STUDIES ON DEVELOPING A FACILE ROUTE FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED QUINOLINE AND INDOLE DERIVATIVES

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In
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In the Faculty of Science
By

Sandhya R.

Under the supervision of

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CERTIFICATE

This is to certify that the thesis entitled **"STUDIES ON DEVELOPING A FACILE ROUTE FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED QUINOLINE AND INDOLE DERIVATIVES"** is a genuine record of research work carried out by **Ms. Sandhya R.** under my supervision, in partial fulfilment of the requirements for the degree of Doctor of Philosophy of Cochin University of Science and Technology, and further that no part thereof has been presented before for the award of any other degree.

Kochi-22
11-11-2013

Dr. Prathapan S.
(Supervising Guide)

DECLARATION

I hereby declare that the work presented in the thesis entitled **"STUDIES ON DEVELOPING A FACILE ROUTE FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED QUINOLINE AND INDOLE DERIVATIVES"** is the result of genuine research carried out by me under the supervision of **Dr. Prathapan S.**, Associate Professor of Organic Chemistry, Department of Applied Chemistry, Cochin University of Science and Technology, Cochin-22, and the same has not been submitted elsewhere for the award of any other degree.

Kochi-22 **Sandhya R.**

11-11-2013

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PREFACE

Heterocyclic compounds have a wide variety of applications. Many of them are key components in biological processes. Most of the pharmaceuticals are heterocyclic in nature besides; these compounds are used as fugisides, herbicides, anti-corrosive agents, photostabilizers, agrochemicals, copolymer, photographic developers, sensitizers, flavouring agents, dyes and pigments. Among the various heterocyclic compounds, the significance of quinolines and indoles lies in their unique applications in various fields. For example, quinoline derivatives are well known for their pharmacological properties, especially many of their derivative exhibit effective anti-malarial activities. Some quinoline derivatives exhibit luminescence properties also. Because of their structural diversity, indole derivatives have become structural constituents of many pharmaceuticals. Among the available methods, 1,3-dipolar cycloaddition reactions are one of the simple techniques that can be used in the synthesis of heterocyclic compounds.

Conventional 1,3-dipolar addition between nitrones and electron deficient acetylenes failed to account for the generation of quinolines and indoles in such reactions. In this situation, the thesis entitled ***"STUDIES ON DEVELOPING A FACILE ROUTE FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED QUINOLINE AND INDOLE DERIVATIVES"*** portrays our attempt to revisit the mechanism of 1,3-dipolar additions with a view to establishing whether it follows a concerted pathway or a stepwise reaction sequence through the formation of a zwitterionic intermediate, which will definitely contribute to the

better use of this technique. Furthermore, we propose to develop novel routes for the synthesis of quinoline and indole derivatives with pre-defined substitution pattern.

The thesis is devided into four chapters. The first chapter briefly describes several aspects of 1,3-dipolar cycloaddition reactions and some of its applications in various fields**.** The research problem is defined at the end of this chapter. The synthesis of various substrates, employed in the present investigation is described in the second chapter. Third chapter reveals our findings on the mechanism of 1,3-dipolar cycloaddition reactions. Here we have investigated the course of nitrone cycloaddition reaction when different substituents are introduced and the effect of medium in controlling the course of the reaction. In the fourth chapter, we utilized our findings on reaction of nitrones with electron deficient acetylenes for developing viable synthetic procedure for the preparation of highly substituted quinoline and indole derivatives having pre-determined substitution pattern. Relevant references are included at the end of individual chapters.

The structural formulae, schemes, tables and figures are numbered chapter-wise as each chapter of the thesis is as an independent unit. All important compounds are fully characterized on the basis of their spectral and analytical data including the single crystal X-ray analysis in many cases. A comprehensive list of references is given at the end of each chapter.

List of Abbreviations

AcOH	: acetic acid
C	: centigrade
D	: debye
d	: doublet
DBA	: dibenzoylacetylene
DBU	: 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	: dichloromethane
DEPT	: distortionless enhancement by polarisation transfer
DMAD	: dimethylacetylenedicarboxylate
DMF	: dimethylformamide
1,3-DC	: 1,3-Dipolar cycloaddition
E	: entgegen
FT IR	: fourier transform infrared
g	: gram
h	: hour
GC-MS	: gas chromatography-mass spectrometry
HOMO	: highest occupied molecular orbital
Hz	: hertz
LUMO	: lowest occupied molecular orbital
m	: multiplet
Me	: methyl
mg	: milligram
min	: minute
mL	: millilitre
mp	: melting point
MS	: mass spectrometry
nm	: nanometre
NMR	: nuclear magnetic Resonance
OLED	: Organic light emitting diode
ORTEP	: oak ridge thermal ellipsoid plot program
m-CPBA	: *m*-chloroperbenzoic acid
MO	: molecular orbital
Ph	: phenyl
RT	: room temperature
s	: singlet
SWNT	: single-wall carbon nanotube
t	: triplet
THF	: tetrahydrofuran
TLC	: thin layer chromatography
TMS	: tetramethylsilane
UV	: ultraviolet
XRD	: X-ray diffraction
Z	: zusammen

CONTENTS

CHAPTER 1

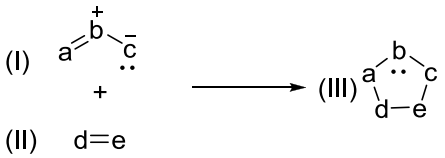
1,3-DIPOLAR CYCLOADDITION: AN OVERVIEW

1.1. Abstract

This chapter briefly describes several aspects of 1,3-dipolar cycloaddition reactions such as nature of 1,3-dipoles and dipolarophiles, mechanism, regioselectivity, reactivity etc. We have also highlighted a few reactions that reveal the synthetic utility of 1,3-dipolar cycloaddition technique.

1.2. 1,3-Dipolar Cycloaddition

The reaction between a 1,3-dipole (**I**) and a dipolarophile (**II**) is termed as a 1,3-dipolar cycloaddition reaction (Scheme 1.1). Normally the product obtained is a five membered heterocyclic compound (**III**). According to Woodward–Hoffmann rules, this is a thermally allowed [4πs + 2πs] cycloaddition reaction.[1] In 1883, Theodor Curtius discovered the first 1,3-dipole, diazoacetic ester.[2] Later, Buchner studied the reactions between ethyl diazoacetate and unsaturated carboxylic esters and it was reported as the first 1,3-dipolar cycloaddition reaction.[3] The concept of this type of reaction was originally suggested by Smith,[4] but it became widely applicable only after the generalisation of it by Rolf Huisgen in the 1960's.[5] Now 1,3-dipolar cycloaddition chemistry has emerged as an important strategy for the synthesis of a wide variety of heterocyclic compounds.



Scheme 1.1

1.2.1. Definition and Classification of 1,3-Dipole

Huisgen defined 1,3-dipole as 'a species that is represented by zwitterionic structures with a positive and negative charge distributed over three atoms and has 4π electrons'.[6] It can be represented either by two octet-structures in which the positive charge is located on the central atom and the negative charge is distributed over the two terminal atoms, or two sextet structures, wherein two of the four 4π electrons are localised at the central atom (Figure 1.1). The sextet formulae contribute little to the electron distribution of the resonance hybrid but illustrate the ambivalence of the 1,3-dipole which is remarkable in understanding the mechanism, reactivity and regiochemistry of 1,3-dipolar cycloaddition.

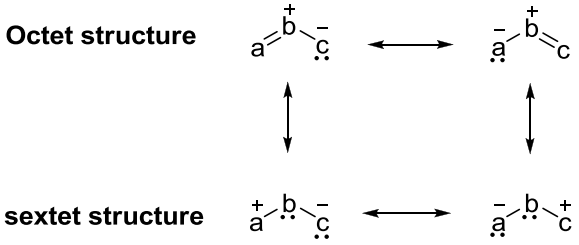
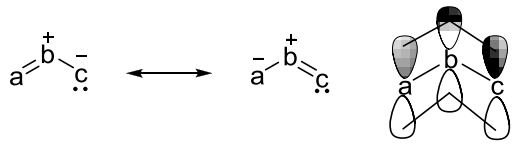


Figure 1.1

Based on electronic makeup, 1,3-dipoles can be classified into two types: the allyl anion type and the propargyl (allenyl) anion type (Figure 1.2). In allyl anion type 1,3-dipoles, the 4π electrons are present

in three parallel *p* orbitals perpendicular to the plane of the dipole. Due to the presence of these π electrons, the molecule possesses a planar, bent structure. Here the central atom can either be a group V (N, P, etc.) or group Vl (O, S) element. In propargyl anion type 1,3-dipoles, presence of an additional π bond (orthogonal to the allyl anion type molecular orbital) makes the dipole linear. Here the central atom is limited to an atom from group V, since they only bear a positive charge in the tetravalent state. Over the years, several 1,3-dipoles have been synthesized and their chemistry is well established. Examples for some of the frequently encountered allyl anion type and propargyl anion type 1,3-dipoles are listed in Table 1.1. Most of these dipoles undergo addition reactions with suitable dipolarophiles.

Allyl anion type



Propargyl/Allenyl anion type

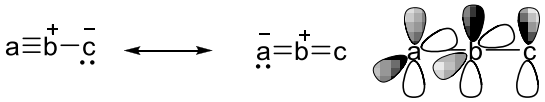
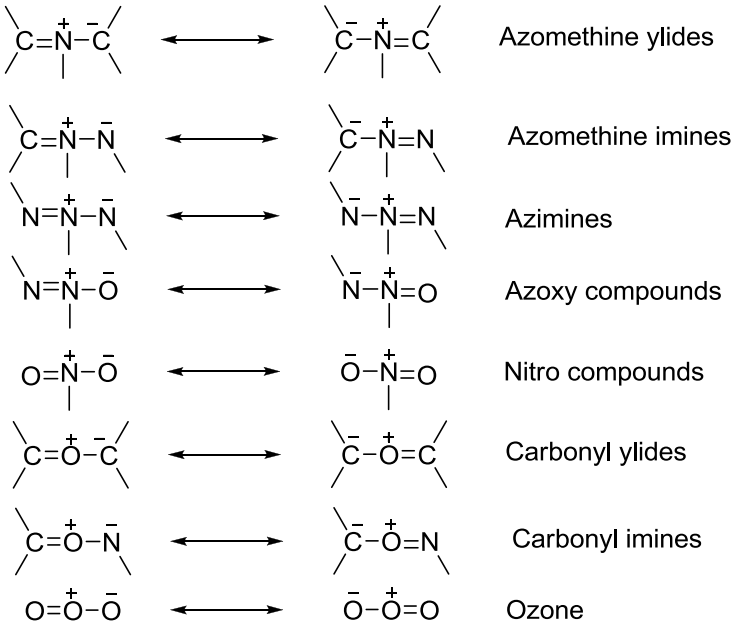


Figure 1.2

Allyl anion type 1,3-dipoles



Propargyl (Allenyl anion) type 1,3-dipoles

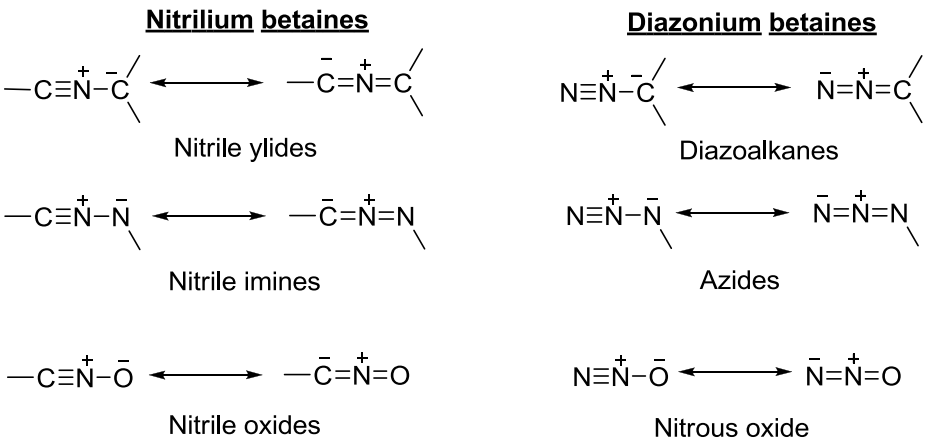


Table 1.1

Interestingly, 1,3-dipoles are not very polar compounds. This can

be explained in terms of an allyl anion type π system, where the negative charge is distributed over the two termini, **a** and **c**, whereas the onium charge is localised on the central atom or group, **b**. The better balanced the distribution of negative charge; the smaller will be the polarity. In another words, relative contribution of the canonical form has a definite say on the dipole moment of various 1,3-dipoles. This was illustrated by measuring the dipole moments of the allenyl anion type dipole diazomethane and the allyl anion type dipole *N*-methyl-*C*-phenylnitrone (Figure 1.3).

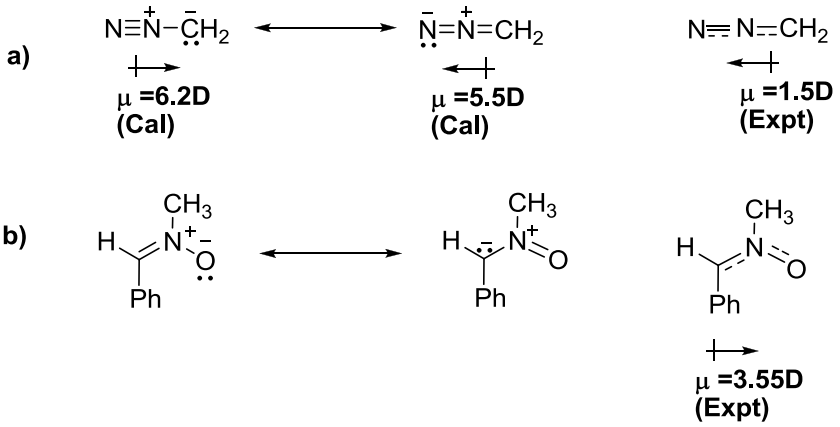


Figure 1.3

The very low experimental value of dipole moment suggests that considerable charge cancellation occurs in the resonance hybrid, which makes it difficult to identify exact electrophilic and nucleophilic centers within the dipolar species. Hence the 1,3-dipole is always an ambivalent compound, which shows both electrophilic and nucleophilic activity at **a** and **c** or reacts in the 1,3-position as a spin coupled diradical. The experimental dipole moment value shows the dominance of an

azomethine *N*-oxide structure for *N*-methyl-*C*-phenylnitrone where, the terminal oxygen carries major fraction of negative charge with respect to the carbon atom.

1.2.2. The Dipolarophile

The multiple-bonded component, which react with 1,3-dipole in a cycloaddition reaction is commonly christened as the dipolarophile. For example, it can contain C≡N, C≡C, C=C, C=N, C=O, C=S. etc. functional groups.[7-10] The π bond in the dipolarophile may be a conjugated one, part of cumulative bond or it can be an isolated one.[11-12] The reactivity of these compounds towards 1,3-dipoles is enriched by the presence of electron withdrawing or electron donating substituents but a combination of both types of substituents in a single system decreases the reactivity of the molecule.

1.3. Mechanism of 1,3-Dipolar Cycloaddition

On the basis of several experimental observations, Huisgen proposed a concerted mechanism for 1,3-dipolar cycloaddition reactions.[13-15] Here, movement of electrons in a closed loop indicated planar arrangement of all five reacting centers. According to Huisgen, the perfect synchrony, the simultaneous formation of the two new sigma bonds, will be attained with symmetrical dipoles and dipolarophiles. So in the case of unsymmetrical reactants, the formation of one sigma bond may lag behind the closure of the second bond in the transition state. Woodward and Hoffmann tried to explain the concerted cycloaddition reactions using conservation of orbital symmetry.[16] The mechanism was

subjected to great deal of discussion and in between, Firestone introduced a stepwise diradical pathway for 1,3-DC (Figure 1.4).[17-19] It was supported by Harcourt and he explained the cycloaddition reaction mechanism with the help of valence bond theory.[20]

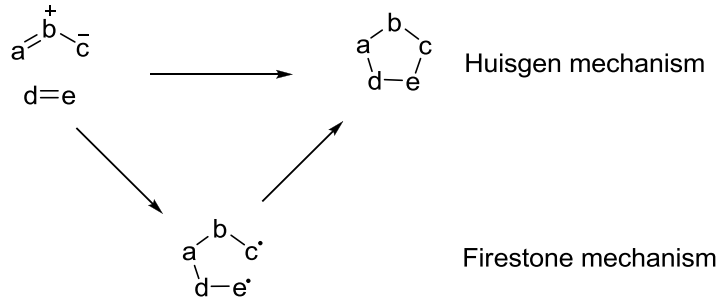
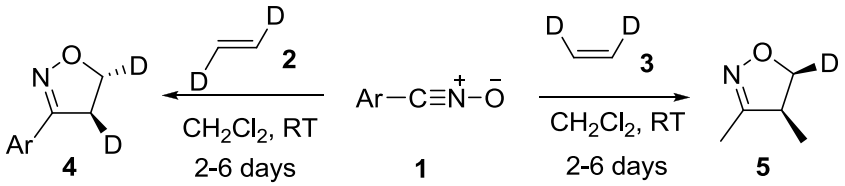


Figure 1.4

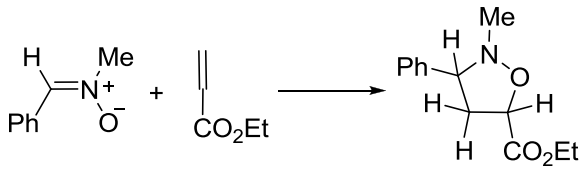
Reaction of benzonitrile oxide **1** with trans dideuterated ethylene **2** gave exclusively the *trans*-isoxazoline **3** (Scheme 1.2).[21] If it follows a radical mechanism, the intermediate can undergo rotation and can yield a mixture of cis and trans isomers. So the dispute was settled in favour of concerted mechanism on the basis of stereospecificity of the reaction.



Scheme 1.2

Effect of solvent on Diels Alder reactions has contributed additional information regarding the 1,3-dipolar cycloaddition reaction mechanism. Many factors such as dipole-dipole attraction, coulumbic

forces, dispersion forces, hydrogen bonding, electrophilic and nucleophilic interactions etc. contribute to the term solvent polarity. If 1,3-dipolar additions proceed through a zwitterionic intermediate, the rate of the reaction should be dependent on solvent polarity. On the other hand, if it is a concerted mechanism, solvent polarity will not affect the rate of the reaction. Huisgen *et al*. studied the cycloaddition reaction between *N*-methyl-*C*-phenylnitrone (**6**) and ethyl acrylate (**7**) in a variety of solvents (Scheme 1.3 and Table 1.2).[22]



6 **7** **8**

Scheme 1.3

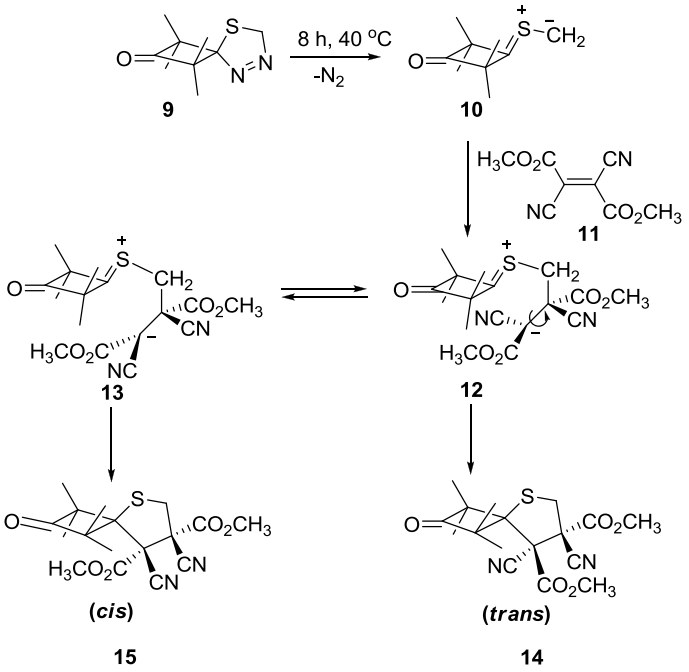
Solvents	E_T (kcalmol^{-1})	10^4 k_2 (Lmol^{-1}sec^{-1})
Toluene	33.9	4.8
Benzene	34.3	4.2
Dioxane	36.0	2.8
Ethyl Acetate	38.1	2.6
Pyridine	40.5	2.2
Acetone	42.2	1.9
Dimethylformamide	43.2	1.7
Dimethyl sulfoxide	45.1	1.8
Acetonitrile	45.6	1.6
Ethanol	51.9	0.86

Table 1.2

They observed that change in solvent polarity did not influence reaction rates appreciably. Slight retardation in the rate of the reaction could be observed while moving from relatively nonpolar toluene to

highly polar ethanol (Table 1.2). Authors proposed that this may be due to the formation of an activated complex. The dipolar cycloaddition reaction of phenyldiazomethane to norbornene and acrylic ester,[23] azomethine imines and DMAD [24], phenyl azide and enamines[25] etc. also revealed similar trends. All the above discussed studies strongly recommended a concerted pathway for 1,3-dipolar cycloaddition reaction.

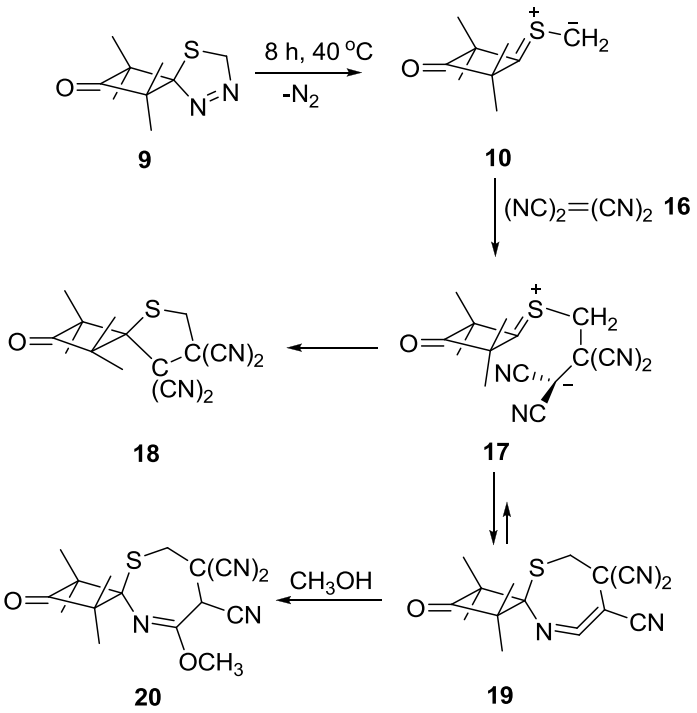
Later in 1986, Huisgen's group themselves showed that, stepwise mechanism is also possible for 1,3-DC reaction and in such case it will not be a stereospecific one.[26] This was illustrated by the cycloaddition reaction of an electron rich thiocarbonyl ylide **10** with dicyanofumarate **11** (Scheme 1.4).



Scheme 1.4

Both cis and trans isomers were obtained in a 48:52 ratio, and the ratio was found to increase in favour of the cis isomer with increasing solvent polarity. Huisgen tried to explain the stepwise phenomenon on the basis of molecular orbital theory. In the language of MO theory the two new σ bonds are formed by two π-HOMO-LUMO interactions. A limiting case is observed when one of the HOMO-LUMO interactions strongly dominates the other. Here the bond energy contribution of the second HOMO-LUMO pair to the transition state is negligible, so it cannot compensate the higher entropy requirements of the concerted process. So a zwitterionic intermediate **12** is generated by the formation of one bond between the reactants as a result of the unilateral electron flow. Huisgen considered the rotation of this ionic intermediate to account for non-stereospecific course of the reaction.

Cycloaddition reaction of the thiocarbonyl ylide **10** with tetracyanoethylene **16** is another case where the formation of the ring enlarged product **20** along with the normal adduct **18** was explained through formation of a zwitterionic intermediate **17** (Scheme 1.5).[27]

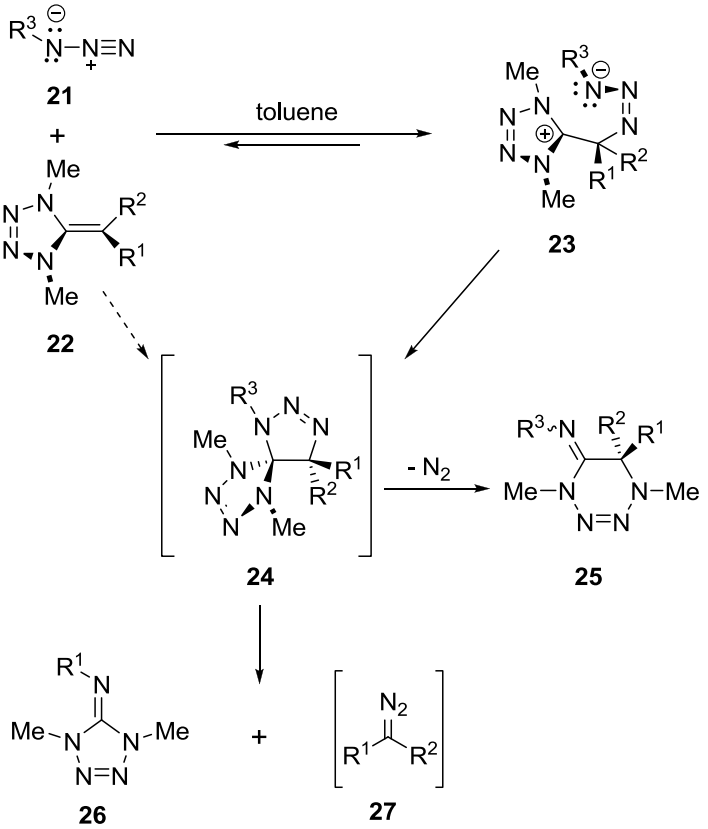


Scheme 1.5

In the formation of the normal adduct thiolane **18,** the trisubstituted carbanion of the ionic intermediate combined with the carbenium-sulfonium center. The unusual adduct **20** was formed by the addition of methanol to the cyclic ketene imine **19** formed from **17** in a competing pathway. According to Huisgen, another condition for a two-step mechanism is the strong steric hindrance at one terminus of the 1,3-dipole.[28] This proposal was later supported by earlier reports from our group.[29]

In 1990, Quast *et al.* reported the first example for a stepwise cycloaddition reaction between strongly electrophilic azides **21** as 1,3-dipoles and electron rich 5-alkylidenedihydrotetrazole **22** as the

dipolarophile (Scheme 1.6).[30] Then azides **21a-c** were treated with 5-alkylidenedihydrotetrazoles in toluene the zwitterion **23** or the 5-iminotetra-hydro-1,2,3,4-tetrazine together with molecular nitrogen are obtained. Here they could not isolate the cycloadduct **24**. The compounds **26** and **27** were assumed as the decomposition product of the intermediate **24**. The yield of the corresponding zwitterions or the tetrazines is given in the Table 1.3.



Scheme 1.6

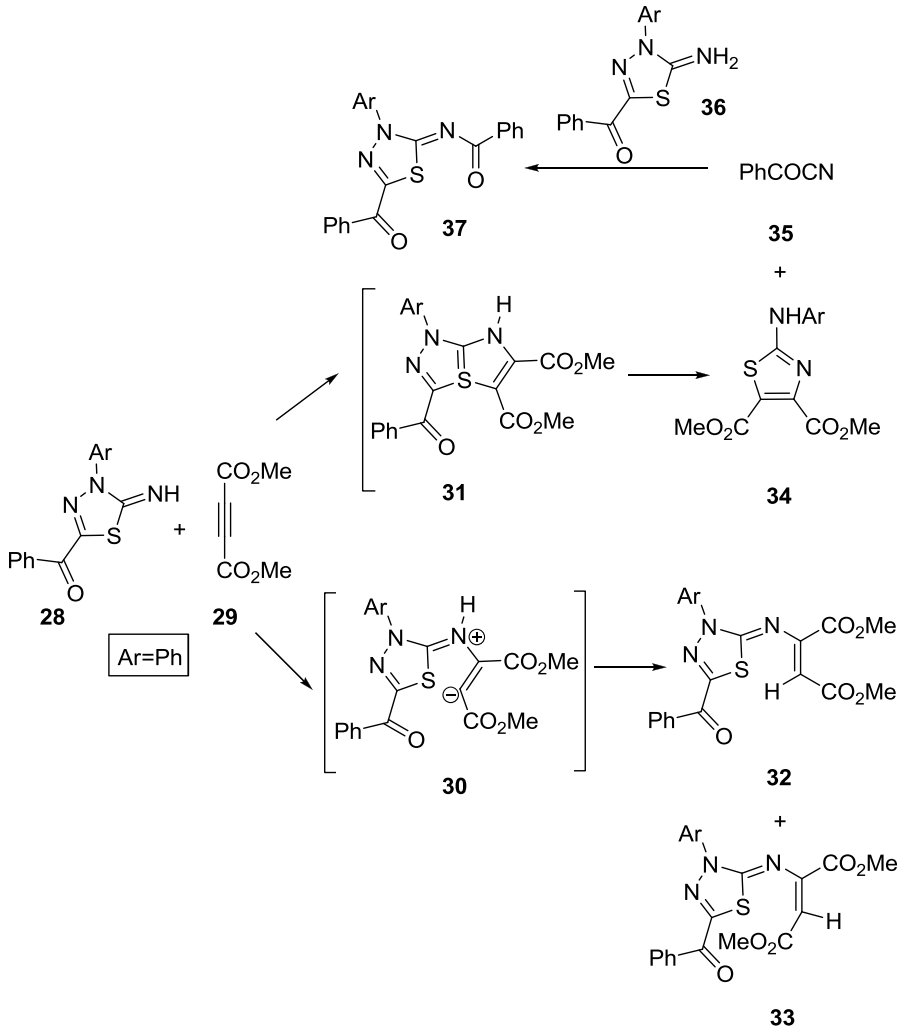
Compound	R^1	R^2	R^3	Yield (%)
23a	Me	Me	2,4,6-$(NO_2)_3$-C_6H_2	90
23b	H	tBu	2,4,6-$(NO_2)_3$-C_6H_2	37
23c	Me	Me	4-Me-C_6H_4-SO_2	quant.
25c	Me	Me	4-Me-C_6H_4-SO_2	73
23d	H	tBu	4-Me-C_6H_4-SO_2	quant.
25d	H	tBu	4-Me-C_6H_4-SO_2	68
23e	H	tBu	Me-SO_2	52
25f	Me	Me	Me-SO_2	86

Table 1.3

Yamamoto *et al*. identified the formation of products resulting from zwitterion intermediate during the reaction of an iminodiathiazoline **28** with dimethyl acetylenedicarboxylate **29** (Scheme 1.7).[31] The iminodiathiazoline **28** can act as a masked 1,3-dipole. Thiazole **34** and benzoyl cyanide **35** were assumed to be formed from the cycloadduct sulfurane **31** and the cis and trans vinyl compounds (**32** and **33**) from the zwitterionic intermediate **30**. Yield of products obtained, when the reaction is conducted in different solvents is given in Table 1.4. From the table it is clear that as the polarity of the solvent increases yield of the product arising through cycloadduct decreases. Vinyl compounds, resulting from zwitterionic intermediate, are produced even in non-polar aprotic solvents, the cis isomer is the major one in aprotic solvents. The ratio of *cis*-vinyl to *trans*-vinyl is dependent on the kind of alcohol used.

Solvent	E_T	**34**	**32**	**33**	**37**
C_6H_6	34.5	86.4	2.1	0.9	10.6
CCl_4	32.5	90.6	3.3	0.1	6.0
THF	37.4	91.6	3.7	0.5	4.2
AcOEt	38.1	84.1	3.1	1.3	11.5
MeCOMe	42.2	72.8	6.3	1.6	19.2
Me_2SO	45.0	76.3	9.4	3.4	11.0
MeCN	46.0	73.9	4.7	1.5	9.9
t-BuOH	43.9	79.0	5.7	4.0	11.3
i-PrOH	48.6	71.9	5.3	12.4	10.4
EtOH	51.9	68.7	13.8	15.8	1.7
MeOH	55.5	41.8	38.5	18.9	0.8

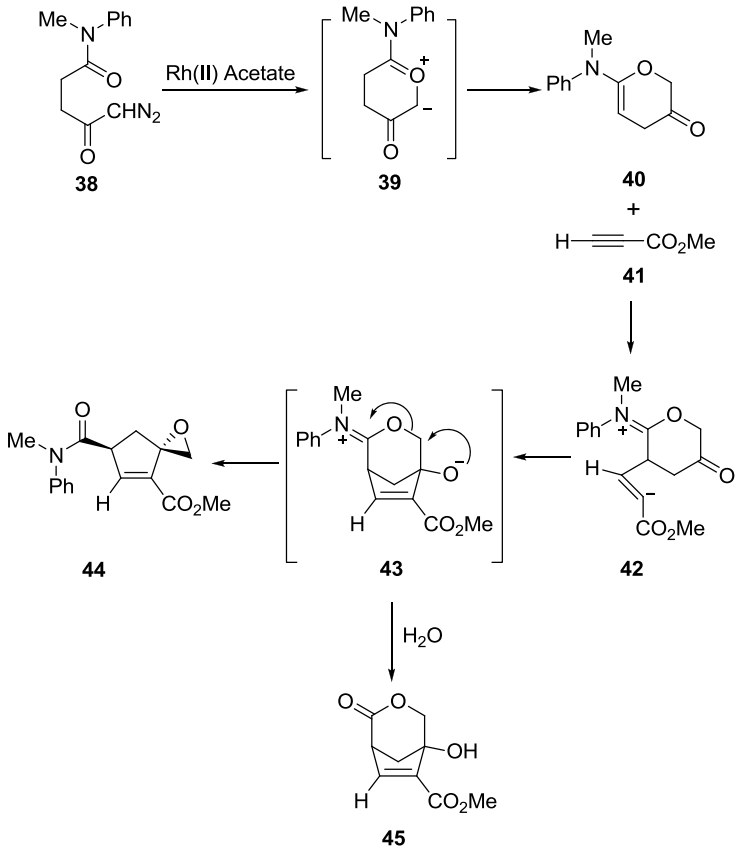
Table 1.4



Scheme 1.7

An unusual zwitterion mediated 1,3-dipolar cycloaddition was observed in the reaction of an α-diazoketoamide **38** with methyl propiolate **41** (Scheme 1.8). Here the reaction was catalysed by Rh(II) acetate.[32] Under anhydrous condition, the cyclic ketene *N,O*-acetal **40**, formed from an *in situ* generated carbonyl ylide **39**, undergoes conjugate

addition with the dipolarophile **41** to produce a zwitterionic intermediate **42**. The anionic part of this ion adds to the adjacent carbonyl group to give another zwitterionic species **43**, which further rearranged to the product **44**. In the presence of trace amount of moisture, lactone **45** was also generated.



Scheme 1.8

As mentioned earlier, a diradical mechanism was also proposed to account for 1,3-dipolar addition reactions. Though the diradical mechanism was completely ruled out, various groups have reported their

findings in favour of a zwitterion mediated stepwise mechanism. So from theoretical studies and experiment observations, it can be concluded that 1,3-dipolar cycloadditions follow both concerted and stepwise paths and they may be in close competition.[33-37]

1.4. Regioselectivity and Reactivity

Both steric and electronic factors contribute to the reactivity as well as to the regioselectivity of 1,3-dipolar cycloaddition reaction.[38-40] Most of the chemical reactions can be successfully explained on the basis of orbital interactions. Fukui used the interaction between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of the reactants to predict the favourable steric pathway.[41] According to him the charge transfer interaction between electron donating part and electron accepting part of the reactants is the driving force for most reactions. Electron donating substituents on either the dipole or the dipolarophile raise the level of both the HOMO and LUMO, electron withdrawing substituents lower the energy of both while conjugating groups raise the HOMO energy but lower the energy of LUMO.

Sustman catagorised 1,3-dipolar cycloaddition reactions into three types based on the nature of substituents present on reactants, that is on the basis of relative FMO energies (Figure 1.5).[42-44] In type I reactions, the HOMO of the dipole can interact with LUMO of dipolarophile. Cycloaddition reaction of azomethine imine and azomethine ylide comes under this category. These types of reactions are known as HOMO controlled or “normal electron demand reactions”. Presence of electron

donating substituent in dipole as well as electron withdrawing substituent in dipolarophile accelerates the rate of the reaction. In type II class of reactions, both reactants have similar FMO energies, hence both HOMO-LUMO interactions are important. In such cases, presence of both electron withdrawing and electron releasing groups on dipole as well as dipolarophile increases the reaction rate. Example for type II cycloaddition reaction is that of nitrones with suitable dipolarophiles. In type III category, the interaction between LUMO of the dipole and HOMO of the dipolarophile is significant. This type of reaction is known as LUMO controlled and is denoted by the term 'inverse electron demand" reactions. In this case the reaction is accelerated by the presence of electron donating substituent on dipolarophile and electron withdrawing substituent on dipoles. 1,3-DC's of ozone and nitrous oxide are example for type III classification. But, the reaction type get changed by the introduction of electron donating or electron withdrawing substituents on dipole or dipolarophile, since it cause a change in the relative FMO energies of the reactants. This is illustrated by the cycloaddition reactions of *N*-methyl-*C*-phenylnirone with methyl vinyl ether as well as with methyl acrylate. In the former case the reaction is controlled by $LUMO_{dipole}$–$HOMO_{dipolarophile}$ interactions, whereas in the second case, the reaction is controlled by the interaction between $HOMO_{dipole}$ –$LUMO_{dipolarophile}$.

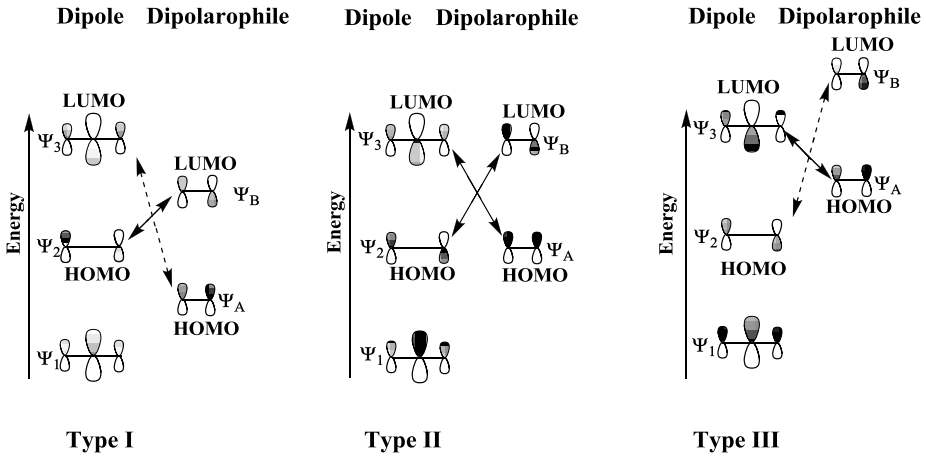


Figure 1.5

Houk combined the term orbital coefficient with frontier orbitals of the interacting atoms.[45-47] According to him the preferred regioisomer will be that one in which the atoms with the larger terminal coefficients interact. Except for nitrone, almost all the 1,3-dipole have larger orbital coefficient for the anionic terminus than the neutral terminus. When the regioselectivity is controlled by HOMO of the dipole, for monosubstituted, conjugated and electron deficient dipolarophiles, the product will be formed with the substituent away from the anionic terminus. But in the case of electron rich dipolarophiles the product will be formed with substituent near the anionic terminus. When the LUMO of the dipole controls the regioselectivity of the reaction, the predominant product will be the one with the substituent near the anionic atom. For example, the reaction of azides with electron rich dipolarophiles is LUMO controlled, here the orbital coefficients are higher on unsubstituted nitrogen in the azide and unsubstituted terminus in the dipolarophiles so the 5-substituted Δ^2-triazolines are favoured (Figure

1.6b). When electron deficient dipolarophile is used, the reaction is HOMO controlled and the product will be 4-substituted Δ^2-triazoline (Figure 1.6a). When electron withdrawing or conjugating substituents are attached to both ends of the dipolarophile, the frontier orbital coefficients at both carbon atoms have nearly identical values. In the case of diazomethanes, with electron deficient dipolarophiles, type I interaction is most significant and as a result of the interaction of larger terminal coefficients on carbon of diazomethane with that on the unsubstituted carbon of the dipolarophile and the favoured products are 3-substituted Δ^1-pyrazolines (Figure 1.6c). The reaction of enol ether with diazomethane is very slow and the product will be a 4-substituted Δ^1-pyrazoline (Figure 1.6d). Nitrous oxide react with conjugated and electron rich alkenes to give the products resulting from the intermediate 5-substituted 1,2,3-oxadiazoline (Figure 1.6e), but it does not react with electron deficient dipolarophiles.

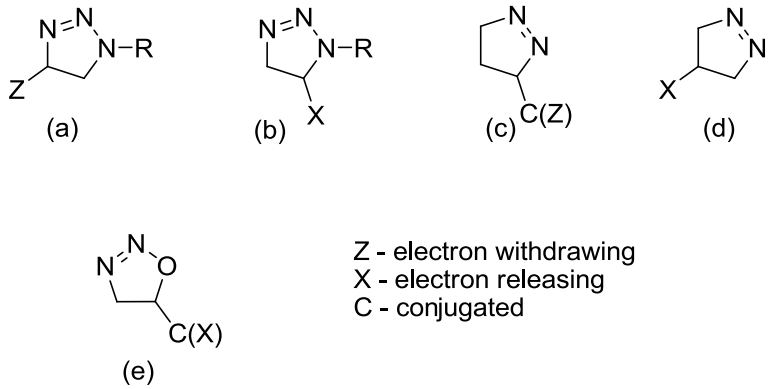


Figure 1.6

The presence of Lewis acids enhance 1,3-dipolar cycloaddition reactions by altering the orbital coefficients of the reacting atoms.[48] Coordination of Lewis acid to dipole or the dipolarophile will lower the FMO energies relative to the uncoordinated reactants (Figure 1.7). This decrease in energy further lowers the energy difference between the interacting molecular orbitals, there by the reactivity of species get increased.[49] This is illustrated by the reaction of *N*-benzyl-*C*-(2-pyridyl)-nitrone **46** with allyl alcohol **47** (Scheme 1.9).[50] By the use of catalyst, the rate of the reaction get doubled and also they could achieve improved diastereoselectivity. The predominant formation of cis isomer **48a** may be due to the substitution of one of the ligands of the Lewis acid by the alcohol group in the exo transition state, such a substitution is very difficult in the endo transition state (Scheme 1.10).

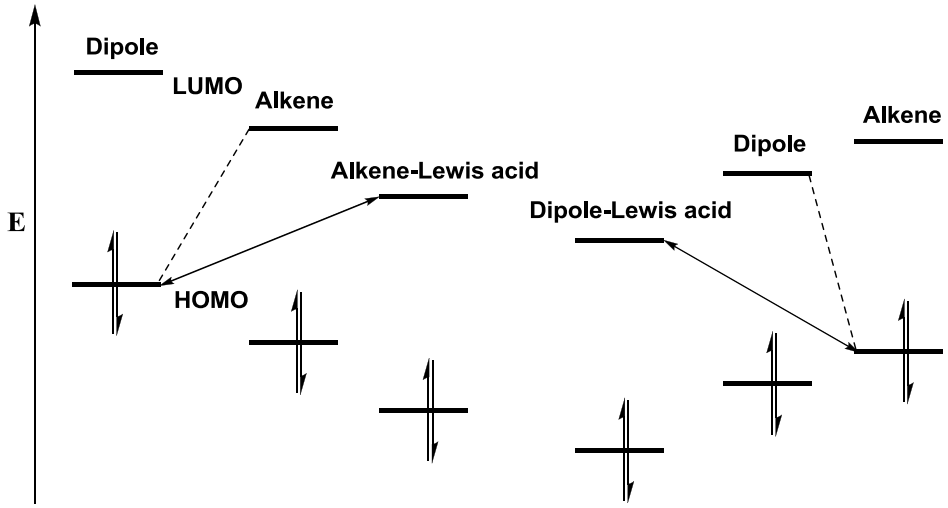
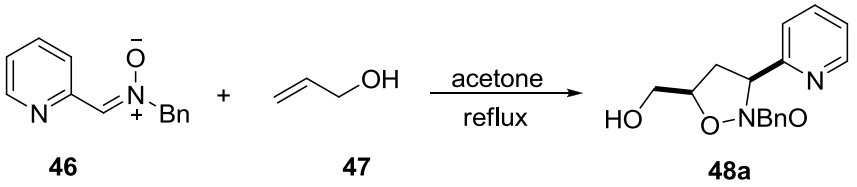
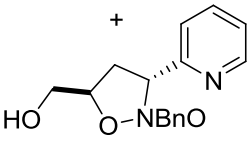


Figure 1.7



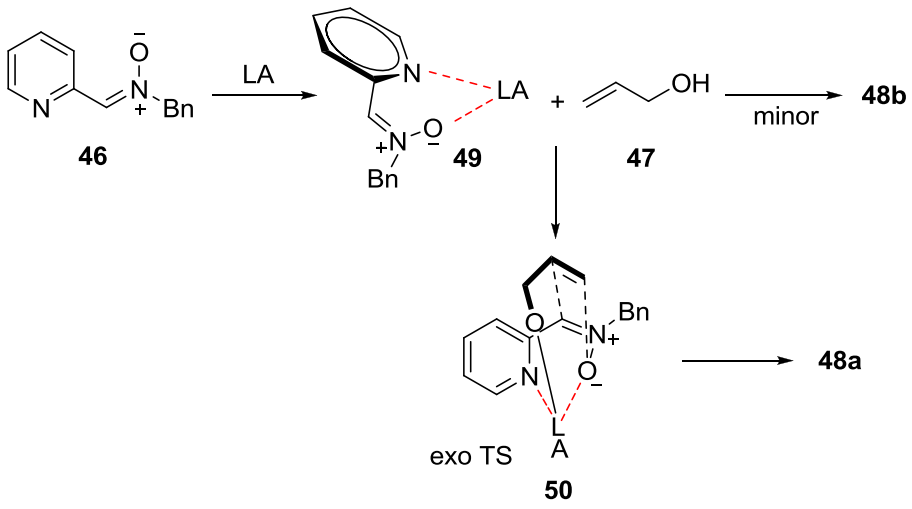
46 47 48a

Lewis acid	time (days)	48a:48b	yield (%)
None	7	70:30	90
AgOTf	3.5	>95:5	100
$[Ag(OClO_3)(PPh_2Me)]$	5	>95:5	92
$Zn(OTf)_2$	3	>95:5	100



48b

Scheme 1.9

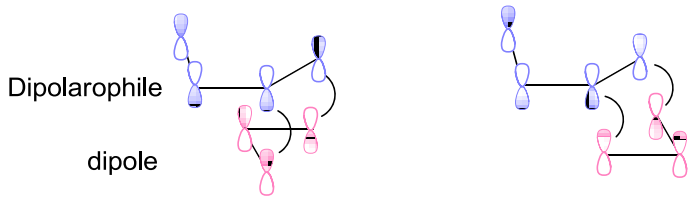


Scheme 1.10

In addition to metal catalysts, use of biocatalysts,[51] microwave radiation[52-54] and ultrasound radiation[55] also enhances the rate of 1,3-dipolar cycloaddition reactions.

