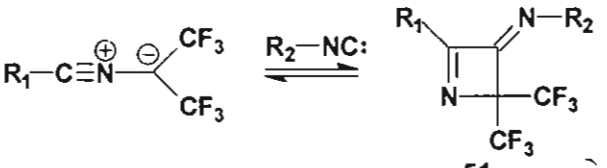


Scheme 1.33

The reaction of isocyanides with acetylenic esters such as dimethyl acetylenedicarboxylate has been studied in detail by a number of groups. The initially formed 1:1 zwitterionic intermediate undergoes further reaction with DMAD and isocyanide in different molar proportions, ultimately leading to a variety of complex heterocyclic systems (for a detailed discussion, see Section 2.9 in Chapter 2)

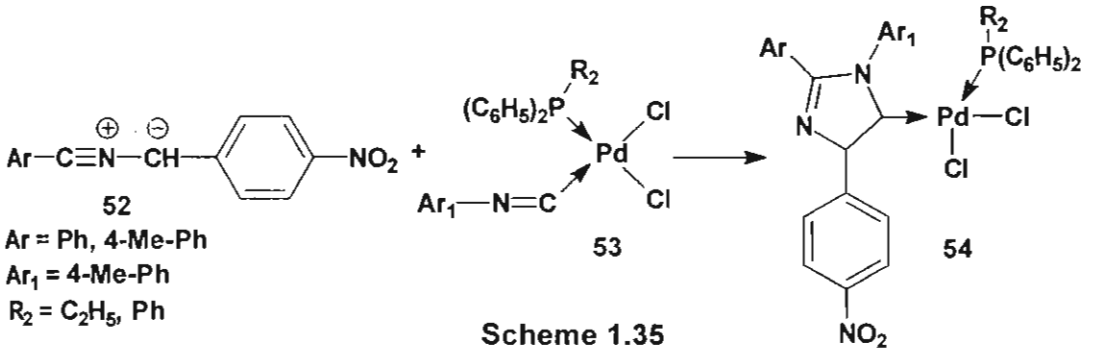
1.4.5.1 Reaction of Isocyanides with Classical 1,3-Dipoles

Nitrile ylides have been shown to produce four membered rings on reaction with isocyanides (Scheme 1.34).[49]



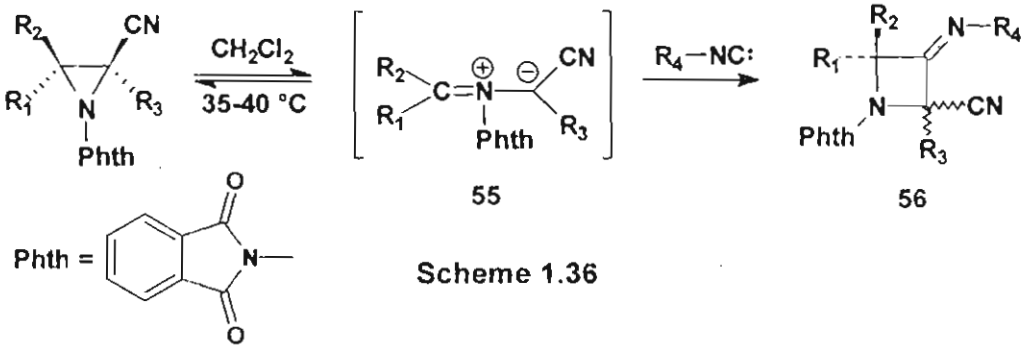
Scheme 1.34

A different reaction course is encountered on treatment of benzo- and *p*-tolunitrile *p*-nitrobenzylide **52** with the isocyanide-palladium complexes **53** (Scheme 1.35).[50]



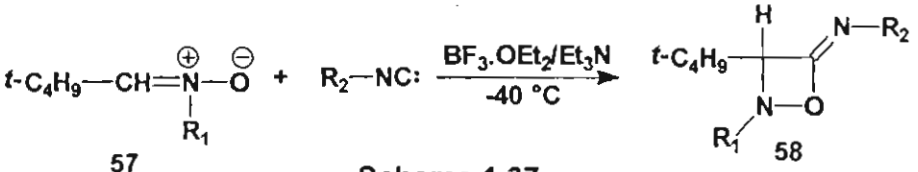
Scheme 1.35

Azomethine ylides **55**, generated either by thermolysis of the triazoline or by the thermal ring opening of the aziridine, have been successfully cyclized with isocyanides to give the 3-iminoazetidines **56** (Scheme 1.36).[51]



Scheme 1.36

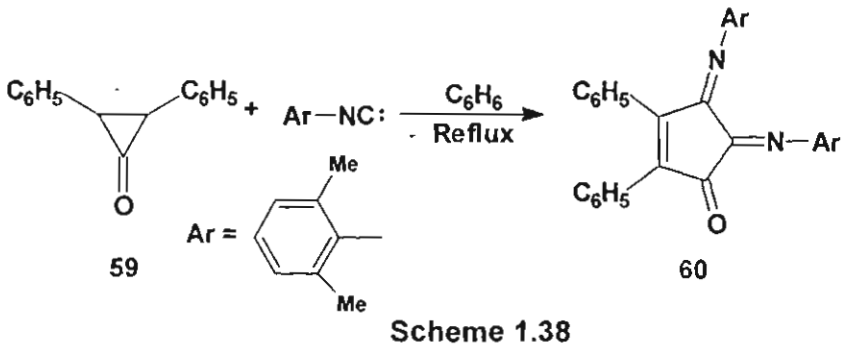
Moderhack and Lorke have shown that using boron trifluoride etherate as catalyst *C,N*-dialkyl nitrones **57** are readily cyclized with isocyanides to yield 4-imino-1,2-oxazetidines **58** (Scheme 1.37).[52]



Scheme 1.37

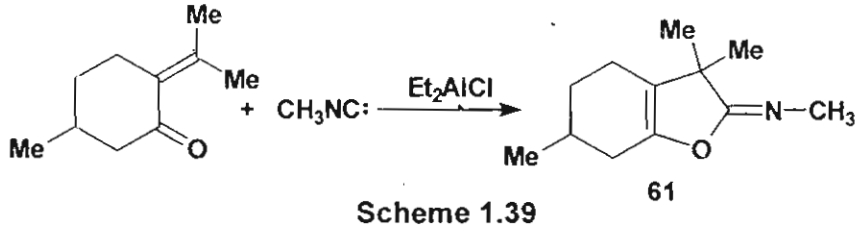
1.4.5.2 [4+1] Cycloaddition Reactions

Diphenyl cyclopropenone **59** on refluxing in benzene with 2,6-dimethylphenyl isocyanide mainly yielded the cyclopentene derivative **60** (Scheme 1.38).[53]



Scheme 1.38

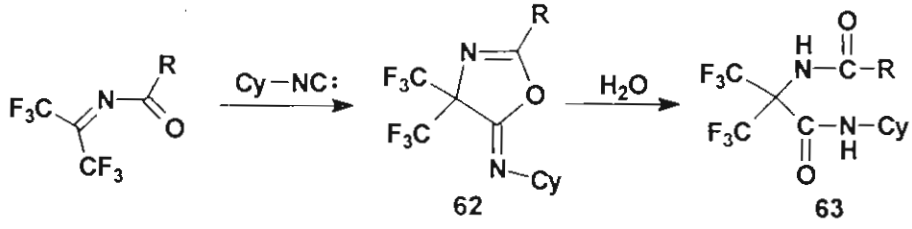
Diethyl aluminium chloride promoted, [4+1] cycloaddition of *α,β-unsaturated carbonyl* compounds with isocyanides to produce unsaturated *N-substituted iminolactones* ***61*** *have been known from the work of Saegusa et al.* (Scheme 1.39).[54]



61

Scheme 1.39

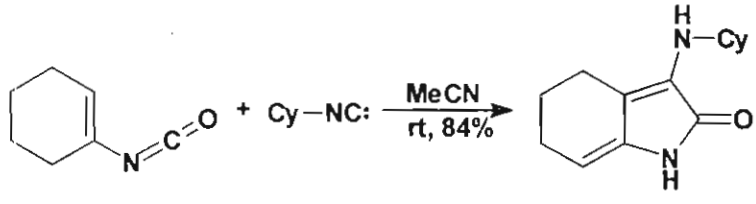
Oxazolines are formed from the reaction of acylimines of hexafluoroacetone and isocyanides. The aminoacid derivative **63** is obtained from **62** after hydrolysis (Scheme 1.40).[55]



62 63

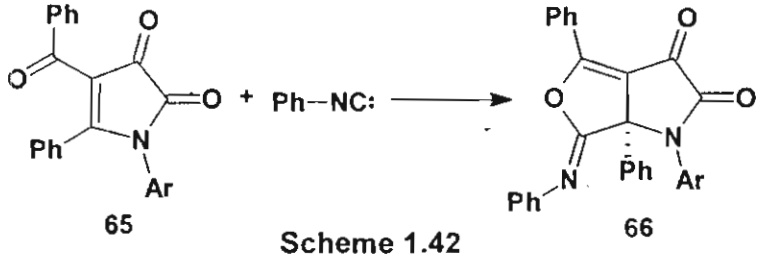
Scheme 1.40

Vinyl isocyanates and alkyl or aryl isocyanides offer the requisite combination for the [4+1] cycloaddition mode as shown by Rigby *et al.* (Scheme 1.41).[56]



Scheme 1.41 64

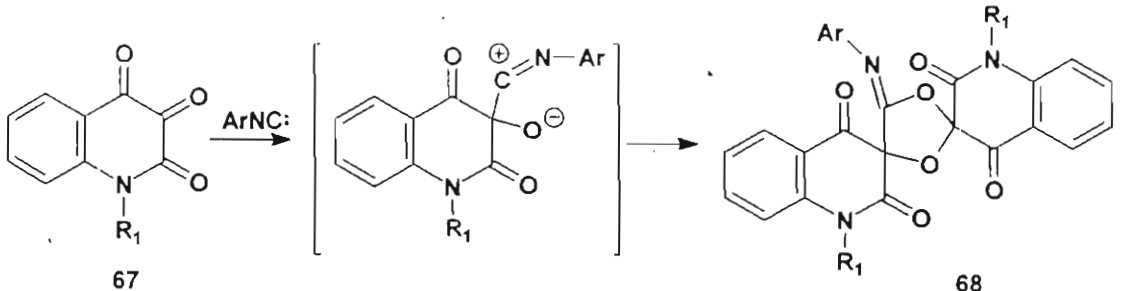
1,5-Diaryl-4-benzoylpyrrole-2,3-diones **65** add one mole of phenyl isocyanide in a reversible thermal [4+1] cycloaddition (Scheme 1.42).[57]



65 66

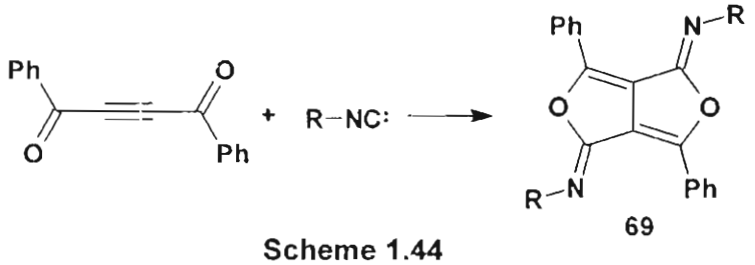
Scheme 1.42

Dispiro-1,3-dioxolanes **68** are obtained from 2,3,4-trioxoquinolines **67** and aromatic isocyanides. The compounds are presumably formed *via* a dipolar intermediate which adds an additional molecule of trioxoquinoline and subsequently undergoes cyclization reaction (Scheme 1.43).[58]



Scheme 1.43

1,4-Diphenylbutyne-1,4-dione adds the isocyanide *via* a criss-cross cycloaddition reaction yielding the 1*H*, 4*H*-furo[3,4-*c*] furan **69** (Scheme 1.44).[59]

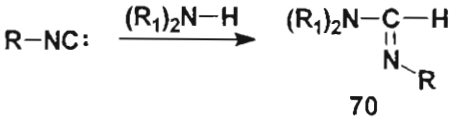


Scheme 1.44

1.4.6 Insertion Type Reactions

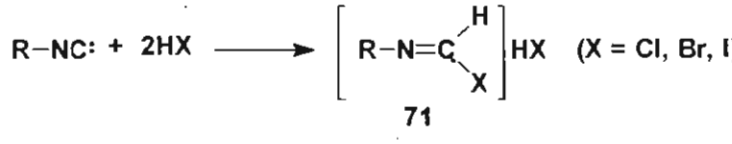
Interestingly, isocyanides undergo insertion reactions manifesting their carbene character. A wide variety of compounds are known to react with isocyanides in this fashion. Depending on the nature of the reactants and of the catalyst, if one is used, different types of reactions have been observed.

Saegusa and co-workers have investigated in detail, the insertion of isocyanides to heteroatom-hydrogen bonds catalyzed by group IB and IIB metal compounds, especially of copper. The isocyanide carbon is inserted into =N-H, =P-H, -O-H, -S-H and Si-H bonds to produce the corresponding derivatives of formimidic acid. A representative example is given in Scheme 1.45.[60]



Scheme 1.45

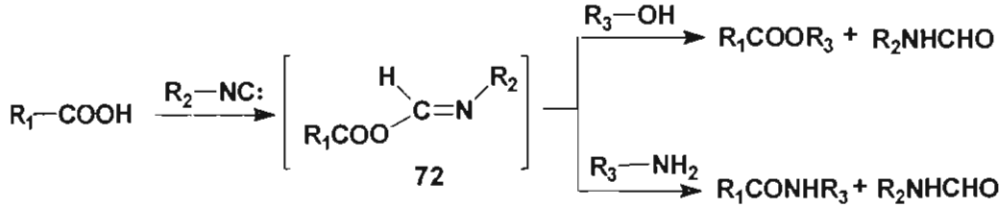
A violent reaction occurs between isocyanides and hydrogen halides. In the reaction carried out at –15 °C, the salts of formimidyl halides **71** were isolated (Scheme 1.46).[61]



71

Scheme 1.46

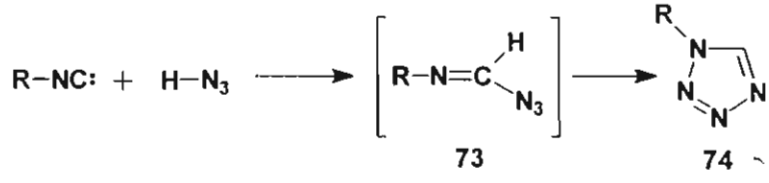
Isocyanides have been employed as activating agents for carboxylic acids in the formation of esters and amides. This reverse reaction of the formation of isocyanide, is assumed to proceed through the primary insertion product **72** (Scheme 1.47).[62]



72

Scheme 1.47

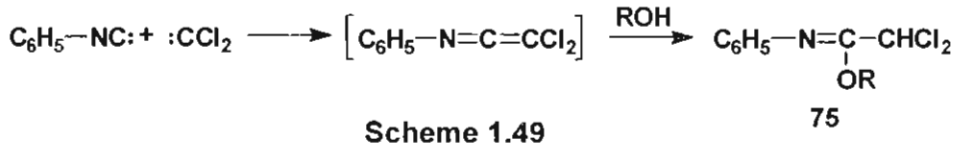
The reaction of isocyanides with hydrazoic acid offers a general synthetic route to 1-substituted tetrazoles **74**. The α-adduct of hydrazoic acid **73** is an unstable intermediate, which is spontaneously converted to **74** (Scheme 1.48).[63]



73 74

Scheme 1.48

Reaction of isocyanides with carbenes have been reported. When chloroform or ethyl trichloroacetate was added dropwise to a mixture of cyclohexyl isocyanide and a potassium alkoxide, *N*-cyclohexyldichloroacetoimidate **75**, presumably derived from *N*-cyclohexyl dichloroketenimine was obtained (Scheme 1.49).[64]

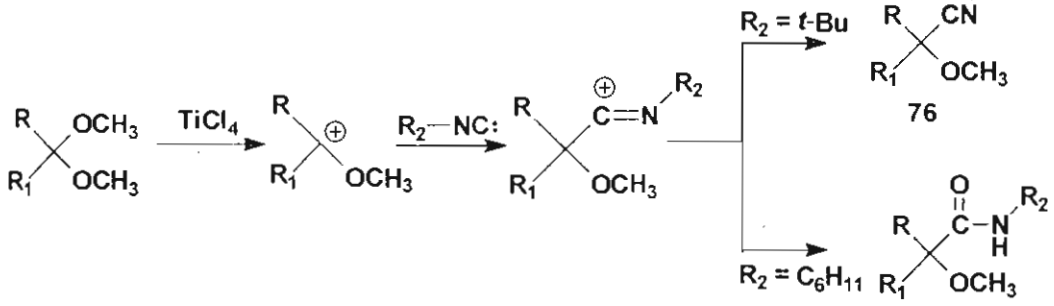


75

Scheme 1.49

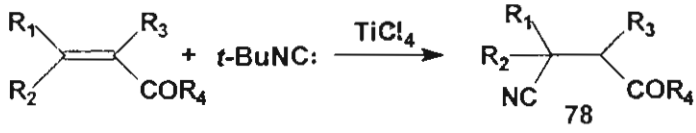
1.4.7 Nucleophilic Addition Reactions

A new cyanation of acetals with the *t*-butyl isocyanide-$TiCl_4$ system producing cyanohydrin ethers **76** or α-alkoxy carboxamide derivatives **77** has been reported by Ito *et al.* (Scheme 1.50).[65]



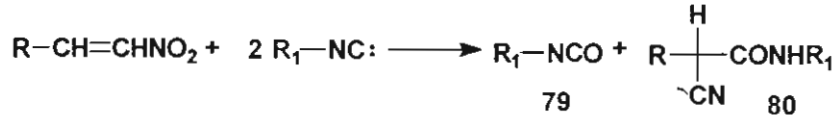
Scheme 1.50

With α-β unsaturated carbonyl compounds, conjugate hydrocyanation was found to take place (Scheme 1.51).[66]



Scheme 1.51

Isocyanides react with β-nitroalkene to produce isocyanate **79** and α-cyano α-substituted carboxamides **80** as shown in Scheme 1.52.[67]



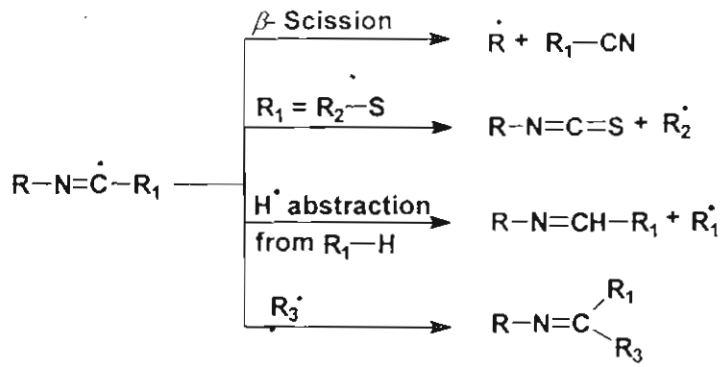
Scheme 1.52

1.4.8 Radical Reactions of Isocyanides

Radical reactions of isocyanides have become interesting recently. In all these reactions, we can consider the formation of an imidoyl radical **81** as a common intermediate (Scheme 1.53).

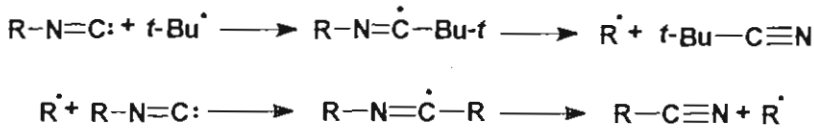
Scheme 1.53

This imidoyl radical can undergo various reactions as depicted in Scheme 1.54.



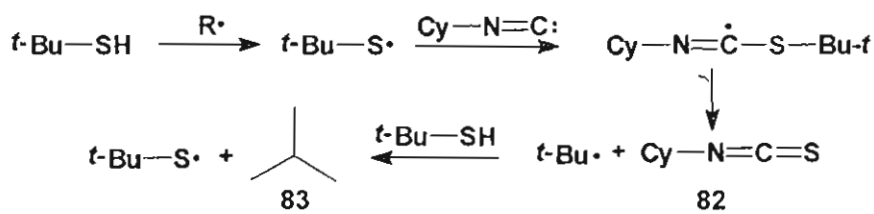
Scheme 1.54

The radical initiated vapor phase isomerization of an alkyl isocyanide to cyanides has been reported.[68] It was initiated by a radical obtained from the decomposition of di-*t*-butylperoxide. The isomerization is a chain reaction corresponding to Scheme 1.55.



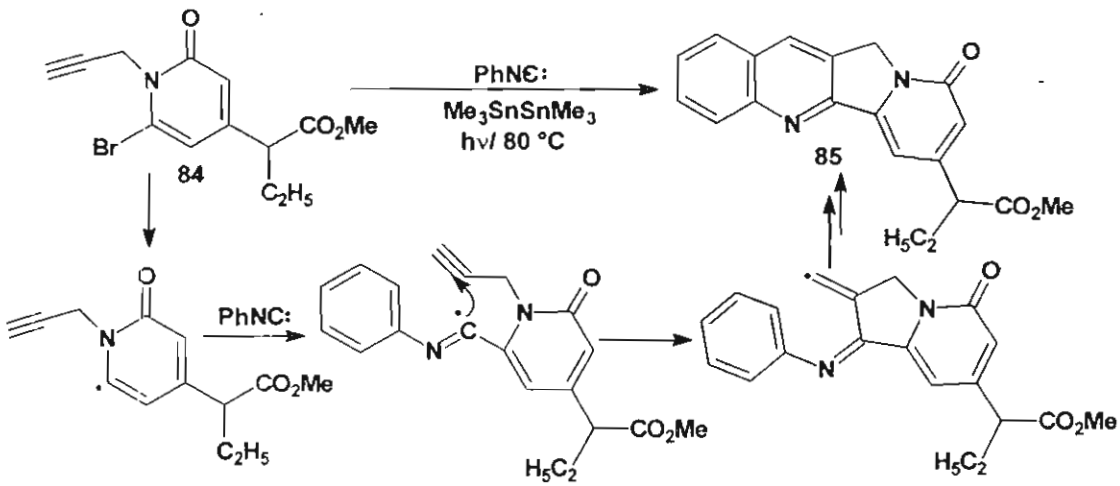
Scheme 1.55

Cyclohexyl isothiocyanate **82** and isobutane **83** are formed from the reaction of 2-methylpropane-2-thiol and cyclohexyl isocyanide (Scheme 1.56).[69]



Scheme 1.56

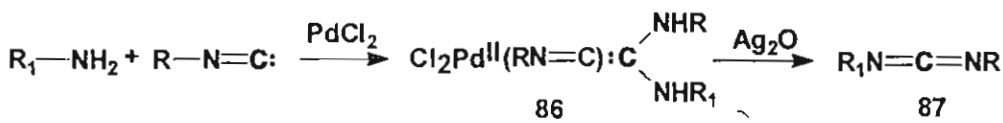
Recently, the radical initiated cyclization of isocyanides has been elegantly used by Curran *et al.* for the preparation of the key intermediate in the synthesis of (±) camptothecin.[18] Reaction of bromopyridone **84**, phenyl isocyanide and hexamethylditin afforded the intermediate **85** after two radical cyclizations and an oxidative rearomatization (Scheme 1.57).



Scheme 1.57

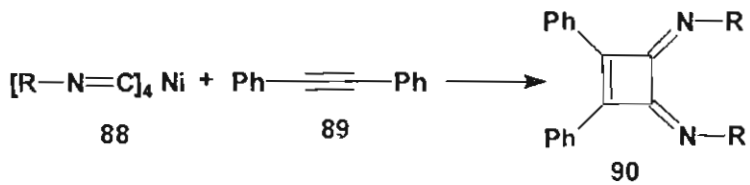
1.4.9 Metal-Isocyanide Complexes

The presence of a non bonding pair of electrons in an *sp*-hybridized orbital on the terminal carbon enables isocyanides to behave as a strong carbon ligand for transition metals. Most of the metal catalyzed reactions of isocyanides involve the heteroatom substituted carbene-metal as the essential intermediate. For example, the carbon coordinated Palladium(II) complex **86** has been obtained from the reaction of primary amines and isocyanides, which on oxidation with Ag_2O afforded carbodiimide **87** (Scheme 1.58).[70]



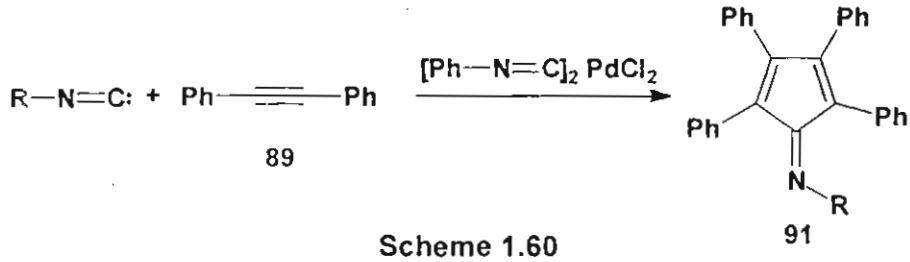
Scheme 1.58

Novel cycloaddition products are obtained from the reaction of isocyanides with diphenylacetylene in the presence of transition metal complexes. An equimolar mixture of **88** and diphenylacetylene **89** gave diiminocyclobutene **90** (Scheme 1.59).[71]



Scheme 1.59

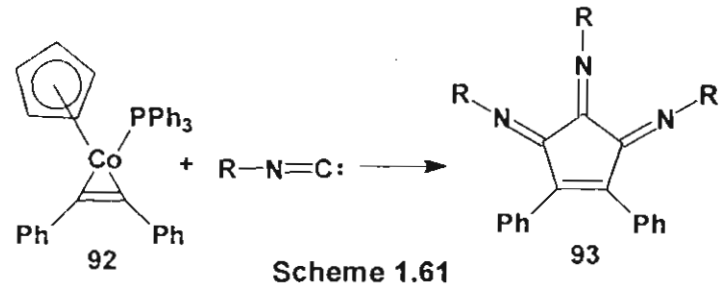
However, the reaction of isocyanides with **89** in the presence of a palladium-isocyanide complex afforded iminocyclopentadiene **91** by a [1+2+2] cycloaddition (Scheme 1.60).[71]



89 91

Scheme 1.60

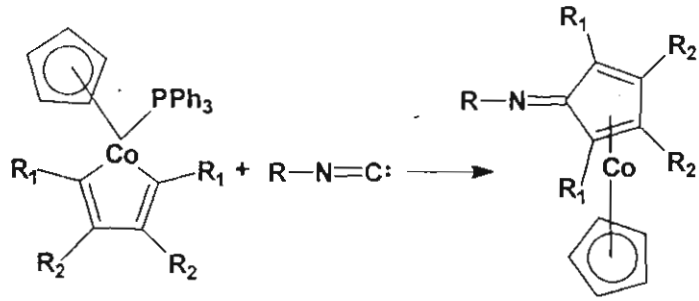
The reaction of 2,6-dimethylphenyl isocyanide with **92** yields 3,4,5-tris(2,6-dimethylphenylimino)diphenylcyclopentene **93** as shown in Scheme 1.61.[72]



92 93

Scheme 1.61

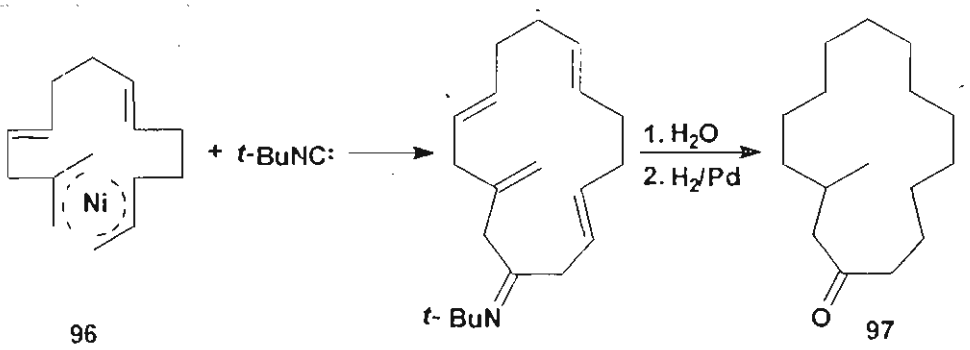
In certain cases the reaction products are isolated as metal complexes. For example, the reaction of **94** with isocyanides yields cobalt complexes **95** in good yields (Scheme 1.62).[73]



94 95

Scheme 1.62

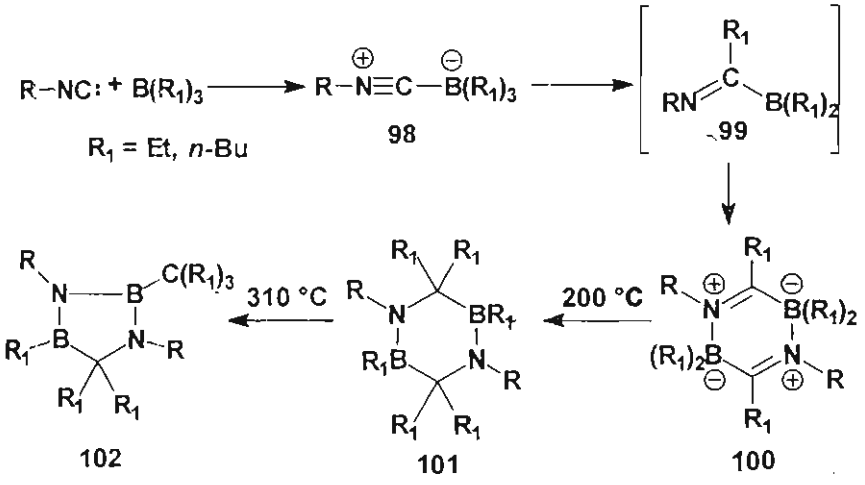
It has been shown that bis-π-allyl nickel complexes undergo insertion reaction with isocyanides to produce cyclic imines. Utilizing this reaction, Baker *et al.* have synthesized (±)muscone **97** from **96** and *t*-butyl isocyanide (Scheme 1.63).[74]



Scheme 1.63

1.4.10 Reaction with Boranes

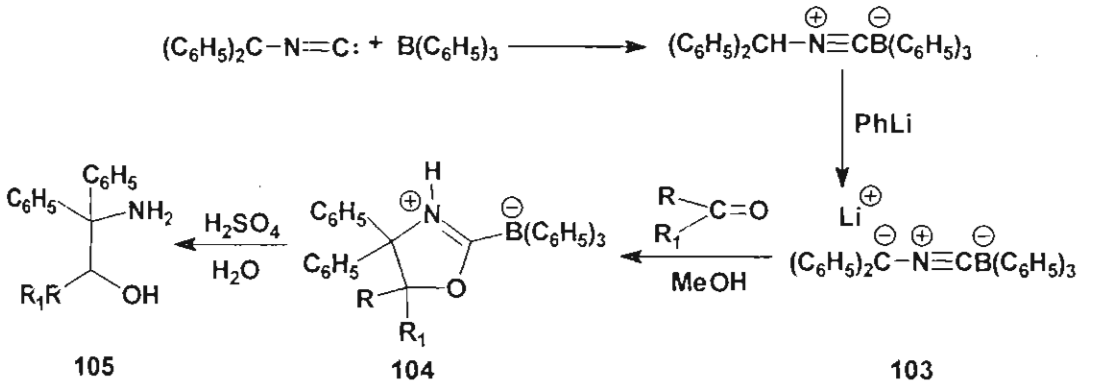
The Lewis base character of isocyanides towards a center of low electron density is manifested in the reactivity of alkyl or aryl isocyanides with diborane and alkyl or aryl boranes. In solution or neat, a 1:1 adduct **98** is formed in an irreversible reaction sequence. The reaction of phenyl isocyanide with ethyl or *n*-butyl borane at room temperature in ether afforded good yields of 2,5-dibora-2,5-dihydro pyrazine **100**.[75] When heated above 200 °C without solvents, **100** rearranges to give isomeric 2,5-dibora-3,6-dihydropyrazines **101**. It has been reported by Cassanova *et al.* that when **101** was heated at 310 °C in vacuum, a new compound **102**, possessing 1,3-diaza-2,4-diborolidine skeleton was formed (Scheme 1.64).[76]



Scheme 1.64

Bittner, Witte and Hesse[77] have devised a novel synthetic application based on adduct **98**. The 1:1 adduct formed from the reaction of benzhydryl isocyanide and triphenylborane on treatment with phenyl lithium is converted to

ylide **103**. This ylide is capable of acting as a 1,3-dipole and adds to aldehydes and ketones producing oxazolinium betaines **104**. More vigorous oxidation leads to β-aminoalcohols **105** (Scheme 1.65).



Scheme 1.65

1.5 Conclusion and Present Work

It is clear from the literature survey presented above that isocyanides are versatile reagents, which can exhibit a broad spectrum of reactivity ranging from multicomponent reactions to radical reactions. The formal divalency of the isocyanide carbon atom is responsible for the peculiarities of isocyanide chemistry. The facile transition of the divalent carbon atom to the tetravalent state makes isocyanides, the most ideal component for multicomponent reactions (MCRs). In this context, it is interesting to note that a range of isocyanide based MCRs have been devised by Ugi *et al.*[78] In contrast to the conventional multistep syntheses which correspond to sequences of chemical reactions of two compounds per each step, MCRs offer the targeted products just by mixing three or more starting compounds in one pot. Such syntheses need minimal preparative work and often give high yields of pure products. MCRs correspond to collection of subreactions of two compounds, which are well known reactions; however, their various combinations can still be new reactions leading to the final products in one pot. Thus, in terms of productivity, number of steps and reagents, MCRs come close to the idea of an 'ideal synthesis' as defined by Wender.[79]

In an attempt to devise novel multicomponent reactions, we investigated the formation zwitterions from activated acetylenes with various nucleophiles

and their trapping with a third component in one pot. The focus of our attention has been zwitterion formation from DMAD with isocyanides. The first phase of the investigation was mainly concerned with the interception of the 1:1 zwitterionic intermediate with aldehydes, which forms the subject matter of the second chapter.

The second phase of the investigation was concerned with the reaction of the zwitterionic intermediate with 1,2- and 1,4-quinones and the details are presented in the third chapter.

The last phase of the work explores the possibility of intercepting the zwitterionic intermediate with the highly reactive C=N double bond of *N*-tosylimines. The results of these studies constitute the fourth chapter.

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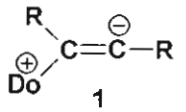
Chapter 2

The Reaction of Cyclohexyl Isocyanide and Dimethyl Acetylenedicarboxylate with Aldehydes: A Novel Synthesis of 2-Aminofurans

2.1 Introduction

The pronounced reactivity of the carbon-carbon triple bond towards nucleophilic reagents is of great significance in organic synthesis. The addition of donors that contain no active hydrogen are generally initiated *via* a dipolar primary complex **1** (Figure 2.1), which can undergo rearrangement, cyclization or addition reactions to result in a stabilized product.[1]



1

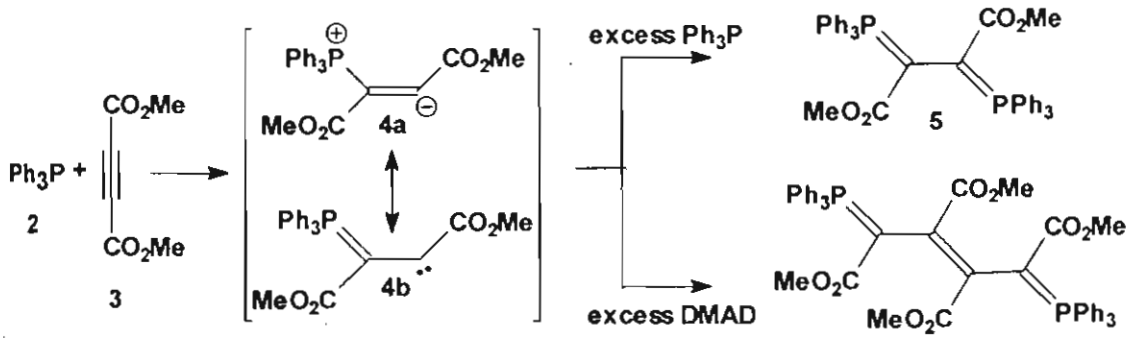
R = CO_2R; CN; CF_3; SO_2R
Do = Donor

Figure 2.1

Various nucleophiles like triphenylphosphine, pyridine, amines, imines, enamines, dimethyl sulfoxide, phosphoranes, isocyanides *etc.* can invoke the zwitterionic intermediate formation. A brief account of these reactions is given in the following sections.

