NUCLEOPHILIC ADDITION OF NITRONES TO ELECTRON DEFICIENT ACETYLENES AND RELATED STUDIES

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In
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By

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Under the supervision of

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CERTIFICATE

This is to certify that the thesis entitled *"***NUCLEOPHILIC ADDITION OF NITRONES TO ELECTRON DEFICIENT ACETYLENES AND RELATED STUDIES***"* is a genuine record of research work carried out by **Mr. Rakesh N.**, 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. All the relevant corrections and modifications suggested by the audience and recommended by the doctoral committee of the candidate during the presynopsis seminar have been incorporated in the thesis.

Kochi-22 **Dr. Prathapan S.**

December 4, 2015 (Supervising Guide)

DECLARATION

I hereby declare that the work presented in the thesis entitled **"NUCLEOPHILIC ADDITION OF NITRONES TO ELECTRON DEFICIENT ACETYLENES AND RELATED STUDIES"** 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, Kochi-22, and the same has not been submitted elsewhere for the award of any other degree.

Kochi-22 **Rakesh N.**

December 4, 2015

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PREFACE

Nitrones or azomethine-*N*-oxides are important precursors for the synthesis of several heterocyclic systems. They belong to the *allyl anion type* 1,3-dipoles and possess unique structural features which make them extraordinarily useful synthons. They behave as 1,3-dipoles in 1,3-dipolar cycloaddition reactions and as electrophiles in reactions with organometallic reagents. These are the two basic reactions given by nitrones. Nitrones also act as '*spin traps*' in which they react with short-lived radicals to furnish stable nitroxide radicals which can be detected and identified by electron paramagnetic resonance (EPR) spectroscopy. Recently SmI_2 catalysed reductive cross-coupling reactions of nitrones have gained significant interest in which the reactions are initiated by single electron transfer (SET) to nitrones. Apart from these reactions, nitrones are also known to participate in reactions which are initiated by the nucleophilic attack of nitrone-oxygen. In our group, we have also explored the nucleophilic character of nitrones through various reactions. The results obtained enabled us to develop a novel two-step one-pot strategy for quinolines and indoles - the heterocycles renowned for their pharmacological applications, from nitrones and electron deficient acetylenes. Using dibenzoylacetylene and phenylbenzoylacetylene as dipolarophiles, we could introduce a desired functional group at a predetermined position of the quinolines or indoles to be synthesised. In this context, the thesis entitled ***"NUCLEOPHILIC ADDITION OF NITRONES TO ELECTRON DEFICIENT ACETYLENES AND RELATED STUDIES"*** portrays our attempt to expand the scope of our

novel synthetic protocol using ester functionalised acetylenes: dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate.

The thesis is organised in to five chapters. The first chapter briefly describes the different classes of reactions that nitrone functionality can tolerate. The research problem is defined at the end of this chapter. The second chapter describes the synthesis of different nitrones used for the present study. The optimisation and expansion of scope of the novel strategy towards quinoline synthesis is discussed in the third chapter. The fourth chapter portrays the synthesis of indole-3-carboxylates using the novel strategy. In the fifth chapter, the reaction of *N*-(2,6-dimethylphenyl) and *N*-(2,4,6-trimethylphenyl)nitrones are discussed. Here we also discuss the mechanistic reinvestigation of Baldwin's proposal in the isoxazoline-oxazoline rearrangement. The major outcome of the work is given at the end of the thesis.

The structural formulae, schemes, tables and figures are numbered chapter-wise since each chapter of the thesis is organized as an independent unit. All new compounds (except two compounds reported in fourth chapter) are fully characterised on the basis of spectral and analytical data and single crystal X-ray analysis on representative examples. Relevant references are included at the end of individual chapters.

List of Abbreviations

AcOH	: acetic acid
br	: broad
C	: centigrade
d	: doublet
DBA	: dibenzoylacetylene
1,3-DCA	: 1,3-Dipolar cycloaddition
DCM	: dichloromethane
DCE	: dichloroethane
DMAD	: dimethyl acetylenedicarboxylate
DMF	: dimethylformamide
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 unoccupied molecular orbital
m	: multiplet
Me	: methyl
m-CPBA	: *m*-chloroperbenzoic acid
mg	: milligram
min	: minute
mL	: millilitre
mp	: melting point
nm	: nanometre
NMR	: nuclear magnetic resonance
ORTEP	: oak ridge thermal ellipsoid plot program
OLED	: organic light emitting diode
KBr	: potassium bromide
Ph	: phenyl
phen	: 1,10-phenanthroline
KOH	: potassium hydroxide
RT	: room temperature
NaOH	: sodium hydroxide
s	: singlet
t	: triplet
TEA	: triethylamine
THF	: tetrahydrofuran
TLC	: thin layer chromatography
TMS	:tetramethylsilane
TsCl	: 4-toluenesulfonyl chloride
UHP	: urea hydrogen peroxide
UV	: ultraviolet
XRD	: X-ray diffraction
Z	: zusammen

CONTENTS

CHAPTER 1

NITRONE: A VERSATILE SYNTHON

1.1. Abstract

Nitrones belong to a unique class of 1,3-dipoles which serve as important building blocks in synthetic organic chemistry. In this chapter we briefly describe a few classes of reactions in which nitrones assume different roles.

1.2. Introduction

Azomethine *N*-oxides, commonly known as *Nitrones*, belong to the *allyl anion type* 1,3-dipoles and are generally used for the construction of nitrogen and oxygen heterocycles (Figure 1.1).[1-3] The extensive use of nitrones in heterocyclic synthesis is due to the fact that most of them are stable compounds and, unlike majority of other dipoles, they do not require *in situ* formation. These 1,3-dipoles were first prepared by Beckmann in 1894[4] and the name '*nitrone*' was formulated by the shortening of 'nitrogen-ketone'[5] since they show significant similarity to carbonyl compounds in reaction with Grignard reagents, oxidation of adjacent methyl group to carbonyl group using selenium dioxide etc.[6-8]

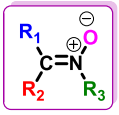


Figure 1.1

The mesomeric effects that predominate in nitrones and ketones clearly show that nitrone (a) behaves as an extended carbonyl function (Figure 1.2).[9]

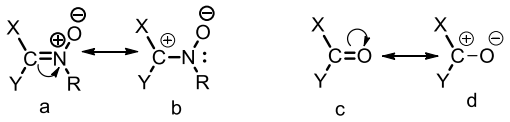


Figure 1.2

Electronic structure of nitrones is influenced by various factors like internal structural characteristics, change in polarity of the solvent, formation of hydrogen bond, complexation, protonation etc.[10] On the basis of theoretical studies, it has been established that the carbon-nitrogen bond in nitrones has almost a pure double bond character while that between N and O atoms has a partial double bond character. Based on this, the zwitterionic structures (i) and (ii), have been proposed for nitrones (Figure 1.3) with (i) as the predominant canonical form.[10]

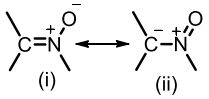


Figure 1.3

Nitrones are broadly classified into two categories: *aldonitrones* and *ketonitrones* (Figure 1.4). In aldonitrones a proton is present on the *α-C*, while in ketonitrones, the *α*-carbon is fully substituted with alkyl or aryl groups.

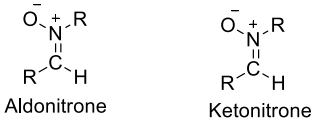
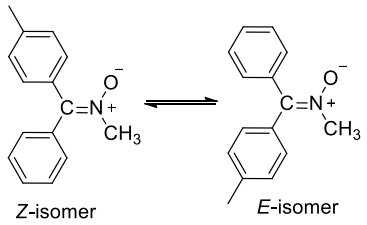


Figure 1.4

Acyclic nitrones exhibit geometrical isomerism[11-13] (*E* and *Z* forms). This was first demonstrated by Semper *et al.* in 1918 for *α*-phenyl-*α*-(4-methylphenyl)-*N*-methylnitrone (Scheme 1.1).[14] Dipole moment studies have been used as a tool to distinguish between the *E* and *Z* –isomers.[6,15]



Scheme 1.1

1.3. Reactivity profile of nitrones

Unique structural features of nitrone described earlier enable this dipole to exhibit broad spectrum of reactivity in various synthetic processes. Among them the most important reactions are: i) *1,3-dipolar cycloaddition reactions* and ii) *electrophilic addition reactions* to organometallic reagents. Nitrones also act as '*spin traps*' in their reaction

with short-lived radicals to furnish stable nitroxide radicals which can be detected and identified by electron paramagnetic resonance (EPR) spectroscopy. Recently SmI_2 catalysed *pinacol-type reductive cross-coupling reactions* of nitrones initiated by single electron transfer (SET) have gained significant interest. Apart from these, nitrones are also known to participate in reactions as *nucleophiles* and in some cases, the reactions are initiated by *nucleophilic attack of nitrone-oxygen* (Figure 1.5).

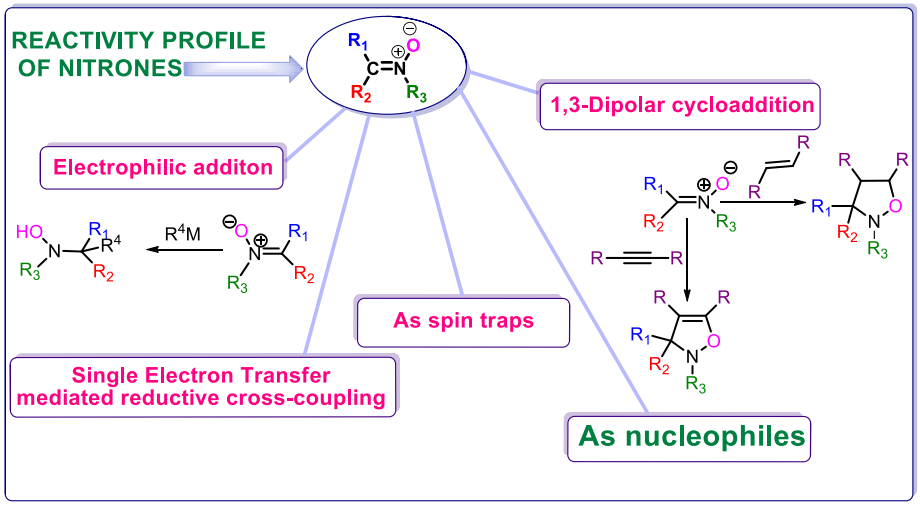


Figure 1.5

Each class of the above mentioned reactions is discussed briefly in the following sessions. Attempts have been made to quote more examples of reactions in which nitrones behave as a nucleophile, since it is more relevant to the present investigation.

1.3.1. 1,3-Dipolar cycloaddition reactions

1,3-Dipolar cycloaddition (DCA) reactions represent the thermal cycloadditions between 1,3-dipoles and dipolarophiles (alkenes or alkynes) to furnish five membered heterocyclic systems[2,16-20] (Figure 1.6).

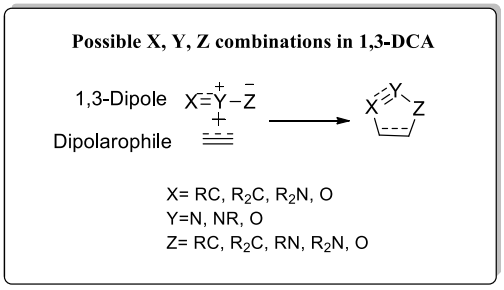


Figure 1.6

1,3-Dipoles used in these reactions are classified into two categories: (i) *allyl-anion* type, having a bent structure and (ii) *propargyl-allenyl anion* type, possessing a linear structure (Figure 1.7).[18] Nitrones belong to the *allyl anion* type 1,3-dipoles.

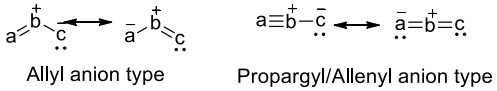


Figure 1.7

Regarding the mechanism of 1,3-DCA, while Huisgen endorsed the concerted mechanistic pathway,[21,22] Firestone came up with a

different proposal: a *diradical* - *stepwise* path way[23-25] (Figure 1.8). Although it started a raging controversy, the former mechanism proved to be the only one which can adequately explain all the experimental observations available at that time. Later in 1986, Huisgen reported the first example of a two-step1,3-DCA reaction involving a zwitterionic intermediate.[26,27] Following this, in 1990's, Quast and Sauer independently reported 1,3-dipolar cycloaddition reactions involving zwitterionic intermediates.[28,29]

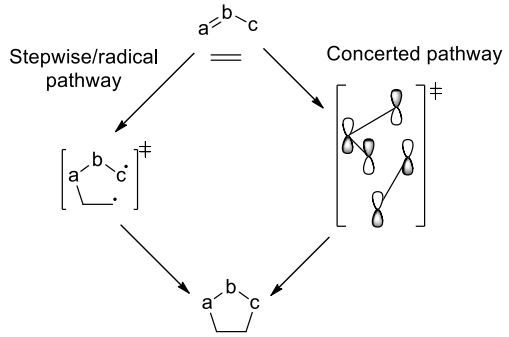
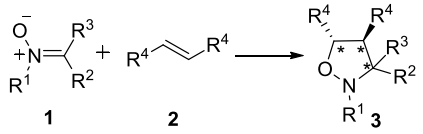


Figure 1.8

Nitrones undergo regioselective[30-33]1,3-DCA reactions with alkenes to furnish isoxazolidines having up to three new chiral centres (Scheme 1.2). The isoxazolines can be easily reduced to amino alcohols retaining all the newly generated asymmetric centres, which serve as building blocks for the synthesis of biologically important molecules.[30] Frontier molecular orbital (FMO) interactions determine the selectivity of reactions. When the dipolarophile is electron - deficient, the HOMO (dipole) - LUMO (dipolarophile) interaction (Normal electron-demand)

is dominant, while in the case of electron-rich dipolarophiles, it is the LUMO (dipole) - HOMO (dipolarophile) interaction (Inverse electron–demand), that assumes the pole position.[30,31]



Scheme 1.2

Depending on the nature of substrates, Lewis acids influence nitrone cycloaddition reactions in two different ways.[34] In normal electron-demand reactions, the LUMO energy of the dipolarophile is lowered by coordination with Lewis acids. This results in reduction of the energy gap between the interacting FMO's facilitating rate acceleration (Figure 1.9).

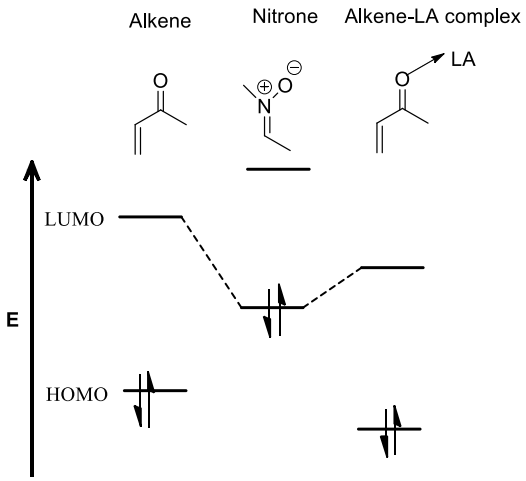


Figure 1.9

In the case of inverse electron-demand reactions, the nitrone is activated to undergo reaction with electron rich alkene. When nitrone is coordinated to the Lewis acid, its LUMO energy is decreased and as a result the energy gap between the two interacting FMO's is reduced. This leads to rate enhancement (Figure 1.10).

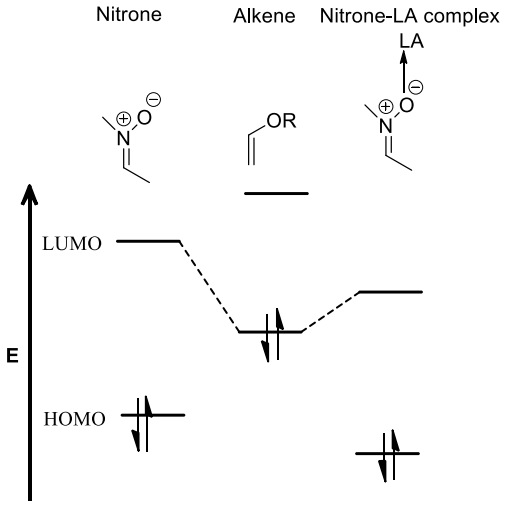


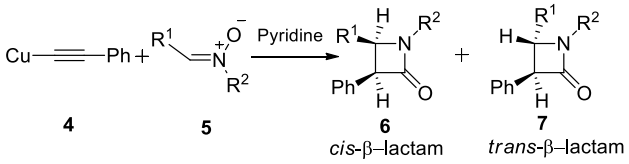
Figure 1.10

The scope of 1,3-DCA reactions of nitrones have been greatly expanded to other dipolarophiles such as allenes[35-39] and alkynes[40-46] and to intramolecular[47-60] versions.

1.3.2. Kinugasa reactions of nitrones

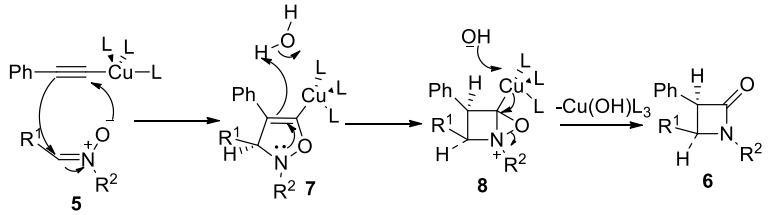
β-Lactams are compounds of considerable synthetic importance since they are present in several antibiotics such as penicillins, carbapenems, cephalosporins etc. They also serve as building blocks for the synthesis of variety of natural products and drugs.[61,62] For example, *β*-lactam is used as an intermediate in the synthesis of Taxol, a potent anti-cancer drug.[63] One of the most important strategies for the synthesis of *β*-lactams that attained significant attention during the past few decades is the *Kinugasa reaction*.

Kinugasa *et al.* in 1972, reported a facile route for the synthesis of β-lactams by the reaction of copper(I) phenylacetylide with *α,N* – diphenylnitrone in anhydrous pyridine under nitrogen atmosphere (Scheme 1.3).[64] Mild reaction conditions and the availability of wide range of nitrones and alkynes are the major advantages of Kinugasa reaction.



Scheme 1.3

A detailed investigation on the scope and limitation of this reaction was done by Ding and Irwin in 1976. They reported that, under the general experimental conditions, the *cis* and *trans* isomers of the *β*-lactam were always obtained in different ratios, the former being the major diastereomer in most cases.[65] They have also proposed a mechanism for the formation of *β*-lactam which suggests the involvement of a highly strained intermediate containing a three-membered oxaziridine and a four-membered azetidine (**8**) (Scheme 1.4). Improved versions of Kinugasa reaction such as the asymmetric version, have been reported, with many of them offering high diastereo- and enantioselectivity.[66-72]

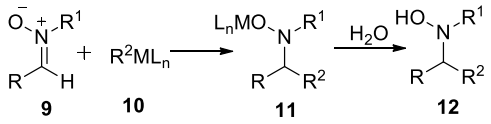


Scheme 1.4

First example for intramolecular variant of Kinugasa reaction was reported by Shintani and Fu in 2003.[73] Inspired by this, a novel route to *β*-lactam fused cyclic enediynes was successfully developed by Basak and Pal in 2006.[74]

1.3.3. Nitrone as electrophile

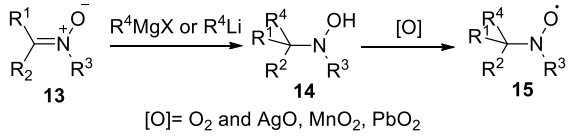
Thanks to two key features, nitrones exhibit good electrophilic character because: the highly polarised C=N bond and the presence of reactive oxygen atom, which acts as an additional chelating centre allowing the formation of five membered ring transition states in the reactions with organometallic reagents.[7,8,75] Nucleophilic addition of organometallic reagents to the azomethine carbon of nitrones furnish *N*,*N*-disubstituted hydroxylamines **12** (Scheme 1.5).



9 **10** **11** **12**

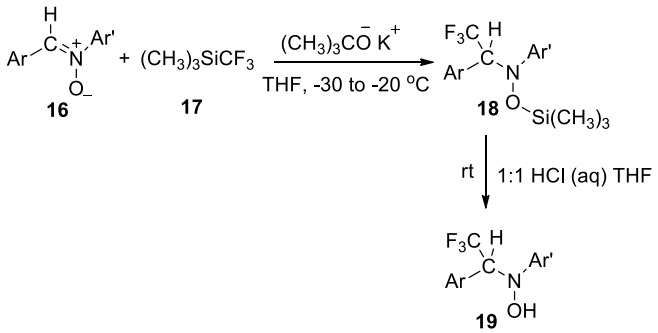
Scheme 1.5

This method serves as an efficient route for the synthesis of primary amines since they can be easily obtained by the reduction of hydroxylamines. A wide range of nitroxyl radicals have also been synthesized using this strategy by the oxidation of hydroxyl amines under mild conditions (Scheme 1.6).[78-83] The organometallic nucleophilic additions of Grignard reagents, organolithium compounds including heterocyclic systems, metal enolates etc., to nitrones have been extensively reviewed.[7,10,75,76] In 2005, Merino described the scope of this reaction in the synthesis of biologically active molecules such as amino acids, nucleosides etc., in a review article.[77]

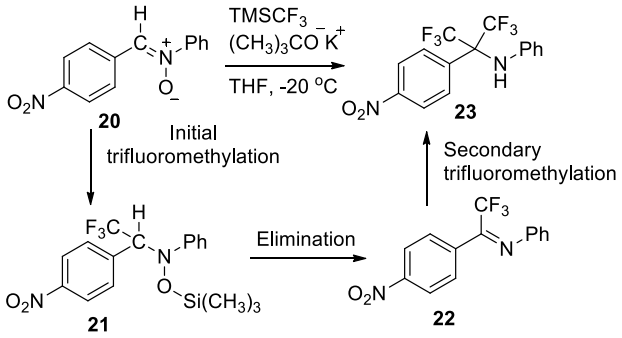


Scheme 1.6

Another important reaction to be considered under electrophilic category is the *perfluoroalkylation* of nitrones. *α,N*-diarylnitrones react with (trifluoromethyl)trimethylsilane ($TMSCF_3$) in the presence of potassium *tert*-butoxide to form *O*-trimethylsilyl ethers of *α*-(trifluoromethyl)hydroxylamines. The protecting group is removed by acid treatment to give *α*-(trifluoromethyl)hydroxylamines (Scheme 1.7). The reaction works well with diarylnitrones and *β,γ*-unsaturated nitrones but α-alkyl and *N*-alkyl nitrones fail to react.[84,85] Certain nitrones, particularly those with strong electron-withdrawing groups on *α*–aryl moiety undergo an elimination/addition sequence to generate *α,α*-bis(trifluoromethyl)amines (Scheme 1.8).



Scheme 1.7



Scheme 1.8

1.3.4. Nitrone as Spin Traps

Spin trapping is a technique used to *trap* and identify the short-lived radical intermediates.[86-96] Free radicals react with spin traps (ST) to form persistent spin adducts (Scheme 1.9) [92] which are stable enough to be detected and identified by electron spin resonance (ESR) spectroscopy. Several oxygen-derived radicals which cannot be detected by ESR under physiological conditions have been identified by this technique.[97]

Scheme 1.9

Nitrones that are commonly used as spin traps include, α-phenyl-*N*-*tert*-butylnitrone (PBN), 5,5-dimethyl-1-pyrroline-*N*-oxide(DMPO), 5-*tert*-butoxycarbonyl-5-methyl-1-pyrroline-*N*-oxide (BMPO) etc., (Figure

1.11). In the case of nitrone spin traps, the stable species formed is the nitroxide radical such as **27** (Scheme 1.10).[98]

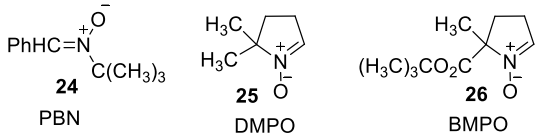
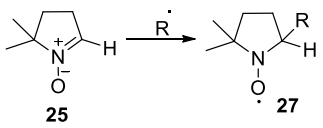
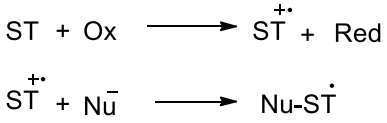


Figure 1.11



Scheme 1.10

One of the limitations of spin trapping technique is possibility of alternative pathways leading to spin adducts. They can be generated by other routes which do not involve R$^{\cdot}$, the radical to be identified, thus causing problems. In some cases the ST is first oxidised to its radical cation (ST$^{\cdot+}$), which then reacts with a nucleophile Nu^{-} to form a stable spin adduct (Scheme 1.11).[92] This phenomenon is known as "*inverted spin trapping"*.[92,98-101]

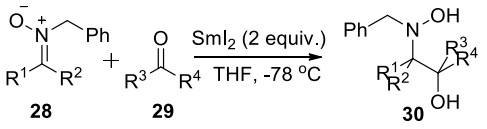


Scheme 1.11

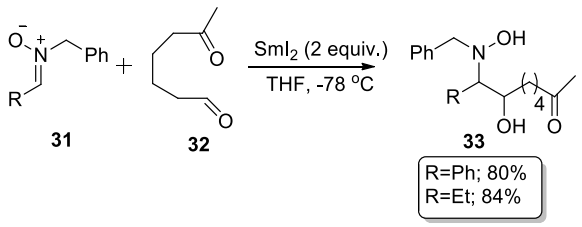
1.3.5. Single electron transfer mediated reductive cross-coupling reactions of nitrones

Samarium(II) iodide, also known as Kagan's reagent,[102] is an important one-electron reducing agent used in current organic synthesis. Mild reaction conditions and high stereoselectivity are the peculiarities of reactions promoted by SmI_2. The range of transformations induced by SmI_2 have been extensively reviewed.[104-112] One among the most important reactions mediated by SmI_2 is the reductive cross-coupling reaction to furnish carbon-carbon bond, which has become an impeccable tool in the hands of synthetic organic chemists.[113]

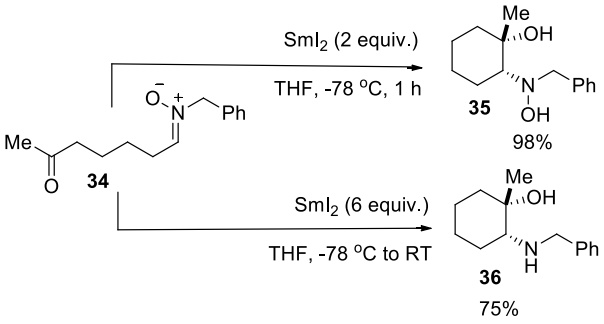
In a pivotal communication, in 2002, Py and Vallee reported a '*nitrone umpolung'* reaction in the synthesis of highly substituted *α-N*-hydroxyaminoalcohols via SmI_2 mediated *pinacol-type heterocoupling* of nitrones with aldehydes and ketones (Scheme 1.12).[114] Here the nitrones served as excellent radical acceptors and SmI_2 as a SET (single electron transfer) agent. The reaction involves a chemoselective SET from SmI_2 to the nitrone group in preference to the carbonyl group. Many aldehydes and ketones tolerated this reaction and when both functionalities were present, the coupling selectively occurred with aldehyde (Scheme 1.13). Using prochiral substrates a mixture of diastereomers was formed. In this communication the authors also reported an intramolecular variant of this reaction producing cyclic *α-N*-hydroxyaminoalcohols (Scheme 1.14).



Scheme 1.12

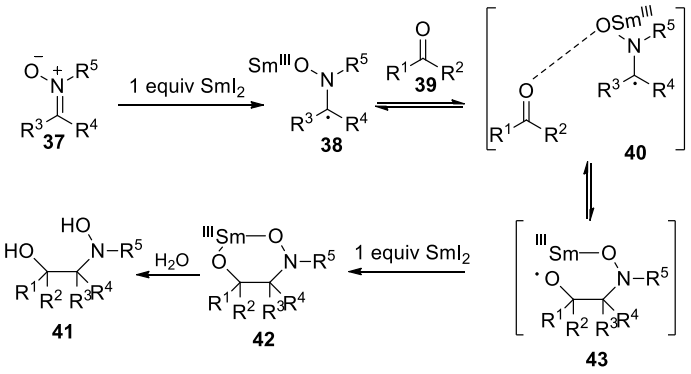


Scheme 1.13



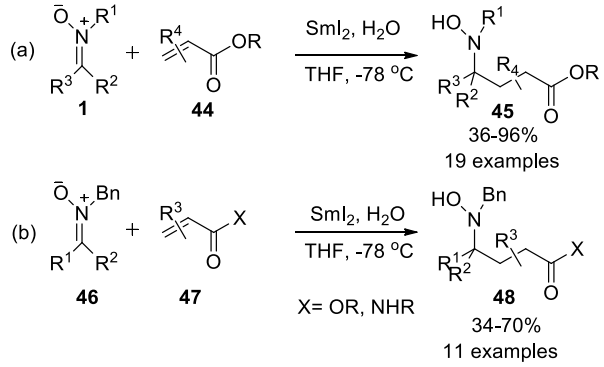
Scheme 1.14

The mechanism involves the reduction of nitrones by SmI_2 to furnish an α-aza-nucleophilic species (radical or anion) which then couples with the carbonyl compounds (Scheme 1.15).



Scheme 1.15

Another important finding came out in 2003, when the groups of Py and Vallee[115,116] and Skrydstrup[117] independently reported the first SmI_2 mediated intermolecular cross-coupling reactions of nitrones with activated olefins (Schemes 1.16). Since then, several reports have appeared on SmI_2 mediated cross-coupling reactions of nitrones with activated olefins and carbonyl compounds, both in inter- and intramolecular versions.[118-129]

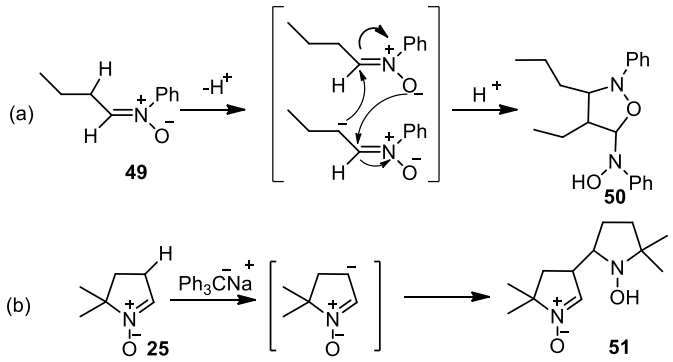


Scheme 1.16

1.3.6. Nitrone as nucleophile

1.3.6.1. Dimerisation of nitrones

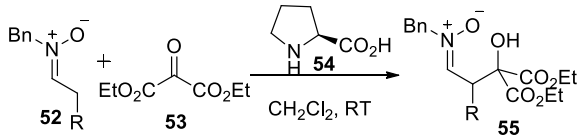
The proton β to $C=N^{+}(O^{-})$ bond is highly acidic in nitrones.[130] This causes some non-cyclic nitrones such as *C*-propyl-*N*-phenylnitrone to undergo *aldol-type* dimerisation spontaneously after its formation [Scheme 1.17(a)].[130,131] However the spontaneous dimerisation[132] is not commonly observed in cyclic nitrones. For DMPO, strong base such as triphenylmethylsodium was required to form aldol-type adduct [Scheme 1.17(b)].[130,133]



Scheme 1.17

1.3.6.2. Asymmetric Nitrone-Aldol reaction

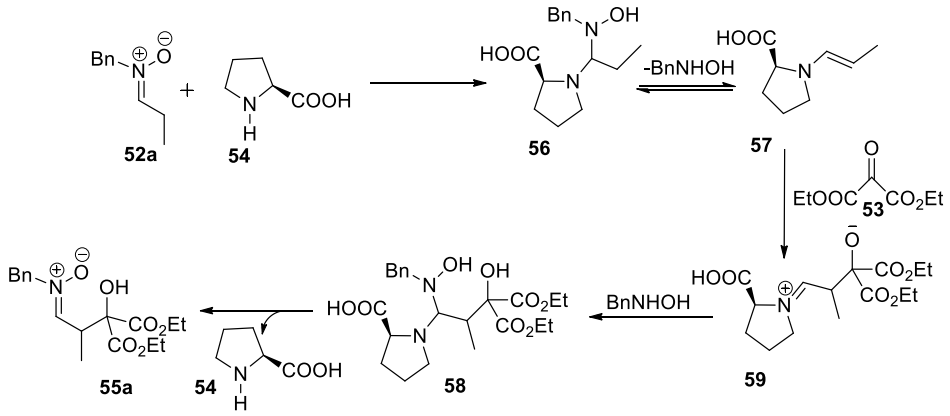
Jorgensen *et al.* reported the synthesis of functionalized *β*-hydroxynitrones via a novel aldol-type reaction of nitrones bearing *α*-hydrogen with activated carbonyl compounds. The reaction rate was not improved by the use of Brønsted and Lewis acids as catalysts. But the use of cyclic secondary amines like pyrrolidine marked a significant enhancement of reaction rate. By using optically active cyclic amines like L-proline, an asymmetric version of this reaction was achieved with up to 80% ee (Table 1.1).[134]



Entry	R	Nitrone	Product	Yield [%]	ee [%]
1	Me	55a	55a	55	76
2	Et	52b	55b	48	80
3	iPr	52c	55c	15	80

Table 1.1

In the first step nitrone **52a** reacts with the catalyst **54** to furnish a chiral enamine intermediate **57**, which then undergoes aldol-type reaction with the activated carbonyl compound followed by the elimination of the catalyst to give the *β*-hydroxynitrone **55a** (Scheme 1.18).

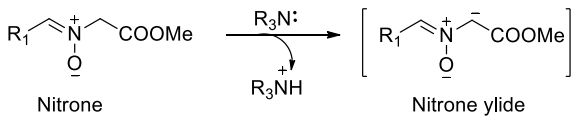


Scheme 1.18

A theoretical investigation of this mechanism was performed by Arno *et al.* using density functional theory (DFT), and the results were in reasonable agreement with the experimental findings.[135]

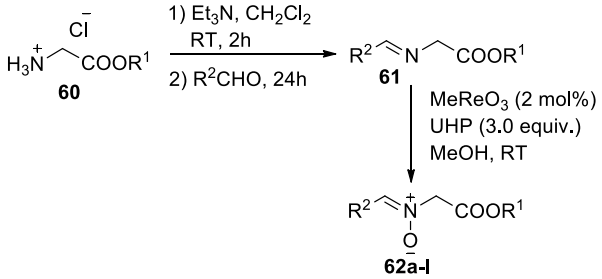
1.3.6.3. Reactions of nitrone ylides

The nitrone ylide/enolate is generated *in situ* when nitrones bearing oxygenated functionalities like ester groups in the *β*-position, reacts with a base (Scheme 1.19).[136,137] The nitrone dipole is then converted to a different dipole (the ylide) which undergoes a nucleophilic addition reaction in preference to the expected 1,3-DCA reaction.