1.5. Stereoselectivity

Most of the 1,3-dipolar cycloaddition reactions are highly stereoselective and this may be due to the concerted nature of the reaction. When two chiral centres are formed, one arising from the dipole and the other from the dipolarophile, diastereomeric products (cis- and trans-) may be produced via endo and exo transition states (Figure 1.8). The predominant formation of each diastereomer depends on attractive *p*-orbital overlap of unsaturated substituents (favouring an endo transition state) and repulsive vanderWaals steric interactions (favouring an exo transition state), in most of the cases, a mixture of diastereomers is obtained.



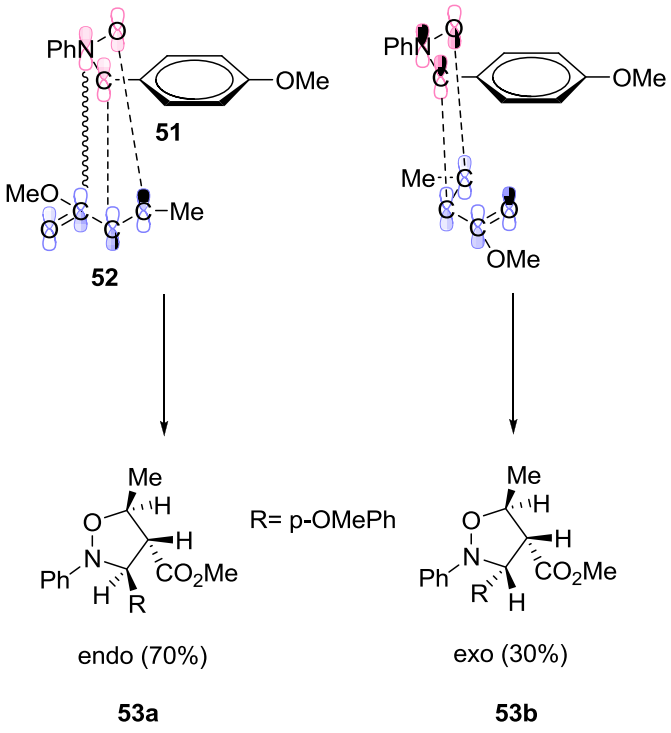
endo selectivity *exo* selectivity

Figure 1.8

This can be demonstrated by the reaction of *C*-(*p*-methoxyphenyl)-*N*-phenylnitrone **51** with methyl crotonate **52**.[56-58] After the reaction, the products were obtained in the diastereomeric ratio 70:30 (endo:exo) (Scheme 1.11). Here the preference for the endo-isomer is due to the stabilising interaction of the nitrogen *p* orbital with the *p*

orbital of the carbonyl carbon. Use of chiral catalyst is another way for achieving non-racemic cycloadducts.[59]

Though secondary orbital interactions are used to explain the endo–exo selectivity in 1,3-dipolar cycloaddition reactions, it is very weak as compared to Diels Alder reactions. Like Diels- Alder reactions, the factors such as the effect of solvent, steric interactions, hydrogen bonding and electrostatic force also affect the endo–exo selectivity in a particular [3+2] cycloaddition reaction. Generally the governing factors of stereoselectivity in a 1,3-dipolar cycloaddition reaction are the structure of the substrate and the presence of the catalyst.[60-62]



Scheme 1.11

1.6. 1,3-Dipolar Cycloaddition: As a Synthetic Tool

1,3-Dipolar cycloaddition can be considered as a device for the synthesis of heterocyclic compounds. Heterocycles constitutes one of the fascinating parts of chemistry. Introduction of a heteroatom into a cyclic structure imparts new properties to the compound. Many of them are key components in biological processes. For example, the genetic material is made up of hetrocycles such as adenine, guanine, cytosine, thymine. Photosynthesizing pigment chlorophyll, the oxygen transporting pigment haemoglobin, vitamins such as thiamine (vitamin B_1), riboflavin (vitamin B_2), pyridoxol (vitamin B_6), nicotinamide (vitamin B_3) and ascorbic acid (vitamin C), the essential amino acids, histidine, proline and tryptophan, hormones kinetin, heteroauxin and cytokinins, neurotransmitter serotonin, histamine and several other bioactive molecules are heterocyclic compounds.[63-69]

Most of pharmaceuticals are heterocyclic in nature. Many natural drugs such as theophylline, papaverine, quinine, emetine, theobromine, atropine, codeine, procaine, morphine, reserpine[70-73] and several of the synthetic drugs such as metronidazole, chloropromazine, diazepam, isoniazid, barbiturates, methotrexate, captopril, antipyrine, and azidothymidine are heterocycles. This class of compounds are used as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV activity, antileishmanial agents, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, antiinflammatory, muscle relaxants anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents.[74-80] Thus the synthesis

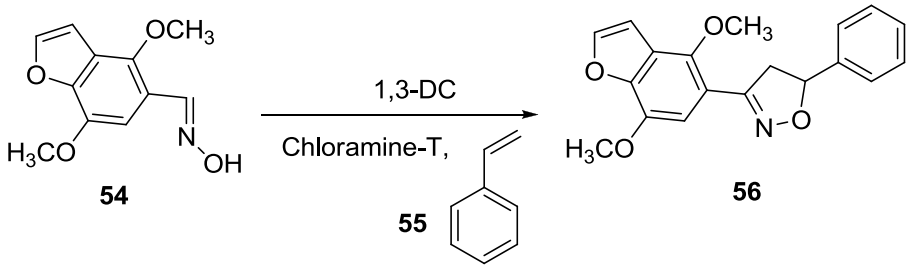
of heterocyclic compound and its application is part of venturing human life.

Heterocyles participate in a wide range of reactions. Depending on the pH of the medium, they behave as acids or bases, forming anions or cations. Some heterocyclic compounds interact readily with electrophilic reagents, others with nucleophiles, yet others with both. Some are easily oxidized, while others can be readily hydrogenated. Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. Another important feature is they can incorporate functional groups either as substituent or as part of the ring system itself. Not surprisingly, several heterocycles are widely used as intermediates in organic synthesis.

The ability of heterocyclic compounds to act as suitable ligands and thereby to produce stable complexes with metal ions has great biochemical significance. For example these compounds are used as chiral ligands for transition metals and the resulting complexes act as catalysts in a variety of asymmetric synthetic reactions. Heterocyclic compounds are also used as fungicides, herbicides, anticorrosive agents, photostabilizers, agrochemicals, copolymer, photographic developers, fluorescent whiteners, sensitizers, booster agent, antioxidant in rubber and flavouring agent, dyes and pigments.[81-85] Wide range of application of heterocyclic compounds reveals the need for a standard synthetic method. Let us see how 1,3-dipolar cycloaddition reaction has emerged as a powerful strategy in synthetic chemistry.

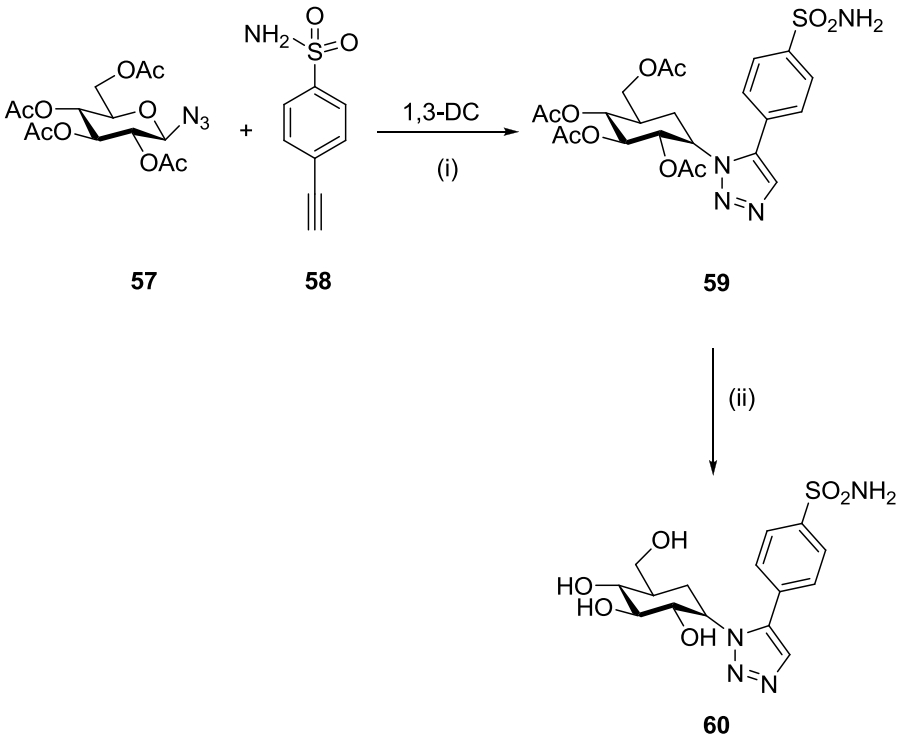
1.6.1. Therapeutics

1,3-Dipolar cycloaddition reaction is used in the synthesis of a large number of compounds having medicinal activity.[86-96] For example, intramolecular 1,3-dipolar cycloaddition reaction act as the key step in the enantioselective synthesis of FR-900482 analogues, that exhibit excellent antitumor activity.[97] Protein tyrosine phosphatase (PTP) dephosphorylates are insulin receptors, which in turn results in diabetes. Ahmad *et al*. reported the use of benzofuran isoxazoline 56 against PTP's.[98] In the synthetic procedure, the oxime derivative **54** undergo cycloaddition with substituted olefins **55** in presence of chloramine T (Scheme 1.12).



Scheme 1.12

By the ruthenium catalysed azide–alkyne 1,3-DC, Salmon *et al*. developed novel series of carbohydrate-based 1,5-disubstituted-1,2,3-triazole benzenesulfonamides **60** (Scheme 1.13).[99] They report that the prepared triazole derivatives show excellent activity against Carbonic anhydrase IX, which is highly expressed in many cancers. This enzyme catalyses the hydration of CO_2 to HCO_3^- and H^+.



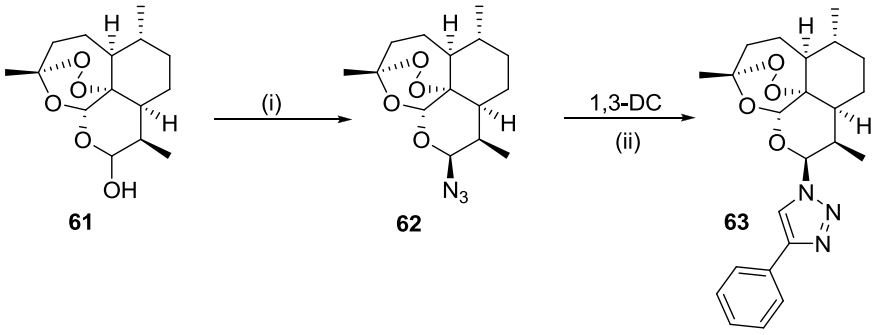
(i) azide 2.6 (0.2 M), alkyne 6 (1.0 -1.5 equiv),
5 mol % [Cp.RuCl(cod)], toluene, N_2, 100^0C, 18 h,
(ii) NaOMe in MeOH (0.05 M, pH 12),
anhydrous MeOH, 0^0C - rt, 30 min-16 h,

Scheme 1.13

Several marine natural products exhibit potential biological properties. Ghosh *et al*. described the total synthesis of a macrolide, Lasonolide A, where an intramolecular 1,3-dipolar cycloaddition is the key step.[100] A series of novel sulfanilamide-derived 1,2,3-triazoles with halobenzyl groups and different lengths of alkyl chains were synthesized successfully via cycloaddition of azides and terminal alkyne by 'click

chemistry.[101] Authors report that the prepared triazole derivatives exhibit promising antibacterial activity.

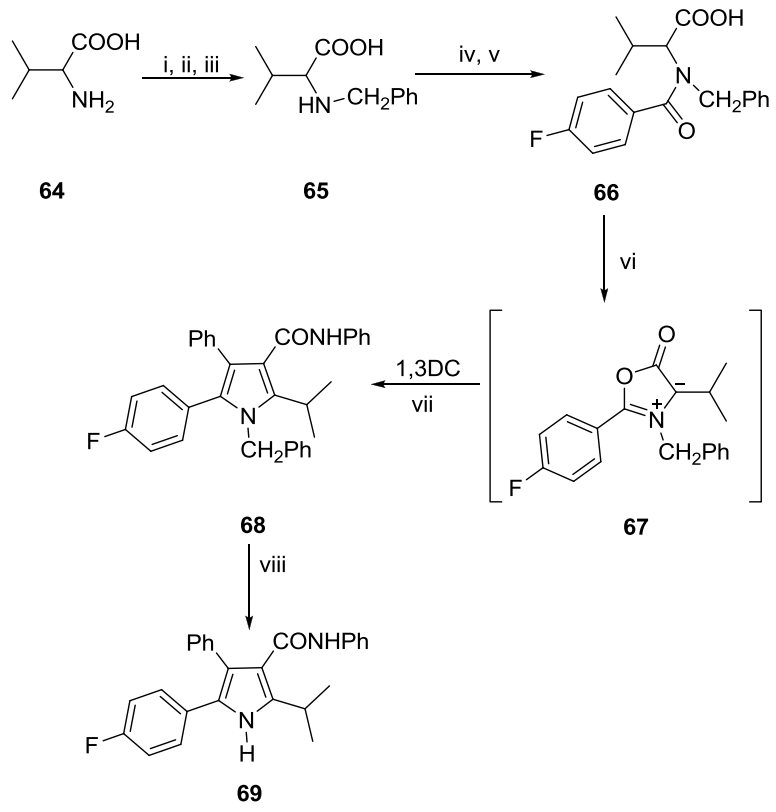
1,3-DC of diastereomeric 10-azidoartemisinin **61** with alkyne afforded 10-substituted triazolylartemisinin **63** (Scheme 1.14), which exhibit strong activity against various cancer cell lines such as DLD-1, U-87, Hela, SiHa, A172, and B16.[102]



(i) trimethylsilyl bromide (2.2 equiv), sodium azide (3 equiv), CH_2Cl_2, rt, 12 h
(ii) $CuSO_4$ (1.1 equiv), sodium ascorbate (2.8 equiv), phenylacetylene (1 equiv), CH_2Cl_2 : H_2O (1:1), rt, 48 h.

Scheme 1.14

Atorvastatin is a commonly used drug against cholesterol, it inhibits the action of HMG-CoA reductase. By the dipolar cycloaddition reaction of 1,3-oxazolium-5-olate **67** with *N*-1,3-diphenyl-2-propynamide, synthesis of an important intermediate of atorvastatin **69** was reported (Scheme 1.15).[103]

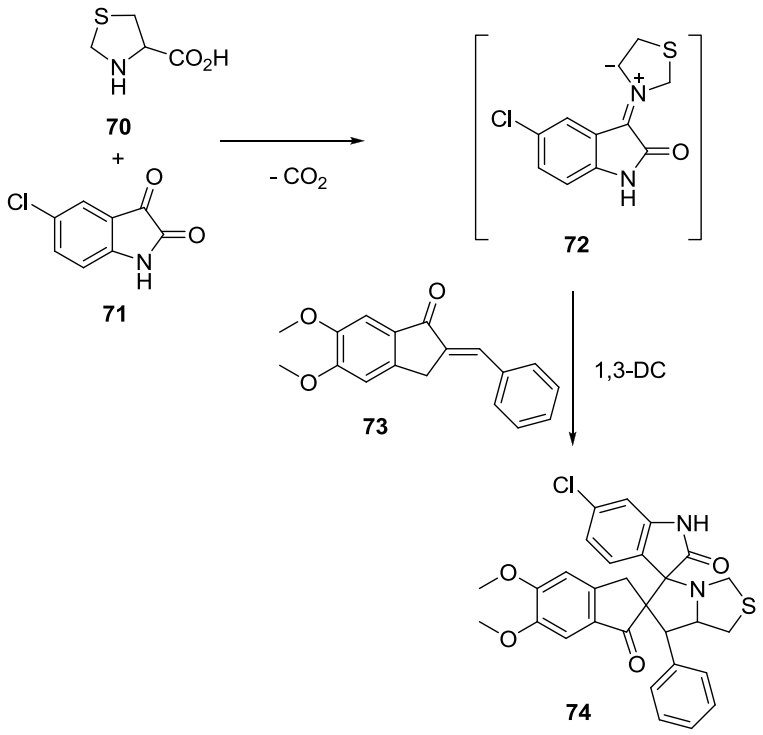


(i) dry HCl gas, CH_3OH, reflux, 4 h (ii) liquor NH_3
(iii) benzyl bromide (1.1 equiv), K_2CO_3 (2 equiv), $CHCl_3$, rt, 12 h
(iv) 4-fluorobenzoyl chloride (1.1 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 ^{0}C to rt, 12 h
(v) NaOH,MeOH–H_2O (4:1), reflux, 3 h
(vi) DCC (1.2 equiv), toluene
(vii) *N*-1,3-diphenyl-2-propynamide (1 equiv), reflux, 7 h
(viii) Na (4 equiv), liquid NH_3, t-BuOH (2 equiv), THF, - 78 ^{0}C, 10 min

Scheme 1.15

Acetylcholinesterase (AchE) is an enzyme which hydrolyses the neurotransmitter acetylcholine. Increasing the level of acetylcholine is an important approach in the treatment of Alzheimer's disease. So, supressing the action of AChE is an important strategy for the treatment of Alzheimer's disease, senile dementia, ataxia, myasthenia gravis and Parkinson's disease. Ali *et al* used 1,3-DC for the synthesis of

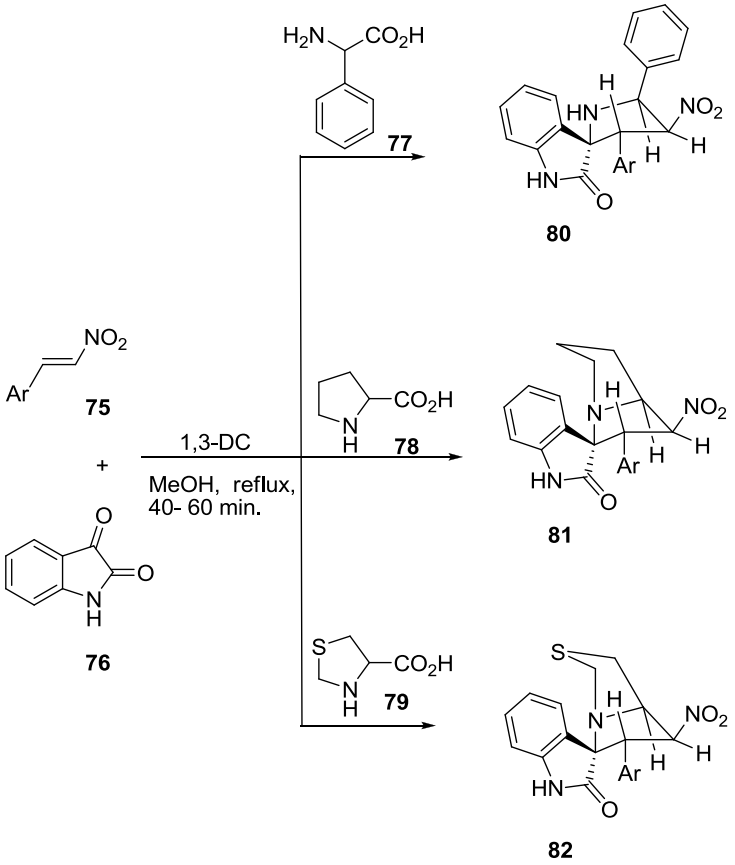
pyralothiazolyloxindole analogues as AChE inhibitors.[104] In the reported procedure an azomethineylide **72**, generated by the decarboxylative condensation of isatin **71** and thiazolidine-4-carboxylic acid **70**, undergoes cycloaddition with the exocyclic double bond of the dipolarophile **73** (scheme 1.16).



Scheme 1.16

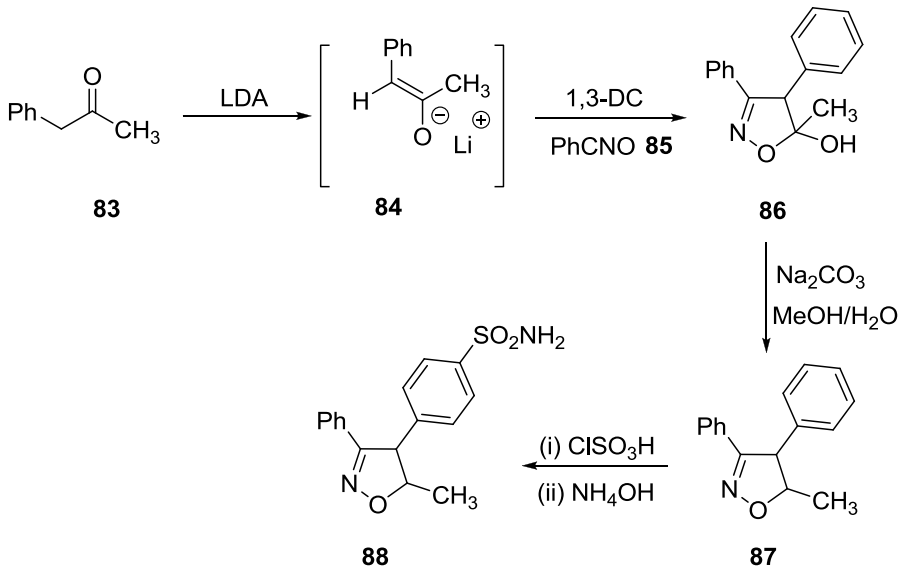
Another successful application of 1,3-DC is the synthesis of spirooxindolo-pyrrolidine, pyrrolizine and pyrrolothiazole hybrid compounds. It was accomplished by the regio- and stereoselective reaction between β-nitrostyrene **75** and non-stabilized azomethineylides, generated *in situ* from isatin **76** and phenylglycine **77,** proline **78** and

thiaproline **79** respectively (Scheme 1.17).[105] These prepared compounds were analysed and they showed good antimycobacterial activity against mycobacterium tuberculosis.



Scheme 1.17

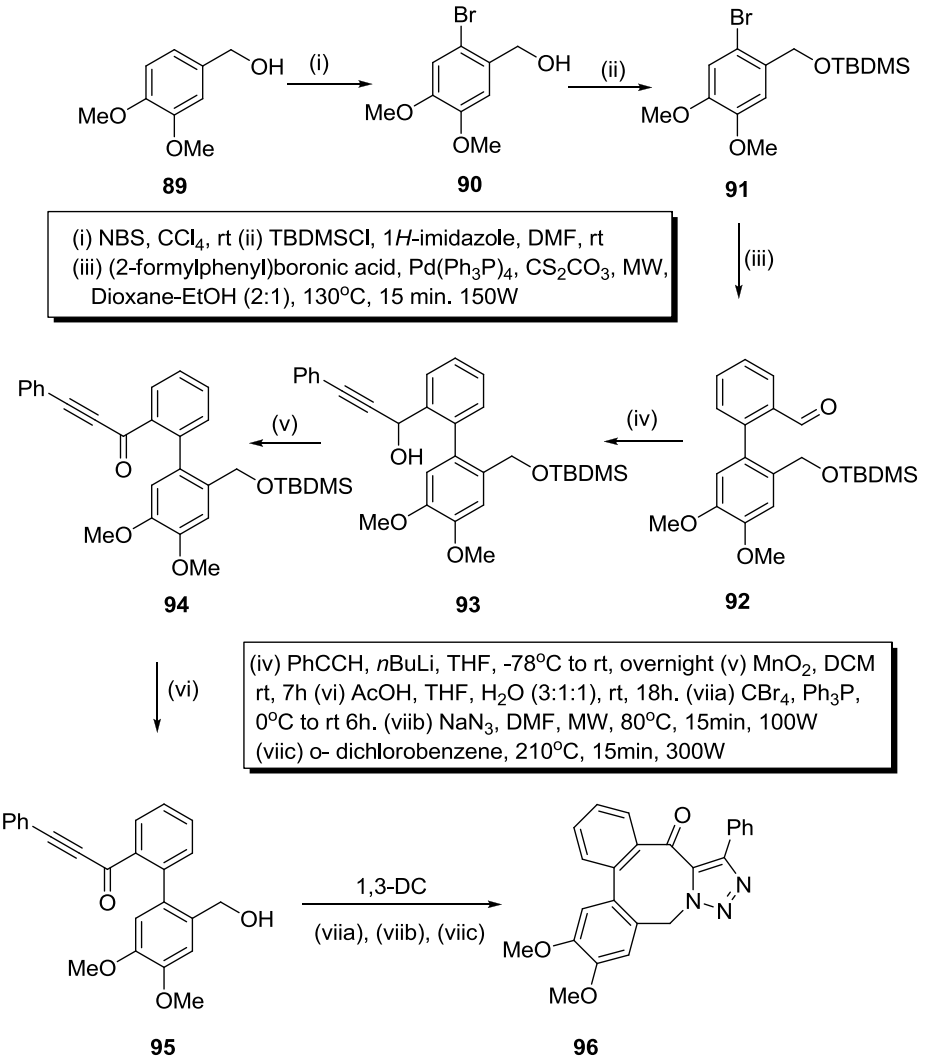
With the help of 1,3-DC, Nunno synthesised analogues of valdecoxib, a cyclooxygenase-2 (COX-2) inhibitor.[106] The procedure includes the reaction of a aryl nitrile oxide **85** with an enolate ion **84**. The enolate ion **84** was generated *in situ* from an alkyl methyl ketone **83** (Scheme 1.18).



83 84 86 88 87

Scheme 1.18

Bisbenzocyclooctadiene lignan lactones and their aza analogues show better activity against leukemia. So the synthesis of these lactones received much attention. Beryozkina *et al*. published a novel microwave assisted synthesis of 7-aza analogues of (-)-steganacin and (-)-steganone, where 1,3-dipolar cycloaddition is an essential step for the construction of the triazole ring in the mentioned derivatives (Scheme 1. 19).[107]

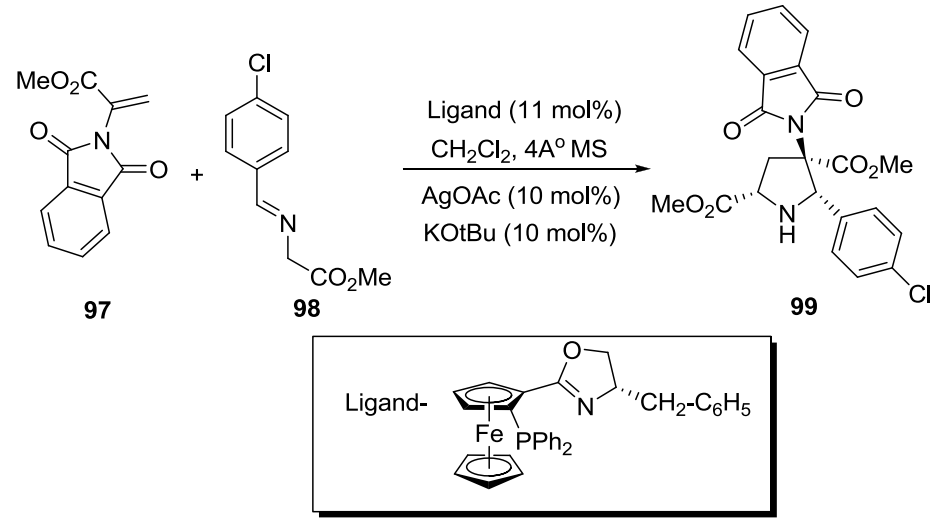


Scheme 1.19

1.6.2. Amino acids and Peptides

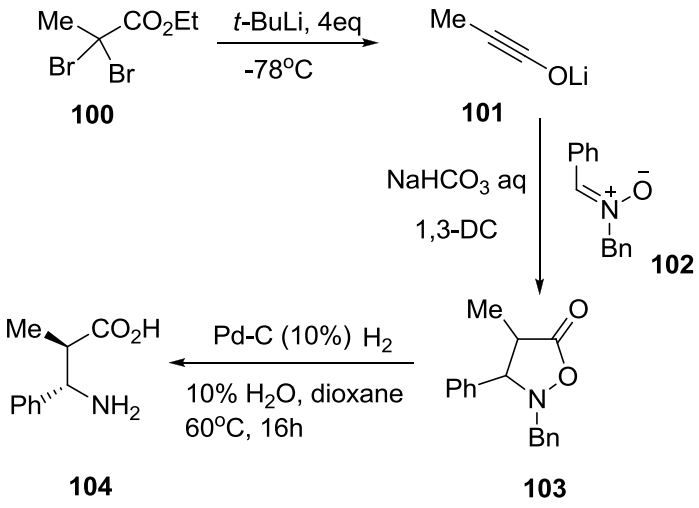
Synthetic amino acids are the key component for recent developments in peptides or proteins research. To enhance proteolytic stability and to confer peculiar properties, these compounds are incorporated into peptides. In addition selectivity, conformational

flexibility, and bioavailability can also be tuned based on well-designed aminoacids. Since they are having metal binding ability, aminoacids are used in the field of nanotechnology. Synthetic amino acids are also used as polymerisation precursors. Using 1,3-dipolar cycloaddition technique, synthesis of structurally important aminoacids were reported by various groups.[108-111] The inclusion of a quaternary α-aminoacid unit can restrict the conformational flexibility also it can improve the lipophilicity of a peptidic chain. Using 1,3-DC, Wang *et al*. synthesized an α-aminoacid analogue.[112] The reaction of azomethine ylide [*N*-(4-chlorobenzylidene)glycine methyl ester] **98** with methyl α-phthalimidoacrylate **97** in presence of the catalyst AgOAc/ferrocenyl oxazolinylphosphine (FOXAP) provided an α-aminoacid analogue **99** in excellent yield (Scheme 1.20).



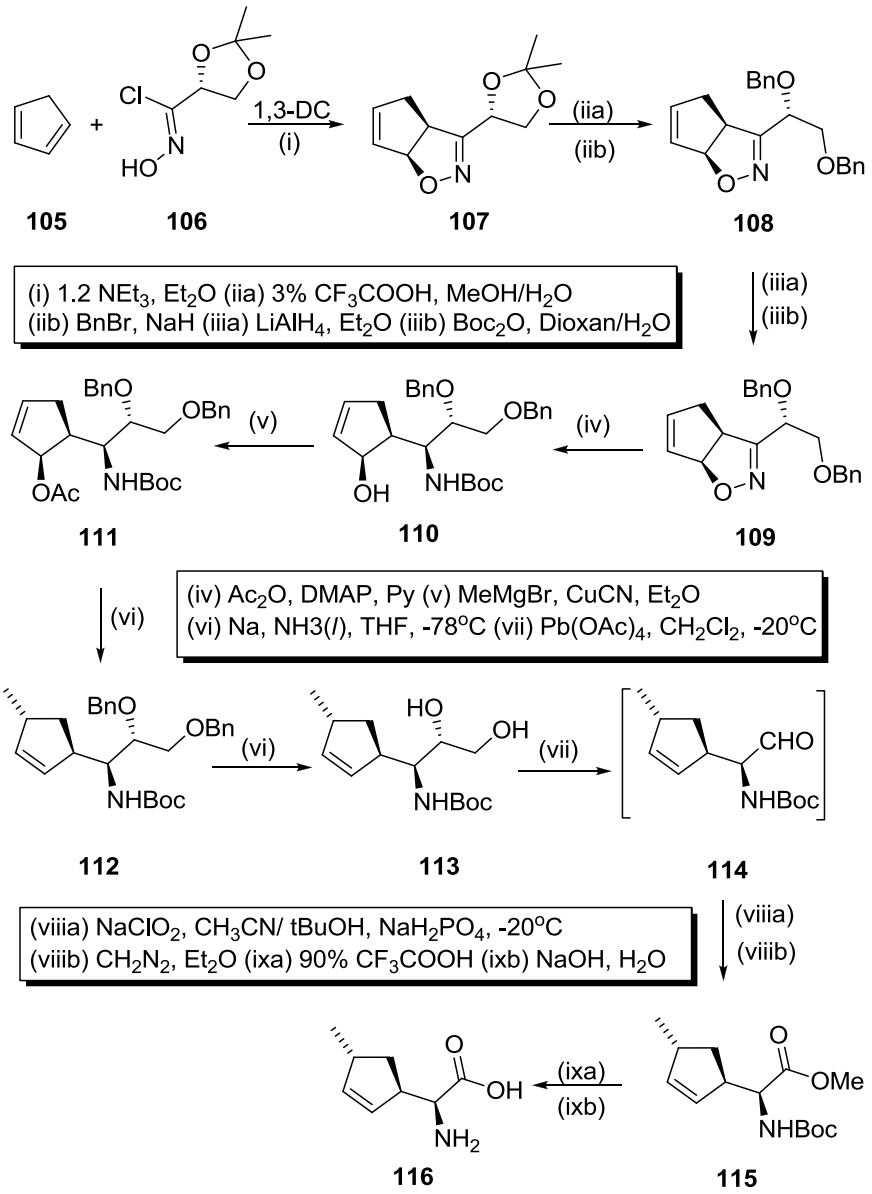
Scheme 1.20

Isoxazolidines are valuable precursors for many organic compounds having biological interest. Shindo *et al.* investigated the synthesis of β- aminoacid **104** from an isoxazolidinone derivative **103**, which was synthesized by an uncatalyzed 1,3-DC of the nitrone **102** and ynolates **101**.[113] Authors have illustrated the first example for an inverse electron demand reaction, where an unactivated nitrone is used (Scheme 1.21).



Scheme 1.21

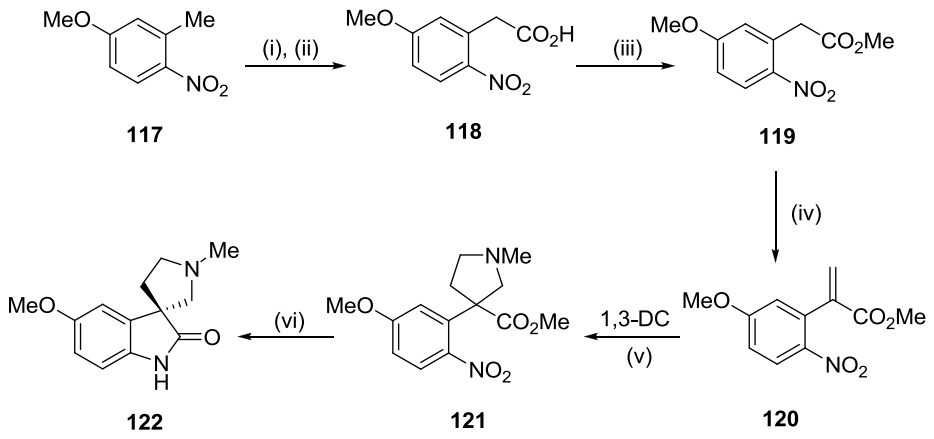
Furanomycin is a natural α-aminoacid, which inhibits bacterial growth. By the cycloaddition strategy the synthesis of carbafuranomycin, a furanomycin analogue **116** was reported.[114] The initial step in the synthetic procedure is the 1,3-DC of a chiral nitrile oxide **106** with cyclopentadiene **105** (Scheme 1.22).


105
106
107
108
(i) 1.2 NEt3, Et2O (iia) 3% CF3COOH, MeOH/H2O
(iib) BnBr, NaH (iiia) LiAlH4, Et2O (iiib) Boc2O, Dioxan/H2O
(iiia)
(iiib)
111
110
109
(iv) Ac2O, DMAP, Py (v) MeMgBr, CuCN, Et2O
(vi) Na, NH3(l), THF, -78°C (vii) Pb(OAc)4, CH2Cl2, -20°C
(vi)
112
113
114
(viiia) NaClO2, CH3CN/ tBuOH, NaH2PO4, -20°C
(viiib) CH2N2, Et2O (ixa) 90% CF3COOH (ixb) NaOH, H2O
(viiia)
(viiib)
(ixa)
(ixb)
116
115

Scheme 1.22

1.6.3. Alkaloids

Various pharmacologically relevant alkaloids can be synthesized by 1,3-dipolar cycloaddition chemistry.[115-120] Horsfiline is a tricyclic oxindole alkaloid famous for its analgesic effect. The total synthesis of this particular alkaloid by the [3+2] cycloaddition of an *in situ* generated azomethine ylide (from sarcosine) with the acrylate dipolarophile **120** is described in scheme 1.23.[121] The dipolarophile was synthesised from 2-nitro-5-methoxytoluene **117** and diethyl oxalate.

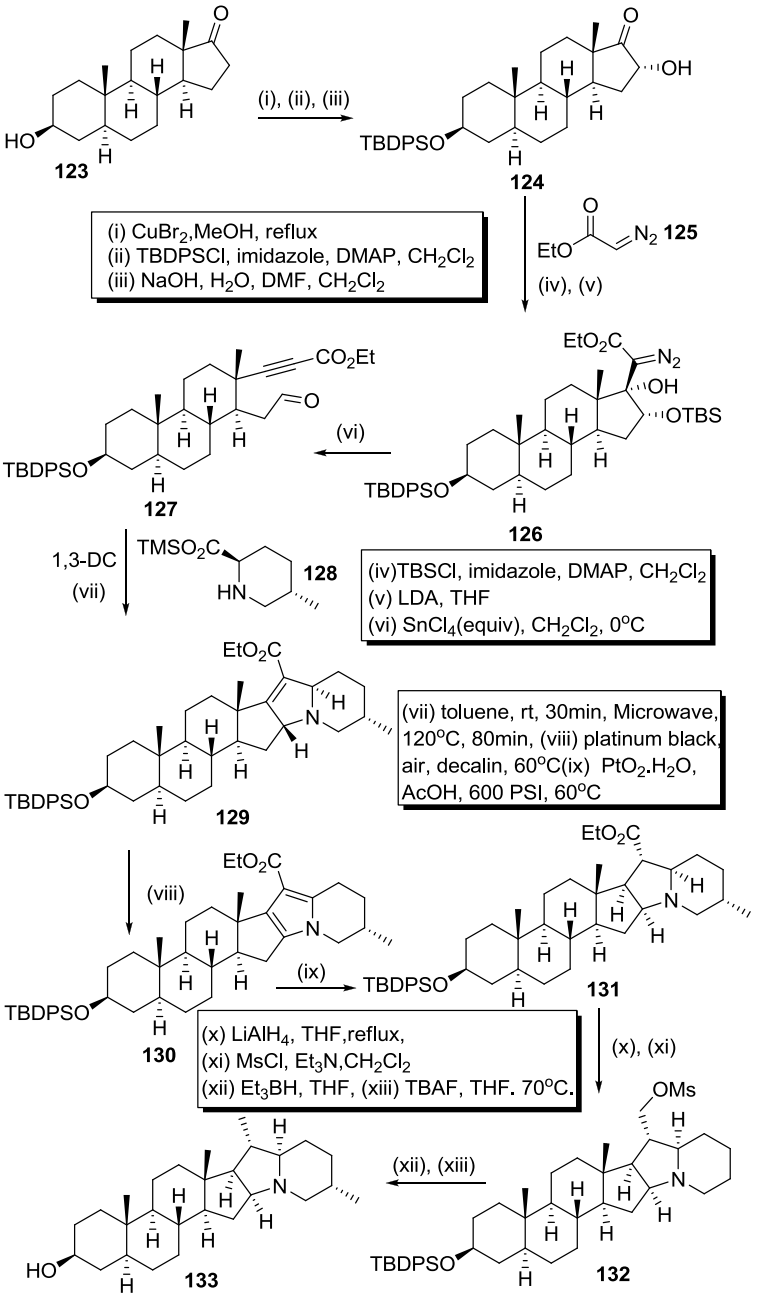


117 118 119 120 121 122

(i) $(CO_2Et)_2$, NaOEt, Et_2O, rt (ii)H_2O_2, NaOH, H_2O, rt, then pH 1
(iii) MeOH, Amberlyst 15, reflux (iv) $(CH_2O)_n$, K_2CO_3, TDA-1, toluene, 85 °C
(v) sarcosine, $(CH_2O)_n$, 3 Å molecular seives, toluene, reflux
(vi) H_2, 10% Pd/C, MeOH

Scheme 1.23

Another example is the synthesis of steroidal alkaloid demissidine (Scheme 1.24).[122] These alkaloids can inhibit acetylcholinesterase, can act as natural insect deterrents and also as antimicrobial agents. Ring fragmentation and 1,3-dipolar cycloaddition reaction are the two key steps in the synthesis of dimissidine.

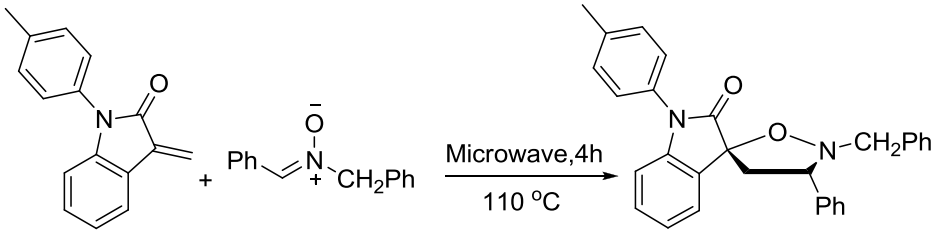

(i), (ii), (iii)
(i) CuBr2,MeOH, reflux
(ii) TBDPSCl, imidazole, DMAP, CH2Cl2
(iii) NaOH, H2O, DMF, CH2Cl2
(iv), (v)
(iv)TBSCl, imidazole, DMAP, CH2Cl2
(v) LDA, THF
(vi) SnCl4(equiv), CH2Cl2, 0°C
1,3-DC
(vii)
(vi)
(vii) toluene, rt, 30min, Microwave, 120°C, 80min, (viii) platinum black, air, decalin, 60°C(ix) PtO2.H2O, AcOH, 600 PSI, 60°C
(viii)
(ix)
(x) LiAlH4, THF,reflux,
(xi) MsCl, Et3N,CH2Cl2
(xii) Et3BH, THF, (xiii) TBAF, THF. 70°C.
(x), (xi)
(xii), (xiii)
123
124
125
126
127
128
129
130
131
132
133

Scheme 1.24

In the synthetic procedure, initially a γ-silyloxy-β-hydroxy-α-diazoester **126** was prepared by starting from epiandrosterone **123**. By the fragmentation of **126**, steroid-based tethered aldehyde ynolate **127** was formed. From compound **128**, and ynoate **127** the pyrrole derivative **129** was obtained through the intramolecular cycloaddition reaction of an *in situ* generated azomethine ylide. The pyrrole derivative **129** thus obtained on successive chemical transformation yielded the alkaloid demissidine **133**.

1.6.4. Lactams

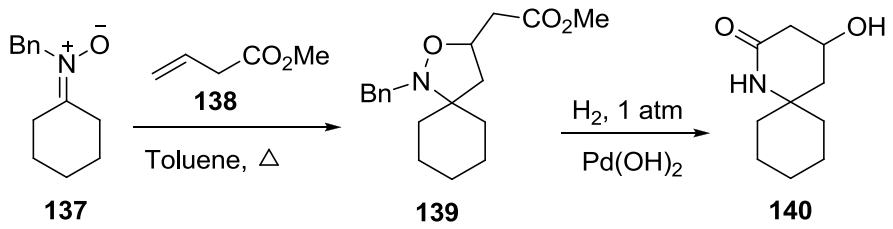
These type of heterocyclic compounds possess anti-inflamatory, anti-tumor, anti-hyperglycemic, anti-HIV, analgesic activities etc. 1,3-Dipolar cycloaddition chemistry has emerged as an ideal tool for the synthesis of such compounds having medicinal value. Various groups have reported the synthesis of β-lactam derivatives through cycloaddition strategy.[123-126] Microwave assisted 1,3-dipolar cycloaddition reaction of exocyclic double bond of methylene isoindolone **134** with *N*-benzyl-*C*-phenylnitrone **135** was used for the synthesis of a spiroisoxazolidinyl lactam **136** (Scheme 1.25).[127]



134 **135** **136**

Scheme 1.25

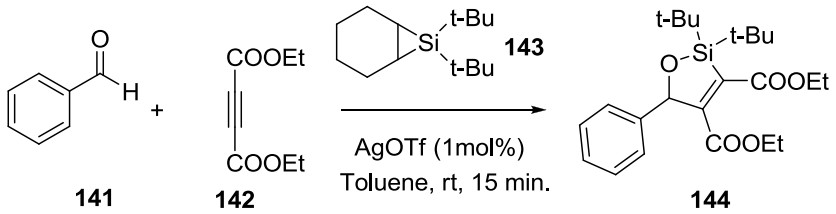
Funk and Daggett reported the cycloaddition reaction of an exocyclic nitrone, **137** derived from cyclohexanone, with unsaturated ester **138** for the synthesis of lactams (Scheme 1.26).[128] Here the lactamization process follows the cleavage of the N-O bond in the isoxazolidine derivative **139**.



Scheme 1.26

1.6.5. Synthetic Intermediates

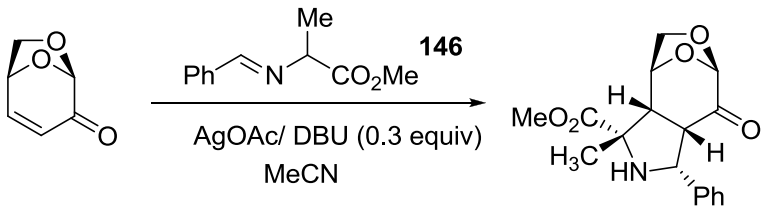
1,3-Dipolar cycloaddition is widely used in organic synthesis. Oxasilacyclopentenes are very useful intermediates in organic syntheses. These can be transformed to useful products by a variety of chemical reactions like protodesilylation, substitution, addition etc. Here an oxasilacyclopentene **144** was formed by the intermolecular cycloaddition reaction of *in situ* generated silylcarbonyl ylide with electron deficient alkyne **142** (Scheme 1.27).[129]



Scheme 1.27

1.6.6. Organocatalysts

Another important application of 1,3-dipolar cycloaddition is in the synthesis of organocatalysts. The *in situ* generated azomethineylide on cycloaddition reaction with levoglucosenone **145** yielded the chiral pyrrolidine derivative **147** (Scheme 1.28).[130] The use of this cellulose derived pyrrolidine as efficient organocatalyst was well established from the success of the asymmetric Diels-Alder reaction catalysed by it.