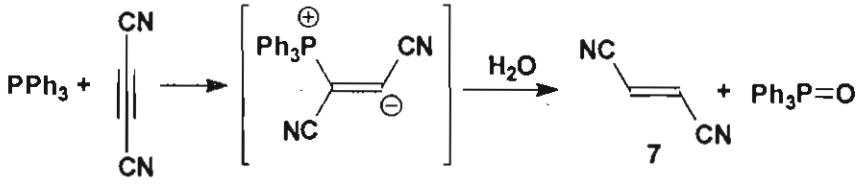
2.2 Addition of Phosphorus Compounds

The reactivity of triphenylphosphine towards various activated acetylenes has been studied in detail by Tebby and co-workers. It has been shown that Ph_3P adds to dimethyl acetylenedicarboxylate (DMAD) to form a 2:1 adduct, a dialkylidene diphosphorane **5** in quantitative yield. In the absence of excess of phosphine, **6** was isolated (Scheme 2.1).[2]



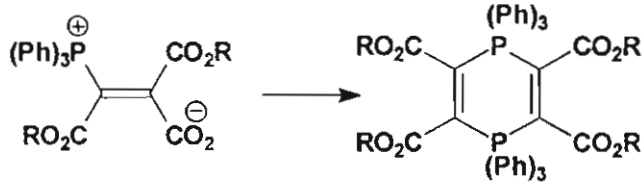
Scheme 2.1

If the reaction was carried out in a protic solvent such as water, the solvent gets added to the zwitterionic species. This is illustrated by the following reaction leading to fumaronitrile **7** and triphenylphosphine oxide (Scheme 2.2).[3]



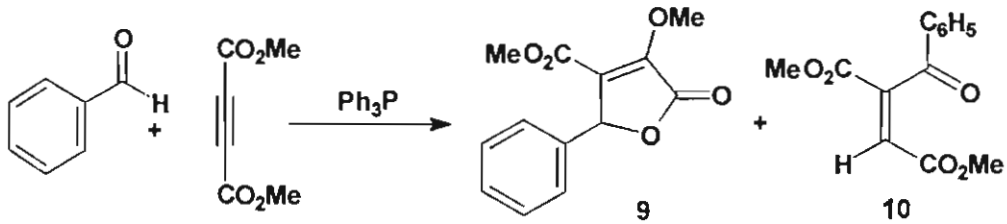
Scheme 2.2

Attempts have been made to trap the zwitterionic intermediate **4** with CO_2 in which case, a betaine is formed. Subsequent decarboxylation gives a product **8** as illustrated in Scheme 2.3.[4]



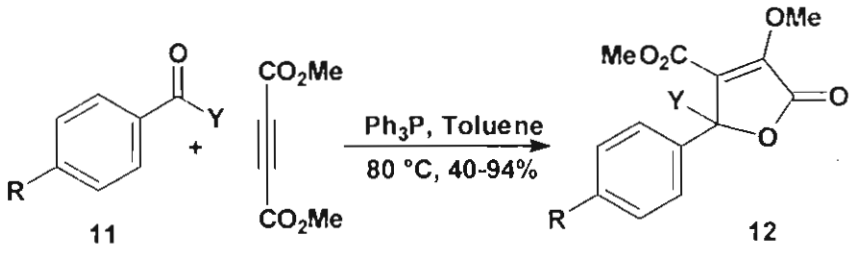
Scheme 2.3 **8**

Similar interception of the 1:1 intermediate derived from DMAD and triphenylphosphine, with benzaldehyde has been reported. Products **9** and **10** were isolated in low yields (Scheme 2.4).[5]



Scheme 2.4

This protocol has been modified recently by Nozaki *et al.* with activated carbonyl compounds such as α-ketoesters, α-ketonitriles *etc.* The use of catalytic amount of triphenylphosphine afforded unsaturated lactones **12** in moderate to high yields (Scheme 2.5).[6]



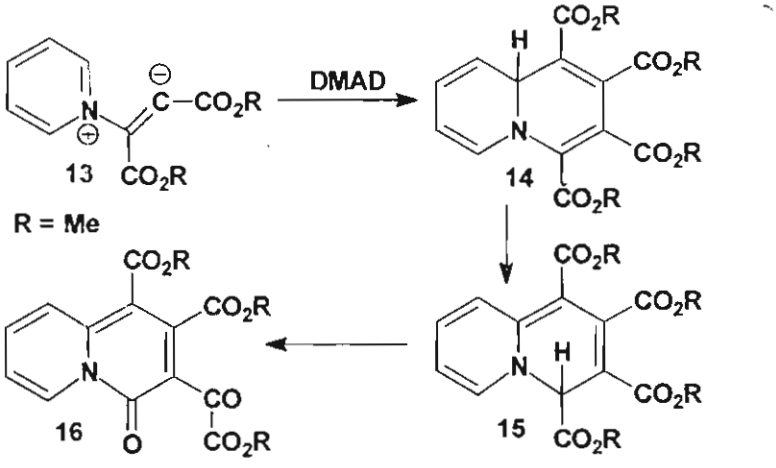
R = NO_2, Cl, Me
Y = CO_2Me, CF_3, CN

Scheme 2.5

We have shown that the zwitterionic intermediate generated by the reaction of triphenylphosphine and DMAD, undergoes a facile addition to 1,2- and 1,4-benzoquinones to afford highly functionalized novel unsaturated γ-spirolactones in good yields (details are given in Chapter 3, Section 3.3).

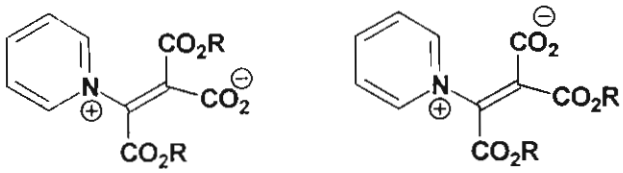
2.3 Addition of Pyridine

As early as 1932, it was shown by Diels and Alder[7] that pyridine can react with DMAD to form adducts. However, the structure of the stable end product was conclusively established only in 1963 by Acheson *et al.* (Scheme 2.6).[8]



Scheme 2.6

In this context, it is noteworthy that Acheson and Plunkett have been able to intercept the 1,4-dipolar species with CO_2, resulting in the isomeric betaines **17** and **18** (Figure 2.2).[9]

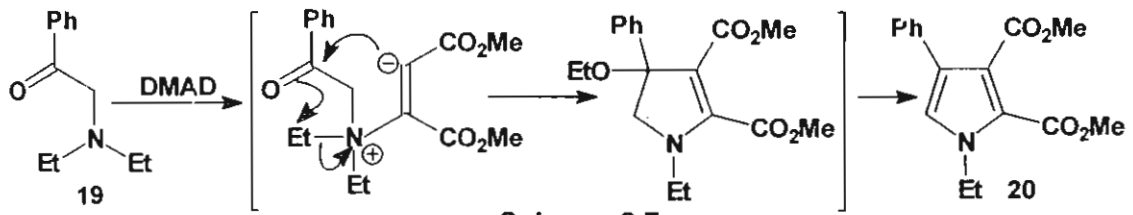


17 18

Figure 2.2

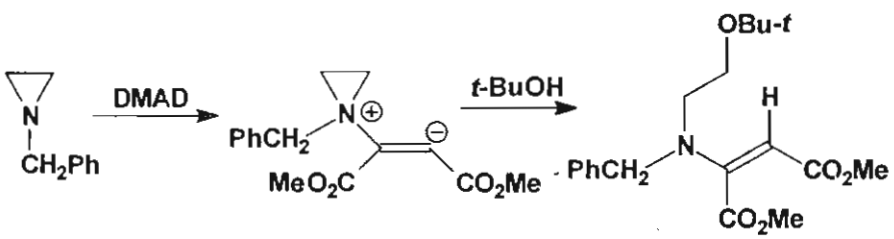
2.4 Addition of Tertiary Amines

Tertiary amines are known to add to activated acetylenes. ω-Diethyl aminoacetophenone **19**, for example, reacts with DMAD in dimethyl sulfoxide to give the pyrrole **20** (Scheme 2.7).[10]



Scheme 2.7

Aziridines react with acetylenic esters to give products, which arise through either a C-N or C-C bond cleavage. *N*-Benzyl aziridine **21** reacts with DMAD in *t*-BuOH to afford the ether derivative **22** by a C-N bond cleavage (Scheme 2.8).[5]

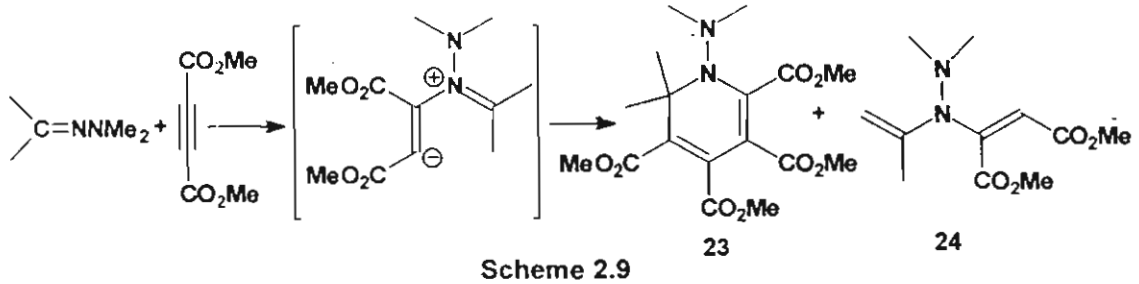


21 22

Scheme 2.8

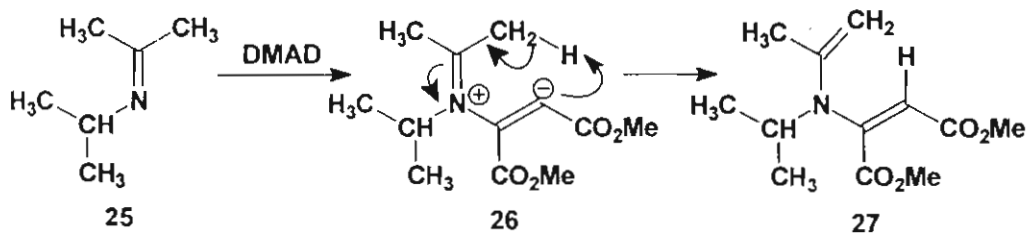
2.5 Addition of Imines

The reaction of imino compounds and activated alkynes has received considerable attention. There are possibilities in the zwitterion for internal or external attacks and these are implicit in several syntheses of heterocycles. A representative example is given in Scheme 2.9.[11]



Scheme 2.9

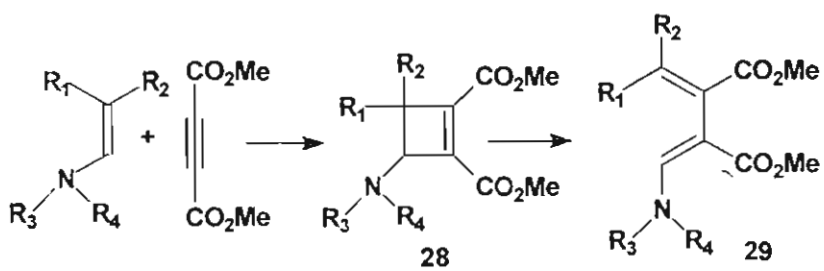
The reaction of ketimine **25** with DMAD gives dimethyl *N*-(1-methyl-vinyl)isopropylaminomaleate **27** presumably through the intermediacy of **26** (Scheme 2.10). [12]



Scheme 2.10

2.6 Addition of Enamines

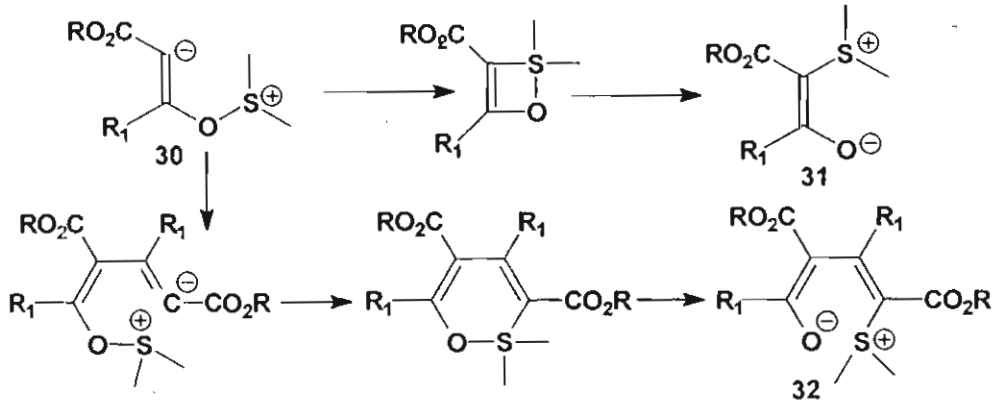
The reaction of enamines with activated alkynes has been investigated by a number of groups.[13] The reaction generally proceeds *via* a four membered ring **28**, which undergoes ring cleavage to form the dienamine **29** (Scheme 2.11).



Scheme 2.11

2.7 Addition of Sulfur Compounds

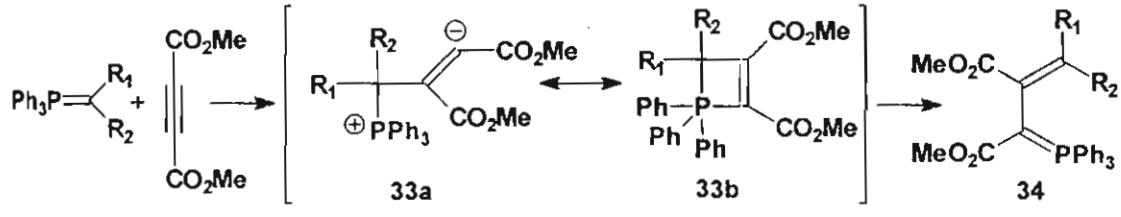
A similar transition state involving a 1,4-dipolar species is accountable for the reaction of activated triple bonds with dimethyl sulfoxide. Methyl propiolate and DMAD give the adducts **31** and **32** when heated in dimethyl sulfoxide. The formation of these products can be explained by invoking a zwitterionic intermediate **30** (Scheme 2.12).[14]



Scheme 2.12

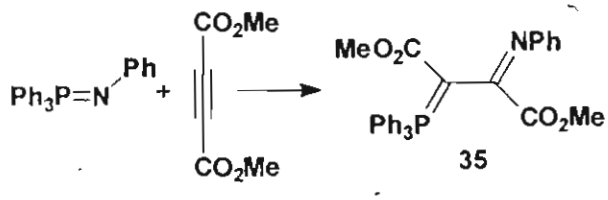
2.8 Addition of Phosphoranes

Alkylidenetriphenyl phosphoranes are known to react with DMAD to produce ylide **34** *via* the intermediate betaine **33a** or phosphacyclobutane **33b** (Scheme 2.13).[15]



Scheme 2.13

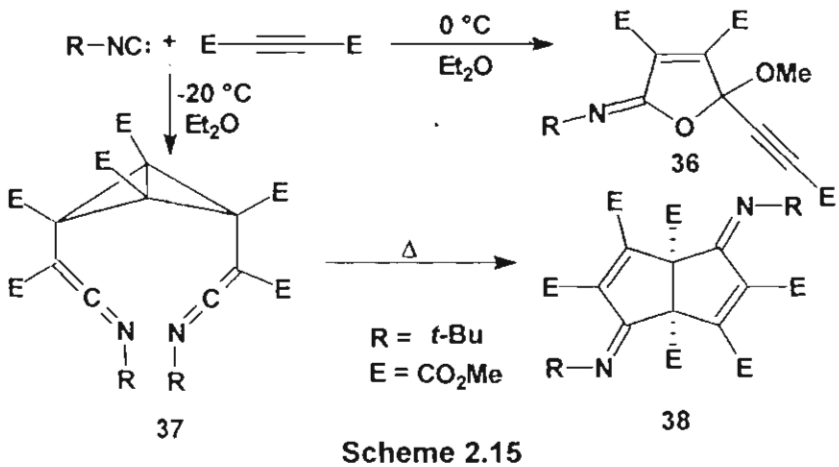
Iminophosphoranes are known to react with DMAD forming 1:1 adducts which have been assigned the structure **35** (Scheme 2.14).[16]



Scheme 2.14

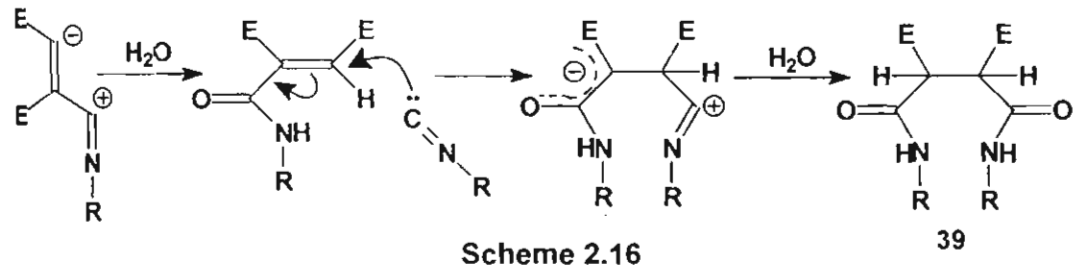
2.9 Addition of Isocyanides

The addition of nucleophilic carbenes such as isocyanides to DMAD has been investigated in detail. Winterfeldt has shown that the reaction of *t*-butyl isocyanide with DMAD at 0 °C gave a 1:2 adduct **36** whereas at –20 °C the reaction led to an interesting bicyclobutane derivative **37**, which on thermal isomerization transformed into a pentalene derivative **38** (Scheme 2.15).[17]



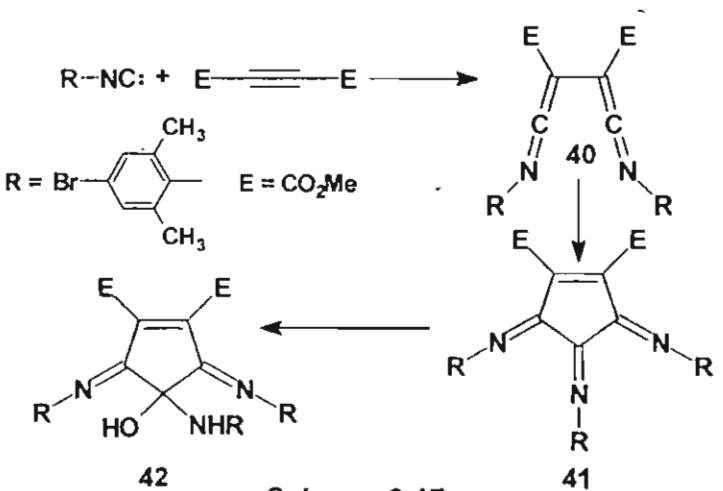
Scheme 2.15

When the reaction was carried out in the presence of a protic solvent such as water, a symmetrical product **39** was isolated (Scheme 2.16).



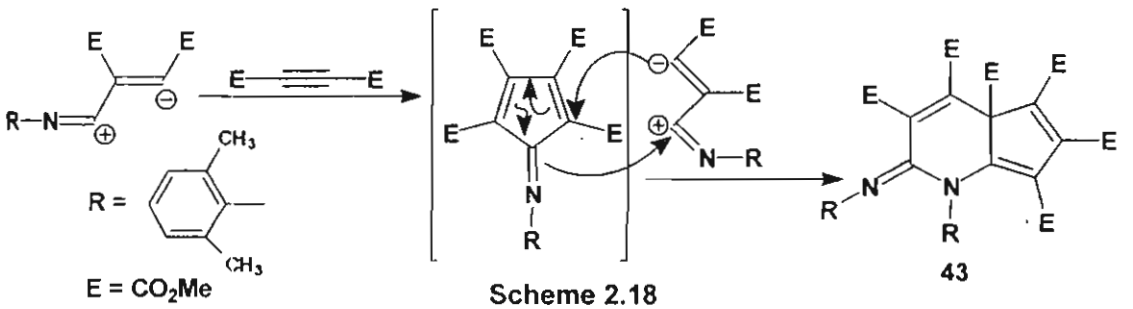
Scheme 2.16

Takizawa and co-workers have shown that cyclopentenetriimine derivatives **41** are formed from the reaction of aromatic isocyanides such as 4-bromo-2,6-dimethylphenyl isocyanide and acetylene derivatives in refluxing benzene. When the reaction was carried out at 0-5 °C, the possible intermediate of this reaction **40** was isolated in addition to compound **42** (Scheme 2.17).[18]



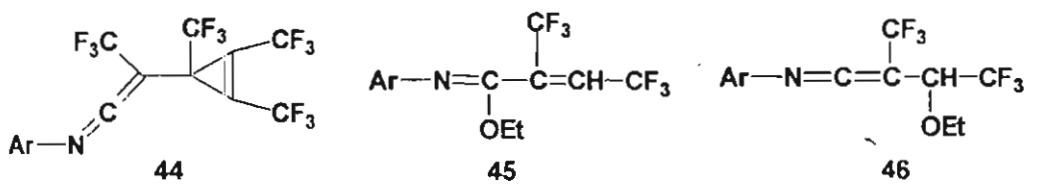
Scheme 2.17

Interestingly, it was found that when the reaction of 2,6-dimethylphenyl isocyanide and dimethyl acetylenedicarboxylate was carried out in benzene at room temperature for 24 h, a 2:3 adduct **43** along with the isomerized products were isolated (Scheme 2.18).[19]



Scheme 2.18

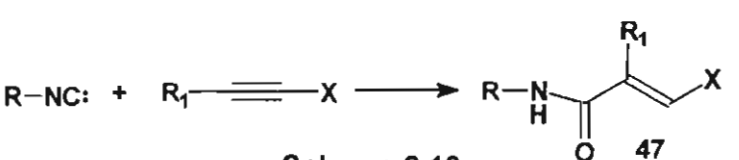
In inert solvents, isocyanides react with 2 moles of hexafluoro-2-butyne to produce cyclopropenyl ketenimines **44**. When the reaction was carried out in ethanol as solvent, two different 1:1:1 adducts (isocyanide:butyne:ethanol), an imino ester **45** and a ketenimine **46** were isolated (Figure 2.3).[20]



44 45 46

Figure 2.3

Similarly, the reaction of 1-halogenoacetylenes with isocyanides in boiling 10% aqueous MeOH gave *N*-substituted 3-halogenoacrylamides **47** (Scheme 2.19).[21]



47

Scheme 2.19

In all these cases, it is reasonable to assume the prior formation of a 1:1 intermediate, which might posses predominantly carbanion (**48a**) or carbene character (**48b**) or perhaps resemble a cyclopropenone imine (**48c**) as given in figure 2.4.[20b]

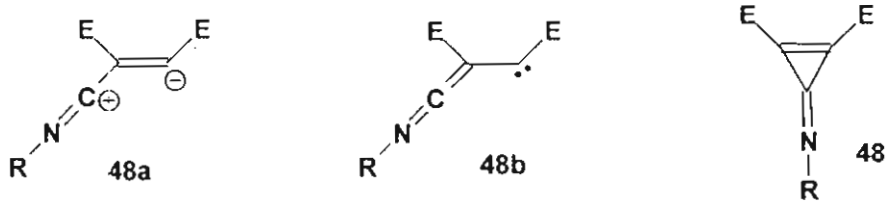
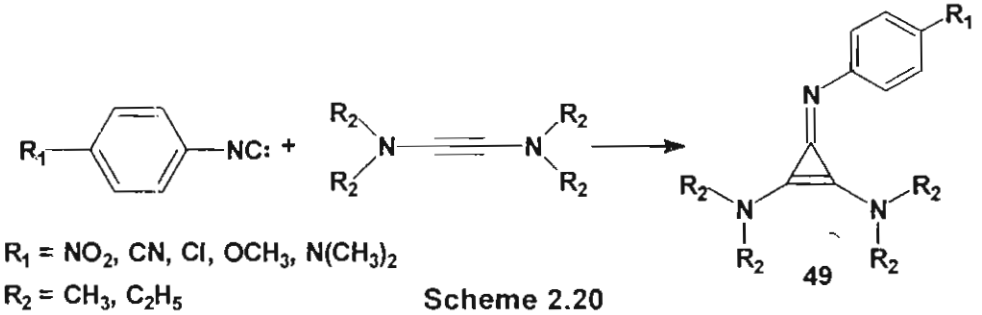


Figure 2.4

Krebs *et al.* have isolated the cyclopropenone imines **49** from the reaction of aryl or aroyl isocyanides with yne diamines in a [2+1] cycloaddition reaction. Electron withdrawing substituents on the aryl group were found to accelerate the reaction (Scheme 2.20).[22]



Scheme 2.20

2.10 Statement of the Problem

Against the literature background given above and in the context of our general interest in the synthesis of heterocyclic compounds by the reaction of dipolar species with carbonyl compounds,[23] we were intrigued by the possibility of trapping the zwitterionic intermediate derived from activated acetylenes and isocyanide with a third component. It was assumed that such a reaction sequence would lead to novel heterocyclic systems, constituting novel multicomponent reactions. Although previous attempts to trap the zwitterionic intermediate with various olefinic dipolarophiles such as dimethylmaleate, cyclohexene *etc.* have failed,[22] we reasoned that experiments using more appropriate trapping agents would be successful.

Following the lines of an ideal MCR,[24] it was expected that the reaction of DMAD and isocyanide will produce a 1:1 intermediate that may react with a

third component (for example, carbonyl compounds) which does not react irreversibly with either isocyanide or DMAD. The rational design here is based on the fact that isocyanides have a high affinity towards activated acetylenes rather than to carbonyl compounds. In this context, it may be mentioned that although the existence of α-iminooxiranes have been suggested from the reaction of isocyanides with carbonyl compounds, to date, no successful attempts at isolating any products from such reactions have been reported.

We have undertaken a thorough investigation of the addition of the zwitterionic intermediate of isocyanide and DMAD with a number of aldehydes. The results of our investigations validating the assumption and the usefulness of the process, leading to novel aminofuran derivatives are presented here.

2.11 Results and Discussion

The aldehydes selected for the studies are listed below (Figure 2.5).

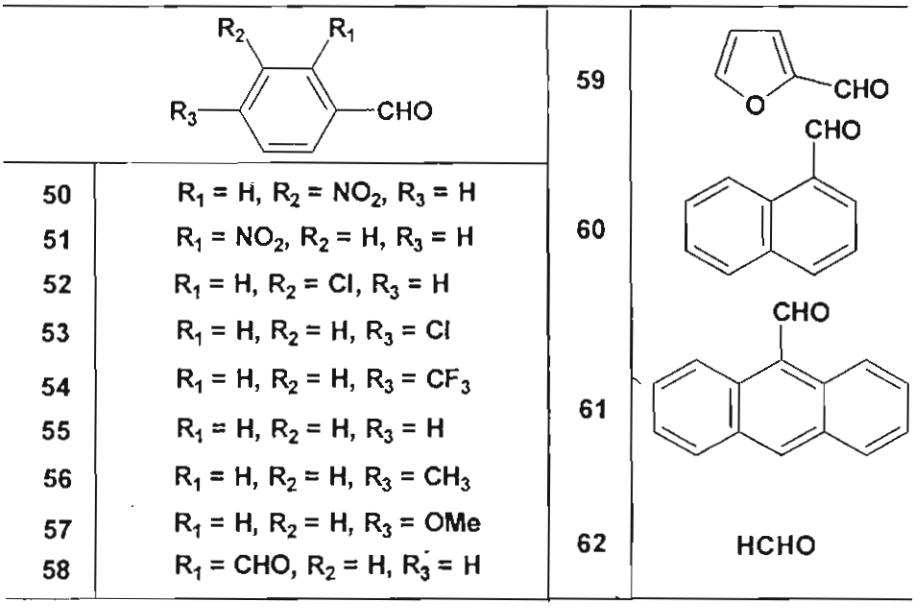
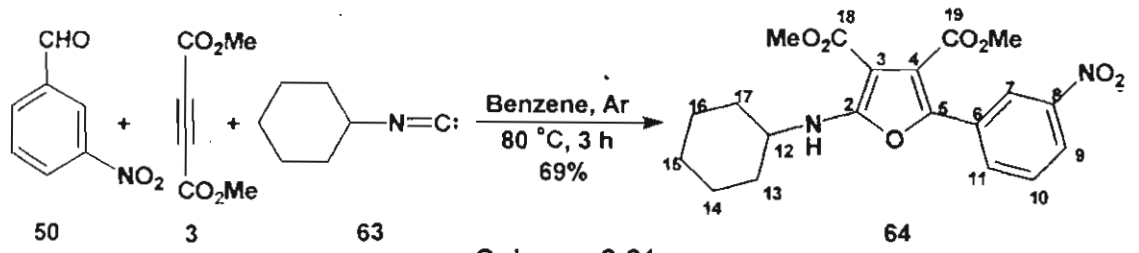


Figure 2.5

Our investigations were initiated with 3-nitrobenzaldehyde **50**, which on treatment with DMAD in presence of stoichiometric amount of cyclohexyl isocyanide **63** in refluxing benzene afforded a product characterized as the aminofuran **64** in 69% yield (Scheme 2.21).[25]



Scheme 2.21

The structure of the product **64** was elucidated by spectroscopic and analytical data. The IR spectrum showed strong absorption at 3367 cm^{-1} indicating the presence of amine functionality. The sharp bands at 1726 and 1663 cm^{-1} were assigned to the two ester carbonyls. In the ^1H NMR spectrum, the signals due to methoxy groups were observed at δ 3.79 and 3.94 as two singlets and the amine hydrogen atom resonated as a doublet at δ 6.70 (exchangeable by D_2O). The tertiary cyclohexyl proton displayed a multiplet at δ 3.79 overlapped with one of the methoxy groups; other protons were discernible as multiplets between δ 1.39-2.07. In the ^{13}C NMR spectrum, the two ester carbonyls were observed at δ 164.62 and 165.20. The methylene carbons of the cyclohexyl group appeared at δ 24.58, 25.53 and 33.59 and the tertiary carbon atom attached to the -NH resonated at δ 51.34. The methoxy carbons were observed at δ 51.70 and 52.84. The signals due to C-3 and C-4 were observed at δ 161.51 and 148.79 and those corresponding to C-2 and C-5 were discernible at δ 116.34 and 88.23 respectively. In the DEPT-135 NMR analysis of the compound **64**, peaks at δ 24.58, 25.53 and 33.59 were negative and the peaks at δ 51.34, 51.70, 52.84, 119.21, 121.73, 129.71 and 130.95 were positive. The ^1H-^{13}C connectivity was established unambiguously by 2D-HETCORE analysis. The cross peaks between δ 24.58, 25.53 and 33.59 with δ 1.39-2.07 shows the presence of cyclohexyl group. The cross peaks at δ 3.79 and 3.94 with δ 51.34 and 51.70 confirm the presence of two methoxy groups. The aromatic protons at δ 7.51, 7.80, 8.06 and 8.33 have cross peaks with the carbon signals at δ 119.21, 121.73, 129.71 and 129.75. The assigned structure was further supported by satisfactory elemental analysis.

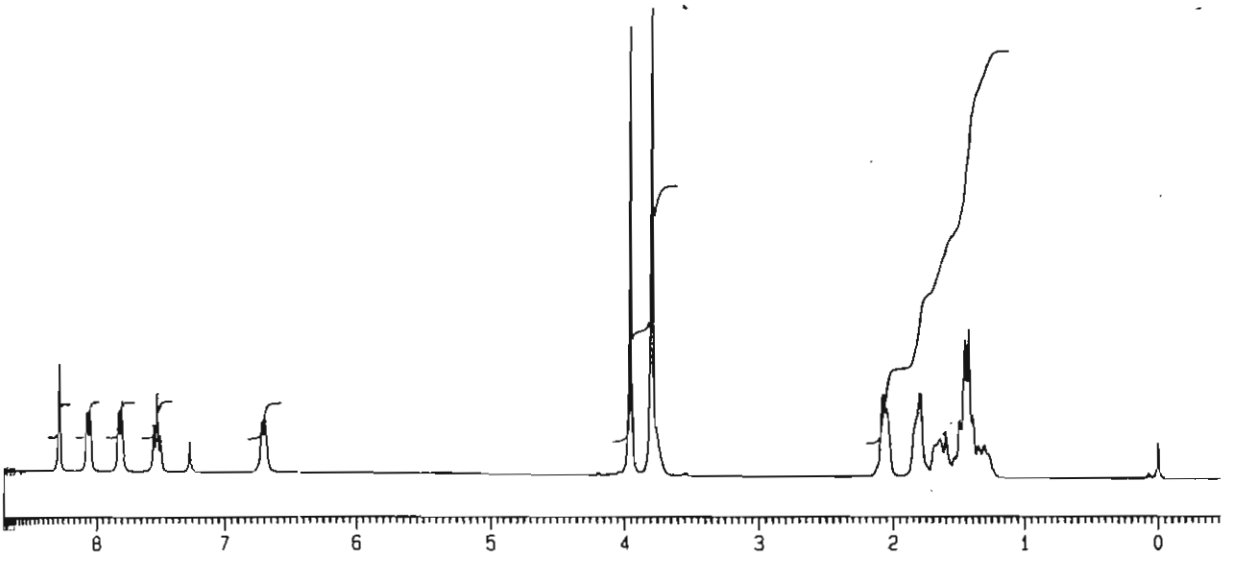


Figure 2.6 ^{1}H NMR spectrum of aminofuran 64

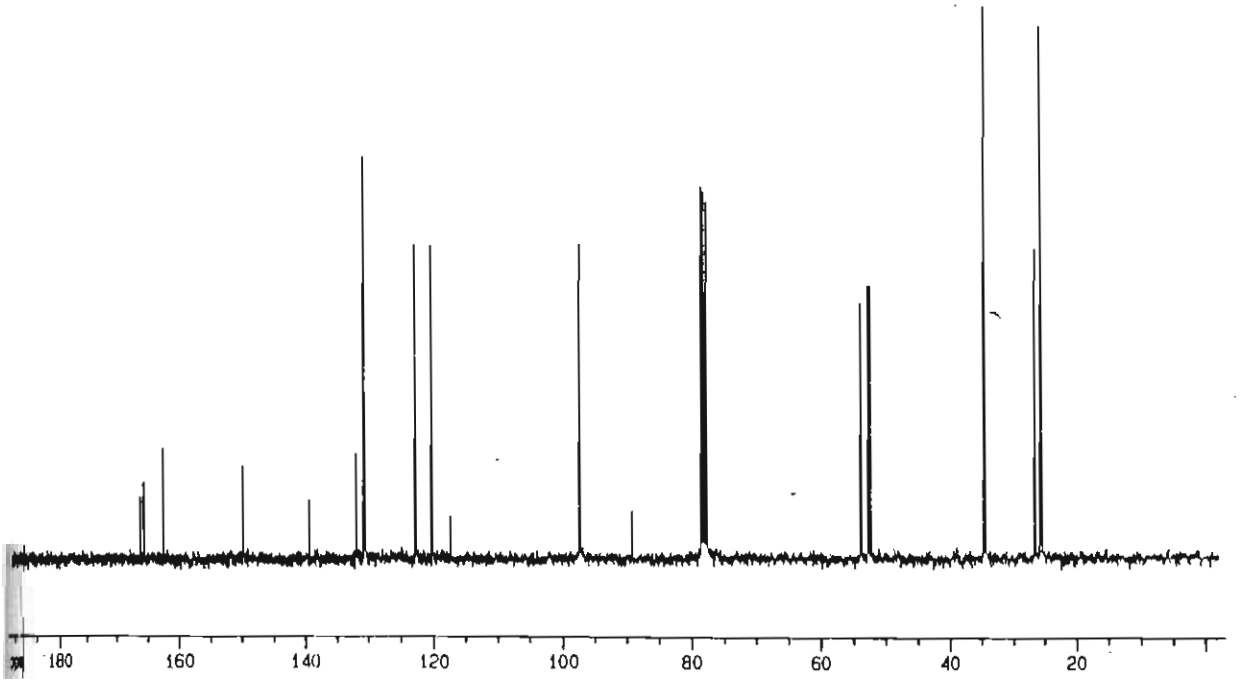


Figure 2.7 ^{13}C NMR spectrum of aminofuran 64

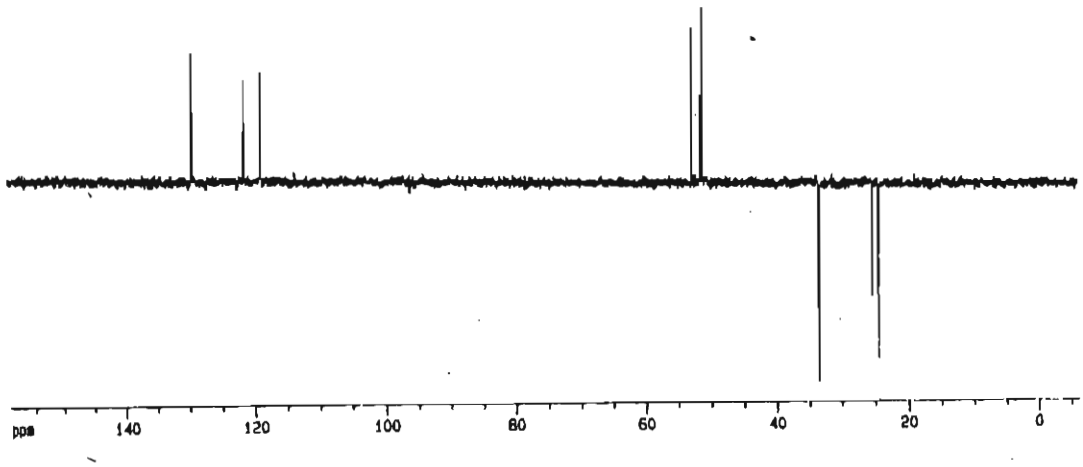


Figure 2.8 DEPT-135 NMR spectrum of aminofuran 64

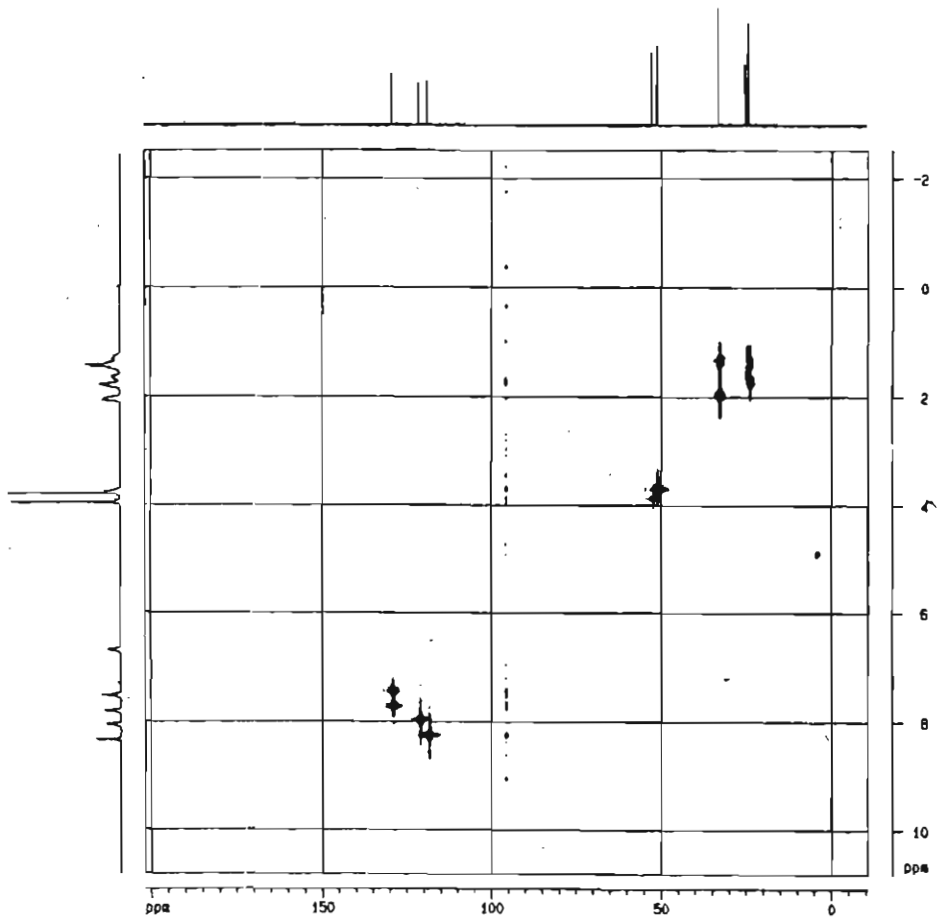
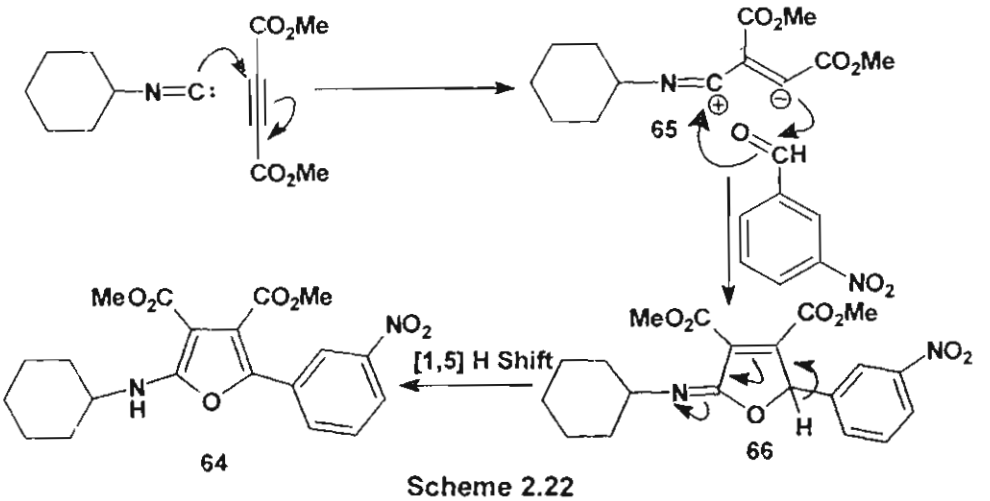