Scheme 1.19

A series of potential substrates for nitrone ylides have been synthesised by Diaz-Martinez *et al.* in 2010.[138] First, the aldimines were synthesised by the treatment of the corresponding aldehydes with the hydrochloride salt of glycinate, and these imines were then oxidised using a catalytic amount of methyltrioxorhenium in presence of urea-hydrogen peroxide complex (UHP), to yield the corresponding nitrones in 65-92% yield (Scheme 1.20, Table 1.2).[138]

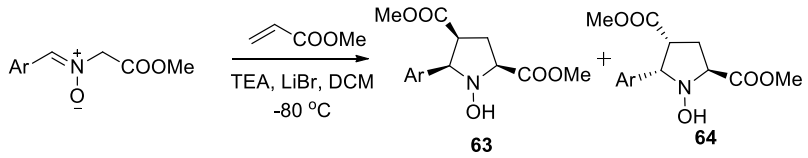


Scheme 1.20

Entry	Nitrone (62)	R^1	R^2	Time (h)	Yield (%)
1	a	Me	Ph	12	88
2	b	Me	4-$MeOC_6H_4$	24	90
3	c	Me	4-BrC_6H_4	48	80
4	d	Me	4-ClC_6H_4	24	79
5	e	Me	4-MeC_6H_4	48	85
6	f	Me	4-PhC_6H_4	48	69
7	g	Me	4-$O_2NC_6H_4$	48	80
8	h	Me	4-NCC_6H_4	48	83
9	i	Me	1-naphthyl	48	65
10	j	Bn	Ph	12	89
11	k	Bn	4-$MeOC_6H_4$	24	81
12	l	Et	Ph	16	92

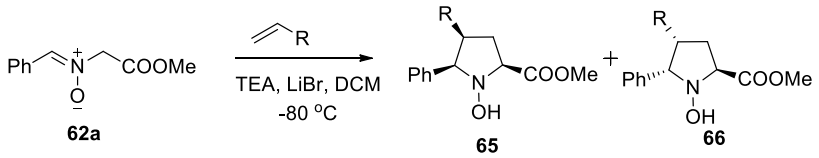
Table 1.2

Merino *et al.* reported the reaction of electron deficient alkenes with a series of *in situ* generated nitrone ylides giving access towards all *cis*-*N*-hydroxypyrrolidones in good yields with high diastereoselectivity. After the preliminary investigation, two optimal conditions were found to be the best for carrying out these reactions: (i) TEA, LiBr, DCM, -80 ^{o}C and (ii) BuLi, THF, -80 ^{o}C (Tables 1.3, 1.4).[137]



Entry	Ar	63:64	Yield
1	Ph	98:2	98
2	4-MeC_6H_4	98:2	94
3	4-PhC_6H_4	80:20	75
4	4-MeOC_6H_4	98:2	92

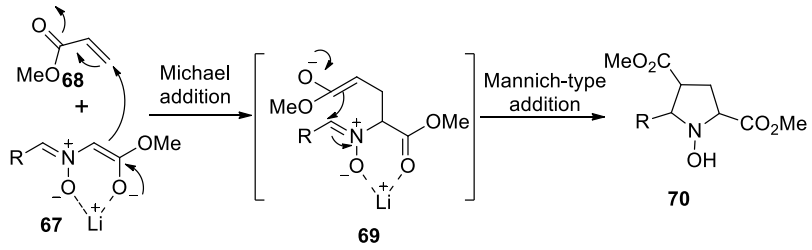
Table 1.3



Entry	R	65:66	Yield
1	COOMe	98:2	98
2	COO_tBu	80:20	96
3	$PhSO_2$	>98:2	98
4	CN	90:10	96

Table 1.4

Based on experimental evidences, a stepwise mechanism is proposed which involves two sequential Michael addition reactions (Scheme 1.21). Later, the authors reported a theoretical investigation of the mechanism using density functional theory (DFT), which was found to be in good agreement with the experimental findings, suggesting a stepwise pathway.[139] A few more examples of such reactions have been reported by the same authors.[140,141.]



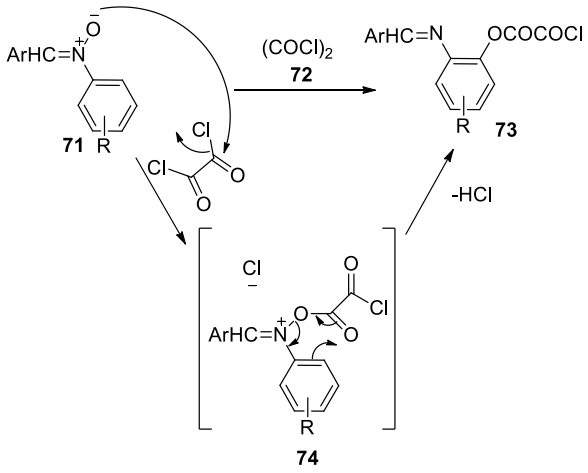
Scheme 1.21

1.3.6.4. Reactions initiated by the nucleophilic attack of nitrone-oxygen

In this section, a few reactions of nitrone nucleophiles that are triggered by the initial nucleophilic attack of the nitrone-oxygen are surveyed. In some cases, the nucleophilic attack is immediately followed by a [3,3]-sigmatropic rearrangement which eventually leads to unconventional products.

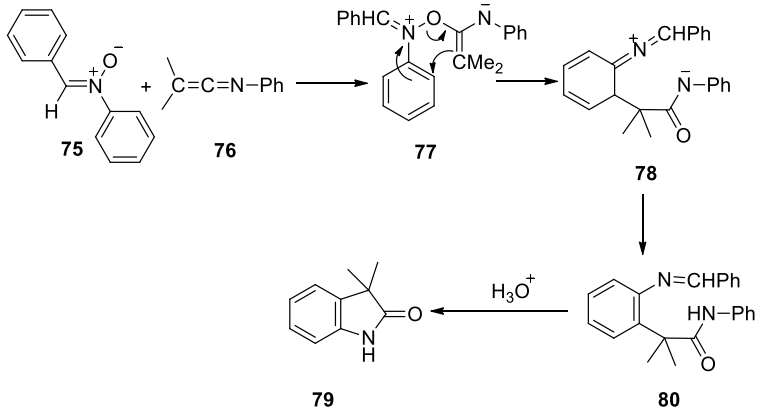
In the reaction of *N*-arylnitrones with electrophiles, regioselective substitution at the ortho position of the *N*-aryl group is observed. This was first reported by Liotta *et al.* in 1974 in the reaction of *N*-arylnitrones

with oxalyl chloride.[142] The chloroglyoxalate group was regioselectively introduced at the ortho position of the *N*-aryl ring. The reaction proceeds through a cyclic six-centered transition state generated by the initial nucleophilic attack of the nitrone-oxygen on oxalyl chloride (Scheme 1.22).



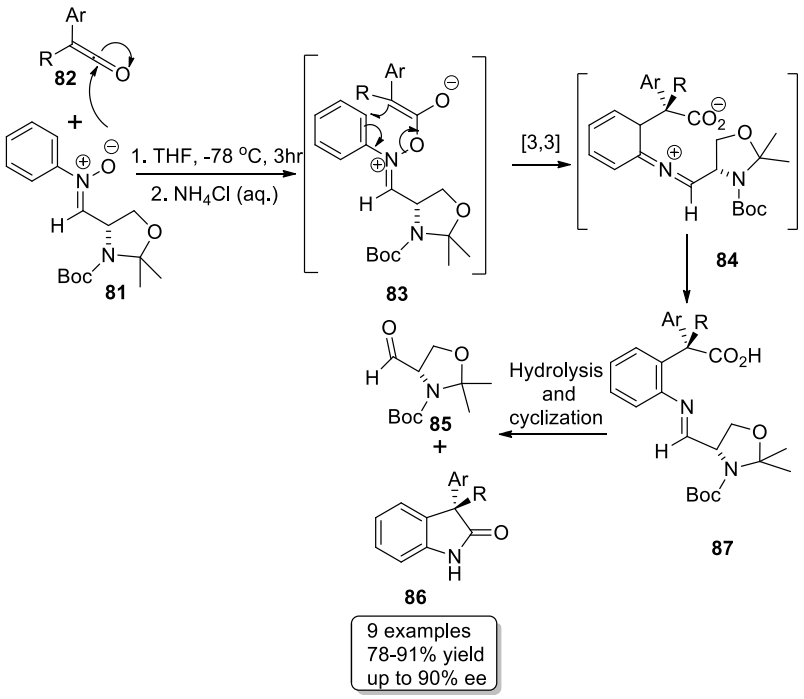
Scheme 1.22

N-Arylnitrones are known to react with ketimines to furnish oxindole derivatives through a multistep process.[143-145] Tsuge *et al.* successfully isolated the 1:1 adduct **80**, the hydrolysis of which furnished oxindole **79**, and subsequently explained the mechanism of the reaction. It involves the initial formation of a zwitterion **77**, which then undergoes a sigmatropic rearrangement to furnish another zwitterion **78**, followed by a hydrogen transfer to give the stable 1:1 adduct **80** (Scheme 1.23).[144]



Scheme 1.23

Numerous reports are also available on *N*-arylnitrone-ketene interactions giving rise to oxindole derivatives.[146-152] In 2009, Duguet *et al.* developed an asymmetric version of this reaction for the synthesis of 3-alkyl-3-aryloxindoles **86**, by the reaction of *N*-phenylnitrone **81** bearing a stereo-directing group (derived from Garner's aldehyde[153,154]) with alkylarylketenes **82**. The reaction marked high yield with excellent enantioselectivity (up to 90% ee).[155] Proposed mechanism for the reaction involves initial nucleophilic attack of the nitrone on ketene followed by a [3,3]-sigmatropic rearrangement which proceeds under the influence of the stereo-directing group, and subsequent aromatization. Imino acid **87**, generated after aromatization undergoes hydrolysis to furnish the enantioenriched oxindole derivative **86** (Scheme 1.24).

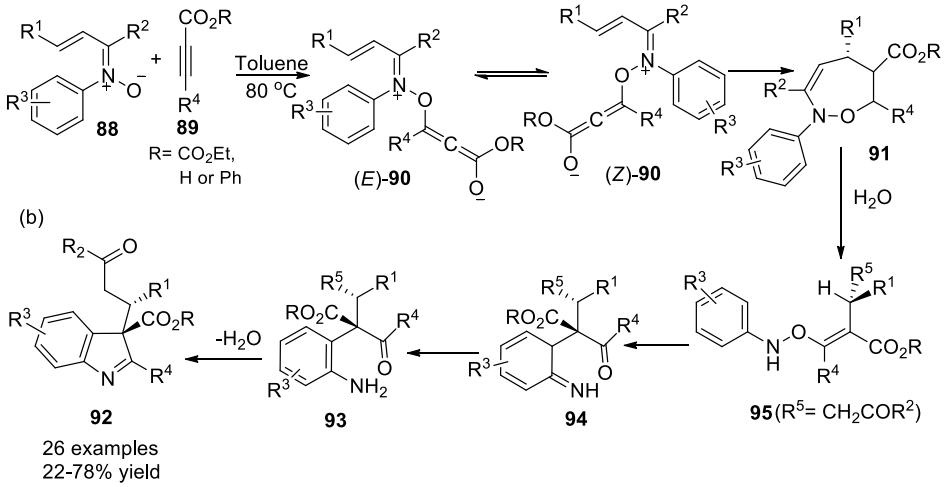


Scheme 1.24

Yang and co-workers reported an efficient strategy for the synthesis of *C*3-quarternary indolenines **92** by the reaction of *α,β*-unsaturated *N*-arylketonitrones **88** with activated alkynes **89**.[156] No transition metal catalysts were used and the reaction described the formation of up to two adjacent quaternary and tertiary stereocenters with high diastereoselectivity. The generality of the reaction was successfully established by using *α,β*-unsaturated *N*-arylketonitrones with or without *β*-substituents and different activated alkynes.

The reaction proceeds through a stepwise process initiated by the nucleophilic Michael attack of the oxygen atom of the nitrone on the

activated alkyne. The resulting seven-membered heterocycle **91** then undergoes eneamine hydrolysis to furnish compound **95**. It then undergoes a [3,3]-sigmatropic rearrangement, tautomerisation and intramolecular condensation to furnish *C*3-quartenary indolenine **92** (Scheme 1.25).

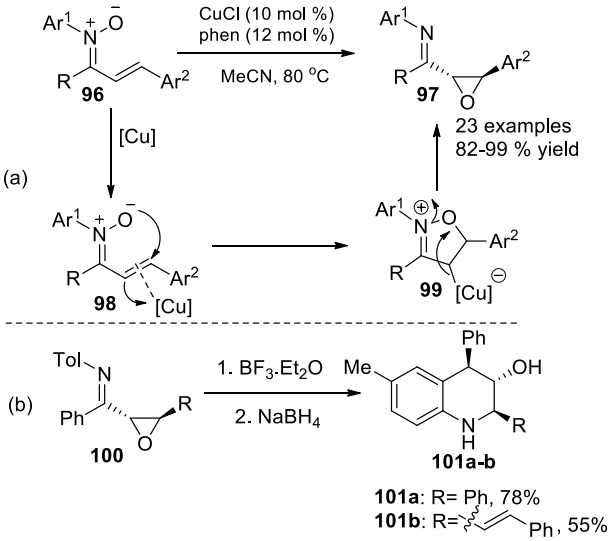


Scheme 1.25

Anderson and co-workers developed a novel strategy for the synthesis of *N*-vinyl and *N*-aryl-*α,β*-unsaturated nitrones by the cross coupling reaction of corresponding oximes with suitable boronic acids. They have also demonstrated the fate of these nitrones in several reactions.[157,158]

In 2013, Anderson reported the conversion of *α,β*-unsaturated nitrones **96** into *α,β*-epoxyketimines **97** by a copper-catalysed oxygen-atom transfer reaction.[158] The proposed mechanism involves the initial

copper-catalysed attack of the nitrone oxygen at the styrenyl group to furnish **99** which undergoes a subsequent N-O bond scission to give the epoxyketimine (Scheme 1.26a). They have also demonstrated that the epoxyketimines can be converted to tetrahydoquinolines by treating them with $BF_3.Et_2O$ and $NaBH_4$ (Scheme 1.32b).

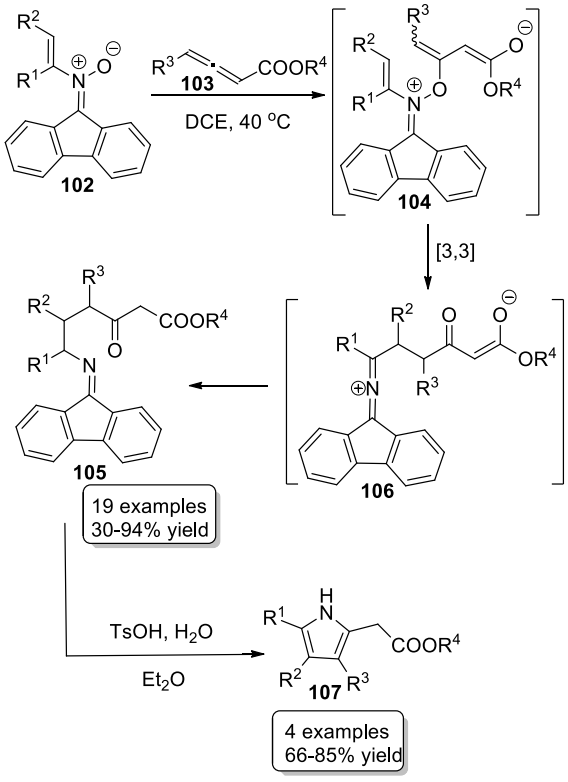


Scheme 1.26

The authors also accomplished the synthesis of 1,4-eneamino ketones **105** through the [3,3]-rearrangement of dialkenylhydroxylamines **104** generated from the reaction between *N*-alkenylnitrones **102** and electron-deficient allenes **103**.[159] The generality of the reaction was established with a series of *N*-alkenylnitrones and different allene components (19 examples, 30-94% yield). The proposed mechanism involves an initial nucleophilic attack of the nitrone to allene forming the

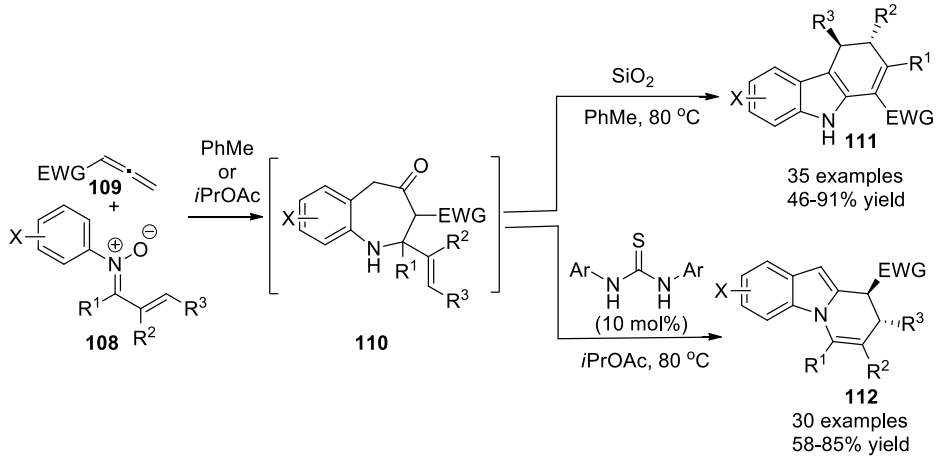
intermediate **104**, which then undergoes a [3,3]-rearrangement to furnish an azalenium intermediate **106**. A subsequent proton transfer generates the stable 1,4-enamino ketone **105**.

Scope of the reaction was extended further, when the 1,4-enaminoketone products were hydrolysed using *p*-toluenesulfonic acid and water in ether to yield tetrasubstituted pyrrole derivatives **107** (4 examples, 66-85% yield) (Scheme1.27).



Scheme 1.27

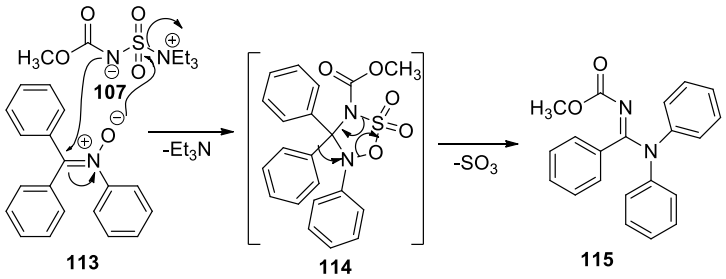
Anderson *et al.* also developed an efficient and selective synthesis of two structurally distinct indole-based heterocycles, dihydrocarbazoles **111** and dihydropyridoindoles **112** from identical starting materials: *N*-aryl-*α,β*-unsaturated nitrones **108** and electron-deficient allenes **109**.[160] The choice of solvent and additives played the crucial role in bringing about two distinct reactions from the common intermediate. Both the reactions marked high yield and high diastereoselectivity (Scheme 1.28).



Scheme 1.28

Burgess reagent is a versatile reagent extensively used in the synthesis of natural products.[161,162] Recently, Burgess reagent mediated novel *C*-to-*N* migration reaction in nitrones was reported from our group.[163] In this communication, by selecting suitable prototypes of aldo- and ketonitrones, Sajitha *et al.* demonstrated that the *C*-to-*N* migration

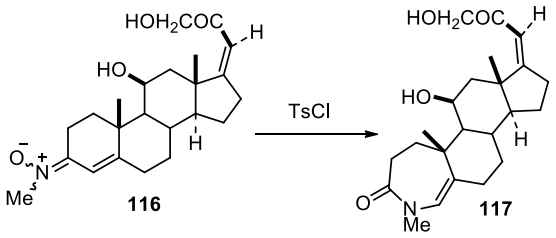
observed in this reaction is a general phenomenon. The proposed mechanism involves a [3+2] annulation across a σ-bond followed by rearrangement involving *C*-to-*N* migration (Scheme 1.29).



Scheme 1.29

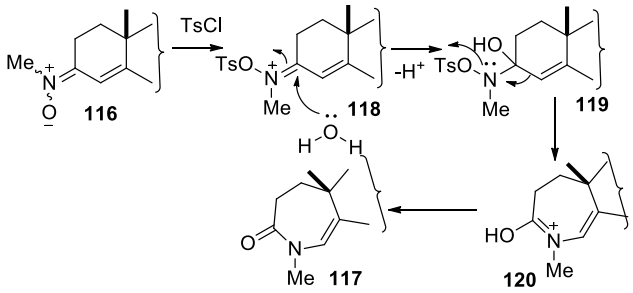
1.3.6.4.1. Beckmann-type rearrangement of nitrones

Nitrones are known to undergo thermal and photochemical rearrangements to imides, oxaziridines etc.[164] In 1972, Barton and co-workers reported a novel rearrangement of ketonitrones to amide using *p*-toluenesulfonyl chloride in pyridine, in the conversion of some steroid unsaturated ketones to the corresponding lactams (Scheme 1.30). They termed this reaction as '*a convenient alternative to the Beckmann rearrangemet'*.[165,166]



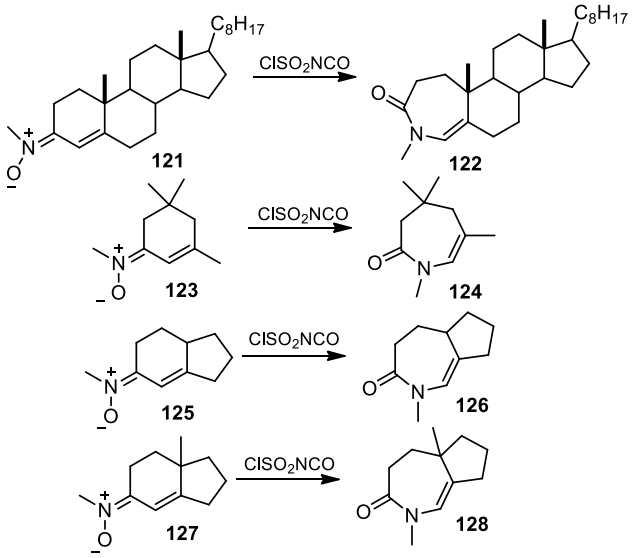
Scheme 1.30

In contrast to the Beckmann rearrangement of oximes, the nitrone-amide rearrangement was not affected by the stereochemistry of the nitrone *ie*. both *syn* and *anti* isomers rearranged to the same lactam (Scheme 1.31).[165-168]



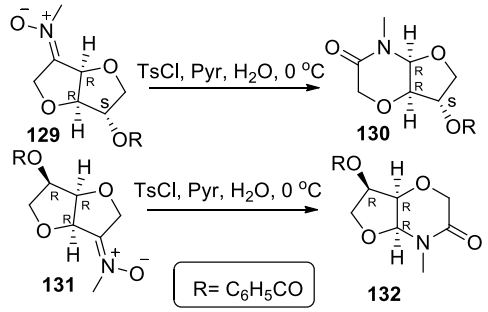
Scheme 1.31

Later in 1988, Dhar *et al.* showed that chlorosulfonyl isocyanate (CSI) can be effectively used for the conversion of nitrones to amides. This was illustrated by the reaction of CSI with different nitrones derived from cyclic conjugated ketones (Scheme 1.32).[169]



Scheme 1.32

Cekovic *et al.* in 2001, reported the synthesis of bicyclic *δ*-lactone **130** and its stereoisomer **132** by the *Beckmann rearrangement* of nitrones **129** and **131** respectively (Scheme 1.33).[170]

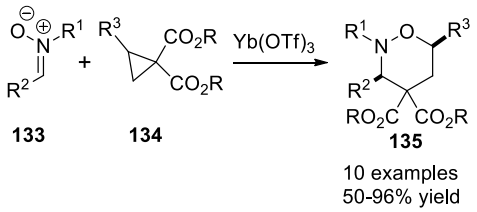


Scheme 1.33

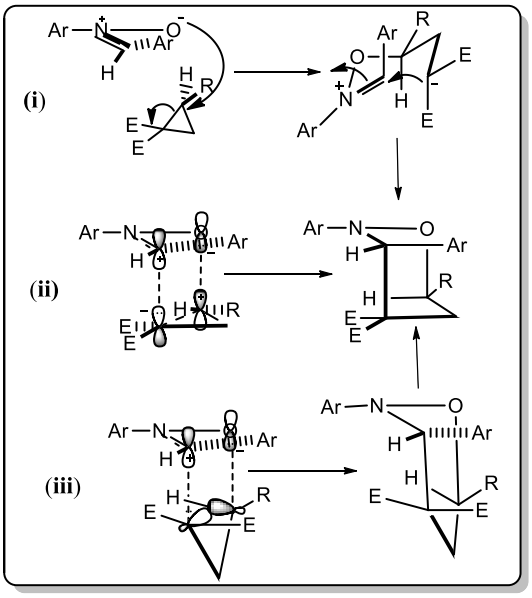
1.3.6.4.2. Reaction of nitrones with cyclopropanes

Recently, [3+3] cycloaddition reactions of donor–acceptor cyclopropanes with nitrones have been developed by several research groups.[171-180] These reactions are also designated as homo [3+2] dipolar cycloaddition reactions.[173] The first report appeared in 2003, in which Young and Kerr described the synthesis of tetrahydro-1,2-oxazine derivatives **135** by the reaction of nitrones with 1,1-cyclopropane diesters, catalysed by $Yb(OTf)_3$ (Scheme 1.34).[173] The reaction was found to be diastereoselective giving products in which the substituents at C-3 and C-6 bore a *cis*-relationship. Since the actual course of the reaction is uncertain, the authors proposed three mechanistic possibilities: (i) a stepwise attack of the nitrone oxygen on the cyclopropane followed by the malonate attack on the resulting iminium ion; (ii) reaction of nitrone with a 1,3-dipolar species generated by the ring opening of cylclopropane; and (iii) the concerted cycloaddition of nitrone across the cyclopropane σ-bond (Scheme 1.35).

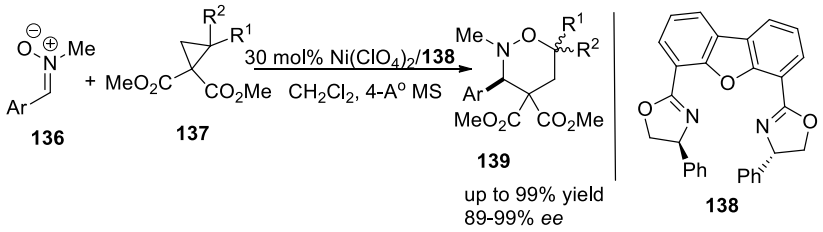
They have also developed a three-component version of this reaction which involves the *in situ* formation of nitrones by the condensation of aldehydes with hydroxylamines.[174] In 2004, Sibi *et al.* reported the first enantioselective version of this reaction, using chiral Lewis acid catalysis (Scheme 1.36).[177] Synthetic utility of this reaction has been demonstrated by using it in the total synthesis of (+)-Nakadomarin A, an uncommon alkaloid possessing a range of potential bioactivities.[180]



Scheme 1.34



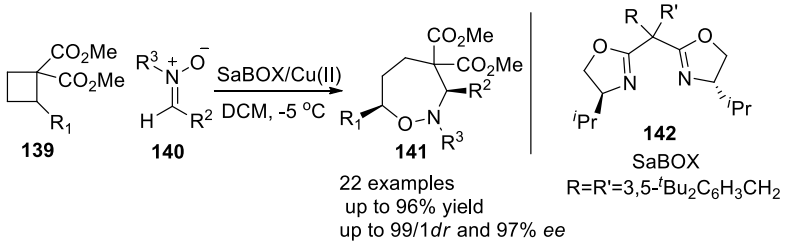
Scheme 1.35



Scheme 1.36

The first intramolecular variant of this reaction was reported by Dias and Kerr in 2009.[181] Apart from $Yb(OTf)_3$, MgI_2,[175] ureas[182] and $Ca(OTf)_2$[183] are also found to be efficient catalysts for carrying out nitrone-cyclopropane reactions.

Recently, a formal [4+3] cycloaddition of nitrones with 1,1-cyclobutane diesters has been developed.[184] The authors described the enantioselective synthesis of 1,2-oxazepane derivatives **141** by the reaction of nitrones **140** with cyclobutane-1,1-dicarboxylates **139**, catalysed by sterically hindered chiral SaBOX/Cu(II) complex (Scheme 1.37). The ring opening of the cyclobutane by the nucleophilic attack of nitrone is presumed to be the rate-determining step of this reaction.



Scheme 1.37

1.3.6.4.3. Reaction of nitrones with electrophilic vinyl carbene intermediates

Vinylcarbenoids, bearing electrophilic character at the vinylogous position, have emerged as a very useful reagent for various transformations (Scheme 1.46). Doyle and co-workers, in 2011, developed a formal [3+3] cycloaddition reaction of nitrones with vinyl

carbenes generated from TBS-protected enol diazoacetate, for the synthesis of 3,6-dihydro-1,2-oxazines **149**, catalysed by chiral dirhodium(II) carboxylates (Figure 1.12).[185]

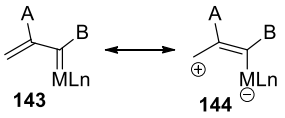
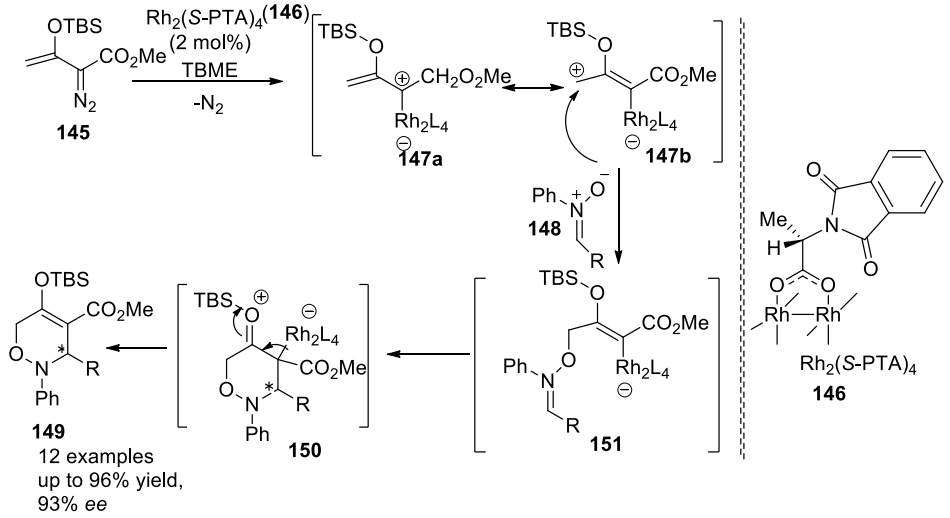


Figure 1.12

The reaction mechanism involves the initial formation of the electrophilic vinyl carbene by the dirhodium carboxylate insertion and loss of dinitrogen. The nucleophilic attack of the nitrone-oxygen at the γ-position of vinyl carbene followed by the intramolecular iminium addition of the catalyst-activated vinyl ether, facilitated by stabilization provided by the TBSO group, and the elimination of the catalyst forms the cycloadduct **149** in a step-wise or concerted manner (Scheme 1.38).



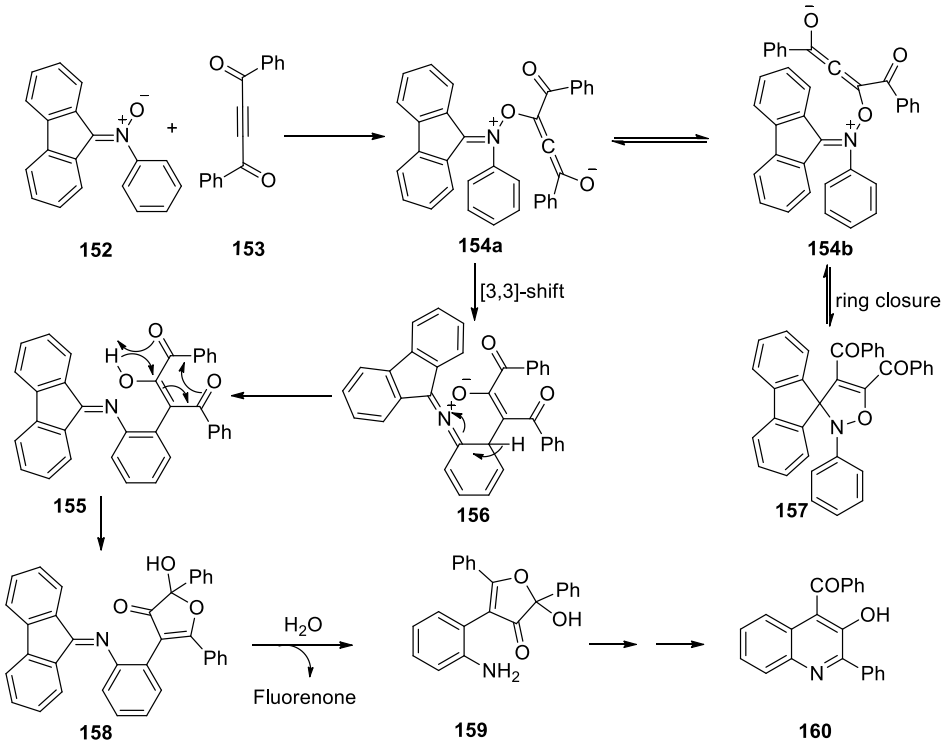
Scheme 1.38

A few more reports are available in the literature which deal with the reaction of nitrones and enol diazoacetates giving 1,2-oxazines.[186-188]

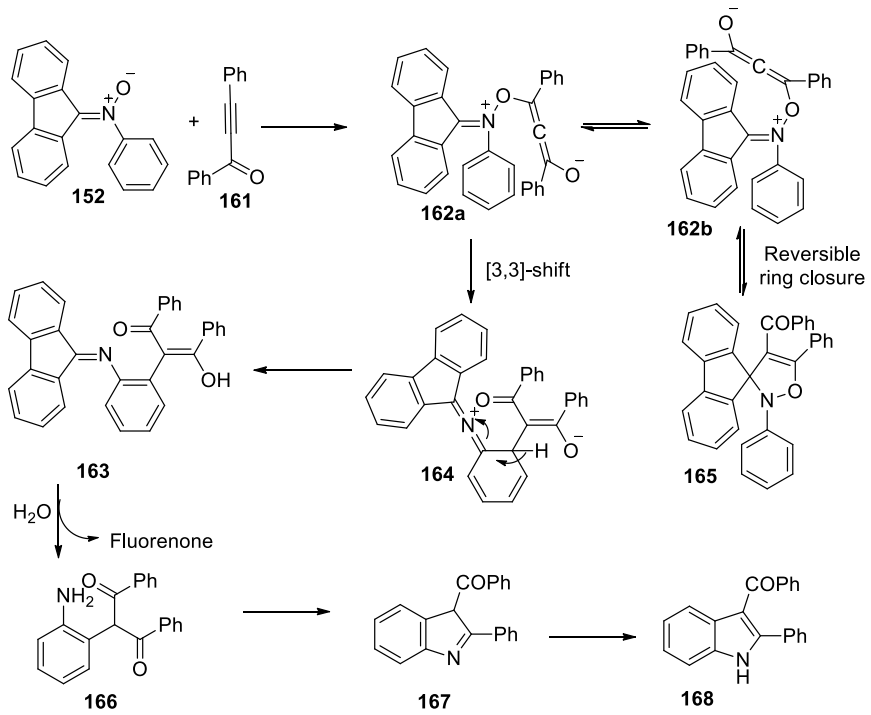
1.4. Definition of the current problem

In our group, we have independently developed an efficient and facile route for the synthesis of highly substituted quinolones and indoles by the reaction of nitrones with electron deficient acetylenes (dibenzoylacetylene and benzoylphenylacetylene).[189,190] Detailed mechanistic study showed that hydrolysis of unconventional primary adducts **158** and **163** formed by nucleophilic addition of nitrones to these electron deficient acetylenes furnished quinolines **160** (Scheme 1.39) and

indoles **168** (Scheme 1.40) respectively. Adducts **158** and **163** were formed by the aza-Cope rearrangement of zwitterionic intermediates which in turn were formed by the initial nucleophilic attack by the nitrone-oxygen on electron deficient acetylenes that are excellent Michael aceptors.[191] We could introduce substituents at predetermined positions of the target molecules quite successfully.