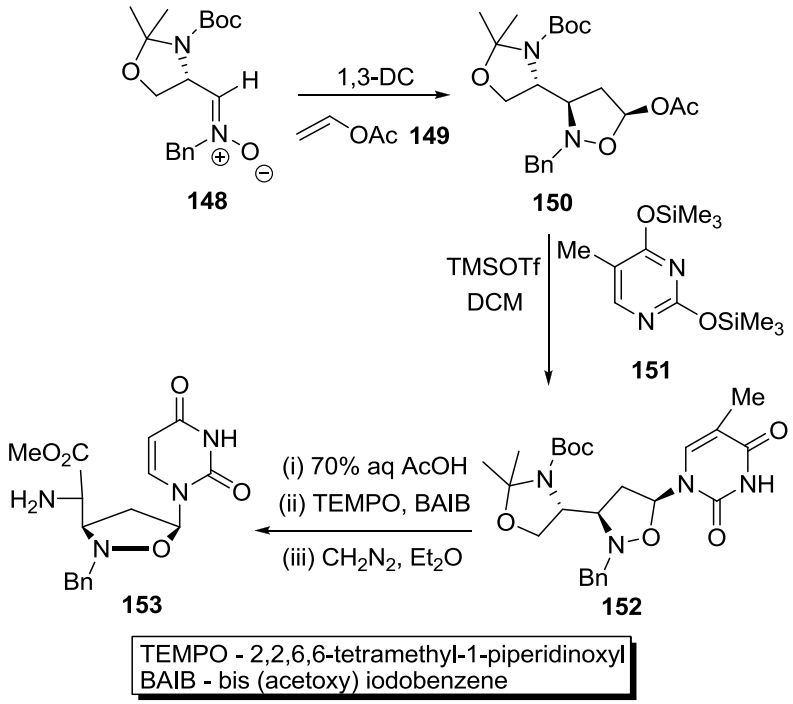


145 **147**

Scheme 1.28

1.6.7. Nucleosides

Nucleosides are potent antitumor, antiviral and anti HIV agents, Nowadays 1,3-dipolar cycloaddition chemistry is extensively used for the synthesis of several nucleosides.[131-134] Merino *et al.* prepared the nucleoside, polyoxin analogues through the cycloaddition of nitrones.[135] Polyoxin is a potent inhibitor of the biosynthesis of chitin, a major structural component of the cell wall of fungi. For substituting the isoxazolidine unit in the pyrimidine nucleoside analogue **153**, the nitrone **148** was treated with vinyl acetate **149** (Scheme 1.29).

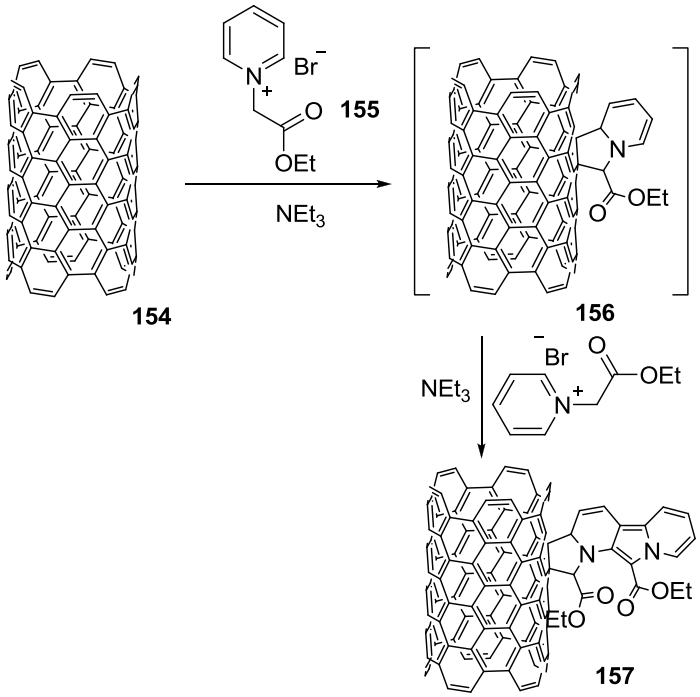


Scheme 1.29

1.6.8. Functionalization of Carbon Nanotubes and Fullerenes

Functionalization is a key process for the integration of carbon nanotubes (CNT) into different systems for technological and biomedical applications. Covalent functionalization of their side walls and tips is one of the most powerful approaches for rendering CNTs soluble in a wide range of solvents. Functionalized CNTs loaded with nucleic acids, proteins, and peptides are able to deliver their 'load' into cells. Covalently functionalised carbon nanotubes have emerged as a tool for the delivery of therapeutic molecules. The molecular targeting of carbon nanotube delivery systems derivatised with a therapeutic agent, without damaging healthy tissues, is an important technique in cancer treatment.

When fluorescent molecules are attached to the nanotube, they provide optical signals for imaging and localisation of the CNT– drug conjugates. 1,3-Dipolar cycloaddition is one among the most versatile routes to the covalent chemical modification of carbon nanotubes.[136-139] An easy protocol for the modification of SWNTs using 1,3-dipolar cycloaddition of pyridinium ylides, readily prepared from pyridinium bromide salts, was reported by Bayazit and co-workers (Scheme 1.30).[140] Here the nanotube **154** is acting as the dipolarophile. The pyridinium ylide **155** first add to the nanotube surface to form a pyrrolidine ring **156,** which further adds a second ylide to afford an indolizine unit **157**.



Scheme 1.30

Fullerenes are used in different fields. In medicinal chemistry, C_{60} has been established as a valuable building block in the synthesis of

novel compounds, not only C_{60} itself exhibit activity against some microorganisms. Because of its high electron affinity and delocalization of electrons in the three dimensional π system, C_{60} is a very good electron acceptor. Though it has a lot of applications, their use is limited in some area due to the solubilty problems. C_{60} is completely insoluble in solvents such as, methanol, water, acetonitrile, tetrahydrofuran and dimethyl sulfoxide. This solubility problem can be diminished by the modification with suitable functional groups. 1,3-Dipolar cycloaddition technique is frequently employed for the introduction of suitable groups on to the fullerene moiety to improve its properties.[141-143]

1.6.9. Miscellaneous

Dendrimers are monodispersed macromolecules having branches or dendrons that grow from a central core. Normally these molecules are 'tree shaped'. Their overall size, morphology and shape are determined by the nature of both branching and surface groups, as well as the number of layers surrounding the core. All the characteristic features make dendrimers suitable platforms for applications in catalysis, cellular imaging, light harvesting, and drug delivery. 1,3-Dipolar cycloaddition technique has been successfully used in the modification of dendrimers.[144-145] Liquid crystalline compounds have extensive applications. They are used as OLEDS, photoconductors, anisotropic networks, flat-panel displays etc. Incorporation of heteroatoms like oxygen, sulphur, nitrogen etc. imparts improved physical properties to liquid crystalline compounds and this can be achieved by the syntheses of these compounds with heterocyclic units, which in turn can be attained

by 1,3-dipolar cycloaddition.[146-147] This technique is widely used in the modification as well as synthesis of polymers[148-150] and self-assembled monolayers[151-152] also.

From the above discussion, it is clear that 1,3-dipolar cycloaddition has emerged as an essential strategy for the synthesis of a large variety of heterocyclic compounds with significant applications.

1.7. Definition of the Problem

What is the mechanism of 1,3-DC? Whether it follows a concerted pathway or a stepwise reaction through the formation of a zwitterionic intermediate is a fundamental question in dipolar cycloaddition chemistry. Majority are in favour of concerted mechanism that are not synchronous, a few describe the possibility of a two-step mechanism. Our group has reported the reaction of dipoles, nitrone and azomethine imine with the dipolarophile, dibenzoylacetylene. There we have obtained results in favour of a stepwise mechanism. Hence, our primary goal was to revisit the mechanism of 1,3-dipolar additions with a view to establishing whether it follows a concerted pathway or a stepwise reaction sequence through the formation of a zwitterionic intermediate.

Another objective is to explore the synthetic utility of 1,3-DC's. The synthetic potential of this type of reaction is clear from the literature analysis. Furthermore, from earlier studies, we have obtained some pharmacologically important heterocyclic compounds such as a highly substituted quinoline as well as a 3(*2H*)-furanone derivative. So another objective of our study is to synthesize more heterocyclic compounds with pre-defined substitution pattern.

Nitrone is an allyl anion type 1,3-dipole. According to the earlier study the reaction between *N*-arylnitrone and the dipolarophile, dibenzoylacetylene, is a zwitterion mediated pathway. In the proposed mechanism for reaction, this zwitterion undergoes [3,3] sigmatropic rearrangement with the ortho position of the *N*-aryl ring. In the present investigation we have repeated the cycloaddition reaction with some other dipolarophiles and employed nitrones with substituents on the *N*-aryl ring. Also we have conducted the reaction of *N*-alkylnitrones so as to block the possibility for [3,3] sigmatropic rearrangement.

When dibenzoylacetylene is used as the dipolarophile, the 1:1 adduct obtained on further chemical transformation gives a highly substituted quinoline. Since derivatives of this heterocyle have wide variety of applications, it is important to synthesis more quinoline derivatives. Another exciting prospect is to check the possibility of generating some other heterocyclic compound by the nitrone cycloaddition reaction. It is clear from the mechanism of the reaction that if we use some monoactivated acetylenes instead of diactivated ones, there is a possibility for the formation of indole derivatives. With a view to exploiting this possibility, we have conducted the reaction between nitrones and a few monoactivated acetylenes such as benzoylphenylacetylene, acetylphenylacetylene and cinnamonylphenyl-acetylene.

1.8. Objectives

1. Synthesis of 1,3-dipoles: nitrones
2. Synthesis of appropriate dipolarophiles: dibenzoylacetylene, benzoylphenylacetylene, cinnamoylphenylacetylene and acetylphenylacetylene.
3. Study the reaction of nitrones with the dipolarophiles.
4. Synthesis of some quinoline derivatives.
5. Synthesis of some highly substituted indoles.

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CHAPTER 2

SYNTHESIS AND CHARACTERISATION OF A FEW NITRONES

2.1. Abstract

Nitrones constitute a unique class of 1,3-dipoles. It can act as a suitable substrate for the synthesis of nitrogen and oxygen heterocycles. In this chapter we briefly describe the synthesis and characterisation of a few nitrones.

2.2. Introduction

Nitrone (azomethine *N*-oxide) is an allyl anion type 1,3-dipole (Figure 1). The name nitrone was coined by Pfeiffer[1] in 1916 from 'nitrogen-ketone' as it shows similarity with carbonyl group in facilitating the removal of a proton from a nearby carbon under basic condition. This 1,3-dipole was first prepared by Beckmann in 1890.[2]

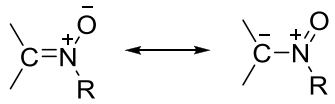


Figure 2.1

The observed dipole moment shows a dominance of azomethine *N*-oxide structure for most of the nitrones, which means the major

fraction of the negative charge is concentrated on terminal oxygen than the α-carbon atom.[3] So this group of compounds show nucleophilic character in majority of its reactions. Based on the presence of a proton on *α*-carbon, nitrones are classified into aldonitrones and ketonitrones (Figure 2.2). Aldonitrones are those having a proton on the *α-C*, but in the case of ketonitrone, the *α*-carbon is substituted with alkyl, aryl or with both alkyl and aryl groups.

Figure 2.2

Due to the presence of a double bond in the structure, nitrones exhibit geometrical isomerism. It was first established in 1918 for *α*-phenyl-*α*-(*p*-tolyl)-*N*-methylnitrone.[4] The configuration of isomers were assigned on the basis of dipole moment measurement.[5] The dipole moment value of *Z*-isomer will be higher than that of the *E*-isomer. By the use of thermal as well as photochemical methods the geometrical isomers can be interconverted. The geometrical isomers of *α*-phenyl-*N*-*t*-butylnitrone are given below (Figure 2.3).[6]

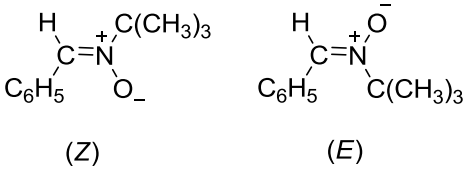
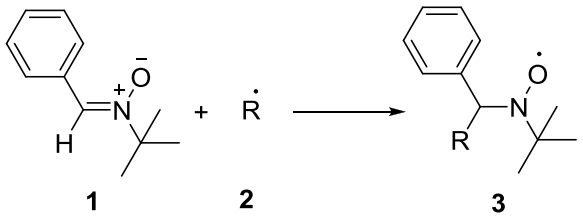


Figure 2.3

2.2.1. Applications of Nitrones

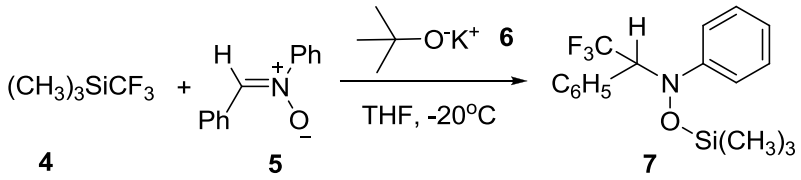
Nitrones are frequently used as spin trapping agents in biological systems.[7-17] Spin trapping is a reliable method to detect free radicals whose life time is too short to identify in the EPR spectrum. This technique is based on the fast reaction between a short lived free radical and a suitable diamagnetic molecule (a spin trap). Here the product will be a relatively long lived paramagnetic species whose EPR signals can be recorded and analysed. Addition of nitrone spin trap to a reactive free radical results the formation of nitroxide, a fairly stable detectable radical (Scheme 2.1). This technique is used to study the effect of reactive oxygen species (ROS) and oxygen centered free radicals (OFR) such as superoxides, alkoxy, peroxy, hydroperoxy and hydroxyl radicals in diseases like arteriosclerosis, neurodegenerative diseases, cellular aging etc. 5,5-Dimethyl-1-pyrroline-*N*-oxide (DMPO), 5-diethoxyphosphoranyl-5-methyl-1-pyrroline-*N*-oxide (DEPMPO) and 5-*tert*-butoxycarbonyl-5-methyl-1-pyrroline *N*-oxide (BMPO) are the commonly used spin trapping agents. Recent studies reveal that nitrones exhibit antioxidant properties also.



1 2 3

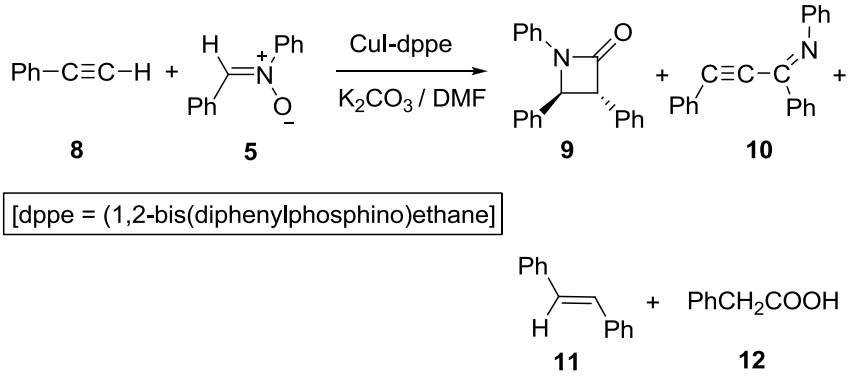
Scheme 2.1

Nitrones are successful candidates in many organic syntheses since they exhibit both electrophilic and nucleophilic character.[18-24] For example, addition of (trifluoromethyl)trimethylsilane (**4**) to *α,N*-diphenylnitrone (**5**) resulted in the formation of an *α*-(trifluoromethyl)-*N*-hydroxyl amine derivative **7**. In this case, the trifluoromethylgroup was added to the electrophilic carbon of the diphenylnitrone **5** (Scheme 2.2).[25]



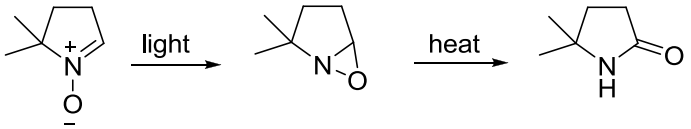
Scheme 2.2

Nucleophilic character of nitrones was illustrated by the reaction of **5** with phenylacetylene (**8**) in presence of CuI-dppe catalyst (Scheme 2.3).[26] Here the coupling products **9** and **12** were obtained in major yield compared to the redox products **11** and **12**.



Scheme 2.3

Nitrones undergo interesting rearrangements under the influence of heat, light and a variety of reagents.[27]



13 14 15

Scheme 2.4

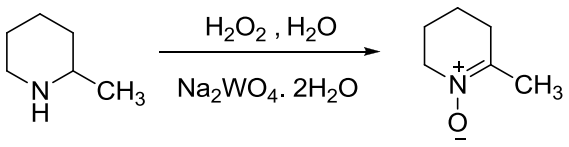
One of the most important class of reactions by nitrones are the 1,3-dipolar cycloaddition reactions, where nitrones react with electron deficient unsaturated compounds to form a wide variety of heterocycles.[28-37] Most of these compounds are as such or precursors of biologically active compounds. Some remarkable reactions of nitrones with Burgess reagent was also reported.[38-39]

2.2.2. Methods for the Synthesis of Nitrones

Numerous methods are available for the synthesis of nitrones since this particular class of compounds have a wide variety of applications.

2.2.2.1. Oxidation of Secondary Amines

Nitrones can be prepared by the oxidation of secondary amines using peroxides as oxidant (Scheme 2.5).[40] Hydrogen peroxide or urea-hydrogen peroxide complex (UHP) is used as the oxidant and selenium dioxide[41] or sodium tungstate[42] is used as the catalyst in many cases.



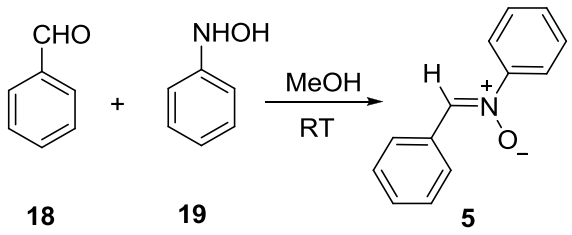
16 **17**

Scheme 2.5

Goti and Murray in independent experiments described the synthesis of nitrones from secondary amines where methyltrioxorhenium was used as the catalyst with UHP.[43-44] An electrochemical oxidation method was also introduced for the synthesis of nitrones from *N*-hydroxy secondary amines where sodium iodide is used as the supporting electrolyte.[45] Carollina *et al.* reported a viable metal-free procedure for the preparation of nitrones from secondary amines using oxone in a biphasic basic medium as the single oxidant.[46]

2.2.2.2. Condensation of Carbonyl Compounds with Hydroxylamines

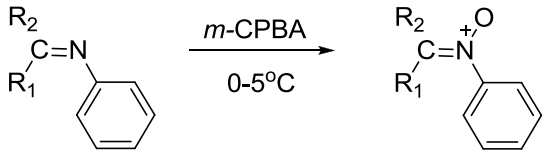
Condensation reaction of aldehyde with *N*-substituted hydroxylamines is a common procedure for the synthesis of diarylnitrones (Scheme 2.6).[47] Here the hydroxylamine derivative **19** is either prepared or formed *in situ* by the reduction of corresponding nitro compounds with zinc powder in presence of weak acids like ammonium chloride or accetic acid. Increased yield of nitrone and significant reduction in reaction time is achieved if microwave irradiation is used in the condensation process.



Scheme 2.6

2.2.2.3. Oxidation of Imines

Imines on oxidation with peracids (Scheme 2.7)[48] or dimethyldioxirane[49] give better yield of nitrone under specific conditions where the possibility for oxaziridine formation is minimized. Potassium permanganate can also be used as oxidising agent under phase transfer condition for the synthesis of nitrones from corresponding imine derivatives.[50]

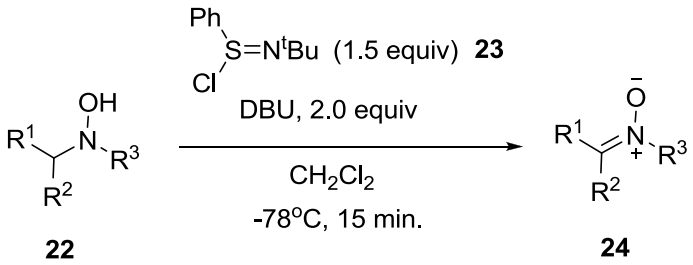


Scheme 2.7

2.2.2.4. Oxidation of *N,N*-Disubstituted Hydroxylamines

Another convenient method for the synthesis of cyclic as well as acyclic nitrones is the oxidation of corresponding *N,N*-disubstituted hydroxylamines with suitable oxidising agents such as yellow mercuric oxide,[51] potassium ferricyanide,[52] *t*-butyl hydroperoxide,[53] molecular oxygen,[54] active lead oxide,[55] potassium permanganate[56] etc. Jun-ichi Matsuo and co-workers reported the use of *N-t-*

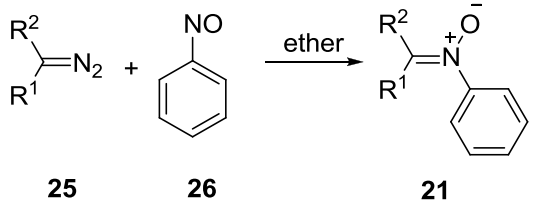
butylbenzenesulfinimidoyl chloride as a suitable oxidant for the synthesis of nitrones from various *N*,*N*-disubstituted hydroxylamines (Scheme 2.8).[57]



Scheme 2.8

2.2.2.5. Condensation of Diazo Compounds with Nitroso Arenes

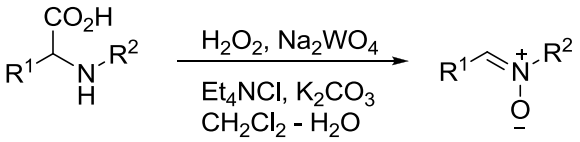
One of the successful methods for the synthesis of ketonitrones is the condensation reaction of corresponding diazo compounds with nitroso arenes (Scheme 2.9).[58] Here the reaction takes place vigorously with the evolution of nitrogen and at the end of the reaction the nitrone derivative is precipitated in appreciable yield.



Scheme 2.9

2.2.2.6. Decarboxylative Oxidation of *N*-Alkyl-α-aminoacids

Murahashi and co-workers reported a novel procedure, where nitrone was synthesized from *N*-alkyl-α-aminoacids (Scheme 2.10).[59] Tungstate-catalyzed oxidation of the aminoacid derivative was attained by the use of H_2O_2 under phase transfer conditions.



27 **28**

Scheme 2.10

In the present investigation, we employed several methods for the preparation of target nitrones. Selection of any particular method was based on availability of appropriate starting materials and reagents.

2.3. Results and Discussion

To study the 1,3-dipolar cycloaddition reaction between nitrone and electron deficient acetylenes, we synthesized a few ketonitrones and one aldonitrone (Figure 2.4) by adapting reported procedures.

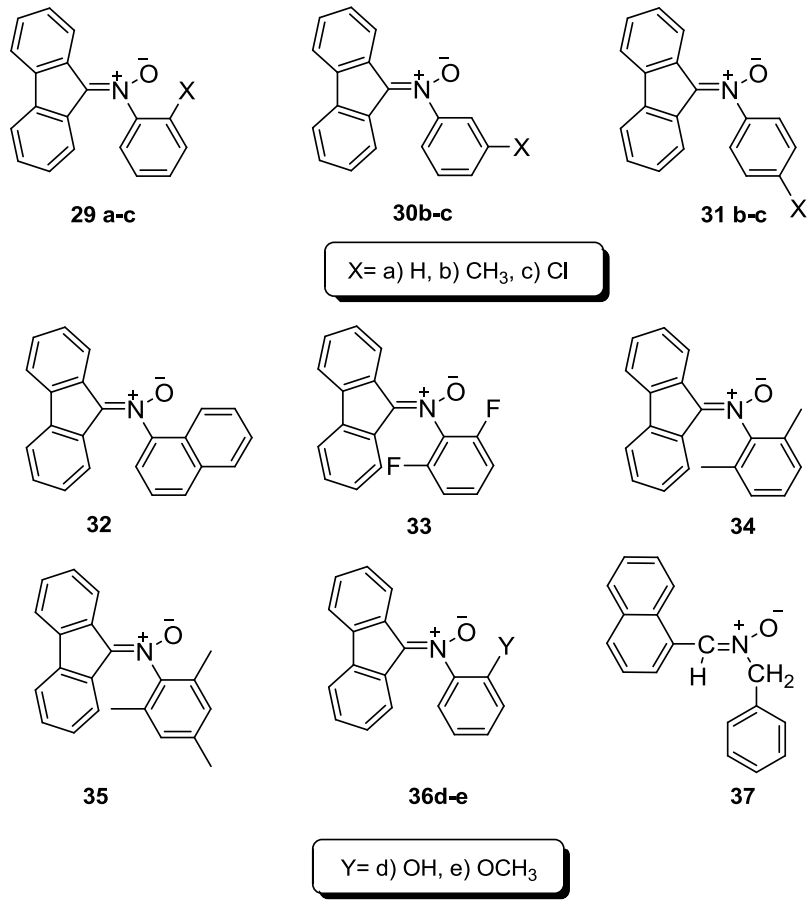
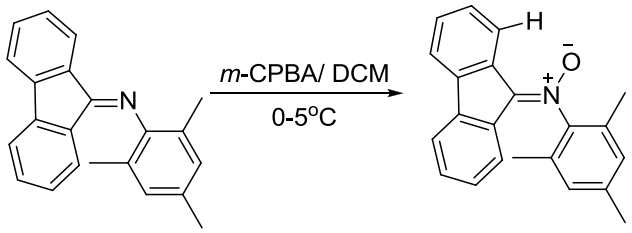


Figure 2.4

2.3.1. Synthesis of *N*-Fluorenylidene-*N*-arylnitrones [29a-b, 30b, 31b, 32, 34, 35, 36d-e.]

For the synthesis of nitrones, we oxidised the corresponding imines with *m*-CPBA. In the procedure, the required amount of *m*-CPBA in DCM was added in small portions to the solution of imines at 0-5°C. The reaction mixture was stirred for 5h. For example, in the synthesis of *N*-fluorenylidene-*N*-(2,4,6-dimethylphenyl)nitrone (**35**), fluorenylidene-*N*-(2,4,6-dimethylphenyl)imine (**38**) in DCM at 0°C was treated with *m*-

CPBA in dichloromethane (Scheme 2.11). The reaction mixture was stirred for 5h maintaining the low temperature. After the completion of the reaction, the pure nitrone derivative **35** was separated by recrystallizing the crude product from a 1:1 mixture of dichloromethane-hexane solvents.



Scheme 2.11

The synthesized nitrone **35** was identified on the basis of elemental analysis, and its structure was further confirmed from spectral data analysis. The peaks at 1540 and 1256 cm^{-1} in the IR spectrum indicated the C=N and the N→O stretching frequencies respectively, which are characteristic peaks for the nitrone group of compounds. In the ^1H NMR spectrum, H-*1* proton of the fluorene ring appeared as a multiplet at δ 9.01-8.99. The high downfield shift of the H-*1* proton is due of the presence of the negatively charged oxygen in its vicinity. The peaks at δ 6.95-6.91 (m, 1H) and at δ 5.82 (d, *J* = 8Hz, 1H) showed the H-*7* and the H-*8* protons respectively. The upfield shift of these protons compared to other aromatic protons may be due to its closeness to the shielding cone of *N*-aryl group. The methyl protons appeared at δ 2.40 (s, 3H) and at δ 2.18 (s, 6H), in the ^1H NMR spectrum (Figure 2.5).

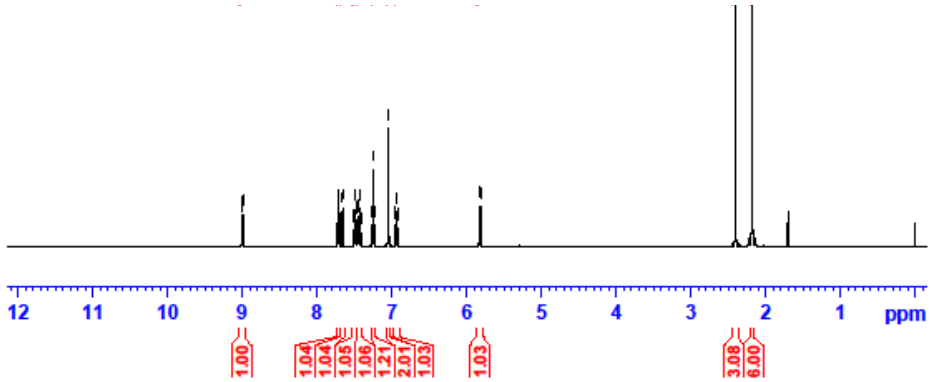


Figure 2.5 ^{1}H NMR spectrum of **35**

The ^{13}C NMR spectrum of **35** showed several signals at δ 145.76, 143.66, 139.50, 139.09, 131.90, 131.22, 131.02, 130.42, 129.87, 129.11, 128.84, 127.92, 127.18, 122.62, 120.17, 119.57, 21.26, 16.50 (Figure 2.6). Of these, the signal at δ 145.76 has been assigned to *C-9* of fluorene ring whereas the signals from δ 143.66 to 119.57 were assigned to aromatic carbons. The peak at δ 21.26 of the ^{13}C NMR spectrum showed the methyl carbon at the para position of the *N*-phenyl ring and the peak at δ 16.50 indicated the methyl carbons at the ortho positions.

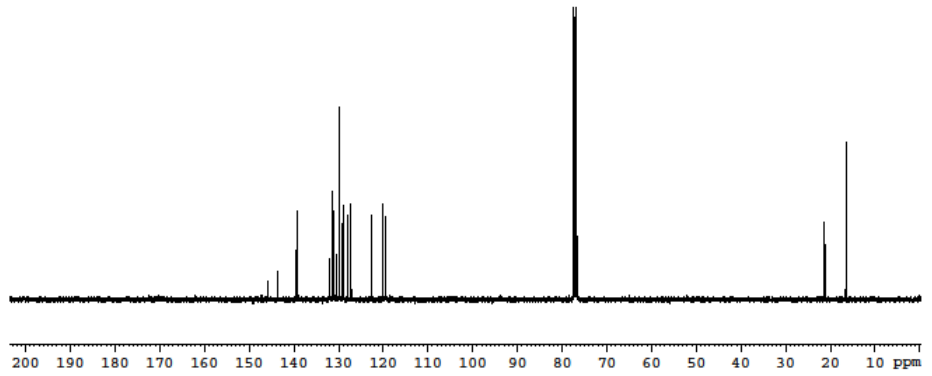
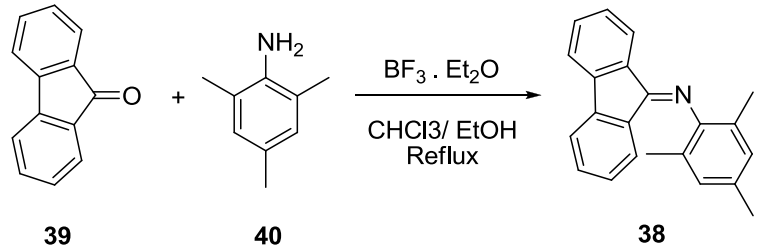


Figure 2.6 ^{13}C NMR spectrum of **35**

Imines were synthesized by the condensation of fluorenone with aryl amines in the presence of an acid catalysts such as BF_3 etherate, *p*-toluene sulphonic acid etc. For example, *N*-fluorenylidene-*N*-(2,4,6-dimethylphenyl)amine (**38**) was prepared by refluxing a mixture of fluorenone **39** and 2,4,6-trimethylaniline (**40**) in chloroform for about 15 min (Scheme 2.12). The reaction mixture was cooled and concentrated. The pure imine derivative was obtained by recrystallizing the crude product from chloroform-ethanol (1:3 ratio) solvent system.



39 **40** **38**

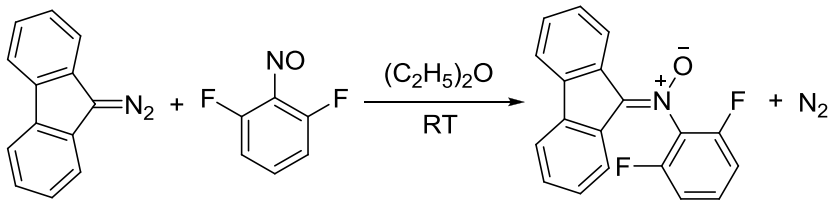
Scheme 2.12

All the imine derivatives prepared were identified by analysing the mass data and these are used as such for the oxidation step.

2.3.2. Synthesis of *N*-Fluorenylidene-*N*-arylnitrones [29 c, 30c, 31c, 33]

Condensation reaction of the corresponding nitrosoarenes with diazofluorene resulted in the formation of nitrones. In the synthesis of **33** diazofluorene (**41**) and 1,3-difluoro-2-nitrosobenzene (**42**) was reacted in diethylether (Scheme 2.13). The reaction was vigorous with nitrogen evolution and after a few minutes, the product precipitated out from the

reaction mixture. Nitrone **33** was purified by recrystallization from ethyl alcohol.



41 **42** **33**

Scheme 2.13

Structure of the nitrone **33** was arrived at on the basis of analytical and spectral data. In the IR spectrum of **33** , the peak at 1249 cm^{-1} showed the N→O stretching frequency, and peak at 1557 cm^{-1} showed presence of the C=N bond. In the ^1H NMR spectrum (Figure 2.7), the H-*1* proton of the fluorenyl ring appeared as multiplet at δ 8.96-8.94 and the H-*7* and the H-*8* protons appeared as multiplet at δ 7.00-6.95 and as doublet at δ 6.03 respectively. All other aromatic protons extended as multiplet from, δ 7.70-7.18 (m, 8H) in the ^1H NMR spectrum.

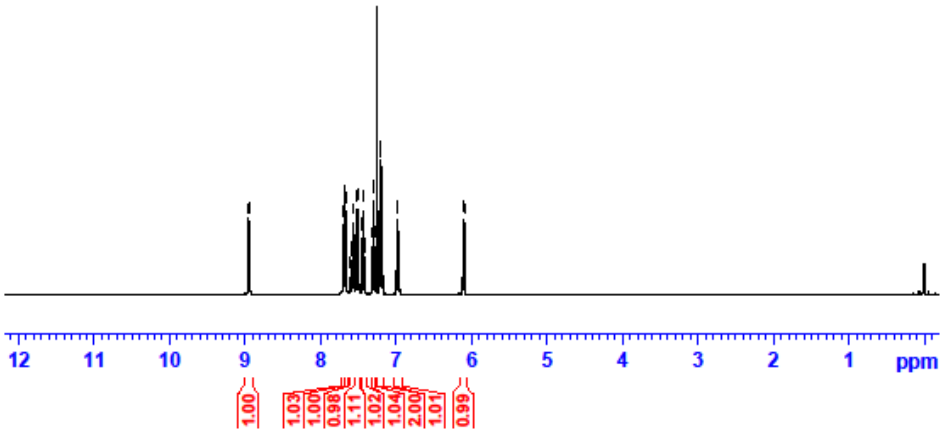


Figure 2.7 ^{1}H NMR spectrum of **33**

The ^{13}C NMR spectrum showed several signals at δ 157.09, 154.56, 139. 73, 139.36, 131.92, 131.83, 131.57, 131.47, 129.95, 129.11, 127.88, 127.62, 122.04, 120.66, 119.78, 113.31, 113.09 and all the signals were assigned to aromatic carbons (Figure 2.8).

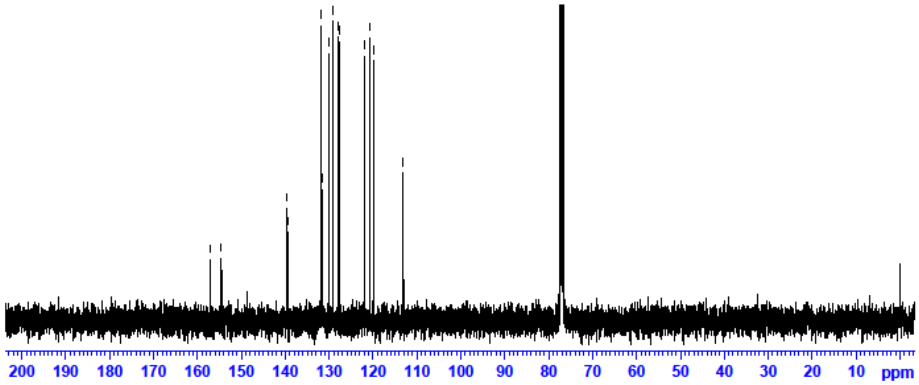
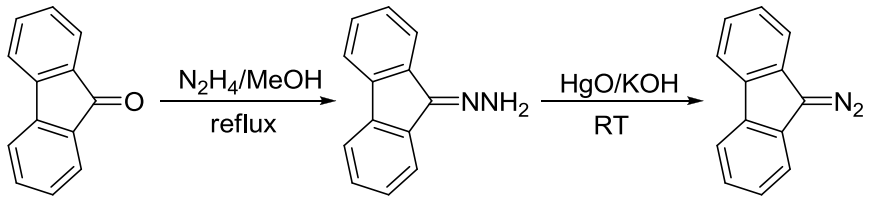


Figure 2.8 ^{13}C NMR spectrum of **33**

Diazofluorene (**41**) was synthesized by the oxidation of fluorenone hydrazone (**43**) with yellow HgO. Here, **43** was prepared by

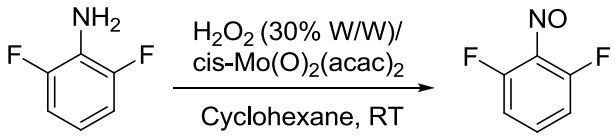
the condensation of fluorenone (**39**) with excess of hydrazine hydrate in refluxing methanol (Scheme 2.14).



39 **43** **41**

Scheme 2.14

For the synthesis of the corresponding nitroso derivatives, we adopted the procedure reported by Porta *et al*. Here 2,6-difluoroaniline (**44)** in cyclohexane was reacted with 30% H_2O_2 in presence of catalytic amount of *cis*-$Mo(O)_2(acac)_2$ at room temperature under aerobic conditions (Scheme 2.15). After 2h, the reaction mixture was filtered and concentrated to obtain the solid mass of nitroso derivative **42**.



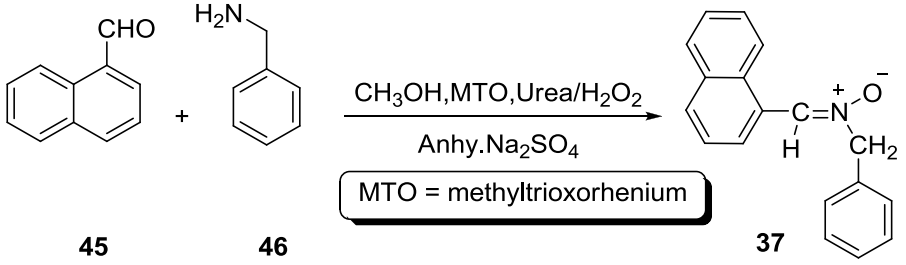
44 **42**

Scheme 2.15

Nitroso derivatives prepared were identified by analysing the mass data and these were used without any further purification for the oxidation step.

2.3.3. Synthesis of *N*-Naphthylidene-*N*-benzylnitrone [37]

Nitrone **37** was prepared by one pot reaction of 1-naphthaldehyde (**45**) with benzylamine (**46**) in presence of urea hydrogen peroxide complex and methyltrioxorhenium catalyst (Scheme 2.16).[5] The product formed was isolated by column chromatography on neutral alumina.



Scheme 2.16

Nitrone **37** obtained was analysed on the basis of analytical and spectral data. In the ^{1}H NMR spectrum (Figure 2.9), the proton attached to the α-C was indicated by the singlet at δ 8.11. The CH_2 protons were indicated by the singlet at δ 5.14 (s, 2H). The doublet at δ 9.45 (d, 1H, *J* = 6.8Hz) showed the H-*1* proton on the naphthyl ring. The presence of negatively charged oxygen near the H-*1* is responsible for its higher δ value compared to other aromatic protons. All other protons appeared as multiplet from δ 7.83-7.35 in the ^{1}H NMR spectrum.

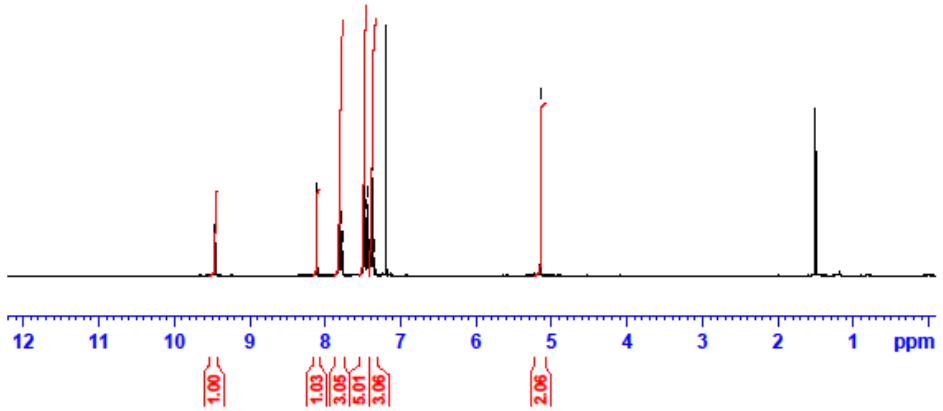


Figure 2.9 ^{1}H NMR spectrum of **37**

The $-CH_2$ carbon in the nitrone was indicated by the peak at δ 72.07 in the ^{13}C NMR spectrum (Figure 2.10). All the other carbons appeared between δ 133.48-121.52.

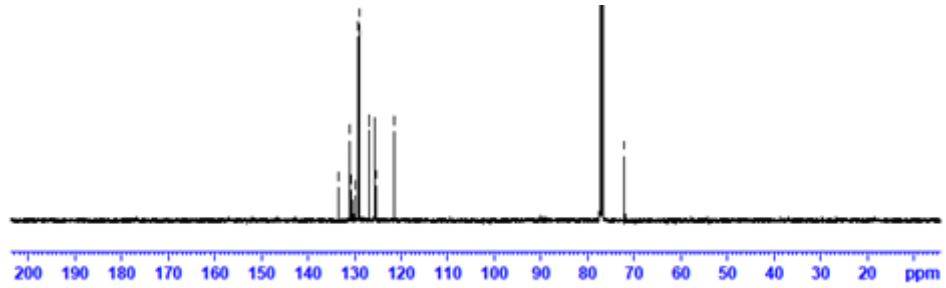


Figure 2.10 ^{13}C NMR spectrum of **37**

2.4. Experimental Section

2.4.1. General Techniques

All reactions were carried out using oven dried glasswares. All experiments were done with distilled and dried solvents by using standard protocols. All starting materials were purchased from either *Sigma-Aldrich*

or *Spectrochem Chemicals* and were used without further purification. Progress of the reaction and chromatographic separations were monitored by dried and activated silica gel TLC plates (aluminium sheets coated with silica gel, *E. Merck*) and alumina plates (TLC grade alumina coated on glass plates) Visualisation of TLC plates was accomplished by exposure to iodine vapours or UV lamp. Separation and purification of compounds were done by column chromatography using either silica gel (*Spectrochem Chemicals*, 60-120 mesh) or neutral alumina (*Spectrochem Chemicals)*. The products were further purified by recrystallization from suitable solvent systems. Solvent eluted from column chromatography was concentrated using *Heidolph* rotary evaporator. Melting points are uncorrected and were determined on a *Neolab* melting point apparatus. Infra-red spectra were recorded using *Jasco 4100* and *ABB Bomem (MB Series)* FT-IR spectrometers. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz *Bruker Avance III* FT-NMR spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS. Elemental analysis was performed using *Elementar Systeme (Vario EL III)*. Molecular mass was determined by electron impact (EI) method using GC-MS (*Agilent GC-7890A, Mass-5975C*) and fast atom bombardment (FAB) using *JMS 600 JEOL* mass spectrometer.

2.4.2. General Procedure for the Synthesis of *N*-Fluorenylidene-*N*-arylamines

A mixture of flurenone (10 mmol), amine (16 mmol) and BF_3-etherate (1 mL) in 30 mL $CHCl_3$ containing EtOH (5 mL) was refluxed for about 15 minutes. The resulting solution was then concentrated and cooled. The residue obtained was recrystallized from a 1:3 mixture of

chloroform-ethanol to give yellow crystals of *N*-fluorenylidene-*N*-arylamines.

2.4.3. General Procedure for the Synthesis of *N*-Fluorenylidene-*N*-arylnitrones from Imines

To a solution of imine (10 mmol) in 10 mL DCM at 0-5^{o}C, *m*-CPBA (11 mmol) in 5 mL DCM was added with stirring. The reaction mixture was then stirred for 5h keeping the low temperature. After the completion, excess *m*-CPBA was removed by filtration, and the filtrate was washed twice with Na_2CO_3 solution and finally with water. After the organic layer was evaporated, the residue obtained was recrystallized from a 1:1 mixture of DCM/hexane to give *N*-fluorenylidene-*N*-arylnitrones in good yield.

2.4.4. General Procedure for the Synthesis of Nitrosobenzenes

The catalyst *cis*-$Mo(O)_2(acac)_2$ (1 mmol) in cyclohexane (50 mL) was stirred for about 10 min at room temperature under aerobic condition. The amine (10 mmol) followed by 30% H_2O_2 (50 mmol) were added to the light orange suspension thus produced. The reaction mixture was then stirred for another one hour under aerobic condition. It was then filtered and dried over anhydrous Na_2SO_4. Filtrate was concentrated and cooled. The solid mass thus obtained was allowed to melt, so that the pure nitroso derivatives got precipitated.

2.4.5. General Procedure for the Synthesis of Nitrones from Nitrosoarenes and Diazofluorene

A mixture of diazofluorene (10 mmol) and appropriate nitrosoarenes (10 mmol) in 40 mL of dry diethyl ether was stirred for about 1h. During the course of reaction, nitrogen was evolved, red colour of the reaction mixture got vanished and yellow precipitate was formed. The precipitate formed was filtered, dried and recrystallized from ethanol to give yellow crystals of nitrone

2.4.6. Spectral and Analytical Data of Significant Compounds

2.4.6.1. Fluorenone Hydrazone (43)

Fluorenone hydrazone was prepared by a reported procedure (81% yield, mp 148 °C).[60]

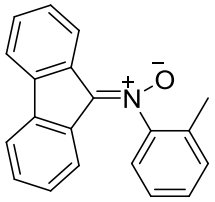
2.4.6.2. 9-Diazofluorene (41)

9-Diazofluorene was prepared by a reported procedure (85% yield, mp 94 °C).[61]

2.4.6.3. *N*-Fluorenylidene-*N*-phenylnitrone (29a)

N-Fluorenylidene-*N*-phenylnitrone was prepared by a reported procedure (85%, mp 194 °C).[58]

2.4.6.4. *N*-Fluorenylidene-*N*-(2-methylphenyl) nitrone (29b)



Yield: 83% ; **mp:** 145 °C.