Figure 2.9 2D-HETEROCOSY spectrum of aminofuran 64

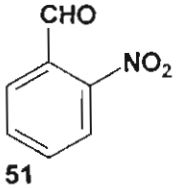
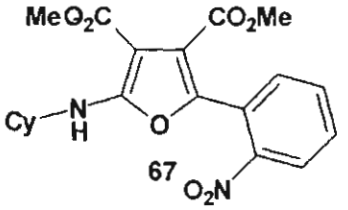
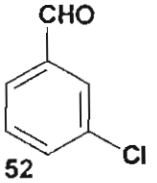
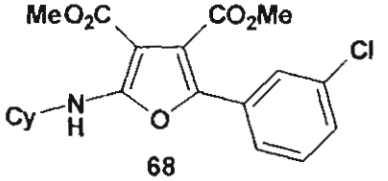
Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate **65** between cyclohexyl isocyanide and DMAD, which adds to the aldehyde carbonyl leading to a dipolar species. Cyclization of the latter leads to the dihydrofuran derivative **66**. Subsequently, it undergoes a [1,5] hydrogen shift to yield the aminofuran derivative **64** as the end product. Alternatively, a cycloaddition of the zwitterion to the C=O can also lead to the dihydrofuran derivative (Scheme 2.22).



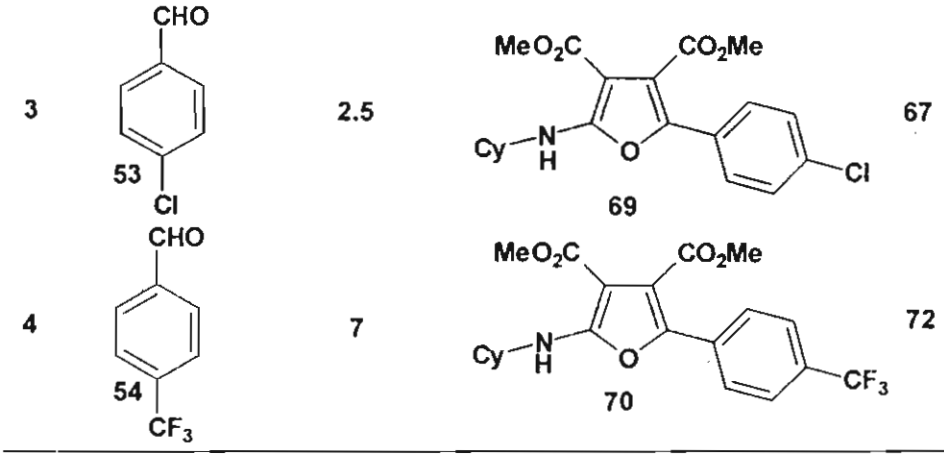
Scheme 2.22

Similar reactivity was observed with other aromatic aldehydes such as 2-nitrobenzaldehyde **51**, 3-chlorobenzaldehyde **52**, 4-chlorobenzaldehyde **53**, 4-trifluromethylbenzaldehyde **54**, which underwent facile reaction with DMAD and cyclohexyl isocyanide yielding the corresponding aminofuran derivatives in good yields. The results obtained are presented in Table 2.1.

Table 2.1

Entry	Aldehyde	t(h)	Product	Yield(%)*
1	 51	3	 67	74
2	 52	2	 68	61

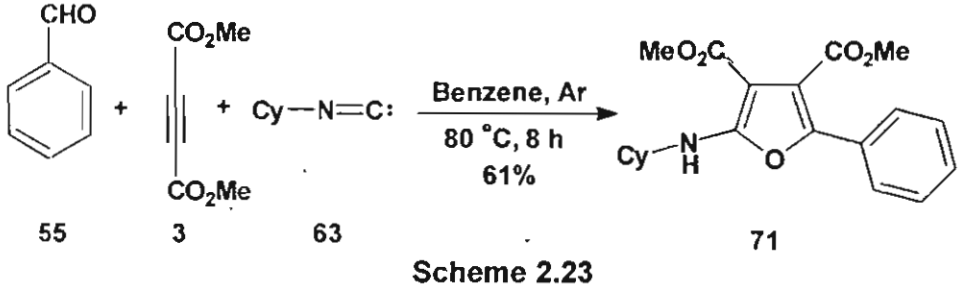
contd.



Reaction conditions: Benzene, Argon, Reflux. Where Cy = Cyclohexyl
*** isolated yield**

In all the cases, the compounds were completely characterized and their structure established by spectroscopic methods. The aminofurans **67-70**, showed characteristic carbomethoxy carbonyls both in the IR and ^{13}C NMR spectra. All other signals were in good agreement with the assigned structure.

Treatment of benzaldehyde **55** with dimethyl acetylenedicarboxylate in the presence of cyclohexyl isocyanide in anhydrous benzene gave the aminofuran **71** in 61% yield (Scheme 2.23).

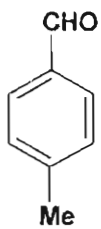
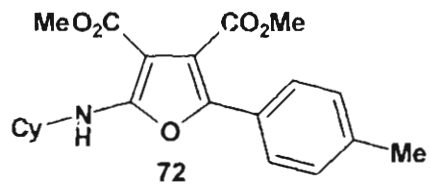
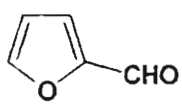
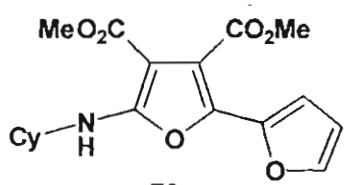
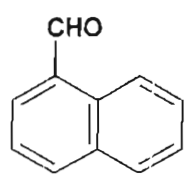
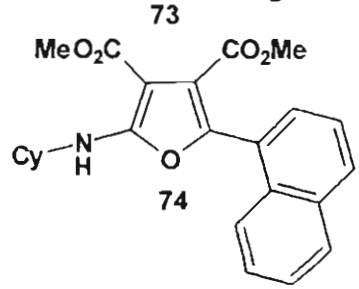
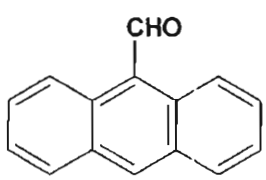
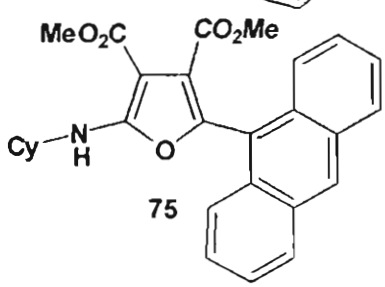
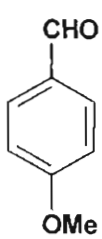
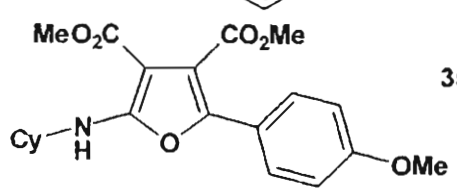


Scheme 2.23

The IR spectrum of **71** showed the two ester carbonyls at 1735 and 1681 cm^{-1}. The absorption at 3353 cm^{-1} can be attributed to the amine functionality. In the ^1H NMR, the carbomethoxy groups resonated as singlets at δ 3.78 and 3.90 respectively and the -NH proton as a doublet at δ 6.60 (exchangeable by D_2O). In the ^{13}C NMR spectrum, the carbomethoxy carbonyls resonated at δ 164.95 and 165.89; the corresponding methyl carbons were discernible at δ 51.17 and 51.59. All other signals were in good agreement with the assigned structure.

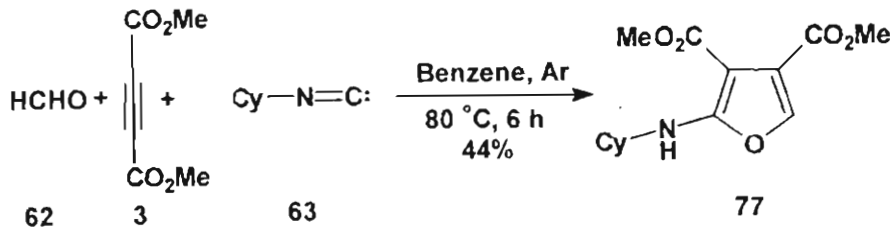
Analogous reaction was observed with 4-methylbenzaldehyde **56**, furfural **59**, 1-naphthaldehyde **60** and 9-anthraldehyde **61**, which on treatment with DMAD and cyclohexyl isocyanide furnished the corresponding aminofurans in good yields. Even the electron rich *p*-anisaldehyde **57** underwent facile reaction. The results are summarized in Table 2.2. As usual, the products **72-76** were completely characterized by spectroscopic analysis.

Table 2.2

Entry	Aldehyde	t(h)	Product	Yield(%)*
1	 **56**	8	 **72**	43
2	 **59**	3	 **73**	68
3	 ***60***	8	 **74**	54
4	 **61**	8	 **75**	57
5	 **57**	9	 **76**	35

Reaction conditions: Benzene, Argon, Reflux. Where Cy = cyclohexyl
*** isolated yield**

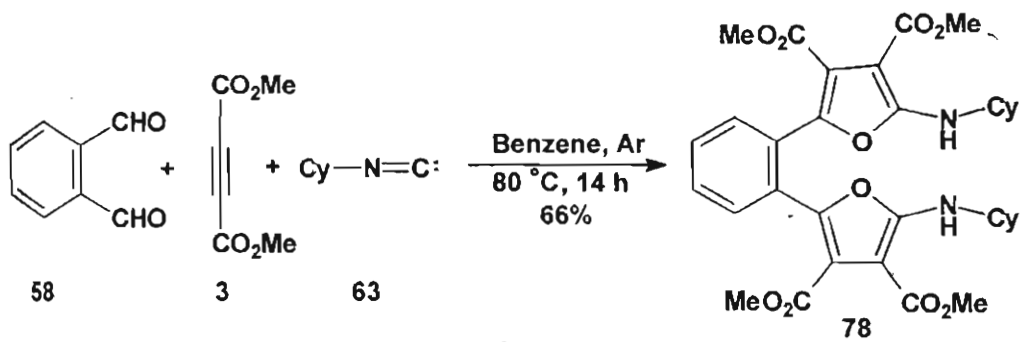
Paraformaldehyde **62** on reaction under similar conditions afforded the product 77 in 44% yield (Scheme 2.24).



Scheme 2.24

As described for the other aminofurans, the IR spectrum of **77** showed strong absorptions at 1744 and 1676 cm^{-1} revealing the presence of two carbomethoxy carbonyls. The absorption at 3355 cm^{-1} can be attributed to the secondary amino group. The ^1H NMR showed two sharp singlets at δ 3.71 and 3.73 corresponding to the methoxy groups. The furanyl proton resonated as a singlet at δ 7.15 and the amino proton as a doublet at δ 6.71. In the ^{13}C NMR spectrum, the two carbonyl carbons appeared at δ 163.47 and 165.44. The carbon atoms bearing the ester groups were seen at δ 84.35 and 118.03. All other signals were also in good agreement with the assigned structure.

Interestingly, phthalaldehyde **58** when treated with two equivalents of DMAD and isocyanide afforded the bis adduct **78** in 66% yield (Scheme 2.25).



Scheme 2.25

The IR spectrum showed absorptions at 3357, 1749 and 1678 cm^{-1} due to the NH group and carbomethoxy carbonyls. ^1H NMR spectrum of **78** showed the two carbomethoxy groups as singlets at δ 3.76 and 3.80. The four aromatic

protons were visible as multiplets in the region δ 7.34-7.59. In the ^{13}C NMR spectrum, the two ester carbonyls were seen at δ 164.64 and 164.83. All other signals were in good agreement with the assigned structure.

2.12 Conclusion

In conclusion, we have found that the one pot reaction of isocyanides and DMAD with aldehydes leads to a facile synthesis of aminofuran derivatives. It may be mentioned that recently aminofurans have been found to undergo facile Diels-Alder reactions leading to hexahydroindolinones;[26] they also serve as useful intermediates in the synthesis of a variety of aromatic as well as aliphatic molecules.[27] It is conceivable that the novel three component reaction described herein will be applicable to the synthesis of a variety of heterocycles.

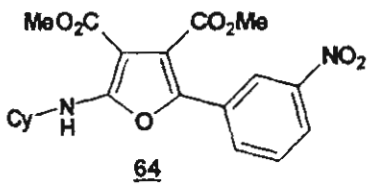
2.13 Experimental Details

General: Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^1H) and 75 (^{13}C) MHz respectively on a Bruker Avance DPX-300 MHz NMR spectrometer. Chemical shifts are reported (δ) relative to TMS (^1H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constant (*J*) is reported in hertz (Hz). Mass spectra were recorded under EI/HRMS (at 5000) resolution using Auto Spec. M mass spectrometer. IR spectra were recorded on Nicolet Impact 400D FT–IR spectrophotometer. Elemental analyses were performed on a Perkin Elmer-2400 Elemental Analyzer. Dimethyl acetylenedicarboxylate was purchased from Aldrich Chemical Co. and was used without further purification. Cyclohexyl isocyanide was prepared by a reported procedure.[28] Commercial grade solvents were distilled prior to use. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate as the binder. Gravity column was performed using 100-200 mesh silica gel and mixtures of hexane-ethyl acetate were used for elution.

Dimethyl 2-(cyclohexylamino)-5-(3-nitrophenyl)-3,4-furandicarboxylate 64

6/2023

A mixture of 3-nitrobenzaldehyde (200 mg, 1.32 mmol) and DMAD (207 mg 1.45 mmol) in anhydrous benzene (15 mL) was purged with argon for 5 min. To this mixture, cyclohexyl isocyanide (159 mg, 1.45 mmol) was added by a syringe and the reaction mixture was refluxed for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate mixture gave the aminofuran **64** as an yellow solid (366 mg, 69%). mp 122-123 °C (recrystallized from CH_2Cl_2-hexane).



64

IR (KBr) ν_{max}: 3367 (NH), 2943, 2849, 1726 (C=O), 1663 (C=O), 1620, 1532 cm^{-1}.

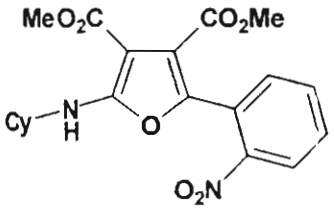
^{1}H NMR: δ 1.39-2.07 (m, 10H), 3.79 (s, 4H), 3.94 (s, 3H), 6.70 (d, J = 7.80, 1H), 7.51 (t, J = 8.01, 1H), 7.80 (d, J = 7.71, 1H), 8.06 (d, J = 8.05, 1H), 8.33 (s, 1H).

^{13}C NMR: δ 24.58, 25.53, 33.59, 51.34, 51.70, 52.84, 88.23, 116.34, 119.21, 121.73, 129.71, 129.75, 130.95, 138.32, 148.79, 161.51, 164.62 (C=O), 165.20 (C=O).

Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.68; H, 5.51; N, 6.96. Found: C, 59.62; H, 5.47; N, 6.71.

Dimethyl 2-(cyclohexylamino)-5-(2-nitrophenyl)-3,4-furandicarboxylate 67

To a refluxing mixture of 2-nitro benzaldehyde (200 mg, 1.32 mmol) and DMAD (207 mg, 1.45 mmol) in anhydrous benzene was added cyclohexyl isocyanide (159 mg, 1.45 mmol) and refluxing was continued at 80 °C for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate as eluant gave **67** as an yellow viscous oil (399 mg, 74%).



67

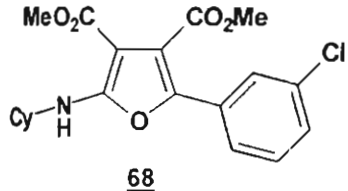
IR (film) ν_{max}: 3355, 2937, 2856, 1732, 1676, 1613, 1470, 1357, 1226 cm^{-1}.

^{1}H NMR: δ 1.22-1.96 (m, 10H), 3.46 (m, 1H), 3.74 (s, 3H), 3.75 (s, 3H), 6.60 (d, J = 7.83, 1H), 7.43-7.58 (m, 3H), 7.81 (d, J = 7.81, 1H).

^{13}C NMR: δ 24.49, 25.37, 33.23, 51.03, 51.64, 52.19, 87.18, 116.70, 123.36, 124.33, 129.00, 130.73, 132.07, 137.92, 148.18, 161.92, 164.06, 164.63.

Dimethyl 2-(cyclohexylamino)-5-(3-chlorophenyl)-3,4-furandicarboxylate 68

To a mixture of 3-chlorobenzaldehyde (200 mg, 1.42 mmol) and DMAD (223 mg, 1.56 mmol) in refluxing anhydrous benzene was added cyclohexyl isocyanide (170 mg, 1.56 mmol) and the reaction mixture was stirred for 2 h. The solvent was removed under vacuum and the residue when purified by chromatography on silica gel using 85:15 hexane-ethyl acetate gave **68** as a highly viscous colorless oil (340 mg, 61%).



68

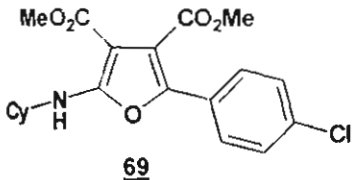
IR (film) ν_{max}: 3355, 2943, 2856, 1745, 1682, 1626, 1482, 1370, 1226 cm^{-1}.

^{1}H NMR: δ 1.26-2.05 (m, 10H), 3.76 (m, 1H), 3.77 (s, 3H), 3.90 (s, 3H), 6.62 (d, J = 8.04, 1H), 7.21-7.46 (m, 4H).

^{13}C NMR: δ 24.60, 25.55, 33.58, 51.24, 51.46, 52.69, 87.90, 114.90, 122.63, 124.55, 127.54, 129.98, 131.03, 134.79, 139.40, 161.31, 164.74, 165.52.

Dimethyl 2-(cyclohexylamino)-5-(4-chlorophenyl)-3,4-furandicarboxylate 69

To a mixture 4-chlorobenzaldehyde (200 mg, 1.42 mmol) and DMAD (223 mg, 1.56 mmol) in anhydrous benzene at 80 °C, cyclohexyl isocyanide (170 mg, 1.56 mmol) was added by a syringe and the refluxing was continued for 2.5 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate gave **69** as a colorless viscous oil (375 mg, 67%).



69

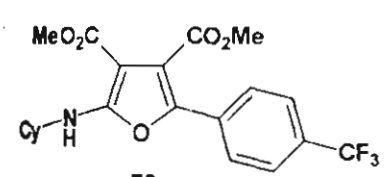
IR (film) ν_{max}: 3349, 2936, 2852, 1735, 1680, 1620, 1585, 1535, 1473, 1362 cm^{-1}.

^{1}H NMR: δ 1.25-2.04 (m, 10H), 3.71 (m, 1H), 3.77 (s, 3H), 3.88 (s, 3H), 6.61 (d, J = 7.90, 1H), 7.13 (d, J = 8.59, 2H), 7.44 (d, J = 8.63, 2H).

^{13}C NMR: δ 24.40, 25.32, 33.38, 50.96, 51.37, 52.36, 87.58, 113.95, 125.79, 127.64, 128.73, 133.24, 139.90, 161.10, 164.58, 165.41.

Dimethyl 2-(cyclohexylamino)-5-(4-trifluoromethylphenyl)-3,4-furandicarboxylate 70

Cyclohexyl isocyanide (120 mg, 1.1 mmol) was added to a refluxing mixture of 4-trifluoromethylbenzaldehyde (174 mg, 1.0 mmol) and DMAD (156 mg, 1.1 mmol) in benzene and the refluxing was continued for 7 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate afforded **70** as a pale yellow viscous oil (306 mg, 72%).



70

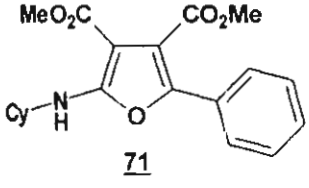
IR (film) ν_{max}: 3349, 2937, 2857, 1754, 1703, 1619, 1530, 1440, 1326, 1267 cm^{-1}.

^{1}H NMR: δ 1.31-2.11 (m, 10H), 3.78 (m, 1H), 3.83 (s, 3H), 3.96 (s, 3H), 6.73 (d, J = 7.91, 1H), 7.65 (m, 4H).

^{13}C NMR: δ 24.40, 25.30, 33.32, 51.00, 51.47, 52.45, 88.00, 115.71, 124.21, 125.49, 125.53, 132.41, 138.95, 161.25, 164.41, 165.26.

Dimethyl 2-(cyclohexylamino)-5-phenyl-3,4-furandicarboxylate 71

To a mixture of benzaldehyde (200 mg, 1.88 mmol) and DMAD (294 mg, 2.07 mmol) in refluxing anhydrous benzene (15 mL) was added cyclohexyl isocyanide (226 mg, 2.07 mmol) and the refluxing was continued for 8 h. The residue obtained after the removal of the solvent, on purification by column chromatography on silica gel using 95:5 hexane-ethyl acetate afforded the aminofuran **71** as a viscous pale yellow oil (407 mg, 61%).



71

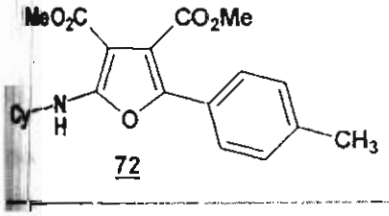
IR (film) ν_{max}: 3353, 2935, 2854, 1735, 1681, 1613, 1472, 1357, 1222 cm^{-1}.

^{1}H NMR: δ 1.26-2.07 (m, 10H), 3.73 (m, 1H), 3.78 (s, 3H), 3.90 (s, 3H), 6.60 (d, J = 7.83, 1H), 7.23-7.53 (m, 5H).

^{13}C NMR: δ 24.69, 25.61, 33.65, 51.17, 51.59, 52.57, 87.72, 113.62, 124.81, 127.71, 128.73, 129.41, 141.12, 161.35, 164.95, 165.89.

Dimethyl 2-(cyclohexylamino)-5-(4-methylphenyl)-3,4-furandicarboxylate 72

A mixture of 4-methylbenzaldehyde (121 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene was purged with argon. To this mixture, cyclohexyl isocyanide (120 mg, 1.1 mmol) was added and refluxed for 8 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 90:10 hexane-ethyl acetate gave **72** as a colorless viscous liquid (158 mg, 43%).



72

IR (film) ν_{max}: 3335, 2930, 2852, 1736, 1682, 1622, 1468, 1362, 1273 cm^{-1}.

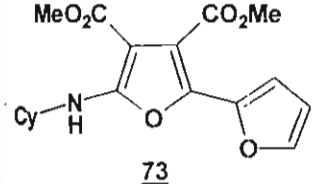
^{1}H NMR: δ 1.11-2.04 (m, 10H), 2.34 (s, 3H), 3.69 (m, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 6.59 (d, J = 7.83, 1H), 7.11 (d, J = 7.80, 2H), 7.37 (d, J = 7.95, 2H).

^{13}C NMR: δ 21.25, 24.29, 24.45, 25.46, 32.22, 33.44, 50.78, 51.22, 52.00, 87.47, 112.77, 124.79, 126.58, 129.12, 137.12, 141.42, 160.97, 164.59, 165.26.

Dimethyl 2-(cyclohexylamino)-5-(2-furyl)-3,4-furandicarboxylate 73

A mixture of furfural (192 mg, 2 mmol) and DMAD (312 mg, 2.2 mmol) in anhydrous benzene was purged with argon. To this mixture, cyclohexyl isocyanide (240 mg, 2.2 mmol) was added by a syringe and refluxed for 3 h. The solvent was removed under vacuum and the residue on chromatography on silica gel using 90:10 hexane-ethyl acetate afforded **73** as a pale brown crystalline solid (470 mg, 68%). mp 136-137 °C (recrystallized from CH_2Cl_2-hexane).

IR (KBr) ν_{max}: 3349, 3130, 2930, 2856, 1732, 1676, 1607, 1483, 1365, 1269, 1237, 1220, 1148 cm^{-1}.



73

^{1}H NMR: δ 1.25-2.04 (m, 10H), 3.70 (m, 1H), 3.76 (s, 3H), 3.88 (s, 3H), 6.42 (s, 1H), 6.58 (d, J = 2.94, 1H), 6.64 (d, J = 7.83, 1H), 7.41 (s, 1H).

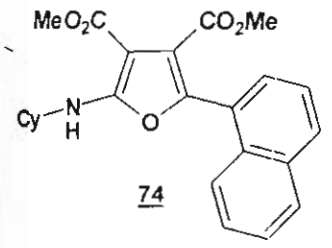
^{13}C NMR: δ 24.51, 25.44, 33.49, 51.04, 51.36, 52.19, 86.69, 107.55, 111.33, 112.81, 134.79, 142.36, 144.05, 161.29, 164.38, 164.86.

HRMS Calcd for $C_{18}H_{21}NO_6$: 347.1368. Found: 347.1375.

Dimethyl 2-(cyclohexylamino)-5-(1-naphthyl)-3,4-furandicarboxylate 74

To a mixture of 1-naphthaldehyde (313 mg, 2 mmol) and DMAD (299 mg, 2.1 mmol) in anhydrous benzene (15 mL) at 80 °C was added cyclohexyl isocyanide (229 mg, 2.1 mmol) and the mixture was heated at the same

temperature for 8 h. The solvent was removed under reduced pressure and the residue obtained on chromatographic separation on silica gel using 90:10 hexane-ethyl acetate gave **74** as a pale yellow viscous oil (439 mg, 54%). Yield based on recovered naphthaldehyde is 84%.



74

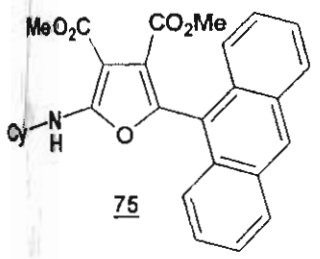
IR (film) ν_{max}: 3332, 2932, 2862, 1736, 1676, 1568, 1439, 1368, 1230 cm^{-1}.

^{1}H NMR: δ 1.24-2.01 (m, 10H), 3.61 (s, 3H), 3.62 (m, 1H), 3.79 (s, 3H), 6.72 (d, J = 8.01, 1H), 7.42-7.61 (m, 4H), 7.82-7.98 (m, 3H).

^{13}C NMR: δ 24.29, 25.22, 33.38, 50.81, 51.17, 51.77, 86.54, 116.28, 124.85, 125.32, 125.85, 126.32, 128.23, 128.27, 129.46, 131.60, 133.53, 142.49, 161.87, 164.44, 164.90.

Dimethyl 2-(9-anthryl)-5-(cyclohexylamino)-3,4-furandicarboxylate 75

A mixture of 9-anthraldehyde (103 mg, 0.5 mmol) and DMAD (78 mg, 0.55 mmol) in benzene was purged with argon for 5 min, followed by the addition of cyclohexyl isocyanide (60 mg, 0.55 mmol). The reaction mixture was refluxed for 8 h and the residue obtained after removal of the solvent, on chromatographic separation using 85:15 hexane-ethyl acetate afforded **75** as an yellow amorphous solid (130 mg, 57%). Yield based on recovered anthraldehyde is 78%.



75

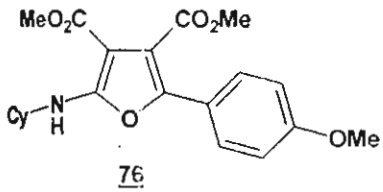
IR (film) ν_{max}: 3338, 3054, 2936, 2848, 1728, 1682, 1568, 1458, 1370, 1310, 1232 cm^{-1}.

^{1}H NMR: δ 1.18-1.98 (m, 10H), 3.32 (s, 3H), 3.55 (m, 1H), 3.84 (s, 3H), 6.84 (d, J = 8.13, 1H), 7.40-7.47 (m, 4H), 7.85-7.98 (m, 4H), 8.48 (s, 1H).

^{13}C NMR: δ 24.38, 25.33, 33.45, 50.94, 51.14, 51.54, 86.05, 118.76, 123.12, 125.25, 125.82, 126.41, 128.41, 129.31, 131.10, 132.10, 162.78, 163.76, 165.34.

Dimethyl 2-(cyclohexylamino)-5-(4-methoxyphenyl)-3,4-furandicarboxylate 76

To a mixture of *p*-anisaldehyde (137 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene at 80 °C, was added cyclohexyl isocyanide (120 mg, 1.1 mmol). The mixture was refluxed for 9 h and the benzene was removed under reduced pressure. The residue on silica gel chromatography using 90:10 hexane-ethyl acetate yielded **76** as a colorless viscous liquid (135 mg, 35%).



76

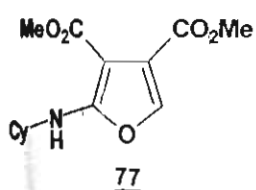
IR (KBr) ν_{max}: 3361, 2937, 2856, 1751, 1688, 1595, 1513, 1439, 1258, 1170 cm^{-1}.

^{1}H NMR: δ 1.27-2.04 (m, 10H), 3.68 (m, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 6.56 (d, *J* = 7.66, 1H), 6.88 (d, *J* = 8.53, 2H), 7.47 (d, *J* = 8.52, 2H).

^{13}C NMR: δ 24.51, 25.44, 33.50, 50.92, 51.38, 52.24, 55.12, 87.20, 111.80, 114.01, 122.04, 126.56, 141.75, 159.25, 161.04, 164.87, 165.74.

Dimethyl 2-(cyclohexylamino)-3,4-furandicarboxylate 77

To a mixture of paraformaldehyde (31 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in refluxing anhydrous benzene was added cyclohexyl isocyanide (120 mg, 1.1 mmol) and the refluxing was continued for 6 h. Chromatography of the residue obtained after removal of the solvent, on silica gel using 95:5 hexane-ethyl acetate afforded **77** as a pale brown viscous liquid (123 mg, 44%).



77

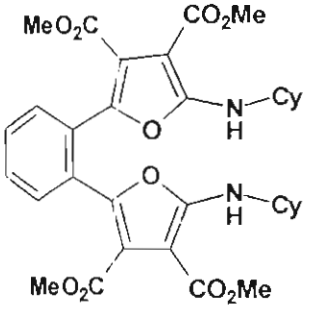
IR (film) ν_{max}: 3355, 2937, 2856, 1744, 1676, 1607, 1470, 1357, 1239 cm^{-1}.

^{1}H NMR: δ 1.18-1.92 (m, 10H), 3.51 (m, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 6.71 (d, *J* = 7.77, 1H), 7.15 (s, 1H).

^{13}C NMR: δ 24.46, 25.31, 33.51, 50.84, 51.11, 51.53, 84.35, 118.03, 136.94, 162.65, 163.47, 165.44.

Dimethyl 2-(cyclohexylamino)-5-{2-[5-cyclohexylamino)-3,4-bis(methoxycarbonyl)-2-furyl]phenyl}-3,4-furandicarboxylate 78

A mixture of phthalaldehyde (67 mg, 0.5 mmol) and DMAD (156 mg, 1.1 mmol) was purged with argon for 5 min. Cyclohexyl isocyanide (120 mg, 1.1 mmol) was added to this mixture by a syringe and the reaction mixture was refluxed for 14 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 85:15 hexane-ethyl acetate afforded the product **78** as a pale yellow solid (209 mg, 66%). mp 145-146 °C (recrystallized from CH_2Cl_2-hexane).



78

IR (KBr) ν_{max}: 3357, 2934, 2854, 1749, 1678, 1610, 1520, 1470, 1449, 1364, 1255 cm^{-1}.

^{1}H NMR: δ 1.10-1.79 (m, 20H), 3.29 (m, 2H), 3.76 (s, 6H), 3.80 (s, 6H), 6.46 (d, J = 8.24, 2H), 7.34-7.37 (m, 2H), 7.56-7.59 (m, 2H).

^{13}C NMR: δ 24.53, 25.32, 33.75, 50.81, 51.26, 52.02, 86.11, 114.91, 127.83, 128.43, 130.22, 141.97, 161.41, 164.64, 164.83.

Anal. Calcd for $C_{34}H_{40}N_2O_{10}$: C, 64.14; H, 6.33; N, 4.40. Found: C, 64.43; H, 6.34; N, 4.28.