Scheme 1.39



Scheme 1.40

For the present study, we propose to further validate and generalize the hypothesis of synthesising quinolines and indoles having predetermined substitution pattern using ester functionalised acetylenes (dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate). The reason for choosing ester group is that it is amenable for transformation to other useful functionalities such as amide, aldehyde, nitrile etc., which would presumably expand the scope of our strategy. So our primary goal was to synthesise ester functionalised quinolines and indoles having predefined substitution pattern. Since the ortho positions of the *N*-aryl ring are active centers for the formation of quinolines[189], we also wanted

to study the reactions between *N*-arylnitrones having both ortho positions of *N*-aryl group blocked and DMAD. Furthermore, we propose to explore the possibility of isolating intermediates such as isoxazolines, aziridines, oxazolines proposed (but not isolated) by Baldwin *et al.* with a similar nitrone.[192]

1.5. Objectives

- Synthesis of nitrone precursors.
- Synthesis of a few quinoline derivatives.
- Synthesis of a few indole-3-carboxylates.
- To study the reaction of *N*-(2,6-dimethylphenyl) and *N*-(2,4,6-trimethylphenyl) nitrones with DMAD.

1.6. References

1. Hamer, J.; Macaluso, A. *Chem. Rev*. **1964**, *64*, 473.
2. Huisgen, R. *Angew. Chem. Int. Ed. Engl*. **1963**, *2*, 565.
3. Tufariello, J. J. *Acc. Chem. Res*. **1979**, *12*, 396.
4. Beckmann, E. *Ber. Dtsch. Chem. Ges*. **1894**, *27*, 1957.
5. Pfeiffer, P. *Liebigs Ann. Chem.* **1916**, *411*, 72.
6. Smith, L. I. *Chem. Rev*. **1938**, *23*, 193
7. Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759
8. Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, *6*, 695.
9. Delpierre, G. R.; Lamchen, M. *Q. Rev. Chem. Soc*. **1965**, *19*, 329
10. Feuer, H. in *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in synthesis*, Second edition, **2008**, John Wiley & Sons, Inc. Chichester, UK
11. Semper, L.; Lichtenstadt, L. *Ber.* **1918**, *51*, 928.
12. Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 5739.
13. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, **1994**.
14. Semper, L.; Lichtenstadt, L. *Chem. Ber.* **1918**, *51*, 928.
15. Sutton, L. E.; Taylor, T. W. J. *J. Chem. Soc.* **1931**, 2190.
16. Huisgen, R. *Angew. Chem. Chem., Int. Ed.* **1963**, *2*, 633.
17. Huisgen, R. *Angew. Chem. Chem., Int. Ed.* **1968**, *7*, 321.
18. Huisgen, R. in *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley and Sons: New York, **1984**; *Vol. 1*.
19. Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781.
20. Ess, H. D.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187.
21. Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291.
22. Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.

23. Firestone, R. A. *J. Org. Chem*. **1968**, *33*, 2285.
24. Firestone, R. A. *J. Org. Chem*. **1972**, *37*, 2182.
25. Firestone, R. A. *Tetrahedron* **1977**, *33*, 3009.
26. Huisgen, R.; Mloston, G.; Langhals, E. *J. Org. Chem.* **1986**, *51*, 4085.
27. Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc*. **1986**, *108*, 6401.
28. Quast, H.; Regnat, D.; Peters, E.; Peters, K.; von Schnering, H. G. *Angew. Chem. Int. Ed.* **1990**, *29*, 695.
29. Weber, A.; Sauer, J. *Tetrahedron Lett*. **1998**, *39*, 807.
30. Tufariello, J. J. in *1,3-Dipolar Cycloaddition Chemistry;* Padwa, A., Ed.; Wiley: New York, **1984**, *Vol 2.*
31. Frederickson, M. *Tetrahedron* **1997**, *53*, 403.
32. Mendez, F.; Tamariz, J.; Geerlings, P. *J. Phys. Chem. A* **1998**, *102*, 6292.
33. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev*. **1998**, *98*, 863.
34. Gothelf, K. V.; Jorgensen, K. A. *Chem. Commun.* **2000**, 1449.
35. Padwa, A.; Kline, D. N.; Koehler, K. F.; Matzinger, M.; Venkatramanan, M. K. *J. Org. Chem*. **1987**, *52*, 3909.
36. Padwa, A.; Kline, D. N.; Norman, B. H. *J. Org. Chem.* **1989**, *54*, 810.
37. Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1989**, *54*, 2862.
38. Zhao, B-X.; Eguchi, S. *Tetrahedron* **1997**, *53*, 9575.
39. Back, T. G.; Clary, K. N.; Gao, D. *Chem. Rev.* **2010**, *110*, 4498.
40. March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milan, S. *J. Chem. Soc., Chem. Commun*. **1995**, 2097.
41. Busque, F.; March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milan, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437.

42. March, P.; Figueredo, M.; Font, J.; Milan, S.; Alvarez-Larena, A.; Piniella, J. F.; Molins, E. *Tetrahedron* **1997**, *53*, 2979.
43. Tomioka, Y.; Nagahiro, C.; Nomura, Y.; Maruoka, H. *J. Heterocycl. Chem*. **2003**, *40***,** 121.
44. Gonzales-Cruz, D.; Tejedor, D.; Armas, P.; Morales, E. Q.; Garcoa-Tellado, F. *Chem. Commun.* **2006**, 2798.
45. Popov, S. A.; Chukanov, N. V.; Romanenko, G. V.; Rybalova, T. V.; Gatilov, Yu. V.; Reznikov, V. A. *J. Heterocycl. Chem*. **2006**, *43*, 277.
46. Popov, S. A.; Reznikov, V. A. *J. Heterocycl. Chem*. **2006**, *43*, 293.
47. Tranmer, G. K.; Keech, P.; Tam, W. *Chem. Commun*. **2000**, 863.
48. Tranmer, G. K.; Tam, W. *J. Org. Chem*. **2001**, *66*, 5113.
49. Aurich, H. G.; Koster, H. *Tetrahedron* **1995**, *51*, 6285.
50. Baskaran, S.; Aurich, H. G.; Biesemeier, F.; Harms, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3717.
51. Aurich, H. G.; Geiger, M.; Gentes, C.; Koster, H. *Tetrahedron Lett.* **1996**, *37*, 841.
52. Aurich, H. G.; Geiger, M.; Gentes, C.; Harms, K.; Koster, H. *Tetrahedron* **1998**, *54*,3181.
53. Roy, B. G.; Maity, J. K.; Drew, M. G. B.; Achari, B.; Mandal, S. B. *Tetrahedron Lett*. **2006**, *47*, 8821.
54. Cordero, F. M.; Gensini, M.; Goti, A.; Brandi, A. *Org. Lett*. **2000**, *2*, 2475.
55. Gravestock, M. B.; Knight, D. W.; Lovell, U. J. S.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3143.
56. Manzoni, L.; Arosio, D.; Belvisi, L.; Bracci, A.; Colombo, M.; Invernizzi, D.; Scolastico, C. *J. Org. Chem*. **2005**, *70*, 4124.
57. Chatterjee, A.; Bhattacharya, P. K. *J. Org. Chem*. **2006**, *71*, 345.

58. Gebarowski, P.; Sas, W. *Chem. Commun*. **2001**, 915.

59. Padwa, A.; Meske, M.;Ni, Z. *Tetrahedron Lett*. **1993**, *34*, 5047.

60. Padwa, A.; Meske, M.; Ni, Z. *Tetrahedron* **1995**, *51*, 89.

61. Ojima, I.; Delaoge, F. *Chem. Soc. Re*v. **1997**, *26*, 377.

62. Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887.

63. Kingston, D. G. I. *Chem. Commun.* **2001**, 867.

64. Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466.

65. Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2382.

66. Okuro, K.; Enna, M.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1107.

67. Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem*. **1995**, *60*, 4999.

68. Basak, A.; Mahato, T.; Bhattacharya, G.; Mukherjee, B. *Tetrahedron Lett.* **1997**, *38*, 643.

69. Basak, A.; Bhattacharya, G.; Bdour, H. M. M. *Tetrahedron* **1998**, *54*, 6529.

70. Basak, A.; Ghosh, S. C.; Bhowmick, T.; Das, A. K.; Bertolasi, V. *Tetrahedron Lett.* **2002**, *43*, 5499.

71. Lo, M. M. -C.; Fu, G. C. *J. Am. Chem. Soc*. **2002**, *124*, 4572.

72. Ye, M. -C.; Zhou, J.; Huang, Z. -Z.; Tang, Y. *Chem. Commun*. **2003**, 2554.

73. Shintani, R.; Fu, G. C. *Angew. Chem. Int. Ed*. **2003**, *42*, 4082.

74. Pal, R.; Basak, A. *Chem. Commun*., **2006**, 2992.

75. Bloch, R. *Chem. Rev.* **1998,** *98*, 1407.

76. Merino, P.; Santiago, F.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442.

77. Merino, P. *C. R. Chimie* **2005**, *8*, 775.

78. Lee, T. D.; Birrel, G. B.; Keana, J. F. W. *J. Am. Chem. Soc*. **1978**, *100*, 1618.
79. Reznikov, V. A.; Volodarsky, L. B. *Tetrahedron* **1993**, *49*, 10669.
80. Bruni, P.; Giorgini, E.; Tommasi, G.; Greci, L. *Tetrahedron* **1998**, *54*, 5305.
81. Reznikov, V. A.; Volodarsky, L. B. *Tetrahedron Lett*. **1994**, *35*, 2239.
82. Kirilyuk, I. A.; Shevelev, T. G.; Morozov, D. A.; Khromovskikh, E. L.; Skurudin, N. G.; Khramtsov, V. V.; Grigorev, I. A. *Synthesis* **2003**, 871.
83. Kalai,T.; Jeko,J.; Hubbell, W. L.; Hideg, K. *Synthesis* **2003**, 2084.
84. Nelson, D. W.; Easley, R. A.; Pintea, B. N. V. *Tetrahedron Lett*. **1999**, *40*, 25.
85. Nelson, D. W.; Owens, J.; Hiraldo, D. *J. Org. Chem*. **2001**, *66*, 2572.
86. Janzen, G. *E. Acc. Chem. Res.* **197*1***, *4*, 31.
87. Perkins, J. M. *Adv. Phys. Org. Chem.* **1980**, *17*, 1.
88. E. G. Janzen, G. E.; Haire, L. D. in *Advances in Free Radical Chemistry*, ed. D. D. Tanner, JAI Press, London, **1990**, vol. 1**,** ch. 6.
89. Buettner, R. G. *Free Radical Biol, Med.* **1987**, *3*, 259.
90. Kotake, Y.; Janzen, E. G. *J. Am. Chem. Soc.* **1991**, *113*, 9503.
91. Knecht, T. K.; Mason, P. R.*Arch. Biochem. Biophys.* **1993**, *303*, 185.
92. Eberson, L.; Hartshorn, P. M.; Persson, O. *J. Chem. Soc., Perkin Trans. 2* **1995**, 141.
93. Taniguchi, H.; Madden, K. P. *Rad. Res.* **2000**, *153*, 447.
94. Davies, J. M.; Hawkins, L. C. *Free Radic. Biol.Med.* **2004**, *36*, 1072.
95. Floyd, R. A.; Castro Faria Neto, H. C.; Zimmerman, G. A.; Hensley, K.; Towner, R. A. *Free Radic. Biol. Med.* **2013**, *62*, 145.
96. Zhai, Z.; Gomez-Mejiba, S. E.; Ramirez, D. C. *Inflammation* **2013**, *36*, 346.

97. Samuni, A.; Carmichael, A. J.; Russo, A.; Mitchell, J. B.; Riesz, P. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 7593.
98. Ranguelova, K.; Mason, P. R. *Magn. Reson. Chem.* **2011**, *49*, 152.
99. Chandra, H.; Symons, R C. M. *J. Chem. Soc., Chem. Commun*. **1986**, 1301.
100. Eberson, L. *J. Chem. Soc. Perkin Tran. 2* **1994**, 171.
101. Eberson, L.; Lind, J.; Merenyi, G. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1181.
102. Girad, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
103. Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573.
104. Kagan, H. B. *New. J. Chem.* **1990**, *14*, 453.
105. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.
106. Molander, G. A. *Org. React.* **1994**, *46*, 211.
107. Molander, G. A.; Harris, C. R. *Chem. Rev*. **1996**, *96*, 307.
108. Skrydstrup, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 345.
109. Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.
110. Krief, A.; Laval, A. M. *Chem. Rev*. **1999**, *99*, 745.
111. Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351.
112. Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959.
113. Masson, G.; Py, S.; Vallee, Y. *Angew. Chem. Int. Ed*. **2002**, *41*, 1772.
114. Masson, G.; Cividino, P.; Py, S.; Vallee, Y. *Angew. Chem. Int. Ed.* **2003**, *42*, 2265.
115. Masson, G.; Zeghida, W.; Cividino, P.; Py, S.; Vallee, Y. *Synlett* **2003**, 1527.
116. Riber, D.; Skrydstrup, T. *Org. Lett.* **2003**, *5*, 229.

117. Johannesen, S. A.; Albu, S.; Hazell, R. G.; Skrydstrup, T. *Chem. Commun*. **2004**, 1962.
118. Cividino, P.; Py, S.; Delair, P.; Greene, A. E. *J. Org. Chem*. **2007**, *72*, 485.
119. Rehak, J.; Fisera, L.; Podolan, G.; Kozisek, J.; Perasinova, L. *Synlett* **2008**, 1260.
120. Rehak, J.; Fisera, L.; Kozisek, J.; Perasinova, L.; Steiner, B.; Koos, M. *ARKIVOC* **2008**, 18.
121. Rehak, J.; Fisera, L.; Pronayova, N. *ARKIVOC* **2009**, 146.
122. Rehak, J.; Fisera, L.; Kozisek, J.; Bellovicova, L. *Tetrahedron* **2011**, *67*, 5762.
123. Xu, C. P.; Huang, P. Q.; Py, S. *Org. Lett*. **2012**, *14*, 2034.
124. Gilles, P.; Py, S. *Org. Lett*. **2012**, *14*, 1042.
125. Burchak, O. N.; Philouze, C.; Chavant, P. Y.; Py, S. *Org. Lett*. **2008**, *10*, 3021.
126. Wu, S. F.; Zheng, X.; Ruan, Y. P.; Huang, P. Q. *Org. Biomol. Chem*. **2009**, *7*, 2967.
127. Wu, S. F.; Ruan, Y. P.; Zheng, X.; Huang, P. Q. *Tetrahedron* **2010**, *66*, 1653.
128. Zhang, H. K.; Xu, S. Q.; Zhuang, J. J.; Ye, J. L.; Huang, P. Q. *Tetrahedron* **2012**, *68*, 6656.
129. Ebran, J. P.; Hazell, R. G.; Skrydstrup, T. *Chem. Commun*. **2005**, 5402.
130. Gibson, J. N.; Forrester, R. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 501
131. Foster, R.; Iball, J.; Nash, R. *Chem. Commun*. **1968**, 1414
132. Black, C. St. D.; Johnstone, M. L. *Aust. J. Chem*. **1984**, *37*, 117.
133. Brown, C. F. R.; Clark, M. V.; Lamchen, M.; Todd, A. *J. Chem. Soc*. **1959**, 2116.

134. Bogevig, A.; Gothelf, K. V.; Jorgensen, K. A. *Chem. Eur. J*. **2002**, *8*, 5652.
135. Arno, M.; Zaragoza, R. J.; Domingo, L. R. *Tetrahedron: Asymmetry* **2004**, *15*, 1541.
136. Stephen Hanessian, S.; Bayrakdarian, M. *Tetrahedron Lett*. **2002**, *43*, 9441.
137. Merino, P.; Tejero, T.; Diez-Martínez, A.; Gültekin, Z. *Eur. J. Org. Chem.* **2011**, *32*, 6567.
138. Diez-Martínez, A.; Gültekin, Z.; Delso, I.; Tejero, T.; Merino, P. *Synthesis* **2010**, 0678.
139. Merino, P.; Tejero, T.; Diez-Martinez, A. *J. Org. Chem*. **2014**, *79*, 2189.
140. Diez-Martinez, A.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2934
141. Merino, P.; Tejero, T. *Synlett* **2011**, 1965.
142. Liotta, D.; Baker, A. D.; Goldman, N. L.; Engel, R. *J. Org. Chem.* **1974**, *39*, 1975.\
143. Murai, N.; Komatsu, M.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1977**, *42*, 448.
144. Tsuge, O.; Watanabe, H.; Matsuda, K.; Yosif, M. *J. Org. Chem.* **1979**, *44*, 4543.
145. Motoyoshiya, J.; Yamamoto, I.; Gotoh, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2727.
146. Hassall, C. H.; Lippmann, A. E. *J. Chem. Soc.* **1953**, 1059.
147. Pratt, R. N.; Taylor, G. A. *J. Chem. Soc. C.* **1968**, 1653.
148. Stokes, D. P.; Taylor, G. A. *J. Chem. Soc. C* **1971**, 2334.
149. Hafiz, M.; Taylor, G. A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1700.

150. Falshaw, C. P.; Hashi, N. A.; Taylor, G. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1837.
151. Evans, A. R.; Hafiz, M.; Taylor, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1241.
152. Takaoka, K.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 3017.
153. Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18.
154. Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609.
155. Duguet, N.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett*. **2009**, *11*, 3858.
156. Huehls, C. B.; Tyler S. Hood, T. S.; Yang, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 5110.
157. Mo, D. -L.; Wink, D. A.; Anderson, L. L. *Org. Lett*. **2012**, *14*, 5180.
158. Mo, D. -L.; Anderson, L. L. *Angew. Chem. Int. Ed*. **2013**, *52*, 1.
159. Pecak, W. H.; Son, J.; Burnstine, A. J.; Anderson, L. L. *Org. Lett.* **2014**, *16*, 3440.
160. Mo, D. - L.; Wink, D. J.; Anderson, L. L. *Chem. Eur. J.* **2014**, *20*, 13217.
161. Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.
162. Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224.
163. Sajitha, T. S.; Prathapan, S.; Unnikrishnan, P. A. *RSC Adv*. **2014**, *4*, 44689.
164. Bonnett, R.; Clark, V.M.; Todd, A. *J. Chem. Soc.* **1959**, 2102.
165. Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *Chem. Comm*. **1971**, 946.
166. Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1764.
167. Jeffs, P. W.; Molina, G.; Cortese, N. A.; Hauck, P. R.; Wolfram, J. *J. Org. Chem.* **1982**, *47*, 3876.

168. McMurry, J. E.; Farina, V.; Scott, W. J.; Davidson, A. H.; Summers, D. R.; Shenvi, A. *J. Org. Chem.* **1984**, *49*, 3803.
169. Joseph, S. P.; Dhar, D.N. *Tetrahedron* **1988**, *44*, 5209.
170. Cekovic, Z.; Vujosevic, T. Z. *Synthesis* **2001**, *13*, 2028.
171. Cardona, F.; Goti, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 7832.
172. Yang, J. *Synlett* **2012**, *23*, 2293.
173. Young, I. S.; Kerr, M. A. *Angew. Chem. Int. Ed*. **2003**, *42*, 3023.
174. Young, I. S.; Kerr, M. A. *Org. Lett*. **2004**, *6*, 139.
175. Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554.
176. Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953.
177. Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc*. **2005**, *127*, 5764.
178. Carson, C. A.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 6560.
179. Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3918.
180. Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc*. **2007**, *129*, 1465.
181. Dias, D. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3664.
182. Hardman, A. M.; So, S. S; Mattson, A. E. *Org. Biomol. Chem*. **2013**, *11*, 5793.
183. Braun, C. M.; Congdon, E. A.; Nolin, K. A. *J. Org. Chem.* **2015**, *80*, 1979.
184. Hu, J-L.; Wang, L.; Xu, H.; Xie, Z.; Tang, Y. *Org. Lett.* **2015**, *17*, 2680.
185. Wang, X.; Xu, X.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc*. **2011**, *133*, 16402.
186. Qian, Y.; Xu, X.; Wang, X.; Zavalij, P. J.; Hu, W.; Doyle, M. P. *Angew. Chem. Int. Ed*. **2012**, *51*, 5900.
187. Xu, X.; Zavalij, P. J.; Doyle, M. P. *Chem. Commun.* **2013**, 10287.
188. Xu, X.; Doyle, M. P. *Acc. Chem. Res*. **2014**, *47*, 1396.

189. John, P. R. *Ph. D Thesis, CUSAT*, **2010**. http://dyuthi.cusat.ac.in/xmlui/handle/purl/1923

190. Sandhya, R. *Ph. D Thesis*, *CUSAT*, **2014**. http://dyuthi.cusat.ac.in/xmlui/handle/purl/3745

191. Radhamani, S.; Natarajan, R.; Unnikrishnan, P. A.; Prathapan, S.; Rappai, J. P. *New J. Chem.* **2015**, *39*, 5580.

192. Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc*. **1968**, *90*, 5325.

CHAPTER 2

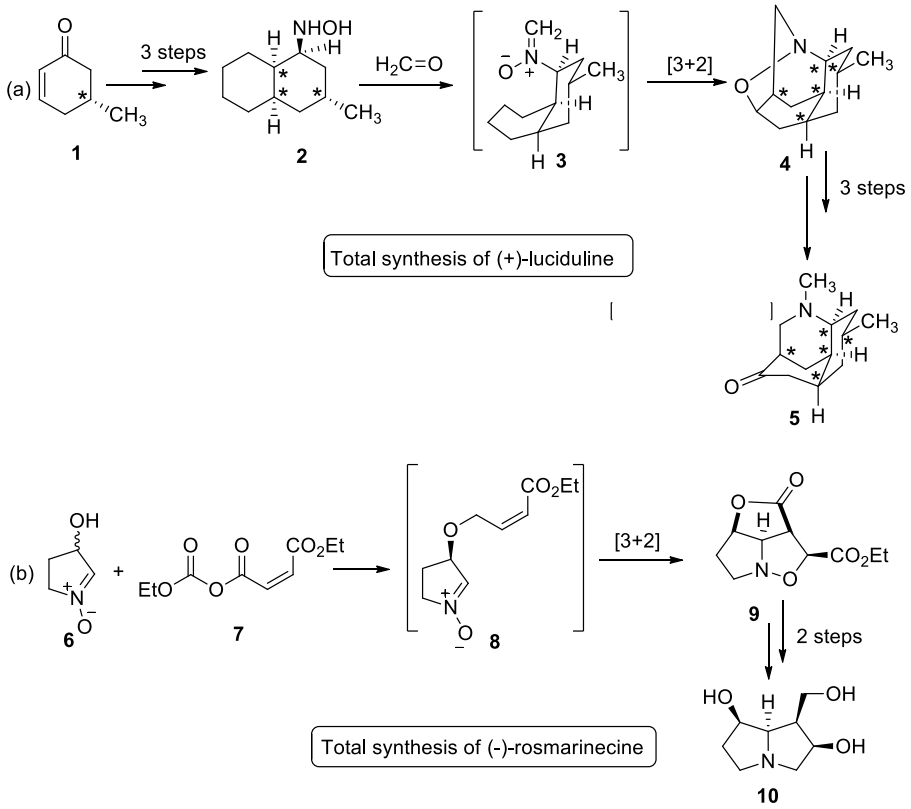
SYNTHESIS AND CHARACTERISATION OF NITRONE PRECURSORS

2.1. Abstract

In this chapter, we describe the synthesis and characterisation of the nitrones used for the present investigation.

2.2. Introduction

Nitrones serve as important intermediates in the synthesis of complex molecules since, (i) they can provide a nitrogen atom in the target molecule and (ii) they show excellent regio- and stereoselectivity in reactions with olefins.[1-11] For example, the total syntheses of (+)-luciduline (**5**) and (-)-rosmarinecine (**10**) involve nitrone [3+2] cycloaddition reaction as a key step (Scheme 2.1).[12,13] Consequently, synthesis of a desired nitrone building block during the course of a total synthesis process is crucial. Hence, development of new synthetic routes as well as improvement of existing strategies for nitrone synthesis is highly desirable.



Scheme 2.1

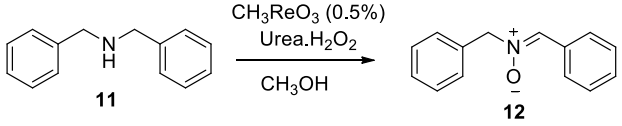
2.3. General methods for nitrone synthesis

General synthetic routes to nitrones are mainly classified in to two categories: (i) *oxidative* methods and (ii) *nonoxidative* methods.

2.3.1. Oxidative methods

2.3.1.1. Oxidation of secondary amines

Oxidation of secondary amines is a direct and general method for the synthesis of nitrones. The greater availability of amines makes this one of the most attractive strategies. Different oxidants such as oxaziridines,[14,15] dioxiranes,[16] urea-hydrogen peroxide (UHP) complex,[17,18] hydrogen peroxide[19-23] etc., in presence of metal catalytic systems are generally used to bring about the transformations (Scheme 2.2).[18] A metal-free procedure for the synthesis of nitrones from secondary amines was reported by Gella *et al*. in 2009.[24] Here, oxone in a biphasic basic medium was used as the single oxidant.

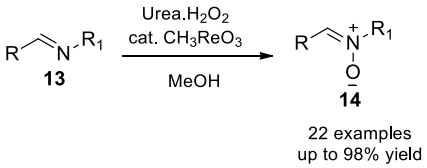


Scheme 2.2

2.3.1.2. Oxidation of imines

Imine oxidation by peroxy acids[25] or dimethyldioxirane[26] gives access to nitrones under certain specific conditions. Potassium permanganate also brings about this transformation under phase transfer conditions.[27] One of the major drawbacks of imine oxidation is that, oxaziridines are formed as the major product with most of the reagents. In 2007, Soldaini *et al.* reported the first example of a high yielding,

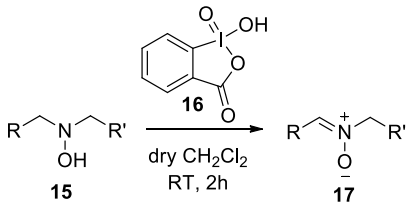
catalytic oxidation procedure for the chemoselective conversion of imines to nitrones. The oxidation was performed with urea hydrogen peroxide (UHP) in presence of catalytic amount of CH_3ReO_3 in methanol at room temperature (Scheme 2.3).[28]



Scheme 2.3

2.3.1.3. Oxidation of *N,N*-disubstituted hydroxylamines

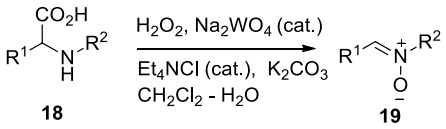
Oxidation of *N,N*-disubstituted hydroxylamines is one of the most common methods used for the synthesis of both cyclic and acyclic nitrones. Various metal salts as well as organic oxidants are used for this purpose.[29-35] Cicchi *et al.* developed a novel strategy for this conversion using an environmentally friendly reagent, Bleach.[36] The same authors developed another efficient methodology in 2001, where the oxidant used was non-toxic MnO_2.[37] Recently, in 2015, Matassini *et al.* reported the oxidation of *N,N*-disubstituted hydroxylamines to nitrones using hypervalent iodine reagents. *o*-iodoxybenzoic acid (IBX), **16** is found to be the best catalyst for the conversion. This strategy allows the synthesis of aldonitrones from suitable hydroxylamines (Scheme 2.4).[38]



Scheme 2.4

2.3.1.4. Decarboxylative oxidation of *N*-alkyl-*α*-aminoacids

Synthesis of nitrones by the catalytic oxidative decarboxylation of *N*-alkyl-*α*-aminoacids was reported by Murahashi *et al.* in 1994.[39] In this procedure, the aminoacid derivative was oxidised by hydrogen peroxide in the presence of a tungstate catalyst, under phase transfer conditions (Scheme 2.5).



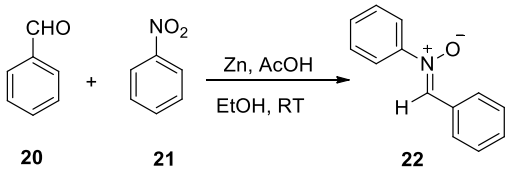
Scheme 2.5

2.3.2. Nonoxidative methods

2.3.2.1. Condensation of carbonyl compounds with hydroxylamines

The condensation of carbonyl compounds with *N*-substituted hydroxylamines is the mildest method for the synthesis of nitrones.[1] To accommodate less stable hydroxylamines in this strategy, Chapoulaud

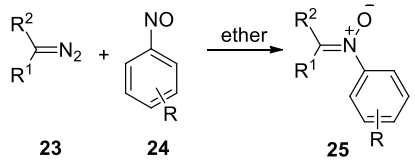
et al. developed a one-pot strategy for the synthesis of *N*-alkyl and *N*-aryl substituted aldonitrones using aldehydes and nitro compounds as precursors. Here the hydroxylamines generated *in situ* by the reduction of nitro compounds subsequently undergo condensation reaction with aldehydes (Scheme 2.6).[40]



Scheme 2.6

2.3.2.2. From nitrosoarenes

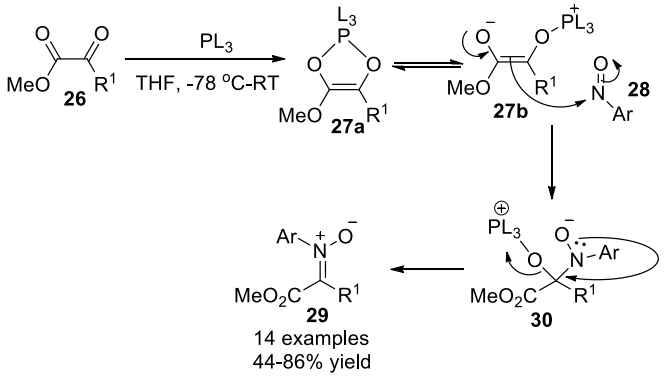
Ketonitrones are successfully synthesised by the condensation reaction between nitrosoarenes and diazo compounds (Scheme 2.7).[41] Spontaneous evolution of nitrogen is the indication of the success of the reaction. Nitrones are generated in good yields by this method.



Scheme 2.7

Chavannavar *et al.* in 2014, described a chemoselective, *umpolung* approach towards nitrone construction using phosphine-

mediated addition of 1,2-dicarbonyls to nitrosoarenes.[42] The optimised condition for conducting the reaction was found to be: $P(NMe_2)_3$ in THF (-78 ^oC to RT). The generality of the reaction was established employing structural diversity in both the substrates. The plausible mechanism involves the formation of oxyphosphorane **27a** which is in equilibrium with zwitterionic phosphonium intermediate **27b**. Subsequently, **27b** undergoes addition to nitrosoarene to furnish the intermediate **30**, which then rearranges to the nitrone **29** (Scheme 2.8).