IR ν_{max} (KBr): 3061cm^{-1} (=C-H stretch), 1540 cm^{-1} (C=N stretch), 1250 cm^{-1} (N→O stretch).

^{1}H NMR ($CDCl_3$): δ 8.97-8.95 (m, 1H), 7.73-7.23 (m, 9H), 5.75 (d, *J* = 8Hz, 2H), 2.28 (s, 3H).

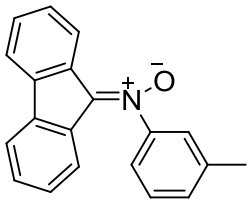
^{13}C NMR ($CDCl_3$): δ: 146.31, 139.23, 139.14, 132.04, 131.95, 131.71, 131.18, 130.59, 130.14, 129.20, 128.91, 127.77, 127.64, 127.19, 123.79, 123.20, 120.21, 119.62, 16.43.

MS: *m/z* 285 (M^+), 286 (M+1).

Elemental analysis calculated for $C_{20}H_{15}NO$:- C: 84.19, H: 5.30, N: 4.91.

Found: C: 84.26, H: 5.22, N: 4.87.

2.4.6.5. *N*-Fluorenylidene-*N*-(3-methylphenyl) nitrone (30b)



Yield: 80%; **mp:** 112 °C.

IR ν_{max} (KBr): 3050 cm^{-1} (=C-H stretch), 1540 cm^{-1} (C=N stretch), 1261 cm^{-1} (N→O stretch).

^{1}H NMR ($CDCl_3$): δ 8.92 (d, *J* = 7.2, 1H), 7.72 -7.23 (m, 9H), 6.94-6.90 (m, 1H), 5.95 (d, *J* = 8 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 140.59, 139.31, 132.42, 131.14, 131.04, 129.91, 129.11,

128.90, 127.30, 127.10, 124.26, 123.97, 120.79, 120.16, 119.60. 21.35.

MS:- *m/z* 285 (M^+), 286 (M+1).

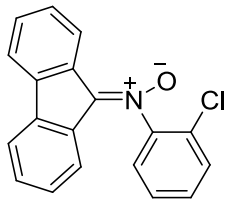
Elemental analysis calculated for $C_{20}H_{15}NO$:- C: 84.19, H: 5.30, N: 4.91.

Found: C: 84.24, H: 5.29, N: 4.94.

2.4.6.6. *N*-Fluorenylidene-*N*-(4-methylphenyl)nitrone (31b)

N-Fluorenylidene-*N*-(4-methylphenyl)nitrone was prepared by a known procedure (83% yield, mp 164 °C).[58]

2.4.6.7. *N*-Fluorenylidene-*N*-(2-chlorophenyl) nitrone (29c)



Yield: 76%; **mp:** 117 °C.

IR ν_{max} (KBr): 3061 cm^{-1} (=C-H stretch), 1548 cm^{-1} (C=N stretch), 1245 cm^{-1} (N→O stretch).

^{1}H NMR ($CDCl_3$): δ δ = 8.96-8.94 (m, 1H), 7.71 -6.90 (m, 10H), 5.82 (d, *J* = 8Hz, 1H).

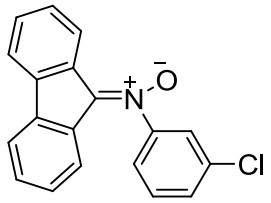
^{13}C NMR ($CDCl_3$): δ: 146.67, 144.37, 139.51, 139.36, 131.90, 131.56, 131.27, 131.23, 130.31, 129.57, 129.03, 128.70, 128.21, 127.71, 127.45, 122.90, 120.40, 119.71.

MS: *m/z* 305 (M^+), 306 (M+1).

Elemental analysis calculated for $C_{19}H_{12}ClNO$:- C: 74.64, H: 3.96, N: 4.58.

Found: C: 74.55, H: 3. 95, N: 4.55.

2.4.6.8. *N*-Fluorenylidene-*N*-(3-chlorophenyl) nitrone (30c)



Yield: 79%; **mp:** 123 °C.

IR ν_{max} (KBr): 3055 cm^{-1} (=C-H stretch), 1538 cm^{-1} (C=N stretch), 1256 cm^{-1} (N→O stretch).

^{1}H NMR ($CDCl_3$): δ 8.90-8.88 (m, 1H), 7.72 -6.93 (m, 10H), 6.01 (d, *J* = 8 Hz, 1H).

^{13}C NMR ($CDCl_3$): δ 147.67, 146.02, 139.45, 139.20, 135.81, 132.22, 131.50, 131. 26, 130.63, 130.48, 129.51, 129.01, 127.48, 127.18, 124.50, 123.74, 122.20, 120.39, 119.73.

MS:- *m/z* 305 (M^+), 306 (M+1).

Elemental analysis calculated for $C_{19}H_{12}ClNO$:- C: 74.64, H: 3.96, N: 4.58. Found: C: 74.58, H: 3.94, N: 4.56.

2.4.6.9. *N*-Fluorenylidene-*N*-(4-chlorophenyl)nitrone (31c)

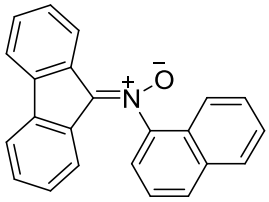
N-Fluorenylidene-*N*-(4-chlorophenyl)nitrone was synthesized by a known procedure (78%, mp 194 ^oC).[58]

2.4.6.10. *N*-Fluorenylidene-*N*-naphthylnitrone (32)

Yield: 79%; **mp:** 157 °C.

IR ν_{max} (KBr): 3050 cm^{-1} (=C-H stretch), 1536 cm^{-1} (C=N stretch), 1250 cm^{-1} (N→O stretch).

^{1}H NMR ($CDCl_3$): δ 9.091 (d, *J* = 8Hz, 1H), 7.139-7.987 (m, 12H), 6.69 (t, *J* = 8Hz, 1H),



5.52 (d, *J* = 8Hz, 1H).

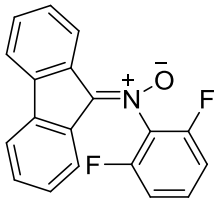
^{13}C NMR ($CDCl_3$): δ 146.84, 143.50, 139.32, 134.58, 132.25, 131.35, 130.41, 130.33, 129.12, 128.98, 128.23, 128.14, 127.44, 127.40, 126.58, 125.58, 123.72, 122.35, 121.17, 120.15, 119.68.

MS:- *m/z* 321 (M^+), 322 (M+1).

Elemental analysis calculated for $C_{23}H_{15}NO$:- C: 85.96, H: 4.70, N: 4.36.

Found: C: 85.87, H: 4.68, N: 4.35.

2.4.6.11. *N*-Fluorenylidene-*N*-(2,6-difluorophenyl)nitrone (33)



Yield: 76%; **mp:** 220 °C.

IR ν_{max} (KBr): 3056 cm^{-1} (=C-H stretch), 1557 cm^{-1} (C=N stretch), 1249 cm^{-1} (N→O stretch).

^{1}H NMR ($CDCl_3$): δ 8.96-8.94 (m, 1H), 7.70-7.18 (m, 8H), 7.00-6.95 (m, 1H), 6.10 (d, *J* = 8Hz, 1H).

^{13}C NMR ($CDCl_3$): δ 157.09, 154.56, 139.73, 139.36, 131.92, 131.83, 131.57, 131.47, 129.95, 129.11, 127.88, 127.62, 122.04, 120.66, 119.78, 113.31, 113.09.

MS:- *m/z* 307 (M^+), 308 (M+1).

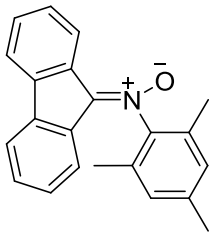
Elemental analysis calculated for $C_{19}H_{11}F_2NO$:- C: 74.26, H: 3.61, N: 4.56.

Found: C: 74.18, H: 3.57, N: 4.54.

2.4.6.12. *N*-Fluorenylidene-*N*-(2,6-dimethylphenyl)nitrone (34)

N-Fluorenylidene-*N*-(2,6-dimethylphenyl)nitrone was prepared by a known procedure (78% yield, mp 154 °C).[62]

2.4.6.13. *N*-Fluorenylidene-*N*-(2,4,6-trimethylphenyl) nitrone (35)



Yield: 79%; **mp:** 213 °C.

IR ν_{max} (KBr): 3055 cm^{-1} (=C-H stretch), 1540 cm^{-1} (C=N stretch), 1256 cm^{-1} (N→O stretch).

^{1}H NMR ($CDCl_3$): δ 9.01-8.99 (m, 1H), 7.72-7.04 (m, 7H), 6.95-6.91 (m, 1H), 5.82 (d, *J* = 8Hz, 1H), 2.40 (s, 3H), 2.18 (s, 6H).

^{13}C NMR ($CDCl_3$): δ 145.76, 143.66, 139.50, 139.09, 131.90, 131.22, 131.02, 130.42, 129.87, 129.11, 128.84, 127.92, 127.18, 122.62, 120.17, 119.57, 21.26, 16.50.

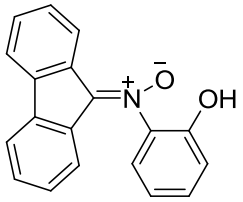
MS:- *m/z* 313 (M^+), 314 (M+1).

Elemental analysis calculated for $C_{22}H_{19}NO$:- C: 84.31, H: 6.11, N: 4.47. Found: C: 84.29, H: 6.09, N: 4.46.

2.4.6.14. *N*-Fluorenylidene-*N*-(2-hydroxyphenyl)nitrone (36d)

Yield: 72%; **mp:** 160 °C.

IR ν_{max} (KBr): 3057 cm^{-1} (=C-H stretch), 1558 cm^{-1} (C=N stretch), 1251 cm^{-1} (N→O stretch).



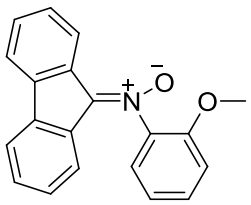
^{1}H NMR ($CDCl_3$): δ 8.92-8.89 (m, 1H), 7.69-6.95 (m, 11H), 6.63 (d, *J* = 8Hz, 1H).

^{13}C NMR ($CDCl_3$): δ 161.04, 152.25, 147.53 140.02, 139.92, 132.82, 132.67, 132.29, 132.11, 130.38, 130.34, 128.98, 127.96, 127.57, 125.12, 124.71, 120.35, 119.83, 119.75, 119.48.

MS:- *m/z* 287 (M^+), 288 (M+1).

Elemental analysis calculated for $C_{19}H_{13}NO_2$:- C: 79.43, H: 4.56, N: 4.88. Found: C: 79.39, H: 4.55, N: 4.85.

2.4.6.15. *N*-Fluorenylidene-*N*-(2-methoxyphenyl)nitrone (36e)



Yield: 80%; **mp:** 134 °C.

IR ν_{max} (KBr): 3056 cm^{-1} (=C-H stretch), 1548 cm^{-1} (C=N stretch), 1266 cm^{-1} (N→O stretch).

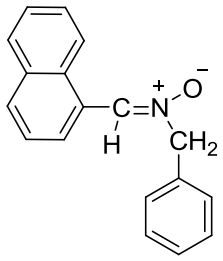
^{1}H NMR ($CDCl_3$): δ 8.99-8.96 (m, 1H), 6.89 (m, 10H), 5.94 (d, *J* = 7.6 Hz, 1H), 3.79 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 152.10, 139.32, 139.15, 136.16, 132.27, 131.46, 131.14, 130.84, 129.13, 128.90, 127.49, 127.40, 125.30, 123.13, 121.61, 120.17, 119.52, 113.05, 56.12.

MS:- *m/z* 301 (M^+), 302 (M+1).

Elemental analysis calculated for $C_{20}H_{15}NO_2$:- C: 79.72, H: 5.02, N: 4.65. Found: C: 79.69, H: 5.01, N: 4.62.

2.4.6.16. *N*-Naphthylidene-*N*-benzyl nitrone (37)



Yield: 77%; **mp:** 82°C.

IR ν_{max} (KBr): 3056 cm^{-1} (=C-H stretch), 1572 cm^{-1} (C=N stretch), 1268 cm^{-1} (N→O stretch).

^{1}H NMR ($CDCl_3$): δ 9.45 (d, *J* = 6.8Hz, 1H), 8.11 (s, 1H), 7.83-7.77 (m, 3H), 7.49-7.35 (m, 8H), 5.14 (s, 2H).

^{13}C NMR ($CDCl_3$): δ 133.48, 133.40, 130.97, 130.63, 129.96, 129.31, 129.29, 129.09, 126.86, 126.83, 125.81, 125.75, 125.41, 121.52, 72.07.

MS:- *m/z* 261 (M^+), 262 (M+1).

Elemental analysis calculated for $C_{18}H_{15}NO_2$:- C: 82.73, H: 5.79, N: 5.36.

Found: C: 82.67, H: 5.76, N: 5.34.

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CHAPTER 3

REACTIONS OF NITRONES WITH ELECTRON DEFICIENT ACETYLENES

3.1. Abstract

This chapter describes our endeavours to unravel the mechanism of 1,3-dipolar cycloaddition reactions. Here we have investigated the course of nitrone cycloaddition reactions when different substituents are introduced and also the effect of medium in controlling the path of the reaction. The experimental observations provide additional evidences for a stepwise addition pathway for 1,3-dipolar cycloaddition reactions.

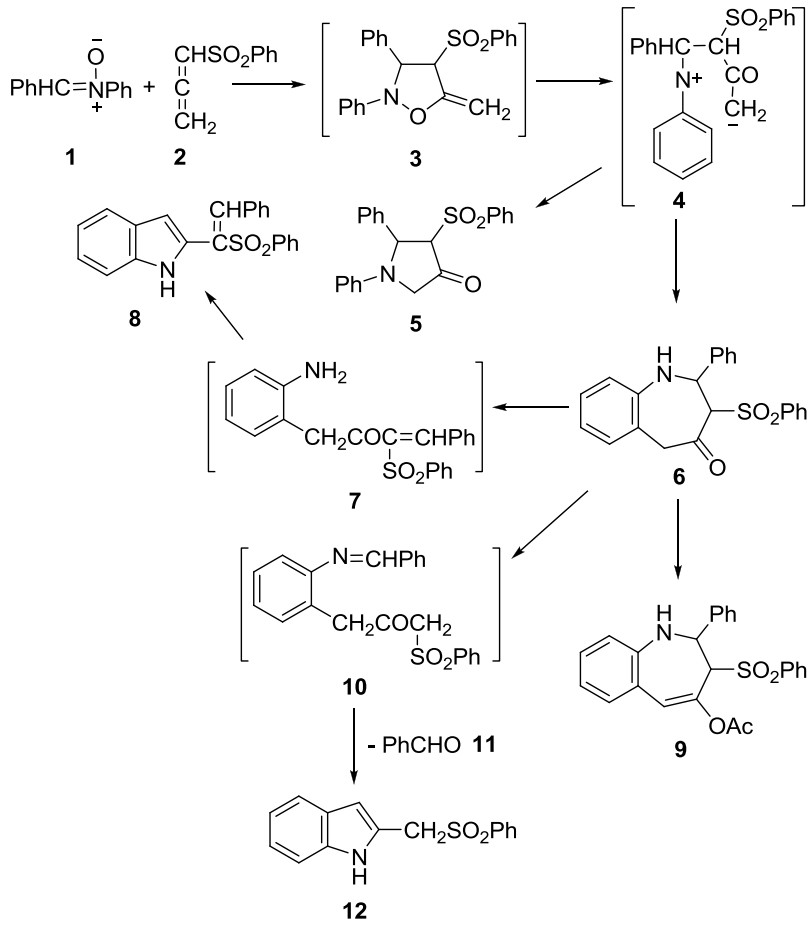
3.2. Introduction

1,3-Dipolar cycloaddition reaction is identified as a promising technique for the synthesis of heterocycles. Using a wide variety of 1,3-dipoles such as diazoalkanes, nitrile oxides, azomethine ylides, azides, nitrones, azomethine imines etc., we can synthesize biologically active heterocyclic compounds.[1-30] So it is important to analyse the mechanism of 1,3-dipolar cycloaddition reactions, which will definitely contribute to the optimal utilization of this technique in various fields. Most of the

earlier reports are in favour of a 'single step concerted process that is not synchronous'.[31] Later Huisgen reported that a stepwise mechanism is also possible for cycloaddition reactions by illustrating the reaction between an electron rich thiocarbonyl ylide and dicyanofumarate, and in such cases a scrambling of stereochemistry was observed.[32] The formation of a ring enlarged product, during the reaction of thiocarbonyl ylide with tetracyanoethylene was explained with the help of an ionic intermediate.[33] Studies on various systems disclosed the possibility for stepwise addition procedure for 1,3-dipolar cycloaddition reactions.[34-36] Preliminary theoretical calculations conducted to analyse the mechanism disclosed that the dipoles follow concerted pathway,[37-40] whereas advanced computational studies revealed that 1,3-dipolar addition reactions follow both stepwise and concerted paths and these paths may be in close competition.[41-45] Our objective of the present study is to find additional evidences for the mechanism of 1,3-dipolar cycloaddition reaction, which will definitely add to the development of cycloaddition chemistry. We selected nitrones as the 1,3-dipole based on several considerations. Since nitrones are a stable class of 1,3-dipoles exhibiting remarkable nucleophilic character,[46-50] we surmised that, its addition with dipolarophiles will certainly reveal the involvement of any transition state or intermediate in the entire process. Regioselctivity observed in several cycloadditions reveals polar nature of the transition state (assuming concerted nature of cycloaddition reaction).[51] It is also possible to introduce different substituents into nitrones. Aldonitrones and ketonitrones, for example, have very different steric environment around one of the reaction centres in cycloaddition reactions. Huisgen

has reported that change in steric environment has a profound effect on facilitating concerted *vs* two-step mechanism for 1,3-dipolar addition.[52] Hence it is reasonable to assume that observed "cycloaddition" reaction of a sterically crowded nucleophilic 1,3-dipole such as ketonitrone can border a two-step reaction sequence. Thus we surmised that detailed analysis of cycloaddition reaction of nitrones will definitely give a clear idea about the mechanistic aspects of 1,3-dipolar cycloaddition reactions.

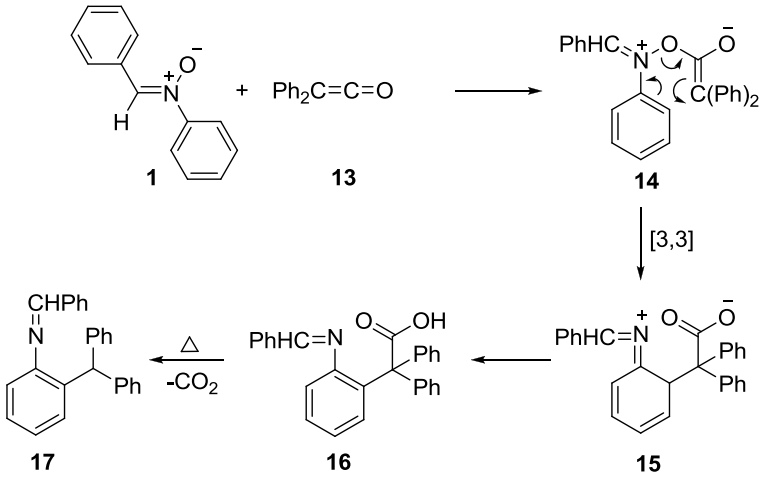
Generally the reaction of nitrones with alkenes and alkynes yields isoxazolidines and isoxazoline respectively as normal cycloadducts.[53-57] But there are exceptions, certain reports describe the formation of interesting heterocyclic compounds by the decomposition of isoxazoline intermediates.[58-61] Parpani and Zecchi reported that the reaction of *C*,*N*-diphenylnitrone with (phenylsulfonyl)alkyne as well as (phenylsulfonyl) propadiene yields a mixture of products other than the expected cycloadducts.[62] When the aldonitrone **1** is treated with (phenylsulfonyl)propadiene (**2**), a mixture of products is obtained. In this case, instead of any isoxazolidine derivative they obtained some unusual products along with a small quantity of benzaldehyde as the stable final products (Scheme 3.1).



Scheme 3.1

According to the authors the major product, benzazepinone **6** was formed from the transient isoxazolidine intermediate **3**. Compound **6** on column chromatography, as well as on standing for a long time in solution decomposed to benzaldehyde and indole **12**. When the benzazepinone derivative **6** was heated, along with **12** a small quantity of the indole **8** was also obtained.

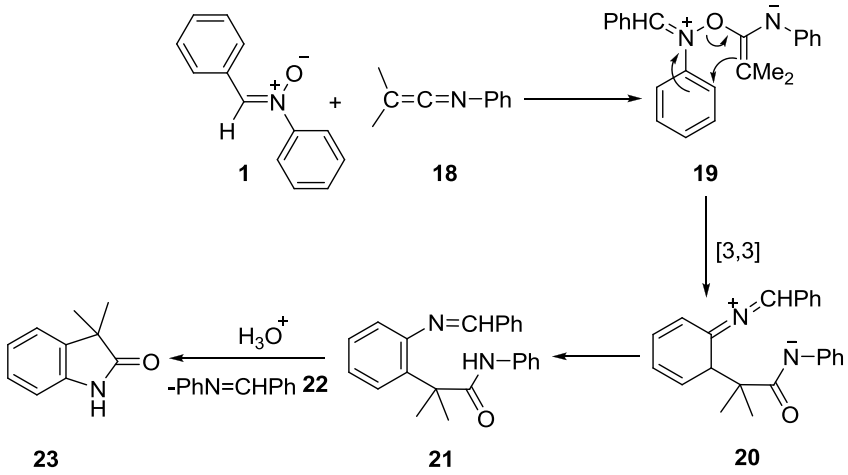
Some reports are in favour of a stepwise addition mechanism, where the products are formed by the rearrangement of ionic intermediate formed in the reaction. For example, a phenylimino derivative **17** was obtained as the stable final product in the reaction between *C*,*N*-diphenylnitrone **1** and diphenylketene **13** (Scheme 3.2).[63] Here the author describes a stepwise pathway for the 1,3-dipolar addition reaction, where the initially formed zwitterion **14** undergoes a [3,3] sigmatropic rearrangement and subsequent rearomatisation to form an imino acid **16**, which on decarboxylation yields the final product **17**.



Scheme 3.2

Another reaction, which illustrates a multistep process is the cycloaddition reaction between the *N*-arylnitrone **1** and ketenimine **18**.[64] Formation of adduct **21** was also explained on the basis of the rearrangement of the initially formed zwitterion **19**. The adduct **21**

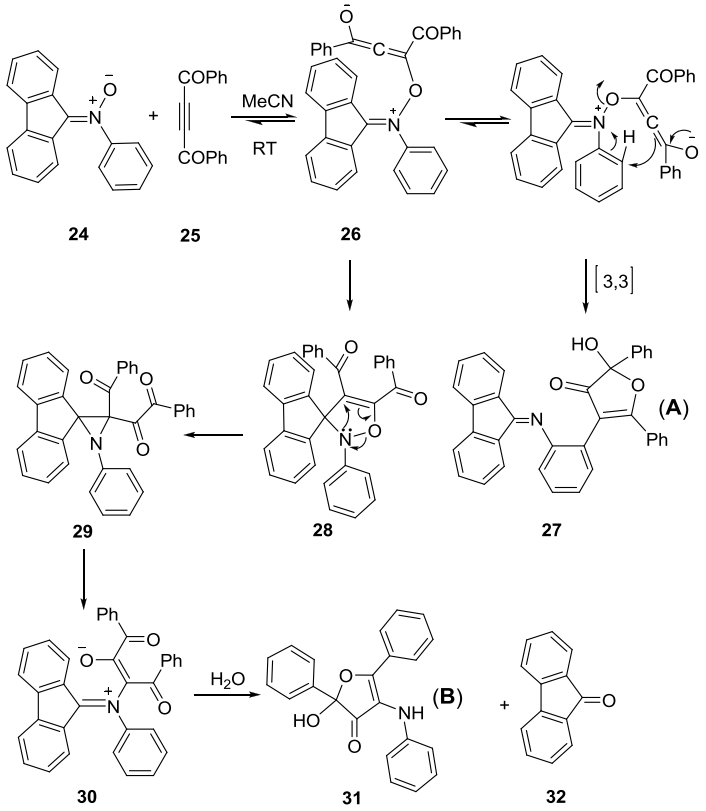
readily undergoes hydrolysis to produce an oxindole derivative **23** as the final product (Scheme 3.3).



Scheme 3.3

So from the above reactions it is clear that all the 1,3-dipolar cycloaddition reactions cannot be explained on the basis of a concerted pathway. From our group it has been proposed earlier that the mechanism of 1,3-dipolar cycloaddition reaction is not concerted, but follows a stepwise procedure with the formation of a zwitterionic intermediate. This was illustrated by the reaction of *N*-fluorenylidiene-*N*-phenylnitrone **24** with dibenzoyl acetylene (DBA) **25** in acetonitrile (Scheme 3.4).[65] Here we isolated a novel 1:1 adduct (furanone-**A, 27**), along with another 3(2H)-furanone (furanone-**B**, **31**) arising through the expected isoxazoline cycloadduct that could not be isolated. Generation of **27** prompted us to propose a stepwise reaction sequence between nitrones and DBA. According to the proposed mechanism, first step is the

nucleophilic addition of nitrone **24** to acetylene **25** to form an ionic intermediate **26**, which further undergoes competing rearrangement as well as cyclization leading to two 3(*2H*)-furanones (**27** and **31**) along with fluorenone **32**. In this report, no evidence is available for the involvement of zwitterionic intermediate **26** in the generation of cycloadduct **28**.



Scheme 3.4

One of the furanones, the 1:1 adduct **(A)** of nitrone **24** and DBA **25**, is formed by the [3,3] sigmatropic rearrangement of the ionic intermediate **26** with one of the ortho positions of the *N*-aryl ring. The

other furanone (**B**) is obtained by the subsequent decomposition of some intermediates formed by the cyclization of the zwitterion. So our present objective is to get further evidences for the proposed stepwise mechanism for 1,3-dipolar cycloaddition reactions.

3.3. Results and Discussion

For the present study we have selected several *N*-arylnitrones and two *N*-alkylnitrones (Figure 3.1). Our group has proposed a stepwise reaction mechanism for 1,3-dipolar cycloaddition reactions. For verifying the proposed reaction pathway, we decided to repeat the cycloaddition reaction of the nitrone **24** with monoactivated acetylene. We assumed that presence of an ionic intermediate in the reaction can provide some additional products in different solvents, so we repeated the 1,3-dipolar cycloaddition reaction of **24** and **25** in different solvents. Since the key step of the suggested mechanism involves a [3,3] sigmatropic rearrangement of the initially generated zwitterion with the ortho position of the *N*-phenyl ring, we planned to check the effect of different substituents in the *N*-phenyl ring, particularly at the ortho position. For this purpose we selected the nitrones **33-37.** Finally for eliminating the possibility for the hetero-Cope rearrangement, we selected the *N*-alkyl nitrones **38** and **39** instead of *N*-arylnitrones for the cycloaddition reactions. We were also interested in isolating the isoxazoline cycloadduct in pure form and subjecting it to further reaction to shed light on some of the mechanisms proposed in Scheme 3.4

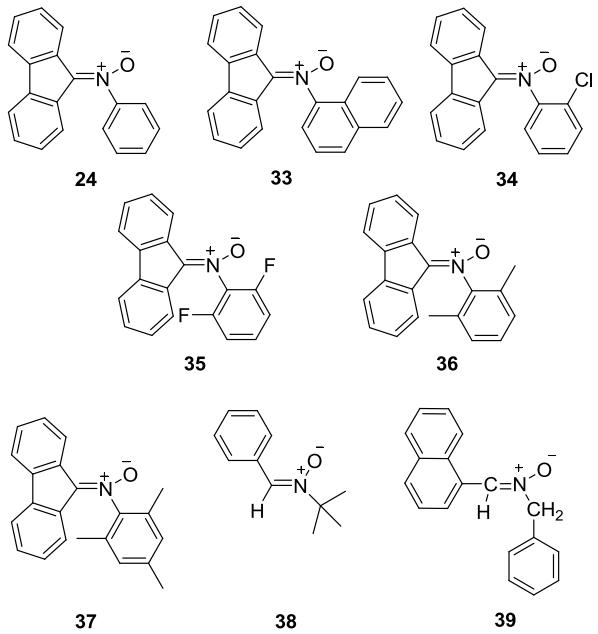


Figure 3.1

We have also prepared some dipolarophiles using the reported literature procedure. One of the dipolarophiles, dibenzoylacetylene (DBA) was synthesized by a known three step procedure.[66] The first step includes Friedel-Crafts acylation of benzene with fumaryl chloride to give *trans*-dibenzoylethylene, which on bromination followed by dehydrobromination using triethylamine gives DBA in high yield. The monoactivated acetylene, benzoylphenylacetylene was prepared by the condensation reaction of sodium salt of phenylacetylene with benzoyl chloride.[67]

3.3.1. Reaction of *N*-Fluorenylidene-*N*-phenylnitrone with Benzoylphenylacetylene

One of our objectives was to gather further evidence for the proposed mechanism. We surmised that if the stepwise reaction sequence proposed by us is correct, 1:1 adducts analogous to **27** will be generated in the reaction between nitrones and other electron deficient acetylenes. In this context, we examined the reaction of **24** with benzoylphenylacetylene instead of DBA. 1,3-Dipolar addition reaction between *N*-fluorenylidene-*N*-phenylnitrone (**24**)and benzoylphenylacetylene (**40**)was conducted (1:1 molar ratio) in refluxing acetonitrile. The reaction was completed in 6h. Using column chromatography, we could isolate three new products along with fluorenone. CHN and MS data of the compounds revealed that two of them are 1:1 adducts and third one is a compound analogous to furanone **B** generated by hydrolytic loss of elements of fluorenone. One of the 1:1 adducts, obtained as the major product, was analysed on the basis of spectral data. A sharp peak at 1649 cm^{-1} indicated the presence of an imine moiety (C=N) in the adduct. A carbonyl group in this compound was indicated by the presence of a peak at 1697 cm^{-1} in the IR spectrum, which was further confirmed by the peak at δ 194.50 in the ^{13}C NMR spectrum (Figure 3.2). A peak at δ 56.96 in the ^{13}C NMR showed the presence of an aliphatic carbon in the compound. The aromatic region in the ^{1}H NMR spectrum extended from δ 7.93-6.90 (m, 21H) and δ 6.69 (d, 1H). On the basis of all the spectral and analytical data, we proposed structure **41** analogous to furanone **A** for the discussed 1:1 adduct. The structure was further confirmed with the help of single crystal X-ray dif-

-fraction analysis (Figure 3.3).

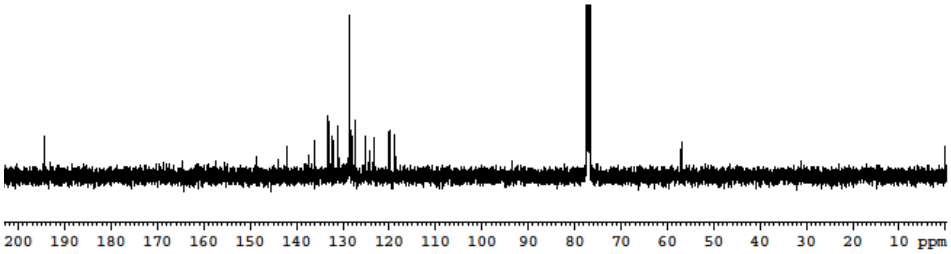


Figure 3.2 ^{13}C NMR spectrum of **41**

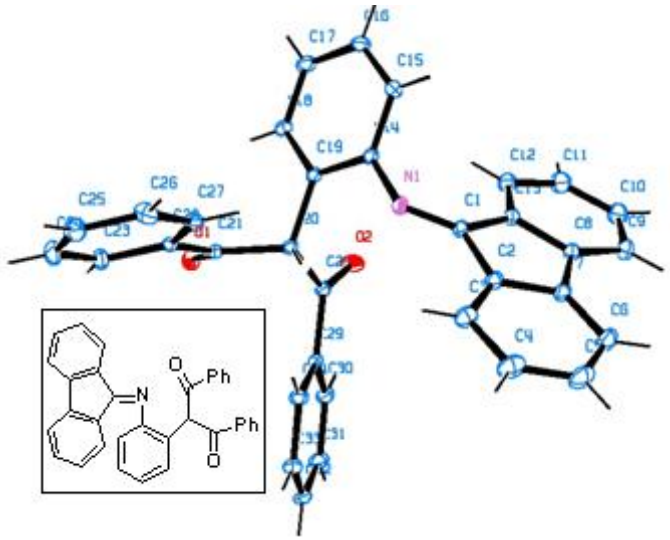


Figure 3.3 ORTEP diagram of molecular structure of **41**

The minor products obtained in the reaction were also identified on the basis of spectral data. The other 1:1 adduct was recognized as an isoxazoline derivative **42** of nitrone and benzoylphenylacetylene with the help of IR, ^{1}H and ^{13}C NMR analysis. The peak at 1633 cm^{-1} indicated the presence of the carbonyl group in **42**, which was supported by the

presence of a peak at δ 189.91 in the ^{13}C NMR spectrum. All the protons in the adduct appeared as multiplet from δ 7.65 to δ 6.62 in the ^{1}H NMR spectrum (Figure 3.4).

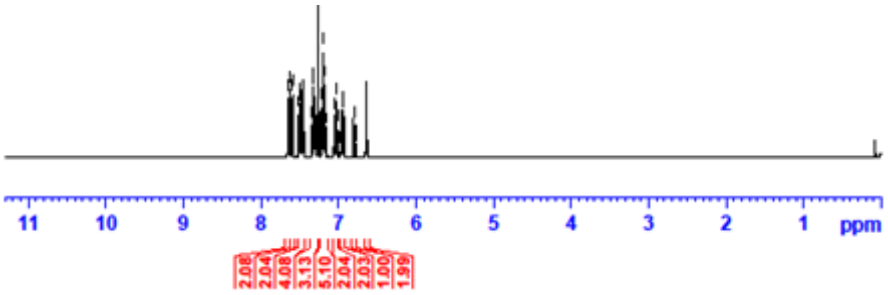


Figure 3.4 ^{1}H NMR spectrum of **42**

The proposed structure **42,** for the second 1:1 adduct was confirmed on the basis of X-ray diffraction studies (Figure 3.5).

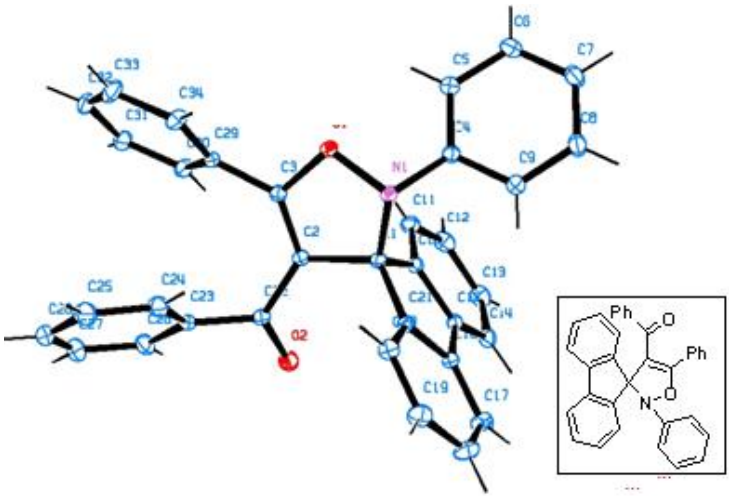


Figure 3.5 ORTEP diagram of molecular structure of **42**

The IR spectrum of the compound analogous to furanone **B** showed a peak at 3373 cm^{-1} corresponding to an –NH functionality, which was further supported by the peak at 1506 cm^{-1} which represents

an –NH bending frequency. Presence of carbonyl group in the compound was indicated by a strong absorption peak at 1661 cm^{-1} , which was further confirmed by a peak at δ 194.87 in the ^{13}C NMR spectrum (Figure 3.6).

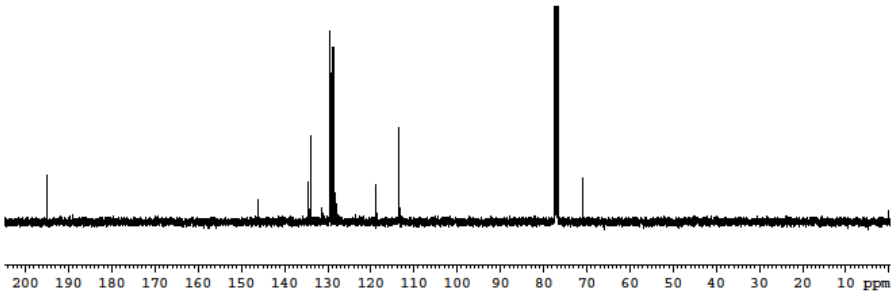


Figure 3.6 ^{13}C NMR spectrum of **43**

In the ^{1}H NMR spectrum of the compound (Figure 3.7), two doublets were observed at δ 5.62 (J = 5.6Hz, 1H) and δ 6.04 (J = 5.6Hz, 1H). On the basis of all the spectral and analytical data we proposed a structure **43** for the above discussed compound.

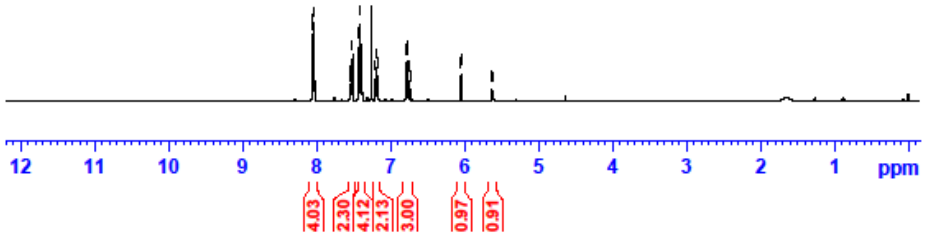
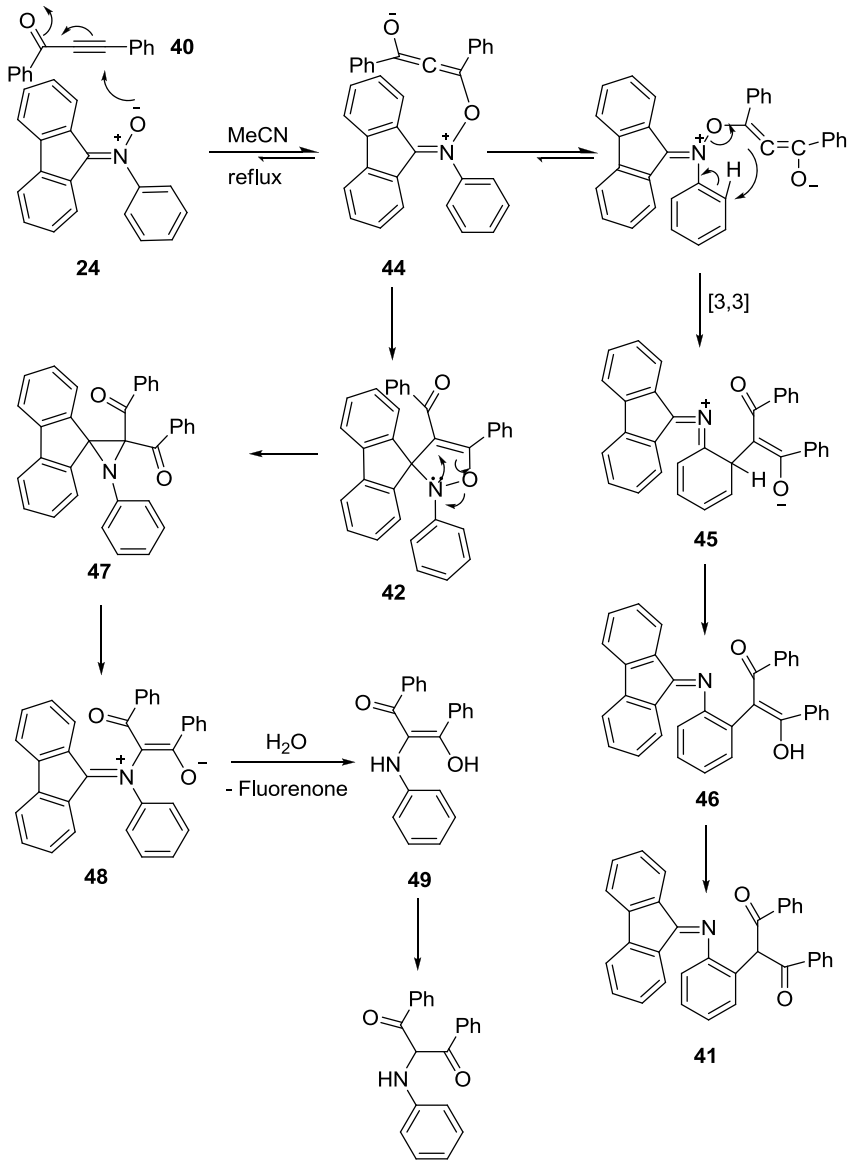


Figure 3.7 ^{1}H NMR spectrum of **43**

Mechanism for the formation of various products in the reaction between 24 and 40 is presented in Scheme 3.5.



Scheme 3.5

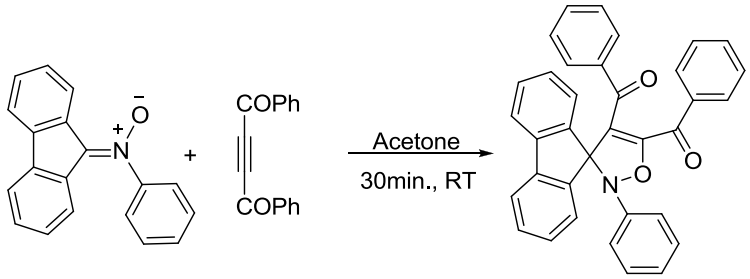
Formation of the 1:1 adduct **41** cannot be explained by a single step concerted mechanism. The reaction between *N*-fluorenylidiene-*N*-

phenylnitrone **24** with benzoylphenylacetylene **40** can be explained on the basis of the mechanism proposed in nitrone-DBA reaction. Initially nitrone adds to benzoylphenylacetylene in a Michael-type addition manner to form a zwitterionic intermediate **44**. This ionic intermediate undergoes a hetero-Cope rearrangement {[3,3] sigmatropic rearrangement} followed by rearomatisation to give the 1:1 adduct **41**. Alternatively, **44** may undergo cyclization to yield isoxazoline derivative **42**. The isoxazoline thus formed rearranges to **48** through an aziridine intermediate **47**. The intermediate **48** on hydrolysis produces **43** along with fluorenone (Scheme 3.5).

3.3.2. Effect of Solvents in Reaction of *N*-Fluorenylidene-*N*-phenylnitrone with DBA

Since the proposed stepwise reaction mechanism (Scheme 3.4) included a charged intermediate **26**, we examined the effect of solvent polarity on the course of the reaction. We assumed that generation of **26** should be favoured in polar solvents whereas a concerted [3+2] cycloaddition pathway should not exhibit substantial solvent effect. When the cycloaddition reaction of *N*-fluorenylidene-*N*-phenylnitrone (**24**) with dibenzoylacetylene (**25**) was conducted in non-polar (*eg*.: benzene) to moderately polar solvents (*eg*.: acetone), by TLC analysis, we could identify the presence of a new compound in the reaction mixture at the early stages of the reaction, and as the reaction progressed, it underwent decomposition and finally we could isolate **31** (furanone **B)** in major yield along with fluorenone and minor amounts of the compound **27** (furanone **A**). We observed that decomposition of the new

compound enhanced with temperature; it remained stable when the reaction temperature was maintained below 10°C. We isolated this new product by precipitating it out of the reaction mixture by adding cold methanol. From the mass spectrum, the compound was identified as a 1:1 adduct of nitrone **24** and DBA **25**. From the spectral data, we identified the compound as the isoxazoline derivative **28** generated through the expected formal dipolar cycloaddition reaction (Scheme 3.6).



24 **25** **28**

Scheme 3.6

The ^{1}H NMR of spectrum of **28** showed signals from δ 7.70-7.54 (m, 7H), 7.41-7.34 (m, 6H), 7.28-7.24 (m, 3H), 7.07-6.80 (m, 5H), and 6.61-6.58 (m, 2H). Carbonyl groups at two different environments in the isoxazoline derivative **28** were displayed by peaks at δ 188.77 and δ 184.25 in the ^{13}C NMR spectrum. The C=O group was indicated by the peak at 1633 cm^{-1} in the IR spectrum. In the ^{13}C NMR spectrum, the quaternary carbon of the isoxazoline ring appeared at δ 85.12 and the other signals from δ 156.35 to 116.57 were assigned to aromatic carbons in the compound. The structure of the isoxazoline derivative **28** was further confirmed from the crystal structure analysis (Figure 3.8).

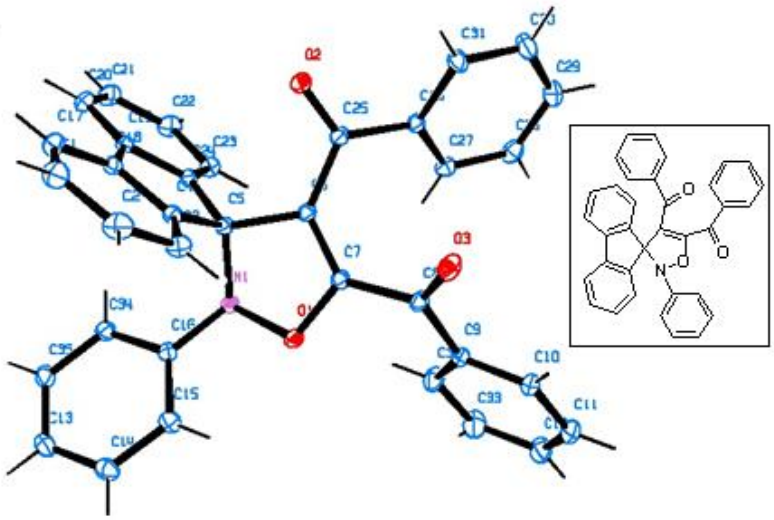


Figure 3.8 ORTEP diagram of molecular structure of **28**

When the polarity of the solvent was increased, that is when highly polar solvents (*eg*.: MeCN and DMSO), were used, we could not isolate the isoxazoline derivative **28**, and in such case the 1:1 adduct **A** was the major product (Table 3.1) along with **31** and fluorenone in minor amounts.