2.14 References

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Chapter 3

The Reaction of Cyclohexyl Isocyanide and Dimethyl Acetylenedicarboxylate with 1,2- and 1,4-Benzoquinones: A Novel Synthesis of Iminolactones

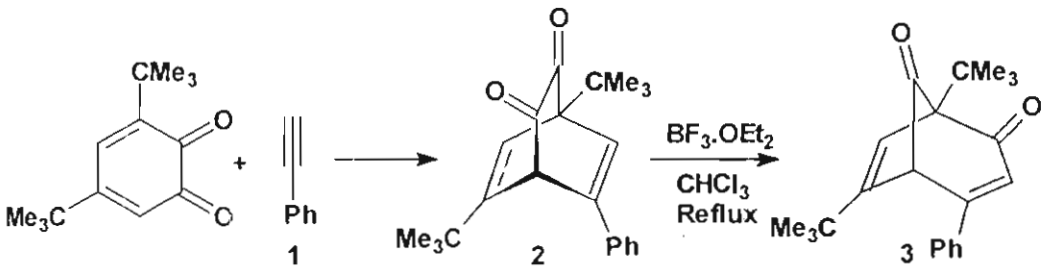
3.1 Introduction

The reactivity of 1,2-benzoquinones in cycloaddition reactions depends on the electronic and steric nature of the substituents.[1] 1,2-Benzoquinones can participate as 4π or 2π components in cycloaddition reactions. The reactivity of 1,2-benzoquinone as a dienophile was reported by Ansell in 1971; the addition occurs preferentially to the more electron deficient C=C bond.[2] In their reaction with electron rich acyclic dienes, 1,2-quinones act as carbodienes, whereas with carbocyclic dienes they act both as carbodienes and heterodienes. 1,2-Benzoquinones afford benzodioxin derivatives with heterocyclic dienes such as furans[3] and pyrroles[4] with the latter participating as dienophiles and the quinones as heterodienes. The HOMO-LUMO energy calculations show that all such reactions may be characterized as inverse electron demand Diels-Alder reactions. Reports from our own laboratory have shown that in dipolar cycloadditions, 1,2-benzoquinones participate preferentially as C=O dipolarophiles.

The different types of reactivity shown by 1,2-benzoquinones in cycloaddition reactions is discussed in the following sections.

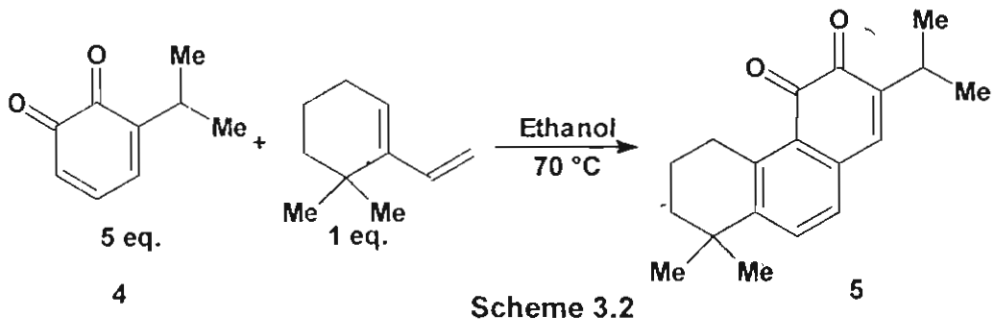
3.1.1 Diels-Alder Reactions of 1,2-Benzoquinones

1,2-Benzoquinone has a highly electron deficient carbodiene moiety and it undergoes facile Diels-Alder reactions with carbocyclic dienes, pentafulvenes, acetylenes *etc.* leading to bicyclo[2.2.2] systems.[2] It is noteworthy that the resulting bicyclo[2.2.2]octenediones undergo a number of interesting and useful transformations. Lewis acid catalyzed rearrangement of such systems afforded bicyclo[3.2.1]octene skeleton **3** which is present in a number of important sesquiterpenes and neolignans (Scheme 3.1).[5]



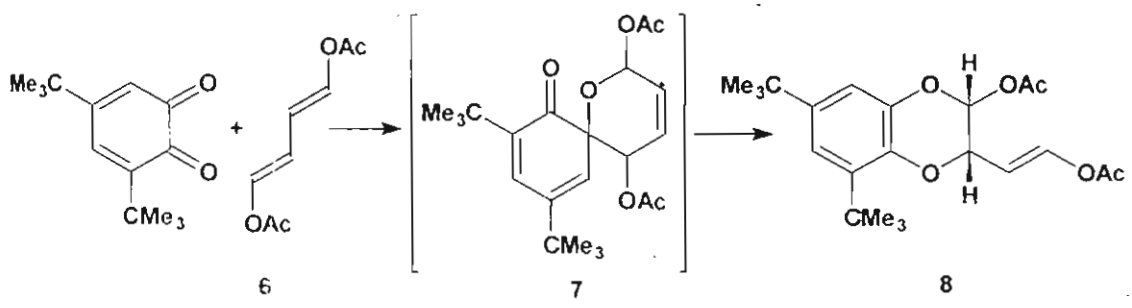
Scheme 3.1

The enone moiety of 1,2-benzoquinone acts as an electron deficient dienophile in its reaction with 2,3-dimethylbutadiene, 1-acetoxybutadiene *etc.* by an inverse electron demand Diels-Alder pathway.[6] This has been utilized in the synthesis of Rosmariquinone **5** (Scheme 3.2).[7]



Scheme 3.2

The presence of two activated carbonyl groups renders *o*-benzoquinone as a heterodienophile. In the reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone with 1,4-diacetoxybutadiene, a primary spiroadduct **7** is obtained which undergoes a [3,3] sigmatropic rearrangement at high temperature yielding the benzodioxin derivative **8** (Scheme 3.3).[6,8]

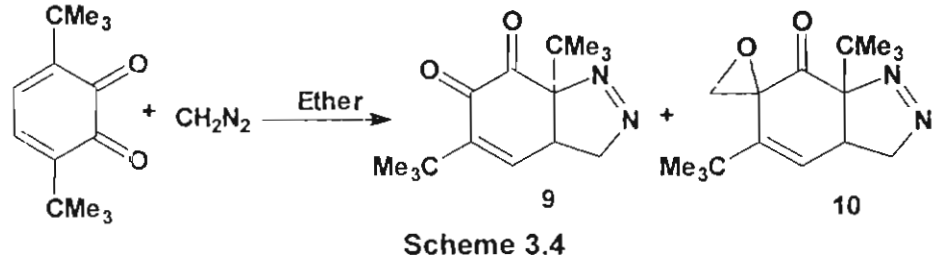


Scheme 3.3

3.1.2 Dipolar Cycloaddition Reactions of 1,2-Benzoquinones

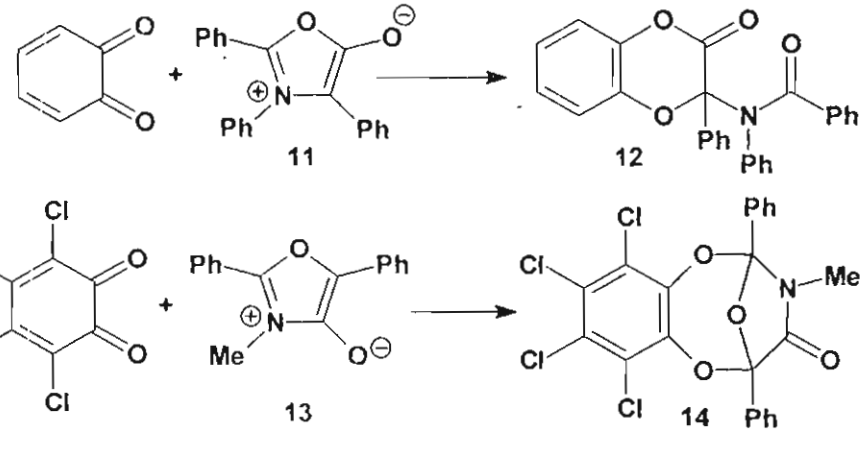
In contrast to the large amount of work on the Diels-Alder cycloadditions of 1,2-quinones, very little is known about their dipolar cycloadditions. The available information is summarized below.

The reaction of diazomethane with 3,6-di-*tert*-butyl-1,2-benzoquinone affords indazole 9. With excess of diazomethane, one of the carbonyl groups is converted to a spirooxirane **10** (Scheme 3.4).[9]



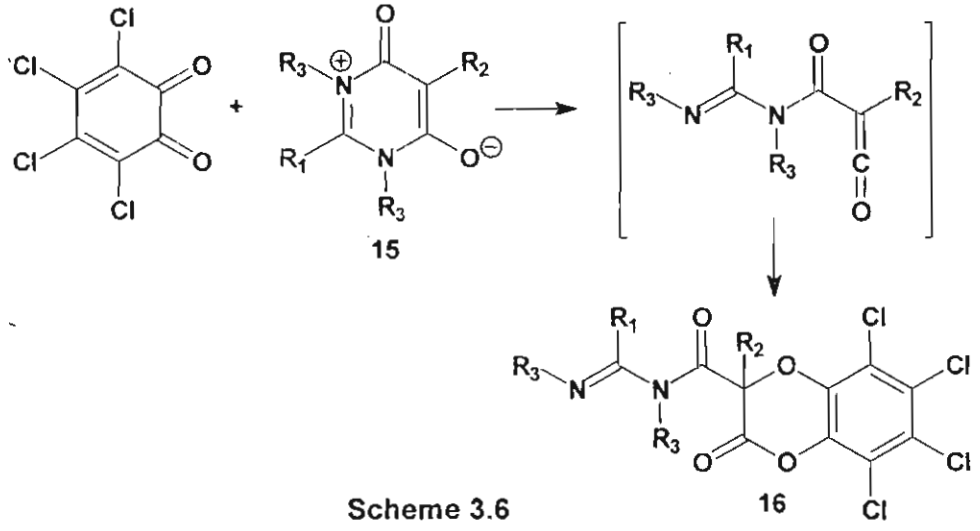
Scheme 3.4

Mesoionic compounds such as münchnones[10] **11** and isomünchnones[11] **13** have been added to 1,2-benzoquinones leading to the formation of interesting heterocycles (Scheme 3.5).



Scheme 3.5

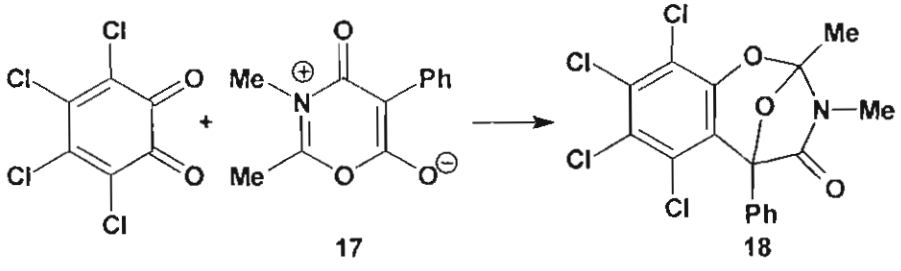
The reaction of 1,3-disubstituted-3,6-dihydro-6-oxopyrimidinium-4-olates **15** with *o*-chloranil afforded the product **16** presumably through the open chain ketene form of the dipole (Scheme 3.6).[12]



15 **16**

Scheme 3.6

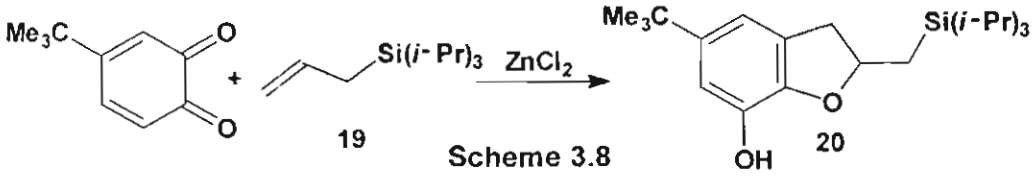
In contrast, the reaction of 4-oxo-4[*H*]-1,3-oxazinium-6-olate **17** with *o*-chloranil ieads to the formation of **18** (Scheme 3.7).[13]



17 **18**

Scheme 3.7

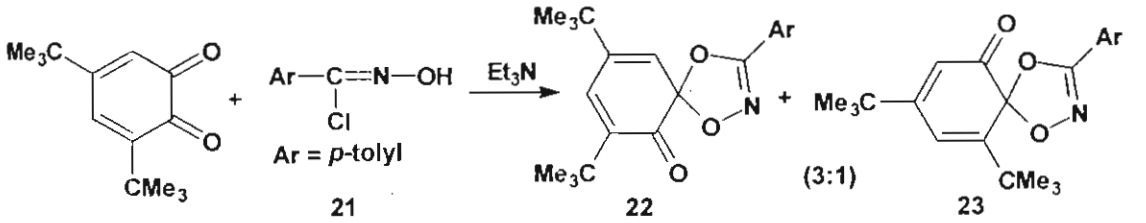
In presence of Lewis acids, allylsilanes undergo a formal [2+3] cycloaddition with 4-*tert*-butyl-1,2-benzoquinone to yield benzofuran derivative **20** (Scheme 3.8).[14]



19 **20**

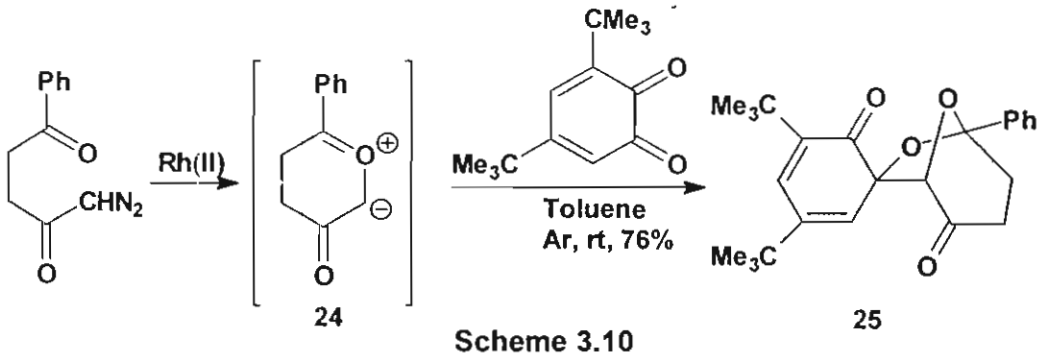
Scheme 3.8

It has been shown that, aryl nitrile oxides undergo facile cycloaddition with 1,2-benzoquinones. 3,5-Di-*tert*-butyl-1,2-benzoquinone on treatment with 4-methyl benzohydroximoyl chloride and triethylamine in benzene at room temperature afforded a regioisomeric mixture of products **22** and **23** in 3:1 ratio (Scheme 3.9).[15]



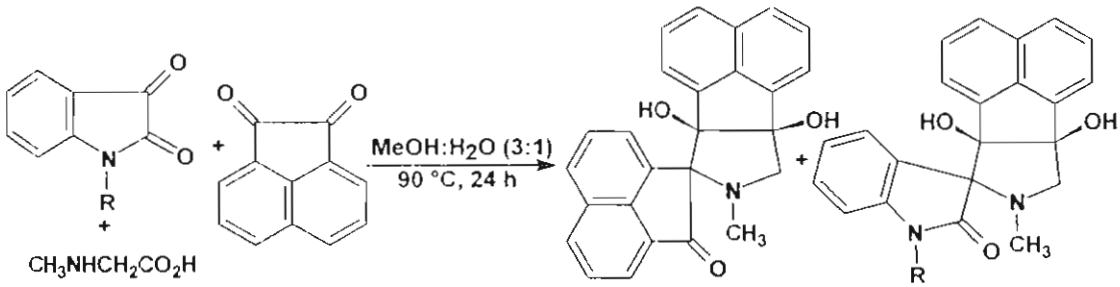
Scheme 3.9

The dipolar cycloaddition reactions of carbonyl ylides with 1,2-diones have been recently reported from our laboratory. The rhodium(II) acetate catalyzed cycloaddition reaction of 1-diazo-5-phenyl-2,5-pentanedione with 3,5-di-*tert*-butyl-1,2-benzoquinone proceeded smoothly to afford a yellow crystalline product **25** in 76% yield (Scheme 3.10).[16]



Scheme 3.10

Grigg *et al.* have shown that azomethine ylides resulting from the condensation of 1,2-dicarbonyl compounds with α-aminoacids or amines undergo cycloaddition reactions with maleimides and acyclic esters.[17] Interestingly, it was found that an isatin derived azomethine ylide reacted with acenaphthenequinone in an unusual mode of cycloaddition to yield the products **26** and **27** (Scheme 3.11).[18]



Scheme 3.11

3.2 1,3-Dipolar Cycloaddition Reactions: Theoretical Considerations

The 1,3-dipole is defined as a species that is represented by zwitterionic octet structures and undergoes 1,3-cycloaddition to multiple bonded systems, the dipolarophile (Figure 3.1).[19]

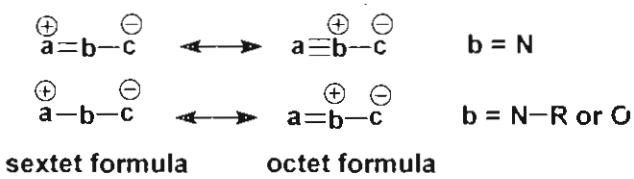


Figure 3.1

Compounds containing an electron sextet at a carbon, nitrogen or oxygen atom is not stable. Stabilization is possible if an unshared pair of electrons at atom **b** can relieve the electron deficiency at center **a** by formation of an additional bond. In the new mesomeric formula in which **b** now has the positive charge, all the centers have completely filled valence shells. Such systems will be designated as 1,3-dipoles with internal octet stabilization.

If the center **b** of the 1,3-dipole **a-b-c** is a carbon functionality, then the internal octet stabilization is prevented by lack of an available free electron pair. However, it is possible for a ligand **f** on the sextet center **a** to posses an unshared electron pair and thus to provide external stabilization (Figure 3.2).

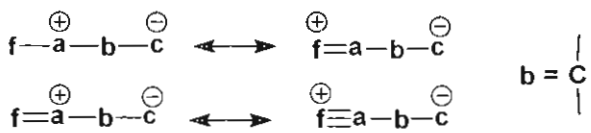
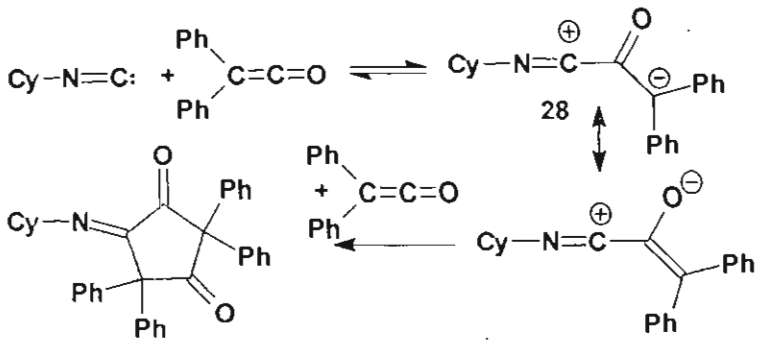


Figure 3.2

The reaction of isocyanides with ketenes may be mentioned as an example; the 1:2 adducts obtained are presumably 1-imino-2,4-cyclopentanediones **30**. A plausible intermediate **28**, which may be formed reversibly can be recognized as an externally stabilized 1,3-dipole, which subsequently combines with a second molecule of the ketene as dipolarophile (Scheme 3.12).[20]

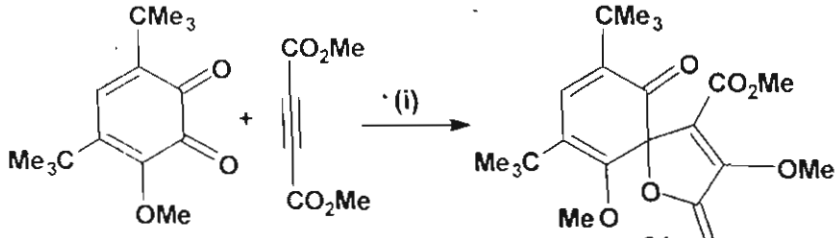


Scheme 3.12

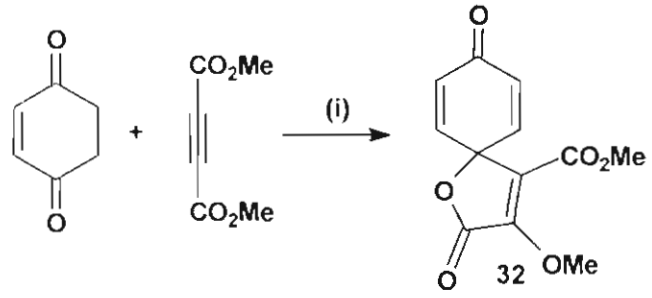
Neither the 1,3-dipole formed from the isocyanide and ketene nor many of the other octet-stabilized 1,3-dipoles are stable enough to be isolated. Such systems therefore are treated with the dipolarophiles *in situ*. Similarly, the 1:1 zwitterionic intermediate generated from DMAD and isocyanide can be considered as an externally stabilized 1,3-dipole.

3.3 Background to the Present Work

In the context of the general interest in the cycloaddition chemistry of 1,2-benzoquinones (*vide supra*), investigations carried out in our laboratory have shown that the zwitterionic intermediate generated by the reaction of triphenylphosphine and DMAD underwent facile addition to 1,2- and 1,4-benzoquinones to afford highly functionalized novel unsaturated γ-spirolactones in high yields (Scheme 3.13).[21]



(i) PPh_3, Benzene, 80 °C , 4 h, 70%



(i) PPh_3, Benzene, rt, 12 h, 88%

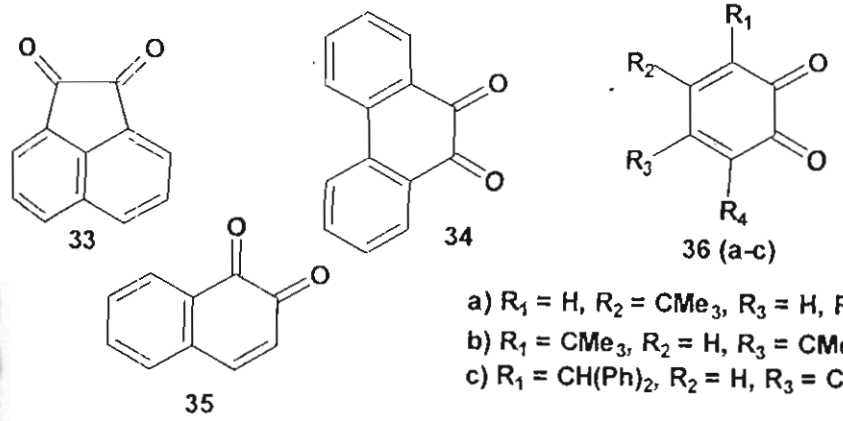
Scheme 3.13

A subject of continuing interest in this area has been the systematic investigation of zwitterion formation involving other nucleophiles and interception of such species with a third component (electrophile). It was surmised that the zwitterionic species derived from isocyanide and DMAD was likely to undergo cycloaddition to quinones leading to heterocycles. The results validating the assumption constitute the subject matter of this chapter.

3.4 Results and Discussion

3.4.1 Reaction of Cyclohexyl Isocyanide and DMAD with 1,2-Benzoquinones

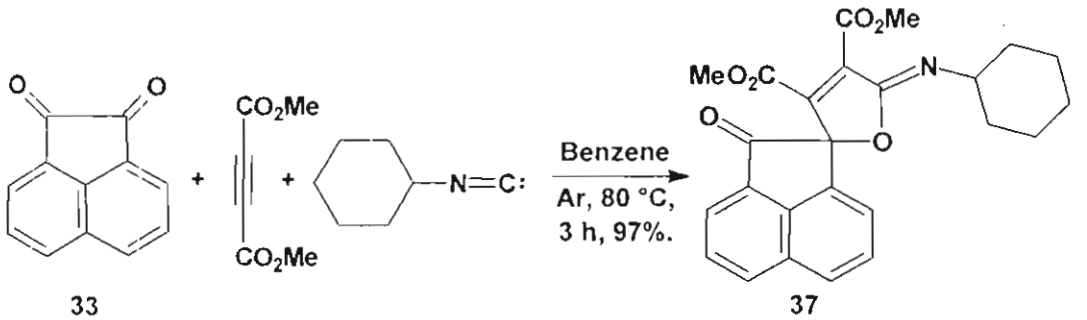
The *o*-quinones selected for our study are listed in Figure 3.3.



a) R_1 = H, R_2 = CMe_3, R_3 = H, R_4 = H
b) R_1 = CMe_3, R_2 = H, R_3 = CMe_3, R_4 = H
c) R_1 = $CH(Ph)_2$, R_2 = H, R_3 = $CH(Ph)_2$, R_4 = OMe

Figure 3.3

In a pilot experiment, we observed that a mixture of acenaphthenequinone **33** and DMAD at 80 °C in anhydrous benzene, when treated with cyclohexyl isocyanide afforded the iminolactone **37** in 97% yield (Scheme 3.14).[22]



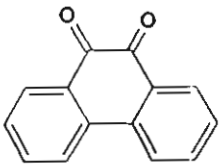
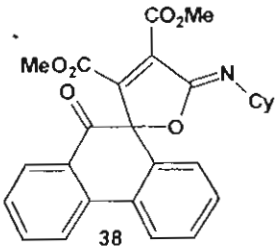
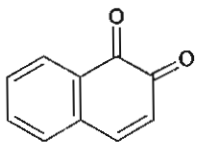
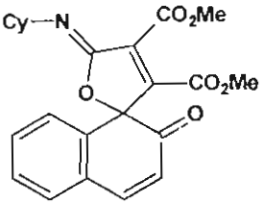
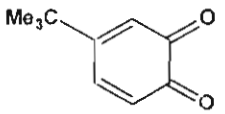
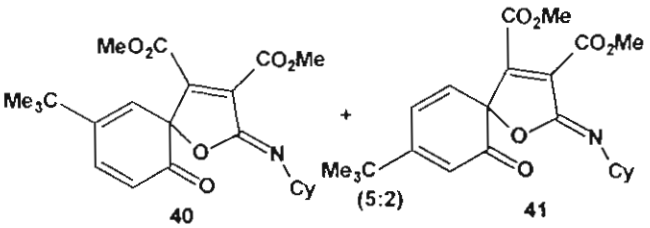
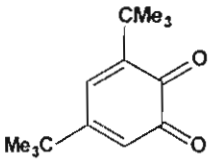
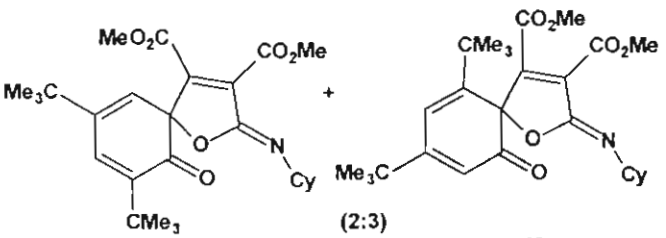
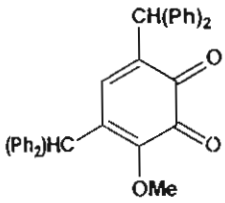
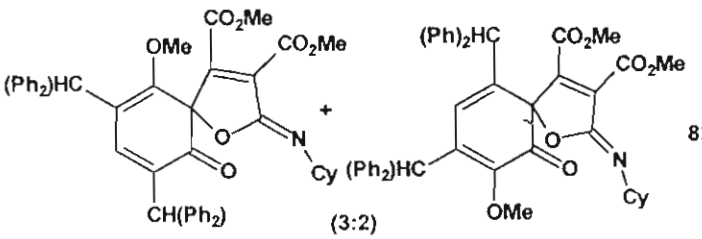
33 37

Scheme 3.14

The product **37** was characterized by spectroscopic and analytical data. The IR spectrum showed strong absorptions at 1755 and 1728 cm^{-1} due to the ester carbonyls. The sharp band at 1688 cm^{-1} was assigned to the keto carbonyl. In the ^1H NMR spectrum, the two carbomethoxy groups resonated at δ 3.46 and 3.97 as singlets. In the ^{13}C NMR spectrum of **37**, the characteristic spirocarbon resonance was observed at δ 90.72. The signals at δ 160.32 and 161.91 revealed the presence of ester carbonyls and the corresponding methoxy carbons were observed at δ 52.74 and 53.22. The keto carbonyl was discernible at δ 195.39 and the imino carbon at δ 154.71. The methylene carbons of the cyclohexyl group appeared at δ 24.87, 25.84, 33.21 and 33.39. The tertiary carbon atom attached to imine N atom resonated at 56.93. The assigned structure was further supported by satisfactory analytical data.

Similar reactivity was observed with 9,10-phenanthrenequinone **34**, 1,2-naphthoquinone **35**, 4-*tert*-butyl-1,2-benzoquinone **36a**, 3,5-di-*tert*-butyl-1,2-benzoquinone **36b**, and 3-methoxy-4,6-bis(1,1-diphenylmethyl)-1,2-benzoquinone **36c** yielding the iminolactones **38-45**. The results obtained are summarized in Table 3.1.

Table 3.1

Entry	Quinone	t(h)	Product(s)	Yield(%)*
1	 34	6	 38	92[b]
2	 35	7	 39	64[b]
3	 36a	3	 40 (5:2) 41	68[c]
4	 36b	8	 42 (2:3) 43	58[c]
5	 36c	5	 44 (3:2) 45	82[c]

Reaction conditions: Benzene, Argon, Reflux. Where Cy = Cyclohexyl

* isolated yield

[b] purified by crystallization

[c] purified by column chromatography

Analogous to the reaction of acenaphthenequinone, 9,10-phenanthrenequinone **34** afforded a single product **38** and it was characterized by spectroscopic analysis. The IR spectrum showed absorptions at 1751 and 1682 cm^{-1} due to the ester carbonyls. The singlets at δ 3.46 and 3.94 in the ^1H NMR

spectrum are diagnostic for the methoxy groups. The ^{13}C signals for the ester and benzoyl carbonyls were seen at δ 160.04, 161.64 and 190.58. The characteristic spirocarbon signal was observed at δ 86.68.

Interestingly, the reaction of 1,2–naphthoquinone **35** afforded a single product **39**, which was purified by crystallization from CH_2Cl_2–hexane mixture. The strong absorption at 1676 cm^{-1} in the IR spectrum, was characteristic of the enone carbonyl; the ester carbonyls were seen at 1757 and 1726 cm^{-1}. In the ^1H NMR spectrum, the olefinic protons resonated as doublets at δ 6.28 (d, J = 9.93) and δ 7.51 (d, J = 9.97) as expected for an enone moiety. The ^{13}C NMR spectrum showed signals at δ 160.04, 161.66 and 191.60 corresponding to carbomethoxy and enone carbonyls. The characteristic resonance for the spirocarbon was seen at δ 85.57. The reactivity preference towards the benzoyl carbonyl rather than to the enone carbonyl is expected.

4-*tert*-Butyl-1,2-benzoquinone **36a** afforded an inseparable mixture of regioisomers **40** and **41** in 5:2 ratio. The IR spectrum showed absorptions at 1769, 1748 and 1739 cm^{-1} due to the ester carbonyls. The absorption at 1646 cm^{-1} was characteristic of the enone carbonyl. In the ^1H NMR spectrum, the two *tert*-butyl groups resonated at δ 1.18 and 1.23 as singlets overlapping with the multiplet of cyclohexyl protons. The six olefinic protons were seen between δ 5.77-7.18. In the ^{13}C NMR spectrum, the characteristic spirocarbons gave signals at δ 77.41 and 83.77. The carbomethoxy carbonyls were seen at δ 161.52, 161.71, 161.79 and 163.62.

Reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone **36b** gave a 2:3 regioisomeric mixture of iminolactones **42** and **43**. The isomers were separated by radial chromatography on a Chromatotron® and characterized by spectroscopic analysis. The IR spectrum of **42** showed absorptions at 1755, 1738, and 1689 cm^{-1} indicating the presence of ester and enone carbonyls. The ^1H NMR spectrum exhibited two singlets at δ 1.17 and 1.24 corresponding to the two tertiary butyl groups. The carbomethoxy methyl groups resonated as singlets at δ

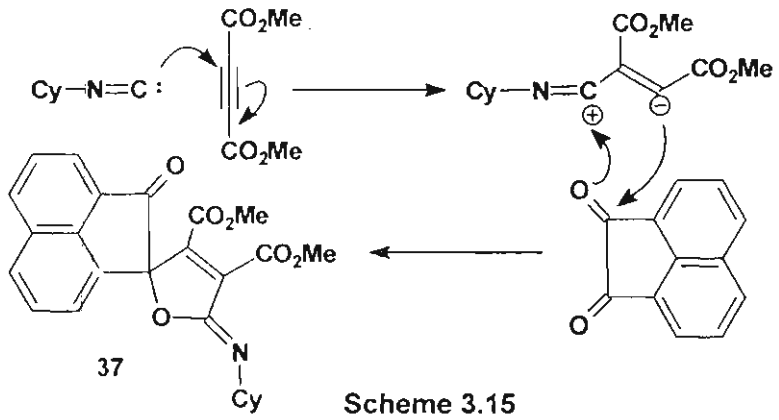
3.67 and 3.89. The peaks at δ 5.69 and 6.95 were assigned to the proton on the carbon β to the carbonyl groups and the one α to the spirocarbon atom respectively. In the ^{13}C NMR spectrum, the signals characteristic of the spirocarbon atom and enone carbonyl were visible at δ 86.84 and 193.06. The carbomethoxy carbonyls were seen at δ 160.30 and 161.91.

The IR spectrum of **43** showed the characteristic ester carbonyl absorptions at 1751 and 1732 cm^{-1} and enone carbonyl at 1676 cm^{-1}. The ^1H NMR spectrum showed two singlets at δ 3.65 and 3.83 corresponding to the methoxy groups. The doublets at δ 5.92 (J = 1.17) and 6.52 (J = 1.07) were attributed to the olefinic protons. The ^{13}C NMR spectrum showed the typical signals at δ 86.02 and 194.35 corresponding to the spiro and enone carbonyl carbon atoms respectively. The carbomethoxy carbonyls were visible at δ 161.40 and 164.97. All other signals are also in good agreement with the proposed structure.

Similar reactivity was observed with 3-methoxy-4,6-bis(1,1-diphenyl methyl)-1,2-benzoquinone **36c** which on treatment with DMAD and cyclohexyl isocyanide in anhydrous benzene at 80 °C for 5 h furnished an inseparable mixture of regioisomers **44** and **45** in 3:2 ratio. The IR spectrum showed three carbonyls at 1751, 1726, and 1682 cm^{-1} indicating the presence of ester and enone carbonyls. In the ^1H NMR spectrum, the methoxy groups were seen at δ 3.33, 3.51, 3.61, 3.71, 3.82 and 3.85. Aromatic protons were visible between δ 6.86-7.31. In the ^{13}C NMR spectrum, the signals at δ 189.73 and 190.68 were attributed to the enone carbonyls. The characteristic carbomethoxy carbonyls were discernible at δ 159.66, 159.72, 161.06 and 161.35. All other signals also agree with the assigned structure.

3.4.1.1 Mechanistic Considerations

The reaction involves the initial formation of a zwitterionic intermediate from cyclohexyl isocyanide and DMAD, which adds to the carbonyl moiety of the quinone in a [3+2] fashion to yield the iminolactone (Scheme 3.15).



Scheme 3.15

Contrary to our experience with the triphenylphosphine catalyzed addition of DMAD to quinones, it is necessary to invoke a *cisoid* 1:1 intermediate **46** for the observed product formation. The 1:1 intermediate **47** generated from triphenylphosphine and DMAD was found to take a reaction course involving *trans* configuration with respect to the ester groups (Figure 3.4).

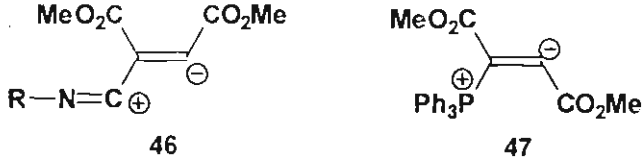


Figure 3.4

The nucleophilic addition to *sp* and sp^2 systems have been studied in detail by a number of groups[23] and in this connection a generalized "rule of trans nucleophilic addition" has been proposed by Truce *et al.*,[24] stating that the *trans* addition mode is the favored one. Some exceptions to this rule have been observed as in the case of the reaction of amines with activated acetylenes.[25] The incoming amine is a neutral species and the nitrogen atom develops a positive charge in the intermediate **48**. Therefore, it seems reasonable to expect a *cisoid* reaction pathway. Similarly, a *cisoid* geometry **49** can be considered for the 1:1 intermediate of isocyanide and DMAD (Figure 3.5).

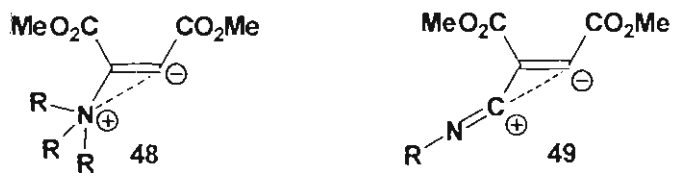


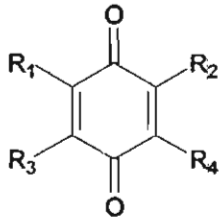
Figure 3.5

The isolation of cyclopropenone imine by Krebs *et al.*[26] strongly supports the presence of such an intermediate.