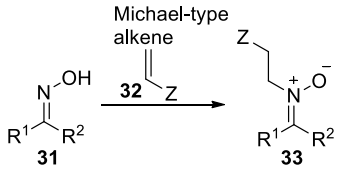


Scheme 2.8

2.3.2.3. From oximes

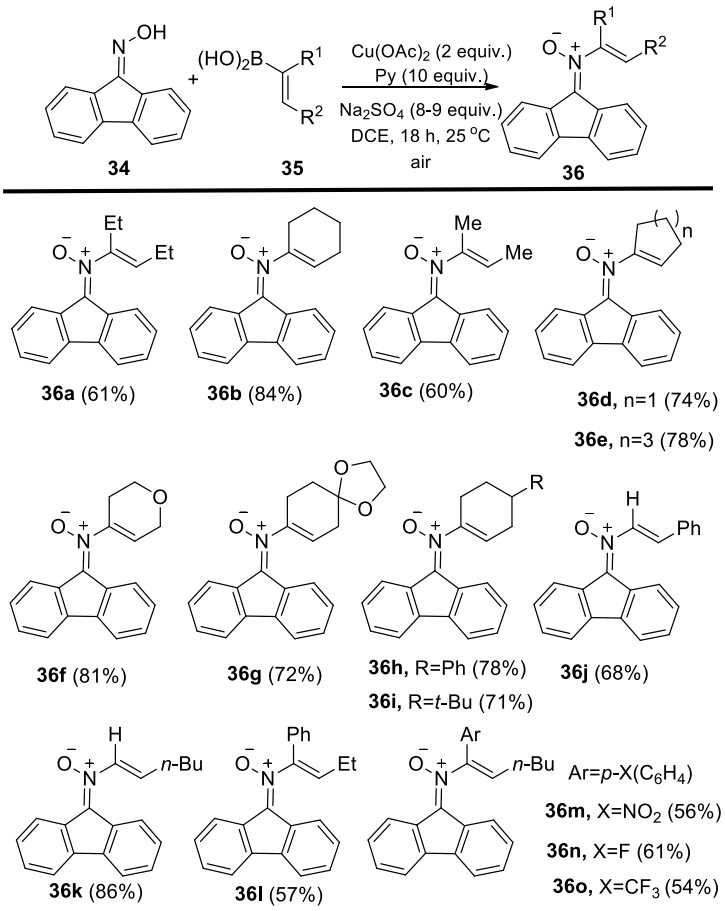
N-Functionalisation of oximes is an important method to accomplish nitrone synthesis. Grigg *et al.* established the synthesis of nitrones by the reaction of oximes with Michael-type acceptors (Scheme 2.9).[43,44] They have successfully used other electrophiles like simple

alkenes[45], epoxides[46], aziridines[47] etc., to expand the scope of the method.

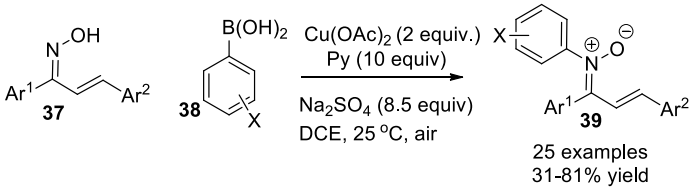


Scheme 2.9

In 2012, Anderson and co-workers reported a single step synthesis of *N*-vinylnitrones via a copper-mediated coupling of fluorenone oxime with vinyl boronic acids.[48] $Cu(OAc)_2$ was identified to be the most effective copper salt after the optimisation studies. To explore the scope of the method, the reaction was carried out with a variety of vinyl boronic acids under the optimised condition. Both cyclic, *trans*-monosubstituted and *cis*-disubstituted boronic acids produced *N*-vinylnitrones in moderate to high yields when treated with fluorenone oxime (Scheme 2.10). Later, the authors successfully synthesised *N*-aryl-α,β-unsaturated nitrones using the same strategy. Here they employed the cross coupling reaction of *α,β*-unsaturated oximes and aryl boronic acids (Scheme 2.11).[49]



Scheme 2.10

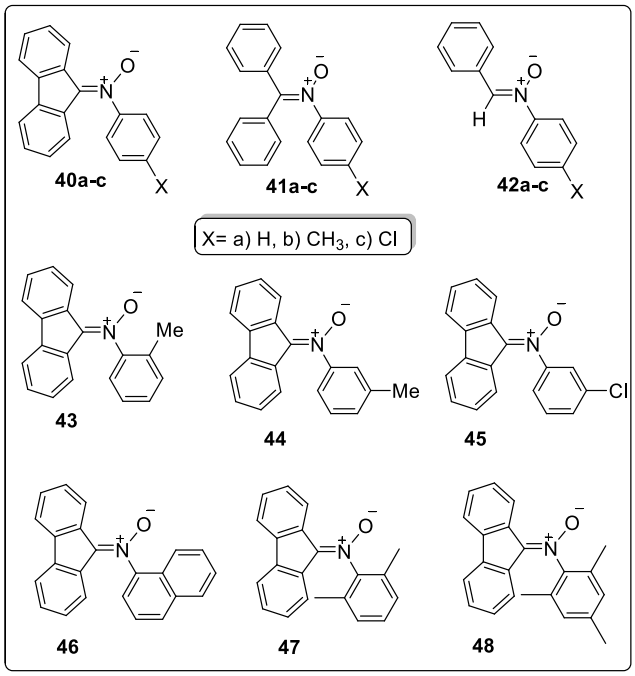


Scheme 2.11

For the present investigation, we have selected different strategies for the synthesis of target nitrones, based on availability of appropriate precursors and reagents.

2.4. Results and discussion

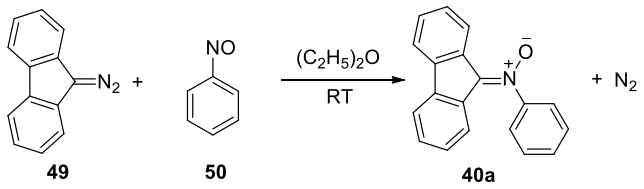
To study the nucleophilic addition of nitrones to electron deficient acetylenes, we synthesised thirteen ketonitrones and three aldonitrones using reported procedures. Structure of nitrones synthesised by us are collected in Figure 2.1.



` Figure 2.1

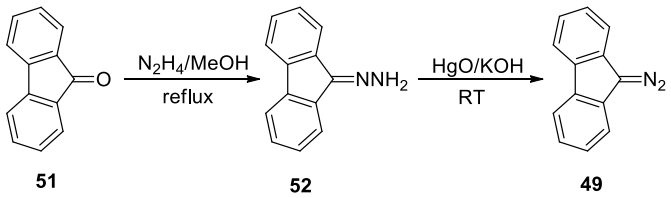
2.4.1. Synthesis of *N*-(9*H*-fluoren-9-ylidene)arylamine oxides (40a-c)

The nitrones were synthesised by the condensation reaction between 9-diazofluorene and corresponding nitrosoarenes.[41] For the synthesis of nitrone **40a**, diazofluorene (**49)** and nitrosobenzene (**50)** were reacted in diethyl ether at RT (Scheme 2.12). A vigorous reaction took place with the evolution of nitrogen and the nitrone precipitated out as a yellow solid. It was purified by recrystallization from ethanol and characterised using spectral and analytical techniques.



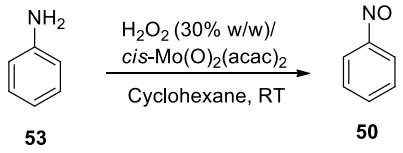
Scheme 2.12

Diazofluorene (**49**) was prepared by the oxidation of fluorenone hydrazone (**52**) with yellow HgO.[50,51] For the synthesis of **52**, condensation reaction between 9-fluorenone (**51**) and hydrazine hydrate in methanol under reflux condition was employed (Scheme 2.13).



Scheme 2.13

Required nitrosoarenes were synthesised by the oxidation of corresponding arylamines using the procedure reported by Porta *et al*.[52] For the synthesis of nitrosobenzene (**50**), aniline (**53**) in cyclohexane was oxidised by 30% H_2O_2 in presence of *cis*-$Mo(O)_2(acac)_2$ catalyst at room temperature under aerobic conditions (Scheme 2.14). After 2h, the reaction mixture was filtered and concentrated to yield solid mass of **50**.

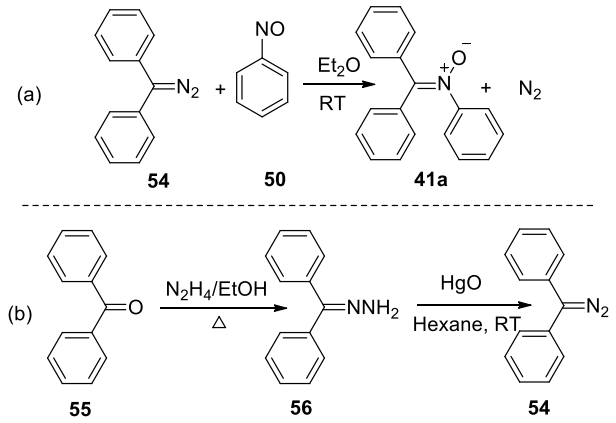


Scheme 2.14

Both the diazo and nitroso derivatives were identified by analysing the mass data and these were used as such without further purification for the nitrone forming condensation reactions.

2.4.2. Synthesis of *N*-(diphenylmethylene)arylamine oxides (41a-c)

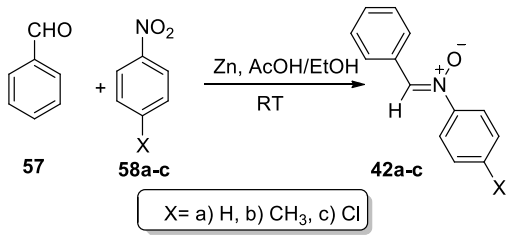
N-(Diphenylmethylene)arylamine oxides (**41a-c**) were synthesised by the condensation reaction between diphenyldiazomethane (**54**) with corresponding nitrosoarenes (Scheme 2.15a).[41] **54** was in turn synthesised by the oxidation of benzophenone hydrazone with yellow HgO (Scheme 2.15b).[51]



Scheme 2.15

2.4.3. Synthesis of (*Z*)-*N*-benzylidenearylamine oxides (42a-c)

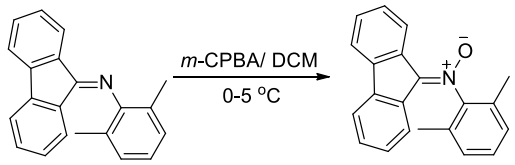
(*Z*)-*N*-Benzylidenearylamine oxides **42a-c** were synthesised by the *one-pot* strategy developed by Chapoulaud *et al.*[40] Here benzaldehyde (**57**) reacts with hydroxylamines generated *in situ* by the reduction of nitroarenes (**58a-c**) (Scheme 2.16).



Scheme 2.16

2.4.4. Synthesis of *N*-(9-*H*-fluoren-9-ylidene)arylamine oxides (43-49)

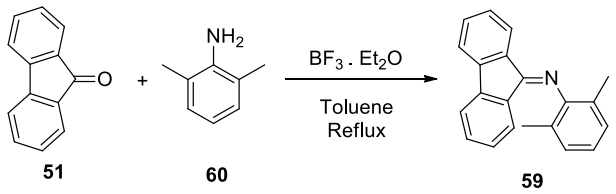
Nitrones **43-49** were synthesised by the oxidation of corresponding imines with *m*-CPBA (*m*-chloroperbenzoic acid).[25] In the synthesis of nitrone **48**, *m*-CPBA in methylene chloride was slowly added to the solution of *N*-(9*H*-fluoren-9-ylidene)-2,6-dimethylaniline (**59**) in DCM at 0-5 ^{o}C (Scheme 2.15). Nitrone **48** was separated by recrystallizing the crude product from a 1:1 DCM/hexane mixture.



59 **48**

Scheme 2.15

Imines were synthesized by the condensation reaction between 9-fluorenone (**51**) and aryl amines in the presence of Lewis acid catalysts like BF_3 etherate. For example, *N*-(9*H*-fluoren-9-ylidene)-2,6-dimethylaniline (**59**) was prepared by refluxing a mixture of 9-fluorenone (**51)** and 2,6-dimethylaniline (**60**) in toluene using a Dean-Stark apparatus in presence of BF_3 etherate (Scheme 2.16). The pure imine derivative was obtained by the recrystallisation of the crude product from a 1:3 chloroform/ethanol mixture.



Scheme 2.16

In some cases the crude product was subjected to column chromatography (neutral alumina) using hexane/ethyl acetate solvent system to get the pure imine. All the imine derivatives prepared were identified using mass spectral data and were used immediately for the oxidation step (*Note: imines underwent slow degradation on standing*).

2.5. Experimental section

2.5.1. General techniques

All reactions were carried out in oven dried glassware. Solvents used for the experiments were distilled and dried by employing standard protocols. All starting materials were purchased from *Sigma-Aldrich, Spectrochem Chemicals* or from *S. D. Fine Chemicals* and were used without further purification. Progress of the reactions were monitored either by thin layer chromatography using dried and activated silica gel TLC plates (aluminium sheets coated with silica gel, E. Merck) or, where applicable, GC-MS. Visualization of TLC plates was done by exposure to iodine vapours or UV lamp. 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 appropriate 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 *Jasco4100* and *ABB Bomem (MB Series)* FT-IR spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz *Bruker AvanceIII* FT-NMR spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). Elemental analysis was performed using *ElementarSysteme (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.

2.5.2. Procedure for the synthesis of diazofluorene

Fluorenone hydrazone (30 mmol) was dissolved in diethylether (150 mL). Anhydrous Na_2SO_4 (60 mmol) and methanol saturated with KOH (3 mL) were added to the solution. Yellow HgO (84 mmol) was then introduced to the reaction mixture in small portions. After the addition was complete, the mixture was stirred for 2h at RT, filtered and dried. The residue was extracted with diethyl ether. On evaporating off ether, bright red crystals of diazofluorene separated out.

2.5.3. Procedure for the synthesis of diphenyldiazomethane

Benzophenone hydrazone (30 mmol) was dissolved in hexane (150 mL). Anhydrous Na_2SO_4 (60 mmol) and methanol saturated with KOH (3 mL) were added to the solution. Yellow HgO (84 mmol) was then introduced to the reaction mixture in small portions. After the addition was complete, the mixture was stirred for 2h at RT, filtered and concentrated to get a pink solution of diphenyldiazomethane which was stored under low temperature for further use.

2.5.4. General procedure for the synthesis of nitrosoarenes

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. To the light orange suspension thus obtained, corresponding aryl amine (10 mmol) and 30% H_2O_2 (50 mmol) were added in quick succession. The reaction mixture was then stirred for another one hour under aerobic condition. It was then filtered and dried over anhydrous Na_2SO_4, concentrated and then kept in freezer to get a solid mass. This was then allowed to melt at room temperature when pure nitroso derivatives got precipitated out.

2.5.5. General procedure for the synthesis of nitrones from diazofluorene and nitrosoarenes

A mixture of 9-diazofluorene (10 mmol) and appropriate nitrosoarenes (10 mmol) was stirred in dry diethyl ether (40 mL) for about 1h. During the course of reaction, nitrogen was evolved, red colour of the reaction mixture got disappeared and yellow precipitate of nitrone was formed. This was then filtered, dried and recrystallized from ethanol.

2.5.6. General procedure for the synthesis of nitrones from diphenyldiazomethane and nitrosoarenes

A concentrated solution of diphenyldiazomethane in hexane was introduced drop wise to the solution of nitrosoarene (10 mmol) in dry diethyl ether (40 mL) with vigorous stirring. Stirring continued for 1h and additional amount of diphenyldiazomethane was added until the pink colour persisted. The precipitate formed was filtered and washed with hexane and dried. It was further purified by recrystallization from ethanol.

2.5.7. General procedure for the synthesis of nitrones from benzaldehyde and nitroarenes

To a stirred solution of benzaldehyde (1 mmol) in ethanol (10 mL, 95%), were introduced nitroarene (2 mmol) and Zn powder (3 mmol) under argon atmosphere at 0 ^{o}C. Glacial acetic acid (6 mmol) was then added dropwise. Reaction temperature was either kept at 0 ^{o}C or

raised to room temperature during the course of the reaction. The progress of the reaction was monitored by TLC. The crude material obtained after filtration on celite pad and evaporation, was purified by column chromatography (silica gel, hexane/ethyl acetate solvent system) to get the required aldonitrones.

2.5.8. General procedure for the synthesis of *N*-(9*H*-fluoren-9-ylidene)arylamines

A mixture of fluorenone (10 mmol), amine (16 mmol) and BF_3-etherate (1 mL) in toluene (30 mL) was refluxed using a Dean-Stark apparatus for about 2 h. The resulting solution was then concentrated and cooled. The residue obtained was column chromatographed (neutral alumina) using mixtures of hexane/ethyl acetate system to give *N*-(9*H*-fluoren-9-ylidene)arylamines. The compound was further purified by recrystallization from a 1:3 mixture of chloroform and ethanol.

2.5.9. General procedure for the synthesis of *N*-(9*H*-fluoren-9-ylidene)arylamine oxides

m-CPBA (11 mmol) in DCM (5 mL) was added to a solution of imine (10 mmol) in DCM (10 mL) at 0-5 ^oC, with stirring. After the addition, the reaction mixture was then stirred for another 5h keeping the temperature low. After the completion of the reaction, excess *m*-CPBA was removed by filtration, and the filtrate was washed twice with Na_2CO_3 solution and finally with water. The organic layer was then evaporated off and the residue obtained was recrystallized from a 1:1

mixture of DCM/hexane to give *N*-(9*H*-fluoren-9-ylidene)arylamine oxides in good yield.

2.5.10. Spectral and analytical data for significant compounds

2.5.10.1. *N*-(9*H*-Fluoren-9-ylidene)aniline oxide (40a)

N-(9*H*-Fluoren-9-ylidene)aniline oxide was prepared by a reported procedure (85% yield, mp 194 °C).[41]

2.5.10.2. *N*-(9*H*-Fluoren-9-ylidene)-4-methylaniline oxide (40b)

N-(9*H*-Fluoren-9-ylidene)-4-methylaniline oxide was prepared by a reported procedure (83% yield, mp 164 °C).[41]

2.5.10.3. 4-Chloro-*N*-(9*H*-fluoren-9-ylidene)aniline oxide (40c)

4-Chloro-*N*-(9*H*-fluoren-9-ylidene)aniline oxide was prepared by a known procedure (83% yield, mp 164 °C).[53]

2.5.10.4. *N*-(Diphenylmethylene)aniline oxide (41a)

N-(Diphenylmethylene)aniline oxide was prepared by a reported procedure (83% yield, mp 164 °C).[41]

2.5.10.5. *N*-(Diphenylmethylene)-4-methylaniline oxide (41b)

N-(Diphenylmethylene)-4-methylaniline oxide was prepared by a known procedure (83% yield, mp 164 °C).[53]

2.5.10.6. 4-Chloro-*N*-(diphenylmethylene)aniline oxide (41c)

4-Chloro-*N*-(diphenylmethylene)aniline oxide was prepared by a known procedure (83% yield, mp 164 °C).[53]

2.5.10.7. (*Z*)-*N*-Benzylideneaniline oxide (42a)

(*Z*)-*N*-Benzylideneaniline oxide was prepared by a reported procedure (83% yield, mp 164 °C).[40,53]

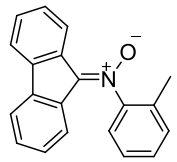
2.5.10.8. (*Z*)-*N*-Benzylidene-4-methylaniline oxide (42b)

(*Z*)-*N*-Benzylidene-4-methylaniline oxide was prepared by a reported procedure.[40,53]

2.5.10.9. (*Z*)-*N*-Benzylidene-4-chloroaniline oxide (42c)

(*Z*)-*N*-Benzylidene-4-chloroaniline oxide was prepared by a reported procedure.[40,53]

2.5.10.10. *N-(9H*-Fluoren-9-ylidene)-2-methylaniline oxide (43)[54]



Yield: 83%; **mp:** 145 °C.

IR ν_{max} (KBr): 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).

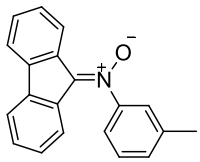
^{13}C NMR ($CDCl_3$): δ 146.3, 139.2, 139.1, 132.0, 131.9, 131.7, 131.2, 130.6, 130.1, 129.2, 128.9, 127.8, 127.6, 127.2, 123.8, 123.2, 120.2, 119.6, 16.4.

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.

2.5.10.11. *N*-(9*H*-Fluoren-9-ylidene)-3-methylaniline oxide (44)[54]



Yield: 80%; **mp:** 112 °C.

IR ν_{max} (KBr): 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 140.6, 139.3, 132.4, 131.1, 131.0, 129.9, 129.1, 128.9, 127.3, 127.1, 124.3, 124.0, 120.8, 120.2, 119.60. 21.4.

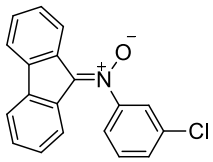
MS:*m/z* 285 (M^+), 286 (M+1).

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.

2.5.10.12. 3-Chloro-*N*-(9-H-fluoren-9-ylidene)aniline oxide (45)[54]



Yield: 79%; **mp:**123 °C.

IR ν_{max} (KBr): 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).

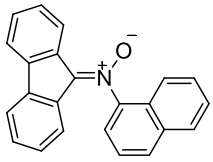
^{13}C NMR ($CDCl_3$): δ 147.7, 146.0, 139.5, 139.2, 135.8, 132.2, 131.5, 131. 3, 130.63, 130.5, 129.5, 129.0, 127.4, 127.2, 124.5, 123.7, 122.2, 120.4, 119.7.

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.

2.5.10.13. *N*-(9*H*-Fluoren-9-ylidene)naphthalen-1-amine oxide (46)[54]



Yield: 79%; **mp:** 157 °C.

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

^{1}H NMR ($CDCl_3$): δ 9.09 (d, *J* = 8Hz, 1H), 7.14-7.99 (m, 12H), 6.69 (t, *J* = 8Hz, 1H), 5.52 (d, *J* = 8Hz, 1H).

^{13}C NMR ($CDCl_3$): δ 146.8, 143.5, 139.3, 134.6, 132.3, 131.4, 130.4, 130.3, 129.12, 129.0, 128.2, 128.1, 127.4, 127.4, 126.6, 125.6, 123.7, 122.4, 121.2, 120.2, 119.7.

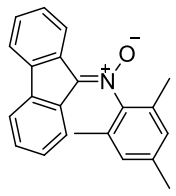
MS:*m/z* 321 (M^+), 322 (M+1).

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.

2.5.7.14. *N*-(9*H*-Fluoren-9-ylidene)-2,6-dimethylaniline oxide (47)

N-(9*H*-Fluoren-9-ylidene)-2,6-dimethylaniline oxide was prepared by a known procedure (78% yield, mp 202 °C).[53]

2.5.10.15. *N*-(9*H*-Fluoren-9-ylidene)-2,4,6-trimethylaniline oxide (48)



Yield: 79%; **mp:** 213 °C.

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

^{1}HNMR ($CDCl_3$): 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 145.8, 143.7, 139.5, 139.1, 131.9, 131.2, 131.0, 130.4, 129.9, 129.1, 128.8, 127.9, 127.2, 122.6, 120.17, 119.6, 21.3, 16.5.

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.

2.6. References

1. Hamer, J.; Macaluso, A. *Chem. Rev*. **1964**, *64*, 473.
2. Huisgen, R. *Angew. Chem. Int. Ed. Engl*. **1963**, *2*, 565.
3. Tufariello, J. J. *Acc. Chem. Res*. **1979**, *12*, 396.
4. Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706.
5. Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497.
6. Werner, K. M.; Santos, J. M.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 4865.
7. Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett*. **2001**, *3*, 953.
8. Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett*. **2001**, *3*, 1367.
9. Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y. *Org. Lett*. **2002**, *4*, 177.
10. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134.
11. Schrittwieser, J. H.; Resch, V. *RSC Adv.* **2013**, *3*, 17602.
12. Wolfgang Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta*. **1978**, *61*, 2755.
13. Akai, S.; Tanimoto, K.; Kanao, Y.; Omura, S.; Kita, Y. *Chem. Commun.* **2005**, 2369.
14. Zajac, W. W.; Walters, T. R.; Darcy, M. G. *J. Org. Chem*. **1988**, *53*, 5856.
15. Cicchi, S.; Ponzuoli, P.; Goti, A.; Brandi, A. *Tetrahedron Lett*. **2000**, *41*, 1583.
16. Murray, R. W.; Singh, M. *J. Org. Chem*. **1990**, *55*, 2954.
17. Murray, R. W.; Iyanar, K. *J. Org. Chem.* **1996**, *61*, 8099.

18. Goti, A.; Cardona, F.; Soldaini, G. *Org. Synth.* **2005**, *81*, 204.

19. Murahashi, S. I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383.

20. Murahashi, S. I.; Mitsui, H.; Shiota, T.; Tomoyasu, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736.

21. Bdistreri, F. P.; Chiacchio, U.; Rescifina, A.; Tomaselli, G. A.; Toscano, R. M. *Tetrahedron* **1992**, *48*, 8677.

22. Murahashi, S. I.; Shiota, T.; Imada, Y. *Org. Synth.* **1992**, *70*, 265.

23. Goti, A.; Nanneili, L. *Tetrahedron Lett.* **1996**, *37*, 6025.

24. Gella, C.; Ferrer, E.; Alibes, R.; Busque, F.; March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6365.

25. Abou-Gharbia, M. A.; Joullie, M. M. *J. Org. Chem.* **1979**, *44*, 2961.

26. Boyd, D. R.; Coulter, P. B.; McGuckin, M. R.; Sharma, N. D. J. *Chem. Soc., Perkin Trans. 1* **1990**, 301.

27. Christensen, D.; Jorgensen, K. A. *J. Org. Chem.* **1989**, *54*, 126.

28. Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2007**, *9*, 473.

29. Brandi, A.; Cicchi, S.; Goti, A.; Koprowski, A.; Pietrusiewicz, K. M. *J. Org. Chem.* **1994**, *59*, 1315.

30. Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571.

31. Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743.

32. Goti, A.; Nannelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025.

33. Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119.

34. Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett.* **1999**, *40*, 1989.

35. Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633.

36. Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, *64*, 7243.

37. Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett*. **2001**, *42*, 6503.
38. Matassini, C.; Parmeggiani, C.; Cardona, F.; Goti, A. *Org. Lett*. **2015**, *17*, 4082.
39. Murahashi, S.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170.
40. Chapoulaud, V. G.; Pandya, S. U.; Cividino, P.; Masson, G.; Py, S.; Vallee, Y. *Synlett* **2001**, *8*, 1281.
41. Johnson, A. W. *J. Org. Chem*. **1963**, *28*, 252.
42. Chavannavar, A. P.; Oliver, A. G.; Ashfeld, B. L. *Chem. Commun.* **2014**, *50*, 10853.
43. Grigg R.; Markandu J.; Perrior T.; Surendrakumar S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929.
44. Grigg R.; Dorrity M. J.; Heaney F.; Malone J. F.; Rajviroongit S.; Sridharan, V.; Surendrakumar S. *Tetrahedron* **1991**, *47*, 8297.
45. Dondas, H. A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Thomas, W. A.; Kennewell, P. *Tetrahedron* **2000**, *56*, 10087.
46. Markandu, J.; Dondas, H. A.; Frederickson, M.; Grigg, R. *Tetrahedron* **1997**, *53*, 13165.
47. Dondas, H. A.; Cummins, J. E.; Grigg, R.; Thornton-Pett M. *Tetrahedron* **2001**, *57*, 7951.
48. Mo, D. -L.; Wink, D. A.; Anderson, L. L. *Org. Lett*. **2012**, *14*, 5180.
49. Mo, D. -L.; Anderson, L. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 6722.
50. Schonberg, A.; Awad, W. I.; Latif, N. *J. Chem. Soc*. **1951**, 1368.
51. Smith, L. I.; Howard, K. L.; *Org. Synth*. **1944**, *24*, 53.
52. Porta, F.; Prati, L. *J. Mol. Cat. A: Chem.***2000**, *157*, 123.
53. John, P. R. *Ph. D Thesis, CUSAT,* **2010**.
54. Sandhya, R. *Ph. D Thesis, CUSAT,* **2014**.

CHAPTER 3

SYNTHESIS AND CHARACTERISATION OF A FEW QUINOLINE DERIVATIVES

3.1. Abstract

In this chapter we describe the synthesis of a few polysubstituted quinolines by the reaction of various nitrones with activated acetylenes using the strategy developed in our lab.

3.2. Introduction

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

3.2.1. Quinolines

Quinoline, also termed as 1-azanaphthalene or benzo[b]pyridine is an aromatic heterocycle constructed by fusing a benzene ring on to a pyridine ring (Figure 3.1).[1-3]

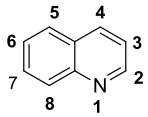


Figure 3.1

3.2.1.1. Applications of quinolines

Several quinoline derivatives are well known for their pharmacological applications.[4-16] For example, quinoline containing molecules such as quinine, chloroquine, primaquine, mefloquine,

amodiaquine etc. are used as antimalerial drugs. The other quinoline derivatives with significant medicinal properties include ciprofloxazin and ofloxacin, used as antimicrobial agents; camptothecin, used as anticancer drug; saquinavir, used in HIV therapy etc.

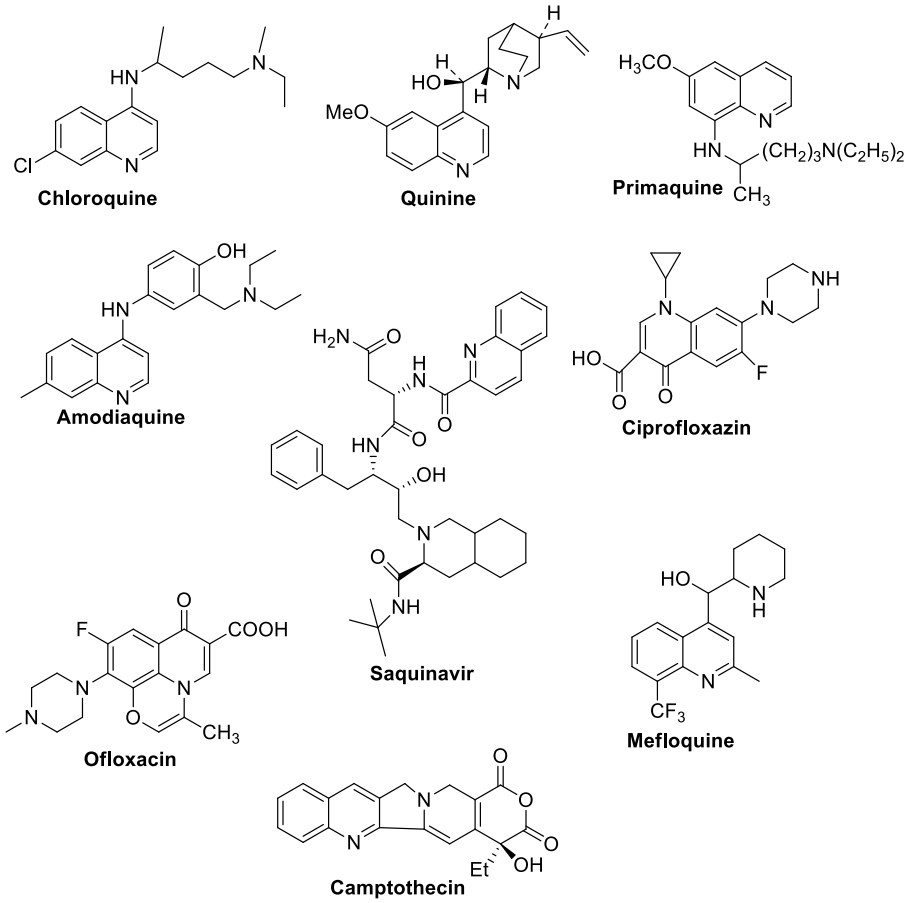


Figure 3.2

Another important application of quinolines is in dye chemistry. Several quinoline based dyes having diverse applications are known. Examples include Quinoline Yellow SS, used in cosmetics; Quinoline Yellow WS, used as a food additive; cyanine dyes, used as sensitizers in photographic emulsions etc. Quinoline containing transition metal complexes are renowned for their applications in targeted drug delivery (eg. ferroquine), organic light emitting diodes (eg. Alq_3) etc.[17-21] Quinoline derivatives also find applications as fungicides in agriculture (eg. ethoxyquin and tebufloquin).

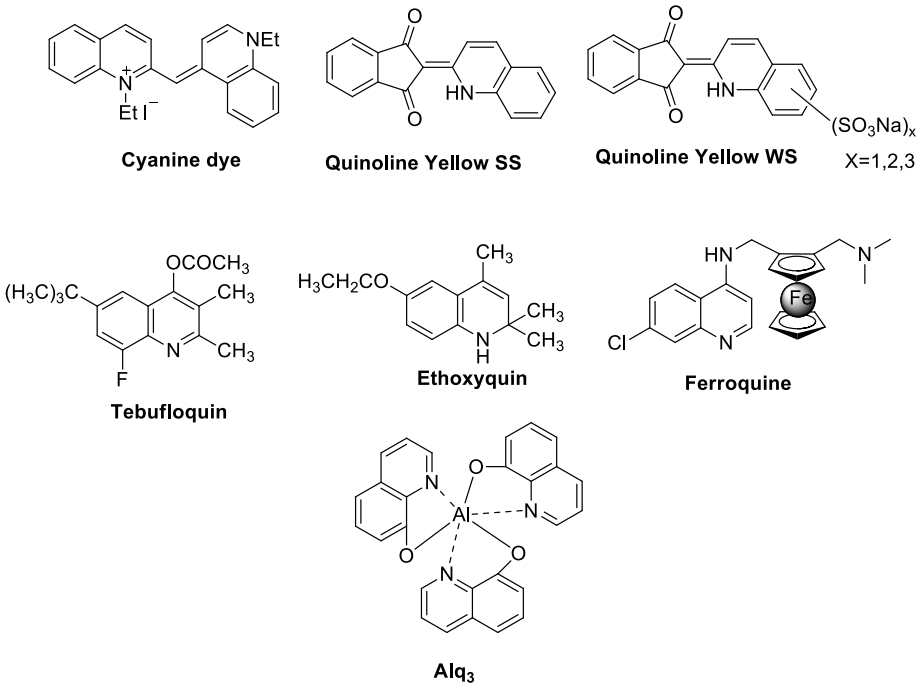


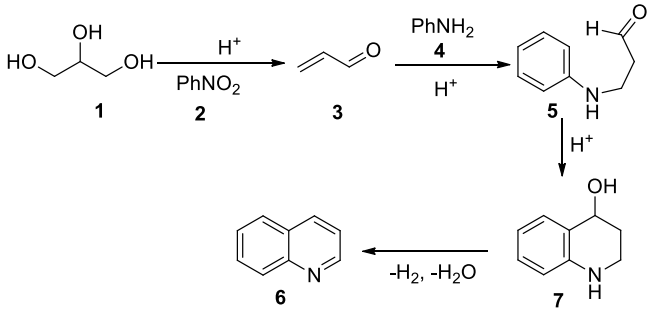
Figure 3.3

3.2.1.2. Methods for the synthesis of quinolines

Synthesis of quinoline core is generally achieved by using various name reactions such as Skraup, Doebner-Miller, Combes, Friedlander synthesis etc. In the first three cases, anilines lacking a C-2 substituent serve as the precursor molecules while in the Friedlander synthesis, the C-2 position of the aniline precursors are equipped with carbonyl groups. Several reviews are available on quinoline synthesis.[22-25] Recent developments in quinoline synthesis is mainly concentrated on the improvement of the well-established strategies using new catalysts, milder conditions etc.[26,27]

(i) Skraup synthesis

In Skraup synthesis, quinoline is formed by heating aniline with glycerol and sulfuric acid in presence of an oxidising agent, nitrobenzene for example (Scheme 3.1).[28] The reaction involves the conjugate addition of acrolein (generated *in situ* by the dehydration of glycerol) to aniline.