Solvents	Compound **A** (%)	Compound **B** (%)
Benzene	17	69
THF	19	68
Dichloromethane	24	62
Acetone	30	58
DMSO	69	19
Acetonitrile	71	18

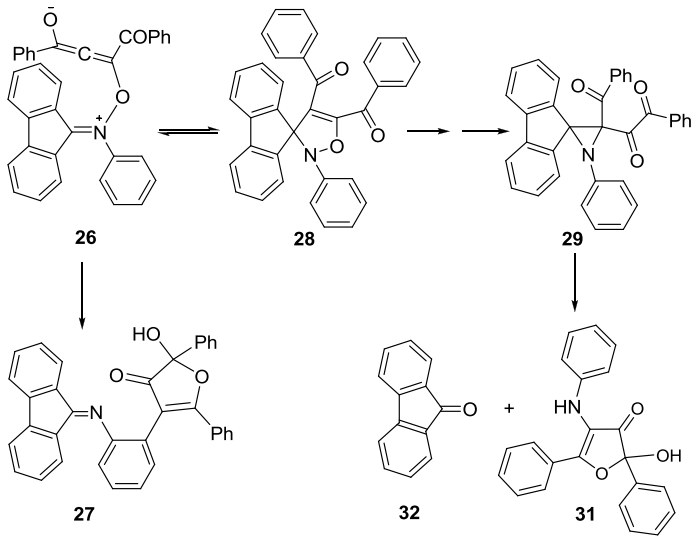
Table 3.1

This can be explained on the basis of solvent-assisted stabilization of the initially formed zwitterion **26**. In less polar solvents, charged

species get destabilized, so it will not get enough life time for rearrangement and successive transformation. So the preferred path will be the cyclization. The experimental observations support the proposed stepwise mechanism.

3.3.3. Decomposition of Isoxazoline Derivative 28

As a control experiment, we conducted the decomposition of the isoxazoline derivative **28** in acetonitrile. After stirring the reaction mixture for about 6h at room temperature, we separated the products by column chromatography. Along with fluorenone, and the 1:1 adduct **A** (32%), we could isolate the compound **B** in maximum yield (58%) (Scheme 3.7).



Scheme 3.7

Generation of **27** from **28** is really remarkable. This is possible only with C-C bond cleavage to regenerate intermediate **26**. On the basis

of theory of microscopic reversibility, we argue that if **26** is involved in the decomposition of **28**, it should also be involved as an intermediate in the generation of **28**. In a highly polar solvent like acetonitrile, we propose that isoxazoline **28** is in tautomeric equilibrium with zwitterionic intermediate **26**. The zwitterion **26**, formed during the decomposition process, get stabilized in this polar solvent and undergo further rearrangement to produce the 1:1 adduct. Comparison of the yield of **27** in the direct reaction between **24** and **25** (71%) with its yield in the decomposition of **28** (51%) is quite revealing. It is evident that an alternative pathway, that is, direct generation of **26** from **24** and **25** is operating in the former case. Thus the decomposition reaction of isoxazoline derivative **28** provides additional evidence for a stepwise mechanism for 1,3-dipolar cycloaddition reaction of nitrones.

3.3.4. Reactions of *N*-Fluorenylidene-*N*-naphthylnitrone with DBA

We observed the course of 1,3-dipolar cycloaddition reaction by replacing *N*-phenylnitrone by *N*-naphthylnitrone. By selecting such a nitrone we could block one of the ortho positions also. The reaction of *N*-fluorenylidene-*N*-naphthylnitrone **33** with dibenzoylacetylene **25** was conducted in acetonitrile at room temperature, and on completion of the reaction, we obtained a single product **50**, which was a 1:1 adduct identified as the analogue of **A** by spectral analysis (Scheme 3.8). The imine (C=N) functionality in the compound was identified by the presence of a peak at 1647cm^{-1} in the IR spectrum. A broad peak at δ 4.38 (s, 1H) in ^{1}H NMR spectrum indicated the presence of an –OH

group in the adduct **50**. The aromatic protons of the compound appeared as a complex multiplet at δ 7.92-6.22 (m, 24H) in the ^{1}H NMR spectrum. The C=O group in the compound was indicated by the peak at δ 199.23 in the ^{13}C NMR spectrum (Figure 3.9) and at 1682 cm^{-1} in the IR spectrum.

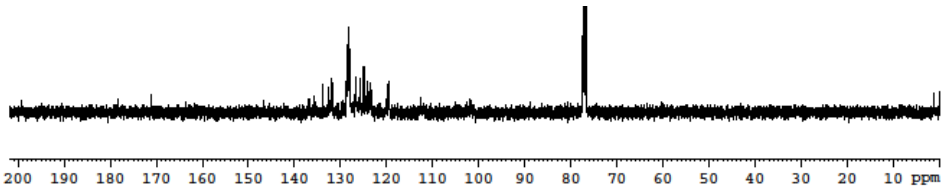
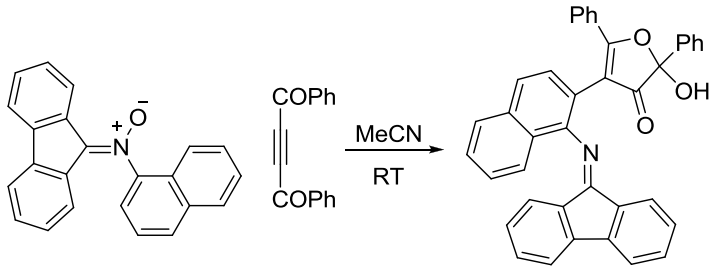


Figure 3.9 ^{13}C NMR spectrum of **50**

When *N*-naphthylnitrone is used for cycloaddition reaction, the zwitterion mediated stepwise mechanism is the preferred pathway. The *N*-naphthyl moiety enables a lower transition state barrier for [3,3] sigmatropic shift.



33 **25** **50**

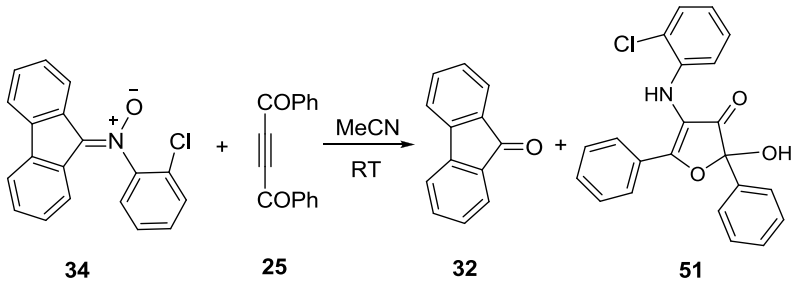
Scheme 3.8

3.3.5. Reactions of Substituted *N*-Arylnitrones

From the above discussed reactions, it is clear that the reaction of *N*-arylnitrones with electron deficient alkynes includes a zwitterion mediated stepwise addition pathway, and for the formation of compound **A** and its analogue **41**, initially formed ionic intermediate undergoes [3,3] sigmatropic rearrangement with the ortho position of the *N*-aryl substituent. So substituents on the *N*-aryl ring, especially the ortho substituents might have some influence on the reaction mechanism. Furthermore, by conducting the reaction of substituted *N*-arylnitrones it is possible to isolate some other intermediate involved in the process. Based on the above expectations, we conducted the cycloaddition reactions of a few nitrones with substituents on the *N*-aryl ring.

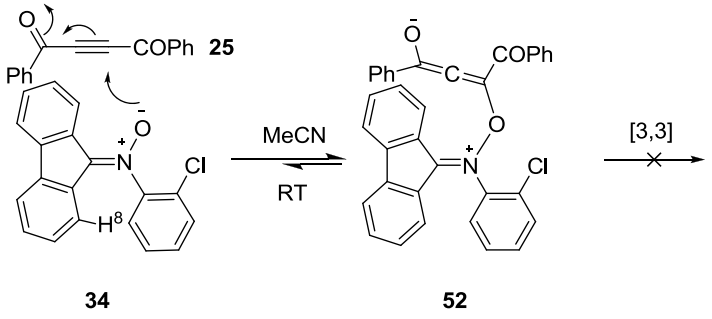
3.3.5.1. Reactions of *N*-Fluorenylidene-*N*-(2-chlorophenyl)nitrone with DBA

The cycloaddition reaction between *N*-fluorenylidene-*N*-(2-chlorophenyl)nitrone and DBA (1:1molar ratio) was done in acetonitrile at RT. We obtained a product corresponding to the mass of compound **B** along with fluorenone. By analysing the spectral data, the product obtained was confirmed as a 3(*2H*)-furanone derivative, analogous to **B** (Scheme 3.9).



Scheme 3.9

When chlorine is substituted at the ortho position, due to steric interaction with the *H*-8 proton of the fluorenyl ring, Cl cannot take the ortho position nearer to the fluorenyl ring. Due to the presence of this bulkier group in the other ortho position, the zwitterion formed cannot undergo rearrangement with the *N*-phenyl ring (Scheme 3.10). So the cyclization of the ionic intermediate takes place, which results in the exclusive formation of **51**.



Scheme 3.10

3.3.5.2. Reactions of *N*-Fluorenylidene-*N*-(2,6-difluorophenyl)nitrone with DBA

When the two ortho positions of the *N*-phenyl ring were substituted by fluorine, the reaction was slow and after completion, we

could isolate two products. One of them was identified as fluorenone. CHN as well as spectral analysis of the second product revealed its identity as **53** analogous to furanone **B**. The –OH and the –NH groups in the compound **53** were indicated by a broad peak at δ 4.32 (s, 0.78H), and a sharp peak at δ 4.97 (s, 1H) respectively in the ^{1}H NMR spectrum (Figure 3.10).

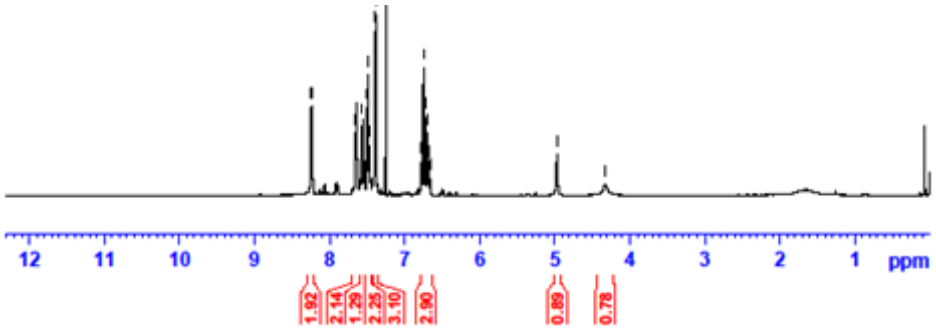


Figure 3.10 ^{1}H NMR spectrum of **53**

The C=O functionality in the product **53** appeared at 1691 cm^{-1} in the IR absorption spectrum, and at δ 197.45 in the ^{13}C NMR spectrum (Figure 3.11).

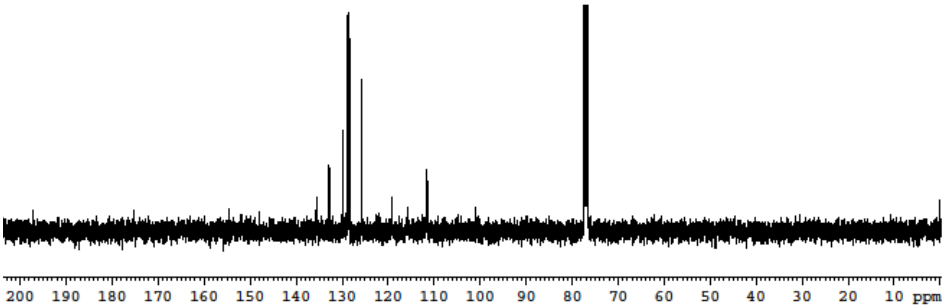
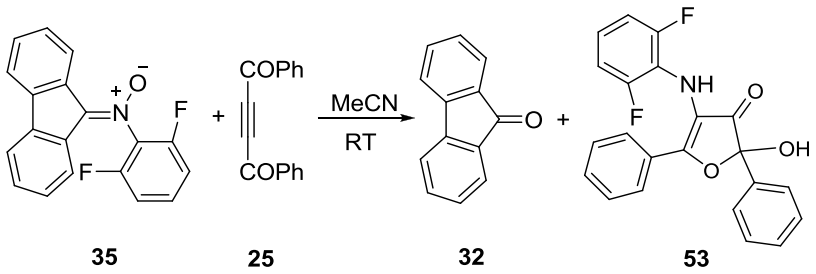


Figure 3.11 ^{13}C NMR spectrum of **53**

So when the two ortho positions were substituted by fluorine, we could not observe any product resulting from the sigmatropic rearrangement of the zwitterion (Scheme 3.11).



Scheme 3.11

3.3.5.3. Reactions of *N*-Fluorenylidene-*N*-(2,6-dimethylphenyl)nitrone with DBA

Reaction between *N*-fluorenylidene-*N*-(2,6-dimethylphenyl)nitrone **36** and DBA **25** was very slow. Even after prolonged stirring, TLC analysis indicated the presence of unchanged nitrone in the reaction mixture. We separated the products of the reaction by column chromatography over silica gel. We obtained four new products along with some amount of unreacted nitrone and a small amount of fluorenone (Scheme 3.12). On analysing the CHN and mass data, we could identify that, among the four products, two are 1:1 adducts of nitrone and DBA, third one is analogous to furanone **B**, and the fourth is a 1:2 adduct, where one equivalent of nitrone is added to two equivalents of DBA.

The structure of 1:2 adduct was analysed on the basis of CHN and spectral data. Presence of a carbonyl group was indicated by a peak at 1671 cm^{-1} in the IR spectrum. In the ^{13}C NMR spectrum peaks at δ 193.91, 192.80, 192.69, and 190.36 showed different carbonyl environments and the peaks at δ 81.14, 56.38 and 52.44 indicated the presence of three quaternary carbon atoms in the compound. Singlets at δ 2.07 (3H) and δ 1.34 (3H) in the ^{1}H NMR spectrum showed the presence of two methyl groups in different environments, which was further confirmed by the peaks at δ 25.29 and δ 15.70 in the ^{13}C NMR spectrum (Figure 3.12). Presence of a CH group was indicated by a multiplet ranging from δ 4.22-4.20 (1H) in the ^{1}H NMR spectrum. On the basis of all the spectral data and the X-ray diffraction studies conducted, we could find out the exact structure as **54** for the 1:2 adduct.

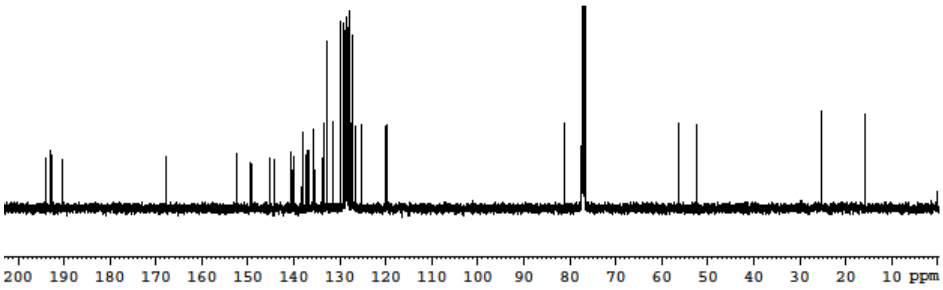


Figure 3.12 ^{13}C NMR spectrum of **54**

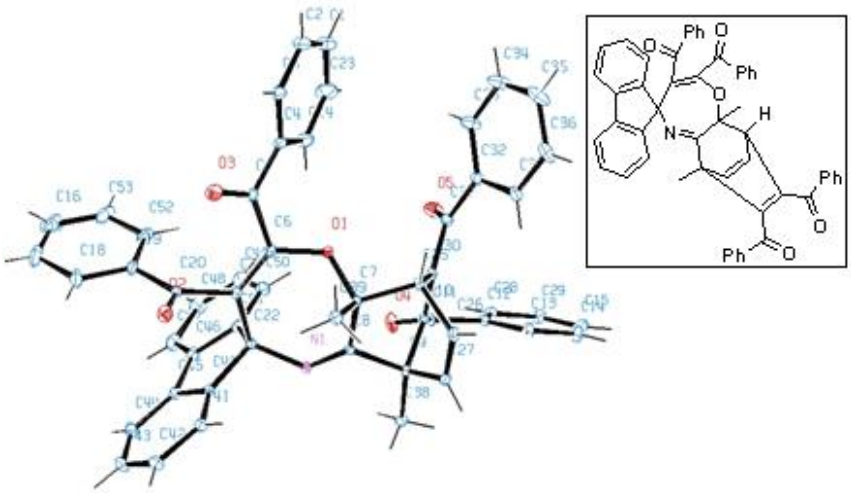


Figure 3.13 ORTEP diagram of molecular structure of **54**

Among the 1:1 adducts the structure of the one, which was obtained in major yield compared to the other, was analysed on the basis of spectral data. This compound was obtained as the third fraction from column chromatography {50% (EtOAc/Hexane)}. Two methyl groups in the cited compound were identified by the presence of a singlet at δ 2.36 (s, 6H) in the ^{1}H NMR, which is supported by a peak at δ 18.62 in the ^{13}C NMR spectrum. The remaining protons in the adduct extend from δ 7.86 to 6.94 in the ^{1}H NMR spectrum. Different carbonyl environments in the 1:1 adduct were revealed by the presence of peaks at δ 203.48, 188.90, and 185.08 in the ^{13}C NMR spectrum. Presence of carbonyl groups in the compound is supported by a sharp peak at 1669 cm^{-1} in the IR spectrum. On the basis of all the spectral and analytical data, we proposed a structure **55** for the mentioned adduct which was further confirmed by the crystal data analysis (Figure 3.14).

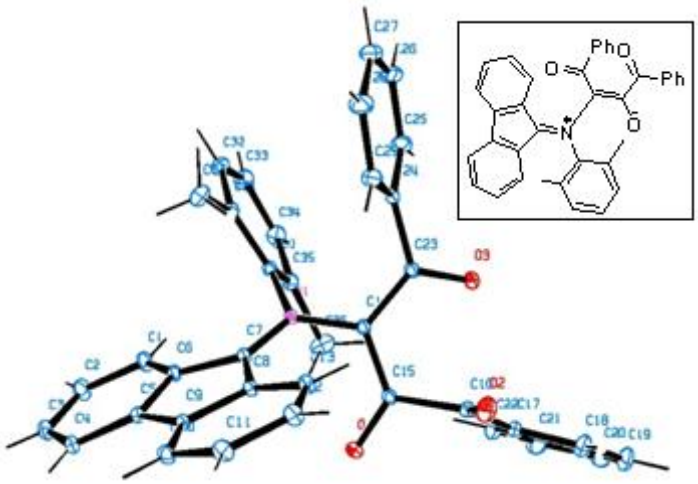


Figure 3.14 ORTEP diagram of molecular structure of **55**

The fourth fraction, the compound analogous to **B** was obtained only in minor quantity. Spectral analysis revealed that, it is a derivative of 3(*2H*)-furanone having the structure **56** similar to **B**.

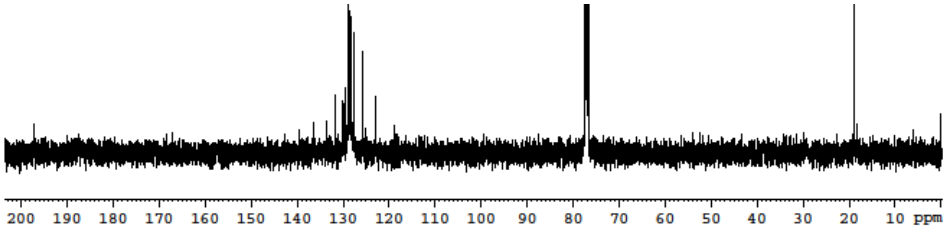


Figure 3.15 ^{13}C NMR spectrum of **56**

The spectral data of the second 1:1 adduct which we obtained in lesser amount was analysed. This was the final fraction and was eluted with 10% methanol in ethyl acetate. A sharp peak at 1389 cm^{-1} in the IR spectrum indicated the presence of a C-N bond in the mentioned compound. ^{13}C NMR spectrum of the adduct showed several signals at δ

198.10, 173.85, 136.76, 135.55, 134.06, 132.31, 130.96, 129.97, 129.47, 128.61, 127.64, 124.00, 122.07, 119.99, 112.54, 22.57 and 18.25. The peak at δ 198.10 in the ^{13}C NMR spectrum showed the presence of a C=O group. This carbonyl group appeared at 1656 cm^{-1} in the IR spectrum. Presence of two methyl groups in different environments was indicated by the peaks at δ 2.32 (s, 3H) and δ 2.01 (s, 3H) in the ^{1}H NMR spectrum, and this appeared at δ 22.57 and δ 18.25 respectively in the ^{13}C NMR spectrum of the said compound. The remaining aromatic protons extended from δ 9.11 to δ 6.72 in the ^{1}H NMR spectrum, which included peaks at δ 9.09 (d, *J* =7.2Hz, 1H), 8.88-8.78 (m, 2H), 8.19 (t, *J* = 7.4Hz, 1H), 7.98-6.72 (m, 17H). Based on all the spectral and analytical data we assumed the structure **57** for this highly polar 1:1 adduct (Scheme 3.12). The structure was finally established from single crystal X-ray diffraction analysis (Figure 3.16).

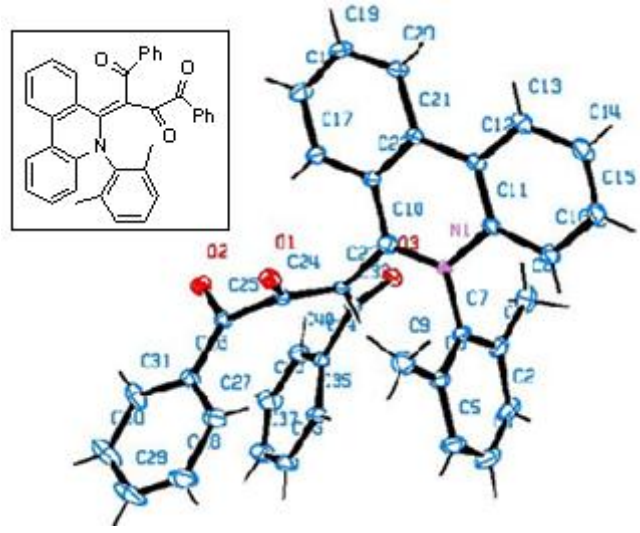
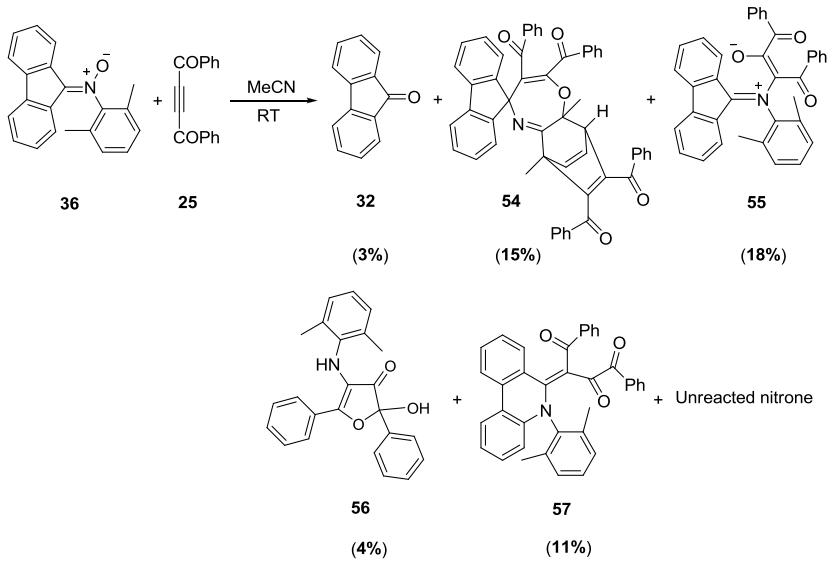


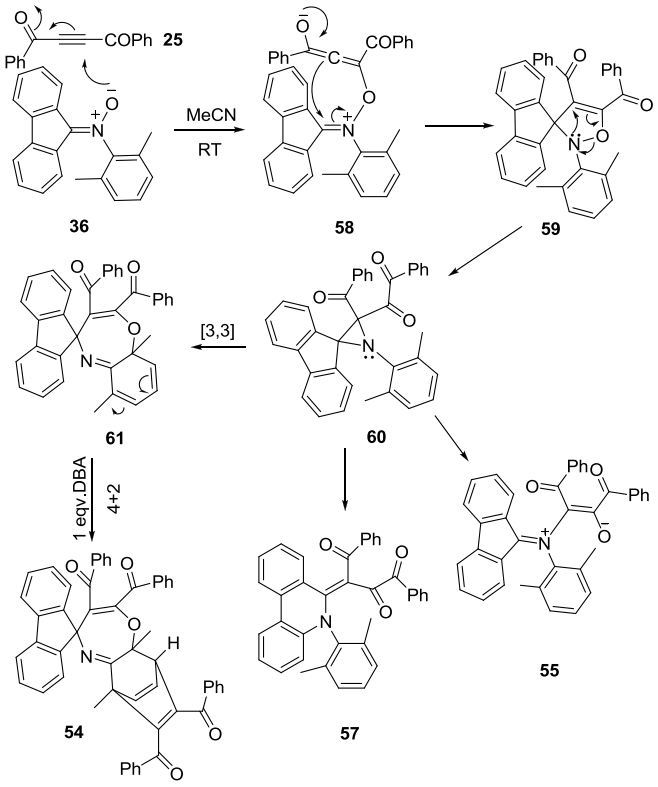
Figure 3.16 ORTEP diagram of molecular structure of **57**



36 25 32 (3%) 54 (15%) 55 (18%) 56 (4%) 57 (11%)

Scheme 3.12

When the two ortho positions of the *N*-phenyl ring are substituted by methyl groups, the initially formed ionic intermediate **58** cannot undergo [3,3] sigmatropic rearrangement with *N*-aryl ring. So it undergoes intramolecular cyclization to produce an isoxazoline intermediate **59**, which readily rearranges to an aziridine intermediate **60**. Subsequent rearrangement of the transient aziridine intermediate results in the formation of dipolar species **55** and **57** where as a [3,3] sigmatropic rearrangement results in the formation of **61**. When an additional molecule of DBA adds to the diene part of the ring enlarged intermediate **61** in a Diels Alder addition manner, 1:2 adduct **54** is formed (Scheme 3.13).



Scheme 3.13

3.3.5.4. Reaction of *N*-Fluorenylidene-*N*-(2,4,6-trimethylphenyl)nitrone with DBA

The reaction between *N*-fluorenylidene-*N*-(2,4,6-trimethylphenyl)nitrone **37** with DBA was quite exceptional. Even though DBA used in the reaction was totally consumed in 48h, we could not observe any significant change in concentration of the nitrone. The products were separated by column chromatography using silica gel. Surprisingly we could observe the formation of derivatives of DBA along with smaller amount of a dipolar species. Among the DBA derived compounds, one is identified as dibenzoylethylene (DBE) **62** by

comparing it with authentic sample. From the analytical and spectral data, the second compound was identified as tetrabenzoylbenzene **63**. In the ^{1}H NMR spectrum (Figure 3.17) the singlet at δ 7.83 corresponds to two equivalent hydrogen atoms present in the benzene ring of the compound **63**.

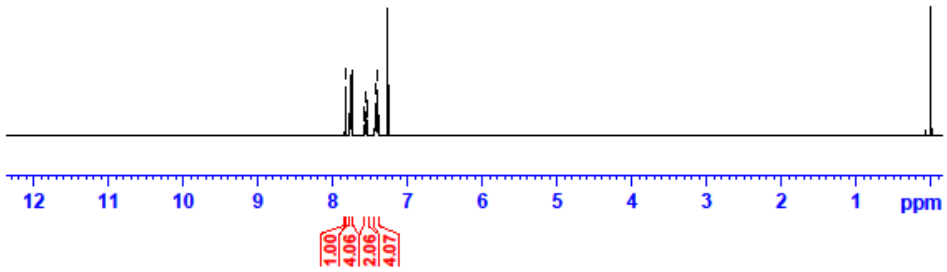
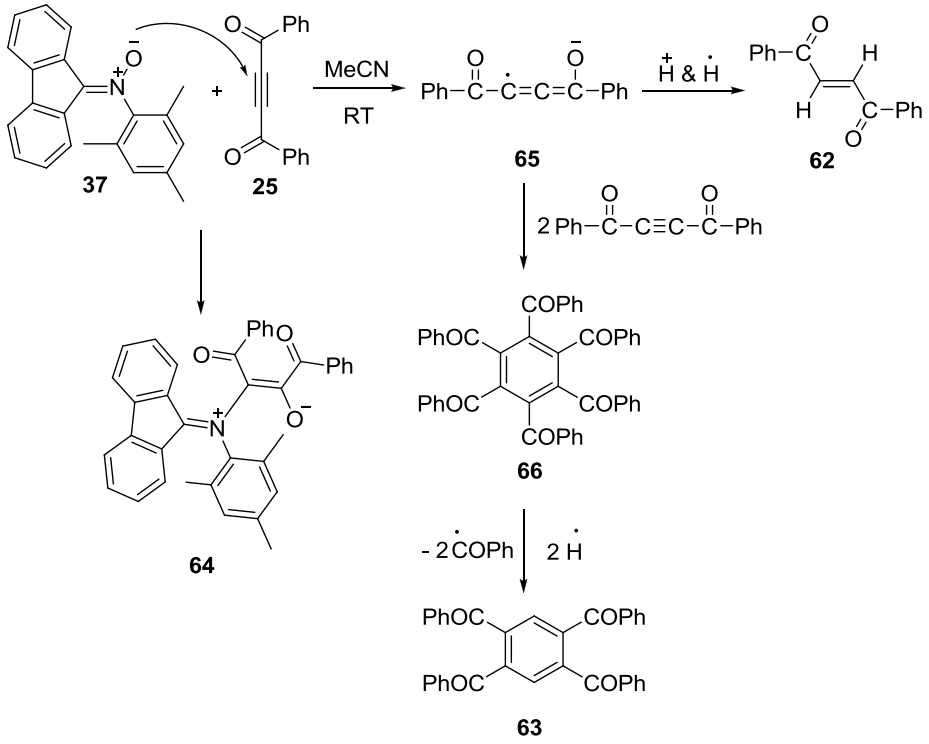


Figure 3.17 ^{1}H NMR spectrum of **63**

The dipolar intermediate was analogous to that obtained in the reaction of *N*-fluorenylidiene-*N*-(2,6-dimethylphenylnitrone) with DBA, and its structure was identified as **64** on the basis of analytical and spectral data. It appears that, when the para as well as the two ortho positions of the *N*-aryl ring are substituted by methyl groups, electron availability on nitrone increases. So electron transfer occurs from nitrone to DBA resulting in the formation of electron transfer-mediated products such as DBE and tetrabenzoylacetylene (Scheme 3.14).

It is assumed that in the reaction of *N*-fluorenylidene-*N*-(2,4,6-trimethyl phenylnitrone) **37** with DBA **25**, an electron is transferred from nitrone to DBA. The radical anion **65** thus formed adds a proton and hydrogen radical to form DBE **62**. And in the case of tetrabenzoylacetylene **63**, the radical anion adds two additional molecules

of DBA to form hexabenzoyl benzene **66**, which further undergoes debenzoylation and subsequent hydrogen radical abstraction to form the tetrabenzoyl derivative **63**.



Scheme 3.14

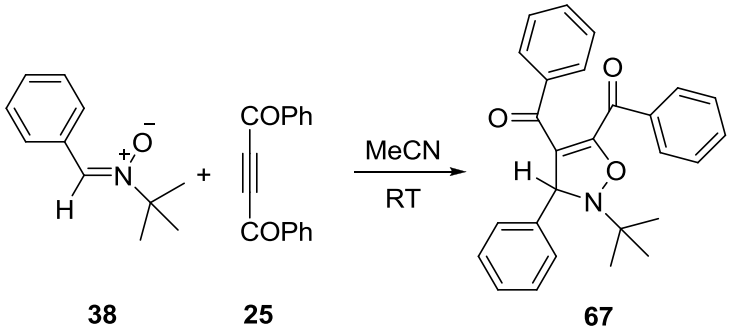
From reaction of substituted *N*-arylnitrones with DBA it can be concluded that, the 1,3-dipolar cycloaddition reaction of nitrone and electron deficient acetylene definitely includes a zwitterion mediated stepwise addition pathway and when both of the ortho positions of the *N*-aryl ring are substituted, one of the pathways, that is the rearrangement of the initially formed zwitterion intermediate gets supressed, and in such cases the products will be formed by the cyclization of the intermediate.

3.3.6 Reactions of *N*-alkylnitrones

Finally we blocked the possibility for a [3,3] sigmatropic rearrangement by the use of *N*-alkyl ring instead of *N*-aryl ring. We conducted the cycloaddition reaction of two different *N*-alkyl nitrones with DBA.

3.3.6.1. Reaction of *C*-Phenyl-*N*-*tert*-butylnitrone with DBA

We conducted the cycloaddition reaction of phenyl-*N*-*tert*-butylnitrone **38** with DBA **25** (1:1 molar ratio) in acetonitrile at RT. The reaction was completed in 6h and we obtained a single product. From mass data, the compound was identified as a 1:1 adduct of the two reactants. Presence of sharp peaks at δ 69.54 and δ 61.84 indicated the presence of quaternary carbon atoms in the compound. One of the peaks, that is at δ 61.84 vanished on recording the DEPT 135 spectrum, indicated the presence of a –CH group in the adduct, which is further established by the singlet at δ 6.00 (s, 1H) in the ^{1}H NMR spectrum. The CH_3 group in the compound was indicated by the singlet at δ 1.27 (s, 9H) in the ^{1}H NMR, and at δ 25.00 in the ^{13}C NMR spectrum (Figure 3.18). All the other aromatic protons appeared as multiplets from δ 7.76-7.70 in the ^{1}H NMR spectrum. On analysing the spectral data we identified the new product as isoxazoline **67** (Scheme 3.15) and this structure was further confirmed from X-ray diffraction studies (Figure 3.19).



38 **25** **67**

Scheme 3.15

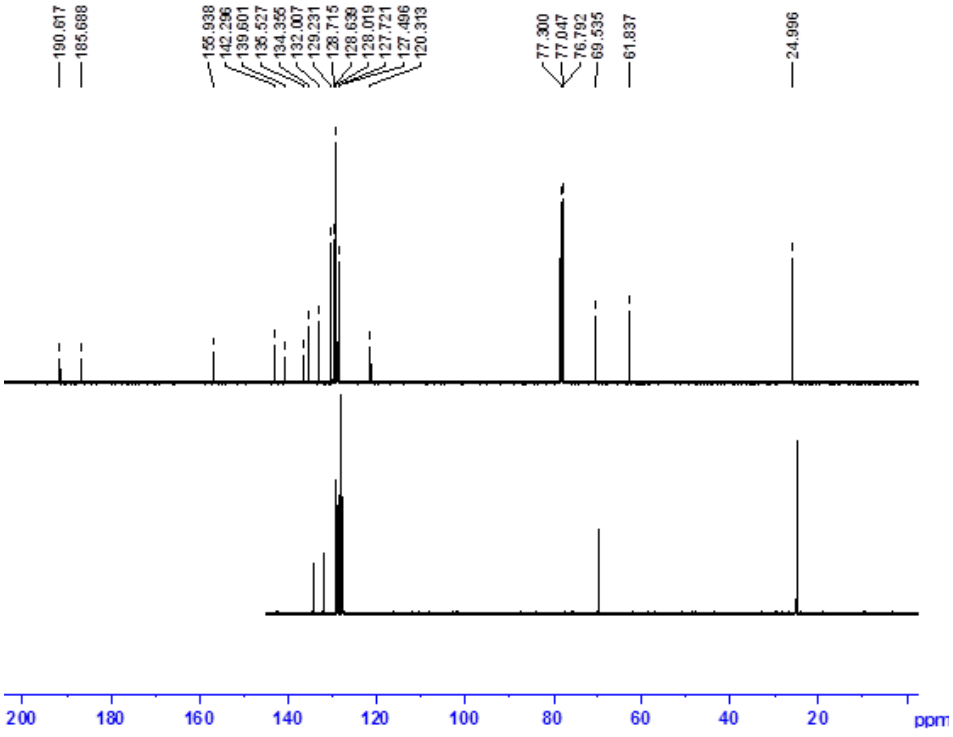


Figure 3.18 ^{13}C NMR and DEPT spectrum of **67**

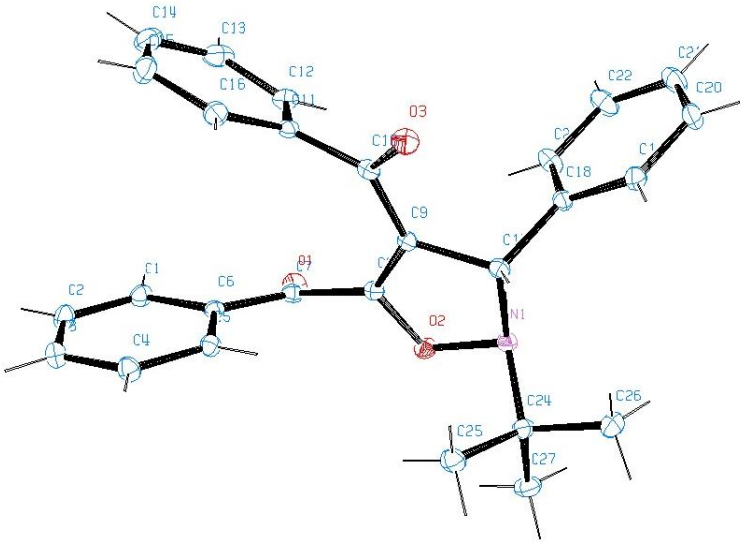


Figure 3.19 ORTEP diagram of molecular structure of **67**

3.3.6.2. Reaction of *N*-Naphthylidene-*N*-benzylnitrone with DBA

In the reaction of *N*-benzylnitrone **39** with DBA **25** also we got a single product **68** and it was identified as isoxazoline **67** on the basis of spectral data (Scheme 3.16). Here we could detect the –CH proton of the isoxazoline ring at δ 6.50 (s, 1H) and at δ 71.65 in the ^{1}H NMR and ^{13}C NMR spectra respectively. The $-CH_2$ protons in **68** are diastereotopic in nature and appeared as two doublets at δ 4.60 (d, J = 13.2 Hz, 1H) and at δ 4.46 (d, J = 13.2 Hz, 1H) in the ^{1}H NMR spectrum (Figure 3.20), which is indicated by a sharp peak at δ 64.13 in the ^{13}C NMR spectrum.

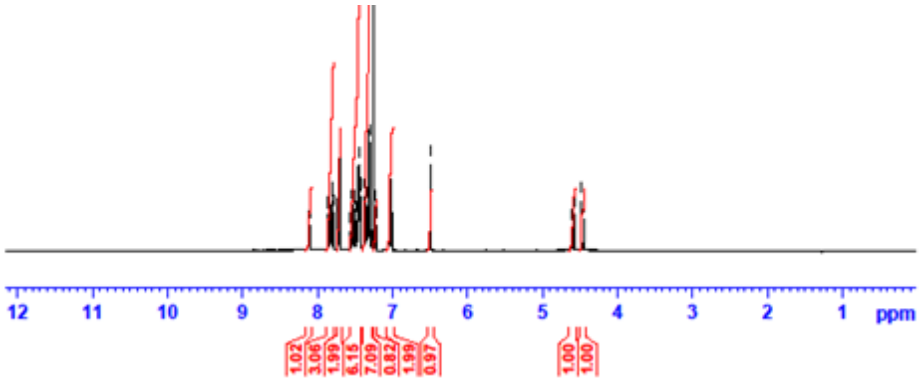


Figure 3.20 ^{1}H NMR spectrum of **68**

Different carbonyl environments were indicated by the peaks at δ 190.45 and 185.73 in the ^{13}C NMR spectrum. The proposed isoxazoline structure **68** was further established using single crystal X-ray diffraction technique (Figure 3.21).

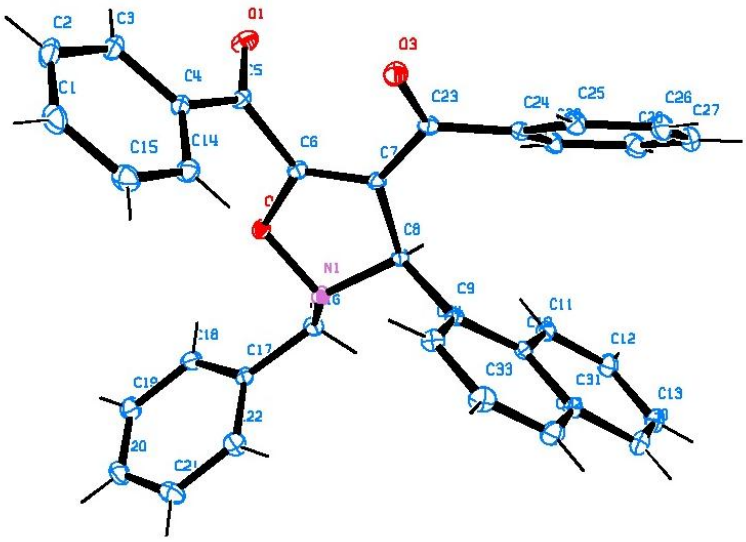
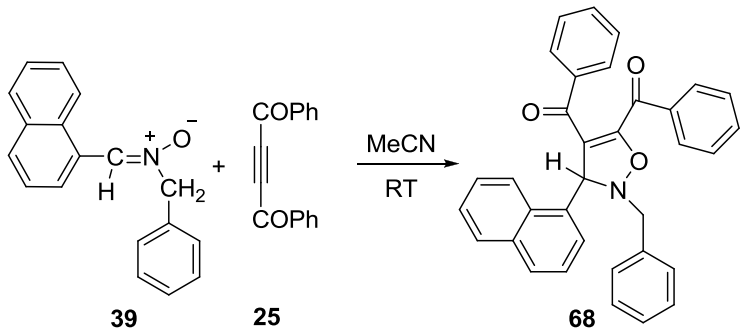
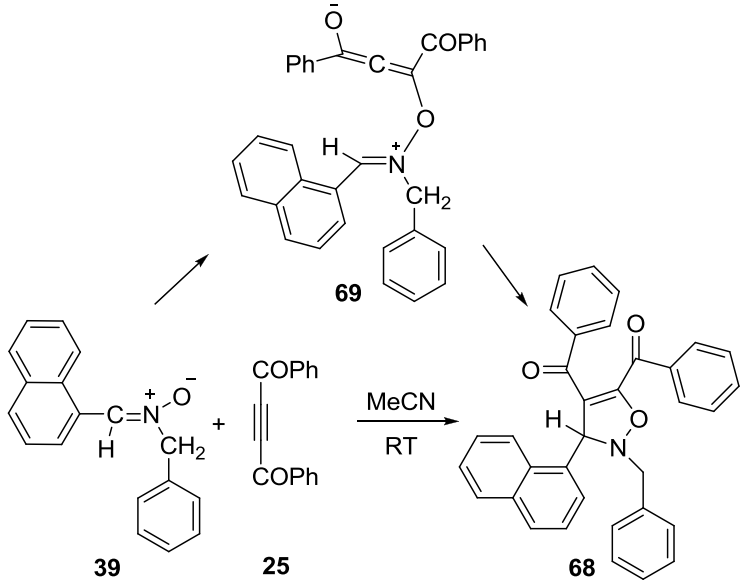


Figure 3.21 ORTEP diagram of molecular structure of **68**



Scheme 3.16

When *N*-alkylnitrone is used, the initially formed zwitterion **69** cannot undergo a [3,3] rearrangement mediated reaction pathway, so it readily undergoes intramolecular cyclization resulting in the formation fairly stable isoxazoline derivatives (Scheme 3.17). Cycloaddition reactions of *N*-alkylnitrones with DBA provide additional evidences for the proposed mechanism.



Scheme 3.17

3.4. Experimental Section

3.4.1. General Techniques

All reactions were carried out utilizing oven dried glasswares. Solvents used for the experiments were distilled and dried by employing standard protocols. All the reagents were purchased from either *Sigma-Aldrich* or *Spectrochem Chemicals* and were used without further purification. Progress of the reaction and chromatographic separations were monitored by dried silica gel TLC plates (Aluminium sheets coated with silica gel, *E. Merck*). Visualisation of TLC plates was achieved by exposure to UV lamp and iodine vapours. Separation and purification of compounds were done by column chromatography using silica gel (*Spectrochem Chemicals*, 60-120 mesh). The products were further purified by recrystallization from suitable solvent systems. Solvent eluted from the column chromatography was concentrated using *Heidolph, IKA or Buchi* rotary evaporators. Melting points were determined on a *Neolab* melting point apparatus and are uncorrected. Infrared spectra were recorded on *Jasco 4100* and *ABB Bomem (MB Series)* FT-IR spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz *Bruker Avance III* FT-NMR spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS. Elemental analysis was performed using *Elementar Systeme (Vario EL III)*. Molecular mass was determined by electron impact (EI) method using GC-MS (*Agilent GC-7890A, Mass-5975C*) and fast atom bombardment (FAB) using *JMS 600 JEOL* mass spectrometer. Here we are giving the spectral and analytical data only for

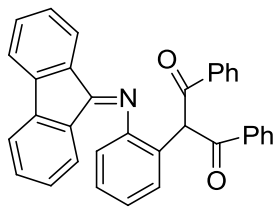
novel compounds and pertinent references are cited for known compounds.

3.4.2. General Procedure for Cycloaddition Reaction.

A mixture of nitrone (4 mmol) and acetylene (4 mmol) in 25 mL of acetonitrile was stirred for about 6h at RT. Progress of the reaction was monitored by TLC. When the reaction was complete, products were isolated by column chromatography over silica gel using mixtures of hexane and ethyl acetate as eluents. The products were further purified by recrystallization from hexane-DCM mixture.

3.4.3. Spectral and Analytical data of Significant Compounds

3.4.3.1. Compound 41



mp: 174°C.

IR ν_{max} (KBr): 3052cm^{-1} (=C-H stretch), 1697cm^{-1} (C=O stretch), 1649cm^{-1} (C=N stretch).

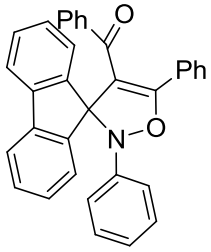
^{1}H NMR ($CDCl_3$): δ 7.93-6.90 (m, 22H), 6.69 (d, *J* = 8Hz, 1H)

^{13}C NMR ($CDCl_3$): δ 194.50, 142.08, 137.25, 136.19, 133.10, 132.16, 130.94, 128.67, 128.59, 128.56, 128.38, 128.00, 127.29, 124.97, 124.06, 123.16, 120.09, 119.68, 118.71, 56.96.

MS: *m/z* 477 (M^+), 478 (M+1).

Elemental analysis calculated for $C_{34}H_{23}NO_2$:- C: 85.51, H: 4.85, N: 2.93 Found: C: 85.45, H: 4.82, N: 2.89.