3.4.2 Reaction of Cyclohexyl Isocyanide and DMAD with 1,4-Benzoquinones

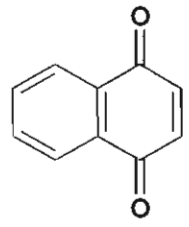
In view of the interesting results obtained by the addition of the zwitterionic intermediate generated from DMAD and cyclohexyl isocyanide to 1,2-benzoquinones, a logical extension of the work was to explore the reactivity of 1,4-benzoquinones towards the zwitterionic intermediate.

The quinones selected for the study are listed in Figure 3.6.

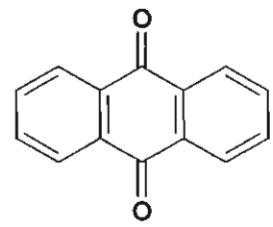


50 (a-d)

a) R_1=H, R_2=CH_3, R_3=CH_3, R_4=H
b) R_1=H, R_2=H, R_3=H, R_4=H
c) R_1=H, R_2=CH_3, R_3=H, R_4=H
d) R_1=Cl, R_2=Cl, R_3=Cl, R_4=Cl



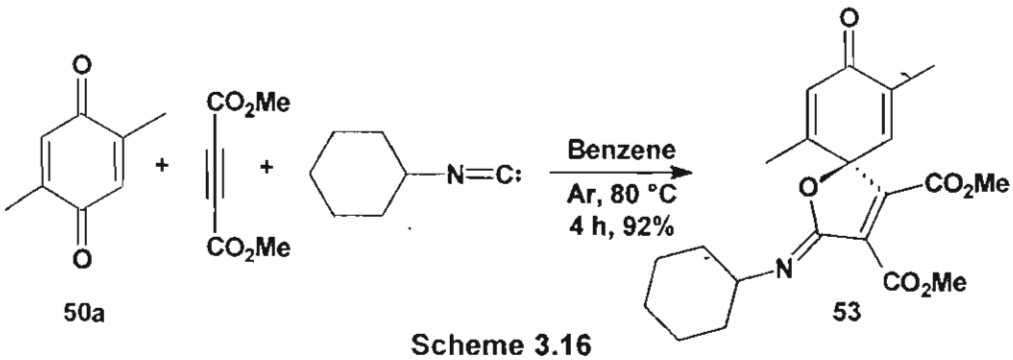
51



52

Figure 3.6

2,5-dimethyl-1,4-benzoquinone **50a** when treated with DMAD and cyclohexyl isocyanide in anhydrous benzene at 80 °C for 4 h afforded the iminolactone **53** in 92% yield (Scheme 3.16).



50a 53

Scheme 3.16

The IR spectrum of **53** showed strong absorptions at 1757 and 1726 cm^{-1} due to the ester carbonyls and the enone carbonyl at 1682 cm^{-1}. The absorption at 1646 cm^{-1} can be attributed to the imino group. In the ^1H NMR spectrum (Figure 3.7), the methyl groups on the cyclohexadiene ring resonated as two doublets at δ 1.85 (J = 1.11) and 1.93 (J = 1.20). The carbomethoxy methyl groups resonated at δ 3.71 and 3.92. The doublets at δ 6.22 (J = 1.22) and 6.32 (J = 1.40) were

assigned to the olefinic protons. In the ^{13}C NMR spectrum (Figure 3.8), the methyl carbons resonated at δ 15.51 and 17.15. The methoxy carbons were seen at δ 52.88 and 56.83. The characteristic signal due to the spirocarbon was discernible at δ 85.08. The carbomethoxy carbonyls resonated at δ 159.85 and 161.61 while the peak at δ 185.31 was assigned to the carbonyl of the dienone. The signal at δ 153.88 can be attributed to the iminocarbon. Finally, the assigned structure was confirmed unambiguously by single crystal X-ray analysis (Figure 3.9).

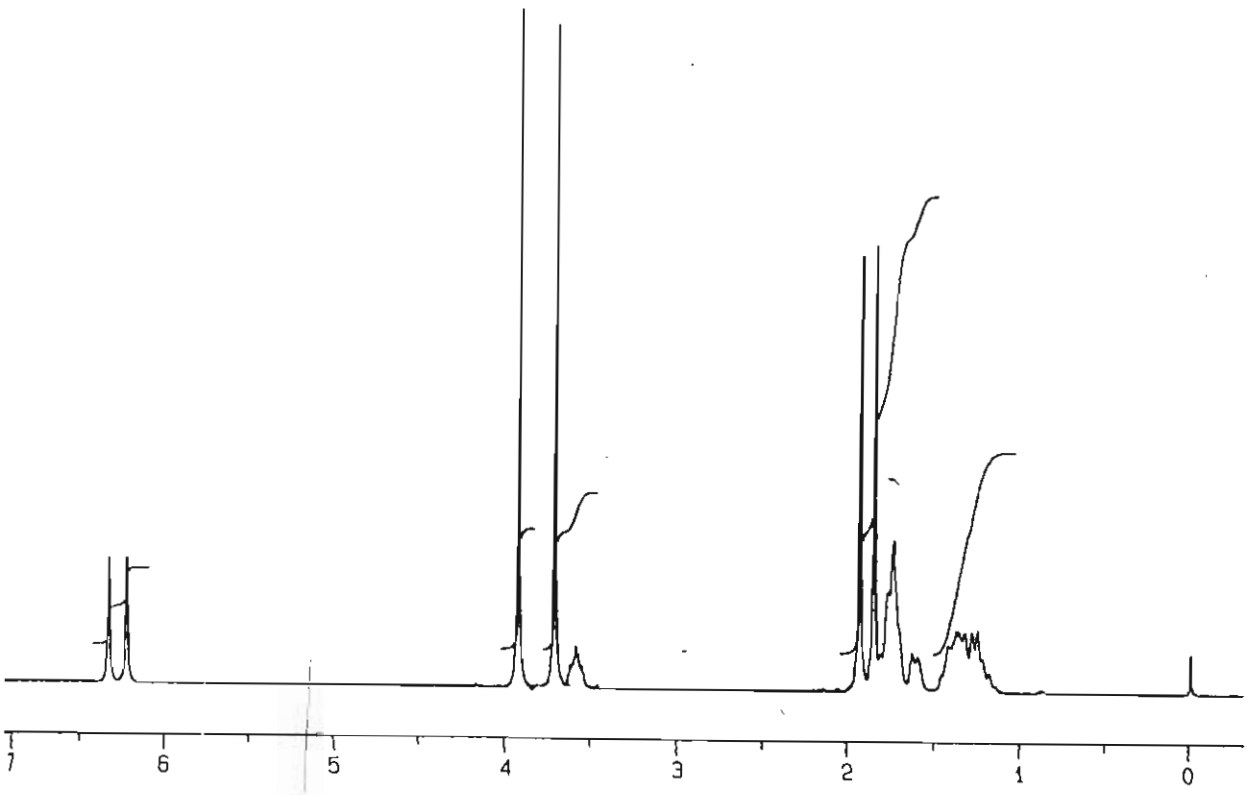


Figure 3.7 ^{1}H NMR spectrum of iminolactone 53

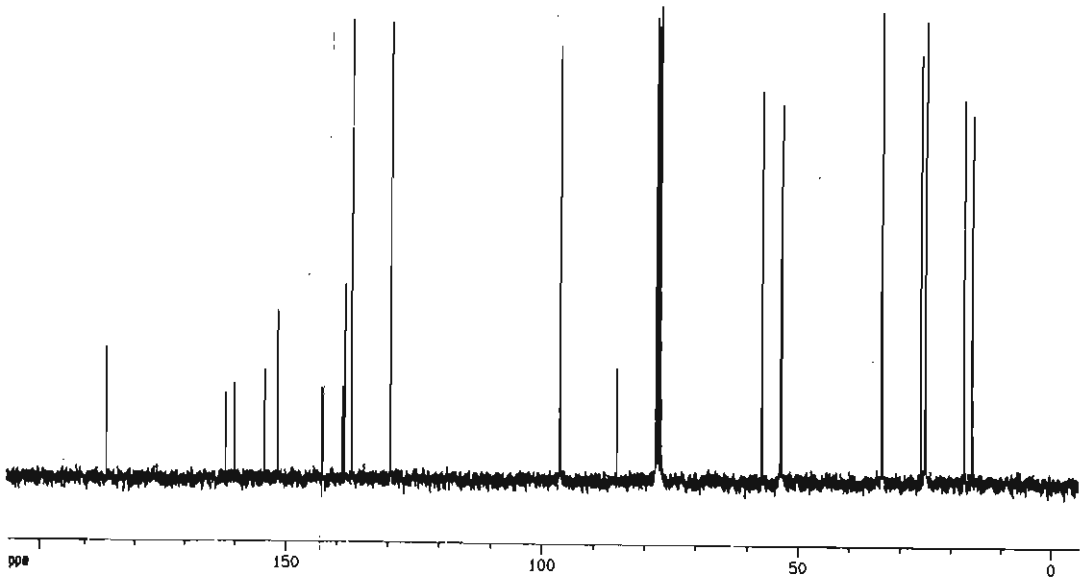


Figure 3.8 ^{13}C NMR spectrum of iminolactone 53

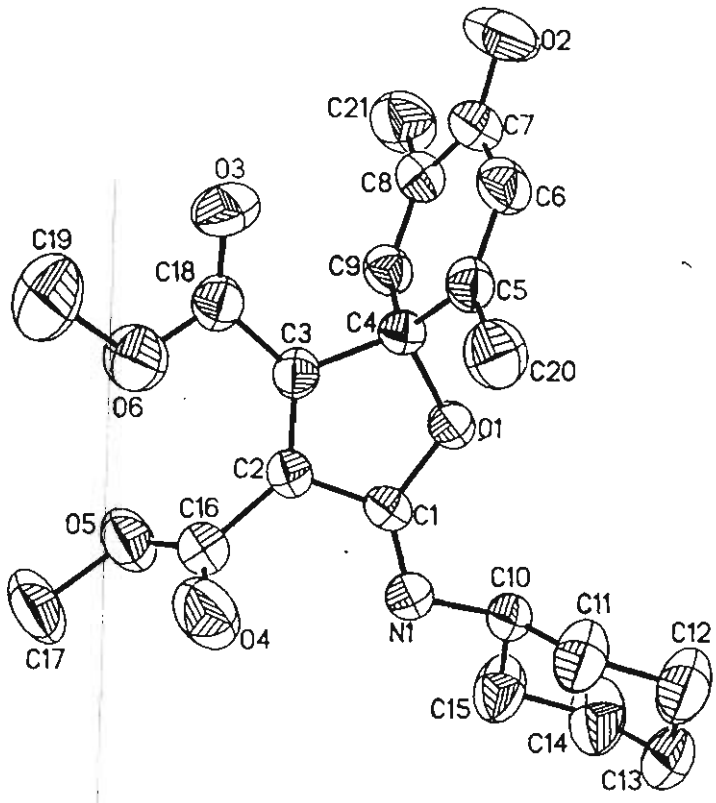
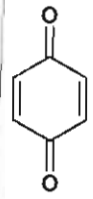
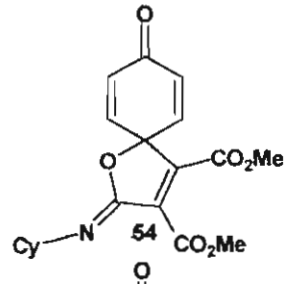
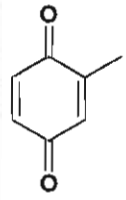
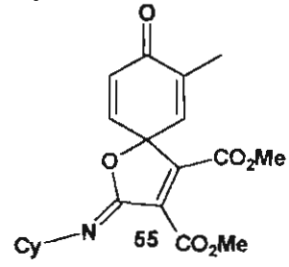
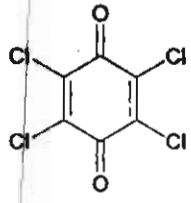
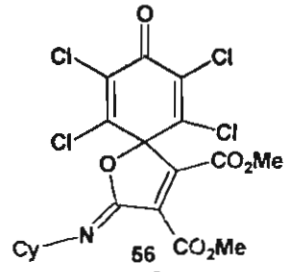
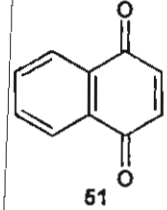
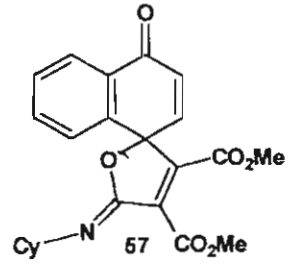
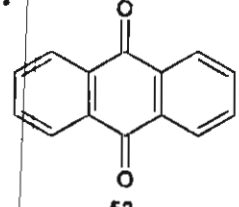
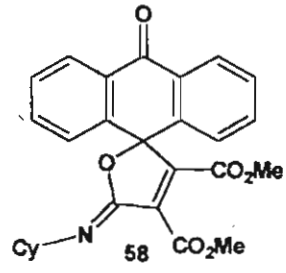


Figure 3.9 X-ray crystal structure of 53

Similar results were obtained with other 1,4-benzoquinones yielding the iminolactones **54-58**; the results are summarized in Table 3.2.

Table 3.2

Entry	Quinone	t(h)	Product	Yield(%)*
1	 50b	5	 54	55
2	 50c	3	 55	67
3	 50d	8	 56	63
4	 51	3	 57	89
5	 52	4	 58	57

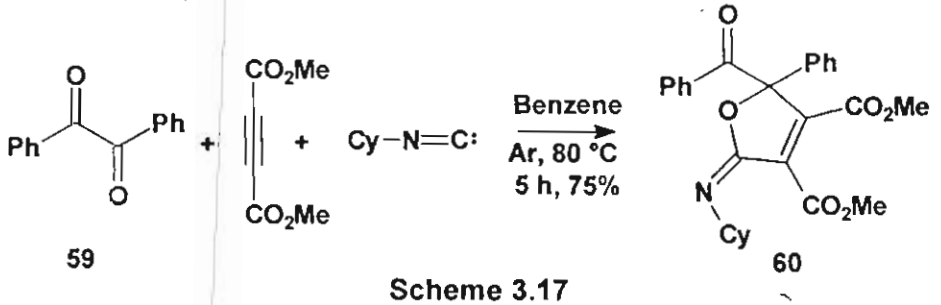
Reaction conditions = Benzene, Argon, Reflux. Where Cy = Cyclohexyl
*** isolated yield**

In all the cases, except anthraquinone **52** the products were purified by crystallization using suitable solvent mixtures. The products were completely characterized by spectroscopic and analytical methods.

The reaction of 2-methyl-1,4-benzoquinone with DMAD and cyclohexyl isocyanide gave only one regioisomer **55** and its structure was assigned on the basis of spectroscopic data. The IR spectrum showed characteristic absorptions at 1732, 1669 and 1642 cm^{-1} indicating the presence of ester and enone carbonyls. In the ^1H NMR spectrum, the carbomethoxy protons were visible at δ 3.75 and 3.96. The olefinic protons were discernible at δ 6.26 as a singlet and two doublets at δ 6.36 and 6.59. The singlet signal at δ 1.90 can be attributed to the methyl group. In the ^{13}C NMR spectrum, the signals at δ 159.37, 161.15 and 184.28 were due to the ester and enone carbonyls respectively. The methyl group resonated at δ 17.08. All other signals are also in accordance with the assigned structure.

3.5 Reaction with Other Diones

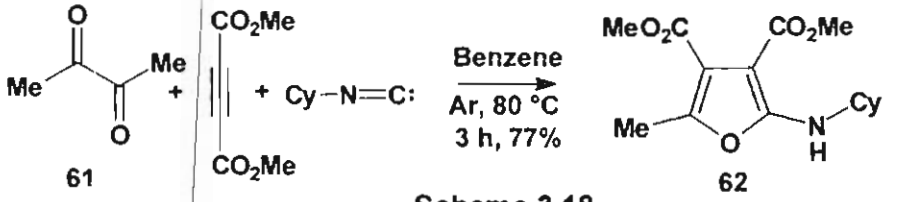
1,2-Diones like benzil **59** on treatment with DMAD and cyclohexyl isocyanide in anhydrous benzene afforded the iminolactone **60** in 75% yield (Scheme 3.17).



Scheme 3.17

As usual, the structure of the product was elucidated by spectroscopic methods. The IR spectrum of **60** showed strong bands at 1740 and 1690 cm^{-1} due to the ester carbonyl groups. The absorption at 1677 cm^{-1} is due to the benzoyl carbon. In the ^1H NMR, the characteristic methyls of the carbomethoxy groups resonated at δ 3.74 and 3.89. In the ^{13}C NMR spectrum, the benzoyl carbonyl resonated at δ 192.83. The ester carbonyls were seen at δ 161.25 and 161.94. The signal at δ 95.59 and 153.85 were assigned to the spirocarbon and imine carbon respectively. All other signals were in good agreement with the assigned structure.

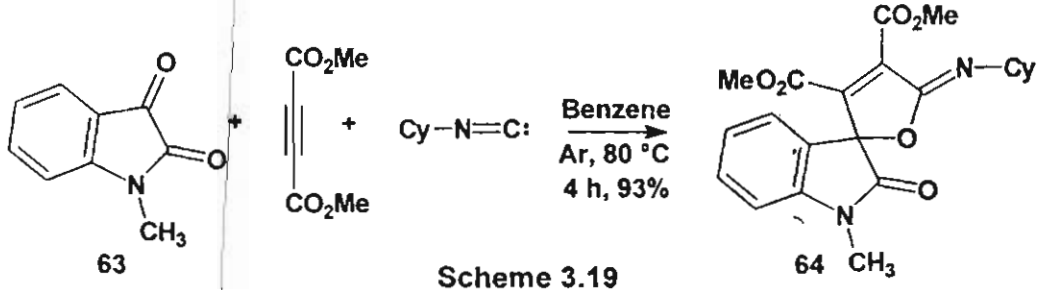
Surprisingly, we found that the reaction of biacetyl **61**, with DMAD and cyclohexyl isocyanide in benzene at 80 °C afforded the aminofuran derivative **62** (Scheme 3.18).



Scheme 3.18

The IR spectrum of **62** showed the amine absorption at 3336 cm^{-1} and the two strong bands at 1726 and 1682 cm^{-1} were assigned to the ester carbonyls. In the ^1H NMR spectrum, the carbomethoxy methyl groups were seen at δ 3.74 and 3.82 respectively. A doublet at δ 6.59 (J = 7.71) was assigned to the amine H- atom. In the ^{13}C NMR spectrum, the methyl group attached to the furan ring resonated at δ 12.66. The ester carbonyls were seen at δ 164.41 and 165.31.

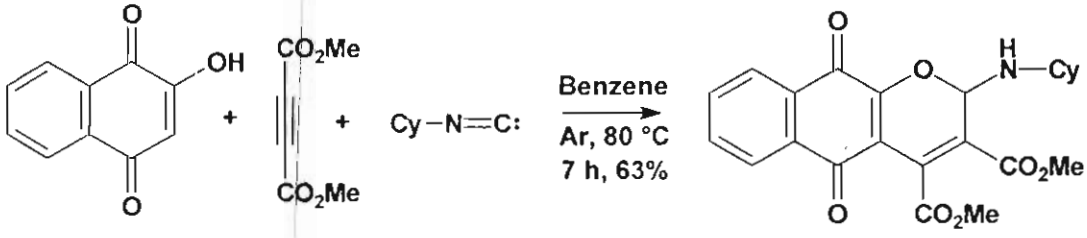
Subsequently, we focused our attention on isatins; *N*-methyl isatin **63** when treated with DMAD and cyclohexyl isocyanide afforded the iminolactone **64** in 93% yield (Scheme 3.19).



Scheme 3.19

The product was purified by chromatography on alumina and characterized by spectroscopic analysis. The IR spectrum of **64** showed the characteristic carbomethoxy carbonyl absorptions at 1732 and 1672 cm^{-1}. The amide carbonyl absorption was seen at 1639 cm^{-1}. In the ^1H NMR spectrum, the -NMe and -OMe protons were seen at δ 3.28, 3.64 and 3.94 respectively. In the ^{13}C NMR spectrum, the three carbonyls resonated at δ 159.91, 161.62 and 170.07. The spirocarbon was discernible at δ 77.19. All the other signals were in agreement with the assigned structure.

A different type of reactivity profile was observed with 2-hydroxy-1,4-naphthoquinone **65**. On treatment with DMAD and cyclohexyl isocyanide in anhydrous benzene **65** yielded a product that was characterized as **66** (Scheme 3.20).

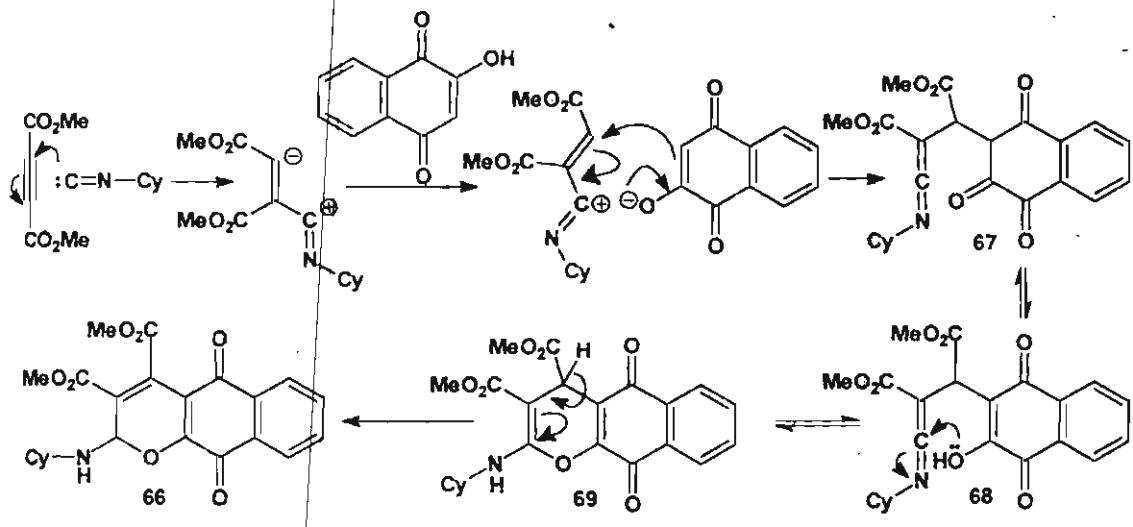


65 **66**

Scheme 3.20

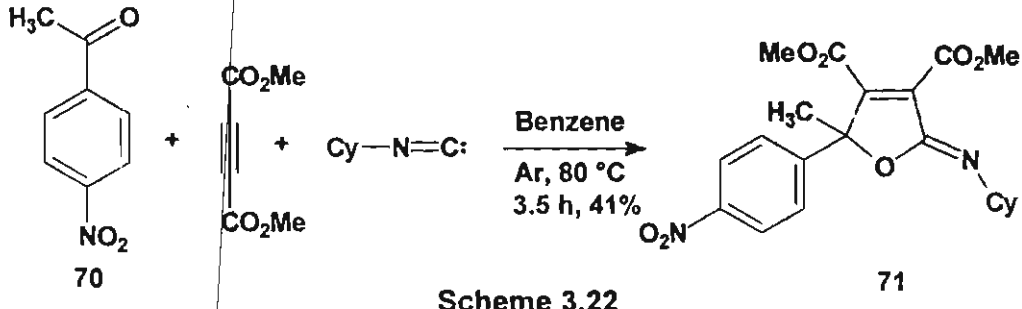
The structure of the product **66** was established by spectroscopic and analytical methods. The IR spectrum of the product showed carbomethoxy carbonyl absorptions at 1732 and 1675 cm^{-1} and the amine absorption at 3261 cm^{-1}. In the ^1H NMR spectrum, the characteristic methoxy protons appeared as singlets at δ 3.67 and 3.74. The signal at δ 4.70 is attributed to the methine proton attached to nitrogen and oxygen. The aromatic protons were visible between δ 7.62-8.14 and the amine hydrogen atom resonated at δ 8.66 (exchangeable by D_2O) indicating extensive intramolecular hydrogen bond formation with the vicinal carbonyl group. In the ^{13}C NMR, the ester carbonyls were observed at δ 169.06 and 172.70. The signals at δ 177.41 and 177.47 can be attributed to the 1,4-naphthoquinone carbonyls. All other signals are in good agreement with the proposed structure. The structure was further supported by satisfactory elemental analysis.

Mechanistically, the reaction may be viewed as shown in Scheme 3.21. The initially formed 1:1 zwitterionic intermediate gets protonated by the highly acidic proton of the 2-hydroxy-1,4-naphthoquinone and concomitant attack of the anion generated gives the ketenimine **67**. Subsequently, it undergoes isomerization under the reaction conditions to give tricyclic pyran system **66**.



Scheme 3.21

Interestingly, even aromatic ketones such as 4-nitroacetophenone **70** on treatment with DMAD and cyclohexyl isocyanide in anhydrous benzene afforded the iminolactone **71** in 41% yield (Scheme 3.22).



Scheme 3.22

As observed for other iminolactones, the IR spectrum of **71** showed strong absorptions at 1732 and 1679 cm^{-1} indicating the presence of two carbomethoxy carbonyls. The ^1H NMR spectrum showed two sharp singlets at δ 3.72 and 3.92 corresponding to the carbomethoxy groups. The methyl group was visible at δ 2.08 and the aromatic protons as two doublets at δ 7.59 (2H, J = 8.82) and 8.22 (2H, J = 8.79). In the ^{13}C NMR spectrum, the carbomethoxy carbonyls were seen at δ 160.80 and 162.26. The spirocarbon characteristically resonated at δ 88.98. All other signals are in good agreement with the proposed structure.

3.6 Conclusion

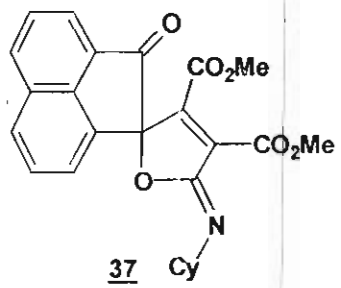
We have observed a novel three component condensation reaction that offers an easy and efficient one pot synthesis of iminolactones, which may be potentially amenable to a number of synthetic transformations.

3.7 Experimental Details

General information about the experiments is given in Section 2.13 (Chapter 2).

Spiro[acenaphthylene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-2-one 37

A mixture of acenaphthenequinone (182 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene was purged with argon for 5 min. To this mixture, cyclohexyl isocyanide (120 mg. 1.1 mmol) was added by a syringe and the reaction mixture was refluxed for 3 h. The solvent was removed under vacuum and the product was crystallized from CH_2Cl_2-hexane mixture. It was washed with hexane (4×3 mL) to give **37** as a pale brown amorphous solid (427 mg, 97%). mp 218-219 °C.



37

IR (KBr) ν_{max}: 2955, 2948, 2854, 1755, 1728, 1688, 1640, 1600, 1431, 1297 cm^{-1}.

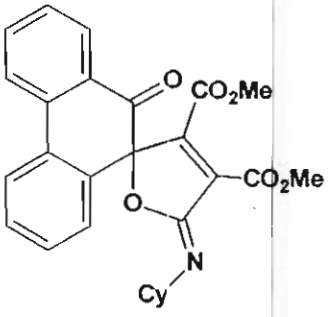
^{1}H NMR: δ 1.16-1.76 (m, 10H), 3.46 (s, 3H), 3.54 (m, 1H), 3.97 (s, 3H), 7.34-8.19 (m, 6H).

^{13}C NMR: δ 24.87, 25.84, 33.21, 33.39, 52.74, 53.22, 56.93, 90.72, 121.50, 123.21, 127.13, 128.70, 128.81, 132.17, 133.77, 138.29, 141.21, 143.06, 154.71, 160.32, 161.91, 195.39.

Anal. Calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23. Found: C, 69.54; H, 5.30; N, 2.84.

Spiro[phenanthrene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-2-one 38

Cyclohexyl isocyanide (120 mg, 1.1 mmol) was added to a refluxing mixture of phenanthrenequinone (208 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene and the refluxing was continued for 6 h. The solvent was removed under reduced pressure and the product was crystallized from CH_2Cl_2-hexane mixture. It was washed with hexane (4×3 mL) to give **38** as a pale yellow crystalline solid (424 mg, 92%). mp 221-222 °C.



38

IR (KBr) ν_{max}: 2924, 2850, 1751, 1719, 1682, 1601, 1451, 1364, 1295, 1270 cm^{-1}.

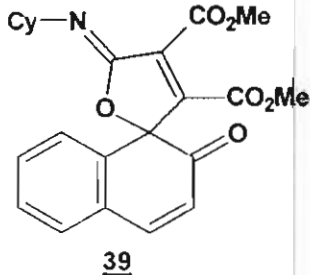
^{1}H NMR: δ 1.19-1.86 (m, 10H), 3.46 (s, 3H), 3.55 (m, 1H), 3.94 (s, 3H), 7.25-7.49 (m, 4H), 7.71-7.73 (m, 1H), 8.04-8.13 (m, 3H).

^{13}C NMR: δ 24.69, 25.68, 32.91, 33.20, 52.48, 52.96, 56.75, 86.68, 123.13, 123.83, 128.24, 128.59, 129.37, 130.04, 131.23, 133.44, 135.40, 144.11, 154.88, 160.04, 161.64, 190.58.

HRMS (EI) Calcd for $C_{27}H_{25}NO_6$: 459.1681. Found: 459.1709.

Spiro[naphthylene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-2-one 39

A mixture of 1,2-naphthoquinone (158 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene at 80 °C was purged with argon for 5 min, followed by the addition of cyclohexyl isocyanide (120 mg, 1.1 mmol). The reaction mixture was refluxed for 7 h and the residue obtained after removal of the solvent was dissolved in CH_2Cl_2-hexane mixture (3+4 mL). The solution was kept in a refrigerator overnight. The crystallized product was separated and washed with hexane to give **39** as pale brown crystals (263 mg, 64%). mp 190-191 °C.



39

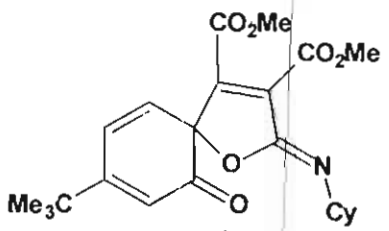
IR (KBr) ν_{max}: 2927, 2853, 1757, 1726, 1676, 1434 cm^{-1}.

^{1}H NMR: δ 1.18-1.72 (m, 10H), 3.54 (m, 1H), 3.61 (s, 3H), 3.94 (s, 3H), 6.28 (d, J = 9.93, 1H), 7.26-7.50 (m, 4H), 7.51 (d, J = 9.97, 1H).

^{13}C NMR: δ 24.68, 24.74, 25.71, 33.02, 33.22, 52.66, 53.02, 56.74, 85.57, 124.29, 127.97, 130.00, 130.42, 130.62, 136.10, 137.30, 143.68, 145.50, 154.89, 160.04, 161.66, 191.60.

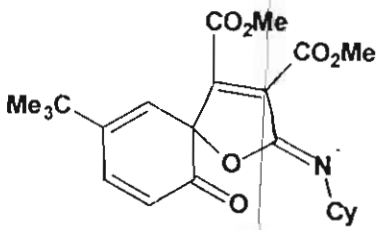
Dimethyl 7-(*tert*-butyl)-2-(cyclohexylimino)-10-oxo-1-oxaspiro[4.5]deca-3,6,8-triene-3,4-dicarboxylate 40 and Dimethyl 8-(*tert*-butyl)-2-(cyclohexylimino)-10-oxo-1-oxaspiro[4.5]deca-3,6,8-triene-3,4-dicarboxylate 41

A mixture of 4-*tert*-butyl-1,2-benzoquinone (152 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene (10 mL) was purged with argon for 5min. Cyclohexyl isocyanide (120 mg, 1.1 mmol) was added to it by a syringe and the reaction mixture was refluxed for 3 h. The solvent was removed under vacuum and the residue on radial chromatography on a Chromatotron® using 95:5 hexane-ethyl acetate afforded an inseparable mixture of regioisomers **40** and **41** as a pale yellow solid (274 mg, 68%).



40

+



41

IR (KBr) ν_{max}: 2932, 2859, 1748, 1739, 1669, 1646, 1573, 1440, 1348, 1275 cm^{-1}.

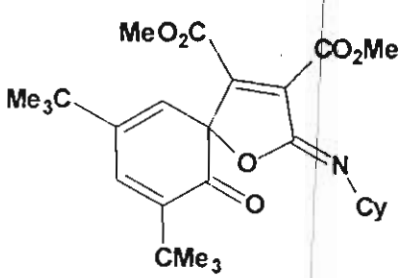
^{1}H NMR: δ 1.12-1.71 (m, 38H), 3.42 (m, 1H), 3.55 (m, 1H), 3.69 (s, 3H), 3.76 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 5.77 (d, J = 1.75, 1H), 6.07 (s, 1H), 6.10 (s, 1H), 6.19 (d, J = 10.27, 1H), 6.55-6.59 (dd, J = 8.43, 1.50, 1H), 7.18-7.23 (dd, J = 7.92, 2.34, 1H).

^{13}C NMR: δ 24.74, 24.79, 24.94, 25.07, 25.78, 28.02, 28.11, 28.38, 32.86, 32.95, 33.01, 33.32, 33.38, 34.42, 34.72, 35.70, 52.39, 52.49, 52.76, 53.01, 56.60, 56.66, 57.10, 57.19, 77.41, 83.77, 116.96, 119.13, 125.18, 125.48, 125.56, 127.23, 127.29, 133.01, 138.29, 142.00, 142.18, 146.49, 153.13, 154.58, 159.94, 161.52, 161.71, 161.79, 163.62, 193.43.

Iminolactones 42 and 43

A mixture of 3,5-di-*tert*-butyl-1,2-benzoquinone (200 mg, 0.91 mmol) and DMAD (142 mg, 1 mmol) in anhydrous benzene (10 mL) at reflux was treated with cyclohexyl isocyanide (109 mg, 1.0 mmol) and the refluxing was continued for 8 h. The solvent was removed under vacuum and the residue on radial chromatography on a Chromatotron® using 95:5 hexane-ethyl acetate afforded a pale yellow puffy solid **42** (96 mg, 22%). Further elution with the same solvent mixture afforded the iminolactone **43** as a low melting pale yellow solid (153 mg, 36%).

Dimethyl 7,9-di(*tert*-butyl)-2-(cyclohexylimino)-10-oxo-1-oxaspiro-[4.5]deca-3,6,8-triene-3,4-dicarboxylate 42



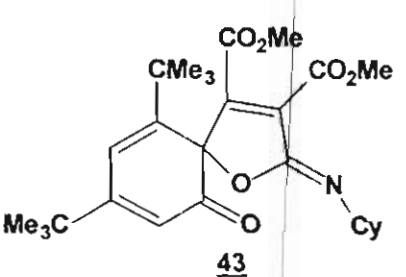
42

IR (KBr) ν_{max}: 2937, 2862, 1755, 1738, 1689, 1445, 1376, 1226 cm^{-1}.

^{1}H NMR: δ 1.17 (s, 9H), 1.24 (s, 9H), 1.18-1.91 (m, 10H), 3.59 (m, 1H), 3.67 (s, 3H), 3.89 (s, 3H), 5.69 (d, J=1.96, 1H), 6.95 (s, 1H).

^{13}C NMR: δ 24.84, 24.86, 28.37, 29.20, 33.01, 33.44, 35.03, 52.35, 53.01, 56.04, 86.84, 123.06, 135.75, 137.14, 143.72, 144.46, 146.87, 153.03, 160.30, 161.91, 193.06.

Dimethyl 6,8-di(*tert*-butyl)-2-(cyclohexylimino)-10-oxo-1-oxaspiro-[4.5]deca-3,6,8-triene-3,4-dicarboxylate 43



43

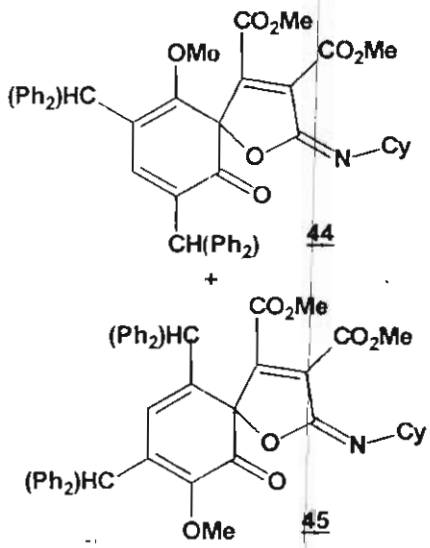
IR (KBr) ν_{max}: 2930, 2850, 1751, 1732, 1676, 1576, 1432, 1351, 1283 cm^{-1}.

^{1}H NMR: δ 1.15 (s, 9H), 1.18 (s, 9H), 1.15-1.82 (m, 10H), 3.60 (m, 1H), 3.65 (s, 3H), 3.83 (s, 3H), 5.92 (d, J = 1.17, 1H), 6.52 (d, J = 1.07, 1H).