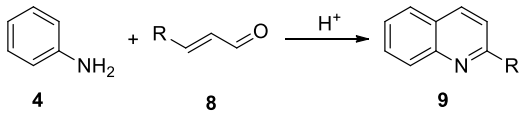


1 2 3 5 6 7

Scheme 3.1

(ii) Doebner-Miller synthesis

This is a generalised version of Skraup synthesis where glycerol is replaced by *α,β*-unsaturated aldehydes such as **8** (Scheme 3.2).[29]

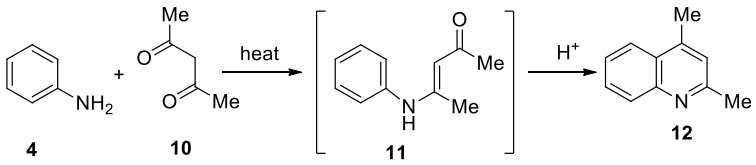


4 **8** **9**

Scheme 3.2

(iii) Combes synthesis

Combes synthesis involves the condensation of aniline with a 1,3-diketone to furnish an enamine intermediate **11**. Enamine **11** then undergoes acid catalysed cyclodehydration to produce a quinoline derivative (Scheme 3.3).[30]

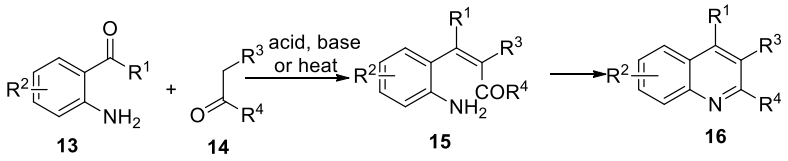


4 **10** **11** **12**

Scheme 3.3

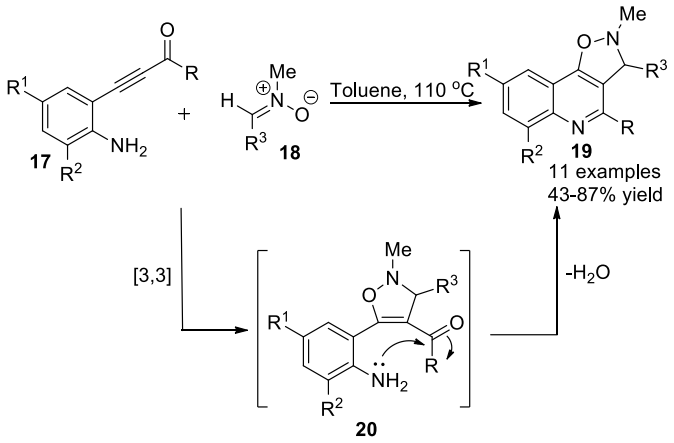
(iv) Friedlander synthesis

It involves acid- or base- catalysed condensation of 2-amino-substituted aromatic carbonyl compound **13** with an *α*-methyleneketone **14** followed by cyclodehydration (Scheme 3.4).[31]



Scheme 3.4

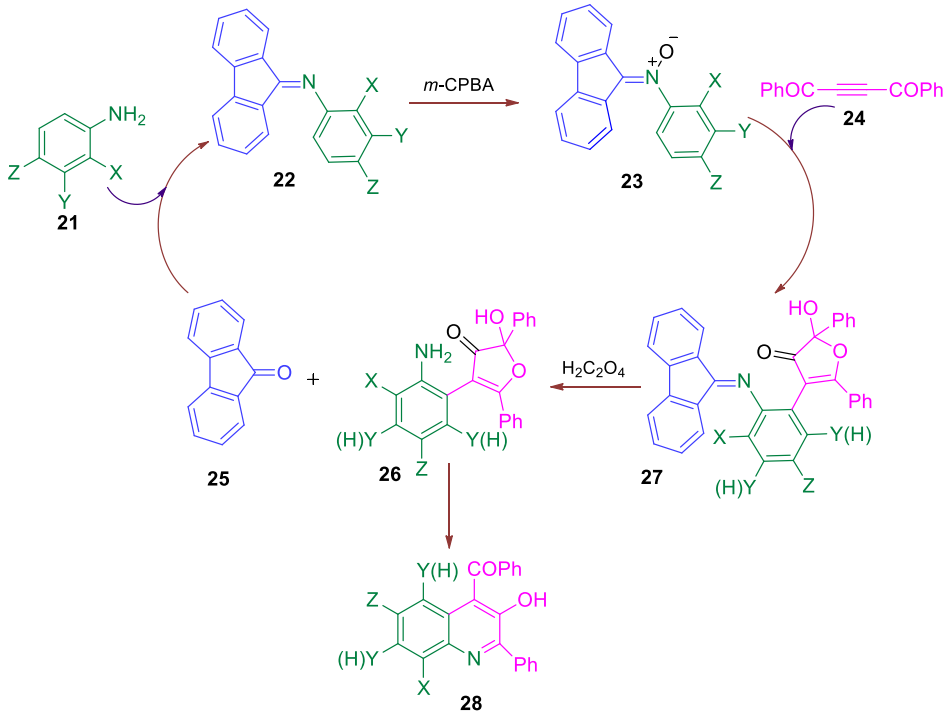
Besides the general synthetic protocols, several elegant approaches involving attempts to produce quinoline core from novel substrates have also been documented in literature.[32,33] In one of such methods, Abbiati *et al.* described the synthesis of isoxazolino[4,5-c]quinoline system via a sequential 1,3-dipolar cycloaddition/annulation reaction between *N*-methylnitrones and *β*-(2-aminophenyl)-*α,β*-ynones.[33] The reactions were carried out in toluene at 110 ^{o}C with 2 equiv. of the nitrone components (Scheme 3.5). Compound **20**, produced by 1,3-DCA reaction between nitrone **18** and acetylene **17** undergoes intramolecular condensation between amino and carbonyl groups to yield the quinoline derivative (**19**) with the expulsion of water molecule.



Scheme 3.5

Recently, we developed a novel nitrone mediated two-step one-pot protocol for the synthesis of highly substituted quinolines (Scheme 3.6).[34,35] As a rule of the thumb, synthesis of nitrones can be understood in terms of carbonyl and amine precursors providing the *C*- and *N*-substituents respectively. In our quinoline synthesis, most of the atoms present in the *N*-substituent of nitrone and the acetylene precursors are retained in the quinoline product and the *C*-substituents on nitrones are eliminated as the carbonyl precursors to nitrone (fluorenone in this case). Recovered carbonyl precursors can be efficiently recycled for the generation of a fresh batch of nitrones. Hence our method of quinoline synthesis is highly atom efficient as well. When we employed dibenzoylacetylene (**24**) as the acetylene component, quinoline product **28** had phenyl, hydroxyl and benzoyl substituents at the 2-, 3-, and 4-positions respectively. Based on Scheme 3.6, it is clear that when other acetylenes are used, a new set of substituents are introduced at the 2-, 3-, and 4- positions of the quinoline product. Substituents at the 5-, 6-, 7-, and 8- positions are decided by the substituents present on the *N*-aryl group of nitrone precursor. Based on these leads, we explored the scope of expanding synthetic potential of quinoline synthesis by using appropriately substituted nitrones and different acetylenes. Since formal 1,3-dipolar cycloaddition is a competing side reaction, it is important to unravel the roles of *C*-substituents on nitrone and nature of solvents in deciding product selectivity and yield. Thus optimization and generalization of the novel nitrone synthesis developed by us warrant further attention. In this chapter, we describe our attempts on

optimisation and expansion of scope of the novel strategy towards quinoline synthesis developed by us.



Scheme 3.6

3.3. Results and Discussion

In order to expand the scope of quinoline synthesis, we selected dimethyl acetylenedicatrboxylate (DMAD) as the reactive acetylene. If DMAD reacts with nitrones in the same way as dibenzoylacetylene (DBA), substituents such as methoxy, hydroxyl, and carbomethoxy can

be introduced at the 2-, 3- and 4- positions of the quinoline product. Carbomethoxy group, in turn, can be easily converted to amide and formyl groups under mild conditions.

3.3.1. Optimisation studies on the synthesis of quinoline derivatives

As mentioned in Chapter 1, in the reaction between *N*-arylnitrones and acetylenes, along with quinolines, products arising through isoxazoline cycloadduct are also formed in varying amounts. In order to improve quinoline yield, formation of isoxazoline should be suppressed. When multiple pathways operate in parallel, changes in substrate structure, reaction temperature, and solvent polarity should play important roles in deciding the major product formed. We systematically explored the role of these variables in deciding product selectivity and yield. Earlier reports from our laboratory indicates negligible role for reaction temperature. In the present investigation, we have explored roles of solvent polarity and substrate structure in deciding the major product. It is also important to identify the ideal nitrone substrate for quinoline synthesis. The 'ideal nitrone' is one that is most easily and economically accessed and gives quinoline as the major product on treatment with activated acetylenes. Since *C*-substituents on nitrones are eliminated as the corresponding carbonyl compounds, as long as *N*-aryl substituents are identical, both aldonitrones and ketonitrones should yield identical quinoline products. Hence, in principle, both aldonitrones and

ketonitrones are suitable precursors for quinoline synthesis. A quick review of methods available for nitrone synthesis reveals that aldonitrones are more easily accessible. As part of optimization studies, we explored the reaction of several *N*-aryl aldonitrones and ketonitrones with DMAD. We examined the reaction of eight different *N*-arylnitrones (Figure 3.4) with DMAD in different solvents.

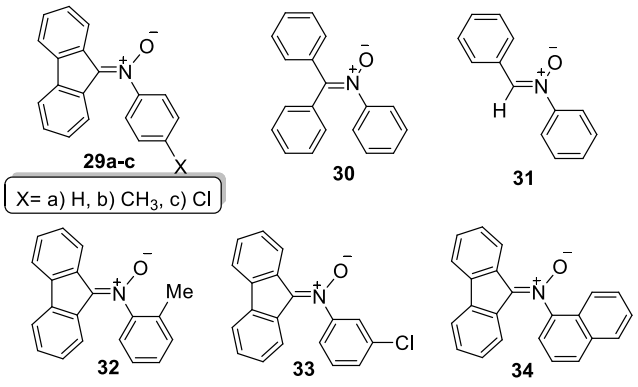


Figure 3.4

The quinoline derivatives produced by the reaction of these nitrones with DMAD are collected in Figure 3.5. As shown in scheme 3.6, we could introduce substituents at the 6-, 7-, and 8- positions of the quinoline by judiciously introducing substituents at appropriate positions on *N*-aryl ring. Acetylene controlled substituents such as methoxy, hydroxyl and carbomethoxy appeared at the 2-, 3-, and 4- positions of the quinoline product.

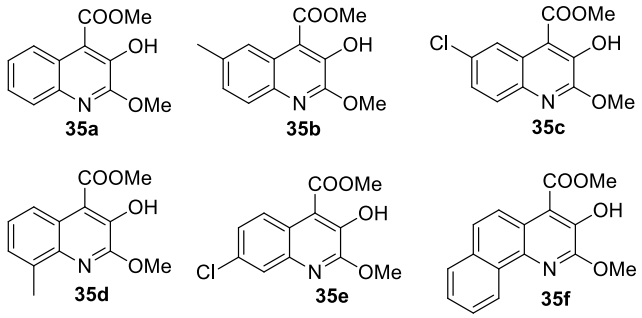
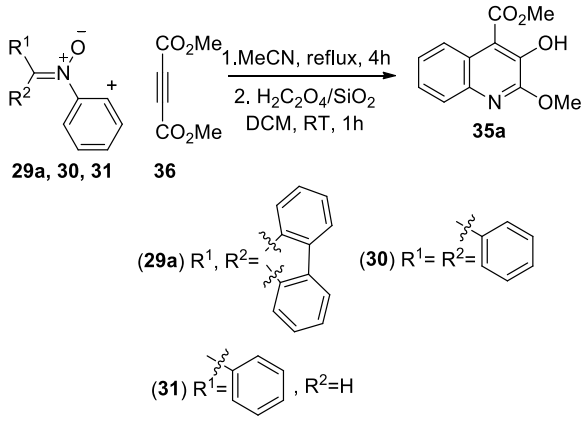


Figure 3.5

3.3.1.1. Role of substrate structure: nature of *C*-substituents on nitrones

We examined the reaction of three *N*-arylnitrones having different *C*-substituents with DMAD in acetonitrile under identical conditions (Scheme 3.7). Nitrones selected include: *N*-(9*H*-fluoren-9-ylidene)aniline oxide (**29a**), *N*-(diphenylmethylene)aniline oxide (**30**) and (*Z*)-*N*-benzylideneaniline oxide (**31**). Unlike in the case of DBA, products arising through formal cycloaddition were not formed when DMAD was employed as the reactive acetylene. Yield of quinoline **35a** formed with nitrones **29a**, **30** and **31** is given in Table 3.1. Based on results presented in Table 3.1, it is clear that fluorenylnitrone **29a** provides higher yield of quinoline. Based on these results, we selected *C*-fluorenylidenenitrones for further optimization studies. Aldonitrones, though easily accessible, gave quinolines in low yields.



Scheme 3.7

Nitrone	Quinoline **35a** (%)
29a	75
30	70
31	8

Table 3.1

3.3.1.2. Role of solvents

In order to unravel the role of solvent polarity on product yield and selectivity, we examine the reaction of fluorenylnitrone **29a** with DMAD in different solvents under identical conditions. In a typical run, a 1:1 mixture of nitrone and DMAD (1 mmol each) in appropriate solvents (10 mL) was stirred magnetically under nitrogen atmosphere at room temperature for 12 h. Solvent was removed under reduced pressure and the residue was redissolved in dichloromethane (10 mL). Oxalic acid

adsorbed on silica gel was added to this solution and the products formed were separated by column chromatography over silica gel. In all the cases, quinoline could be isolated along with unchanged starting material. Yield of quinoline **35a**, fluorenone **25** and unchanged **29a** are tabulated in Table 3.2. In general, polar solvents gave quinolone in higher yields. Among polar solvents, acetonitrile was identified as the best solvent for quinoline synthesis.

Solvent	Quinoline **35a** (%)	Fluorenone **25** (%)	Unchanged nitrone **29a** (%)
Benzene	16	20	75
THF	52	55	40
Dichloromethane	55	58	38
Acetone	65	66	30
DMSO	68	69	26
Acetonitrile	75	78	18

Table 3.2

3.3.1.3. Role of temperature

Reaction between nitrone **29a** and DMAD was carried out in acetonitrile at room temperature, at reflux and at 40 ^{o}C. Changes in reaction temperature did not influence product selectivity. However, rate of product formation increased with reaction temperature. Best results were obtained in refluxing acetonitrile.

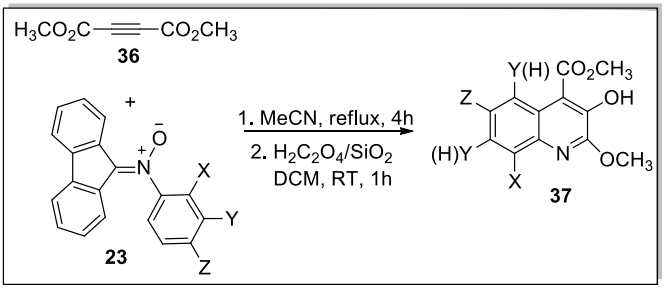
3.3.1.4. Role of substrate concentration.

We carried out the reaction between nitrone and DMAD at 1mM, 5 mM, 10 mM and 100 mM (saturation) concentration of substrates in refluxing acetonitrile. Cleanest and fastest reaction was observed at 100 mM concentration and all further reactions were performed at this concentration.

Based on optimization studies listed above, we selected the following protocol for quinoline synthesis: reaction of a 1:1 mixture of *C*-fluorenylidenenitrone and DMAD (100 mM in each substrate) in acetonitrile at reflux for 4h.

3.3.2. Expanding the scope of quinoline synthesis

Based on previous reports from our laboratory, a generalized scheme for quinoline synthesis involving a suitably substituted nitrone and DMAD may be formulated as follows (Scheme 3.8):

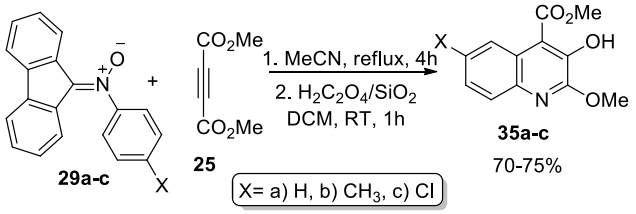


Scheme 3.8

In principle, substituents present at the 2-position of the *N*-aryl group of parent nitrone ends up at the 8-position of quinoline product. Similarly, substituents present at the 4-position of the *N*-aryl group will appear at the 6-position of the product. Substituents present at the 3-position of the *N*-aryl group may end up at either the 5- or 7- position of the quinoline product. In order to broaden the scope of our methodology, we propose to introduce different substituents at predetermined positions of the quinoline product.

3.3.2.1. Introduction of groups specifically at the 6-position of quinolines

We selected three different nitrones **29a-c** to achieve our goal of introducing a group specifically at the 6-postion of quinolines (Scheme 3.9). When nitrone **29a** was reacted with DMAD under optimized reaction conditions, quinoline **35a** was generated in good yields.



Scheme 3.9

In the IR spectrum of **35a**, the ester carbonyl was identified by the peak at 1723 cm^{-1} and the –OH group at 3299 cm^{-1}. In the ^{1}H NMR

spectrum (Figure 3.6), the singlet signal at δ 9.31 (D_2O-exchangeable) was assigned to the –OH proton. The six methoxy protons were identified by the singlet signal at δ 4.0. All the other four protons of **35a** appeared in the δ 8.07- 7.27 range in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum (Figure 3.7), the signals at δ 164.6 and δ 161.4 were assigned to the ester carbonyl carbon and the C=N attached to the methoxy group respectively.

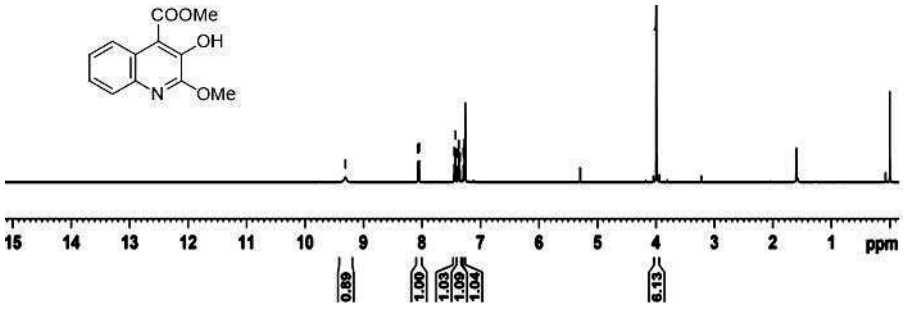


Figure 3.6 ^{1}H NMR spectrum of **35a**

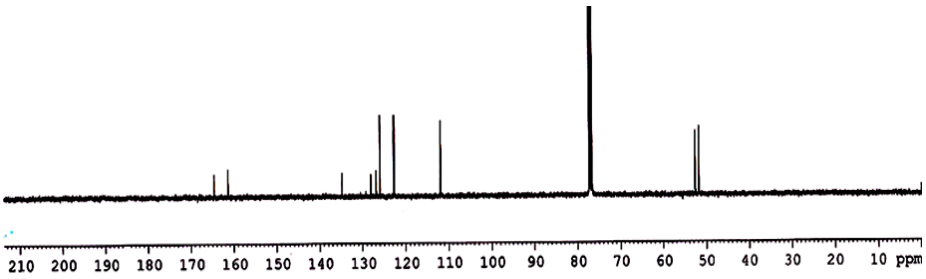


Figure 3.7 ^{13}C NMR spectrum of **35a**

When nitrone **29b** bearing a methyl group at the 4-position of the *N*-aryl group was reacted with DMAD under optimized reaction

condtions, quinoline **35b** bearing a methyl substituent at the 6-position was exclusively generated in good yields. In the ^{1}H NMR spectrum of **35b** (Figure 3.8), the –OH group was identified by the singlet signal at the δ 9.22. The methyl group was identified by the singlet signal at δ 2.47 (s, 3H) and the two methoxy groups were identified at δ 3.99 (s, 3H) and δ 3.98 (s, 3H) in the ^{1}H NMR spectrum. The aromatic protons attached to C-5, C-7 and C-8 were identified by the singlet at δ 7.83, doublet of a doublet at δ 7.20 and doublet at δ 7.32 respectively. The presence of signals at δ 164.7 and δ 161.3 in the ^{13}C spectrum of **35b** confirmed the presence of ester carbonyl and C=N attached to methoxy group respectively (Figure 3.9).

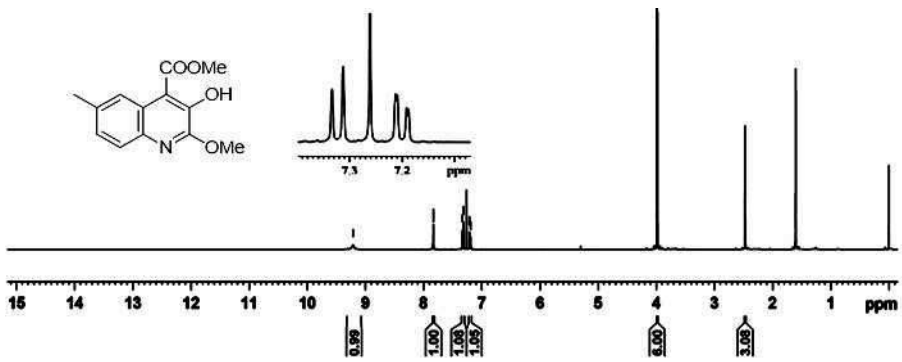


Figure 3.8 ^{1}H NMR spectrum of **35b**

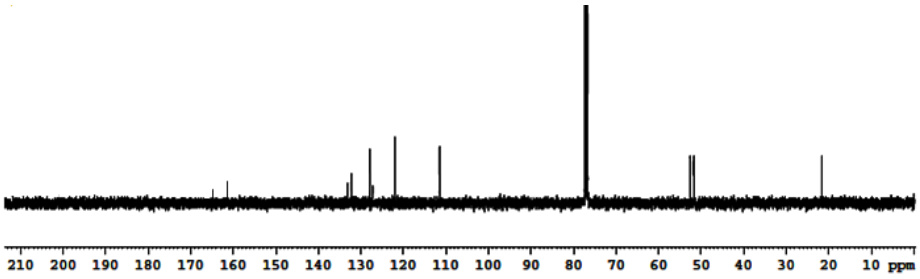


Figure 3.9 ^{13}C NMR spectrum of **35b**

Similarly, when nitrone **29c** bearing a chlorine at the 4-position of the *N*-aryl group was reacted with DMAD under optimized reaction condtions, quinoline **35c** bearing a chlorine substituent at the 6-position was exclusively generated in yields comparable with those obtained for **35a,b**. In the ^{1}H spectrum of **35c**, the –OH group was identified by the peak at δ 9.22 and in the ^{13}C spectrum, the ester carbonyl and C=N group were identified by the signals at δ 163.7 and δ 161.0 (Figure 3.10 and 3.11).

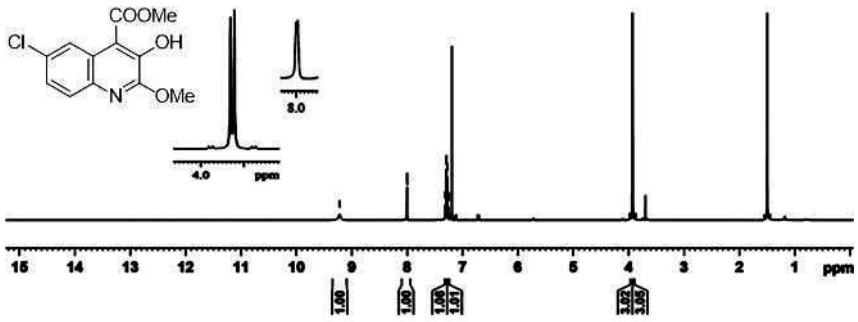


Figure 3.10 ^{1}H NMR spectrum of **35c**

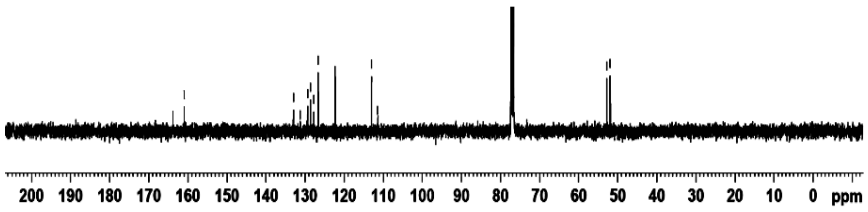
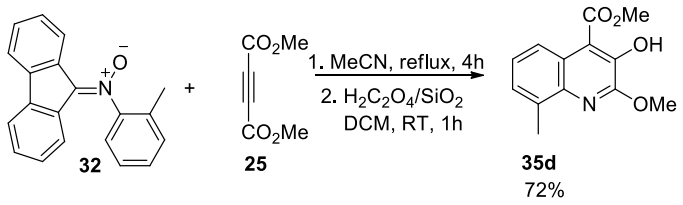


Figure 3.11 ^{13}C NMR spectrum of **35c**

We could, thus, successfully introduce both inductively electron withdrawing and electron releasing groups specifically at the 6-postion of quinolines.

3.3.2.2. Introduction of a methyl group specifically at the 8-position of quinolines

We carried out the reaction of *N*-(9*H*-fluoren-9-ylidene)-2-methylaniline oxide (**32)** with DMAD in acetonitrile under reflux condition for 4 h. Quinoline **35d** bearing the methyl substituent at the 8-position was formed as the only isolable product in high yields (Scheme 3.10).



Scheme 3.10

Presence of -OH group in the quinoline derivative **35d** was indicated by the broad band at 3371 cm^{-1} in the IR absorption spectrum,

which was further confirmed by presence of a singlet (D_2O-exchangeable) at δ 9.16 in the ^1H NMR spectrum. The -CH_3 group in the compound appeared as a singlet at δ 2.46 and the two –OCH_3 groups were identified at δ 3.92 and δ 3.91 in the ^1H NMR spectrum. Other three protons of **35d** appeared in the δ 7.81 to δ 7.07 range in the ^1H NMR spectrum (Figure 3.12). In the ^{13}C NMR spectrum, the ester carbonyl carbon and the C=N group were assigned by the signals at δ 163.6 and δ 160.6 respectively (Figure 3.13).

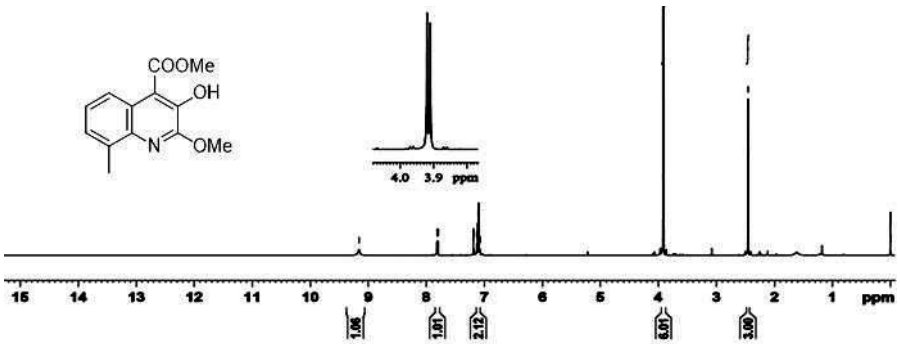


Figure 3.12 ^1H NMR spectrum of **35d**

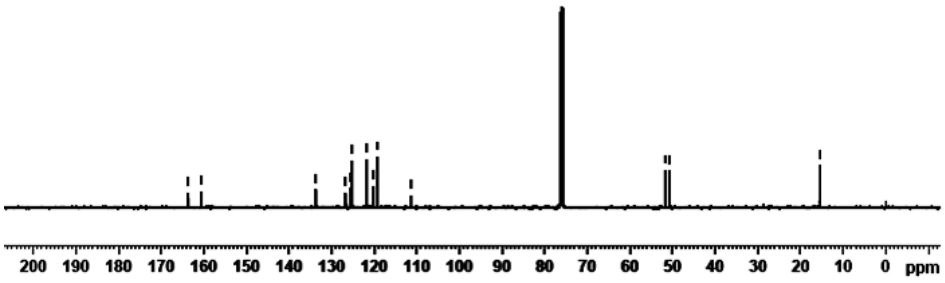
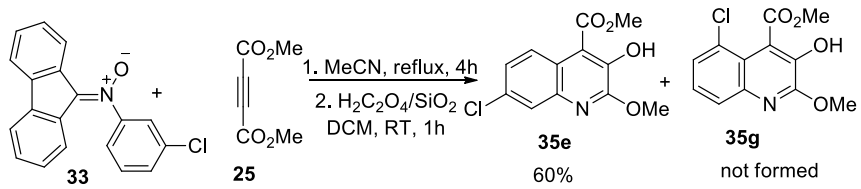


Figure 3.13 ^{13}C NMR spectrum of **35d**

3.3.2.3. Introduction of chlorine at 7- or 8-position of quinolines

When we conducted the reaction of 3-chloro-*N*-(9*H*-fluoren-9-ylidene)aniline oxide (**33**) with DMAD in acetonitrile under reflux condition, we were expecting two isomeric quinoline derivatives **35e** and **35g**. But a single isomer bearing the chloro substituent at the 7-position was exclusively generated in this reaction (Scheme 3.11). Generation of **35g** was not evident even in the GC-MS analysis of the reaction mixture.



Scheme 3.11

Structure of **35e** was assigned on the basis of spectral and analytical data. The broad peak at 3303 cm^{-1} was assigned to the –OH group in the IR absorption spectrum of **35e**. The ester carbonyl was indicated by the peak at 1738 cm^{-1}. In the ^{1}H NMR spectrum of **35e**, the singlet signal at δ 9.18 was assigned to the –OH proton (Figure 3.14). The protons attached to C-6 and C-8 appeared at δ 7.91 (d, *J* = 8.8Hz, 1H) and δ 7.37 (s, 1H) respectively. The proton attached to C-5 appeared as a doublet at δ 7.18 (d, *J* = 8.8Hz, 1H) and the two methoxy groups appeared as singlets at δ 3.93 and δ 3.92. The ^{1}H NMR spectrum obtained for **35e** is consistent with that expected for a 7-substituted quinoline. In the ^{13}C

NMR spectrum of **35e**, the ester carbonyl carbon was indicated by the signal at δ 164.1 (Figure 3.15).

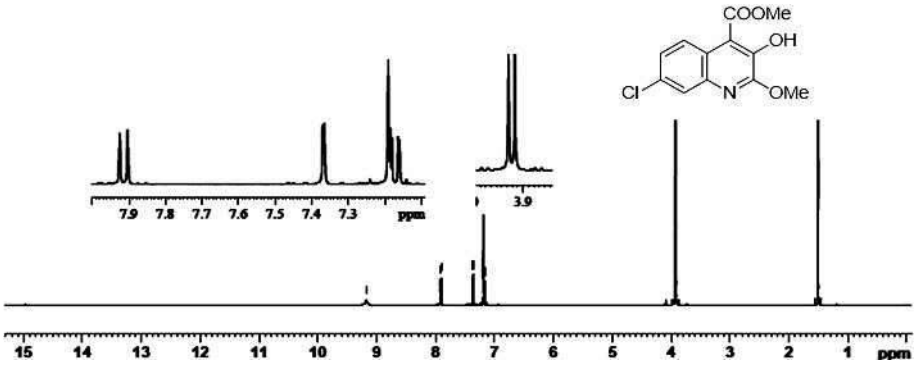


Figure 3.14 ^{1}H NMR spectrum of **35e**

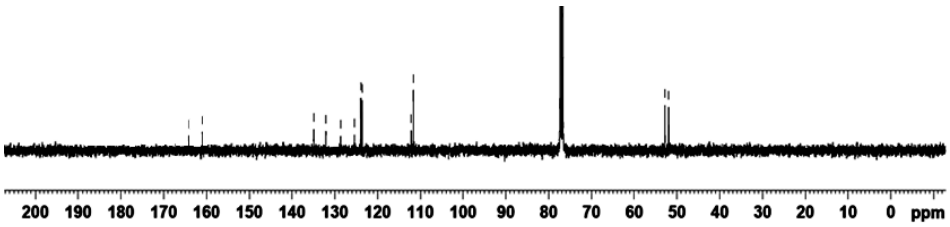
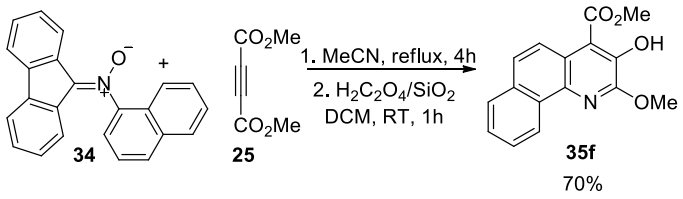


Figure 3.15 ^{13}C NMR spectrum of **35e**

3.3.2.4. Synthesis of benzo(*h*)quinoline derivative

Versatility of our quinoline synthesis protocol was further demonstrated by near-quantitative generation of benzo(*h*)quinoline derivative **35f** by the reaction of *N*-(9*H*-fluoren-9-ylidene)naphthalen-1-oxide (**34**) with DMAD (Scheme 3.12). The reaction was conducted in acetonitrile under reflux followed by hydrolysis in the same pot. The

benzo(*h*)quinoline was separated out along with fluorenone by silica gel column chromatography.



Scheme 3.12

The –OH group and the ester carbonyl group were indicated by the broad peak at 3356 cm^{-1} and the sharp peak at 1732 cm^{-1} respectively in the IR spectrum of **35f**. The –OH group was confirmed by the singlet signal (D_2O-exchangeable) at δ 10.19 in the ^1H NMR spectrum (Figure 3.16). The signal at δ 164.8 in the ^{13}C NMR spectrum of **35f** indicated the ester carbonyl carbon (Figure 3.17).