3.4.3.2. Compound 42



mp: 142°C.

IR ν_{max} (KBr): 3062cm^{-1} (=C-H stretch), 1633cm^{-1} (C=O stretch).

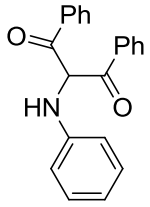
^{1}H NMR ($CDCl_3$): δ 7.65-7.28 (m, 11H), 7.21-7.16 (m, 5H), 7.06-6.93 (m, 4H), 6.82-6.78 (m, 1H), 6.65-6.62 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 189.91, 162.45, 145.90, 144.57, 140.81, 138.40, 131.00, 129.84, 129.30, 129.15, 128.14, 127.78, 127.72, 127.29, 124.97, 123.54, 120.16, 117.01, 115.32, 85.84.

MS: *m/z* 477 (M^+), 478 (M+1).

Elemental analysis calculated for $C_{34}H_{23}NO_2$:- C: 85.51, H: 4.85, N: 2.93. Found: C: 85.48, H: 4.83, N: 2.88.

3.4.3.3. Compound 43



mp: 70°C.

IR ν_{max} (KBr): 3373cm^{-1} (N-H stretch), 3054cm^{-1} (=C-H stretch), 2854cm^{-1} (-C-H stretch), 1661cm^{-1} (C=O stretch), 1506cm^{-1} (N-H) bend.

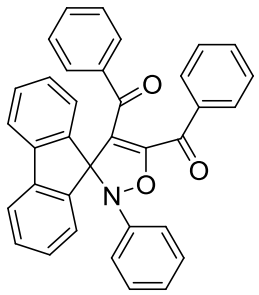
^{1}H NMR ($CDCl_3$): δ 8.05-8.03 (m, 4H), 7.55-7.51 (m, 2H), 7.40 (t, *J* = 7.8Hz, 4H), 7.20-7.16 (m, 2H), 6.79-6.73 (m, 3H), 6.04 (d, *J* = 5.6Hz, 1H), 5.62 (d, *J* = 5.6Hz, 1H).

^{13}C NMR ($CDCl_3$): δ: 194.87, 145.99, 134.60, 134.02, 131.22, 129.47, 129.40, 129.34, 128.71, 128.16, 128.10, 118.81, 113.59, 113.10, 70.90.

MS: *m/z* 315 (M^+), 316 (M+1).

Elemental analysis calculated for $C_{21}H_{17}NO_2$:- C: 79.98, H: 5.43, N: 4.44. Found: C: 79.95, H: 5.41. N: 4.42.

3.4.3.4. Compound 28



mp: 120°C.

IR ν_{max} (KBr): 3061cm^{-1} (=C-H stretch), 1641cm^{-1} (C=O stretch).

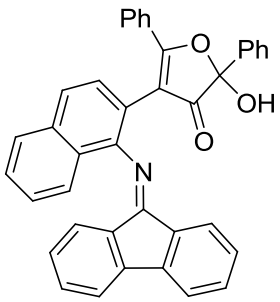
^{1}H NMR ($CDCl_3$): δ 7.70-7.54 (m, 7H), 7.41-7.34 (m, 6H), 7.28-7.24 (m, 3H), 7.07-6.80 (m, 5H), 6.61-6.58 (m, 2H).

^{13}C NMR ($CDCl_3$): δ: 188.77, 184.25, 156.35, 145.71, 143.97, 140.60, 139.43, 135.99, 134.36, 132.15, 129.67, 129.43, 128.78, 128.26, 128.16, 128.04, 127.99, 125.32, 123.69, 122.61, 120.35, 116.57, 85.12.

MS: *m/z* 505 (M^+), 506 (M+1).

Elemental analysis calculated for $C_{35}H_{23}NO_3$:- C: 83.15, H: 4.59, N: 2.77. Found: C: 83.11, H: 5.56, N: 2.75.

3.4.3.5. Compound 50



mp: 132°C.

IR ν_{max} (KBr): 3281cm^{-1} (O-H stretch), 1682cm^{-1} (C=O stretch), 1647 cm^{-1}(C=N stretch).

^{1}H NMR ($CDCl_3$): δ 7.92-6.22 (m, 24H), 4.38 (s, 1H).

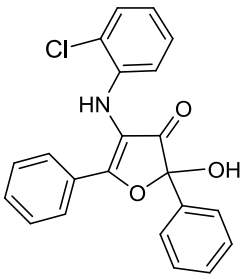
^{13}C NMR ($CDCl_3$): 199.23, 178.21, 171.19, 146.62, 135.60, 133.83, 132.53, 131.85,

128.61, 128.31, 128.18, 127.86, 126.67, 126.52, 125.72, 124.91, 124.43, 124.24, 123.63, 123.28, 119.67, 119.37, 112.71.

MS: *m/z* 555 (M^+), 556 (M+1).

Elemental analysis calculated for $C_{39}H_{25}NO_3$:- C: 84.31, H: 4.54, N: 2.52. Found: C: 83.26, H: 5.53, N: 2.49.

3.4.3.6. Compound 51



mp: 142°C.

IR ν_{max} (KBr): 3356cm^{-1} (N-H stretch), 3071cm^{-1} (=C-H stretch), 1707cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 8.14-6.38 (m, 14H), 5.57 (s, 1H) 4.82 (s, 1H).

^{13}C NMR ($CDCl_3$): δ: 197.92, 177.49, 140.46, 135.52, 133.28, 129.81, 129.49, 128.94, 128.82, 128.34, 128.13, 127.65, 125.68, 120.50, 119.88 113.99, 113.63, 101.39.

MS: *m/z* 377 (M^+), 378 (M+1).

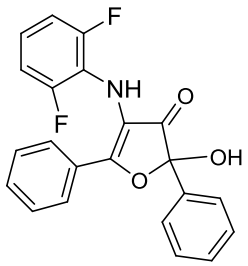
Elemental analysis calculated for $C_{22}H_{16}ClNO_3$:- C: 69.94, H: 4.27, N: 3.71. Found: C: 69.88, H: 4.26, N: 3.67.

3.4.3.7. Compound 53

mp: 90°C.

IR ν_{max} (KBr): 3341cm^{-1} (N-H stretch), 3066cm^{-1} (=C-H stretch), 1691cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 8.24 (d, *J* = 7.6Hz, 2H), 7.66-6.66 (m, 11H), 4.97 (s, 1H), 4.32



(s, 1H).

^{13}C NMR ($CDCl_3$): δ: 197.45, 175.26, 172.14, 163.18, 154.87, 152.28, 147.99, 137.61, 135.60, 132.82, 129.68, 128.75, 128.67, 128.26, 125.75, 119.20, 116.04, 111.73, 111.50, 101.26.

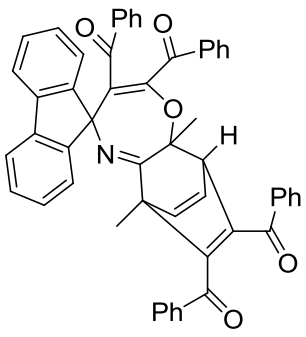
MS: *m/z* 379 (M^+), 380 (M+1).

Elemental analysis calculated for $C_{22}H_{15}F_2NO_3$:- C: 69.65, H: 3.99, N: 3.69. Found: C: 69.58, H: 3.97, N: 3.65.

3.4.3.8. Compound 54

mp: 242°C.

IR ν_{max} (KBr): 3055cm^{-1} (=C-H stretch), 2875cm^{-1} (-C-H stretch), 1671cm^{-1} (C=O stretch).



^{1}H NMR ($CDCl_3$): δ: 7.77-7.74 (m, 3H), 7.57-7.24(m, 18H), 7.15-7.07 (m, 5H), 6.98-6.89 (m, 3H), 6.50-6.48 (m, 1H), 4.22-4.20 (m, 1H), 2.07 (s, 3H), 1.34 (s, 3H).

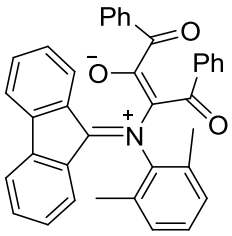
^{13}C NMR ($CDCl_3$): δ: 193.91, 192.80, 192.69, 190.36, 167.87, 152.47, 149.49, 149.20, 145.13, 144.22, 140.15, 138.17, 137.27, 137.10, 136.84, 135.75, 135.60, 133.84, 133.44, 132.83, 131.46, 129.84, 129.19, 128.82, 128.76, 128.62, 128.45, 128.34, 128.15, 128.01, 127.43, 127.18, 126.55, 125.36, 119.92, 119.86, 81.14, 56.38, 52.44, 25.29, 15.70.

MS: *m/z* 767 (M^+), 768 (M+1).

Elemental analysis calculated for

$C_{53}H_{37}NO_5$:- C: 82.90, H: 4.86, N: 1.82. Found: C: 82.85, H: 4.82, N: 1.79.

3.4.3.9. Compound 55



mp: 236°C.

IR ν_{max} (KBr): 3055cm^{-1} (=C-H stretch), 1669cm^{-1} (C=O stretch).

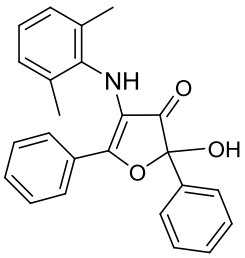
^{1}H NMR ($CDCl_3$): δ 7.86-7.84 (m, 2H), 7.52-7.47 (m, 3H), 7.40-7.04 (m, 14H), 6.86 (t, *J* =7.6Hz, 2H), 2.36 (s, 6H).

^{13}C NMR ($CDCl_3$): δ: 203.48, 188.90, 185.08, 141.49, 140.69, 134.57, 134.29, 133.17, 132.96, 130.34, 130.22, 129.42, 128.14, 127.74, 126.98, 123.70, 120.62, 18.62.

MS: *m/z* 533 (M^+), 534 (M+1).

Elemental analysis calculated for $C_{37}H_{27}NO_3$:- C: 83.28, H: 5.10, N: 2.62. Found: C: 83.25, H: 5.07, N: 2.60.

3.4.3.10. Compound 56



mp: 138°C

IR ν_{max} (KBr): 3374cm^{-1} (N-H stretch), 3062cm^{-1} (=C-H stretch), 1671cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 7.94 (d, 2H, *J* =7.2Hz), 7.66-6.80 (m, 11H), 4.67 (s, 1H), 3.98 (s, 1H), 2.09 (s, 6H).

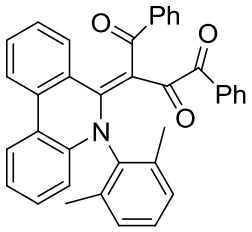
^{13}C NMR ($CDCl_3$): δ: 197.18, 168.33, 142.60, 139.58, 136.31, 133.59, 131.61, 130.17, 129.87, 129.63, 128.92, 128.78, 128.70, 128.46, 128.28, 127.62, 125.79,

122.94, 118.91, 18.85.

MS: *m/z* 371 (M^+), 372 (M+1).

Elemental analysis calculated for $C_{24}H_{21}NO_3$:- C: 77.61, H: 5.70, N: 3.77, O: 12.92; Found: C: 77.58, H: 5.69, N: 3.75.

3.4.3.11. Compound 57



mp: 238°C.

IR ν_{max} (KBr): 3061cm^{-1} (=C-H stretch), 1656cm^{-1} (C=O stretch), 1389cm^{-1} (C-N stretch).

^{1}H NMR ($CDCl_3$): δ 9.09 (d, *J* =7.2Hz, 1H), 8.88-8.78 (m, 2H), 8.19 (t, *J* =7.4Hz, 1H), 7.98-6.72 (m, 17H), 2.32 (s, 3H), 2.01 (s, 3H).

^{13}C NMR ($CDCl_3$): δ: 198.10, 173.85, 136.76, 135.55, 134.06, 132.31, 130.96, 129.97, 129.47, 128.61, 127.64, 124.00, 122.07, 119.99, 112.54, 22.57, 18.25.

MS: *m/z* 533 (M^+), 534 (M+1).

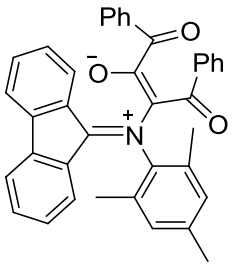
Elemental analysis calculated for $C_{37}H_{27}NO_3$:- C: 83.28, H: 5.10, N: 2.62, O: 8.99; Found: C: 83.25, H: 5.08, N: 2.57.

3.4.3.12. Compound 64

mp: 210°C.

IR ν_{max} (KBr): 2962cm^{-1} (-C-H stretch), 1671cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 7.85-7.83 (m, 2H), 7.52-7.46 (m, 3H), 7.40-7.11 (m, 11H), 6.96 (t, *J* =7.4Hz, 2H), 6.85 (s, 2H) 2.29 (s, 3H), 2.31 (s, 6H).

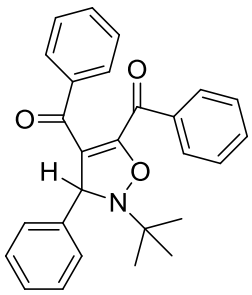


^{13}C NMR ($CDCl_3$): δ: 203.78, 192.31, 188.90, 142.04, 140.59, 134.36, 133.10, 132.85, 132.25, 131.85, 129.65, 128.87, 128.42, 128.32, 128.25, 127.79, 127.62, 127.39, 127.29, 127.07, 126.98, 126.84, 126.64, 126.16, 125.93, 119.52, 118.86, 28.68, 17.46.

MS: *m/z* 547 (M^+), 548 (M+1).

Elemental analysis calculated for $C_{38}H_{29}NO_3$:- C: 83.34, H: 5.34, N: 2.56. Found: C: 83.26, H: 5.33, N: 2.55

3.4.3.13. Compound 67



mp: 110°C.

IR ν_{max} (KBr): 3054 cm^{-1} (=C-H stretch), 1655cm^{-1} (C=O stretch).

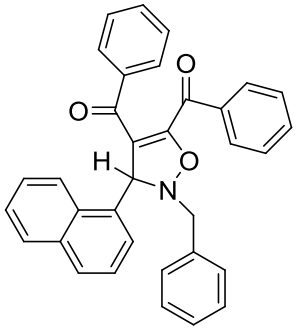
^{1}H NMR ($CDCl_3$): δ 7.76-7.703 (m, 15H), 6.00 (s, 1H), 1.27 (s, 9H).

^{13}C NMR ($CDCl_3$): δ: 190.62, 185.69, 155.94, 142.30, 139.60, 135. 53, 134.36, 132.01, 129.23, 128.72, 128.64, 128.02, 127.72, 127.50, 120.31, 61.84, 24.30.

MS: *m/z* 411 (M^+), 412 (M+1).

Elemental analysis calculated for $C_{27}H_{25}NO_3$:- C: 78.81, H: 6.12, N: 3.40. Found: C: 78.75, H: 6.09, N: 3.39.

3.4.3.14. Compound 68



mp: 134°C.

IR ν_{max} (KBr): 3057 cm^{-1} (-C-H stretch), 1677cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 8.12-8.10 (m, 1H), δ: 7.86-7.79 (m, 3H), 7.72-7.70 (m, 2H), 7.56-7.01 (m, 16H), 6.50 (s, 1H), 4.60 (d, *J* = 13.2Hz, 1H), 4.46 (d, *J* = 13.2Hz, 1H).

^{13}C NMR ($CDCl_3$): 190.45, 185.73, 155.88, 139.18, 135.71, 134.91, 134.51, 134.17 132.35, 131.26, 129. 90, 129. 47, 129.26, 128.92, 128.82, 128.81, 128.33, 128.23, 128.19, 126.46, 125. 82, 125.63, 123.50, 120.21, 71.65, 64.13.

MS: *m/z* 495 (M^+), 496 (M+1).

Elemental analysis calculated for $C_{34}H_{25}NO_3$:- C: 82.40, H: 5.08, N: 2.83

Found: C: 82.36, H: 5.05, N: 2.82.

3.5 References

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CHAPTER 4

SYNTHESIS OF SOME HIGHLY SUBSTITUTED QUINOLINE AND INDOLE DERIVATIVES

4.1. Abstract

This chapter briefly describes the synthesis of a few quinoline and indole derivatives using nucleophilic addition of nitrones to electron deficient acetylenes.

4.2. Introduction

In this section a brief introduction to the synthesis of quinolines and indoles is presented.

4.2.1. Quinolines

Quinoline (Figure 4.1) or 1-azanaphthalene is an aromatic heterocyclic compound in which a benzene ring is fused to a pyridine ring through two adjacent carbon atoms. Its chemical formula is C_9H_7N. It is a colourless hygroscopic liquid. Quinoline is naturally isolated from coal tar. It is slightly soluble in cold water, but readily in hot water and in most organic solvents. In lab, this compound is used as a high boiling basic solvent.

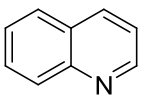


Figure 4.1

Quinoline itself has limited use, but its derivatives have a lot of applications in various field. This heterocyclic compound is used as the 'parental' compound to synthesize various pharmacologically active compounds with antimalarial, antibacterial, antiasthmatic, antiviral, antifungal, anti-inflammatory, antileishmanial, antimicrobial, anticancer activities.[1-20]

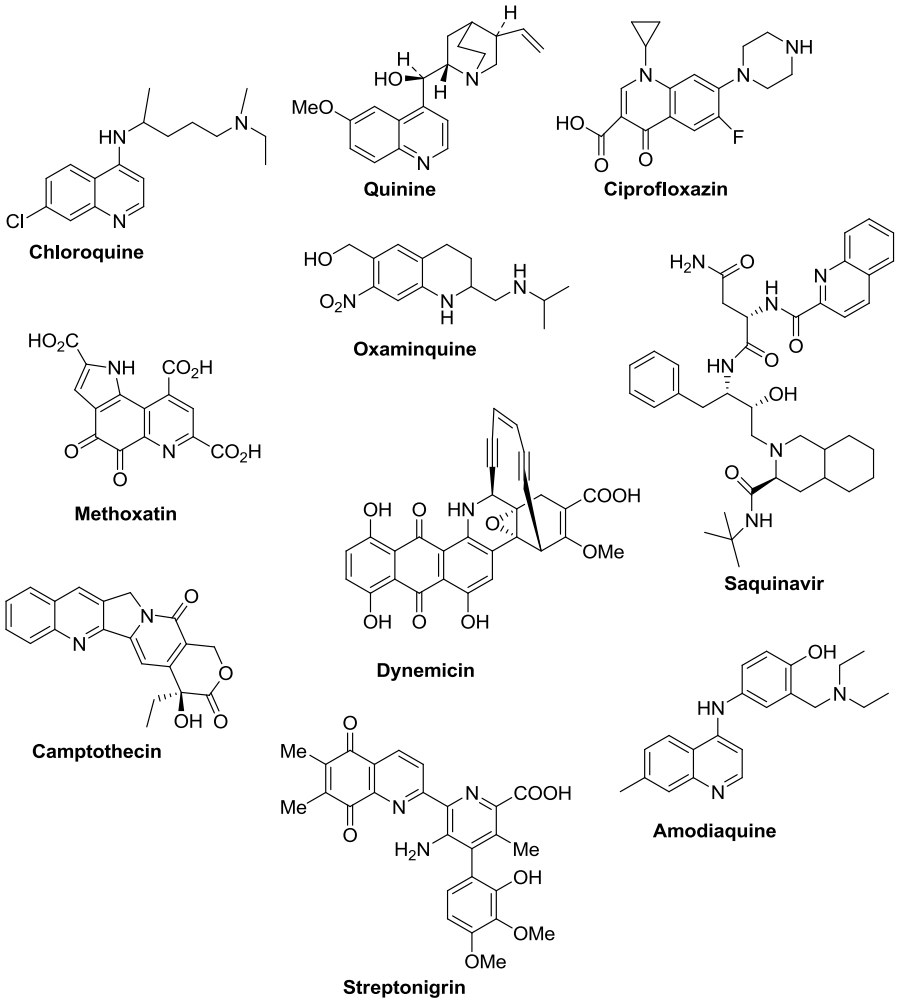
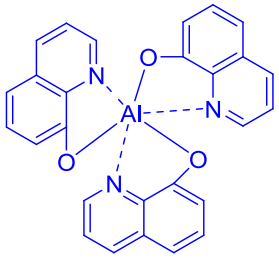


Figure 4.2

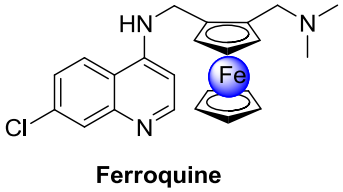
The alkaloid quinine, which is used in tonics, is a traditional anti-malarial drug. chloroquine, amodiaquine etc. are examples for synthetic drugs which exhibit significant antimalarial activity. Ciprofloxazin contains a 4-quinolone unit which is an antibiotic used in the infection of bones and joints, urinary tract as well as respiratory tract infections. Methoxatin is another quinoline derivative, act as a redox co-factor in alcohol dehydrogenase; it also acts as an antioxidant. Oxaminquine is a tetrahydroquinoline derivative used to eradicate blood flukes. Quinoline derivatives such as streptonigrin, dynemicin, camptothecin etc. exhibit effective anticancer activities. Saquinavir is an example for a quinoline based drug used in HIV therapy.

Quinolines find application in transition metal chemistry also.[21-24] Many quinoline derivatives are used in the synthesis of ligands, which form interesting complexes with transition metals (eg. salen complexes). In some cases transition metals provide additional stability to the drug and act as a better means of delivery to their desired targets. In ferroquine, a ferrocene moiety is incorporated into the lateral side chain of chloroquine. The hydrophobic ferrocene core enhances the lipophilicity and in turn enhances trans membrane interactions. Quinoline derivatives exhibit luminescence properties. **Alq_3** {**(**tris-(8-hydroxy-quinolinato) aluminium(III)} is an example for a quinoline based complex used in organic light emitting diodes.[25] Another application of these type of compounds is in the synthesis of dyes with vital applications. For example, cyanine dyes are used as sensitizers in photographic emulsions. This particular dye is formed by the base catalysed reaction of a methyl substituted quinolinium salt with *N*-ethyl-

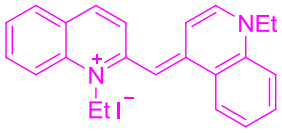
-quinolinium iodide.



Alq_3



Ferroquine



Cyanine dye

Figure 4.3

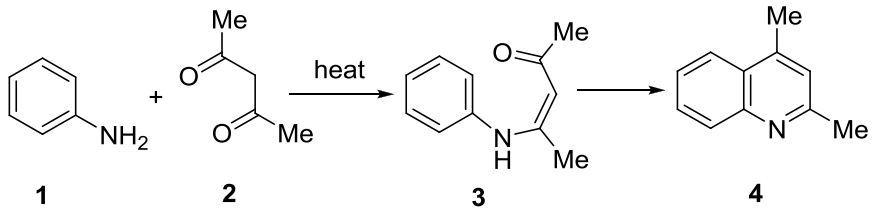
4.2.1.1. Methods for the Synthesis of Quinolines

Conventional methods for the synthesis of quinolines include: (a) Combes synthesis (b) Conrad–Limpach–Knorr synthesis (c) Doebner Miller synthesis (d) Scraup synthesis (e) Friedlander synthesis etc. In these five methods, aniline or its derivatives is used as the starting material.[26] Interestingly, in all these methods, except Friedlander synthesis, -CN bond formation arising through condensation or nucleophilic addition involving the amine functionality is the first step. In Friedlander synthesis, -CN bond formation is accomplished at a later stage.

(a) Combes synthesis

Here aniline is reacted with a 1,3-diketone such as **2** in the presence of an acid. The *β*- aminoenone **3** formed by the condensation of

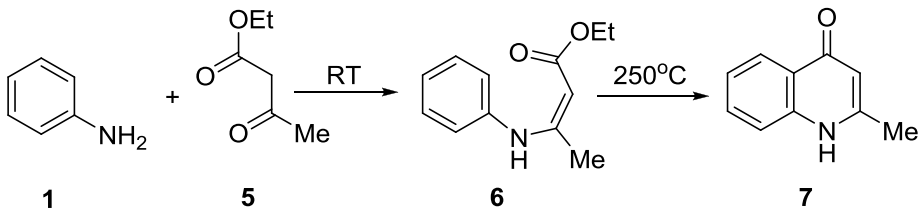
aniline with the carbonyl compound undergoes cyclization with concentrated H_2SO_4, which is followed by the loss of a water molecule to produce quinoline derivative **4** (Scheme 4.1).



Scheme 4.1

(b) Conrad–Limpach–Knorr synthesis

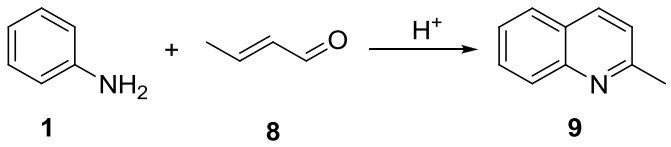
In Conrad–Limpach–Knorr synthesis, aniline is treated with a *β*-ketoester **5** at low temperature to give a *β*-aminoacrylate **6**. Cyclization of *β*-aminoacrylate gives a 4-quinolone derivative **7** (Scheme 4.2).



Scheme 4.2

(c) Doebner Miller synthesis

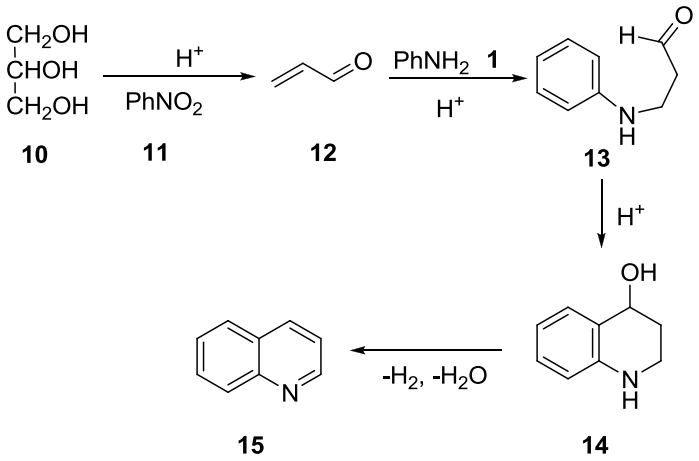
In this reaction, an *α*, *β*-unsaturated aldehyde such as **8** is added to aniline in a conjugate fashion. The process is catalysed by HCl or $ZnCl_2$ (Scheme 4.3).



Scheme 4.3

(d) Scraup synthesis

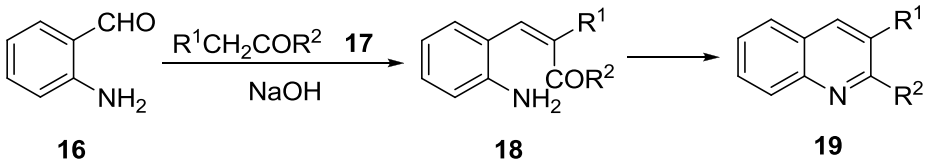
In Scraup synthesis aniline is heated with glycerol and sulphuric acid. At first glycerol is dehydrated to acrolein, which then adds to aniline in a conjugate addition manner. The intermediate is then cyclized, dehydrated, and then oxidized to give quinoline (Scheme 4.4).



Scheme 4.4

(e) Friedlander synthesis

Here 2-aminobenzaldehyde is cyclized with an α-methyleneketone **17** in the presence of a base (Scheme 4.5).

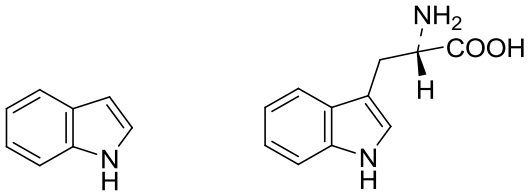


16 18 19

Scheme 4.5

4.2.2. Indoles

The indole unit (Figure 4.4) occurs naturally in a wide variety of structures and many of them have important physiological activities. It is a volatile crystalline solid, having a persistent odour. Indole is a very weakly basic compound. Most of the indole alkaloids are derived from the amino acid 'tryptophan.' Substituted indoles can bind to many receptors with high affinity.



Indole Tryptophan

Figure 4.4

Most of the naturally existing indole derivatives have medicinal applications.[27-34] For example, indole-3-acetic acid, a monosubstituted indole derivative, acts as a plant growth regulator. Indolone, a simple indole derivative occuring in some mushrooms, is a pigment involved in photosynthesis. Serotonin is another naturally occurring derivative of indole having a wide range of pharmacological properties. It helps in the contraction of blood vessels by the stimulation of smooth muscle and blood platelet aggregation, also act as a constrictor of arteries in the

brain. Variation in serotonin concentration in the brain produce changes in mood and in appetite. The indole derivative sumatriptan is used as a drug in the treatment of migraine. Ondansetron is a potent 5HT-3 antagonist, used to treat vomiting caused by cancer chemotherapy. Most of the important indole alkaloids have more complex structures than simple tryptamine derivatives. This is illustrated by ergot alkaloids. Ergotamine is a tetra cyclic indole alkaloid with a complex peptide based side chain unit. It is an effective vaso constrictor and is used as its tartrate salt in the treatment of migraine.

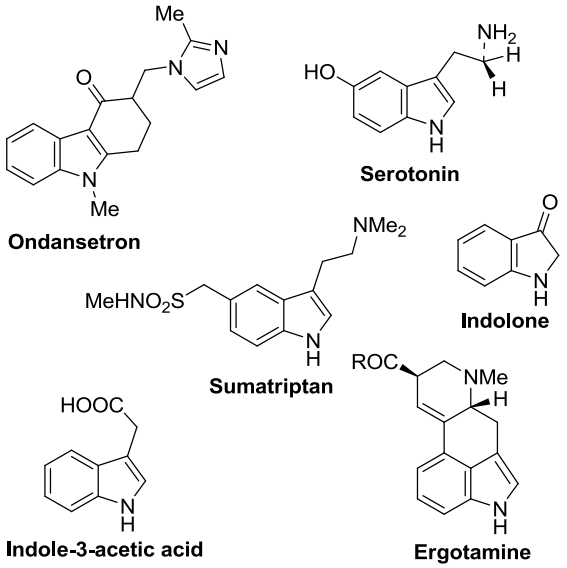


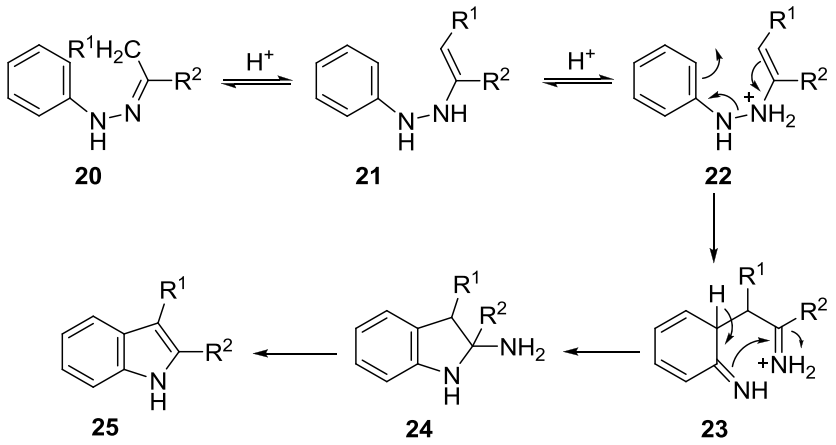
Figure 4.5

4.2.2.1. Methods for the Synthesis of Indoles

Among the reported procedures, some important synthetic methods include (a) Fischer synthesis (b) Bartoli synthesis and (c) Madelung synthesis.[35]

(a) Fischer synthesis

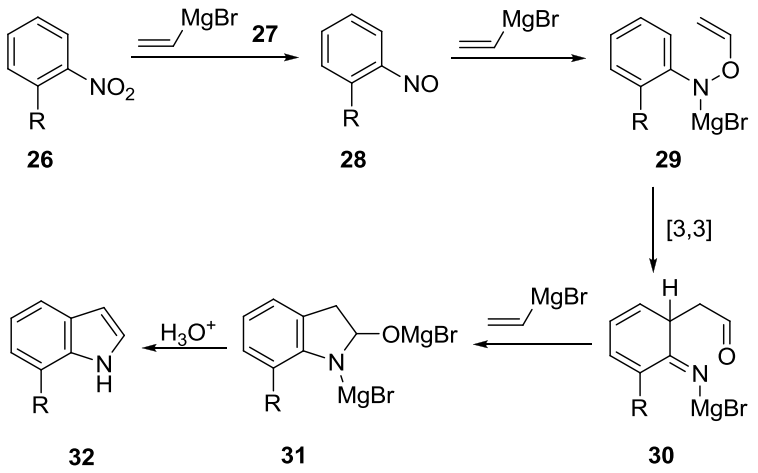
In this method, an arylhydrazone **20** is cyclized by heating with either a Brőnstead or Lewis acid catalyst (Scheme 4.6). $ZnCl_2$ is the most commonly used catalyst.



Scheme 4.6

(b) Bartoli synthesis

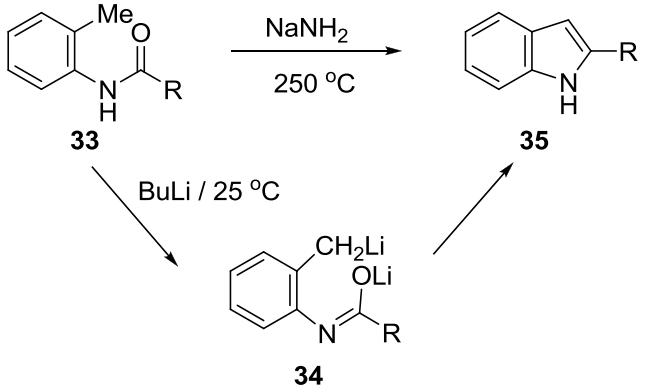
Here an ortho substituted nitrobenzene is reacted with 3 moles of vinylmagnesium bromide. The key step in this reaction also is a [3,3] sigmatropic rearrangement (Scheme 4.7).



Scheme 4.7

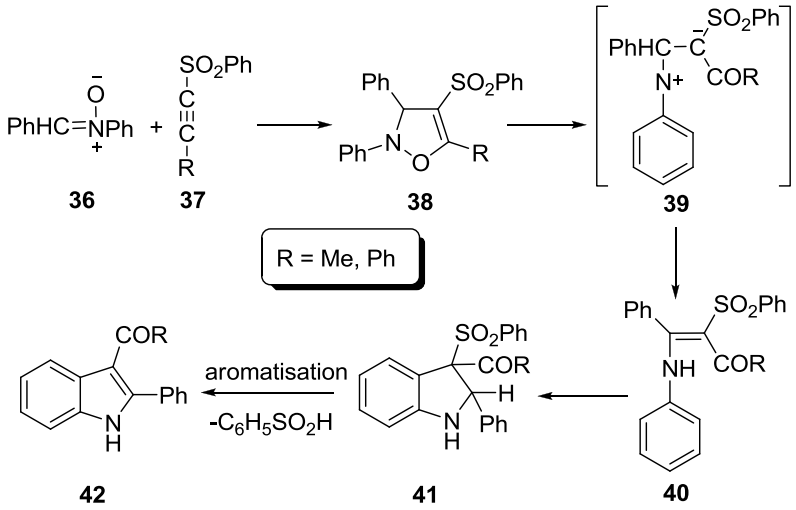
(c) Madelung synthesis

It involves the cyclization of 2-(acylamino)toluene **33** by strong base in the absence of air. High temperature is needed for the cyclization reaction. In a modified version of this method, butyllithium is used as the base at room temperature (Scheme 4.8).



Scheme 4.8

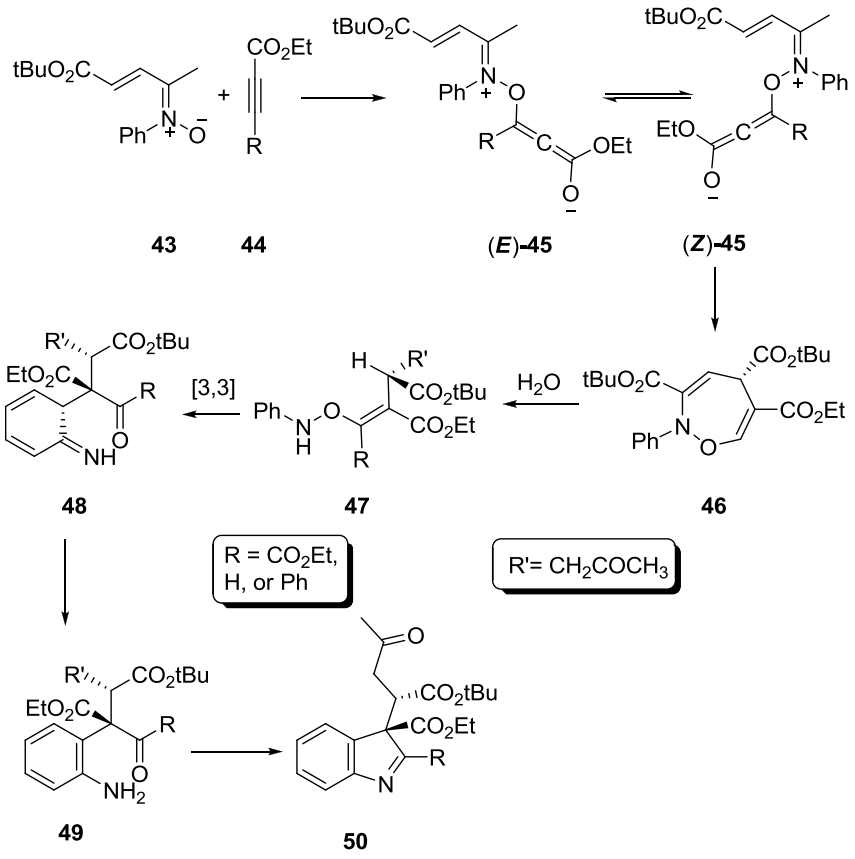
Apart from these general methods, several procedures are reported for the synthesis of specific indole derivatives. Parpani *et al*. reported the synthesis of 3-acylindole derivatives by the 1,3-dipolar cycloaddition of *C*,*N*-diphenylnitrone with (phenylsulfonyl) alkynes (Scheme 4.9).[36] According to authors, the isoxazoline derivative **38** formed at the initial stage, decomposed to **40** by the N-O bond cleavage and hydrogen migration. Then **40** underwent 1,5-cyclization on to the ortho position of the *N*-phenyl ring to form a dihydroindole derivative **41**. Aromatisation of **41** by the elimination of benzenesulfinic acid resulted in the formation of indole derivative **42**.



Scheme 4.9

Synthesis of a C3-quaternary indolenine was reported by the reaction of α, β-unsaturated *N*-arylketonitrones with activated alkynes (Scheme 4.10).[37] The proposed mechanism included the formation of a zwitterionic intermediate **45** by the nucleophilic addition of the oxygen atom of the nitrone **43** to the activated alkyne **44.** The zwitterion

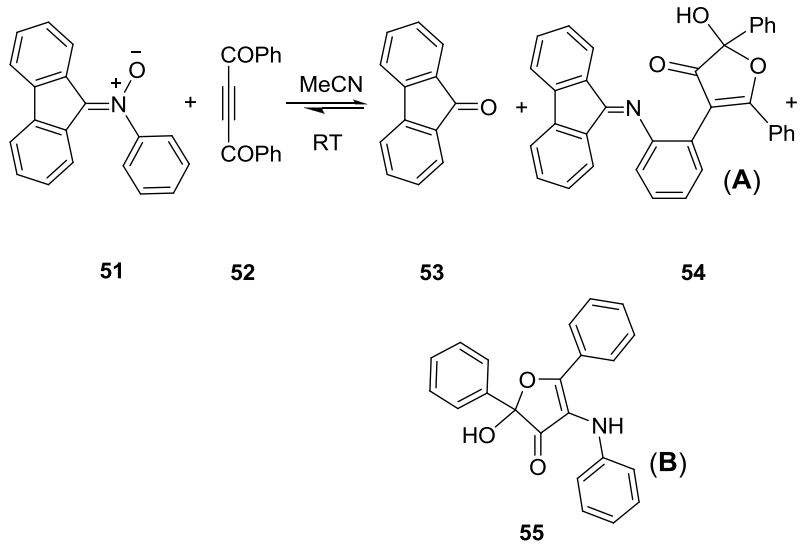
isomerised to the *Z* form, which cyclized to the seven membered heterocycle **46** then hydrolysed to **47,** which on [3,3] sigmatropic shift produced **48**. The intermediate **48** then tautomerized to **49** which on intramolecular condensation produced the indolenine **50**.



Scheme 4.10

Our interest in quinoline and indole synthesis was ignited by chance. We observed that reaction of *N*-fluorenylidene-*N*-phenylnitrone **51** with dibenzoylacetylene **52** resulted in the formation of two 3(*2H*)-

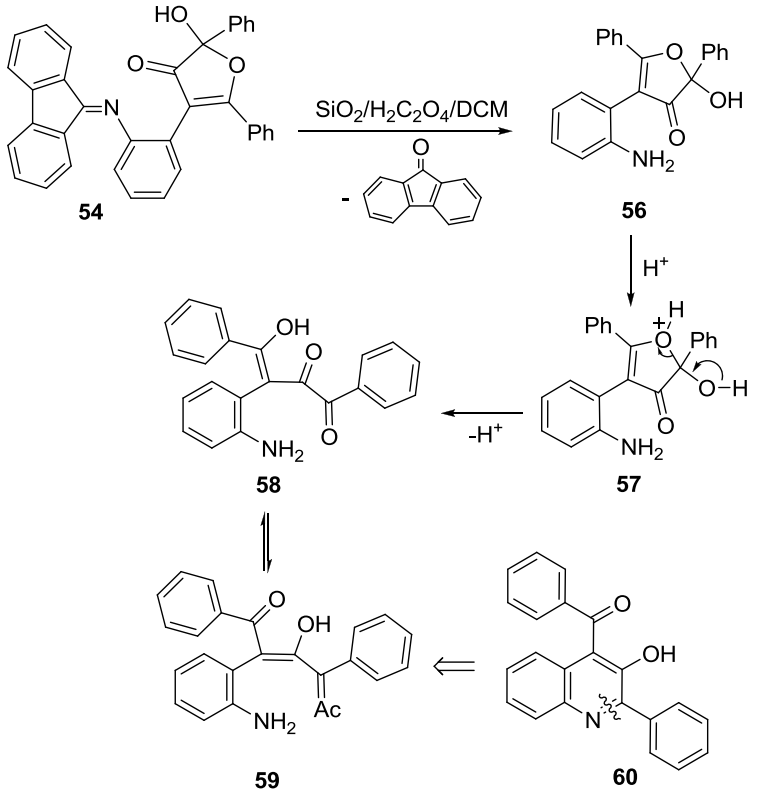
furanone derivatives (**54** and **55**) along with fluorenone (**53**) (Scheme 4.11).[38]



51 **52** **53** **54** **55**

Scheme 4.11

We were intrigued by the interesting structural features of furanone **54**. Close examination of the structural features of **54** revealed its potential as viable staring material for highly substituted quinoline derivatives. A retrosynthtic analysis for the generation of quinoline derivatives testified our hypothesis (Scheme 4.12).

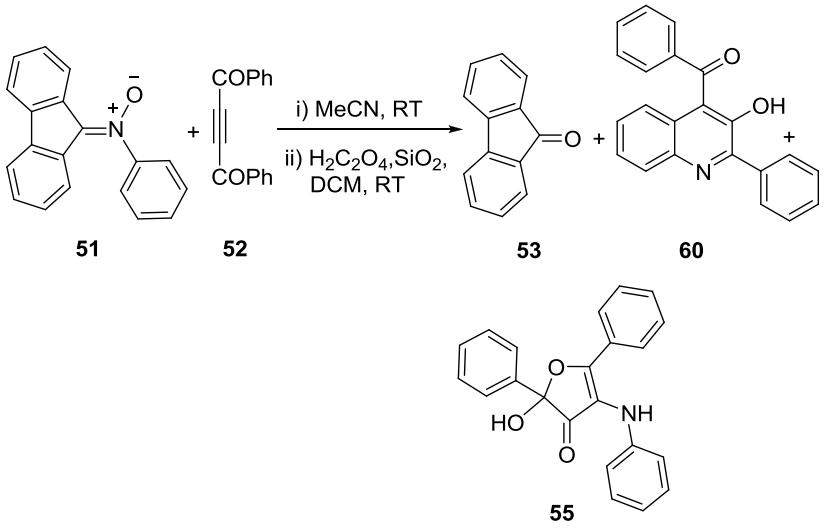


Scheme 4.12

It is easily discernible that mild hydrolysis of **54** might generate intermediate **58** that is structurally similar to intermediate **18** involved in Friedlander synthesis. Consequently, intramolecular condensation between the amino and carbonyl functionalities in **58** should generate the corresponding quinoline derivative **60**. Indeed, hydrolysis of **54** using oxalic acid adsorbed on silica gel yielded a highly substituted quinoline derivative **59**.

A major disadvantage of the new protocol developed by us was the difficulty in separating furanone **54** in the pure form. Soon we recognized that isolation of **54** is redundant. A more practical method is

to carry out the reaction in one-pot. In a repeat run, reaction between a 1:1 mixture of **51** and **52** in acetonitrile was closely monitored by TLC analysis. When TLC analysis indicated complete consumption of starting materials, we removed the solvent, redissolved the residue in dichloromethane and added oxalic acid adsorbed on silica gel to the product mixture. Under these conditions, quinoline could be isolated in higher yield proving our assumption that it is not necessary to isolate **54** in pure form. In short, we could develop a one-pot, two-step synthesis of quinolines from *N*-arylnitrones and DBA (Scheme 4.13).



Scheme 4.13

From the reaction between *N*-fluorenylidene-*N*-phenylnitrone with dibenzoylacetylene and formal *in situ* hydrolysis of the product obtained, we recognized that it is possible to synthesize a variety of quinoline derivatives with predetermined substitution pattern by using appropriately substituted nitrones and diactivated acetylenes. When

dibenzoylacetylene (DBA) is used as the acetylene component, depending on the *N*-arylnitrone employed, a variety of 2-phenyl-3-hydroxy-4-benzoylquinolines are conveniently generated (Figure 4.6). The boon and bane of the protocol is that substituents on 2,3,4-positions are determined by the diactivated acetylene employed. Ready availability of a variety of diactivated acetylenes such as DBA, dimethyl acetylenedicarboxylate etc. provides easy access to several quinolines. In this investigation, we restricted our choice of diactivated acetylenes to DBA.