^{13}C NMR: δ 24.73, 25.73, 28.07, 31.02, 32.80, 33.74, 35.94, 38.12, 52.38, 52.71, 56.89, 86.02, 116.41, 123.38, 135.70, 146.29, 153.11, 154.93, 160.47, 161.40, 164.97, 194.35.

Dimethyl 7,9-dibenzhydryl-2-(cyclohexylimino)-6-methoxy-10-oxo-1-oxaspiro[4.5]deca-3,6,8-triene-3,4-dicarboxylate 44 and Dimethyl 6,8-dibenzhydryl-2-(cyclohexylimino)-9-methoxy-10-oxo-1-oxaspiro[4.5]deca-3,6,8-triene-3,4-dicarboxylate 45

To a mixture of 3-methoxy-4,6-bis(1,1-diphenylmethyl)-1,2-benzoquinone (200 mg, 0.43 mmol) and DMAD (67 mg, 0.47 mmol) in refluxing anhydrous benzene (10 mL) was added cyclohexyl isocyanide (52 mg, 0.47 mmol) and the refluxing was continued for 5 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel using 90:10 hexane-ethyl acetate to afford an inseparable mixture of iminolactones **44** and **45** as an yellow solid (255 mg, 82%).



IR (KBr) ν_{max}: 2924, 2856, 1751, 1726, 1682, 1495, 1445 cm^{-1}.

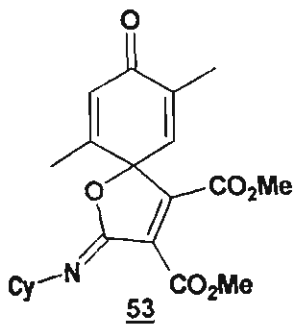
^{1}H NMR: δ 1.05-1.07 (m, 20H), 3.33 (s, 3H), 3.40 (m, 1H), 3.51 (s, 3H), 3.61 (s, 4H), 3.71 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.67 (s, 1H), 5.36 (s, 1H), 5.58 (s, 1H), 5.79 (s, 1H), 5.84 (s, 1H), 6.52 (s, 1H), 6.86-7.31 (m, ArH).

^{13}C NMR: δ 24.53, 24.61, 25.66, 32.80, 32.99, 33.35, 47.89, 48.53, 48.93, 51.48, 52.10, 52.45, 52.67, 52.81, 56.38, 56.56, 59.74, 62.54, 88.60, 87.54, 126.36, 126.82, 128.06, 128.13, 128.23, 128.38, 128.42, 128.52, 128.62, 128.71, 128.81, 128.97, 129.55, 135.92, 137.30, 139.01, 139.46, 140.06, 140.72

140.80, 141.02, 141.27, 141.48, 143.29, 143.44, 144.06, 146.63, 152.11, 154.27, 154.80, 159.66, 159.72, 161.06, 161.35, 189.73, 190.68.

Dimethyl 2-(cyclohexylimino)6,9-dimethyl-8-oxo-1-spiro[4.5]deca-3,6,9-triene-3,4-dicarboxylate 53

A mixture of 2,5-dimethyl-1,4-benzoquinone (272 mg, 2 mmol) and DMAD (312 mg, 2.2 mmol) in anhydrous benzene (15 mL) was purged with argon for 5 min. To this mixture, cyclohexyl isocyanide (239 mg, 2.2 mmol) was added *via* a syringe and the reaction mixture was refluxed for 4 h. The solvent was removed under vacuum. The product **53** was crystallized from CH_2Cl_2-hexane mixture and washed with hexane (4×5 mL) to give a white crystalline solid (712 mg, 92%). mp 167-168 °C.



53

IR (KBr) ν_{max}: 2930, 2856, 1757, 1726, 1682, 1646, 1439, 1357, 1283 cm^{-1}.

^{1}H NMR: δ 1.25-1.84 (m, 10H), 1.85 (d, *J* = 1.11, 3H), 1.93 (d, *J* = 1.20, 3H), 3.59 (m, 1H), 3.71 (s, 3H), 3.92 (s, 3H), 6.22 (d, *J* = 1.22, 1H), 6.32 (d, *J* = 1.40, 1H).

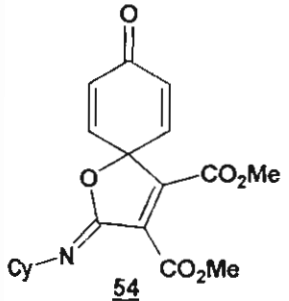
^{13}C NMR: δ 15.51, 17.15, 24.76, 24.83, 25.76, 33.31, 33.50, 52.88, 53.20, 56.83, 85.08, 129.21, 136.83, 138.12, 138.71, 142.57, 151.34, 153.88, 159.85, 161.61, 185.31.

HRMS(EI) Calcd for $C_{21}H_{25}NO_6$: 387.1681. Found: 387.1690.

Crystal data for **53**: $C_{21}H_{25}NO_6$. *M* = 387.42. The crystal used for X-ray study has the dimensions of 0.36 x 0.30 x 0.22 mm. *M* = 387.42, monoclinic, space group $P2_1$, unit cell dimensions: a =13.5925 (2) Å, b = 9.4664 (2) Å, c = 16.2656 (2) Å, a = 90°, b = 91.052 (1)°, y = 90°, *V* = 2092.576 (6) $Å^3$, *D*c 1.230 Mg /m^3.

Dimethyl 2-(cyclohexylimino)-8-oxo-1-spiro[4.5]deca-3,6,9-triene-3,4-dicarboxylate 54

To a refluxing mixture of 1,4-benzoquinone (108 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene (10 mL), cyclohexyl isocyanide (120 mg, 1.1 mmol) was added and heating was continued for 5 h. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2-hexane mixture. After triturating, it was kept in a refrigerator for 24 h. The product was separated, washed with hexane to give **54** as a colorless solid (198 mg, 55%). mp 145-146 °C.



54

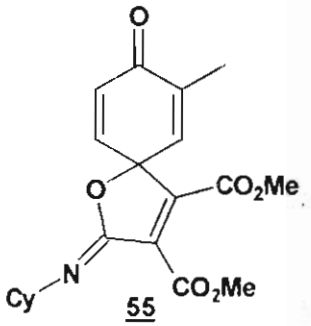
IR (KBr) ν_{max}: 2939, 2859, 1739, 1682, 1646, 1507, 1407, 1341 cm^{-1}.

^{1}H NMR: δ 1.28-1.88 (m, 10H), 3.58 (m, 1H), 3.73 (s, 3H), 3.94 (s, 3H), 6.38 (s, 2H), 6.59 (s, 2H).

^{13}C NMR: δ 24.63, 24.79, 25.64, 33.25, 52.79, 53.18, 56.74, 82.33, 129.41, 131.03, 139.14, 140.99, 141.79, 153.13, 159.57, 161.52, 183.83.

Dimethyl 2-(cyclohexylimino)-7-methyl-8-oxo-1-spiro[4.5]deca-3,6,9-triene-3,4-dicarboxylate 55

To a mixture of 2-methyl-1,4-benzoquinone (244 mg, 2 mmol) and DMAD (312 mg, 2.2 mmol) in refluxing anhydrous benzene (20 mL) cyclohexyl isocyanide (240 mg, 2.2 mmol) was added and the refluxing was continued for 3 h. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2-hexane mixture (2+3 mL). On keeping in a refrigerator for two days, the product crystallized out and it was separated by filtration. It was washed with hexane to give **55** as a white crystalline solid (250 mg, 67%). mp 156-157 °C.



55

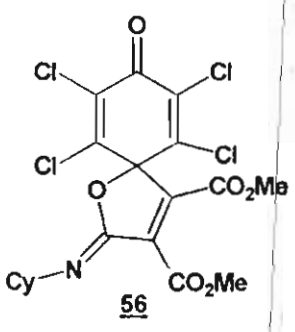
IR (KBr) ν_{max}: 2932, 2853, 1732, 1669, 1642, 1507, 1454, 1394 cm^{-1}.

^{1}H NMR: δ 1.27-1.97 (m, 10H), 1.90 (s, 3H), 3.62 (m, 1H), 3.75 (s, 3H), 3.96 (s, 3H), 6.26 (s, 1H), 6.36 (dd, J = 9.89, 1.41, 1H), 6.59 (d, J = 9.87, 1H)

^{13}C NMR: δ 17.08, 24.38, 24.45, 25.38, 32.95, 33.11, 52.61, 52.49, 56.55, 84.05, 129.00, 130.50, 138.84, 141.46, 141.81, 151.31, 153.31, 159.37, 161.15, 184.28.

Dimethyl 6,7,9,10-tetrachloro-2-(cyclohexylimino)-8-oxo-1-spiro[4.5]deca-3,6,9-triene-3,4-dicarboxylate 56

To a refluxing mixture of *p*-chloranil (245 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene was added cyclohexyl isocyanide (120 mg, 1.1 mmol) and the refluxing was continued at 80 °C for 8 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 90:10 hexane-ethyl acetate gave iminolactone **56** as a colorless solid (315 mg, 63%). mp 151-152 °C (recrystallized from CH_2Cl_2-hexane).



56

IR (KBr) ν_{max}: 2934, 2859, 1751, 1732, 1695, 1589, 1434, 1346, 1278 cm^{-1}.

^{1}H NMR: δ 1.25-1.77 (m, 10H), 3.62 (m, 1H), 3.79 (s, 3H), 3.96 (s, 3H).

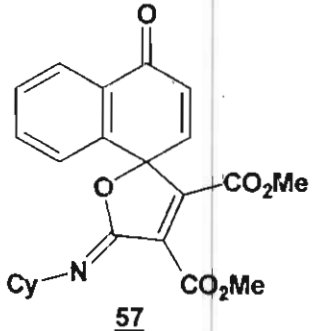
^{13}C NMR: δ 24.46, 25.52, 32.97, 53.34, 57.31, 86.61, 133.01, 138.17, 141.30, 144.16, 151.71, 158.65, 160.42, 168.95.

HRMS (EI) Calcd for $C_{19}H_{17}NO_6Cl_4$: 497.1563. Found: 497.9636.

Anal. Calcd for $C_{19}H_{17}NO_6Cl_4$: C, 45.90; H, 3.44; N, 2.81. Found: C, 45.55; H, 3.03; N, 2.66.

Spiro[naphthylene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-8-one 57

To a mixture of 1,4-naphthoquinone (200 mg, 1.27 mmol) and DMAD (198 mg, 1.40 mmol) in refluxing anhydrous benzene (10 mL), cyclohexyl isocyanide (153 mg, 1.40 mmol) was added and the refluxing was continued for 3 h. The residue obtained after the removal of the solvent was dissolved in CH_2Cl_2-hexane mixture. The crystallized product was separated and washed with hexane (4x5 mL) to give **57** as a white crystalline solid (464 mg, 89%). mp 155-156 °C.



57

IR (KBr) ν_{max}: 2934, 2859, 1751, 1732, 1676, 1599, 1435, 1348 cm^{-1}.

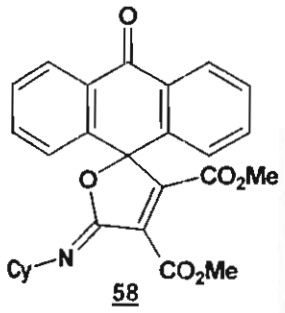
^{1}H NMR: δ 1.24-1.74 (m, 10H), 3.56 (s, 3H), 3.60 (m, 1H), 3.95 (s, 3H), 6.56 (d, J = 10.10, 1H), 6.72 (d, J = 10.14, 1H), 7.27 (d, J = 7.26, 1H), 7.52-7.61 (m, 2H), 8.15 (d, J = 6.98, 1H).

^{13}C NMR: δ 24.62, 25.60, 33.09, 33.30, 52.59, 53.12, 56.78, 83.41, 125.61, 126.90, 129.49, 130.80, 131.22, 133.15, 137.39, 141.80, 143.09, 154.00, 159.47, 161.69, 183.14.

HRMS (EI) Calcd for $C_{23}H_{23}NO_6$: 409.4357. Found: 409.1525.

Spiro[anthracene-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-8-one 58

A mixture of anthraquinone (200 mg, 0.96 mmol) and DMAD (150 mg 1.06 mmol) in anhydrous benzene (15 mL) was purged with argon for 5 min. To this mixture, cyclohexyl isocyanide (116 mg, 1.06 mmol) was added and the reaction mixture was refluxed for 4 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 70:30 hexane-ethyl acetate mixture gave the iminolactone **58** as a white crystalline solid (254 mg, 57%). mp 224-225 °C (recrystallized from CH_2Cl_2-hexane).



58

IR (KBr) ν_{max}: 2927, 2853, 1745, 1732, 1676, 1600, 1448, 1430, 1322, 1286 cm^{-1}.

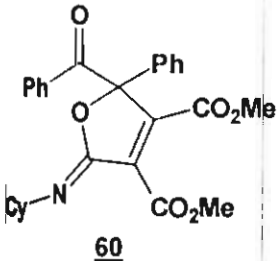
^{1}H NMR: δ 1.21-1.82 (m, 10H), 3.41 (s, 3H), 3.67 (m, 1H), 3.96 (s, 3H), 7.44 (d, J = 7.52, 2H) 7.55-7.70 (m, 4H), 8.34 (d, J = 7.31, 2H).

^{13}C NMR: δ 24.74, 25.67, 33.27, 52.59, 53.25, 57.03, 84.81, 125.84, 127.56, 129.66, 131.31, 133.72, 135.78, 138.30, 146.20, 155.12, 159.70, 162.12, 182.58.

HRMS (EI) Calcd for $C_{27}H_{25}NO_6$: 459.4955. Found: 459.1681.

Dimethyl 2-benzoyl-5-(cyclohexylimino)-2-phenyl-2,5-dihydro-3,4-furandicarboxylate 60

To a refluxing mixture of benzil (200 mg, 0.95 mmol) and DMAD (149 mg, 1.05 mmol) in anhydrous benzene, cyclohexyl isocyanide (115 mg, 1.05 mmol) was added and the refluxing was continued for 5 h. The solvent was removed under vacuum and the residue on silica gel chromatography with 80:20 hexane-ethyl acetate afforded the iminolactone **60** as a colorless solid (349 mg, 75%). mp 102-103 °C (recrystallized from CH_2Cl_2-hexane).



60

IR (KBr) ν_{max}: 2930, 2850, 1740, 1690, 1677, 1448, 1432 cm^{-1}.

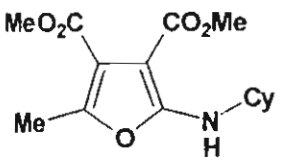
^{1}H NMR: δ 1.13-1.87 (m, 10H), 3.57 (m, 1H), 3.74 (s, 3H), 3.89 (s, 3H), 7.35 (m, 7H), 7.48 (m, 1H), 7.87 (m, 2H).

^{13}C NMR: δ 24.80, 25.03, 25.80, 33.17, 33.37, 52.58, 53.02, 57.38, 95.59, 126.35, 128.31, 128.66, 129.32, 131.02, 133.60, 133.70, 134.18, 136.09, 146.27, 153.85, 161.25, 161.94, 192.83.

Dimethyl 2-(cyclohexylimino)-5-methyl-3,4-furandicarboxylate 62

A mixture of biacetyl (173 mg, 2 mmol) and DMAD (294 mg, 2.1 mmol) in anhydrous benzene was purged with argon for 5 min, followed by the addition of cyclohexyl isocyanide (229 mg, 2.1 mmol). The reaction mixture was refluxed

for 3 h. The residue obtained after removal of the solvent was purified by silica gel chromatography with 85:15 hexane-ethyl acetate to afford the aminofuran **62** as a colorless solid (455 mg, 77%). mp 89-90 °C (recrystallized from CH_2Cl_2-hexane).



62

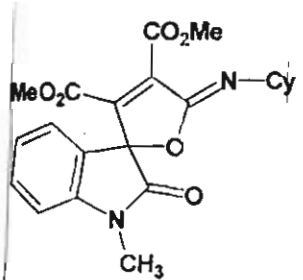
IR (KBr) ν_{max}: 3336, 2943, 2856, 1726, 1682, 1621, 1595, 1475, 1440 cm^{-1}.

^{1}H NMR: δ 1.25-1.98 (m, 10H), 2.33 (s, 3H), 3.57 (m, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 6.59 (d, J = 7.71, 1H).

^{13}C NMR: δ 12.66, 24.54, 25.42, 33.60, 50.71, 51.13, 51.48, 84.89, 112.73, 146.10, 161.63, 164.41, 165.31.

Spiro[1'-methylindole-1(2*H*)-4-cyclohexylimino-2,3-bis(methoxycarbonyl)furan]-2-one 64

To a refluxing mixture of *N*-methyl isatin (161 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene, cyclohexyl isocyanide (120 mg, 1.1 mmol) was added and the refluxing was continued for 4 h. The reaction mixture was concentrated under vacuum and the residue on chromatography on neutral alumina with 80:20 hexane-ethyl acetate afforded the iminolactone **64** as a colorless solid (381 mg, 93%). mp 162-163 °C (recrystallized from CH_2Cl_2-hexane).



64

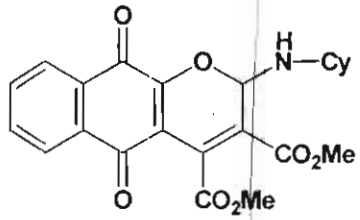
IR (KBr) ν_{max}: 2925, 2854, 1732, 1672, 1639, 1606, 1493, 1434, 1367, 1302, 1238 cm^{-1}.

^{1}H NMR: δ 1.19-1.72 (m, 10H), 3.28 (s, 3H), 3.57 (m, 1H), 3.64 (s, 3H), 3.94 (s, 3H), 6.89 (d, J = 7.77, 1H), 7.05-7.43 (m, 3H).

^{13}C NMR: δ 24.71, 24.78, 25.75, 26.80, 33.14, 33.23, 52.79, 53.06, 56.84, 77.19, 108.87, 123.36, 124.19, 124.43, 131.53, 138.41, 144.71, 154.17, 159.91, 161.62, 170.07.

Dimethyl 5-(cyclohexylamino)-5,10-dioxo-5,10-dihydro-2H-benzo[g]chromene-3,4-dicarboxylate 66

A mixture of 2-hydroxy-1,4-naphthoquinone (174 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene at 80 °C was purged with argon for 5 min, followed by the addition of cyclohexyl isocyanide (120 mg, 1.1 mmol). The reaction mixture was refluxed for 7 h and the residue obtained after removal of the solvent was dissolved in CH_2Cl_2-hexane mixture (3+4 mL) and kept in a refrigerator overnight. The crystallized product was separated and washed with hexane to give **66** as a wine red crystalline solid (269 mg, 63%). mp 152-153 °C (recrystallized from CH_2Cl_2-hexane).



66

IR (KBr) ν_{max}: 3261, 2949, 2856, 1732, 1675, 1641, 1602, 1447, 1365, 1301, 1176 cm^{-1}.

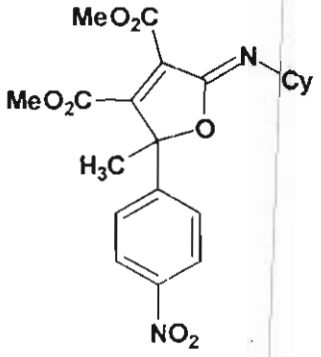
^{1}H NMR: δ 1.36-2.09 (m, 10H), 3.67 (s, 3H), 3.74 (s, 3H), 3.87 (m, 1H), 4.70 (s, 1H), 7.62-7.76 (m, 3H), 8.14 (d, J = 7.53, 1H), 8.66 (d, J = 7.50, 1H, D_2O exchangeable).

^{13}C NMR: δ 24.27, 24.35, 25.36, 33.35, 33.68, 34.90, 50.59, 51.12, 52.48, 72.35, 114.30, 123.69, 129.89, 131.64, 135.21, 156.71, 158.08, 169.06, 172.70, 177.41, 177.47.

Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.44; N, 3.29. Found: C, 64.44; H, 5.12; N, 3.21.

Dimethyl 5-(cyclohexylimino)-2-methyl-2-(4-nitrophenyl)-2,5-dihydro-3,4-furandicarboxylate 71

A mixture of 4-nitroacetophenone (165 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene at reflux was treated with cyclohexyl isocyanide (120 mg, 1.1 mmol) and the refluxing was continued for 3.5 h. The solvent was removed under vacuum and the residue on chromatography on silica gel with 80:20 hexane-ethyl acetate mixture afforded the iminolactone **71** as a white solid (170 mg, 41%). mp 118-119 °C (recrystallized from CH_2Cl_2-hexane).



71

IR (KBr) ν_{max}: 2932, 2853, 1759, 1732, 1679, 1646, 1606, 1520, 1440, 1354, 1295 cm^{-1}.

^{1}H NMR: δ 1.20-1.74 (m, 10H), 2.08 (s, 3H), 3.63 (m, 1H), 3.72 (s, 3H), 3.92 (s, 3H), 7.59 (d, J = 8.82, 2H), 8.22 (d, J = 8.79, 2H).

^{13}C NMR: δ 24.22, 24.78, 25.67, 33.34, 52.85, 53.14, 56.78, 88.98, 123.71, 127.00, 135.93, 145.64, 146.43, 147.87, 154.28, 160.80, 162.26.

3.8 References

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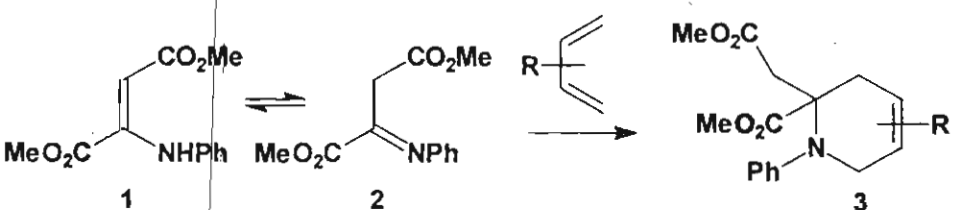
Chapter 4

The Reaction of Isocyanides and Dimethyl Acetylenedicarboxylate with *N*-Tosylimines: A Novel Synthesis of 2-Aminopyrroles

4.1 Introduction

The reactivity of carbon-nitrogen double bond has been successfully exploited in cycloaddition reactions. Substitution with electron withdrawing groups, especially the *N*-sulfonyl or *N*-acyl and activation by iminium salt formation have been shown to be effective in increasing the reactivity of the otherwise sluggishly reactive imines.[1] This is a consequence of an increase of HOMO(dipole)-LUMO(dipolarophile) interaction due to the enhanced electrophilicity of dipolarophiles. It was Alder who reported the first example of the dienophilic activity of imino compounds in 1943.[2] Tetrahydropyridine **3** was formed in the reaction of the enaminodiester **1** and various dienes, instead of the expected carbocyclic adduct, presumably *via* an imino tautomer **2** as illustrated in Scheme 4.1.



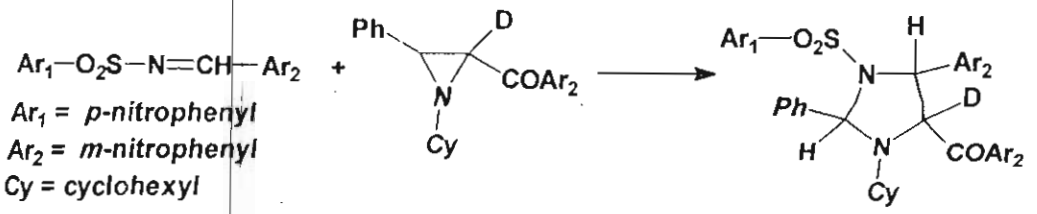
Scheme 4.1

A variety of heterocyclic systems are produced from the dipolar and Diels-Alder cycloadditions involving imines as 2π components. A brief account of such reactions is given in the following sections.

4.2 Dipolar Cycloaddition Reactions with Imines

4.2.1 Addition of Azomethine Ylides

Although Schiff bases react with azomethine ylides, the more strongly polarized sulfonylimines react more readily and regiospecifically to give *N*-sulfonyl imidazolidines **6** in excellent yields.[3] The regiochemistry of the product was established unambiguously by addition of a sulfonylimine **4** to specifically 3-deuterated aziridinyl ketone **5** (Scheme 4.2).

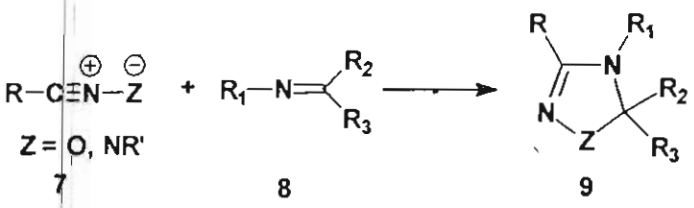


4 5 6

Scheme 4.2

4.2.2 Addition of Nitrile Oxides and Nitrile Imines

Good to excellent yields of Δ^2-1,2,4-oxadiazoline and 1,2,4-triazoline derivatives **9** were obtained by the cycloaddition of aromatic and aliphatic nitrile oxides and imines to acyclic and cyclic imino compounds (Scheme 4.3).[4]

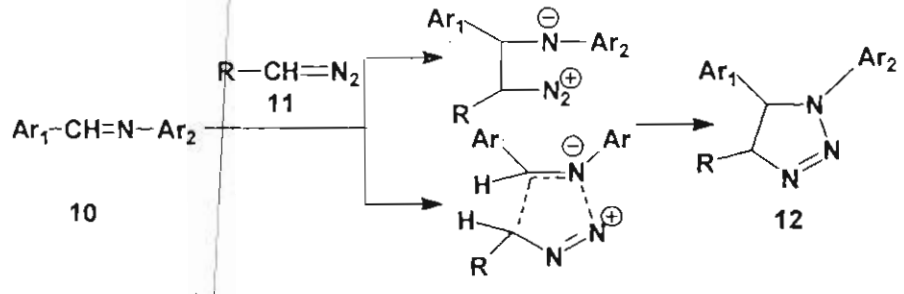


7 8 9

Scheme 4.3

4.2.3 Addition of Diazoalkanes

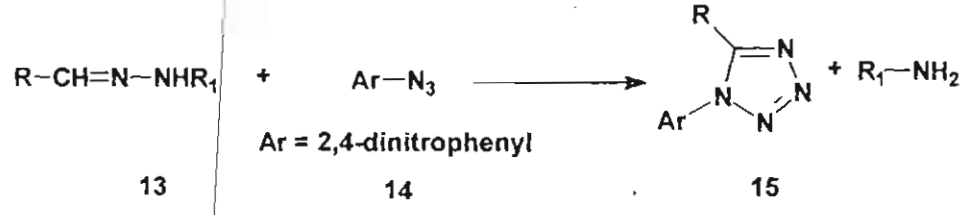
1,3-Dipolar cycloaddition of imines **10** and diazoalkanes **11** afford triazolines **12** (Scheme 4.4). Diazomethane adds rapidly to electron deficient imines. The [3+2] cycloaddition of diazomethane to the somewhat unreactive benzalaniline takes place even at very low temperatures, if catalyzed by organoaluminium compounds.[5]



Scheme 4.4

4.2.4 Addition of Azides

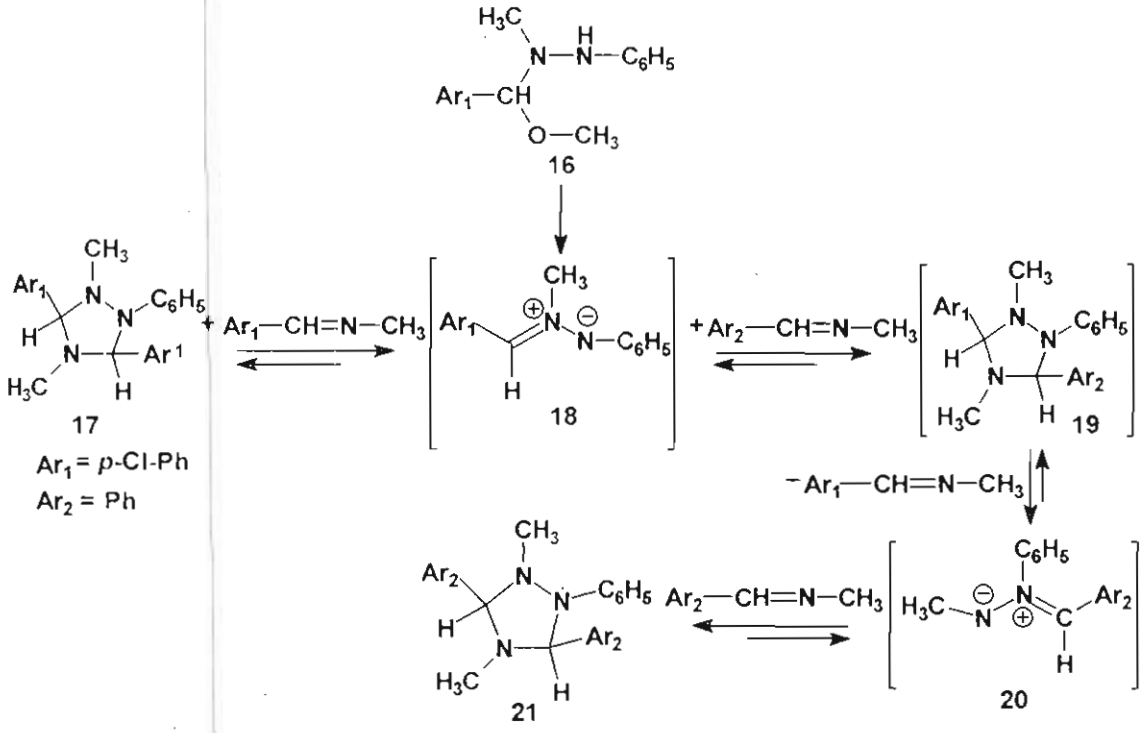
Aldehyde hydrazones gave tetrazoles on dipolar cycloaddition with 2,4-dinitrophenyl azide in moderate yields after the elimination of R_1-NH_2 (Scheme 4.5).[6]



Scheme 4.5

4.2.5 Addition of Azomethine Imines

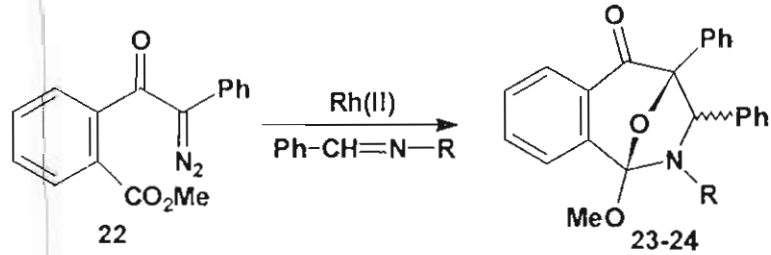
Treatment of the azomethine imine precursor, hydrazino ether **16** with *p*-chlorobenzylidene methylamine in refluxing acetonitrile yielded 99% of the triazolidine **17**. Reacting **17** with other dipolarophiles demonstrated the reversibility of the cycloaddition. Interestingly, it has been found that with an excess of benzylidene methylamine, 68% yield of the chlorine free triazolidine **21** was obtained. One possible explanation is that the adduct **19**, besides undergoing cycloreversion to give **18**, also forms the less favored 1,3-dipole **20** which then reacts with excess of azomethine to give **21** (Scheme 4.6).[7]



Scheme 4.6

4.2.6 Addition of Carbonyl Ylides

The dipolar cycloaddition of carbonyl ylides across -C=N- bonds has been studied by Padwa *et al.*[8] The rhodium(II) catalyzed reaction of **22** with both *N*-benzylidene benzene sulfonamide and methylamine afforded a mixture of *endo* (major) and *exo* (minor) cycloadducts. The diastereomers were separated and the stereochemistry of the *endo* isomer **23** was unequivocally established by X-ray crystallography (Scheme 4.7).



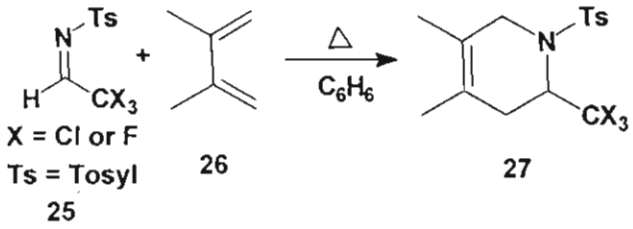
23a; *endo* (80%); R = SO_2Ph, 23b; *exo* (10%); R = SO_2Ph

24a; *endo* (60%); R = Me, 24b; *exo* (30%); R = Me

Scheme 4.7

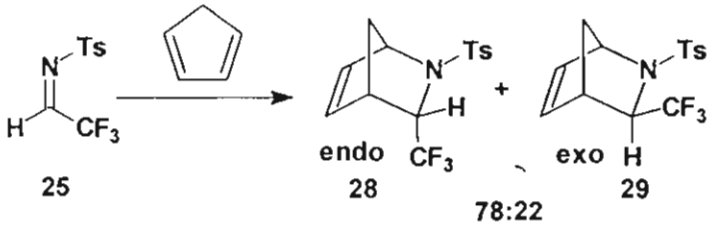
4.3 [4+2] Cycloaddition Reactions with Imines

The first example of [4+2] cycloaddition of *N*-sulfonylimines was reported by Albrecht as early as 1964. Tosylimines **25**, prepared from chloral or fluoral and *p*-toluene sulfonamide, reacted with 2,3-dimethyl butadiene **26** to give the cycloadduct **27** in high yields as illustrated in Scheme 4.8.[9]



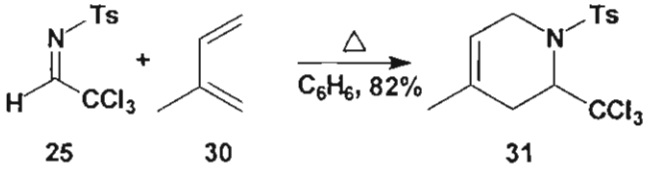
Scheme 4.8

Cycloaddition of cyclic dienes such as cyclopentadiene with *N*-tosyl trifluoromethylimine affords *exo* and *endo* adducts **28** and **29** in the ratio 78:22 (Scheme 4.9).[10]



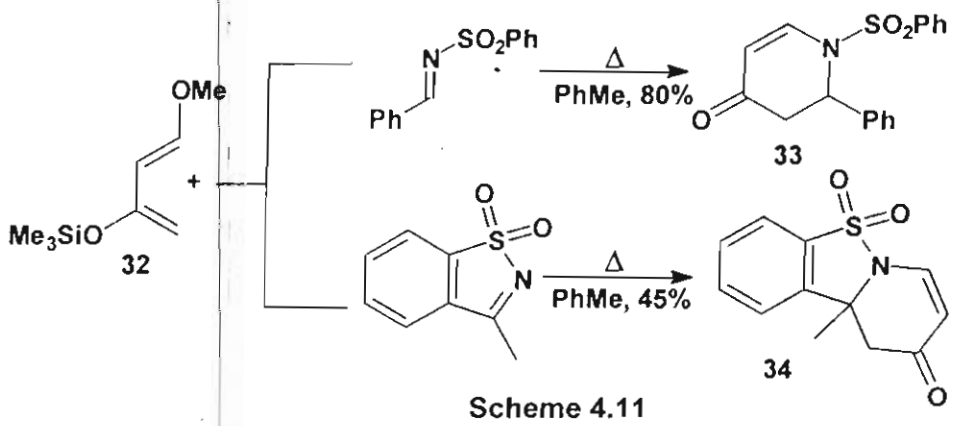
Scheme 4.9

Several examples of cycloadditions with unsymmetrical dienes have been reported.[11] The diene **30** on reaction with **25** gave only one regioisomer **31** as shown in Scheme 4.10.