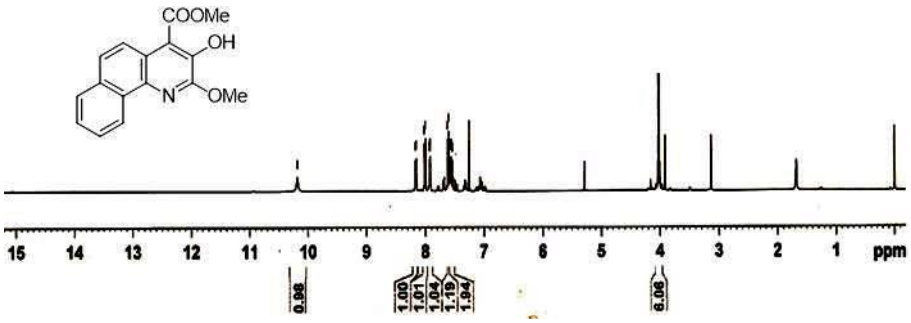


Figure 3.16 ^1H NMR spectrum of **35f**

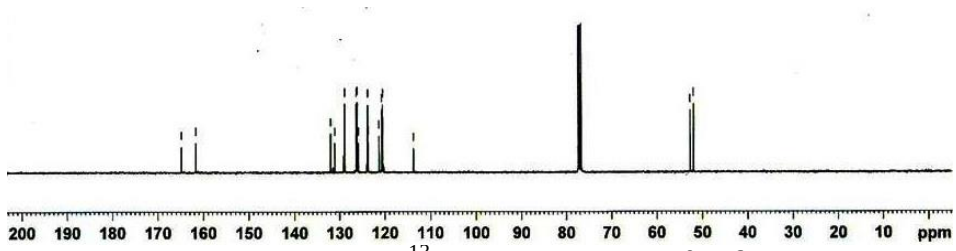


Figure 3.17 ^{13}C NMR spectrum of **35f**

3.4. Experimental section

3.4.1. General techniques

The general techniques employed are described in Chapter 2 of this thesis.

3.4.2. Optimization studies.

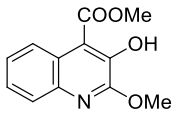
In all experiments, 1:1 mixture of respective nitrones and dimethylacetylenedicarboxylate (DMAD) in suitable solvents was stirred under different condition for 4-12h. Different substrates, solvents, concentration, reaction time and reaction temperature were used and optimal conditions were used in individual runs. Workup of the reaction mixture involved: removal of solvent under reduced pressure, redissolving the residue in minimal amount of dichloromethane, treatment with oxalic acid adsorbed on silica gel and separation and purification of products by column chromatography.

3.4.3. Optimized general procedure for one-pot synthesis of quinoline derivatives.

In all reactions, a 1:1 mixture (1 mmol each) of respective nitrones and dimethyl acetylenedicarboxylate (DMAD) in 10 mL of acetonitrile was stirred under reflux for 4 h. After the complete consumption of starting materials, solvent was evaporated off and the residue was redissolved in dichloromethane (10 mL) in the same flask. Oxalic acid (1 mmol) adsorbed on silica gel (1 g) was added to the same pot and the mixture was stirred at room temperature for 1 h. After the completion of the reaction, solvent was removed and the products were isolated by column chromatography over silica gel using mixtures of hexane and ethyl acetate as eluents. In all reactions, fluorenone was formed as a by-product in yields comparable to those cited for quinolines. Optimal consumption of starting materials was achieved by recycling fluorenone.

3.4.3. Spectral and analytical data of significant Compounds

3.4.3.1 Quinoline 35a



Off-white solid**,** 75%.

mp: 130-132 °C.

IRν_{max} (KBr): 3299, 2952, 2853, 1723, 1631, 1614, 1526, 1333, 1172, 1089, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (br s,

1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.27-7.45 (m, 3H), 4.0 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 161.4, 134.8, 128.1, 126.9, 126.0, 122.8, 122.6, 112.0, 111.9, 52.7, 51.8.

MS: *m/z* 233 (M^+), 234 (M+1).

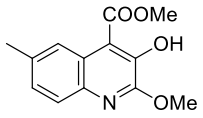
Elemental analysis calculated for $C_{12}H_{11}NO_4$: C: 61.81, H: 4.76, N: 6.02. Found: C: 61.76, H: 4.73, N: 5.94.

3.4.3.2. Quinoline 35b

Yellow solid, 75%.

mp: 135-137 °C.

IRν_{max} (KBr): 3294, 2946, 2553, 1717, 1691, 1592, 1380, 1256, 1182, 1063, 773 cm^{-1}.



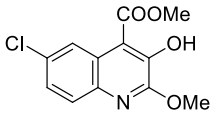
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (br s, 1H), 7.83 (s, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.20 (dd, *J* = 8.8, 1.2 Hz, 1.6Hz, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 161.3, 133.2, 132.2, 127.9, 127.2, 122.0, 111.5, 52.6, 51.8, 21.6.

MS: *m/z* 247 (M^+), 248 (M+1).

Elemental analysis calculated for $C_{13}H_{13}NO_4$: C: 63.17, H: 5.31, N: 5.69. Found: C: 63.22, H: 5.33, N: 5.73.

3.4.3.3. Quinoline 35c



Dark yellow solid, 70%.

mp: 155-158 °C.

IRν_{max} (KBr): 3330, 2982, 2853, 1701, 1675, 1588, 1526, 1448, 1274, 1110, 997, 768 cm^{-1}.

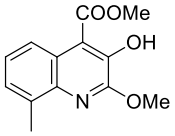
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (br s, 1H), 8.00 (s, 1H), 7.30 (d, J = 8.8Hz, 1H), 7.26 (dd, J = 8.8, 2Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 161.0, 133.0, 131.3, 129.4, 128.6, 127.8, 126.6, 122.4, 113.0, 111.4, 52.9, 51.9.

MS: *m/z* 267 (M^+), 268 (M+1).

Elemental analysis calculated for $C_{12}H_{10}ClNO_4$: C: 53.84, H: 3.77, N: 5.28. Found: C: 53.89, H: 3.78, N: 5.28.

3.4.3.4. Quinoline 35d



Yellow solid, 72%.

mp: 140-143 °C.

IRν_{max} (KBr): 3371, 2937, 1753, 1686, 1588, 1453, 1339, 1287, 1240, 1095, 804 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (br s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.07-7.13 (m, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 160.6, 133.6, 126.7, 125.5, 121.8, 120.2, 119.3, 111.4, 51.7, 50.8, 15.5.

MS: *m/z* 247 (M^+), 248 (M+1).

Elemental analysis calculated for $C_{13}H_{13}NO_4$: C: 63.14, H: 5.31, N: 5.66. Found: C: 63.19, H: 5.38, N: 5.71.

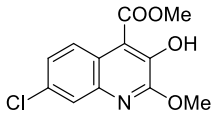
3.4.3.5. Quinoline 35e

Dark yellow solid, 60%.

mp: 160-162 °C.

IRν_{max} (KBr): 3303, 2941, 2853, 1738, 1681, 1588, 1380, 1250, 1105, 814, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (br s, 1H), 7.91 (d, *J* = 8.8Hz, 1H), 7.37 (s, 1H), 7.16-7.19 (d, *J* = 8.8Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H).

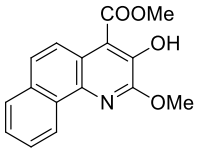


^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 161.0, 134.9, 132.1, 128.7, 125.4, 124.0, 123.7, 112.1, 111.6, 90.3, 52.8, 52.0.

MS: *m/z* 267 (M^+), 268 (M+1).

Elemental analysis calculated for $C_{12}H_{10}ClNO_4$: C: 53.87, H: 3.79, N: 5.24. Found: C: 53.80, H: 3.73, N: 5.19.

3.4.3.6. Quinoline 35f



Brown solid, 70%.

mp: 180-182 °C.

IRν_{max} (KBr): 3356, 2946, 2848, 1732, 1649, 1603, 1448, 1240, 1053, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (br, s, 1H), 8.16 (d, J = 8Hz, 1H), 8.0 (d, J = 9.2Hz, 1H), 7.92 (d, J = 7.2Hz, 1H), 7.54-7.63 (m, 3H), 4.02 (s, 3H), 4.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 161.7, 132.0, 131.1, 128.9, 126.3, 126.1, 125.8, 123.8, 123.7, 121.3, 120.7, 120.5, 113.7, 52.7, 52.0.

MS: *m/z* 283 (M^+), 284 (M+1).

Elemental analysis calculated for $C_{16}H_{13}NO_4$: C: 67.87, H: 4.65, N: 4.95. Found: C: 67.93, H: 4.69, N: 5.04.

3.5 References

1. Manske, R. H. *Chem. Rev.* **1942**, *30*, 113.
2. Jones, G. *Chemistry of Heterocyclic Compounds*: *Quinolines*, *Wiley Interscience*, *London*, **1977**, *32*, p.1
3. Marella, A.; Tanwar, O. P.; Saha, R.; Ali, M. R.; Srivastava, S.; Akhter, M.; Shaquiquzzaman, M.; Alam, M. M. *Saudi. Pharm. J.* **2013**, *21*, 1.
4. Craig, J. C.; Person, P. E. *J. Med. Chem*. **1971,** *14*, 1221.
5. Dillard, R. D.; Pavey, D. E.; Benslay, D. N. *J. Med. Chem*. **1973,** *16*, 251.
6. Fournet, A.; Vagneur, B.; Richomme, P.; Bruneton, J. *Can. J. Chem.* **1989**, *67*, 2116.
7. Fournet, A.; Hocquemiller, R.; Roblot, F.; Cavé, A.; Richomme, P.; Bruneton, J. *J. Nat. Prod.* **1993**, *56*, 1547.
8. Nicolaou, K. C.; Gross, J. L.; Kerr, M. A. *J. Heterocycl. Chem*. **1996**, *33*, 735.
9. Doube, D.; Blouin, M.; Brideau, C.; Chan, C.; Desmarais, C.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Tagari, P.; Young, R. N. *Bioorg. Med. Chem. Lett*. **1998,** *8*, 1255.
10. Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, H. *Eur. J. Med. Chem*. **2000**, *35*, 1021.
11. Chen, Y. -L.; Fang, K. -C.; Sheu, J. -Y.; Hsu, S. -L.; Tzeng, C. -C. *J. Med. Chem*. **2000**, *44*, 2374.
12. Fang, K. -C.; Chen, Y. -L.; Sheu, J. -Y.; Wang, T. -C.; Tzeng, C. -C. *J. Med. Chem*. **2000**, *43*, 3809.
13. Chevalier, J.; Atifi, S.; Eyraud, A.; Mahamoud, A.; Barbe, J.; Pages, J. – M. *J. Med. Chem*. **2001**, *44*, 4023.
14. Graves, P. R.; Kwiek, J. J.; Fadden, P.; Ray, R.; Hardeman, R. K.; Coley, A. M.; Foley, M.; Haystead, T. A. *Mol. Pharmacol*. **2002**, *62*, 1364.

15. Michael, J. P. *Nat. Prod. Rep.***2007**, *24*, 223.
16. Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166.
17. Li, Y.; Kock, C.; Smith, P. J.; Guzgay, H.; Hendricks, D. T.; Naran, K.; Mizrahi, V.; Warner, D. F.;Chibale, K.; Smith, G. S. *Organometallics* **2013**, *32*, 141.
18. Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S.; Domarle, O.; Blampain, G.; Millet, P.; Georges, A. J.; Abessolo, H.; Dive, D.; Lebibi, J. *J. Med. Chem.* **1997**, *40*, 3715.
19. Biot, C.;Taramelli, D.; Forfar-Bares, I.; Maciejewski, L. A.; Boyce, M.; Nowogrocki, G.; Brocard, J. S.; Basilico, N.; Olliaro, P.; Egan, T. *J. Mol. Pharmaceutics* **2005**, *2*, 185.
20. Biot, C.; Delhaes, L.; Abessolo, H.; Domarle, O.; Maciejewski, L. A.; Mortuaire, M.; Delcourt, P.; Deloron, P.; Camus, D.; Dive, D.; Brocard, J. S. *J. Organomet. Chem.* **1999**, *589*, 59.
21. Montes, V. A.; Pohl, R.; Shinar, J.; Anzenbacher, P. Jr. *Chem. Eur. J.* **2006**, *12*, 4523.
22. Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141.
23. Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811.
24. Barluenga, J.; Rodriguez, F.; Fananas, F. J. *Chem. Asian J.* **2009**, *4*, 1036.
25. Marco-Contelles, J.; Perez-Mayoral, E.; Samadi, A.; Carreiras, M. C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652.
26. Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.***2008**, *12*, 1116.
27. Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. *RSC Adv.* **2014**, *4*, 24463.
28. Skraup, H. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2086.

29. Doebner, O.; von Miller, W. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2812.
30. Combes, A. *Bull. Soc. Chim. Fr.* **1988**, *49*, 89.
31. Friedlander, P. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2572.
32. Broggini, G.; Colombo, F.; De Marchi, I.; Galli, S.; Martinelli, M.; Zecchi, G. *Tetrahedron: Asymmetry* **2007**, *18*, 1495.
33. Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E.; Verdecchia, M. *Eur. J. Org. Chem.* **2009**, 1027.
34. John, P. R. *Ph. D Thesis, CUSAT*, **2010**.
35. Sandhya, R. *Ph. D Thesis, CUSAT*, **2014**.

CHAPTER 4

SYNTHESIS AND CHARACTERISATION OF A FEW INDOLE-3-CARBOXYLATES

4.1. Abstract

In this chapter we describe the synthesis of a few indole derivatives by the reaction of various nitrones with monoactivated acetylenes using the strategy developed in our lab.

4.2. Introduction

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

4.2.1. Indoles

Indole unit, consisting of a benzene ring fused to a pyrrole system is found in many naturally occurring compounds having physiological activities. Prototypical example is tryptophan, an essential amino acid needed for maintaining nitrogen balance and biosynthesis of neurotransmitter serotonin[1], which is believed to provide 'mood balance' (Figure 4.1).

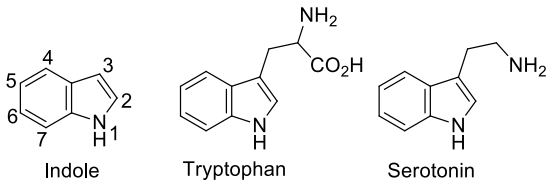


Figure 4.1

Many naturally occurring as well as synthetic indole-containing compounds have profound medicinal applications.[2-14] An important class is 'triptans' used for the treatment of migraine. They include sumatriptan, rizatriptan, zolmitriptan, frovatriptan etc. Other examples of indole-based drugs include indomethacin, used for the treatment of rheumatoid arthritis; ondasetron, used in the treatment of vomiting caused by chemotherapy; fluvastatin, used for the treatment of cardiovascular disease etc., (Figure 4.2). Indole derivatives also find application in dye industry, perfume industry, agriculture etc.[15]

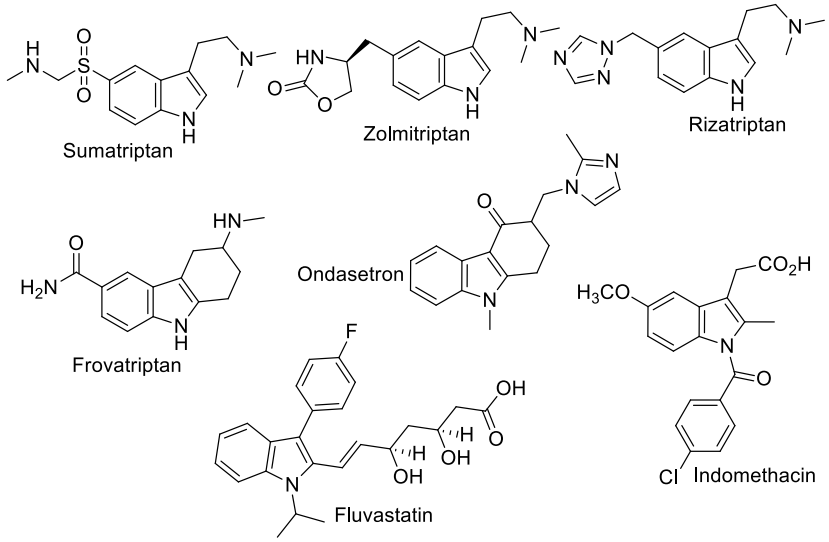
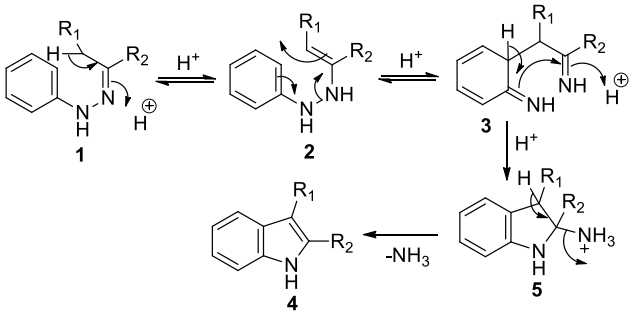


Figure 4.2

4.2.1.1. General strategies for indole synthesis

One of the pioneering as well as the most renowned procedure is the Fischer synthesis.[16,17] This involves the conversion of arylhydrazones to indoles in the presence of Brønsted or Lewis acid catalysts (Scheme 4.1). Subsequently numerous strategies were developed for the synthesis of this versatile heterocycle. Over the past twenty years, several review articles on indole synthesis have appeared in literature.[18-29]



Scheme 4.1

In 2011 Taber *et al.* published a review article with a view to categorise the existing methodologies for indole synthesis in a systematic manner.[29] They assembled the strategies for indole synthesis into nine groups. The nine classes as well as the well-known reactions associated with each class are depicted in Figure 4.3.

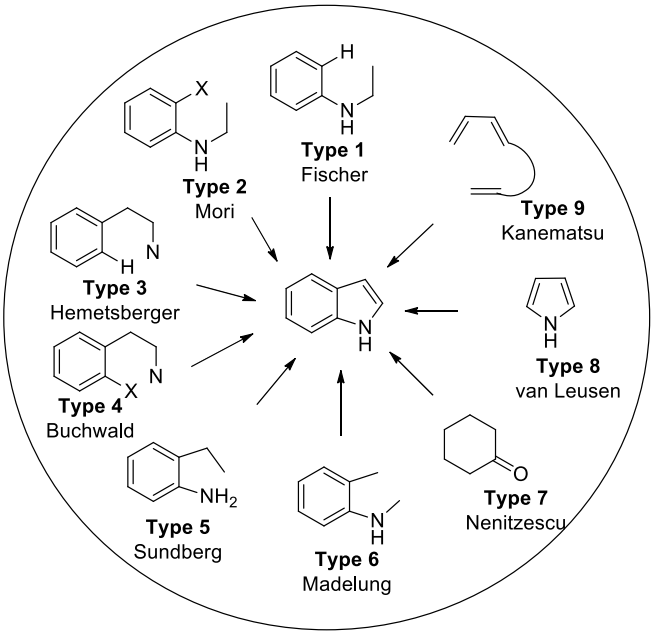
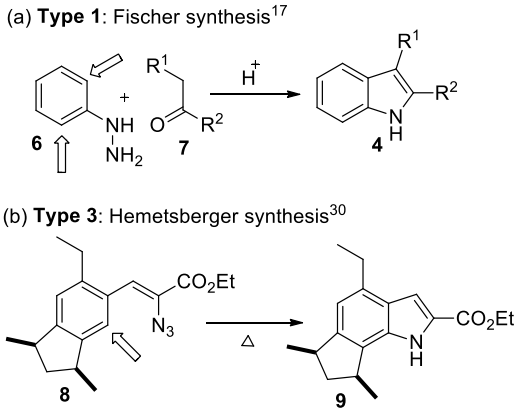
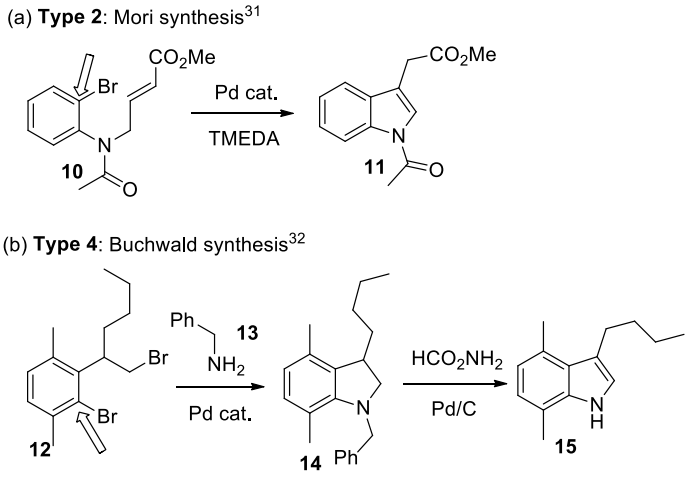


Figure 4.3

Taber classified indole synthesis strategies to nine different types based on how the 'last bond' is formed. While **type 1** and **type 3** focus on forming a bond to an unsubstituted aromatic carbon (Scheme 4.2), **type 2** and **type 4** discuss the bond formation to a substituted aromatic carbon (Scheme 4.3).

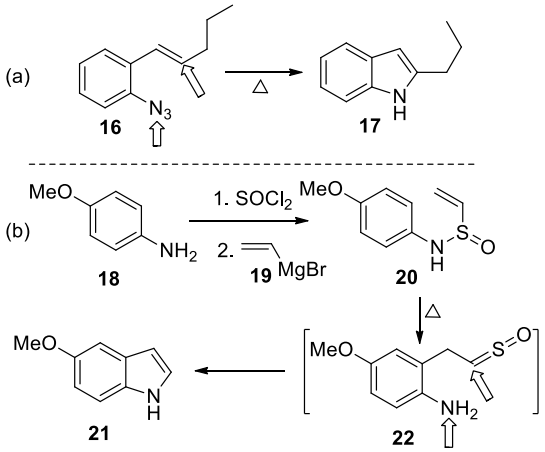


Scheme 4.2



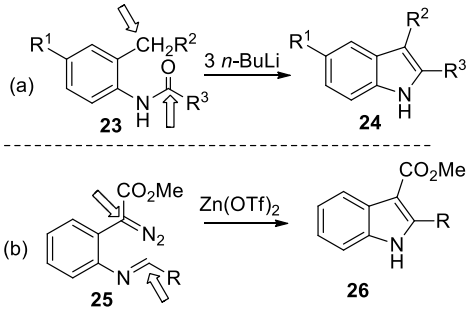
Scheme 4.3

In the **type 5** classification, the last step is the C-N bond formation. Sundberg indole synthesis[33] (Scheme 4.4a), and Julia indole synthesis[34] (Scheme 4.4b) belong to this category.



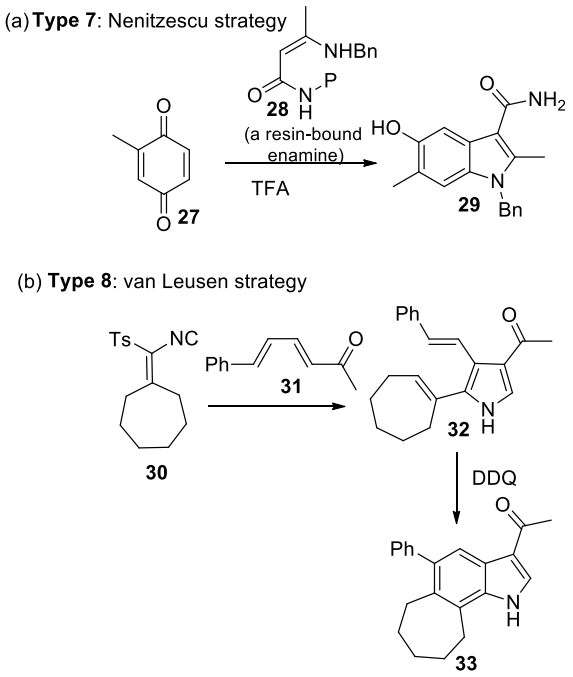
Scheme 4.4

The **type 6** class involves the formation of C-C bond as the last step. The famous Madelung indole synthesis comes under this category, in which *N*-(alkylphenyl)alkanamides and related compounds are converted to indoles in presence of a strong base (Scheme 4.5a).[35] In 2009, Doyle *et al.* reported an alternate route involving the Lewis acid catalysed indole synthesis via intramolecular nucleophilic attack of phenyldiazoacetates to iminium ions (Scheme 4.5b).[36]



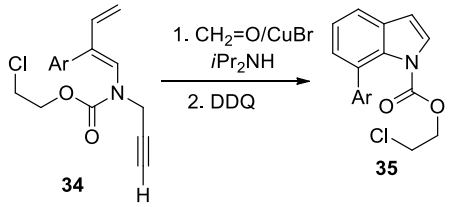
Scheme 4.5

The **type 7** category includes the synthesis of indoles from cycloalkanes[37] (Scheme 4.6a) whereas in **type 8**, the reactions involving construction of benzene ring fused onto the existing pyrrole system, are included (Scheme 4.6b).[38]



Scheme 4.6

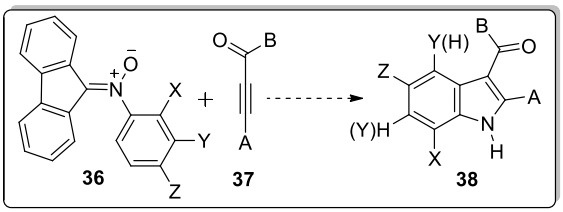
In the **type 9** category, the simultaneous construction of both rings of indole is included. This strategy was pioneered by Kanematsu *et al.* in 1986 (Scheme 4.7).[39,40]



Scheme 4.7

A few examples for indole synthesis employing nitrones as precursor molecules have already been reviewed in *Chapter 1* of this thesis. In the present work, we describe another nitrone-mediated synthesis of indole derivatives using the strategy developed in our lab (Scheme 4.8). Our method fits into **type 5** indole synthesis formulated by Taber. Methyl propiolate and methyl phenylpropiolate were used for the present study intending to synthesise ester functionalised indoles. Indole synthesis described herein bears close resemblance to quinoline synthesis reported in *Chapter 3* of this thesis. Our motivation behind indole synthesis reported herein is also similar to that for quinoline synthesis described in *Chapter 3*. Finding optimized reaction conditions, introduction of ester functionality at the 3-position, and selective introduction of desired functional groups at a particular position are common themes for both *Chapter 3* and *Chapter 4*. Since optimization studies are described in *Chapter 3*, the same are not described in this chapter. For indole synthesis, as in the case of quinoline synthesis, reaction of *N*-aryl-*C*-fluorenylnitrone with acetylenic esters at 100 mM concentration in refluxing acetonitrile for 4h was identified as the most

appropriate condition. Synthesis of various indole targets were achieved in excellent yields under these conditions.



Scheme 4.8

4.3. Results and Discussion

Various nitrones used in this study are listed in Figure 4.4. Though nitrones **40** and **41** also gave the corresponding indoles in good yields, we found fluorenylnitrones as better substrates for indole synthesis. Hence **40** and **41** were eliminated at the optimization stage itself.

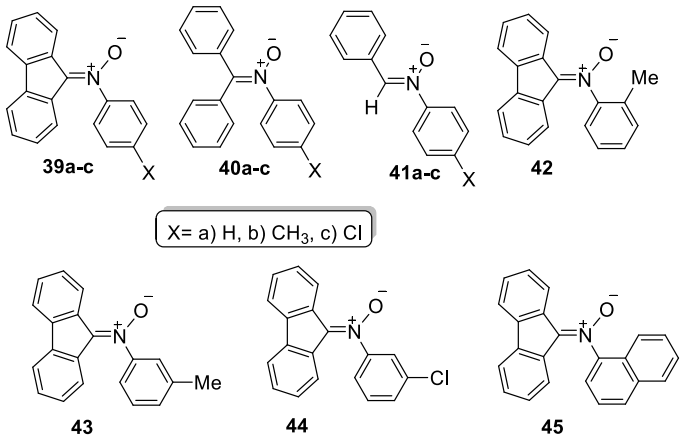


Figure 4.4

Since one of our primary goals was to introduce an ester functionality at the 3-position, we employed two acetylenic esters viz. methyl propiolate and methyl phenylpropiolate. Structure of indoles synthesized by us are given in Figure 4.5. Though methyl propiolate gave expected indoles **46-54** in excellent yield, methyl phenylpropilate behaved differently. In the reaction with **39a**, methyl phenylpropiolate gave 2-hydroxy-3-benzoylindole (**55**) instead of the expected methyl 2-phenylindole-3-carboxylate (**56**) (*vide infra*). Hence we did not use methyl phenylpropiolate for further investigations.

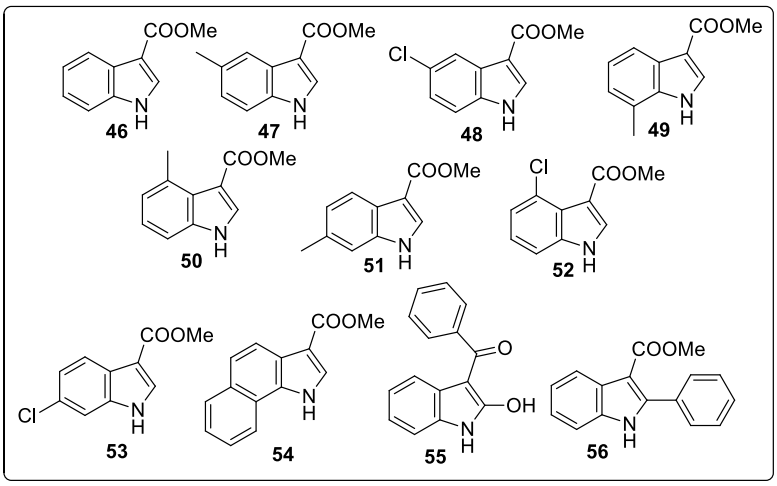


Figure 4.5

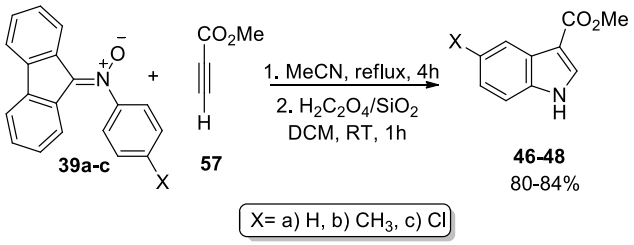
4.3.1. Expanding the scope of Indole synthesis

Reaction between *N*-fluorenylidene-*N*-arylnitrones and methyl propiolate provides indoles with a carbomethoxy substituent at the 3-position. Scope of indole synthesis is further enhanced by introduction of

substituents selectively at the 4-, 5-, 6-, and 7- positions of indoles. Herein, we describe our attempts in this direction.

4.3.1.1. Introduction of substituent specifically at the 5- position of Indoles

We carried out the reaction of nitrones **39a-c** having different substituents at the 4-position of *N*-aryl group with methyl propiolate (**57**) (1:1 molar ratio) in acetonitrile under reflux condition. After the reaction was complete, solvent was removed and hydrolysis of the products was done in dichloromethane at room temperature, using oxalic acid adsorbed on silica gel. The products were isolated by column chromatography over silica gel using hexane/ethyl acetate mixture.



Scheme 4.9

In the reaction of *N*-(9*H*-fluoren-9-ylidene)aniline oxide (**39a**) with methyl propiolate (**57**), indole **46** was obtained in excellent yield. Structure of **46** was ascertained on the basis of spectral and analytical data. In the IR spectrum of **46**, the ester carbonyl appeared at 1664 cm^{-1}

and the –NH group at 3229 cm^{-1}. In the ^{1}H NMR spectrum (Figure 4.6), the singlet signals at δ 8.66 and δ 3.86 indicated the –NH proton and $–CH_3$ protons respectively. The five aromatic protons appeared in the δ 7.17-8.14 region in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum (Figure 4.7), the signal at δ 166.5 was assigned to the ester carbonyl carbon.

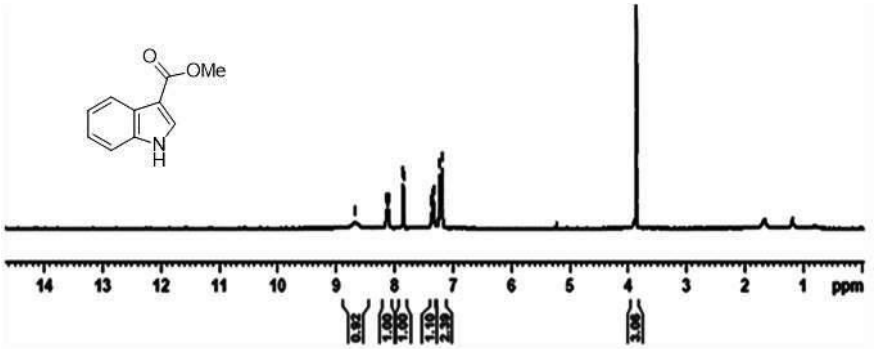


Figure 4.6 ^{1}H NMR spectrum of **46**

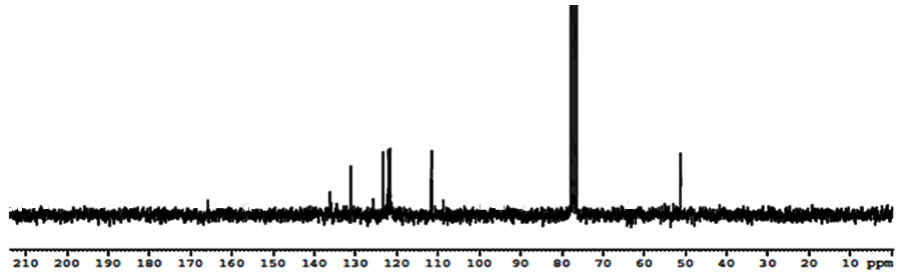


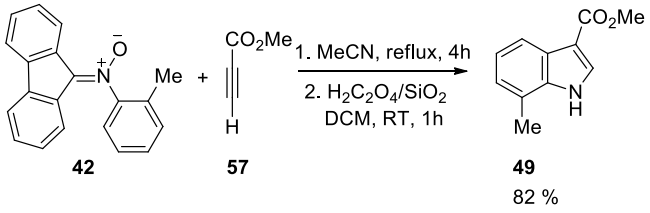
Figure 4.7 ^{13}C NMR spectrum of **46**

In continuation, we examined the reaction of *N*-(9*H*-fluoren-9-ylidene)-4-methylaniline oxide (**39b**) with methyl propiolate. As expected, indole **47** having a methyl substituent at the 6- position was generated as the only product. Similarly, reaction between 4-chloro-*N*-

(9*H*-fluoren-9-ylidene)aniline oxide (**39c**) and methyl propiolate gave indole **48** having a chloro substituent at the 6- position. Indoles **47** and **48** were identified by comparing their physical and spectral data with those reported in literature.[41,42] As in the case with quinolines reported in Chapter 3, we could successfully introduce different groups at the 6-position of indoles as well.