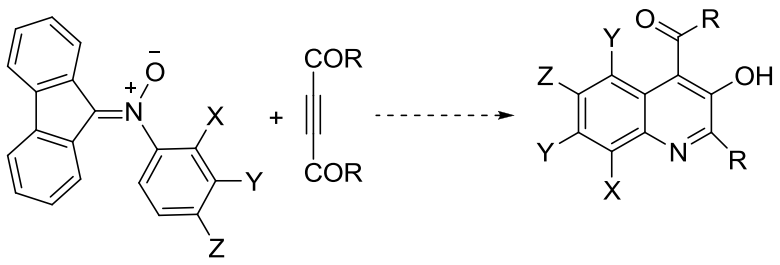
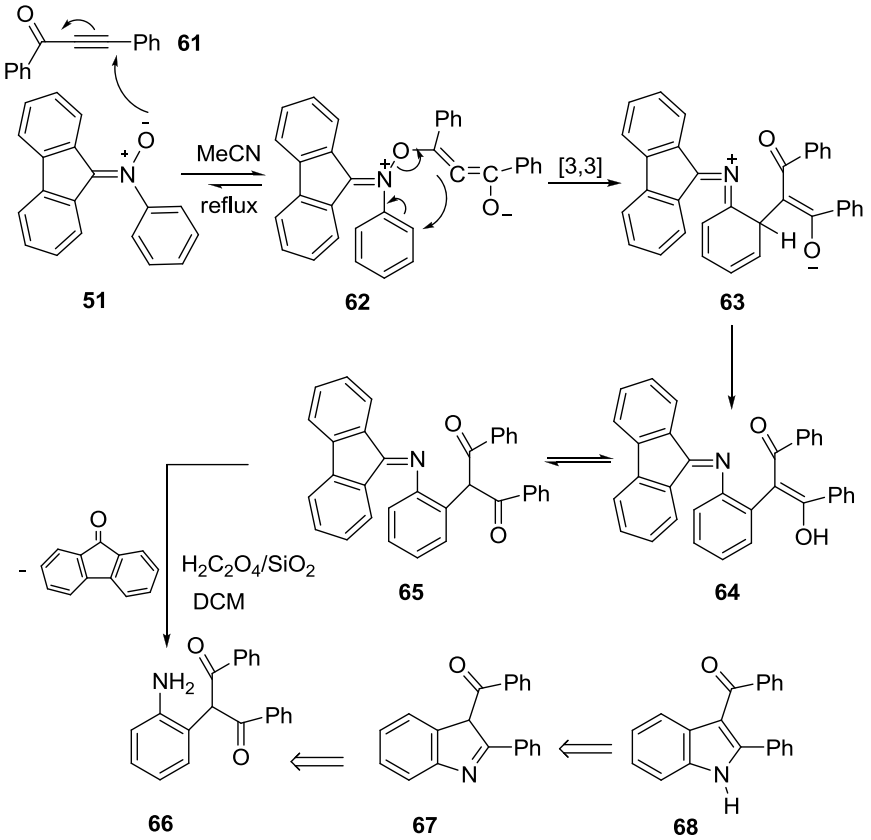


Figure 4.6

Closer examination of the mechanism of the reaction between *N*-fluorenylidene-*N*-phenylnitrone with dibenzoylacetylene offered us another exciting possibility: *if monoactivated acetylenes are used, instead of DBA, it may be possible to generate indoles*! Retrosynthetic analysis for indole and mechanism of the reaction between *N*-arylnitrones and a mono activated acetylene (Scheme 4.14) converge to reveal a novel indole synthesis protocol.



Scheme 4.14

So another objective is to synthesize a few indole derivatives using monoactivated acetylenes such as benzoylphenylacetylene, acetylphenylacetylene and cinnamoylphenylacetylene.

4.3. Results and Discussion

We selected *N*-fluorenylidene-*N*-phenylnitrone along with a few substituted nitrones (Figure 4.7) for the synthesis of suitably substituted quinoline and indole derivatives. By the use of a nitrone with an ortho

substituent in the *N*-aryl ring we could prepare a quinoline derivative with substituent at the 8th position. We could also prepare quinoline derivatives with substituent at the 6th position by the use of nitones with substituent in the para position of the *N*-aryl ring. On the other hand, a mixture of 5-substituted and 7-substituted quinolines were generated in the reaction of nitrone with substituent at the meta position of the *N*-aryl ring. However, when a bulky substituent was introduced at the meta position of the *N*-aryl ring, 7-substituted quinoline was exclusively generated. Thus, we could introduce a substituent of our choice at a predetermined position in the quinoline product. The fluorenone by-product can be recycled to enhance atom efficiency of our protocol. However, our protocol has its own limitations. It is not possible to introduce a bulky substituent at the 5- and 8-positions. Neither is it possible to generate 5-substituted quinolines exclusively. Nevertheless, the inherent simplicity and excellent atom efficiency makes this new method for quinoline synthesis truly remarkable.

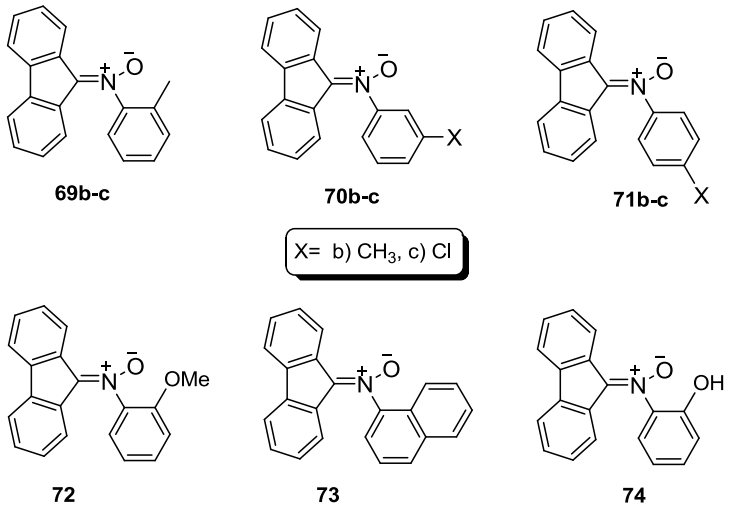


Figure 4.7

Dibenzoylacetylene (DBA) was synthesized by a known three step procedure.[39] In addition to dibenzoylacetylene, we prepared a few monoactivated acetylenes for the synthesis of indole derivatives. We prepared monoactivated acetylenes, such as benzoylphenylacetylene, acetylphenylacetylene and cinnamoylphenylacetylene by the condensation reaction of sodium salt of phenylacetylene with benzoyl chloride, acetyl chloride and cinnamoyl chloride respectively.[40]

We prepared a few quinoline derivatives (Figure 4.8) by starting from the *N*-fluorenylidene-*N*-arylnitrones with substituents at different positions in the *N*-aryl ring.

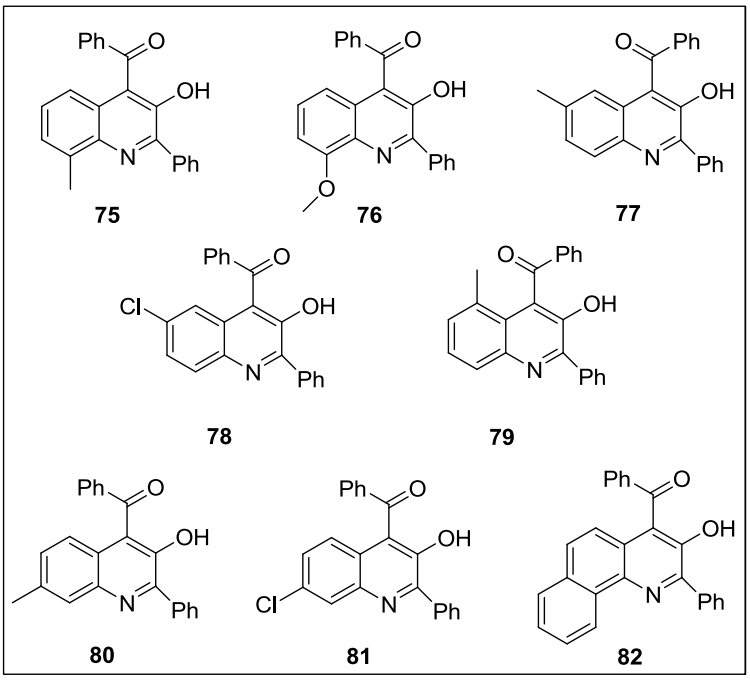
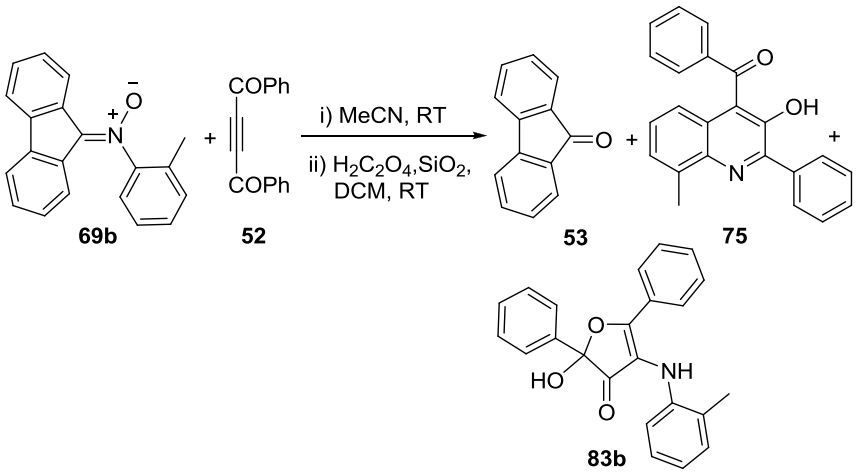


Figure 4.8

4.3.1. Synthesis of 8-Substituted Quinoline Derivatives 75, 76.

We carried out the reaction of *N*-fluorenylidene-*N*-arylnitrones (**69b** and **72**) with a substituent at the ortho position of the *N*-aryl ring with DBA (1:1 molar ratio) in acetonitrile at room temperature. After the completion of the reaction, the solvent was removed and the hydrolysis of the products was accomplished by stirring the reaction mixture with oxalic acid adsorbed on silica gel in dichloromethane at RT for 2h. The products were separated by column chromatography. For example, in the synthesis of 8-methylquinoline derivative **75**, *N*-fluorenylidene-*N*-(2-methylphenyl)nitrone (**69b**) was treated with DBA (**52**) (1:1 molar ratio) in acetonitrile at RT. Solvent was removed, and the reaction mixture together with oxalic acid adsorbed on silica gel in DCM was stirred for another 2h and the products were separated by column chromatography (Scheme 4.15). We obtained 8-methyl substituted quinoline **75** along with fluorenone **53** and the 3(*2H*)-furanone derivative **83b**.



Scheme 4.15

Presence of -OH group in the quinoline derivative **75** was indicated by the broad band at 3480 cm^{-1} in the IR absorption spectrum, which was further confirmed by presence of a singlet (D_2O-exchangeable) at δ 9.14 in the ^1H NMR spectrum. The $-CH_3$ group in the compound appeared as a singlet at δ 2.86 in the ^1H NMR spectrum. Other protons of **75** appeared in the δ 8.18 to δ 7.17 range in the ^1H NMR spectrum (Figure 4.9).

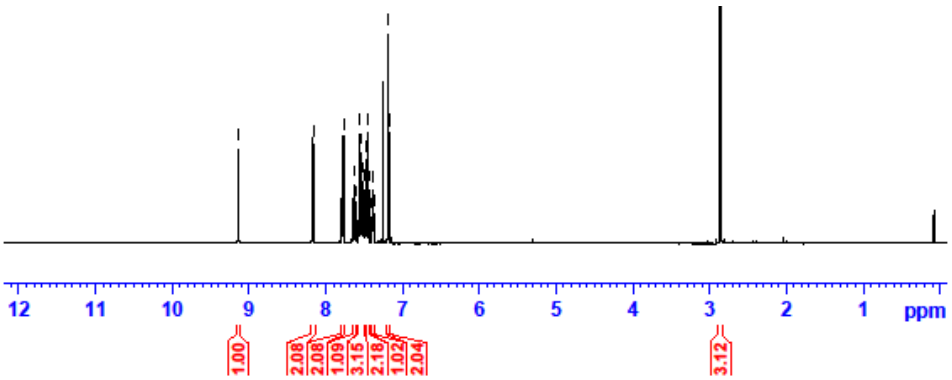


Figure 4.9 ^1H NMR spectrum of **75**

The carbonyl functionality in the quinoline derivative **75** was confirmed by a peak at δ 198.21 in the ^{13}C NMR spectrum (Figure 4.10).

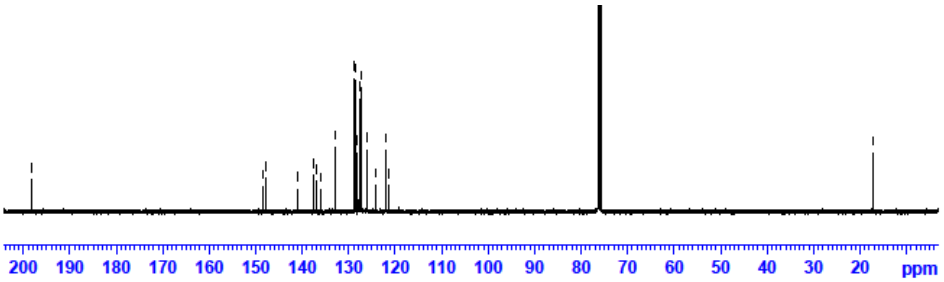


Figure 4.10 ^{13}C NMR spectrum of **75**

The carbonyl group appeared at 1666 cm^{-1} in the IR spectrum, and the methyl carbon (-CH_3) appeared at δ 17.21 in the ^{13}C NMR spectrum of **75**. Structure of the 3(*2H*)-furanone derivative **83b** obtained was confirmed on the basis of spectral data. The carbonyl group in the compound **83b** appeared at 1701 cm^{-1} in the IR spectrum, which was confirmed by a peak at δ 197.54 in the ^{13}C NMR spectrum (Figure 4.11).

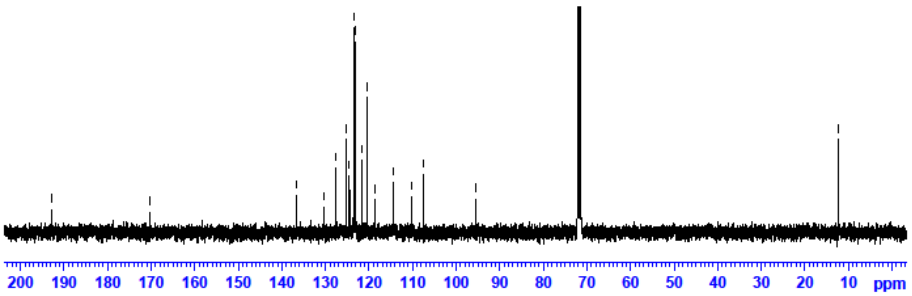


Figure 4.11 ^{13}C NMR spectrum of **83b**

In the ^{13}C NMR spectrum of **83b**, the methyl carbon appeared at δ 12.33 and all the other carbons appeared in the δ 95.56 to 170.22 range. Appearance of a peak at 95.56 is significant since it confirms the presence of a ketal-type carbon. The IR spectrum of the compound showed peaks at 3367 cm^{-1} and 3304 cm^{-1} corresponding to the –OH and the –NH functionalities, which were further confirmed by the presence of small singlets at δ 4.45 and δ 4.85 in the ^{1}H NMR spectrum (Figure 4.12). The singlet at δ 2.24 (s, 3H) in the ^{1}H NMR spectrum indicated the methyl protons of **83b**.

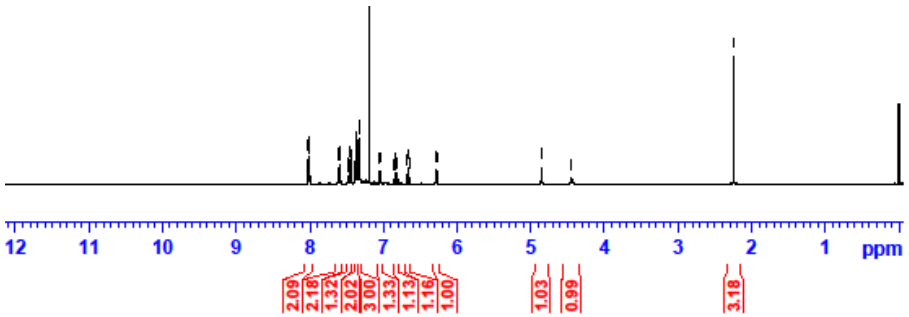
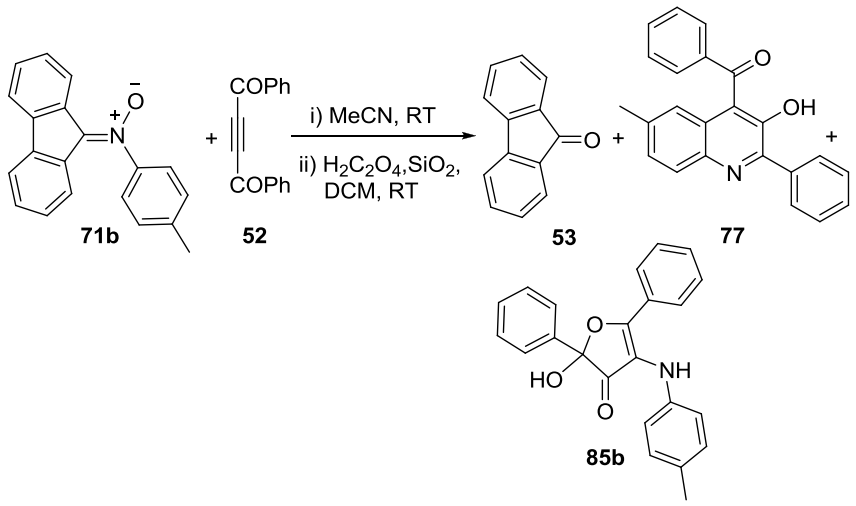


Figure 4.12 ^{1}H NMR spectrum of **83b**

4.3.2. Synthesis of 6-Substituted Quinoline Derivatives 77, 78.

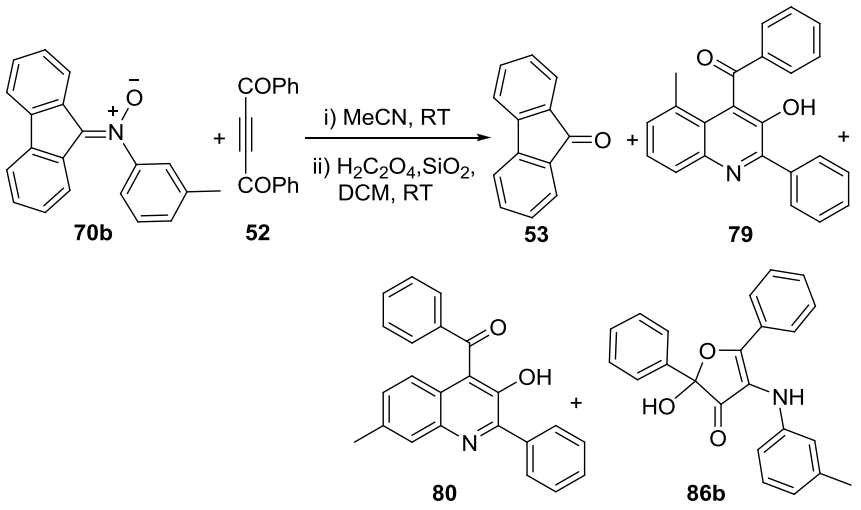
We could synthesize the 6-substituted quinoline derivatives **77** and **78** by conducting the hydrolysis of the reaction mixture obtained in the reaction of corresponding nitrones **71b-c** with DBA[38] (Scheme 4.16). Along with the quinoline derivatives, we obtained the corresponding 3(2*H*)-furanones (**85b-c)** also.



Scheme 4.16

4.3.3. Synthesis of 5- and 7-Substituted Quinoline Derivatives 79 and 80.

We synthesized quinoline derivatives with substituent at either the 5- or 7-position by the hydrolysis of products obtained in the reaction of nitrones having substituent at the meta position of the *N*-aryl group with dibenzoylacetylene. This was illustrated by the reaction between *N*-fluorenylidene-*N*-(3-methylphenyl)nitrone (**70b**) with DBA. After the hydrolysis of the reaction mixture, we obtained a 1:1 mixture of 5- and 7-methyl substituted quinoline derivatives **79** and **80** along with the corresponding 3(*2H*)-furanone **86b** and fluorenone (Scheme 4.17). Structures of all the products were identified on the basis of spectral and analytical data.



70b 52 53 79 80 86b

Scheme 4.17

For the 7-methyl substituted quinoline derivative **80**, the phenolic -OH proton appeared as a singlet at δ 9.11 and the methyl group appeared at δ 2.49 in the ^{1}H NMR spectrum (Figure 4.13).

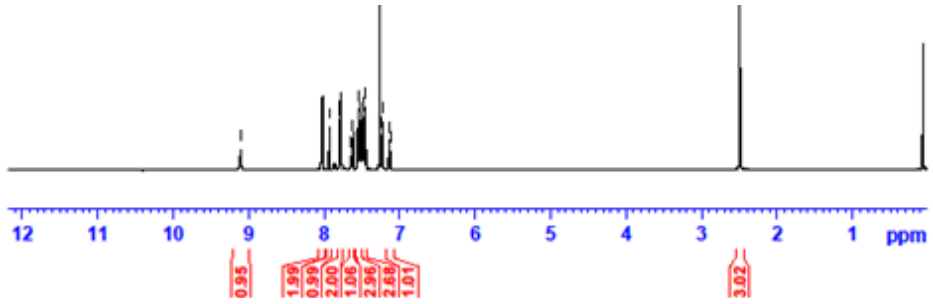


Figure 4.13 ^{1}H NMR spectrum of **80**

In the ^{1}H NMR spectrum of 5-methyl substituted quinoline **79** (Figure 4.14), the phenolic –OH proton appeared considerably upfield at δ 6.30 (D_2O-exchangeable) indicating profound variation in hydrogen bonding and ensuing conformational preferences among quinolines **79** and **80**.

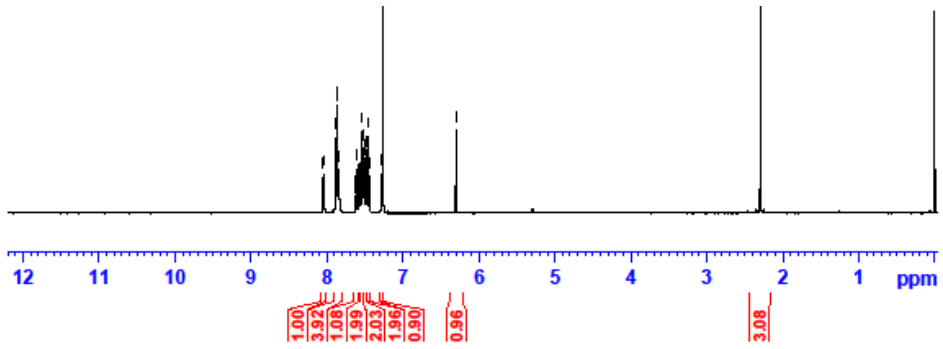


Figure 4.14 ^{1}H NMR spectrum of **79**

In the case of **79**, due to steric repulsion, the phenyl ring of the -COPh group is positioned away from the 5-methyl substituent forcing the carbonyl group to orient itself towards the 5-substituent. Consequently, intramolecular hydrogen bonding between the -OH group at 3-position and carbonyl group is disrupted. But in the case of quinoline derivatives without substituents at the 5-position, the -OH and carbonyl groups are appropriately oriented ensuring strong intramoleclular *H*-bonding between the two resulting in substantial downfield shift in phenolic OH resonance. This effect is also evident in the IR spectrum of 5-substituted quinolines, where the -OH and C=O groups appeared as sharp peaks at 3676 cm^{-1} and 1671 cm^{-1} respectively. Further evidence for the preferential orientation of substituents in **79** is provided by single crystal X-ray diffraction analysis (Figure 4.15).

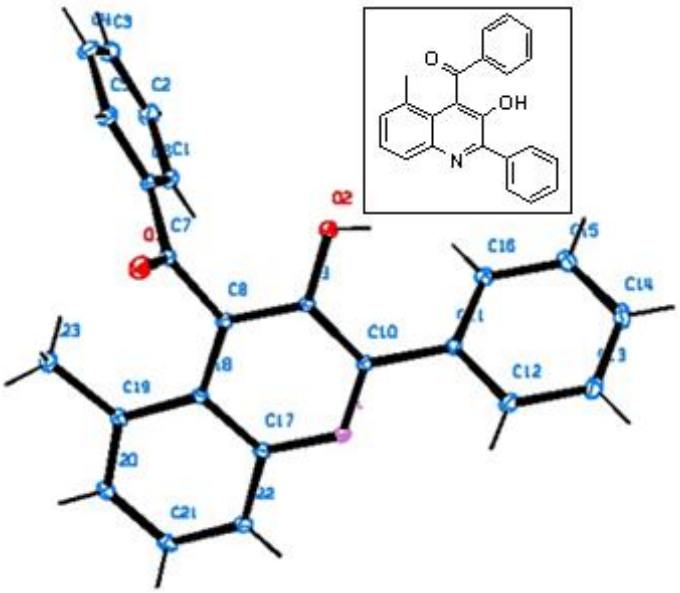
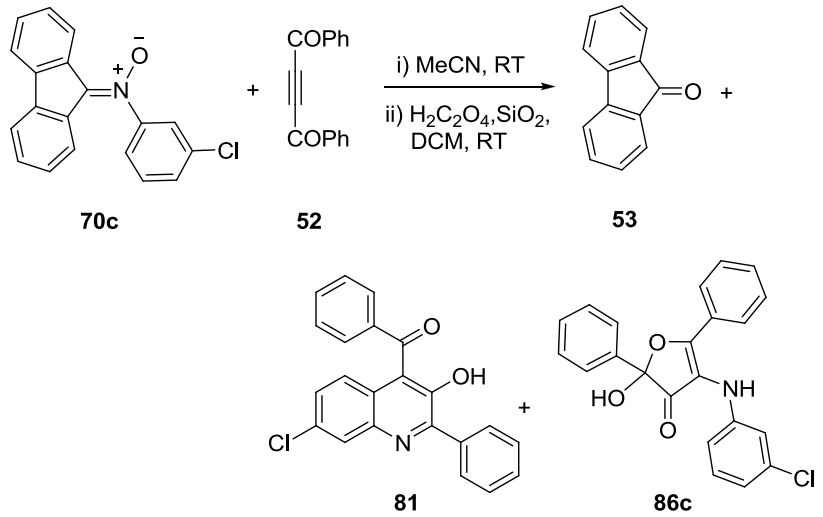


Figure 4.15 ORTEP diagram of molecular structure of **79**

4.3.4. Synthesis of 7-Substituted Quinoline Derivative 81.

When the *meta* position of the *N*-aryl ring was substituted by larger atom or group, we could eliminate the possibility for the formation of 5-substituted quinoline derivative along with the corresponding 7-substituted quinoline. This was illustrated by the reaction between *N*-fluorenylidene-*N*-(3-chlorophenyl)nitrone (**70c**) with DBA (Scheme 4.18).

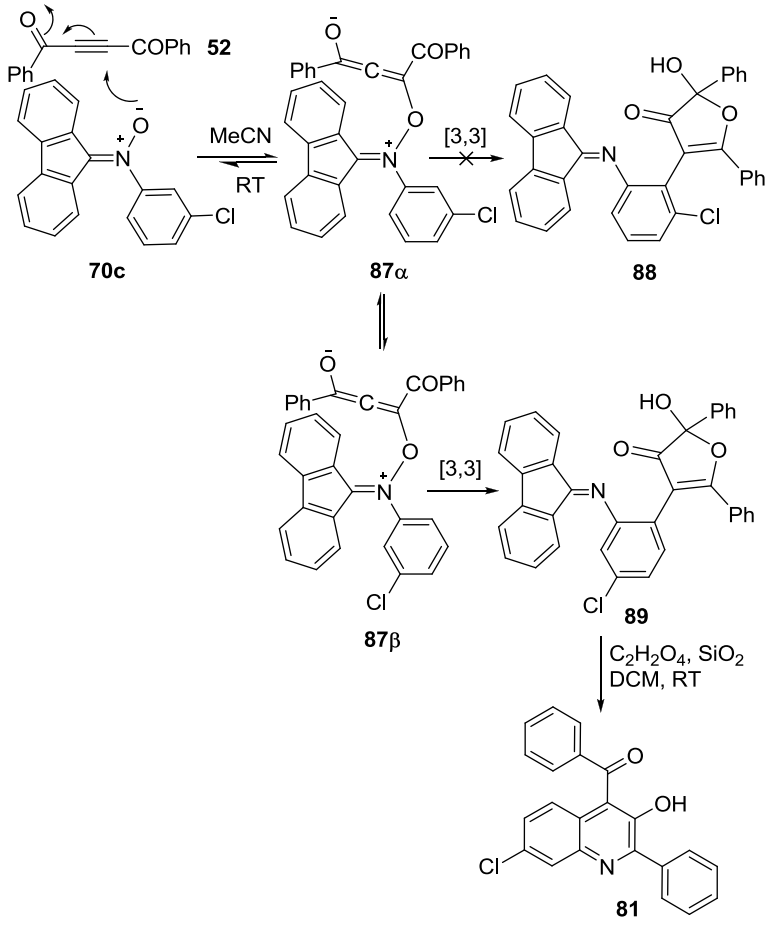


70c **52** **53** **81** **86c**

Scheme 4.18

When a bulky group like chlorine is substituted at one of the meta positions, formation of 1:1 adduct **88** is not favoured. Two rotamers (α and β) are conceivable for the zwitterionic intermediate **87**. Steric interaction with chlorine restricts the anionic centre of the zwitterion **87** (α) from approaching the 2-position of the *N*-aryl ring for [3,3] sigmatropic rearrangement. Consequently, [3,3] sigmatropic shift is restricted to the other rotamer **87**(β) with 6-position as the possible

location of attack resulting in the formation of 1:1 adduct **89** (Scheme 4.19). When smaller groups are present at the meta position, rotamers analogues to **87*α,β*** leading to 5- and 7-substituted quinolines respectively are almost equally populated.

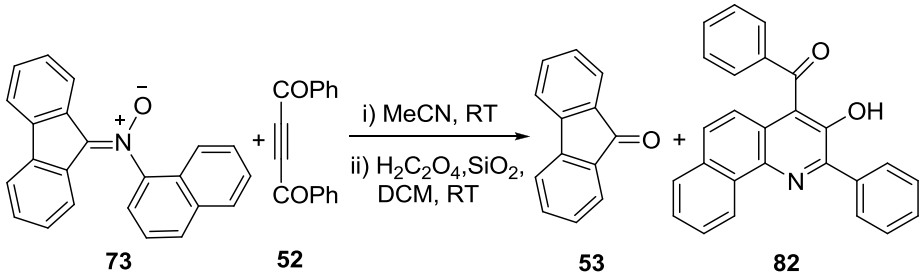


Scheme 4.19

4.3.5. Synthesis of Benzo(*h*)quinoline Derivative 82

We conducted one-pot addition followed by hydrolysis reaction of *N*-fluorenylidene-*N*-naphthylnitrone (**73**) with DBA. After the

completion of the reaction, we separated benzo(*h*)quinoline **82** along with fluorenone **53** in near-quantitative amounts (Scheme 4.20).



Scheme 4.20

The –OH and the C=O functionalities in the quinoline derivative **82** were indicated by a broad peak at 3491 cm^{-1} and a sharp peak at 1763 cm^{-1} respectively in the IR spectrum. The phenolic –OH proton appeared as a singlet (D_2O-exchangeable) at δ 8.70 in the ^1H NMR spectrum of **82** (Figure 4.16).

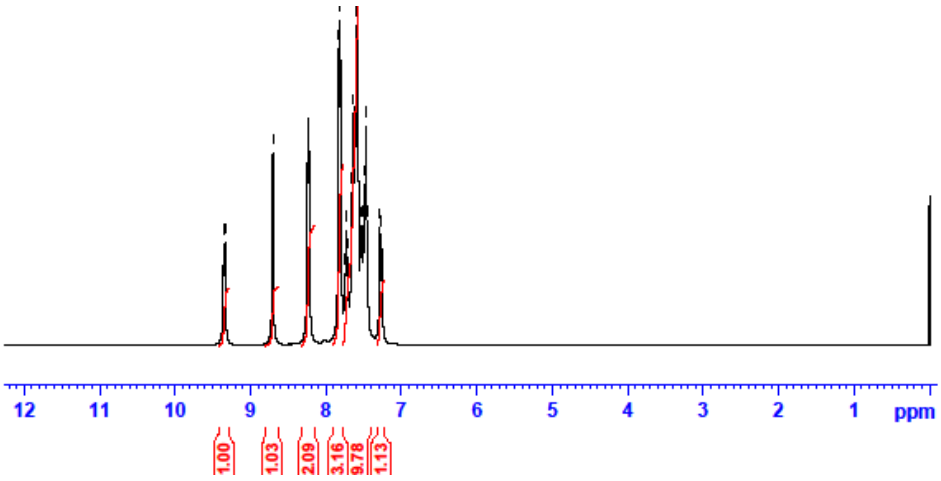


Figure 4.16 ^1H NMR spectrum of **82**

The ^{13}C NMR spectrum of **82** showed several signals at δ 198.79, 148.75, 148.23, 140.06, 138.30, 137.07, 134.13, 132.01, 131.65, 129.92, 129.68, 129.37, 128.90, 128.60, 128.49, 127.69, 127.59, 127.45, 124.47, 124.32, 123.37, 122.65. Of these, the signal at δ 198.79 was assigned to the carbonyl carbon and all the other signals were assigned to aromatic carbons. The structure of the compound was further confirmed from single crystal X-ray diffraction data (Figure 4.17).

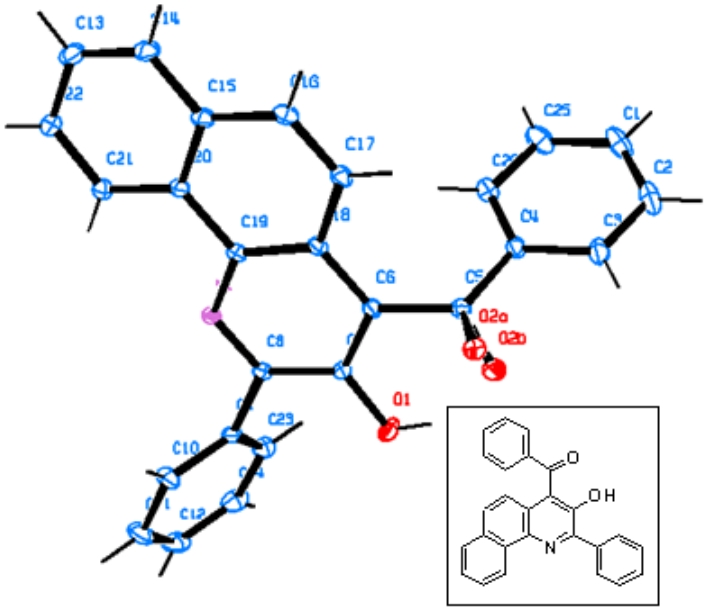
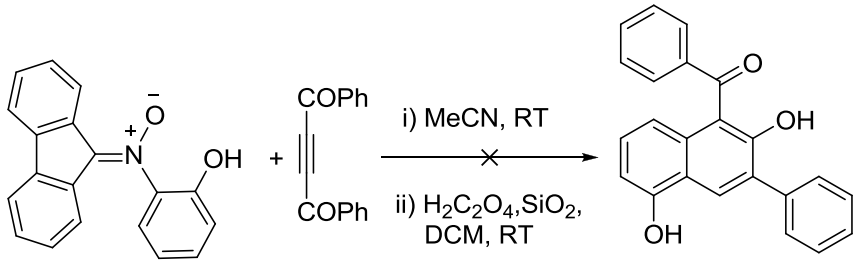


Figure 4.17 ORTEP diagram of molecular structure of **82**

4.3.6. Attempted the Synthesis of 8-Hydroxyquinoline Derivative 90

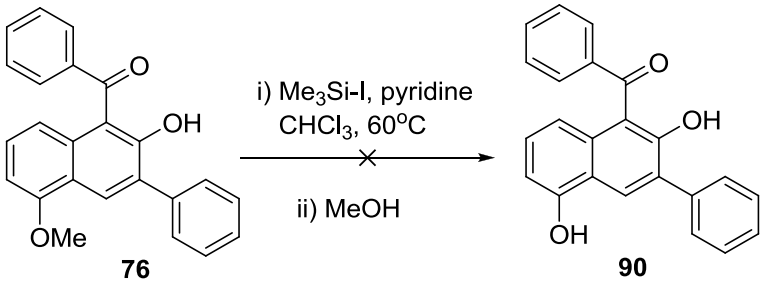
For the synthesis of 8-hydroxyquinoline derivative **90**, we conducted the reaction of *N*-fluorenylidene-*N*-(2-hydroxyphenyl)nitrone (**74**) with DBA (Scheme 4.21). After the completion of the reaction, the solvent was removed. Hydrolysis of the reaction mixture was tried by

adding oxalic acid adsorbed on silica gel. Unfortunately, the reaction mixture decomposed to an intractable mixture and we could not isolate any quinoline derivative. Continuous reaction monitoring by mass spectral analysis indicated the generation of a 1:1 adduct of nitrone and DBA in the initial stages of the reaction. But as the reaction advanced, the 1:1 adduct itself decomposed.



Scheme 4.21

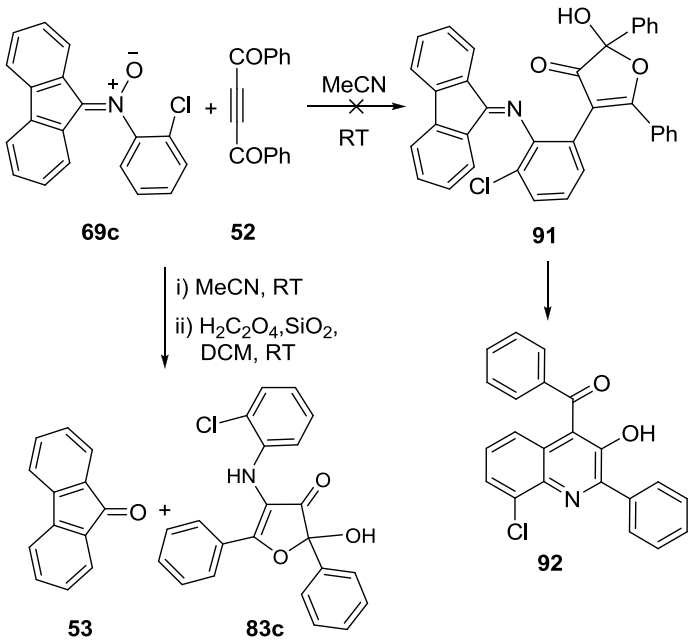
We attempted the alternative synthesis of 8-hydroxyquinoline derivative **90** by the hydrolysis of -OMe group of 8-methoxy quinoline **76** with the reagent iodotrimethylsilane (Scheme 4.22).[41] Since the reactant remained unchanged after several hours, we arrived at the conclusion that the reagent is not suitable for the transformation of **76** to the product.



Scheme 4.22

4.3.7. Attempted the Synthesis of 8-Chloroquinoline Derivative 92

We have already described (in chapter 3 of this thesis) the reaction between *N*-fluorenylidene-*N*-(2-chlorophenyl)nitrone **69c** with DBA **52**. Fluorenone **53** and 3(*2H*)-furanone **83c** were the only products formed in this reaction. The expected 1:1 adduct **91** was not formed in detectable amounts. We repeated the reaction employing the one-pot protocol developed by us. This reaction also gave rise to **53** and **83c** in near quantitative amounts. Neither the 1:1 adduct **91** nor the 8-substiuted quinoline **92** derived thereof were formed in detectable amounts (Scheme 4.23)



Scheme 4.23

During the synthesis of derivatives of quinoline, we could isolate some derivatives of 3(*2H*)-furanone also (Figure 4.18).

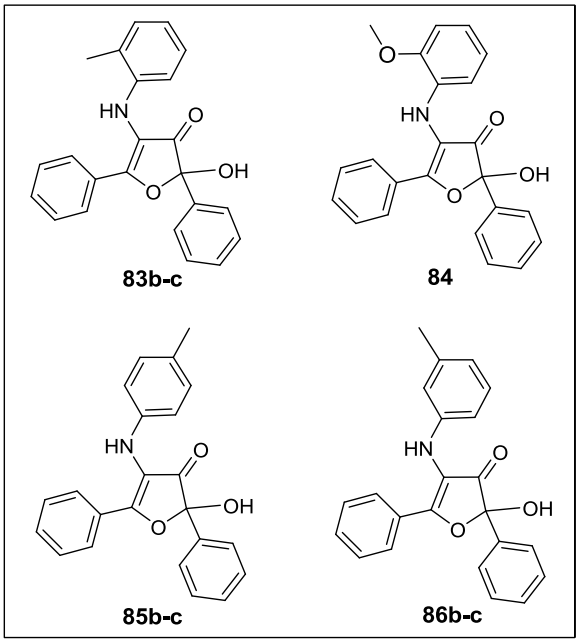
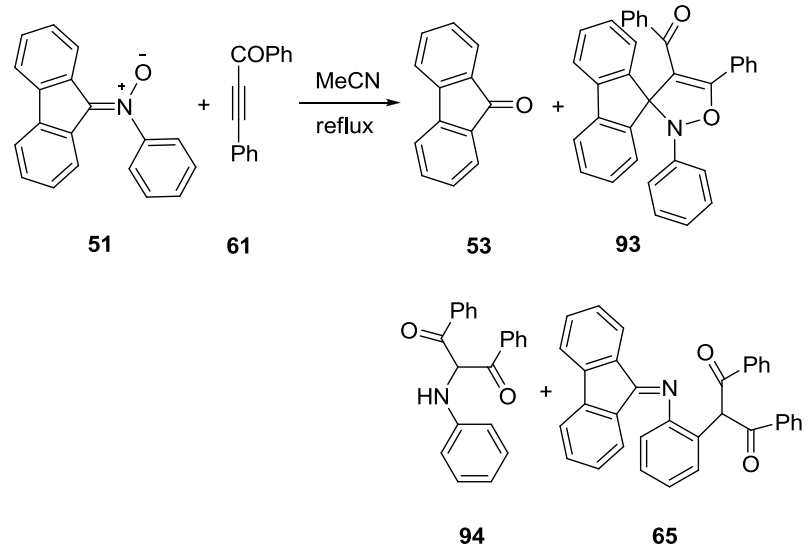


Figure 4.18

4.3.8. Synthesis of Highly Substituted Indoles

We established that it is possible to synthesize indoles if we use monoactivated acetylenes instead of dibenzoylacetylene in the reaction of *N*-arylnitrones. This was illustrated by the reaction between *N*-fluorenylidene-*N*-phenylnitrone **(51)** and benzoylphenylacetylene **(61)** (Scheme 4.24).

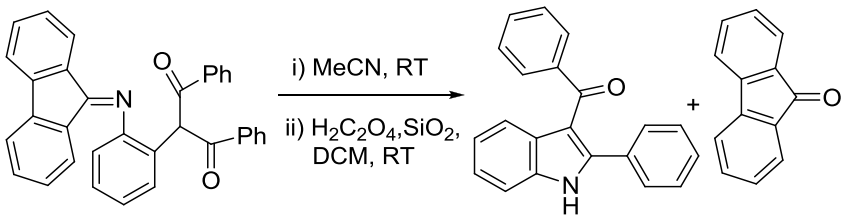


51 61 53 93

94 65

Scheme 4.24

Hydrolysis of compound **65** was accomplished by stirring the reaction mixture and oxalic acid adsorbed on silica gel in dichloromethane at RT for 2h. The products formed were separated by column chromatography. We obtained a highly substituted indole derivative **68** along with fluorenone **53** (Scheme 4.25). Similar results were obtained when the reaction was carried out in one pot as reported for quinolines.



65 68 53

Scheme 4.25

We identified the structure of indole derivative **68** on the basis of analytical and spectral data.[41] In the ^{1}H NMR spectrum, the singlet at δ 8.57 indicated the -NH proton in **68**. All the other fourteen protons appeared as multiplet from δ 7.96-7.16. In the IR spectrum, the carbonyl group appeared at 1593 cm^{-1} and NH group at 3149 cm^{-1}. Carbonyl stretching frequencies rarely appear below 1600 cm^{-1}. So, we were hesitant to assign the 1593 cm^{-1} peak to a carbonyl group. We searched for reported values for carbonyl stretching frequencies in 3-acylindoles and found that these appear around 1600 cm^{-1}. Based on these reports and ^{13}C NMR spectral data we confirmed the presence of a carbonyl group in **70**. The ^{13}C NMR spectrum of **68** showed signals at δ 193.15, 143.54, 139.68, 135.46, 131.72, 131.57, 129.66, 129.22, 128.82, 128.69, 128.41, 127.76, 123.64, 122.23, 121.82, 110.94. Of these, the signal at δ 193.15 was assigned to the carbonyl carbon in **68**. The structure was further confirmed from the SCXRD analysis (Figure 4.19).

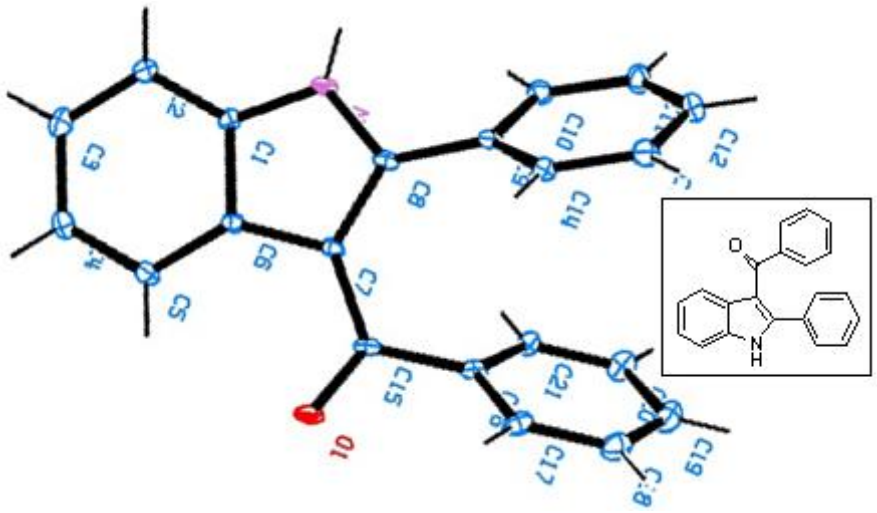


Figure 4.19 ORTEP diagram of molecular structure of **68**

We synthesized a few derivatives of indole (Figure 4.20) using procedure analogous to that we adopted in the preparation of quinoline derivatives.