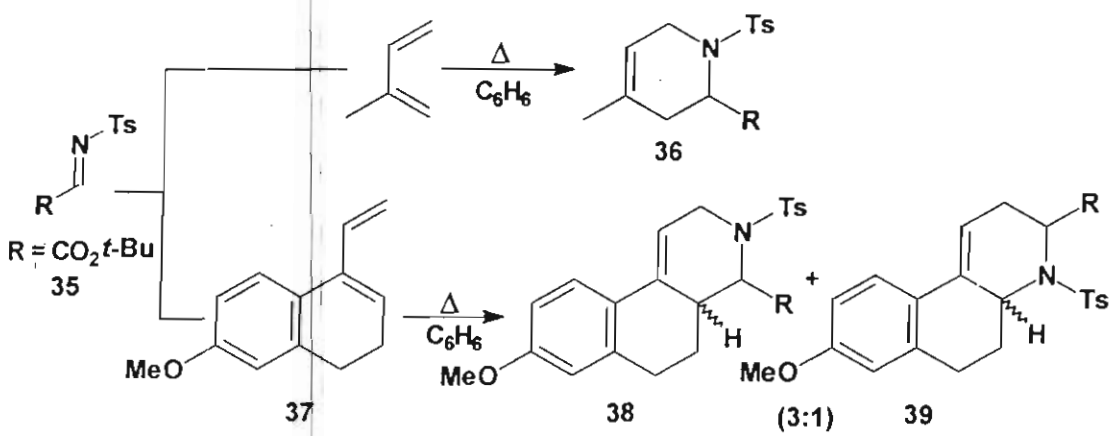
Scheme 4.10

Similarly, Danishefsky-Kitahara diene **32** showed good regioselectivity in its cycloaddition with both acyclic and cyclic *N*-sulfonylimines (Scheme 4.11).[12]



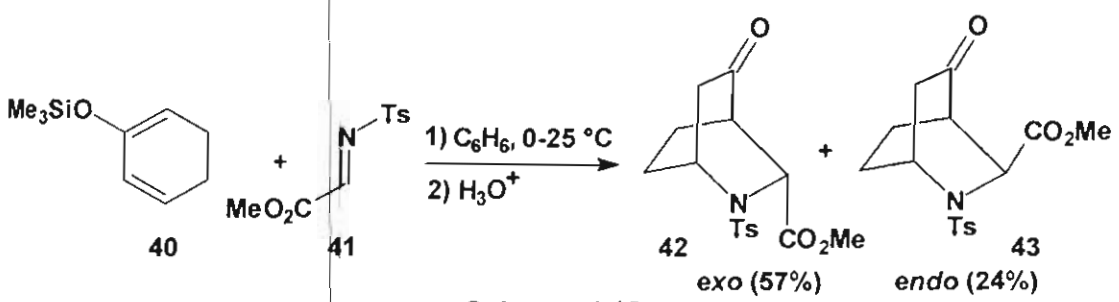
Scheme 4.11

Carboxyl substituted *N*-sulfonylimines have been used in [4+2] cycloadditions. The imine **35** adds regioselectively to isoprene to give only one adduct **36**, but diene **37** surprisingly afforded a 3:1 mixture of adducts **38** and **39** (Scheme 4.12).[13]



Scheme 4.12

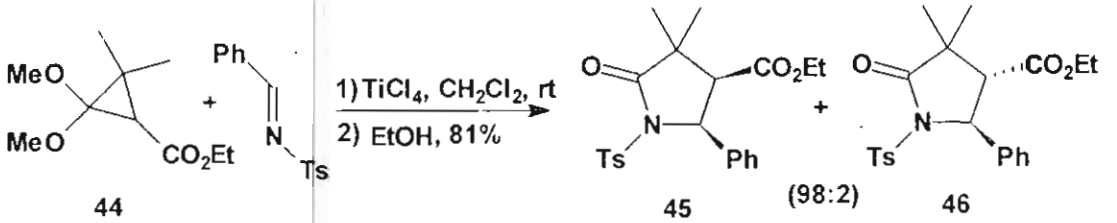
The silyloxy cyclohexadiene **40** on reaction with **41** afforded **42** and **43** (Scheme 4.13). The major adduct has served as an intermediate in the total synthesis of piperidine alkaloids isoprosopinine B and deoxyprosopinine.[13d]



Scheme 4.13

4.4 Other Cycloaddition Reactions Involving *N*-sulfonylimines

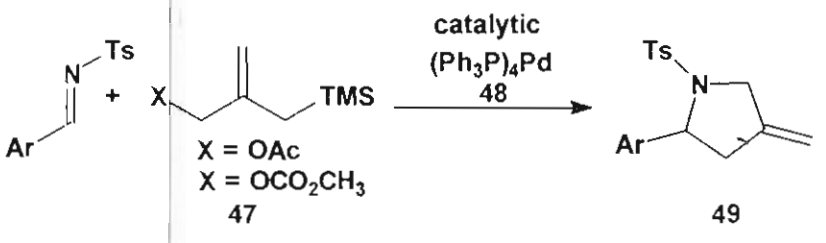
In the presence of titanium(IV) chloride, ethyl 2,2-dialkoxy cyclopropanecarboxylate **44** reacted with imines to give γ-lactams. Especially, when *N*-tosyl aldimines were employed, *cis*-3,4-disubstituted γ-lactams were obtained in good yields with high diastereoselectivity (Scheme 4.14).[14]



44 45 46

Scheme 4.14

Cycloaddition of trimethylenemethane (TMM) palladium complexes to imines possessing an electron withdrawing group has been studied in detail by Trost *et al.* The reaction of imines with the TMM precursor **47** using tetrakis (triphenylphosphine) palladium **48**, afforded a nearly quantitative yield of methylene pyrrolidine **49** (Scheme 4.15).[15]

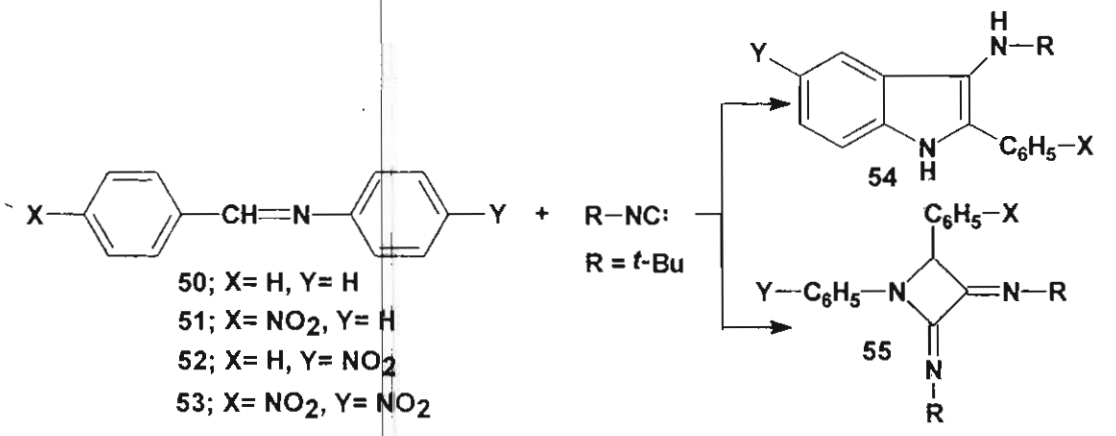


47 49

Scheme 4.15

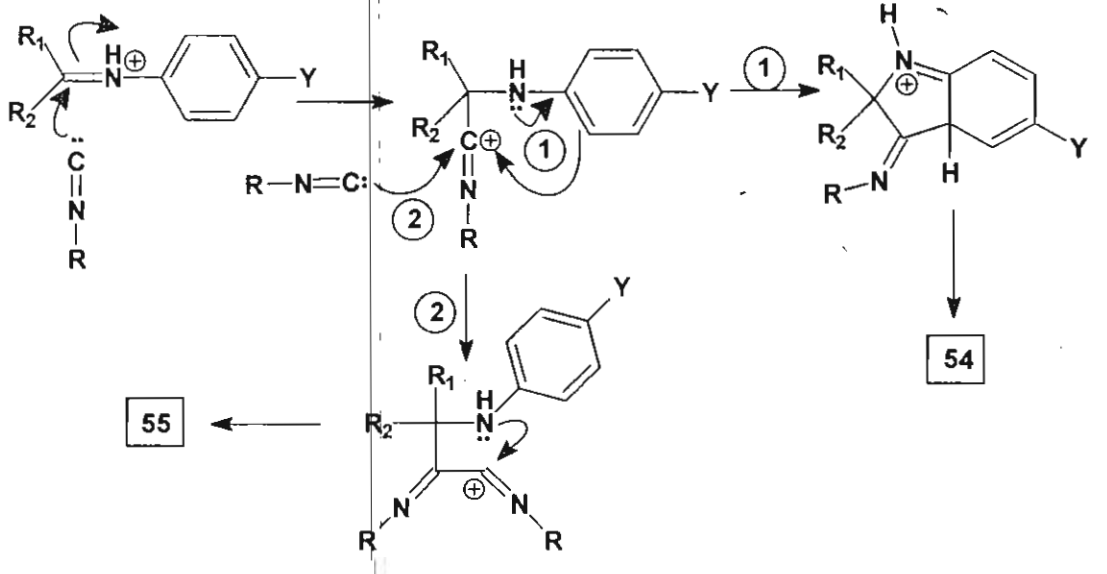
4.5 Reactions Related to the Present Work

The reaction between *N*-arylimines **50-53** and *tert*-butyl isocyanide has been studied by Deyrup *et al.* Two principal types of products *via* 3-*tert*-butylimino-2-phenylindoles **54** and 2,3-bis(*tert*-butylimino)azetidines **55** have been identified from these reactions (Scheme 4.16).[16]



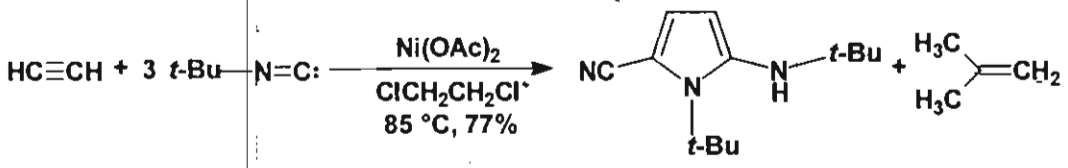
Scheme 4.16

With imines **50** and **51**, 1:1 adducts **54** were obtained as major products and the 2:1 adducts in poor yields. Imines **52** and **53** yielded 2:1 isocyanide:imine adducts **55** in high yields. Acid catalysis is essential for the reaction; mechanistically the formation of the products can be rationalized as shown in Scheme 4.17.



Scheme 4.17

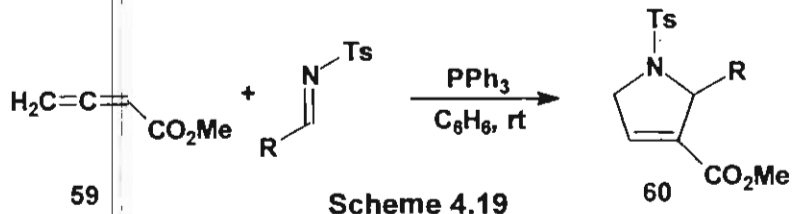
It has been reported that 2-aminopyrrole **57** is formed from the reaction of acetylene **56** and *tert*-butyl isocyanide in the presence of nickel acetate as catalyst (Scheme 4.18).[17]



56 57 58

Scheme 4.18

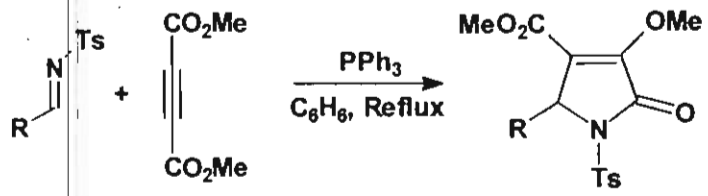
The reaction of methyl 2,3-butadienoate **59** with *N*-tosylimines in the presence of catalytic amount of triphenylphosphine afforded pyrrolidine derivatives **60** in excellent yields (Scheme 4.19).[18]



59 60

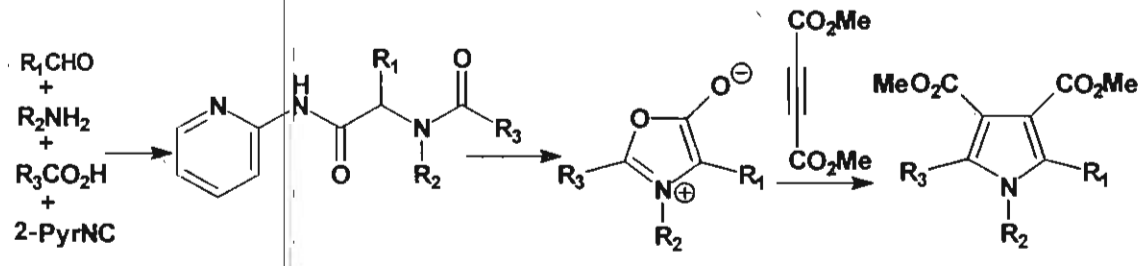
Scheme 4.19

Similarly, the reaction of DMAD and *N*-tosylimines with catalytic amount of triphenylphosphine furnished pyrrolidinones **61** in good yields (Scheme 4.20).[18]



Scheme 4.20 61

In this context, it is interesting to note that somewhat similar type of pyrrole systems **63** are formed from the dipolar cycloaddition reactions of münchnones with DMAD. Münchnones **62** can be derived by a Ugi-4CR (Scheme 4.21).[19]



62 63

Scheme 4.21

4.6 The Present Work

Prompted by the success in developing a synthesis of aminofuran derivatives by the reaction of aldehydes and the zwitterionic intermediate formed between DMAD and isocyanide *(vide supra)*, we reasoned that the latter would react with *N*-tosylimines to afford aminopyrrole derivatives, thus constituting a novel multicomponent reaction. The resurgence of interest on MCRs by virtue of their convergence, productivity, facile execution, and generally high yields of products is noteworthy in this context.

4.7 Results and Discussion

The tosylimines selected for our study are shown in Figure 4.1.

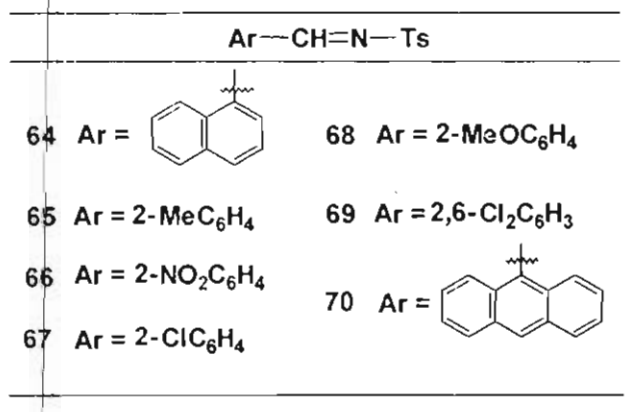
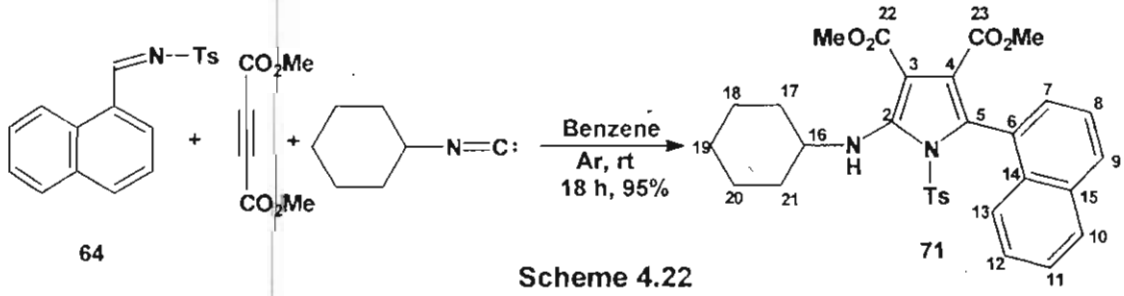


Figure 4.1

Initially, we carried out the reaction of *N*-tosyl 1-naphthaldimine **64**, DMAD and cyclohexyl isocyanide in anhydrous benzene at room temperature; the adduct **71** was obtained in 95% yield (Scheme 4.22).



Scheme 4.22

The structure of the adduct **71** was confirmed by spectroscopic and analytical data. In the IR spectrum, the strong absorption at 3328 cm^{-1} is due to the amine functionality. The sharp bands at 1734 and 1681 cm^{-1} were assigned to

the ester carbonyls. In the ^{1}H NMR spectrum (Figure 4.2), the two carbomethoxy groups were observed at δ 3.30 and 3.74 as two singlets and the -NH proton resonated at δ 6.15 as a broad singlet (exchangeable with D_2O). The aromatic protons were visible between δ 7.25-7.85. The carbon signals at δ 25.13, 25.79, 34.04 and 59.49 in the ^{13}C NMR spectrum (Figure 4.3) have been assigned to the cyclohexyl group. The methoxy carbons were observed at δ 51.42 and 51.80 and the two ester carbonyls were seen at δ 164.70 and 165.21. The signals due to C-3 and C-4 were observed at δ 150.25 and 145.24 and those corresponding to C-2 and C-5 were discernible at δ 121.48 and 99.88 respectively. The assigned structure was further supported by satisfactory analytical data.

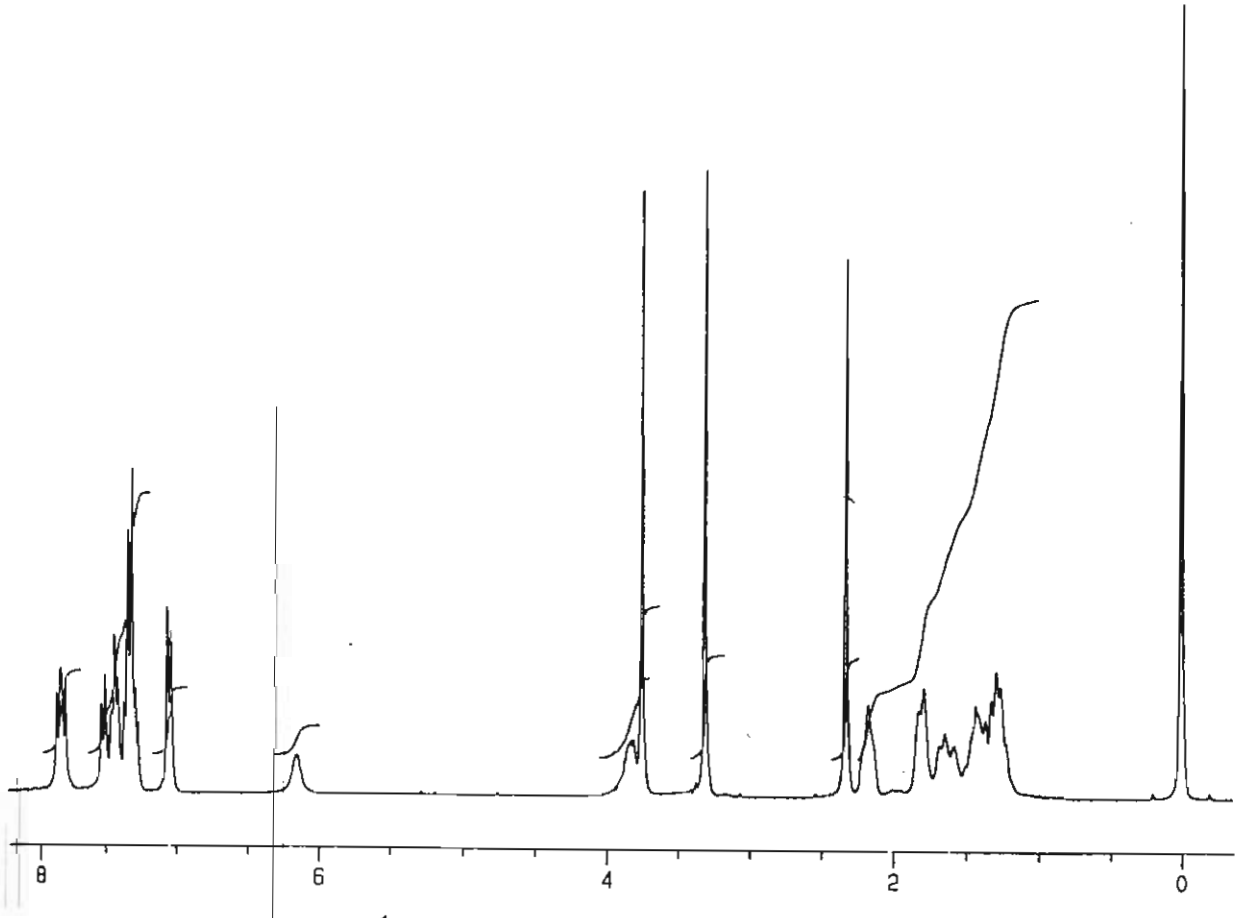


Figure 4.2 ^{1}H NMR spectrum of aminopyrrole 71

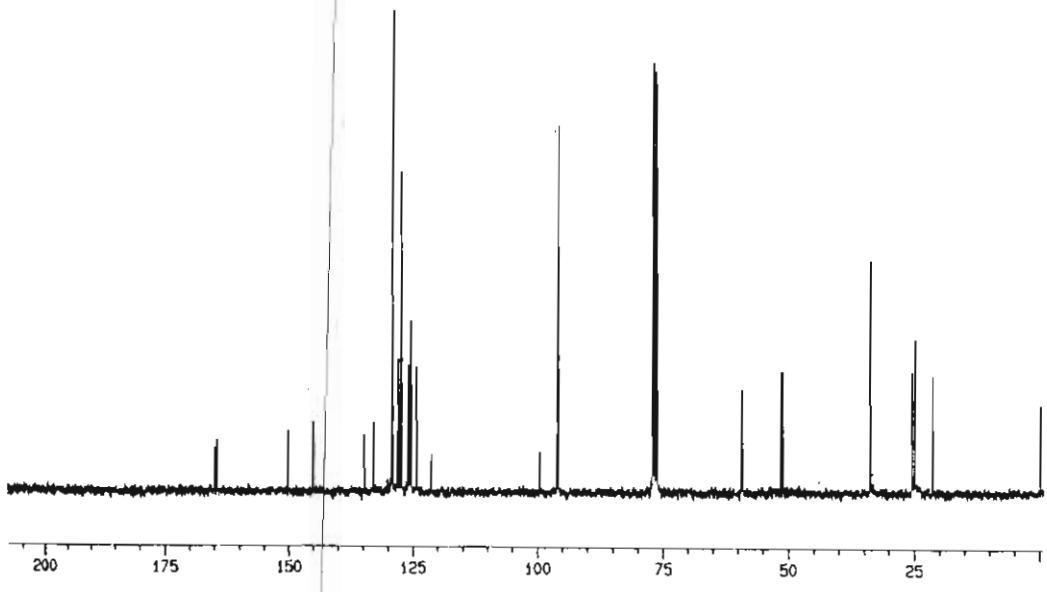
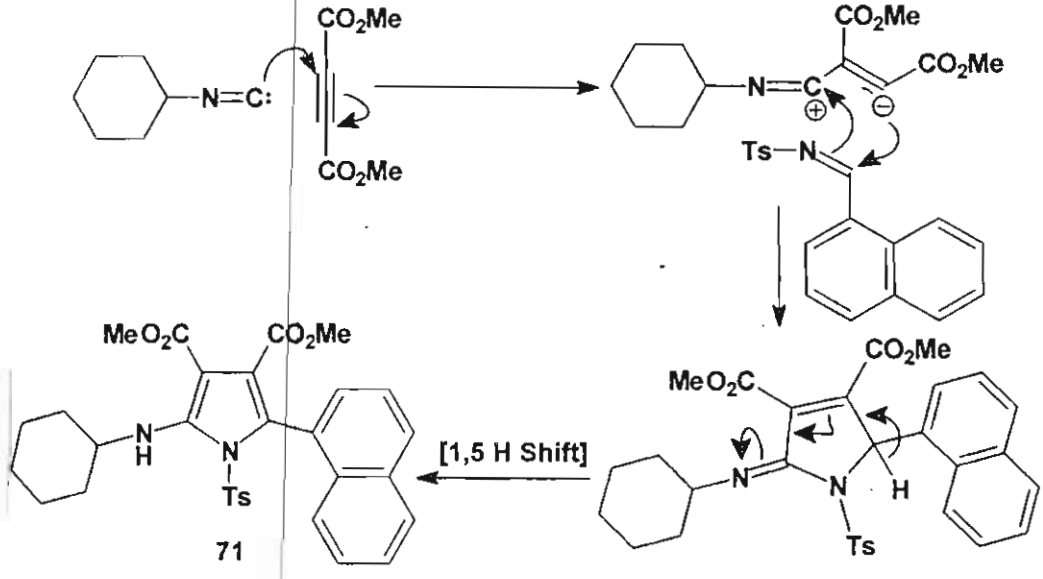


Figure 4.3 ^{13}C NMR spectrum of aminopyrrole 71

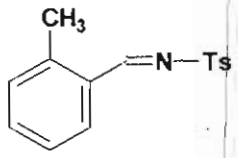
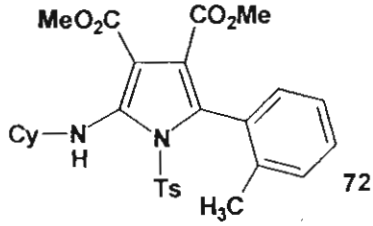
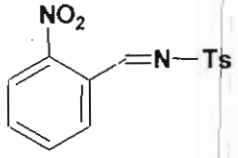
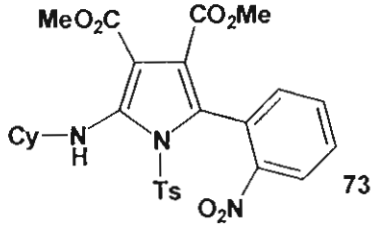
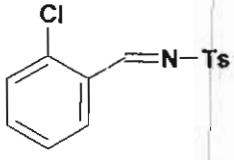
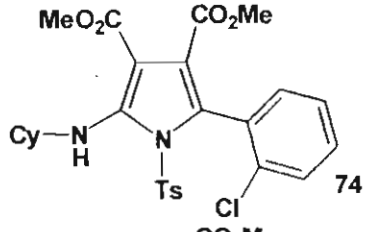
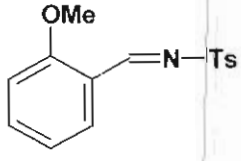
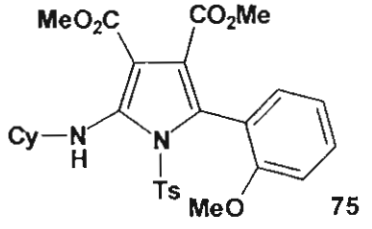
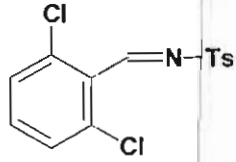
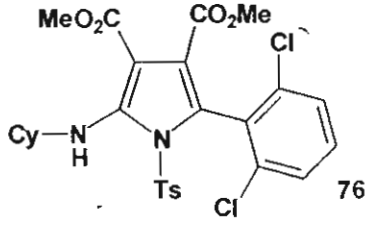
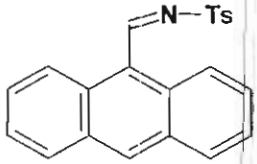
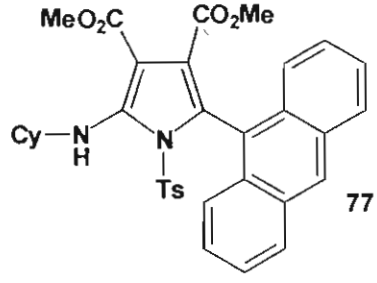
Mechanistically, the transformation presumably proceeds *via* addition of the nucleophilic isocyanide to DMAD to afford a 1:1 zwitterionic intermediate, which adds to the carbon-nitrogen double bond of the tosylimine to yield an intermediate iminolactam. The latter undergoes a [1,5] H shift under the reaction conditions to yield the aminopyrrole as illustrated in Scheme 4.23.



Scheme 4.23

The reaction was found to be general and efficient. Interestingly, it was found that only the tosylimines, derived from *ortho* substituted aldehydes gave stable, isolable products. The results are summarized in Table 4.1.

Table 4.1

Entry	Tosylimines	t(h)	Product	Yield(%)*
1	 65	22	 72	92
2	 66	20	 73	87
3	 67	16	 74	82
4	 68	15	 75	79
5	 69	21	 76	94
6	 70	2 Reflux	 77	93

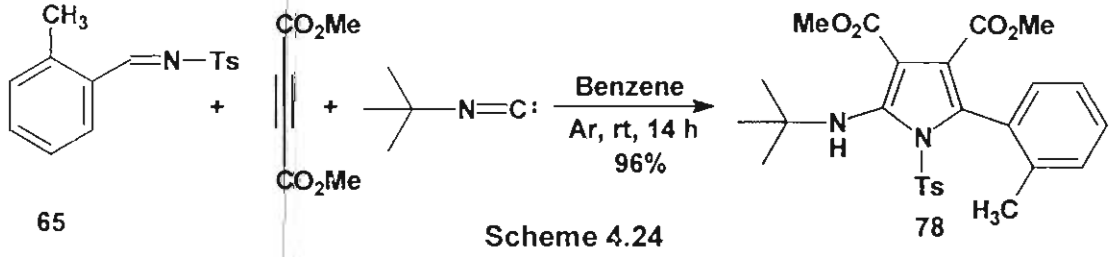
Reaction conditions: Benzene, Argon, rt. Where Cy = Cyclohexyl

***isolated yield**

The adducts **72-77** were characterized by spectroscopic methods. The ^{1}H and ^{13}C NMR spectra of compounds are similar to those of **71**, which exhibited characteristic signals with appropriate chemical shifts. All these compounds revealed peaks in the region δ 4.5-6.0, which can be attributed to the -NH proton, based on the characteristic broadness and facile exchange with D_2O. Satisfactory CHN/ high resolution mass data were also obtained in each case.

The reaction could be easily extended to employ *tert*-butyl isocyanide as the nucleophile without compromising chemical efficiency.

Thus, *N*-tosyl 2-methylbenzaldimine **65**, on treatment with DMAD and stoichiometric amount of *tert*-butyl isocyanide in benzene at ambient temperature for 14 h afforded the aminopyrrole **78** in 96% yield (Scheme 4.24).



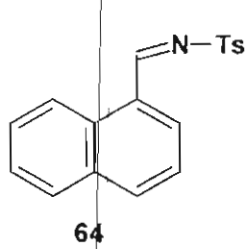
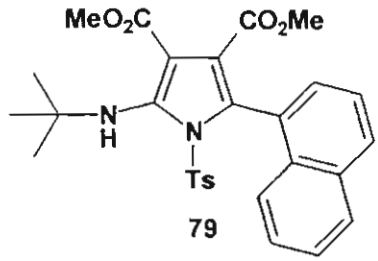
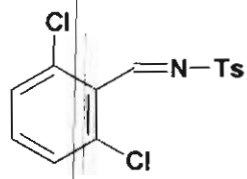
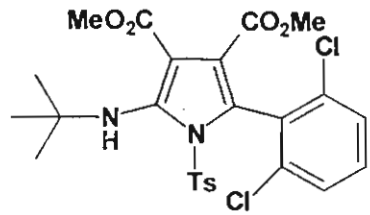
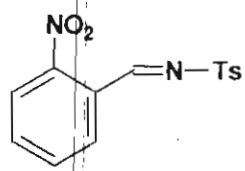
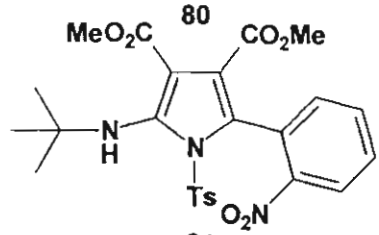
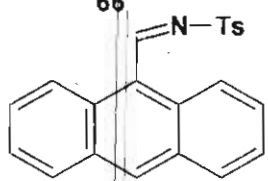
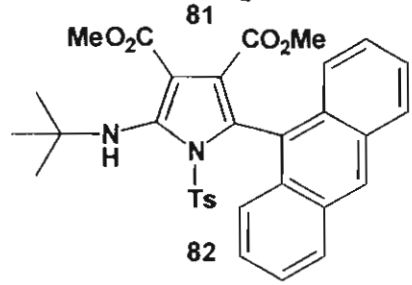
65 78

Scheme 4.24

The structure of the adduct was elucidated by spectroscopic and analytical methods. The IR spectrum of **78** showed a strong absorption at 3334 cm^{-1} indicating the presence of an amine functionality. The peaks at 1756 and 1707 cm^{-1} were attributed to the carbomethoxy groups. In the ^{1}H NMR, the nine protons of the *tert*-butyl group appeared as a singlet at δ 1.34. The *ortho*-methyl protons of the phenyl ring and *p*-methyl protons of the tosyl group resonated as singlets at δ 2.23 and 2.39 respectively. The signals due to the carbomethoxy groups were observed at δ 3.48 and 3.74. In the ^{13}C NMR spectrum, the characteristic carbomethoxy carbonyls appeared at δ 164.36 and 164.89. The methyl carbons on the phenyl rings resonated at δ 20.36 and 21.62 while the peak at δ 30.16 was assigned to the methyl carbons of the *tert*-butyl group. Analytical data further supported the integrity of the compound.

Other *N*-tosylimines also reacted with *tert*-butyl isocyanide and DMAD under similar conditions and the results are summarized in Table 4.2.

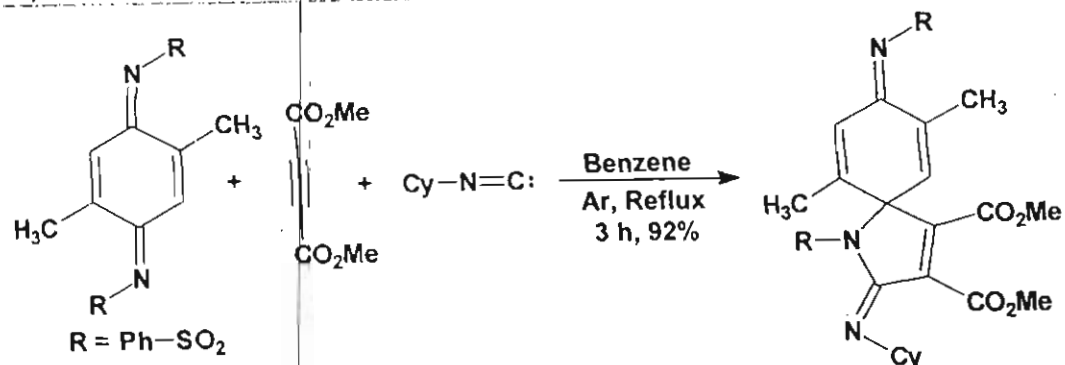
Table 4.2

Entry	Tosylimines	t(h)	Product	Yield(%)*
1	 64	19	 79	72
2	 69	15	 80	93
3	 66	24	 81	71
4	 70	3 reflux	 82	68

Reaction conditions: Benzene, Argon, rt.
***isolated yield**

When tosylmethyl isocyanide (TosMIC) was used in place of cyclohexyl or *tert*-butyl isocyanide, there was no reaction, implying that its nucleophilicity was inadequate to trigger the formation of zwitterionic intermediate.

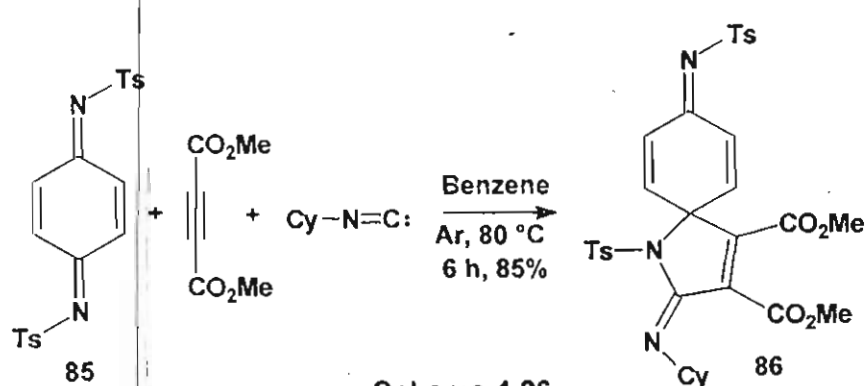
Subsequent to the above investigations and to explore the scope of this reaction, we have extended the studies to quinoneimines. 2,5-Dimethyl-*p*-quinoneimine **83** on reaction with DMAD and cyclohexyl isocyanide afforded the iminolactam **84** (Scheme 4.25).



83 Scheme 4.25 84

The IR spectrum of **84** showed strong ester carbonyl absorptions at 1738 and 1663 cm^{-1}. In the ^1H NMR spectrum, the signals due to carbomethoxy protons appeared at δ 3.62 and 3.82. The methyl groups resonated at δ 1.95 and 1.99. The two olefinic protons on the cyclohexadiene ring resonated as singlets at δ 6.26 and between δ 7.41 and 7.56 overlapping with the signals of the aromatic protons. In the ^{13}C NMR spectrum, the peak at δ 69.26 was assigned to the spirocarbon atom. The sp^3 carbon signals at δ 17.14 and 18.78 were due to the methyl groups. The diagnostic signals for the carbomethoxy carbonyls were seen at δ 163.53 and 165.35. Satisfactory elemental analysis was also obtained.

Analogous reaction was observed with *p*-quinoneimine **85**, which on treatment with DMAD and cyclohexyl isocyanide in anhydrous benzene at 80 °C for 6 h furnished the adduct **86** in 85% yield (Scheme 4.26).