4.3.1.2. Introduction of methyl group specifically at the 7- position of indoles

For the synthesis of 7-methylindole derivative **49**, we conducted the reaction of *N*-(9*H*-fluoren-9-ylidene)-2-methylaniline oxide (**42**) with methyl propiolate (**57**) (Scheme 4.10). After completion of the reaction, solvent was removed and the residue was hydrolyzed using oxalic acid adsorbed on silica gel in dichloromethane. Indole **49** was isolated by column chromatography over silica gel.



42 **57** **49**
82 %

Scheme 4.10

The peaks at 1697 cm^{-1} and 3289 cm^{-1} in the IR spectrum of **49** correspond to the ester carbonyl and –NH group respectively. In the

^{1}H NMR spectrum (Figure 4.8), the –NH proton appeared as a singlet at δ 8.62. The methoxy and methyl protons appeared at δ 3.84 and δ 2.42 respectively. The singlet at δ 7.82 was assigned to the proton attached to C-2. The doublet signals at δ 7.94 and δ 6.98 were assigned to protons attached to C-4 and C-6 respectively. The proton at C-5 appeared as a triplet at δ 7.11. The ^{13}C NMR spectrum of **49** (Figure 4.9) showed signals at δ 164.8, 134.7, 129.7, 124.4, 122.7, 121.2, 119.6, 118.2, 108.2, 50.0 and 15.5. Of these, the signal at δ 164.8 was assigned to the ester carbonyl carbon. The methyl and methoxy carbons were indicated by the signals at δ 15.5 and δ 50.0 respectively.

Figure 4.8 ^{1}H NMR spectrum of **49**

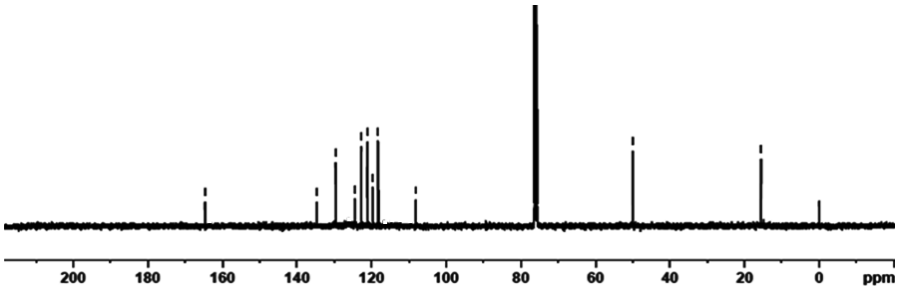
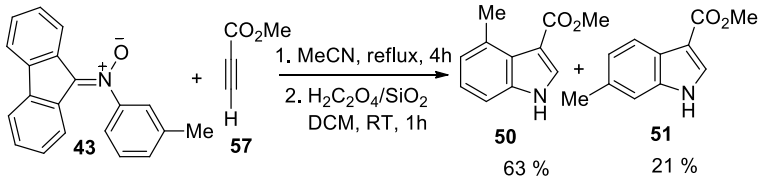


Figure 4.9 ^{13}C NMR spectrum of **49**

4.3.1.3. Introduction of substituents at 4- and 6-positions of indoles

For the synthesis of indole derivatives with substituents either at 4- or 6- positions we conducted the hydrolysis of the products obtained by the reaction of nitrones bearing meta substituent with methyl propiolate. This is illustrated by the reaction of *N*-(9*H*-fluoren-9-ylidene)-3-methylaniline oxide (**43**) with methyl propiolate (**57**) (Scheme 4.11). After the hydrolysis we obtained a 3:1 mixture of 4- and 6-methyl substituted indole derivatives **50** and **51**. The structures of these isomers were established on the basis of spectral and analytical data.



Scheme 4.11

In the ^{1}H NMR spectrum of **50** (Figure 4.10), the singlet signals at δ 8.64, δ 3.88 and δ 2.88 were assigned to –NH proton, methoxy protons and methyl protons respectively. The singlet at δ 7.94 and the doublet at δ 7.05 were assigned to protons attached to C-2 and C-5 respectively. The protons at C-6 and C-7 were indicated by triplet signals at δ 7.17 and δ 7.26 respectively.

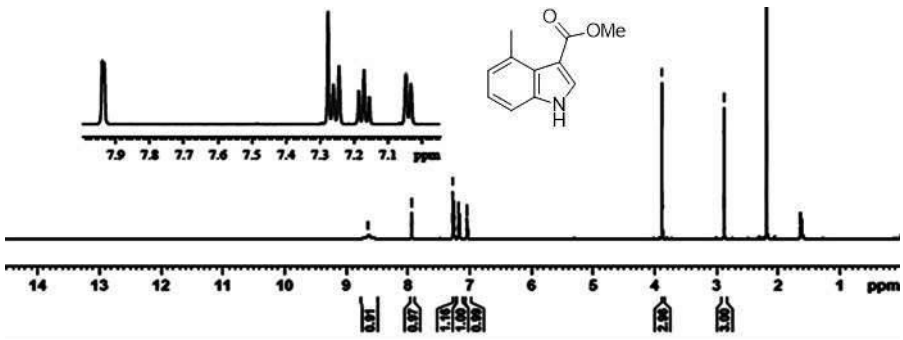


Figure 4.10 ^{1}H NMR spectrum of **50**

The ^{1}H NMR spectrum of **51** (Figure 4.11) contained singlet signals at δ 8.41, δ 3.91 and δ 2.47 are attributable to the –NH, methoxy and methyl protons. The singlet signals at δ 7.85 and δ 7.20 were assigned to the protons attached to C-2 and C-7 respectively. The doublet signals at δ 8.06 and δ 7.09 were assigned to the protons at C-4 and C-5 respectively.

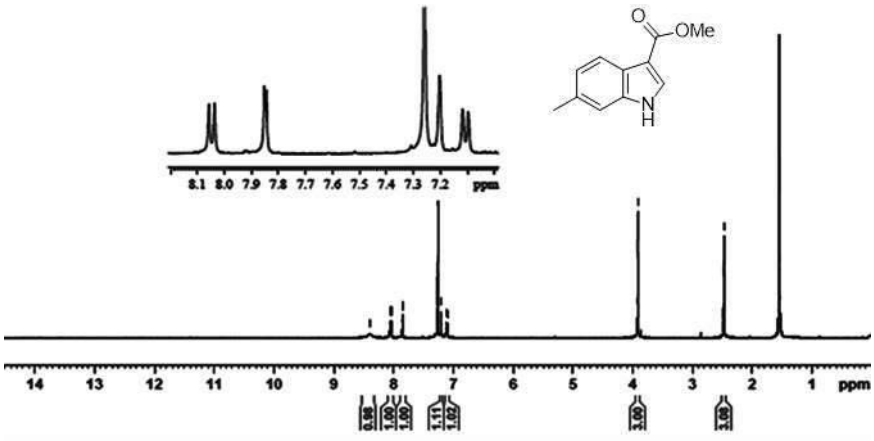


Figure 4.11 ^{1}H NMR spectrum of **51**

Existence of the isomers in a 3:1 ratio was indicated by GC-MS analysis of the reaction mixture (Figure 4.12).

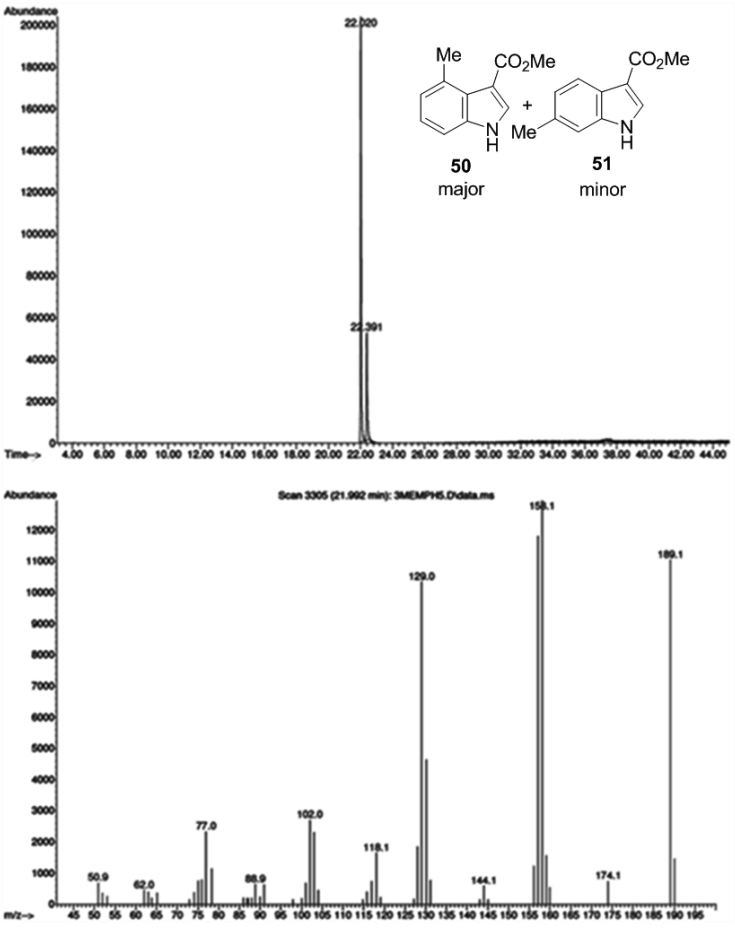


Figure 4.12 GC-MS spectrum of the mixture of **50** and **51**

Similarly, in the reaction of 3-chloro-*N*-(9*H*-fluoren-9-ylidene)aniline oxide (**44**) with methyl propiolate (**57**), 4- and 6-substituted indole derivatives **52** and **53** were formed. Though we could not separate these compounds in pure form, GC-MS analysis of the

mixture showed the existence of these compounds in 3:1 ratio (Figure 4.13). The results obtained in the reaction between *N*-(9*H*-fluoren-9-ylidene)-3-methylaniline oxide (**43**) and methyl propiolate, prompted us to assign 4-substituted indole **52** as the major isomer.

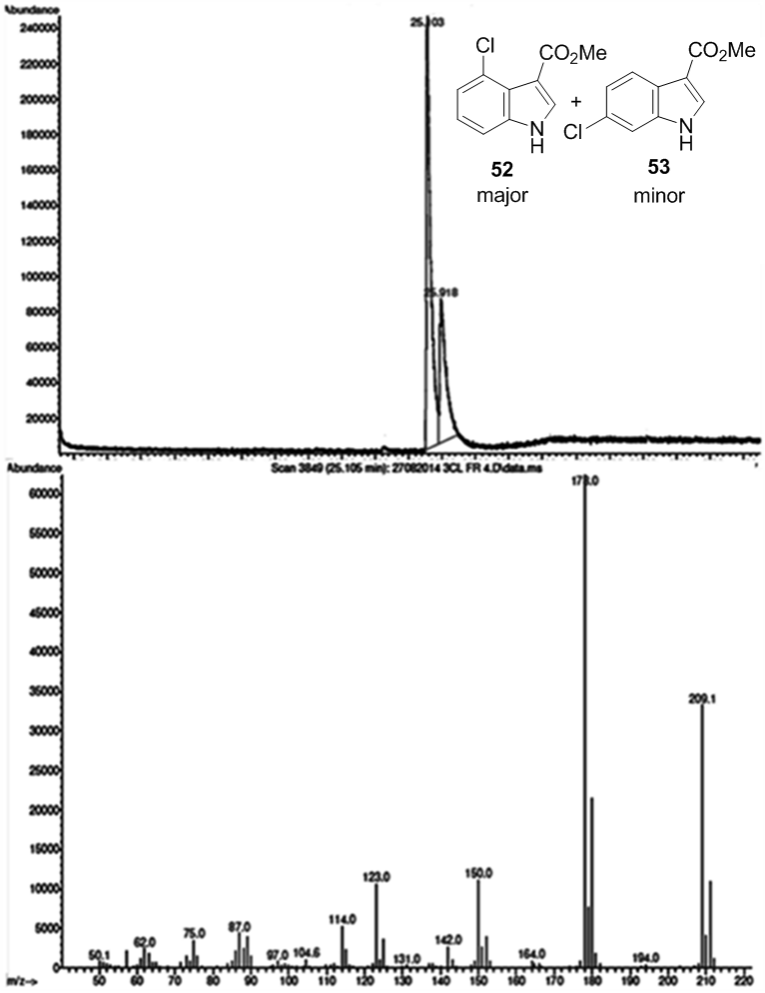
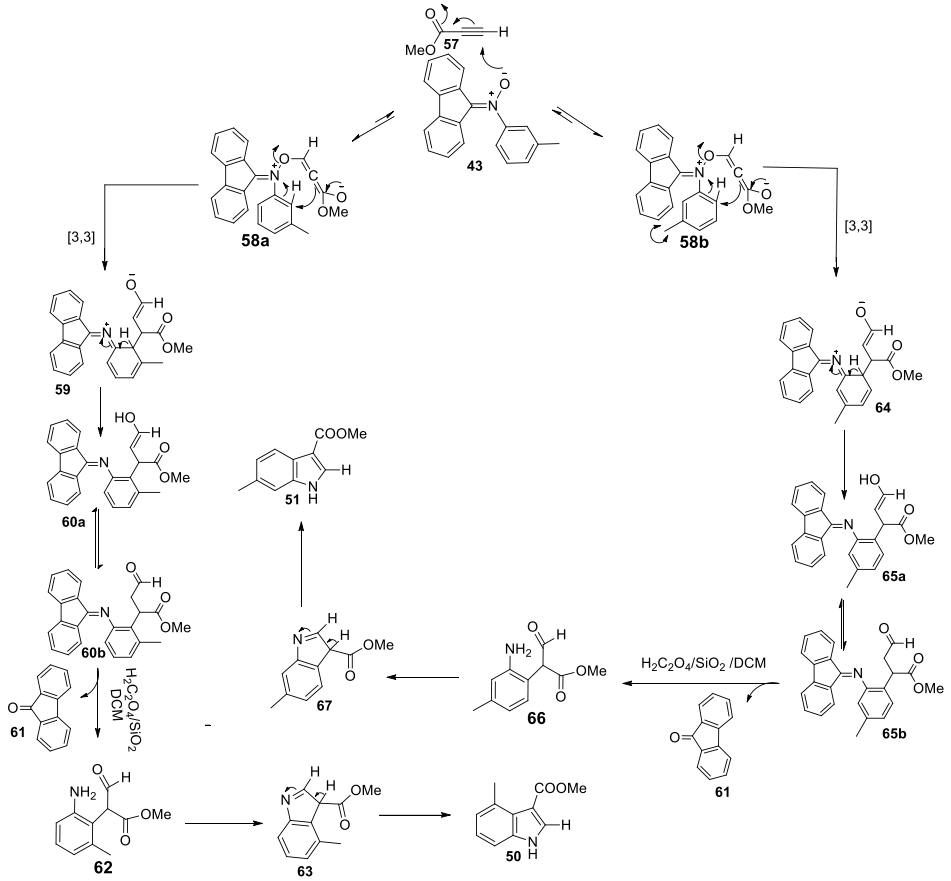


Figure 4.13 GC-MS spectrum of the mixture of **52** and **53**

4.3.1.3.1. Proposed mechanism for the formation of 4- and 6- substituted indoles

Mechanism for the generation of 4- and 6-substituted indoles is demonstrated in Scheme 4.12 by taking the reaction between **43** and methyl propiolate (**57**) as an illustrative example. The zwitterionic intermediate formed by the reaction of nitrone **43** with methyl propiolate has two possible orientations, **58a** and **58b**. Due to van der Waals repulsion, **58b** is the less favoured and hence less populated rotamer. Both rotamers undergo aza-Cope rearrangement followed by aromatisation to furnish adducts **60b** and **65b**. These adducts then undergo hydrolysis, with the expulsion of fluorenone to generate the corresponding indole derivatives **50** and **51**. Based on the spectral and analytical measurements, indole derivative **50**, generated from the major rotamer **58a**, is identified as the major product.

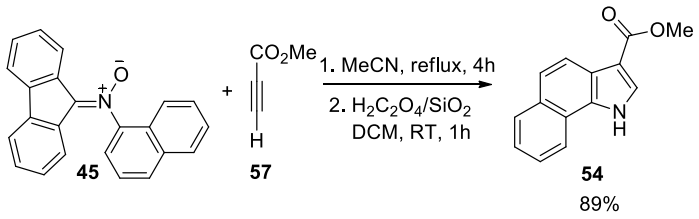


Scheme 4.12

4.3.1.4. Synthesis of benzo[g]indole derivative 54

In order to further broaden the scope of the novel indole synthesis protocol, we attempted synthesis of a benzo[g]indole derivative. We conducted the 'one-pot, addition followed by hydrolysis' strategy for the synthesis of bezo[g]indole derivative **54**, using *N*-(9*H*-fluoren-9-ylidene)naphthalene-1-oxide (**45**) and methyl propiolate (**57**) as precursors (Scheme 4.13). The product was isolated after column

chromatography over silica gel, along with fluorenone in near-quantitative amounts.



Scheme 4.13

In the IR spectrum of **54**, the ester carbonyl was indicated by the peak at 1598 cm^{-1}. In the ^{1}H NMR spectrum (Figure 4.14), the –NH proton was assigned at δ 9.67. The ester carbonyl carbon was assigned by the signal at δ 162.4 in ^{13}C NMR spectrum (Figure 4.15).

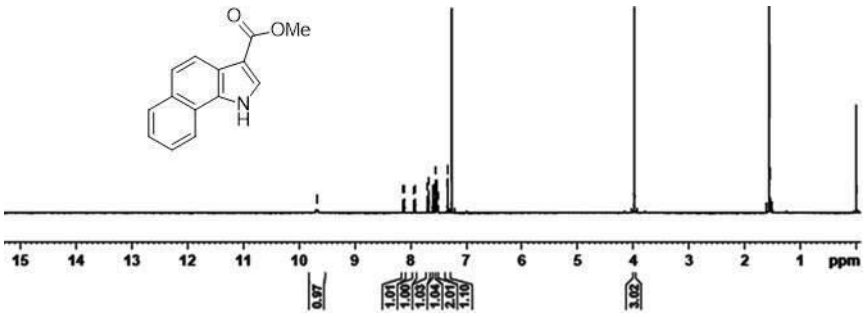


Figure 4.14 ^{1}H NMR spectrum of benzo[g]indole **54**

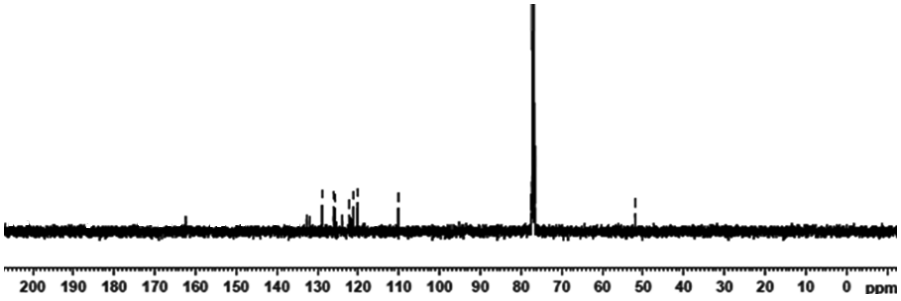
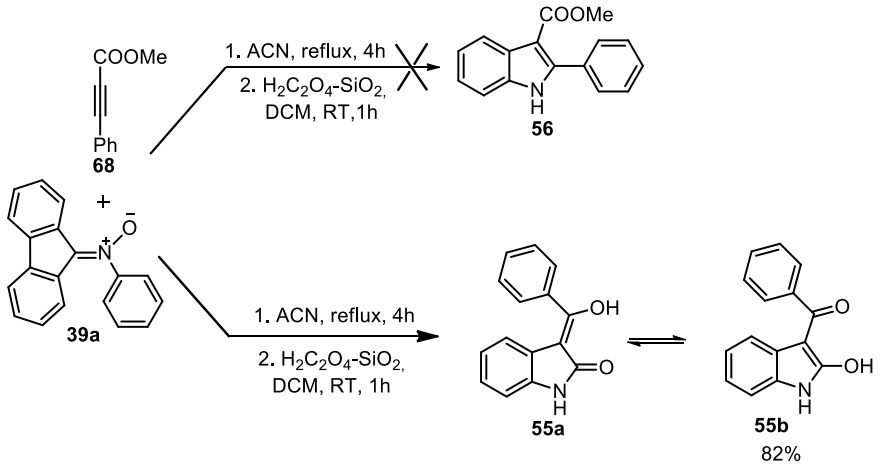


Figure 4.15 ^{13}C NMR spectrum of benzo[g]indole **54**

4.3.1.5. Reaction of *N*-fluorenylidene-*N*-phenylnitrone (39a) with methyl phenylpropiolate (68)

In the reaction of *N*-(9*H*-fluoren-9-ylidene)aniline oxide (**39a**) with methyl phenylpropiolate (**68**), based on our earlier experience with methyl propiolate (**57**), we were expecting the formation of indole-3-carboxylate **56**. Contrary to our expectation, the reaction took a different course leading to another product identified as indole **55**.



Scheme 4.14

Structure of indole **55** was arrived at on the basis of spectral and analytical data. In the IR spectrum of **55** carbonyl stretching frequency was observed at 1659 cm^{-1}. In the ^{1}H NMR spectrum (Figure 4.16), the signal at δ 8.87 (D_2O-exchangeable) corresponds to –NH proton. Aromatic protons appeared in the δ 6.86-7.81 region. Interestingly, signal corresponding to the methyl group was missing here indicating further transformation of the ester functionality. In the ^{13}C NMR spectrum (Figure 4.17), two signals corresponding to carbonyl carbons are observed at δ 173.7 and δ 171.8. It appears that **55** is existing in solution as an equilibrium mixture of tautomers **55a** and **55b**.

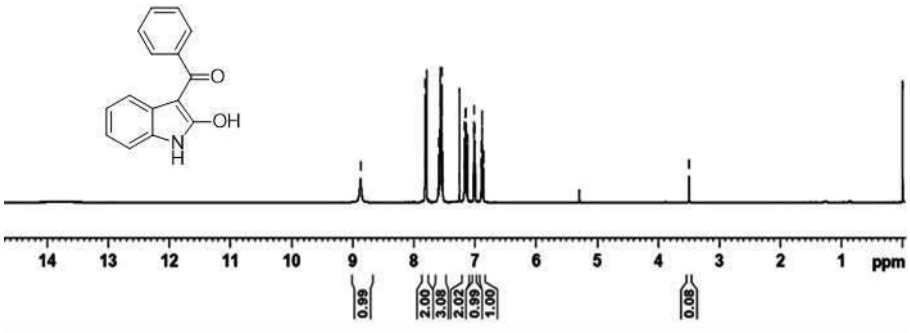


Figure 4.16 ^{1}H NMR spectrum of **55**

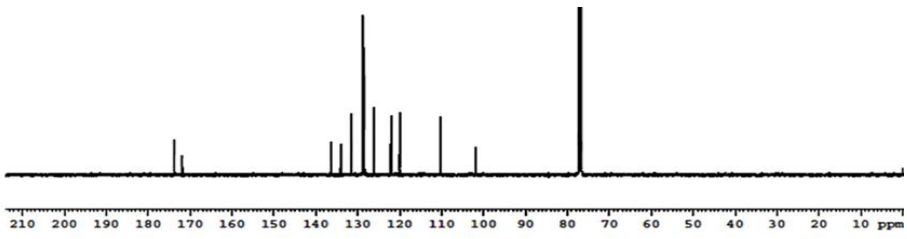


Figure 4.17 ^{13}C NMR spectrum of **55**

Structure of **55** was further confirmed from X-ray diffraction studies (Figure 4.18). It appears that, in the solid state, the compound exists exclusively as tautomer **55a**.

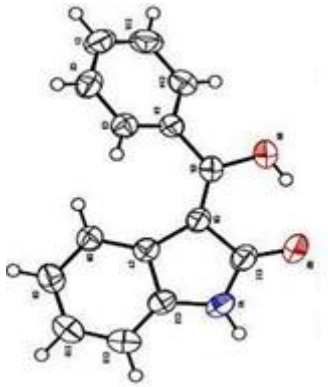
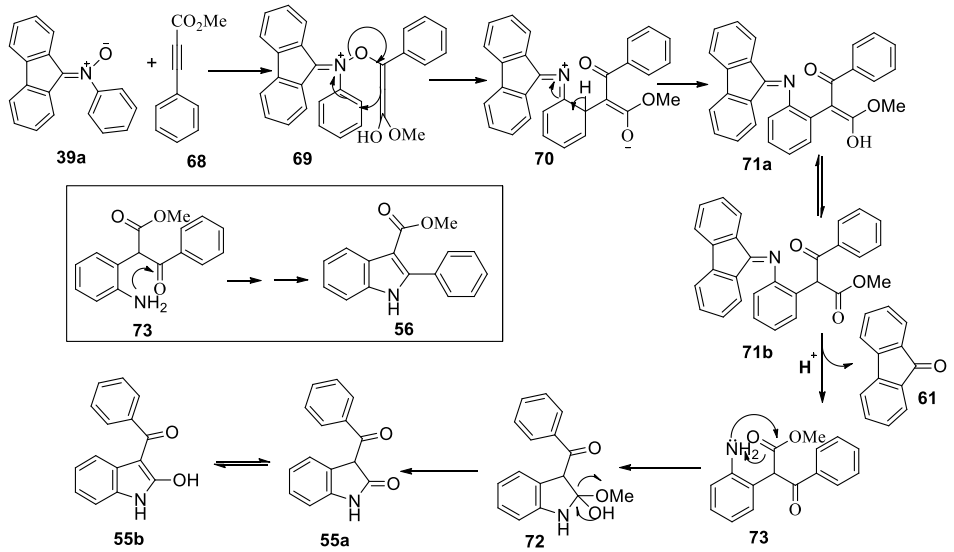


Figure 4.18 ORTEP diagram of molecular structure of **55**

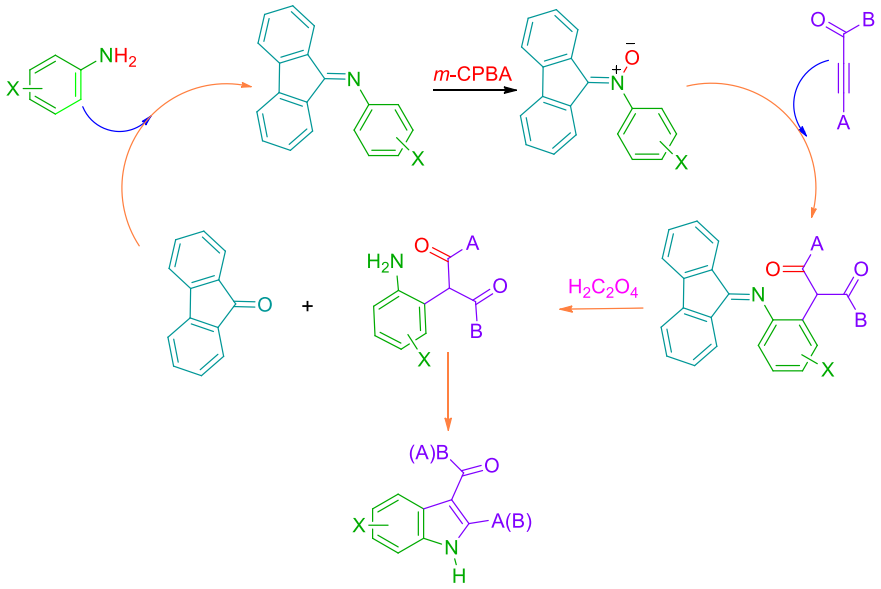
Mechanism for the generation of **55** is understood in terms of the pathways indicted in Scheme 4.15. The zwitterionic intermediate **69** is generated through Michael type addition of nitrone (**39a**) to methyl phenylpropiolate (**68**). It then undergoes an aza-Cope rearrangement to furnish **71b**, which upon hydrolysis, with the expulsion of fluorenone (**61**), generates anilinoketoester **73**. Compound **73** has two potential sites for intramolecular attack by the amine nucleophile: the ester-carbonyl and the keto-carbonyl. Attack on ketocarbonyl will produce the expected indole **56** (see inset in Scheme 4.15), while attack on ester carbonyl will lead to the generation of **55**. It appears that intramolecular nucleophilic substitution leading to cyclization with loss of methoxy group is the preferred pathway here.



Scheme 4.15

4.3.2. Summary

We have successfully expanded the scope of the '*simple and highly atom-efficient strategy for the synthesis of highly substituted indole derivatives'* developed in our lab, by the reaction of *N*-(9*H*-fluoren-9-ylidene)arylamine oxides with methyl propiolate and methyl phenylpropiolate (Scheme 4.16).



Scheme 4.16

Based on the current results we could deduce the merits and limitations of this novel strategy as follows:

(i) This strategy allows introducing a desired substituent at a predetermined position.

(ii) The substituents at C-2 and C-3 positions solely depend up on the dipolarophiles used. However the substituent at the C-3 position, by default, should be an electron withdrawing group. In some cases it is not possible to predict the C-2 and C-3 substituents.

(iii) It is not possible to introduce substituents exclusively at C-4 and C-6 positions – a mixture of C4- and C-6 substituted indoles are generated.

4.4. Experimental section

4.4.1. General techniques

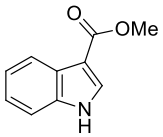
Described in Chapter 2 of this thesis.

4.4.2. General procedure for the one-pot synthesis of indole derivatives.

In all reactions, a 1:1 mixture (1 mmol each) of nitrone and acetylene in 10 mL of acetonitrile was stirred under reflux for 4 h. After the complete consumption of starting materials, solvent was evaporated off and the residue was redissolved in dichloromethane (10 mL) in the same flask. Oxalic acid (1 mmol) adsorbed on silica gel (1 g) was added to the same pot and the mixture was stirred at room temperature for 1 h. After the completion of the reaction, solvent was removed and the products were isolated by column chromatography over silica gel using mixtures of hexane and ethyl acetate as eluents. In all reactions, fluorenone was formed as a by-product in yields comparable to those cited for indoles. Optimal consumption of starting materials was achieved by recycling fluorenone.

4.4.3. Spectral and analytical data of significant Compounds

4.4.3.1. Indole 46



Off-white solid[41-44], 84%.

mp: 145-147 °C.

IR (KBr): 3229, 3005, 2936, 1664, 1525, 1440, 1201, 739 cm^{-1}.

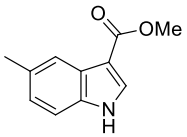
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (br s, 1H), 7.17-8.14 (5H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.4, 136.1, 131.1, 125.8, 123.2, 122.1, 121.5, 111.6, 51.2.

MS: *m/z* 175 (M^+), 176 (M+1).

Elemental analysis calculated for $C_{10}H_9NO_2$: C: 68.54, H: 5.19, N: 8.01. Found: C: 68.49, H: 5.14, N: 8.03.

4.4.3.2. Indole 47



Pale yellow solid[41,42], 84%.

mp: 163-164 °C.

IR (KBr): 3242, 2920, 2848, 1671, 1531, 1448, 1359, 1152, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 7.91 (s, 1H), 7.79 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.02 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 3.85 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7,

133.4, 130.6, 129.9, 125.1, 123.8, 120.2, 110.1, 107.3, 49.9, 20.5.

MS: *m/z* 189 (M^+), 190 (M+1).

Elemental analysis calculated for $C_{11}H_{11}NO_2$: C: 69.84, H: 5.85, N: 7.41. Found: C: 69.88, H: 5.87, N: 7.44.

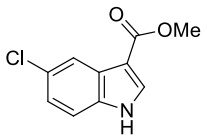
4.4.3.3. Indole 48

Yellow solid, 80%.

mp: 190-195 °C.

IR (KBr): 3304, 2946, 1675, 1592, 1531, 1448, 1385, 1198, 892, 768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (br s, 1H), 8.16 (s, 1H), 7.92 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.23 (dd, J = 2, 8.8 Hz, 1H), 3.93 (s, 3H).



^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 134.4, 132.0, 128.1, 126.9, 123.7, 121.2, 112.5, 108.8, 51.2.

MS: *m/z* 209 (M^+), 210 (M+1).

Elemental analysis calculated for $C_{10}H_8ClNO_2$: C: 57.31, H: 3.86, N: 6.67. Found: 57.29, H: 3.85, N: 6.68.

4.4.3.4. Indole 49

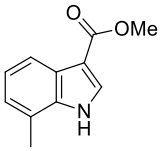
Pale yellow solid[41,43], 82%.

mp: 161-163 °C.

IR (KBr): 3289, 3019, 2952, 1697, 1614, 1531, 1442, 1318, 1204, 1131,

783, 711 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (br s, 1H), 7.94 (d, J = 8 Hz, 1H), 7.83 (s, 1H), 7.11 (t, J = 8 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 3.84 (s, 3H), 2.42 (s, 3H).



^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 134.7, 129.7, 124.4, 122.7, 121.2, 119.6, 118.2, 108.2, 50.0, 15.5.

MS: *m/z* 189 (M^+), 190 (M+1).

Elemental analysis calculated for $C_{11}H_{11}NO_2$: C: 69.83, H: 5.86, N: 7.40. Found: C: 69.77, H: 5.80, N: 7.43.

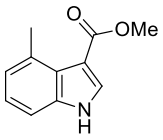
4.4.3.5. Indole 50

Off-white solid[41], 63%.

mp: 160-163 °C.

IR (KBr): 3289, 2920, 2853, 1673, 1614, 1514, 1442, 1406, 1354, 1178, 1053 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (br s, 1H), 7.94 (s, 1H), 7.26 (t, J = 6.4 Hz, 1H), 7.17 (t, J = 6.4 Hz, 1H), 7.05 (d, J = 5.6 Hz, 1H), 3.87 (s, 3H), 2.87 (s, 3H).



^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 136.9, 132.5, 131.9, 124.5, 124.0, 123.4, 109.7, 109.2, 51.1, 30.9.

MS: *m/z* 189 (M^+), 190 (M+1).