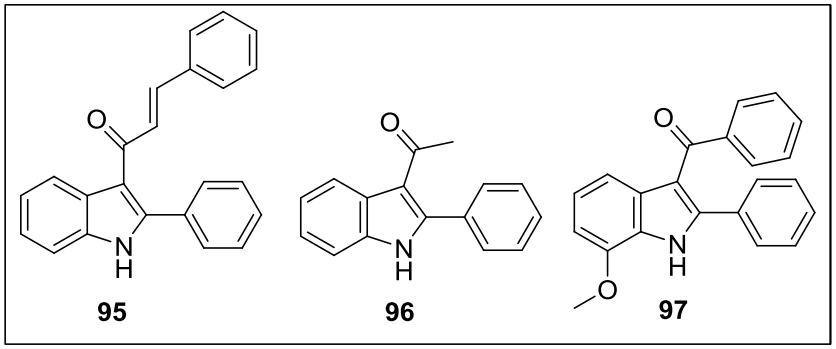


Figure 4.20

4.3.9. Reaction of *N*-Fluorenylidene-*N*-phenylnitrone with Cinnamoylphenylacetylene

Reaction between *N*-fluorenylidene-*N*-phenylnitrone **51** and cinnamoylphenylacetylene **98** (1:1 molar ratio) was conducted in acetonitrile at refluxing condition. The reaction completed in 6h. Solvent was removed, and the reaction mixture together with oxalic acid adsorbed on silica gel in DCM was stirred for another 2h and after the completion of the reaction, we could separate four products. On analysing CHN and mass data, we could identify that, along with the indole derivate **95** (56%) and fluorenone, a 1:1 adduct of **51** and **98** (18%) and a compound having *m/z* = 339 (4%) were also formed. Structure of the indole derivative **95** was arrived at on the basis of spectral data. In the ^{1}H NMR spectrum (Figure 4.21), the -NH proton appeared as singlet at δ 8.53. The doublet at δ 6.80 (*J* = 15.6 Hz, 1H)

indicated one of the vinylic protons in this compound. The other vinylic proton appeared along with the aromatic protons in **95**. This was confirmed by analysing the COSY spectrum of the indole derivative (Figure 4.22), where the proton at δ 6.80 showed a strong interaction with a proton at δ 7.66-7.62.

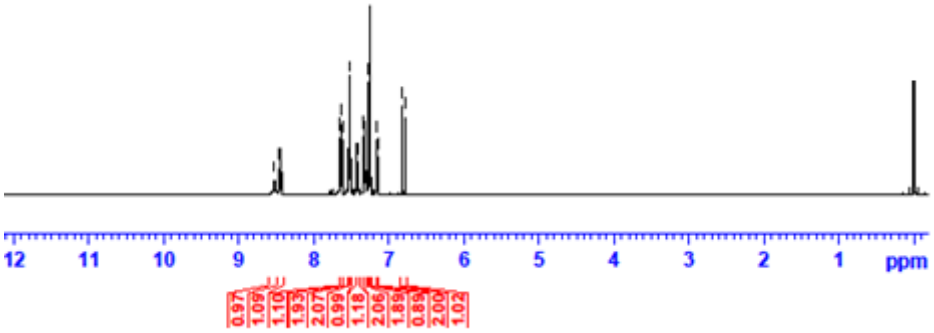


Figure 4.21 ^{1}H NMR spectrum of **95**

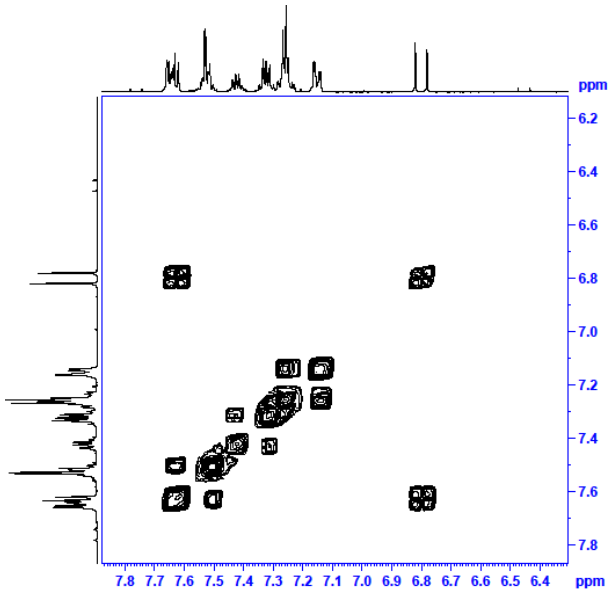


Figure 4.22

The ^{13}C NMR spectrum of **95** showed signals at δ 187.25, 143.89, 140.33, 135.47, 135.38, 132.61, 130.06, 129.64, 129.60, 128.88, 128.65,

128.06, 127.99, 126.65, 123.93, 122.72, 122.66, 116.37, 110.91. Of these, the signal at δ 187.25 has been assigned to the carbonyl carbon, whereas the eighteen signals from δ 143.89-110.91 were assigned to aromatic and vinylic carbons. In the IR spectrum, the carbonyl group appeared at 1634 cm^{-1}. The proposed structure of the indole derivative **95** was further confirmed from crystal structure analysis (Figure 4.23).

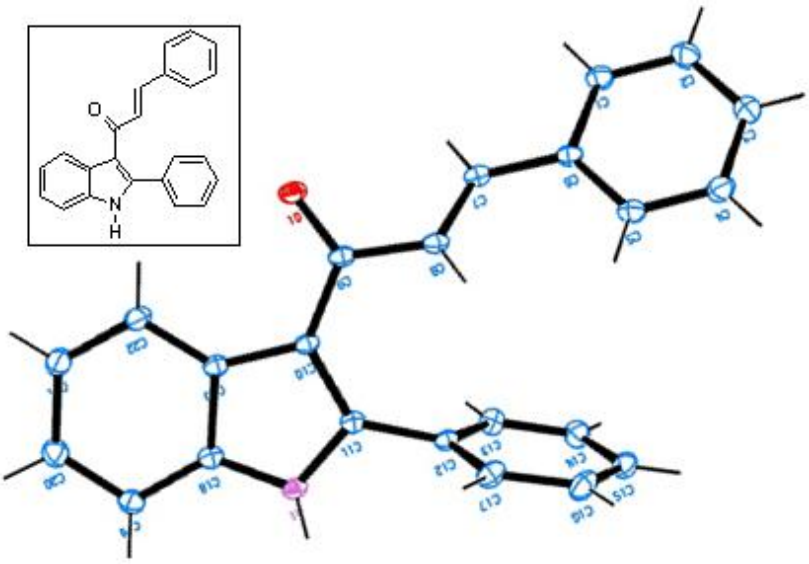


Figure 4.23 ORTEP diagram of molecular structure of **95**

By analysing the spectral data, the 1:1 adduct obtained in the above discussed reaction was identified as an isoxazoline derivative **99**. The ^1H NMR spectrum of the compound showed several peaks at δ 7.89-7.86 (m, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.64-7.60 (m, 1H), 7.57-7.53 (m, 4H), 7.36-7.32 (m, 2H), 7.27-7.16 (m, 6H), 6.99-6.91 (m, 4H), 6.81-6.76 (m, 1H), 6.61-6.58 (m, 2H), 6.36 (d, *J* = 15.6 Hz, 1H). Of these, the signal at δ 6.36 was assigned to one of the vinylic protons in **99**.

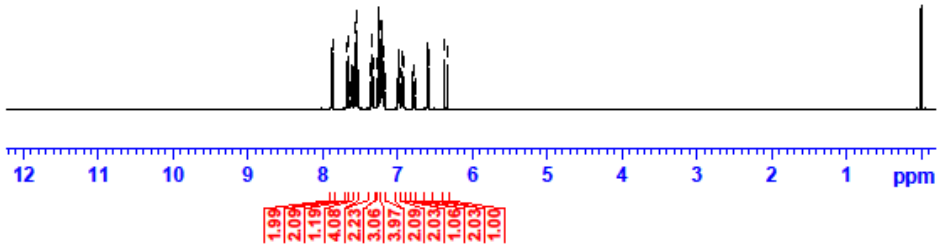


Figure 4.24 ^{1}H NMR spectrum of **99**

The ^{13}C NMR of the compound showed several peaks from δ 183.86 to δ 84.98. Of these, the peak at δ 183.86 showed the carbonyl carbon, and the peak at δ 84.98 indicated the quaternary carbon of the isoxazoline ring. Structure of this isoxazoline derivative **99** was further confirmed from X-ray diffraction analysis (Figure 4.25).

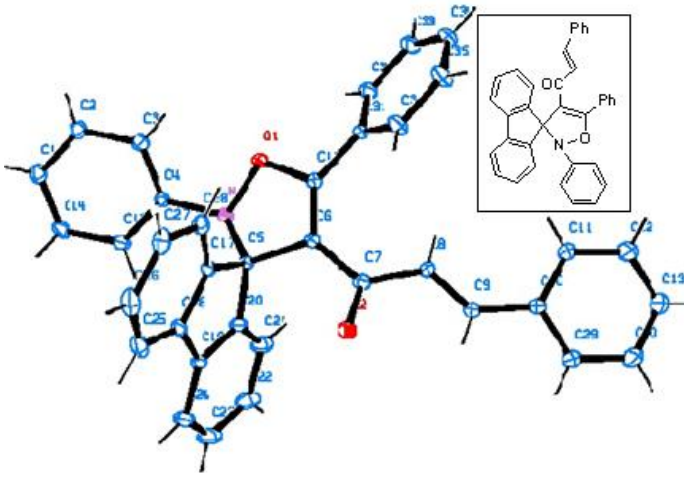


Figure 4.25 ORTEP diagram of molecular structure of **99**

On the basis of spectral data and the single crystal X-ray diffraction studies, we identified the final fraction (*m/z* = 339) as the pyrrole derivative **100**. The ^{1}H NMR spectrum of **100** (Figure 4.26) showed a broad peak at δ 11.17 (s, 1H) indicating the presence of an -OH

group in the compound. Signals due to other protons were observed at δ 7.22-7.08 (m, 6H), 7.04-6.87 (m, 7H), 6.79-6.77 (m, 2H), 6.18 (s, 1H). Here the singlet at δ 6.18 indicated the NH proton in the pyrrole ring.

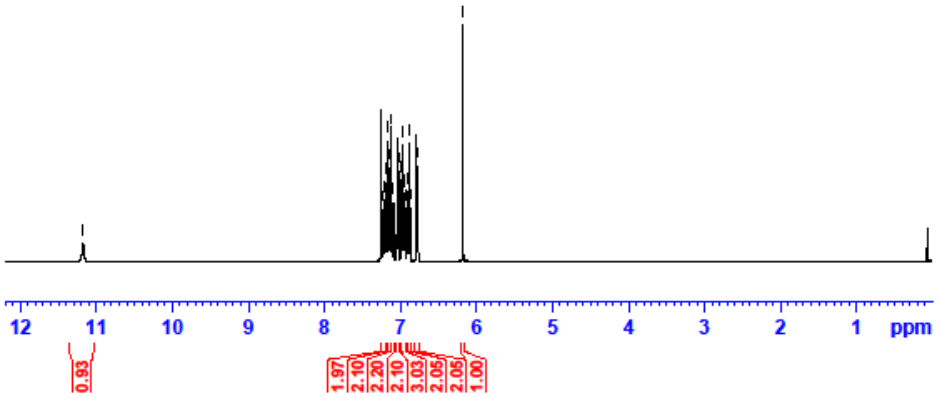


Figure 4.26 ^{1}H NMR spectrum of **100**

The ^{13}C NMR spectrum showed signals at δ 187.80, 160.88, 142.49, 138.50, 137.61, 131.56, 129.75, 129.36, 128.73, 128.29, 128.23, 128.07, 127.55, 127.34, 127.27, 120.10, and 99.69. Among these signals, the peak at δ 187.80 indicated the presence of a carbonyl group in the compound. So the reaction of *N*-fluorenylidene-*N*-phenylnitrone **51** with cinnamoylphenylacetylene **98** and subsequent hydrolysis of the reaction mixture resulted in the formation of a substituted pyrrole derivative also (Scheme 4.26). Finally the crystal structure analysis (Figure 4.27) confirmed the structure of **100**.

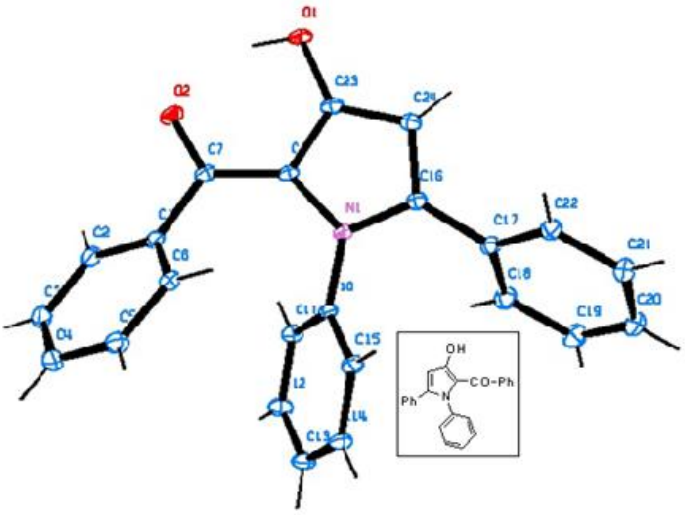
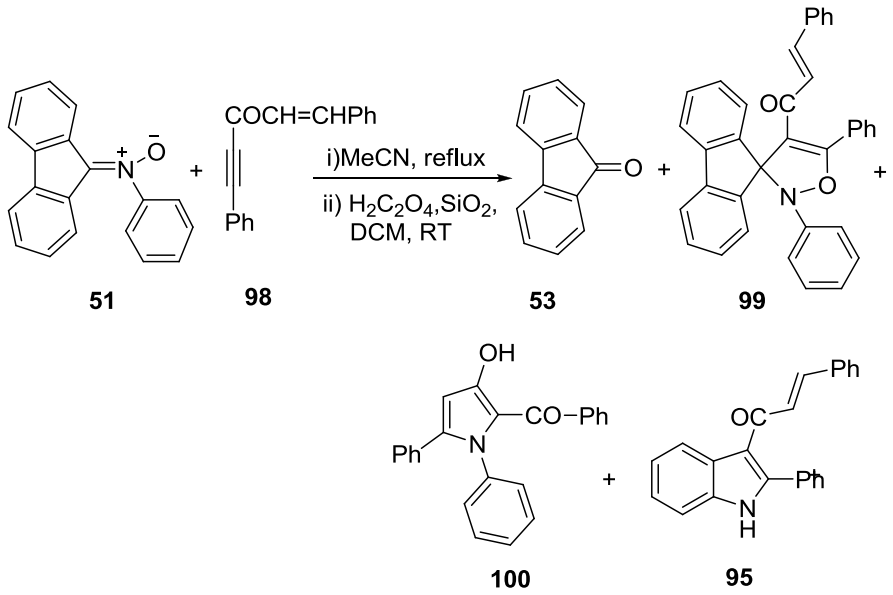
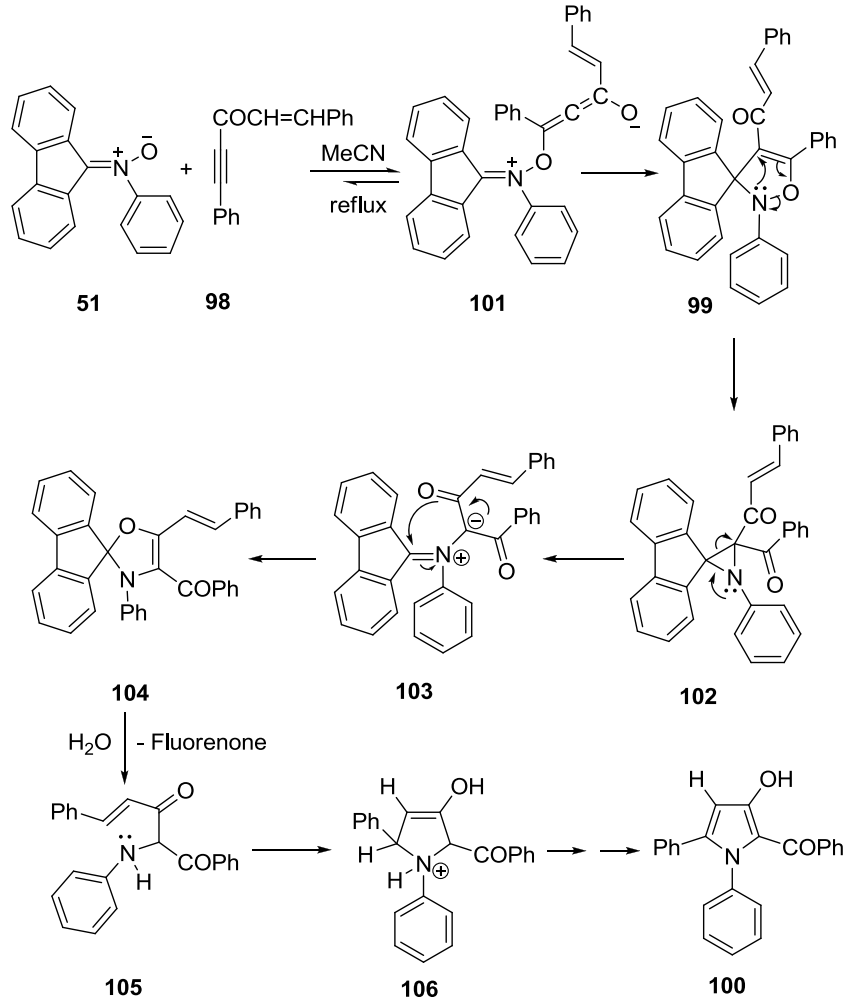


Figure 4.27 ORTEP diagram of molecular structure of **100**



Scheme 4.26

The pyrrole derivative **100** was formed by the hydrolysis of an oxazoline intermediate.[42] The proposed mechanism for the formation of **100** is given in the Scheme 4.27.

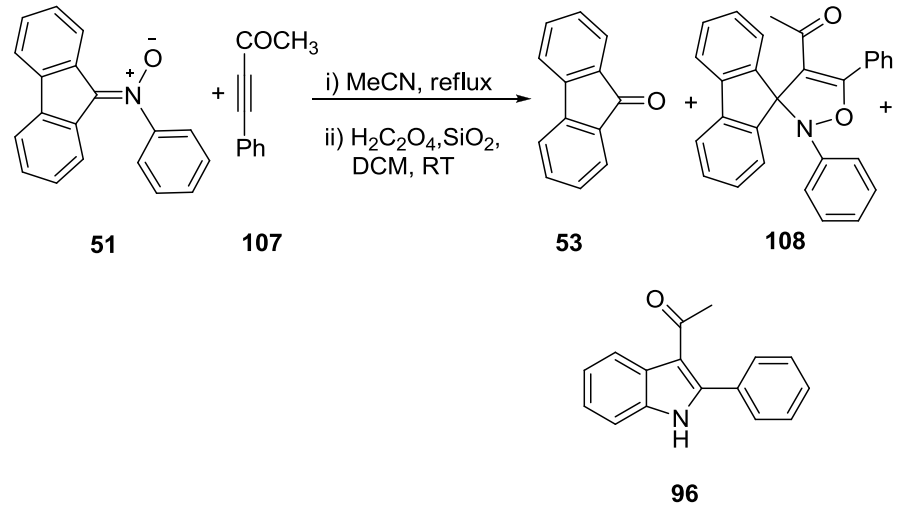


Scheme 4.27

The observed pyrrole formation reaction is a variation of the mechanism illustrated for the generation of 3(*2H*)-furanones **83-86**. This was confirmed by a control experiment where **99** was refluxed in moist acetonitrile for 6h. Under these conditions, **100** was formed in low yields.

4.3.10. Reaction of *N*-fluorenylidene-*N*-phenylnitrone with acetylphenylacetylene

We obtained 3-acylindole **96** along with an isoxazoline derivative **108** by the hydrolysis of the products obtained in the reaction of *N*-fluorenylidene-*N*-phenylnitrone **51** with acetylphenylacetylene **107** (Scheme 4.28).



Scheme 4.28

4.3.11. Targeted Synthesis of 7-Substituted Indole 97

Using the same methodology that we applied in the synthesis of quinoline derivatives, it is possible to synthesize indole derivatives in a pre-planned manner. In the reaction between *N*-arylnitrone and DBA, by replacing DBA with monoactivated acetylenes, we can prepare a variety of substituted indoles (Figure 4.28).

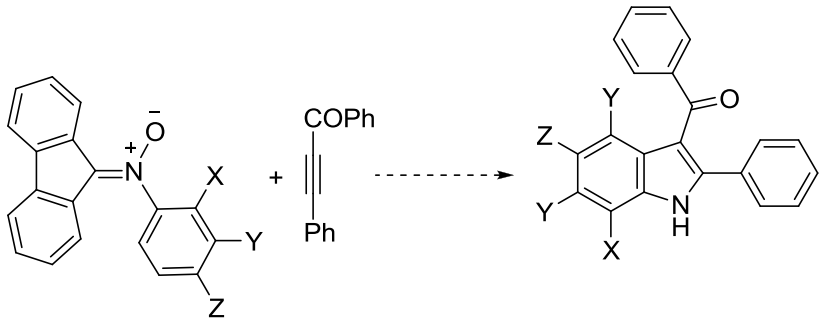


Figure 4.28

In order to establish the power of this new methodology, we attempted the targeted synthesis of an indole derivative with predetermined substituent at a predetermined position. For the synthesis of 7-methoxyindole derivative **97**, for example, we conducted the reaction between *N*-fluorenylidene-*N*-(2-methoxyphenyl)nitrone **72** (X = OCH_3, Y = Z = H) and benzoylphenylacetylene **61**. Hydrolysis of the reaction mixture yielded the expected indole derivative **97** in quantitative amount. The ^{1}H NMR spectrum of the compound showed the -NH proton as a singlet at δ 8.72. The methoxy protons were displayed by the signal at δ 4.00 (s, 3H), and the remaining protons appeared in the δ 7.67 to δ 6.74 in the aromatic region of the ^{1}H NMR spectrum of the compound. In the ^{13}C NMR spectrum, the carbonyl group was indicated by the signal at δ 193.33, and the –OCH_3 carbon was indicated the signal at δ 55.52. All the other carbons appeared from δ 145.85 to δ 103.43 in the ^{13}C NMR spectrum. The structure of the compound was confirmed as **97** on the basis of spectral and analytical data.

4.4. Experimental Section

4.4.1. General Techniques

All reactions were carried out utilizing oven dried glasswares. Solvents used for the experiments were distilled and dried by employing standard protocols. All the reagents were purchased from either *Sigma-Aldrich* or *Spectrochem Chemicals* and were used without further purification. Progress of the reaction and chromatographic separations were monitored by dried silica gel TLC plates (Aluminium sheets coated with silica gel, *E. Merck*). Visualisation of TLC plates was achieved by exposure to UV lamp and iodine vapours. Separation and purification of compounds were done by column chromatography using silica gel (*Spectrochem Chemicals*, 60-120 mesh). The products were further purified by recrystallization from suitable solvent systems. Solvent eluted from the column chromatography was concentrated using *Heidolph, IKA or Buchi* rotary evaporators. Melting points were determined on a *Neolab* melting point apparatus and are uncorrected. Infrared spectra were recorded on *Jasco 4100* and *ABB Bomem (MB Series)* FT-IR spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz *Bruker Avance III* FT-NMR spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS. Elemental analysis was performed using *Elementar Systeme (Vario EL III)*. Molecular mass was determined by electron impact (EI) method using GC-MS (*Agilent GC-7890A, Mass-5975C*) and fast atom bombardment (FAB) using *JMS 600 JEOL* mass spectrometer.

4.4.2. General Procedure for Hydrolysis of 1:1 Adducts

A mixture of oxalic acid (0.25 g, 2 mmol) and silica gel (2 g) in 20 mL of DCM was stirred for about 15 min. The solvent was evaporated off and about 2 mmol of 1:1 adduct in 30 mL of DCM was added to it and the mixture was stirred for about 1h. The progress of the reaction was monitored by TLC. When the reaction was complete, the products were isolated by column chromatography over silica gel using mixtures of hexane and DCM as eluents. The products were further purified by recrystallization from hexane:DCM mixture.

4.4.3. General Procedure for the One-pot Synthesis of Quinolines and Indoles.

A mixture of nitrone (2 mmol) and acetylene (2 mmol) in 25 mL of acetonitrile was stirred for about 6h at RT. The progress of the reaction was monitored by TLC. When the reaction was complete the solvent was removed. The residue was redissolved in 30 mL DCM. A mixture of oxalic acid (2 mmol) adsorbed on silica gel (2 g) was added to the reaction mixture and stirred for about 1h. The progress of the reaction was monitored by TLC. When the reaction was complete, the products were isolated by column chromatography over silica gel using mixtures of hexane and ethyl acetate as eluents. The products were further purified by recrystallization from hexane:DCM mixture.

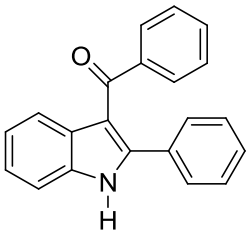
4.4.4. Decompostion of Isoxazoline 99

In a control experiment, a solution of **99** (503 mg, 1 mmol) in moist acetonitrile (10 mL) was refluxed for 6h. Solvent was removed

under reduced pressure and the residue was separated by column chromatography. Most of the isoxazoline **99** was recovered unchanged along with trace amounts of fluorenone and pyrrole **100**.

4.4.5. Spectral and Analytical Data of Significant Compounds

4.4.5.1 Indole 68



mp: 202°C.[43]

IR ν_{max} (KBr): 3149 cm^{-1} (N-H stretch), 3050cm^{-1} (=C-H stretch), 1593cm^{-1} (C=O stretch).

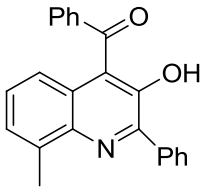
^{1}H NMR ($CDCl_3$): δ 8.57 (s, 1H), 7.96-7.94 (m, 1H), 7.66-7.64 (m, 2H), 7.47-7.16 (m, 11H).

^{13}C NMR ($CDCl_3$): δ: 193.15, 143.54, 139.68, 135.46, 131.72, 131.57, 129.66, 129.22, 128.82, 128.69, 128.41, 127.76, 123.64, 122.23, 121.82, 110.94.

MS: *m/z* 297 (M^+), 298 (M+1).

Elemental analysis calculated for $C_{21}H_{15}NO$:- C: 84.82, H: 5.08, N: 4.71. Found: C: 84.77, H: 5.05, N: 4.69.

4.4.5.2. Quinoline 75



mp: 132°C.

IR ν_{max} (KBr): 3480cm^{-1} (-OH stretch), 1666cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 9.14(s, 1H), 8.18-8.15 (m, 2H), 7.79-7.17 (m, 11H), 2.86 (s, 3H).

^{13}C NMR ($CDCl_3$): δ: 198.21, 148.54, 147.71, 140.88, 137.48, 137.07, 136.08, 132.84, 128.77, 128.67, 128.35, 127.73, 127.42, 126.15, 125.96, 124.16, 121.97,

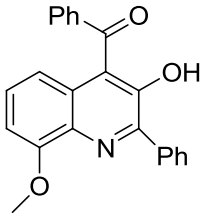
121.36. 17.26.

MS: *m/z* 339 (M^+), 340 (M+1).

Elemental analysis calculated for $C_{23}H_{17}NO_2$:- C: 81.40, H: 5.05, N: 4.13.

Found: C: 81.33, H: 5.02, N: 4.11.

4.4.5.3. Quinoline 76



mp: 176°C.

IR ν_{max} (KBr): 3395cm^{-1} (-OH stretch), 1673cm^{-1} (C=O stretch).

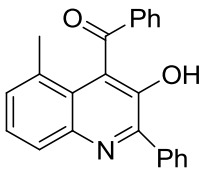
^{1}H NMR ($CDCl_3$): δ 8.65(s, 1H), 8.04-8.02 (m, 2H), 7.80-7.78 (m, 2H), 7.62 (t, 1H, J=7.4), 7.54-7.44 (m, 5H), 7.24-7.22 (m, 1H), 6.91 (t, 2H, J=7.6), 4.07 (s, 3H).

^{13}C NMR ($CDCl_3$): δ: 198.50, 155.89, 150.06, 148.65, 138.18, 136.67, 134.87, 133.98, 129.81, 129.66, 129.45, 128.81, 128.67, 127.75, 126.76, 122.95, 116.90, 105.80, 56.17.

MS: *m/z* 355 (M^+), 356 (M+1).

Elemental analysis calculated for $C_{23}H_{17}NO_3$:- C: 77.73, H: 4.82, N: 3.94, O: 13.51%; Found: C: 77.65, H: 4.79, N: 3.91.

4.4.5.4. Quinoline 79



mp: 160°C.

IR ν_{max} (KBr): 3626cm^{-1} (-OH stretch), 1671cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 8.05(d, J = 8.4Hz, 1H), 7.89-7.84 (m, 4H), 7. 62-7.44 (m, 7H), 7.28-7.27 (m, 1H), 6.30 (s, 1H) 2.30 (s, 3H).

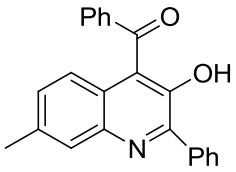
^{13}C NMR ($CDCl_3$): δ: 197.89, 149.98, 145.03, 144.26, 137.85, 135.89, 134.03,

133.01, 130.28, 129.77, 129.44, 129.27, 129.04, 128.96, 128.68, 127.28, 127.09, 125.55, 22.81.

MS: *m/z* 339 (M^+), 340 (M+1).

Elemental analysis calculated for $C_{23}H_{17}NO_2$:- C: 81.40, H: 5.05, N: 4.13. Found: C: 81.35, H: 5.04, N: 4.12

4.4.5.5. Quinoline 80



mp: 134°C.

IR ν_{max} (KBr): 3478cm^{-1} (-OH stretch), 1668cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 9.11(s, 1H), 8.04-8.02 (m, 2H), 7.93 (s, 1H), 7.80-7.12 (m, 10H), 2.49 (s, 3H).

^{13}C NMR ($CDCl_3$): δ: 198.99, 151.63, 148.51, 143.28, 138.49, 136.97, 136.77, 133.90, 129.77, 129.47, 129.44, 129.38, 129.22, 128.81, 128.58, 124.60, 123.09, 121.98, 21.35.

MS: *m/z* 339 (M^+), 340 (M+1).

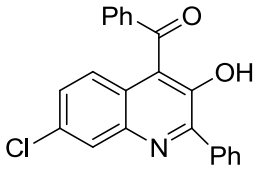
Elemental analysis calculated for $C_{23}H_{17}NO_2$:- C: 81.40, H: 5.05, N: 4.13. Found: C: 81.37, H: 5.04, N: 4.10.

4.4.5.6. Quinoline 81

mp: 105°C.

IR ν_{max} (KBr): 3315cm^{-1} (OH stretch), 1666 cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 9.29 (s, 1H), 8.14-8.01 (m, 3H), 7.78-7.46 (m, 8H), 7.29-7.23 (m,



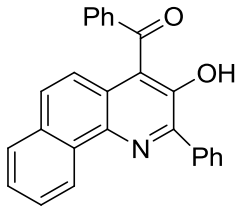
2H).

^{13}C NMR ($CDCl_3$): δ: 198.42, 152.92, 149.30, 143.34, 138.20, 136.22, 134.19, 132.68, 129.85, 129.75, 129.51, 129.02, 128.96, 128.64, 127.97, 126.05, 123.62, 121.88.

MS: *m/z* 359 (M^+), 360 (M+1).

Elemental analysis calculated for $C_{22}H_{14}ClNO_2$:- C: 73.44, H: 3.92, N: 3.89. Found: C: 73.37, H: 3.91, N: 3.87.

4.4.5.7. Benzo(*h*)quinoline 82



mp: 152°C.

IR ν_{max} (KBr): 3491cm^{-1} (-OH stretch), 1673cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 9.34 (d, J=7.6, 1H), 8.70 (s, 1H), 8.23 (d, J=6.8Hz, 2H), 7.83-7.45 (m, 12H), 7.28 (d, J=9.2Hz, 1H).

^{13}C NMR ($CDCl_3$): δ: 198.79, 148.75, 148.23, 140.06, 138.30, 137.07, 134.13, 132.01, 131.65, 129.92, 129.68, 129.37, 128.90, 128.60, 128.49, 127.69, 127.59, 127.45, 124.47, 124.32, 123.37, 122.65.

MS: *m/z* 375 (M^+), 376 (M+1).

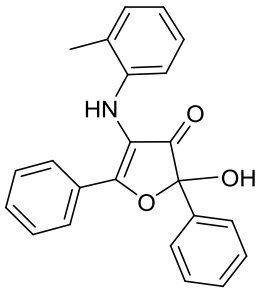
Elemental analysis calculated for $C_{26}H_{17}NO_2$:- C: 83.18, H: 4.56, N: 3.73, O: 8.52%; Found: C: 83.11, H: 4.52, N: 2.72.

4.4.5.8. 3(*2H*)-Furanone 83b

mp: 155°C.

IR ν_{max} (KBr): 3374cm^{-1} (-OH stretch), 1671cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 8.02-8.00 (m, 2H),



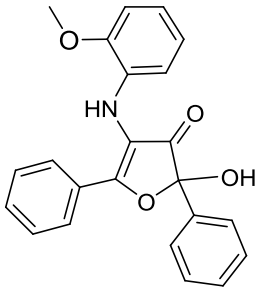
7.61-7.59 (m, 2H), 7.48-7.32 (m, 6H), 7.05-6.64 (m, 3H), 6.28 (d, J=7.6, 1H), 4.85 (s, 1H), 4.45 (s, 1H), 2.24 (s, 3H).

^{13}C NMR ($CDCl_3$): δ: 192.90, 170.22, 158.62, 136.75, 130.50, 127.53, 125.36, 124.51, 123.53, 123.13, 121.56, 120.45, 118. 75, 114.52, 110.19, 107.57, 95.56, 12.33.

MS: *m/z* 357 (M^+), 358 (M+1).

Elemental analysis calculated for $C_{23}H_{19}NO_3$:- C: 77.29, H: 5.36, N: 3.92. Found: C: 77.25, H: 5.35, N: 3.88

4.4.5.9. 3(*2H*)-Furanone 84



mp: 138°C.

IR ν_{max} (KBr): 3367cm^{-1} (-OH stretch), 3304cm^{-1}(-NH stretch), 1701 (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 8.17-8.14 (m, 2H), 7.69-7.40 (m, 8H), 6.85-6.66 (m, 3H), 6.30-6.29 (m, 1H), 5.66 (s, 1H), 3.99 (s, 1H), 3.90 (s, 3H).

^{13}C NMR ($CDCl_3$): δ: 197.82, 175.81, 147.72, 135.75, 133.63, 132.82, 129.77, 128.82, 128.80, 128.46, 128.35, 125.69, 120.85, 119.16, 115.07, 112.52, 110.52, 110.17, 100.58, 55.64.

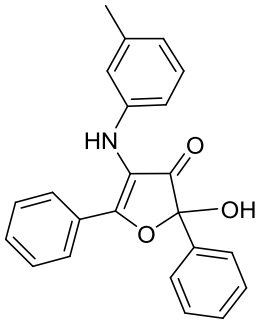
MS: *m/z* 373 (M^+), 374 (M+1).

Elemental analysis calculated for $C_{23}H_{19}NO_4$:- C: 73.98, H: 5.13, N: 3.75, Found: C: 73.95, H: 5.11, N: 3.72.

4.4.5.10. 3(*2H*)-Furanone 86b

mp: 125°C.

IR ν_{max} (KBr): 3388cm^{-1} (-OH stretch),



1691cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 8.07 (d, J=7.6, 2H), 7.60-7.31 (m, 8H), 6.92 (t, J=7.8, 1H), 6.53 (d, J=7.6, 1H), 6.36 (s, 1H), 6.31 (d, 8Hz, 1H), 4.96 (s, 1H), 4.76 (s, 1H), 2.11 (s, 3H).

^{13}C NMR ($CDCl_3$): δ: 197.56, 175.25, 143.14, 138.05, 134.69, 131.89, 128.70, 128.04, 127.77, 127.74, 127.46, 124.69, 119.73, 114.60, 114.23, 110.66, 100.06, 20.47.

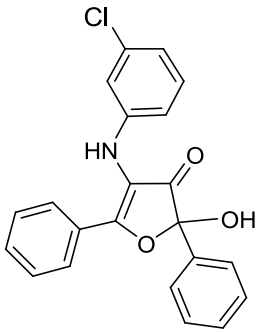
MS: *m/z* 357 (M^+), 358 (M+1).

Elemental analysis calculated for $C_{23}H_{19}NO_3$:- C: 77.29, H: 5.36, N: 3.92. Found: C: 77.26, H: 5.33, N: 3.89.

4.4.5.11. 3(*2H*)-Furanone 86c

mp: 80°C.

IR ν_{max} (KBr): 3423 cm^{-1} (-OH stretch), 1697cm^{-1} (C=O stretch).



^{1}H NMR ($CDCl_3$): δ 8.12 (d, J=7.6, 1H), 7.65-7.63(m, 1H), 7.57(t, J=7.4Hz, 2H), 7.48-7.39 (m, 5H), 7.17 (t, J=7.8, 1H), 6.99(t, J=8Hz, 1H), 6.74-6.44 (m, 3H), 5.21 (s, 1H), 5.09 (s, 1H).

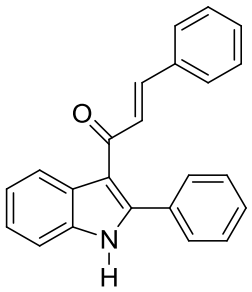
^{13}C NMR ($CDCl_3$): δ: 198.59, 177.45, 145.69, 135.44, 134.99, 133.56, 133.32, 130.28, 130.16, 129.83, 128.93, 128.84, 128.46, 128.16, 128.08, 125.65, 119.73, 114.63, 114.27, 112.57, 101.51.

MS: *m/z* 377 (M^+), 378 (M+1).

Elemental analysis calculated for $C_{22}H_{16}ClNO_3$:- C: 69.94, H: 4.27, N: 3.71,

Found: C: 69.87, H: 4.25, N: 3.70.

4.4.5.12. indole 95



mp: 152°C.

IR ν_{max} (KBr): 3175 cm^{-1} (N-H stretch), 3057cm^{-1} (-C-H stretch), 1634cm^{-1} (C=O stretch).

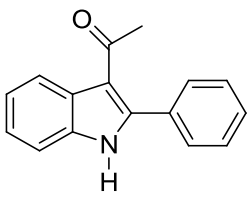
^{1}H NMR ($CDCl_3$): δ 8.53 (s, 1H), 8.46-8.44 (m, 1H), 7.66-7.14 (m, 14H), 6.80 (d, J=15.6 Hz, 1H).

^{13}C NMR ($CDCl_3$): δ: 187.25, 143.89, 140.33, 135.47, 135.38, 132.61, 130.06, 129.64, 129.60, 128.88, 128.65, 128.06, 127.99, 126.65, 123.93, 122.72, 122.66, 116.37, 110.91.

MS: *m/z* 323 (M^+), 324 (M+1).

Elemental analysis calculated for $C_{23}H_{17}NO$:- C: 85.42, H: 5.30, N: 4.33. Found: C: 85.39, H: 5.26, N: 4.31.

4.4.5.13. indole 96



mp: 168°C. [44]

IR ν_{max} (KBr): 3174 cm^{-1} (N-H stretch), 3058cm^{-1} (=C-H stretch), 1594cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ 8.43 (s, 1H), 7.77-7.75 (m, 2H), 7.57-7.32 (m, 5H), 7.20-7.06 (m, 2H), 2.57 (s, 3H).

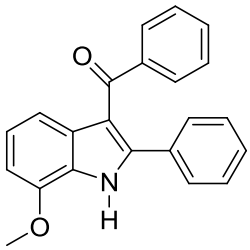
^{13}C NMR ($CDCl_3$): δ: 192.99, 143.65, 141.25, 134.59, 131.50, 128.91, 128.28, 122.48, 121.57, 121.07, 110.50, 14.51.

MS: *m/z* 235 (M^+), 236 (M+1).

Elemental analysis calculated for

$C_{16}H_{13}NO$:- C: 81.68, H: 5.57, N: 5.95. Found: C: 81.63, H: 5.56, N: 5.93.

4.4.5.14. indole 97



mp: 198°C.

IR ν_{max} (KBr): 3150 cm^{-1} (N-H stretch), 3081cm^{-1} (=C-H stretch), 1608cm^{-1} (C=O stretch).

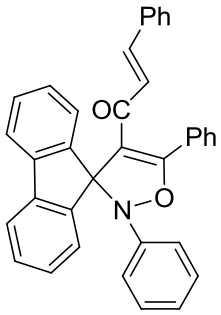
^{1}H NMR ($CDCl_3$): δ 8.72 (s, 1H), 7.67-7.64 (m, 2H), 7.48 (d, J= 8.4Hz, 1H), 7.40-7.38 (m, 2H), 7.34-7.29 (m, 1H), 7.23-7.12 (m, 6H), 6.76-6.74 (m, 1H), 4.00 (s, 3H).

^{13}C NMR ($CDCl_3$): δ: 193.33, 145.85, 142.92, 139.77, 131.85, 131.53, 129.97, 129.68, 129.23, 128.74, 128.39, 127.75, 122.64, 114.31, 103.43, 55.52.

MS: *m/z* 327 (M^+), 328 (M+1).

Elemental analysis calculated for $C_{22}H_{17}NO_2$:- C: 80.71, H: 5.23, N: 4.28. Found: C: 80.66, H: 5.20, N: 4.26.

4.4.5.15. Isoxazoline 99



mp: 105°C.

IR ν_{max} (KBr): 3058cm^{-1} (=C-H stretch), 1649cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ: 7.89-7.86 (m, 2H), 7.67 (d, J=7.6, 2H), 7.64-7.60 (m, 1H), 7.57-7.53 (m, 4H), 7.36-7.32 (m, 2H), 7.27-7.16 (m, 6H), 6.99-6.91 (m, 4H), 6.81-6.76 (m, 1H), 6.61-6.58 (m, 2H), 6.36 (d, J=15.6, 1H).

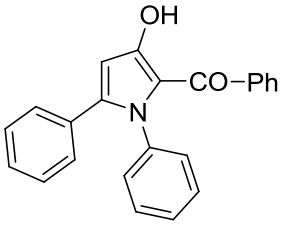
^{13}C NMR ($CDCl_3$): δ : 183.86, 163.14, 145.94, 144.89, 140.77, 140.72, 134.94,

131.69, 130.23, 129.75, 129.36, 128.75, 128.60, 128.12, 127.98, 127.94, 127.93, 125.38, 124.66, 123.59, 120.08, 118.34, 117.04, 84.98.

MS: *m/z* 503 (M^+), 504 (M+1).

Elemental analysis calculated for $C_{36}H_{25}NO_2$:- C: 85.86, H: 5.00, N: 2.78. Found: C: 85.82, H: 4.98, N: 2.75.

4.4.5.16. Pyrrole 100



mp: 130°C.

IR ν_{max} (KBr): 3061cm^{-1} (=C-H stretch), 1598cm^{-1} (C=O stretch).

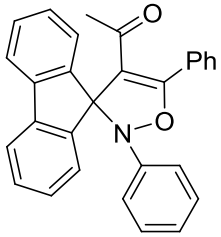
^{1}H NMR ($CDCl_3$): δ 11.17 (s, 1H), 7.22-7.08 (m, 6H), 7.04-6.87 (m, 7H), 6.79-6.77 (m, 2H), 6.18 (s,1H).

^{13}C NMR ($CDCl_3$): δ: 187.80, 160.88, 142.49, 138.50, 137.61, 131.56, 129.75, 129.36, 128.73, 128.29, 128.23, 128.07, 127.55, 127.34, 127.27, 120.10, 99.69.

MS: *m/z* 339 (M^+), 340 (M+1).

Elemental analysis calculated for $C_{23}H_{17}NO_2$:- C: 81.40, H: 5.05, N: 4.13.; Found: C: 81.26, H: 5.02, N: 4.11.

4.4.5.17. Isoxazoline 108



mp: 124°C.

IR ν_{max} (KBr): 3058cm^{-1} (=C-H stretch), 1649cm^{-1} (C=O stretch).

^{1}H NMR ($CDCl_3$): δ: 7.84-7.81 (m, 2H), 7.65-7.52 (m, 6H), 7.37-7.33 (m, 2H), 7.26-7.22 (m, 3H), 6.93-6.89 (m, 2H), 6.79-6.75 (m, 1H), 6.56-6.53 (m, 2H), 2.28 (s, 3H)

^{13}C NMR ($CDCl_3$): δ: 192.37, 163.37, 145.90, 144.89, 140.62, 131.44, 129.74, 129.43, 128.64, 128.28, 128.01, 127.94, 125.52, 123.64, 120.15, 117.26, 117.09, 84.49, 28.70.

MS: *m/z* 415 (M^+), 416 (M+1).

Elemental analysis calculated for $C_{29}H_{21}NO_2$:- C: 83.83, H: 5.09, N: 3.37. Found: C: 83.78, H: 5.05, N: 3.35.

4.5 References

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List of Publications

1. (2-*tert*-Butyl-3-phenyl-2,3-dihydroisoxazole-4,5-diyl)bis-(phenyl methanone), **R**. **Sandhya**, M. Sithambaresan, S. Prathapan and M. R. P. Kurup, *Acta Cryst*.(2013).E**69**, o1284.
2. 1,3-Dipolar Cycloadditions: Mechanism revisited. Rappai, J. P.; **Sandhya**, **R**.; Rakesh, N.; Prathapan, S.; Unnikrishnan, P. A. *Tetrahedron Lett*. (under preparation).
3. Atom Efficient Synthesis of Highly Substituted Quinolines. **Sandhya**, **R**.; Rappai, J. P.; Rakesh, N.; Prathapan, S.; Unnikrishnan, P. A. *Org. Lett*. (under preparation).
4. (2-benzyl-3-(naphthalen-1-yl)-2,3-dihydroisoxazole-4,5-diyl)bis-(phenylmethanone), **R**. **Sandhya**, M. Sithambaresan, and M. R. P. Kurup, *Acta Cryst.,* Section **E** (under preparation).

Posters in Conferences

1. 1,3-Dipolar Cycloaddition Leading to Isoxazoline, **Sandhya**, **R**.; Rakesh, N.; Prathapan, S. *International Conference on Materials for the new Millennium*, *MatCon 2010*.
2. Novel Cycloaddition Reaction Between Nitrone and Electron Deficient Acetylenes, **Sandhya**, **R**.; Unnikrishnan, P. A.; Prathapan, S. *Current Trends in Chemistry*, *CTriC 2012*.
3. Rearrangement and Cyclization of Isoxazoline to Some Biologically Active Compounds, **Sandhya**, **R**.; John, P. R.; Unnikrishnan, P. A.; Prathapan, S. *Current Trends in Chemistry*, *CTriC 2013*.