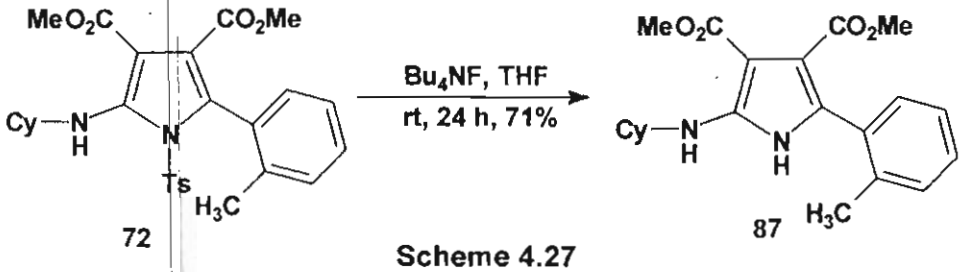


85 Scheme 4.26 86

As described for the above iminolactam **84**, the IR spectrum of **86** showed strong bands at 1740 and 1669 cm^{-1} due to the ester carbonyls. In the ^1H NMR spectrum, the two carbomethoxy groups were discernible as singlets at δ 3.67

and 3.85. In the ^{13}C NMR spectrum, the ester carbonyls were seen at δ 163.23 and 163.57. Other signals in the ^{1}H and ^{13}C NMR spectra were also in agreement with the assigned structure. Analytical data further supported the integrity of the compound.

Interestingly, it was found that detosylation of **72** could be effected using TBAF in THF at room temperature to afford the aminopyrrole **87** in 71% yield (Scheme 4.27).



72 87

Scheme 4.27

4.8 Conclusion

In conclusion, we have uncovered a novel and efficient multicomponent condensation reaction of *N*-tosylimines, DMAD and isocyanides for the synthesis of 2-aminopyrroles. It may be mentioned that there are only isolated reports available on 2-aminopyrrole synthesis.[20] Interestingly, it has been reported that the reaction of sodium salt of various substituted 2-aminopyrroles with appropriate electrophiles gave pyrrole nucleosides which served as common intermediates to both 7-deazaadenosine and the 7-deazaguanosine series. Several of these 5- and 5,6-substituted pyrrolo[2,3-d]pyrimidine nucleosides have shown potent activity against HIV in preliminary *in vitro* screens.[21]

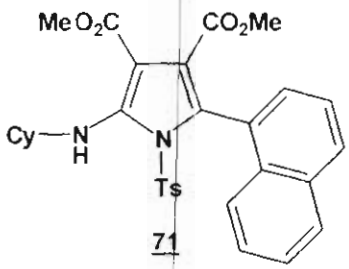
4.9 Experimental Details

General information about the experiments is given in Section 2.13 (Chapter 2).

Dimethyl 2-(cyclohexylamino)-1-[(4-methylphenyl)sulfonyl]-5-(1-naphthyl)-1*H*-pyrrole-3,4-dicarboxylate 71

A mixture of *N*-tosyl 1-naphthaldimine (309 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene was purged with argon at room

temperature. To this mixture, cyclohexyl isocyanide (120 mg, 1.1 mmol) was added by a syringe and the reaction mixture was stirred for 18 h. The solvent was removed under vacuum and the product **71** was recrystallized from CH_2Cl_2-hexane mixture; it was washed with hexane (4×5 mL) to give a colorless crystalline solid (554 mg, 95%). mp 149-150 °C.



71

IR (KBr) ν_{max}: 3328, 2927, 2850, 1734, 1681, 1575, 1449, 1377, 1222 cm^{-1}.

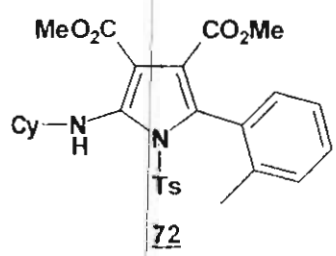
^{1}H NMR: δ 1.25-2.16 (m, 10H), 2.32 (s, 3H), 3.30 (s, 3H), 3.74 (s, 3H), 3.80 (m, 1H), 6.15 (br s, 1H), 7.03 (d, J = 7.98, 2H), 7.25-7.52 (m, 7H), 7.79-7.85 (m, 2H).

^{13}C NMR: δ 21.63, 25.13, 25.79, 34.04, 51.42, 51.80, 59.49, 99.88, 121.48, 124.46, 125.58, 126.14, 127.56, 128.10, 128.71, 129.35, 133.09, 133.17, 134.96, 145.24, 150.25, 164.70, 165.21.

Anal. Calcd for $C_{31}H_{32}N_2O_6S$: C, 66.41; H, 5.75; N, 4.99; S, 5.71. Found: C, 66.03; H, 5.88; N, 5.18; S, 5.77.

Dimethyl 2-(cyclohexylamino)-5-(2-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 72

To a mixture of *N*-tosyl 2-methylbenzaldimine (274 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene (15 mL) was added cyclohexyl isocyanide (120 mg, 1.1 mmol) and the mixture was stirred at room temperature for 22 h. The solvent was removed under vacuum and the product was recrystallized from CH_2Cl_2-hexane mixture. It was washed with hexane (4×3 mL) to give **72** as a white crystalline solid (485 mg, 92%). mp 135-136 °C.



72

IR (KBr) ν_{max}: 3324, 2930, 2859, 1732, 1655, 1596, 1495, 1442, 1360, 1295 cm^{-1}.

^{1}H NMR: δ 1.15-1.93 (m, 10H), 2.21 (s, 3H), 2.40 (s, 3H), 3.48 (s, 3H), 3.72 (s, 3H), 3.76 (m, 1H),

5.99 (br s, 1H), 6.82 (d, J = 7.02, 1H), 7.04-7.28 (m, 5H), 7.44 (d, J = 8.31, 2H).

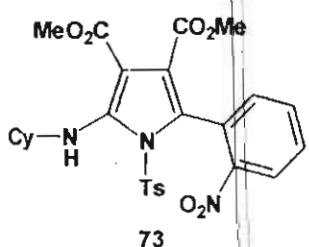
^{13}C NMR: δ 19.06, 21.54, 24.44, 24.50, 25.57, 34.87, 34.89, 52.57, 52.93, 58.92, 107.89, 126.01, 127.51, 128.16, 128.27, 128.90, 129.48, 131.01, 131.68, 133.79, 136.02, 137.86, 143.45, 145.47, 161.07, 164.34.

Anal. Calcd for $C_{28}H_{32}N_2O_6S$: C, 64.10; H, 6.14; N, 5.33; S, 6.11. Found: C, 64.21; H, 6.15; N, 5.66; S, 6.48.

Dimethyl 2-(cyclohexylamino)-5-(2-nitrophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 73

To a mixture of *N*-tosyl 2-nitrobenzaldimine (304 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene (15 mL) was added cyclohexyl isocyanide (120 mg, 1.1 mmol) and the reaction mixture was stirred at rt for 20 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 80:20 hexane-ethyl acetate afforded an yellow crystalline solid (486 mg, 87%). mp 76-77 °C (recrystallized from CH_2Cl_2-hexane).

IR (KBr) ν_{max}: 3386, 2930, 2856, 1736, 1689, 1563, 1530, 1450, 1384, 1344, 1230 cm^{-1}.



73

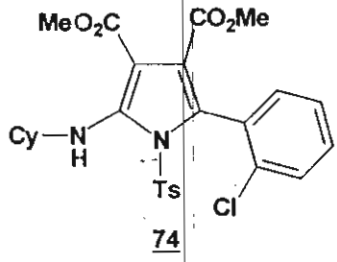
^{1}H NMR: δ 1.12-2.16 (m, 10H), 2.41 (s, 3H), 3.52 (s, 3H), 3.73 (s, 4H), 5.82 (d, J = 9.25, 1H), 7.13-7.26 (m, 3H), 7.46-7.56 (m, 4H), 8.14-8.17 (m, 1H).

^{13}C NMR: δ 21.65, 24.94, 25.03, 25.67, 33.68, 51.39, 51.94, 59.68, 100.80, 124.72, 127.44, 129.39, 129.51, 132.08, 132.45, 134.89, 145.52, 148.68, 150.05, 164.41, 164.56.

HRMS (EI) Calcd for $C_{27}H_{29}N_3O_8S$: 555.1675. Found: 555.1655.

Dimethyl 2-(cyclohexylamino)-5-(2-chlorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 74

Cyclohexyl isocyanide (120 mg, 1.1 mmol) was added to a mixture of *N*-tosyl 2-chlorobenzaldimine (294 mg, 1.1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene and the reaction mixture was stirred for 16 h. The solvent was removed under vacuum and the residue on chromatographic separation on neutral alumina column with 80:20 hexane-ethyl acetate mixture afforded **74** as a pale yellow solid (452 mg, 82%). mp 106-107 °C (recrystallized from CH_2Cl_2-hexane).



74

IR (KBr) ν_{max}: 3295, 2929, 2852, 1736, 1689, 1571, 1453, 1382, 1234, 1181 cm^{-1}.

^{1}H NMR: δ 1.11-2.15 (m, 10H), 2.39 (s, 3H), 3.55 (s, 3H) 3.72 (s, 4H), 5.84 (d, J = 8.73, 1H) 7.20-7.55 (m, 8H).

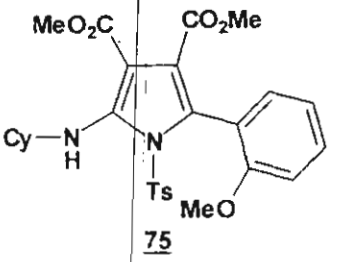
^{13}C NMR: δ 21.70, 25.04, 25.14, 25.71, 33.90, 33.94, 51.50, 52.08, 59.70, 100.62, 121.26, 125.88, 126.89, 127.62, 129.32, 129.57, 129.89, 130.56, 132.03, 134.83, 135.19, 145.59, 149.93, 164.68, 164.96

Anal. Calcd for $C_{27}H_{29}N_2O_6SCl$: C, 59.49; H, 5.36; N, 5.13; S, 5.88. Found: C, 59.76; H, 5.45; N, 5.18; S, 6.29.

Dimethyl 2-(cyclohexylamino)-5-(2-methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 75

To a mixture of *N*-tosyl 2-methoxybenzaldimine (290 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene (15 mL) at room temperature, cyclohexyl isocyanide (120 mg, 1.1 mmol) was added by a syringe and stirred for 15 h. The solvent was removed under vacuum and the residue on

chromatographic separation on basic alumina using 80:20 hexane-ethyl acetate afforded **75** as a pale yellow solid (427 mg, 79%). mp 73-74 °C (recrystallised from CH_2Cl_2-hexane).



75

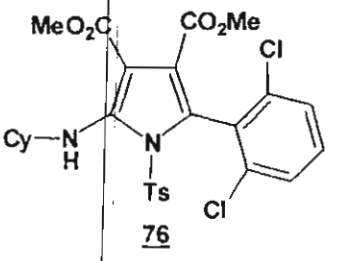
IR (KBr) ν_{max}: 3321, 2932, 2852, 1747, 1662, 1610, 1506, 1453 cm^{-1}.

^{1}H NMR: δ 1.16-2.15 (m, 10H), 2.37 (s, 3H), 3.54 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 3.85 (m, 1H), 5.92 (br s, 1H), 6.81-7.44 (m, 8H).

^{13}C NMR: δ 21.69, 25.15, 25.80, 33.85, 34.04, 51.29, 51.75, 55.27, 59.49, 100.15, 110.27, 119.67, 120.23, 120.41, 126.98, 127.51, 129.27, 130.09, 131.46, 135.19, 144.90, 150.32, 157.89, 164.76, 165.42.

Dimethyl 2-(cyclohexylamino)-5-(2,6-dichlorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 76

A mixture of *N*-tosyl 2,6-dichlorobenzaldimine (164 mg, 0.5 mmol) and DMAD (78 mg, 0.55 mmol) in anhydrous benzene (10 mL) at room temperature was purged with argon for 5 min, followed by the addition of cyclohexyl isocyanide (60 mg, 0.55 mmol). The mixture was stirred for 21 h. The solvent was removed under vacuum and the product was recrystallized from CH_2Cl_2-hexane mixture. It was washed with hexane (4x2 mL) to give **76** as a colorless crystalline solid (274 mg, 94%). mp 170-171 °C.



76

IR (KBr) ν_{max}: 3289, 2927, 2853, 1738, 1689, 1564, 1446, 1377, 1228 cm^{-1}.

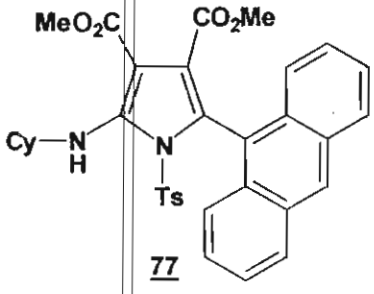
^{1}H NMR: δ 1.06-2.03 (m, 10H), 2.41 (s, 3H), 3.58 (s, 3H), 3.65 (m, 1H), 3.74 (s, 3H) 5.38 (br s, 1H), 7.22-7.37 (m, 5H), 7.76 (d, J = 8.04, 2H).

^{13}C NMR: δ 21.74, 25.15, 25.77, 33.79, 51.53, 51.91, 59.10, 102.16, 120.04, 125.26, 127.65, 128.33, 129.45, 130.11, 130.50, 135.35, 136.66, 145.51, 147.63, 163.94, 164.71.

Anal. Calcd for $C_{27}H_{28}N_2O_6SCl_2$: C, 55.96; H, 4.86; N, 4.83. Found: C, 56.10; H, 4.89; N, 4.58.

Dimethyl 2-(9-anthryl)-5-(cyclohexylamino)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 77

To a mixture of *N*-tosyl 9-anthraldimine (125 mg, 0.34 mmol) and DMAD (55 mg, 0.38 mmol) in anhydrous benzene (8 mL), cyclohexyl isocyanide (42 mg, 0.38 mmol) was added and the reaction mixture was refluxed for 2 h. The solvent was removed under vacuum and the product was recrystallized from CH_2Cl_2-hexane to afford 77 as colorless crystals (198 mg, 93%). mp 169-170 °C.



77

IR (KBr) ν_{max}: 3319, 3054, 2930, 2853, 1726, 1678, 1566, 1454, 1383, 1318, 1224 cm^{-1}.

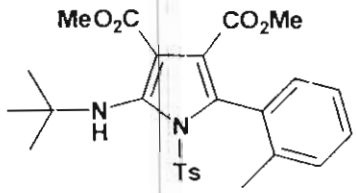
^{1}H NMR: δ 1.23-2.23 (m, 10H), 2.28 (s, 3H), 3.09 (s, 3H), 3.79 (s, 3H), 3.85 (m, 1H), 6.15 (br s, 1H), 6.84 (d, J = 7.99, 2H), 7.04 (d, J = 8.25, 2H), 7.22-7.50 (m, 6H), 7.95 (d, J = 8.37, 2H), 8.46 (s, 1H).

^{13}C NMR: δ 21.59, 25.22, 25.85, 34.05, 51.57, 52.16, 58.58, 99.87, 121.75, 124.31, 124.93, 125.39, 125.81, 126.01, 126.36, 127.72, 128.30, 128.83, 129.19, 130.95, 132.44, 134.95, 145.14, 148.42, 164.72, 164.81.

Anal. Calcd for $C_{35}H_{34}N_2O_6S$: C, 68.83; H, 5.61; N, 4.58. Found: C, 68.84; H, 5.68; N, 4.55.

Dimethyl 2-(*tert*-butylamino)-5-(2-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 78

To a mixture of *N*-tosyl 2-methylbenzaldimine (137 mg, 0.5 mmol) and DMAD (78 mg, 0.55 mmol) in anhydrous benzene (10 mL), *tert*-butyl isocyanide (46 mg, 0.55 mmol) was added and the reaction mixture was stirred for 14 h at room temperature. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 80:20 hexane-ethyl acetate gave the aminopyrrole **78** as an yellow solid (267 mg, 96%). mp 122-123 °C (recrystallized from CH_2Cl_2-hexane).



78

IR (KBr) ν_{max}: 3334, 2957, 1756, 1707, 1585, 1435, 1330, 1291 cm^{-1}.

^{1}H NMR: δ 1.34 (s, 9H), 2.23 (s, 3H), 2.39 (s, 3H), 3.48 (s, 3H), 3.74 (s, 3H), 6.74 (d, J = 7.35, 1H), 7.03-7.39 (m, 7H).

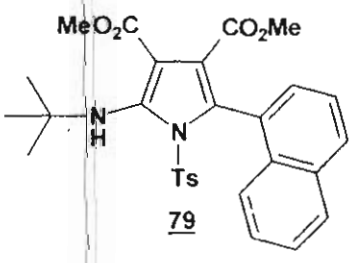
^{13}C NMR: δ 20.36, 21.62, 30.16, 51.42, 51.73, 57.91, 108.07, 120.02, 124.68, 127.37, 128.84, 129.34, 129.60, 129.82, 130.79, 131.88, 135.60, 138.95, 145.02, 146.73, 164.36, 164.89.

Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.33; H, 6.06; N, 5.61; S, 6.43; Found: C, 62.11; H, 6.28; N, 5.67; S, 6.14.

Dimethyl 2-(*tert*-butylamino)-1-[(4-methylphenyl)sulfonyl]-5-(1-naphthyl)-1*H*-pyrrole-3,4-dicarboxylate 79

A mixture of *N*-tosyl 1-naphthaldimine (309 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene (20 mL) was purged with argon at room temperature. To this, *tert*-butyl isocyanide (92 mg, 1.1 mmol) was added by a syringe and the reaction mixture was stirred for 19 h. The solvent was removed under vacuum and the residue dissolved in 5 mL of benzene. The solution was allowed to stand overnight. The crystallized product was separated

and washed with hexane (4x2 mL) to give colorless crystals of **79** (396 mg, 72%). mp 129-130 °C.



79

IR (KBr) ν_{max}: 3344, 2952, 1739, 1695, 1558, 1446, 1384, 1210 cm^{-1}.

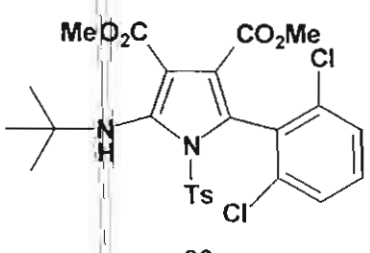
^{1}H NMR: δ 1.41 (s, 9H), 2.30 (s, 3H), 3.28 (s, 3H), 3.77 (s, 3H), 5.06 (br s, 1H), 7.00 (d, J = 8.22, 2H), 7.24-7.48 (m, 7H), 7.79-7.86 (m, 2H).

^{13}C NMR: δ 21.59, 30.26, 51.59, 51.75, 58.12, 108.46, 120.92, 124.46, 125.22, 125.59, 126.15, 127.47, 128.16, 128.31, 129.20, 129.27, 129.40, 130.54, 132.93, 133.06, 135.36, 145.03, 146.85, 164.57, 164.82.

Anal. Calcd for $C_{29}H_{30}N_2O_6S$: C, 65.15; H, 5.65; N, 5.23. Found: C, 65.18; H, 5.68; N, 4.99.

Dimethyl 2-(*tert*-butylamino)-5-(2,6-dichlorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 80

A mixture of *N*-tosyl 2,6-dichlorobenzaldimine (164 mg, 0.5 mmol) and DMAD (78 mg, 0.55 mmol) in anhydrous benzene (8 mL) was purged with argon at room temperature. To this mixture, *tert*-butyl isocyanide (46 mg, 0.55 mmol) was added by a syringe and stirred for 15 h. The solvent was removed under vacuum and the residue on chromatographic separation on neutral alumina with 80:20 ethyl acetate in hexane as eluant gave the aminopyrrole **80** as a white crystalline solid (268 mg, 93%). mp 172-173 °C.



80

IR (KBr) ν_{max}: 3344, 2959, 1732, 1707, 1539, 1452, 1371, 1178 cm^{-1}.

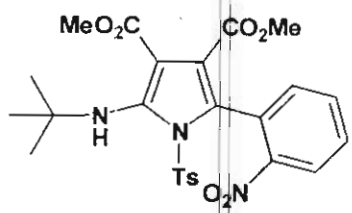
^{1}H NMR: δ 1.26 (s, 9H), 2.40 (s, 3H), 3.58 (s, 3H), 3.76 (s, 3H), 3.94 (br s, 1H), 7.20-7.38 (m, 5H), 7.73 (d, J = 8.15, 2H).

^{13}C NMR: δ 21.71, 30.00, 51.71, 51.89, 57.71, 111.26, 119.21, 127.70, 128.05, 128.41, 129.32, 130.07, 130.70, 136.14, 143.84, 145.28, 163.45, 164.55.

Anal. Calcd for $C_{25}H_{26}N_2O_6SCl_2$: C, 54.25; H, 4.73; N, 5.06. Found: C, 54.14; H, 4.73; N, 4.76.

Dimethyl 2-(*tert*-butylamino)-5-(2-nitrophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 81

tert-Butyl isocyanide (46 mg, 0.55 mmol) was added to a mixture of *N*-tosyl 2-nitrobenzaldimine (152 mg, 0.5 mmol) and DMAD (78 mg, 0.55 mmol) and stirred for 24 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column with 80:20 hexane-ethyl acetate as eluant gave a pale yellow amorphous solid **81** (188 mg, 71%). mp 82-83 °C.



81

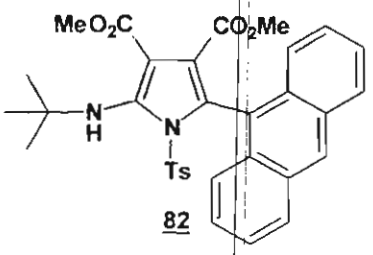
IR (KBr) ν_{max}: 3356, 2932, 2857, 1728, 1678, 1542, 1448, 1344, 1220 cm^{-1}.

^{1}H NMR: δ 1.34 (s, 9H), 2.40 (s, 3H), 3.52 (s, 3H), 3.76 (s, 3H), 4.78 (br s, 1H), 7.17-7.56 (m, 7H), 8.15-8.18 (m, 1H).

^{13}C NMR: δ 21.74, 30.11, 51.66, 52.01, 58.30, 108.74, 124.80, 126.53, 127.47, 129.52, 130.31, 132.18, 132.40, 135.57, 145.42, 147.06, 148.77, 164.28, 164.35.

Dimethyl 2-(9-anthryl)-5-(*tert*-butylamino)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate 82

To a mixture of *N*-tosyl 9-anthraldimine (125 mg, 0.34 mmol) and DMAD (55 mg, 0.38 mmol) in anhydrous benzene (10 mL), *tert*-butyl isocyanide (32 mg, 0.38 mmol) was added and the reaction mixture was refluxed for 3 h. The solvent was removed under vacuum and the product **82** was recrystallized from CH_2Cl_2-hexane mixture. It was washed with hexane (4x2 mL) to give colorless crystals (135 mg, 68%). mp 156-157 °C.



82

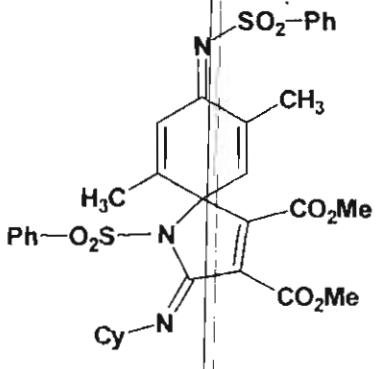
IR (KBr) ν_{max}: 3328, 3044, 2928, 2846, 1728, 1682, 1572, 1443, 1376, 1320, 1248 cm^{-1}.

^{1}H NMR: δ 1.43 (s, 9H), 2.26 (s, 3H), 3.04 (s, 3H), 3.82 (s, 3H), 4.74 (br s, 1H), 6.80 (d, J = 8.01, 2H), 7.04 (d, J = 8.19, 2H), 7.24-7.47 (m, 6H), 7.95 (d, J = 8.37, 2H), 8.47 (s, 1H).

^{13}C NMR: δ 21.50, 30.18, 51.51, 51.75, 57.84, 110.18, 120.87, 124.55, 124.91, 125.85, 125.98, 127.82, 128.32, 128.41, 128.82, 129.02, 129.14, 130.93, 132.04, 135.39, 144.63, 144.99, 164.19, 164.85.

Dimethyl 2-(cyclohexylimino)-6,9-dimethyl-1-(phenylsulfonyl)-8-[(phenylsulfonyl)imino]-1-azaspiro[4.5]deca-3,6,9-triene-3,4-dicarboxyalate 84

A mixture of 2,5-dimethyl *p*-quinoneimine **83** (42 mg, 0.1 mmol) and DMAD (16 mg, 0.11 mmol) in anhydrous benzene was purged with argon. To this mixture, cyclohexyl isocyanide (12 mg, 0.11 mmol) was added by a syringe and the reaction mixture was refluxed for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel using 80:20 hexane-ethyl acetate mixture as eluant gave the iminolactam **84** as a pale yellow solid (62 mg, 92%). mp 165-166 °C (recrystallized from CH_2Cl_2-hexane).



84

IR (KBr) ν_{max}: 2934, 2846, 1738, 1663, 1625, 1550, 1444 cm^{-1}.

^{1}H NMR: δ 1.15-1.81 (m, 10H) 1.95 (s, 3H), 1.99 (s, 3H), 3.17 (m, 1H), 3.62 (s, 3H), 3.82 (s, 3H), 6.26 (s, 1H), 7.41-7.56 (m, 7H), 7.98-8.00 (m, 4H).

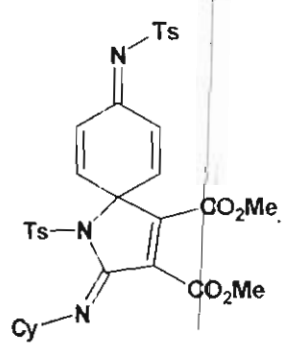
^{13}C NMR: δ 17.14, 18.78, 24.51, 25.35, 34.71, 34.75, 53.01, 53.18, 59.61, 69.26, 123.58, 126.91,

128.02, 128.69, 129.52, 132.47, 133.61, 134.66, 137.83, 138.84, 140.12, 141.89, 143.84, 153.22, 159.84, 163.53, 165.35.

Anal. Calcd for $C_{33}H_{35}N_3O_8S_2$: C, 59.53; H, 5.30; N, 6.31. Found: C, 59.12; H, 5.46; N, 5.94.

Dimethyl 2-(cyclohexylimino)-1-[(4-methylphenyl)sulfonyl]-8-{[(4-methylphenyl)sulfonyl]imino}-1-azaspiro[4.5]deca-3,6,9-triene-3,4-dicarboxyalate 86

To a refluxing mixture of *p*-quinoneimine **85** (83 mg, 0.2 mmol) and DMAD (32 mg, 0.22 mmol) in anhydrous benzene was added cyclohexyl isocyanide (24 mg, 0.22 mmol) and the refluxing was continued at 80 °C for 6 h. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel using 80:20 hexane-ethyl acetate as eluant to afford the iminolactam **86** as a colorless solid (114 mg, 85%). mp 156-157 °C (recrystallized from CH_2Cl_2-hexane).



86

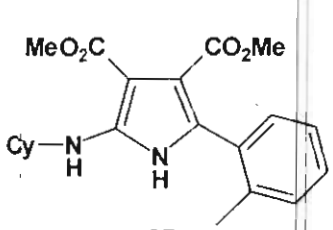
IR (KBr) ν_{max}: 2927, 2840, 1740, 1669, 1619, 1556, 1444, 1362 cm^{-1}.

^{1}H NMR: δ 1.11-1.86 (m, 10H), 2.44 (s, 6H), 3.18 (m, 1H), 3.67 (s, 3H), 3.85 (s, 3H), 6.52 (d, J = 8.91, 1H), 6.64 (d, J = 9.75, 2H), 7.25-7.34 (m, 4H), 7.81 (d, J = 9.21, 1H), 7.88-7.93 (m, 4H).

^{13}C NMR: δ 21.56, 21.61, 24.45, 25.33, 34.59, 52.59, 53.16, 59.54, 66.45, 76.48, 124.96, 127.28, 128.72, 129.41, 129.54, 131.26, 135.08, 135.86, 141.96, 142.59, 143.31, 143.64, 144.55, 159.81, 163.23, 163.57.

Detosylation of 72 with Bu_4NF. Procedure for the preparation of Dimethyl 2-(cyclohexylamino)-5-(2-methylphenyl)-1*H*-pyrrole-3,4-dicarboxylate 87

To a solution of **72** (100 mg, 0.19 mmol) in THF (3 mL) was added a solution of Bu_4NF (1M, 0.2 mL, 3equiv.) in THF and the mixture was stirred at room temperature for 24 h. Methanol was added and the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate *(10 mL)* and washed with saturated $NaHCO_3$ and the aqueous layer was extracted twice with ethyl acetate. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to afford **87** as a colorless solid (50 mg, 71%). mp 165-166 °C (recrystallized from CH_2Cl_2-hexane).



87

IR (KBr) ν_{max}: 3355, 3218, 2930, 2850, 1657, 1595, 1557 cm^{-1}.

^{1}H NMR: δ *1.30-1.95* (m, *10H*), 2.26 (s, 3H), *3.13* (m, 1H), 3.61 (s, 3H), 3.76 (s, 3H), 6.51 (br s, 1H), 7.17-7.27 (m, 4H), 7.50 (s, 1H).

^{13}C NMR: δ 19.54, 23.94, 24.95, 32.92, 49.96, 50.47, 50.63, 89.14, 111.05, 124.48, 126.67, 127.44, 129.12, 130.37, 131.60, 137.47, 147.35, 165.46, 165.59.

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SUMMARY

The thesis entitled "**Novel Multicomponent Reactions Based on Isocyanides**" embodies the results of extensive investigations carried out to gain some insight into the reactivity of *in situ* generated 1:1 zwitterionic intermediate between DMAD and isocyanide with various dipolar traps such as aldehydes, quinones and *N*-tosylimines.

A general introduction to the chemistry of isocyanides laying special emphasis on multicomponent reactions is presented in chapter 1. A definition of the present work is also incorporated in this chapter.

The second chapter describes the addition of zwitterionic intermediate derived from DMAD and cyclohexyl isocyanide to aromatic aldehydes. The addition of zwitterionic intermediate to 3-nitrobenzaldehyde furnished 2-aminofuran derivative **64** in 69% yield. The reaction was found to be general and similar aminofurans were obtained in good yields from a variety of aldehydes. Paraformaldehyde on reaction under similar conditions afforded the aminofuran **77** in 44% yield. Interestingly, phthalaldehyde when treated with two equivalents of DMAD and isocyanide afforded the bis adduct **78** in 66% yield.

Mechanistically, the reaction sequence involves the addition of 1:1 intermediate to the aldehyde carbonyl to afford a dihydrofuran derivative. Subsequently, it undergoes a [1,5] H shift to yield the aminofuran derivatives.

In the third chapter, the interception of 1:1 zwitterionic intermediate with 1,2-and 1,4-quinones is described. It was found that the *in situ* generated 1:1 intermediate undergoes facile addition with acenaphthene quinone to afford iminolactone **37** in 97% yield. Similar reactivity was observed with 9,10-phenanthrenequinone, 1,2-naphthoquinone, 4-*tert*-butyl-1,2-benzoquinone, 3,5-di-*tert*-butyl-1,2-benzoquinone, and 3-methoxy-4,6-

bis(1,1-diphenylmethyl)-1,2-benzoquinone yielding the iminolactones in good yields. The addition of the zwitterionic intermediate to 1,4-benzoquinones also afforded similar adducts in good yields. The reaction of 2,5-dimethyl *p*-benzoquinone with DMAD and cyclohexyl isocyanide afforded the iminolactone **53** in 92% yield. The structure of **53** was unambiguously confirmed by X-ray crystallographic analysis. A rationalization of the reaction is also incorporated.

The reaction of the zwitterionic intermediate with other 1,2-diones such as benzil and isatin found to follow the same reactivity pattern. A different type of reactivity profile was observed with 2-hydroxy-1,4-naphthoquinone. A pyran annulated product **66** was isolated in this case.

The fourth chapter contains the results of investigations aimed at studying the reactivity of zwitterionic intermediate towards the highly reactive C=N double bond of *N*-tosylimines. *N*-tosylimines **64-70** when treated with stoichiometric amounts of DMAD and cyclohexyl isocyanide in anhydrous benzene afforded the corresponding aminopyrroles in 79-95% yield. *tert*-Butyl isocyanide also elicited the same reactivity pattern. Although tosylmethyl isocyanide, ethyl propiolate, dibenzoyl acetylene, TCNE *etc.* were used in place of their respective components, no stable products could be isolated.

The reaction was extended to quinoneimines which yielded the corresponding iminolactams. Interestingly, it was found that detosylation of 2-aminopyrrole **72** could be effected using TBAF in THF at room temperature to afford the aminopyrrole **87** in 71% yield.

In conclusion, we have developed some novel and efficient multicomponent reactions by exploiting the reactivity of the *in situ* generated zwitterionic intermediate from DMAD and isocyanides. It was found that the one pot reaction of isocyanides and DMAD with aldehydes, quinones and *N*-tosylimines will lead to aminofurans, iminolactones and

aminopyrroles respectively. It may be mentioned that recently aminofurans have been found to undergo facile Diels-Alder reactions leading to hexahydroindolinones; they also serve as useful intermediates in the synthesis of a variety of aromatic as well as aliphatic molecules. Iminolactones can be easily hydrolyzed to their corresponding spirolactones, a recurring structural motif present in a number of biologically active natural products such as chlorothricin, kijanolide and tetranolide. Interestingly, it has been reported that the reaction of sodium salt of various substituted 2-aminopyrroles with appropriate electrophiles gave pyrrole nucleosides which served as common intermediates to both 7-deazaadenosine and the 7-deazaguanosine series. Several of these 5- and 5,6-substituted pyrrolo[2,3-d]pyrimidine nucleosides have shown potent activity against HIV in preliminary *in vitro* screens. It is conceivable that the novel multicomponent reactions described herein will be applicable to the synthesis of a variety of heterocycles.

List of Publications

[1] Triphenylphosphine Promoted Addition of Dimethyl Acetylenedicarboxylate to 1,2-Benzoquinones: Facile Synthesis of Novel γ-Spirolactones. V. Nair, J. S. Nair, **A. U. Vinod**, N. P. Rath. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3129.

[2] Novel Cycloaddition Reactions of *o*-Benzoquinones and Related Chemistry. V. Nair, S. Kumar, A. G. Nair, G. Anilkumar, K. V. Radhakrishnan, J. S. Nair, D. Maliakal, K. C. Sheela, B. Mathew, P. M. Treesa, **A. U. Vinod**, J. Prabhakaran, V. Sheeba, A. Thomas. *Proc. Indian Acad. Sci. (Chem. Sci.)* **1998**, *110*, 507.

[3] Novel Heterocyclic Construction *via* Dipolar Cycloadditions to 1,2-Dicarbonyl Compounds. V. Nair, K. C. Sheela, K. V. Radhakrishnan, **A. U. Vinod**, C. Rajesh, P. M. Treesa. *J. Het. Chem.* **2000**, *37*, 659.

[4] Triphenylphosphine Catalyzed Addition of Dimethyl Acetylenedicarboxylate to 1,2 and 1,4-Benzoquinones: Synthesis of Novel γ-Spirolactones. V. Nair, J. S. Nair, **A. U. Vinod**. *Synthesis* **2000**, 1713.

[5] The Reaction of Cyclohexyl Isocyanide and Dimethyl Acetylenedicarboxylate with Aldehydes: A Novel Synthesis of Aminofuran Derivatives. V. Nair, **A. U. Vinod**. *Chem. Commun.* **2000**, 1019.

[6] The Reaction of Cyclohexyl Isocyanide and Dimethyl Acetylenedicarboxylate with *o*-and *p*-Quinones: A Novel Synthesis of Iminolactones. V. Nair, **A. U. Vinod**, J. S. Nair, A. R. Sreekanth, N. P. Rath. *Tetrahedron Lett.* **2000**, *41*, 6675.

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[8] A Novel Synthesis of 2-Aminopyrroles Using a Three Component Reaction. V. Nair, **A. U. Vinod**, C. Rajesh. *J. Org. Chem.* **2001**, 0000.

[9] Aminoisocyanides in Multicomponent Reactions (MCRs): A Facile Synthesis of Substituted 3(5*H*)-Pyrrolin-2-ones *via* a Dimroth Type Rearrangement. V. Nair, J. S. Mathen, **A. U. Vinod**, R. Luxmi Varma (communicated to *Chem. Lett.*).

Published Contributions to Academic Conferences

[1] Novel Cycloaddition Chemistry of *o*-Benzoquinones. J. S. Nair, K. V. Radhakrishnan, D. Maliakal, P. M. Treesa, **A. U Vinod**, B. Mathew, K. C. Sheela, V. Nair. National Symposium on Emerging Trends in Organic Chemistry, Trivandrum, India, November **1996**, Poster # P-21.

[2] Triphenylphosphine Catalyzed Addition of Dimethyl Acetylenedicarboxylate to 1,2 and 1,4-Benzoquinones: Synthesis of Novel γ-Spirolactones. J. S. Nair, **A. U. Vinod**, V. Nair. 16th International Conference on Heterocyclic Chemistry, Bozeman, USA, August **1997**, Poster # PO II, 180.

[3] Novel Heterocyclic Construction *via* Dipolar Cycloadditions to 1,2-Dicarbonyl Compounds. V. Nair, K. C. Sheela, **A. U. Vinod**, C. Rajesh, J. S. Nair. International Symposium on Trends in Medicinal Chemistry and Biocatalysis, New Delhi, India, January **2000**, IL-47.

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