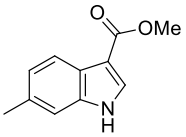
Elemental analysis calculated for $C_{11}H_{11}NO_2$: C: 69.85, H: 5.85, N: 7.41. Found: C: 69.89, H: 5.87, N: 7.44.

4.4.3.6. Indole 51

Off-white solid[44], 21%.

mp: 158-161 °C.

IR (KBr): 3247, 2920, 1675, 1540, 1437, 1364, 1198, 1147, 1043 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (br s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.20 (s, 1H) 7.09 (d, J = 8Hz, 1H), 3.91 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 142.0, 141.1, 134.1, 133.4, 130.3, 123.8, 121.2, 111.3, 51.0, 21.63.

MS: *m/z* 189 (M^+), 190 (M+1).

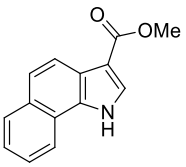
Elemental analysis calculated for $C_{11}H_{11}NO_2$: C: 69.83, H: 5.85, N: 7.40. Found: C: 69.75, H: 5.80, N: 7.36.

4.4.3.7. Benzo[g]indole 54

Pale brown solid[46,47], 89%.

mp: 202-205 °C.

IR (KBr): 3346, 2937, 2853, 1598, 1406, 1376, 1115, 1074, 991 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (br s, 1H), 8.10 (d, J = 8 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.32-7.60 (m, 4H), 3.98 (s, 3H).

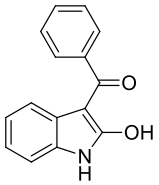
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4,

132.7, 132.0, 129.0, 126.1, 125.7, 125.5, 123.8, 122.2, 121.8, 121.26, 120.3, 110.2, 52.0.

MS: *m/z* 225 (M^+), 226 (M+1).

Elemental analysis calculated for $C_{14}H_{11}NO_2$: C: 74.65, H: 4.92, N: 6.23. Found: C: 74.61, H: 4.88, N: 6.20.

4.4.3.8. Indole 55



Off-white solid[45], 82%.

mp: 179-180 °C.

IR (KBr): 3184, 3048, 1659, 1617, 1459, 1310, 1200, 964 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (br s, 1H), 7.52-7.81 (5H), 6.86-7.17 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 171.8, 136.4, 134.1, 131.5, 128.7, 128.4, 126.0, 122.1, 121.9, 120.0, 110.3, 101.8.

MS: *m/z* 237 (M^+), 238 (M+1).

Elemental analysis calculated for $C_{15}H_{11}NO_2$: C: 75.94, H: 4.67, N: 5.90. Found: C: 75.88, H: 4.63, N: 5.87.

4.5 References

1. Berger, M.; Gray, J.A.; Roth, B.L. *Annu. Rev. Med.* **2009**, *60*, 355.
2. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, **1970**.
3. Sugden, J. K.; Yoloye, T. O. *Pharm. Acta Helv.* **1978**, *53*, 65.
4. Sundberg, R. J. *Indoles*; Ed.; Academic Press: London, **1996**.
5. Rahman, A.; Basha, A. *Indole Alkaloids*; Harwood Academic: Amsterdam, **1998**, 141.
6. Gupta, R. R. *Heterocyclic Chemistry*; Vol. 2; Springer: New York, **1999**, *2*, 193.
7. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, *103*, 893.
8. Somei, M.; Yamada, F. *Nat. Prod. Rep*. **2004**, *21*, 278.
9. Somei, M.; Yamada F. *Nat. Prod. Rep*. **2005**, *22*, 73.
10. Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep*. **2007**, *24*, 843.
11. Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.
12. Gribble, G. W. *Heterocyclic Scaffolds II: Reactions and Applications of Indoles (Topics in Heterocyclic Chemistry*), Springer, **2010**, *26*.
13. Biswal, S.; Sahoo, U.; Sethy, S.; Kumar, H. K. S.; Banerjee, M. *Asian J. Pharm. Clin. Res.* **2012**, *5*, 1.
14. Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620.
15. Barden, T. C. *Top. Heterocycl. Chem*. **2011**, *26*, 31.
16. Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241.
17. Robinson, B. *Chem. Rev*. **1969**, *69*, 227.
18. Gribble, G. W.; *Contemp. Org. Synth.* **1994**, *1*, 145.

19. Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2849.
20. Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
21. Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417.
22. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev*. **2006**, *106*, 2875.
23. Kruger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal*. **2008**, *350*, 2153.
24. Russel, J. S.; Pelkey, E. T. *Prog. Heterocycl. Chem*. **2009**, *20*, 122.
25. Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem*. **2009**, *16*, 2531.
26. Palmisano, G.; Penoni, A.; Sisti, M.; Tibiletti, F.; Tollari, S.; Nicholas, K. M. *Curr. Org. Chem.* **2010**, *14*, 2409.
27. Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641.
28. Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.* **2011**, *18*, 615.
29. Taber, D. F.; Tirunaharai, P. V. *Tetrahedron*, **2011**, *67*, 7195.
30. MacLeod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391.
31. Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *18*, 1037.
32. Aoki, K.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc*. **1998**, *120*, 3068.
33. Sundberg, R. J.; Lin, L.-S.; Blackburn, D. E. *J. Heterocycl. Chem*. **1969**, 6 441.
34. Baudin, J.-B.; Julia, S. A. *Tetrahedron Lett*. **1986**, *27*, 837.
35. Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511.
36. Zhou, L.; Doyle, M. P. *J. Org. Chem*. **2009**, *74*, 9222.
37. Ketcha, D. M.; Wilson, L. J.; Portlock, D. E. *Tetrahedron Lett*. **2000**, *41*, 6253.
38. Moskal, J.; van Leusen, A. M. *J. Org. Chem*. **1986**, *51*, 4131.
39. Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 1837.
40. Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1987**, *28*, 5895.

41. Hopkins, C. R.; Czekaj, M.; Kaye, S. S.; Gao, Z.; Pribish, J.; Pauls, H.; Liang, G.; Sides, K.; Cramer, D.; Cairns, J.; Luo, Y.; Lim, H-K.; Vaz, R.; Rebello, S.; Maignan, S.; Dupuy, A.; Mathieue, M.; Levella, J. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 2734.
42. Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011.
43. Ji, X.; Huang, H.; Wu, W.; Li, X.; Jiang, H. *J. Org. Chem*. **2013**, *78*, 11155.
44. Satoshi Hirano, S.; Akai, R.; Shinoda, Y.; Nakatsuka, S-i. *Heterocycles* **1995**, *41*, 255.
45. Mongel, A.; Palopl, J.; Ramirez, C.; Font, M.; Fernandez-A. E. *Eur. J. Med. Chem.* **1991**, *26*, 179.
46. Mitchell, G.; Rees, C. W. *J. Chem. Soc. Chem. Commun.* **1986**, 399.
47. Mitchell, G.; Rees, C. W. *J. Chem. Soc. Perkin. Trans.* **1987**, 413.
48. Natarajan, R.; Rappai, J. P.; Unnikrishnan, P. A.; Radhamani, S.; Prathapan, S. *Synlett* **2015**, *26*, 2467.

CHAPTER 5

REACTION OF *N*-(2,6-DIMETHYLPHENYL) AND *N*-(2,4,6-TRIMETHYLPHENYL)NITRONES WITH DMAD

5.1. Abstract

In this chapter we describe the reaction of N-(2,6-dimethylphenyl) and N-(2,4,6-trimethylphenyl)-C-fluorenylidenenitrones with DMAD. Our aim is to revisit the mechanism of isoxazoline-oxazoline rearrangement proposed by Baldwin et al. in the reaction of a similar nitrone with DMAD.

5.2. Introduction

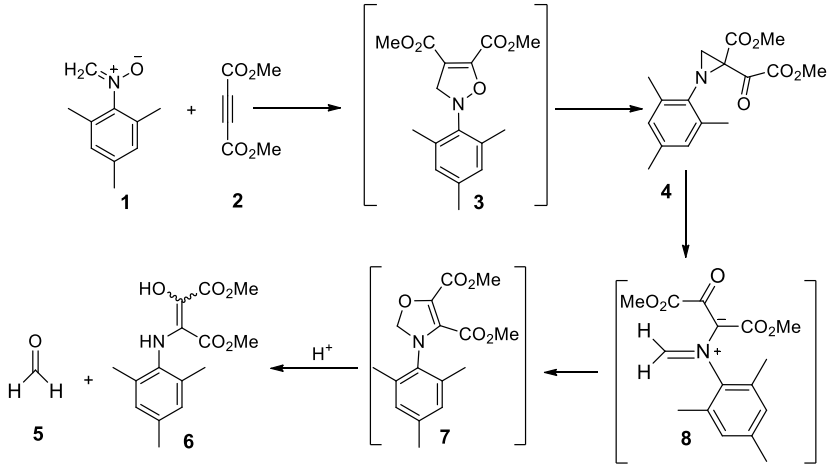
Nucleophilic addition of *N*-arylnitrones to electron deficient acetylenes followed by [3,3]-sigmatropic shift involving the *ortho*-position of the *N*-aryl substituent lie at the core of novel indole and quinoline synthesis discovered by us.[1] Since formal dipolar addition to give the corresponding isoxazolines is a competing reaction for nitrones, improving product selectivity towards quinolines and indoles is key to improving the utility of our method. Our attempts to maximize the yield of the aforementioned heterocycles are described in previous chapters of this thesis. Since the ortho-positions are involved in the ensuing sigmatropic rearrangement, blocking the key *ortho*-positions of the *N*-aryl substituent can drive the reaction to other directions. In this chapter we describe our investigations on a *N*-arylnitrones bearing methyl substituents at the 2,6- and 2,4,6-positions. Mechanistic studies on our novel two-step one-pot strategy for quinolines and indoles have revealed

that at least one of the ortho positions should be free in the *N*-phenyl ring of the nitrone precursors to facilitate the cyclisation process leading to the target molecules. So we decided to carry out reactions of nitrones bearing substituents at both ortho positions with DMAD so that we would possibly be able to isolate isoxazolines or related systems which were not obtained in earlier cases. Earlier reports suggest that isoxazolines are unstable and hence undergo facile *in situ* rearrangement to the corresponding oxazolines or products derived thereof. Baldwin *et al*. in 1968, proposed a mechanism for isoxazoline-oxazoline rearrangement in the reaction of *N*-(2,4,6-trimethylphenyl)-*C*-methylenenitrone with DMAD.[2,3] By using similar nitrones with *C*-fluorenyl counterpart, we wanted to check whether it would be possible to isolate any of the intermediates proposed by Baldwin.

5.2.1. Baldwin's proposal and related literature

Baldwin *et al*. in a pivotal communication, described the rearrangement of isoxazoline to oxazoline in the reaction of nitrone **1** with DMAD (**2**).[2] The initially isolated acylaziridine intermediate **4** under thermal condition (toluene, reflux) rearranged to the oxazoline **7** via a zwitterionic intermediate (azomethine ylide **8**). Oxazoline **7** was not isolated; apparently it readly got hydrolysed to an eneamine **6** along with formaldehyde (**5**). Isolation of the eneamine **6** was considered as an indirect evidence for the existence of oxazoline **7** (Scheme 5.1). Ironically, though the mechanism is proposed for isoxazoline to

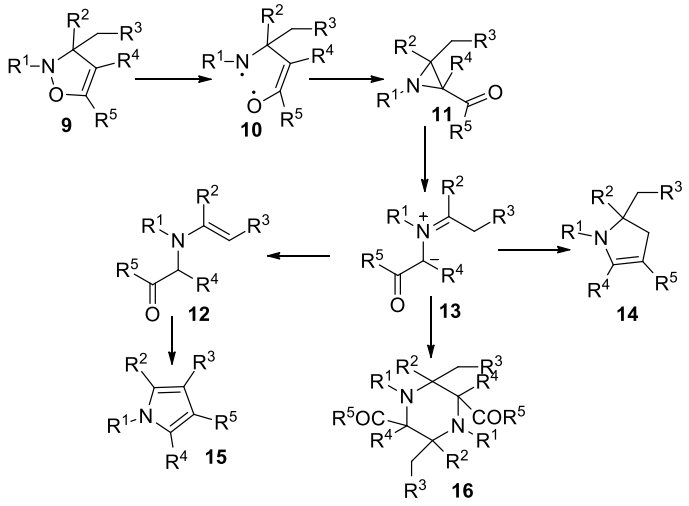
oxazoline rearrangememt, neither of these could be isoalted and their formation is postulated on the basis of situational evidence. Reactions similar to these transformations were later reported by El-Din[4] and Romeo.[5]



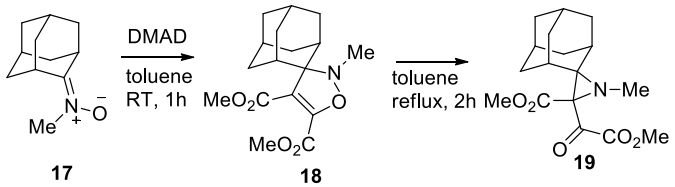
Scheme 5.1

Rearrangement of isoxazoline to oxazoline was initiated by the cleavage of N-O bond having low thermochemical stability which was furthur weakened by the *N*-aryl substitution. On the other hand, *N*-alkylisoxazolines are stable and could be isolated in high yields.[6] For the ring opening of isoxazolines, two possibilities *viz.* a concerted pathway[7] and the homolytic cleavage of the N-O bond at the rate limiting step,[8-10] have been proposed.[11] Isolation of the intermediates in isoxazoline-acylaziridine-azomethine ylide sequence is often difficult since secondary interactions usually lead to a number of products such as pyrroles (**15**),[10,12-29] 2,3-dihydrooxazoles (**14**),[3] piperazines (**16**)[3] etc.

(Scheme 5.2).[30] Georgiev *et al*. in 1990, reported an additional proof for this reaction sequence by isolating acylaziridine from a nitrone-DMAD reaction (Scheme 5.3).[31] Recently a microwave assisted rearrangement of isoxazolines to *cis*-acylaziridines was reported by Vrancken and Campagne.[32] Eberbach *et al.* in 2003, reported the access to isolable azomethine ylides by the photochemical transformation of 2,3-dihydroisoxazoles.[30] The reactivity profile of isoxazoline, aziridine derivatives, and azomethine ylides have been reviewed recently.[11,33-35]

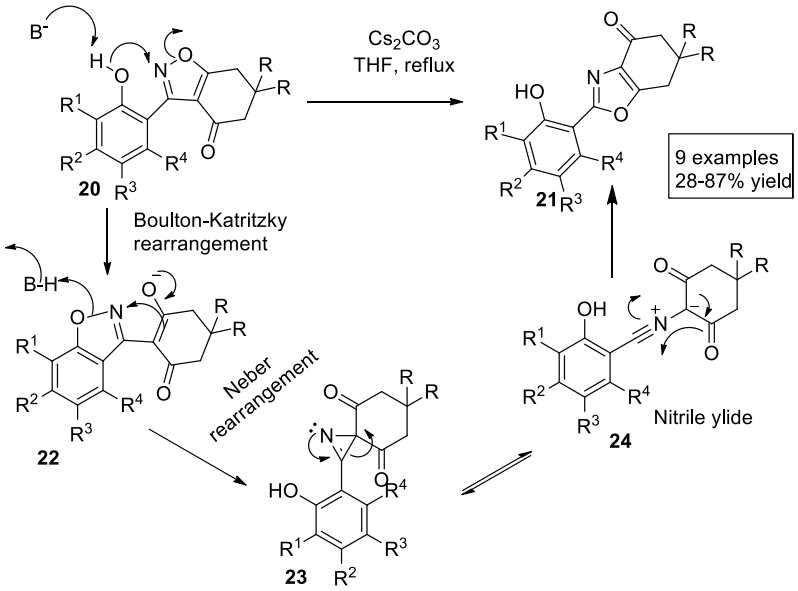


Scheme 5.2



Scheme 5.3

Jones *et al.* in 2015 reported a base catalysed rearrangement of 3-aryltetrahydrobenzisoxazoles to 2-aryltetrahydrobenzoxazoles.[36] Initial step in this conversion is the Boulton–Katritzky ring transposition[37,38] forming **22**. It then undergoes a Neber rearrangement[39] to produce an aziridine intermediate **23** which is expected to be in equilibrium with a nitrile ylide **24**. Finally, **24** rearranges to the oxazole system (Scheme 5.4).



Scheme 5.4

5.3. Results and discussion

We have selected two fluorenylidene nitrones **25** and **26** for the present study (Figure 5.1). Nitrones **25** and **26** were prepared by the procedures described in Chapter 2 of this thesis.

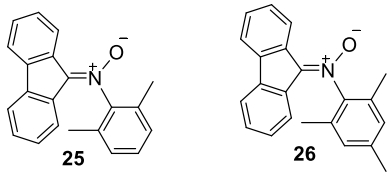


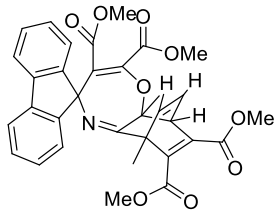
Figure 5.1

5.3.1. Reaction of *N*-(9*H*-fluoren-9-ylidene)-2,6-dimethylaniline oxide with DMAD

Reaction of *N*-(9*H*-fluoren-9-ylidene)-2,6-dimethylaniline oxide (**25**) with DMAD (**27**) was conducted in acetonitrile under reflux condition. When the starting materials were completely consumed, the reaction mixture was concentrated and subjected to column chromatography over silica gel. We obtained three products and on analysing CHN and mass data, two of them were identified as 1:1 adducts of nitrone and DMAD and the remaining one as a 1:2 adduct (one equivalent of nitrone is added to two equivalents of DMAD) (Scheme 5.5).

Structure of 1:2 adduct obtained as the first fraction from column chromatography {20-30% (EtOAc/hexane)} was arrived at on the basis of spectral data. In the IR spectrum, the ester carbonyl group appeared at

1698 cm.$^{-1}$ In the ^{13}C NMR spectrum (Figure 5.4) the peaks at δ 166.8, 166.5, 165.2, 164.1 and 163.6 indicated three different ester carbonyls and the -C=N group. Appearance of two singlets at δ 1.87 (3H) and δ 1.24 (3H) in the ^{1}H NMR spectrum (Figure 5.3) indicated the presence of two methyl groups in different environments, which was further confirmed by the peaks at δ 24.0 and δ 14.7 in the ^{13}C NMR spectrum. Presence of four methoxy groups was indicated by the singlets at δ 3.84 (3H), δ 3.70 (6H), and δ 3.06 (3H) respectively in the ^{1}H NMR spectrum. Presence of quaternary carbon atoms and the methoxy carbons was indicated by the peaks at δ 80.8, 55.3, 52.7, 52.4, 52.0, 51.8 and 49.5 in the ^{13}C NMR spectrum. Presence of a -CH group was indicated by the signal at δ 4.40 (dd, J = 1.6, 6.4 Hz, 1H) in the ^{1}H NMR spectrum. On the basis of all the spectral data, we propose the structure **28** (Figure 5.2) for the 1:2 adduct. It may be mentioned here that earlier investigators from our lab had isolated a similar 1:2 adduct in the reaction between nitrone **25** and dibenzoylacetylene.[40]



28

Figure 5.2

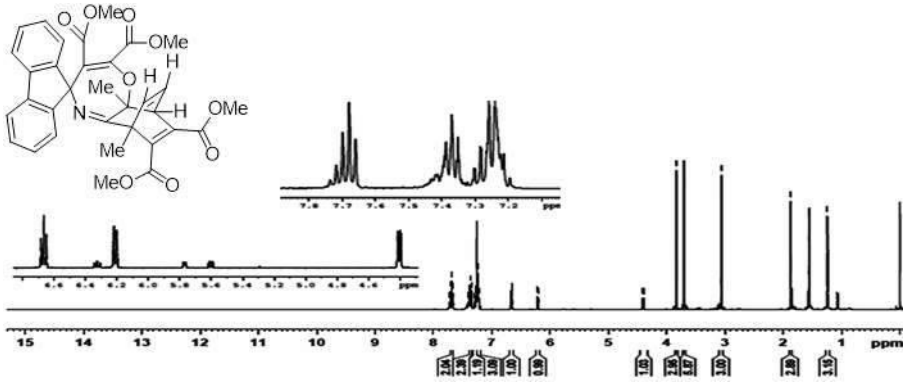


Figure 5.3 ^{1}H NMR spectrum of **28**

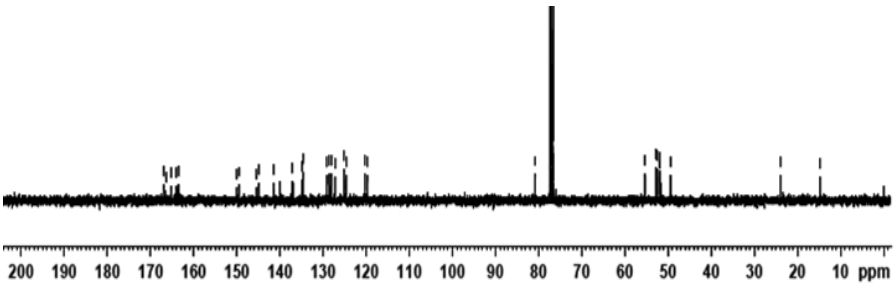


Figure 5.4 ^{13}C NMR spectrum of **28**

Among the two 1:1 adducts, the major dipolar species was obtained as the second fraction from column chromatography {50-80% (EtOAc/hexane)}. The peak at 1678 cm^{-1} in the IR spectrum indicated the presence of ester carbonyl. ^{13}C NMR spectrum (Figure 5.7) revealed different carbonyl environments in the compound by the peaks at δ 170.6, 168.0, 164.1 and 162.5. Presence of two methyl groups was indicated by the signal at δ 2.27 (s, 6H) in the ^{1}H NMR spectrum (Figure 5.6) and confirmed by the peak at δ 18.1 in the ^{13}C NMR spectrum. It is interesting to note that unlike in the case of **28**, the two methyl groups are chemical shift equivalent in the case of **29**. The methoxy groups were

identified by the singlet signals at δ 3.88 and δ 3.52, and all the remaining protons were observed in the δ 7.50 to δ 7.06 region. Based on the spectral and analytical data, we assigned the structure **29** for the mentioned adduct which was further confirmed by single crystal XRD analysis (Figure 5.5).

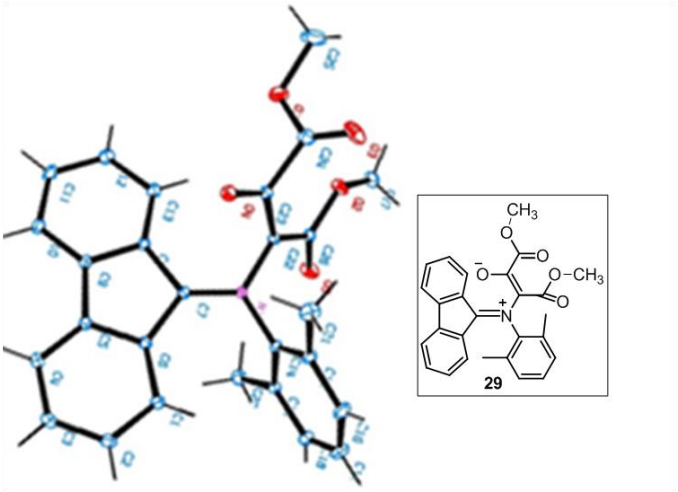


Figure 5.5 ORTEP diagram of **29**

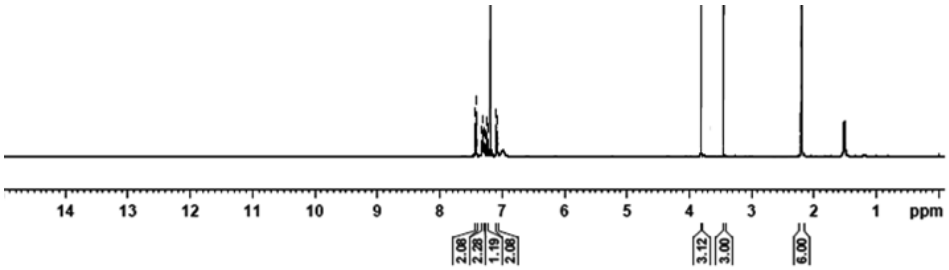


Figure 5.6 ^{1}H NMR spectrum of **29**

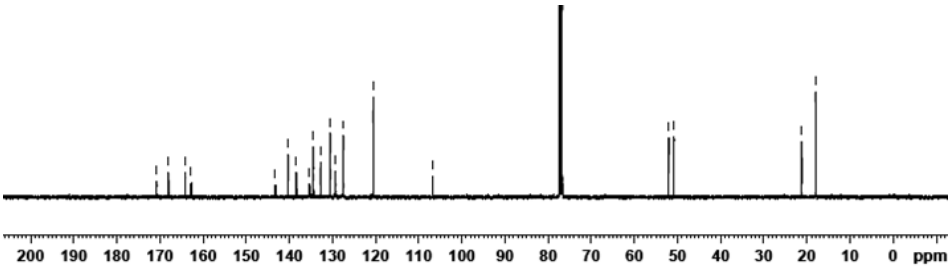


Figure 5.7 ^{13}C NMR spectrum of **29**

A highly polar and dark-coloured (red) 1:1 adduct eluted out as the third fraction from the column chromatography {10% (MeOH-EtOAc)}. Presence of ester group in this compound was indicated by the peak at 1687 cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum (Figure 5.10) showed the presence of different carbonyl environments by signals at δ 179.4, 169.1, 168.5 and 166.8. Presence of two methyl groups was indicated by the signals at δ 1.98 (s, 3H) and δ 1.78 (s, 3H) in the ^{1}H NMR spectrum (Figure 5.9) and confirmed by the signal at δ 18.0 in the ^{13}C NMR spectrum. Signals at δ 3.71 (3H) and 3.26 (3H) in the ^{1}H NMR spectrum indicated the presence of two methoxy groups which was further corroborated by signals at δ 51.7 and 49.9 in the ^{13}C NMR spectrum. All the remaining protons appeared in the δ 8.70 to δ 7.16 region { δ8.70 (d, *J* = 8.4 Hz, 2H), 8.64 (d, *J* = 8 Hz, 1H), 8.05 (t, *J* = 7.6 Hz, 1H), 7.74-7.81 (m, 2H), 7.59 (t, *J* = 8.8 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.16-7.24 (m, 3H)} in the ^{1}H NMR spectrum. Based on the spectral and analytical data, structure **30** was assigned for this highly polar 1:1 adduct. The structure was finally established from single crystal XRD

analysis (Figure 5.8). It may be noted that two possible canonical forms contribute to the structure of **30** (Scheme 5.6).

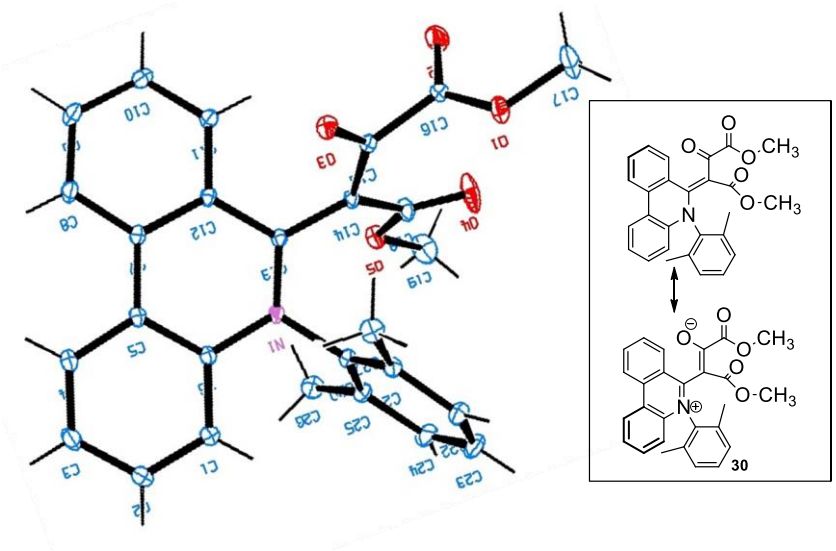


Figure 5.8 ORTEP diagram of **30**

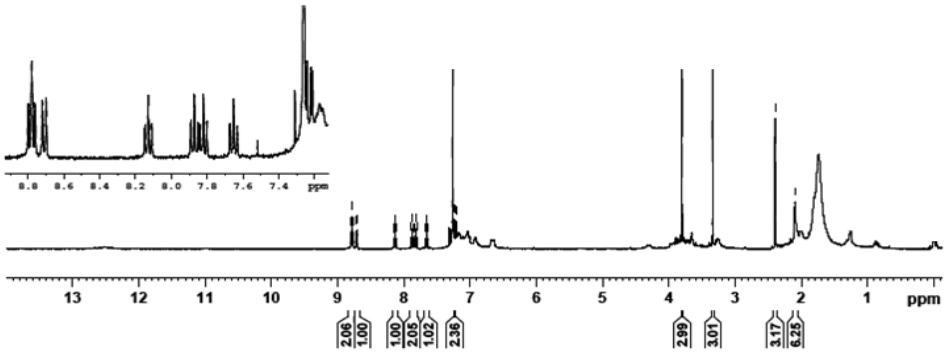


Figure 5.9 ^{1}H NMR spectrum of **30**

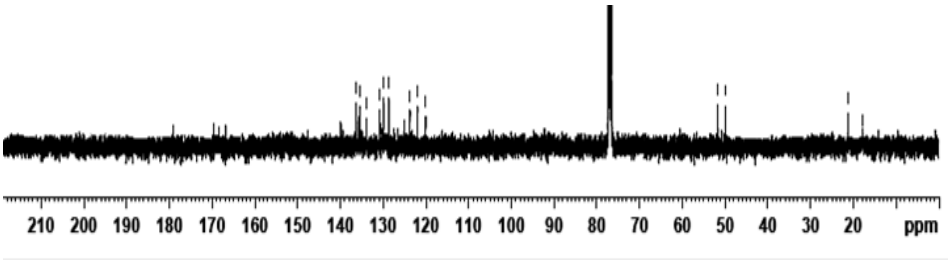
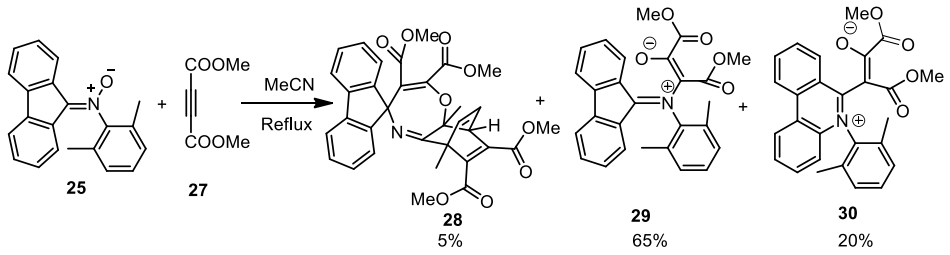


Figure 5.10 ^{13}C NMR spectrum of **30**

Overall reaction between **25** and **27** is given in Scheme 5.5.



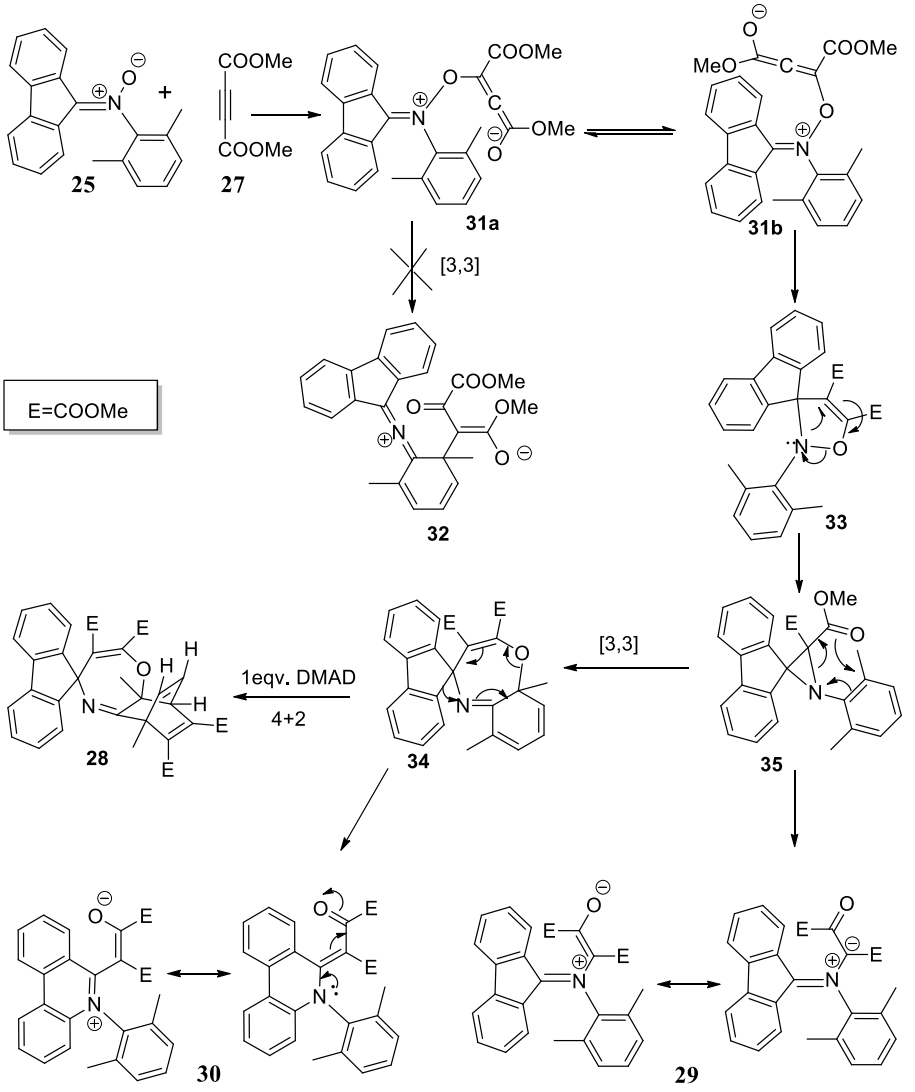
Scheme 5.5

5.3.2. Proposed mechanism for the formation of the products 28, 29 and 30

In a recent article, we had described compelling evidence in favour of a two-step mechanism to account for the formation of isoxazolines in the reaction between nitrones and electron deficient acetylenes.[6] Similarly, initial nucleophilic addition step is invoked as the first step in the reaction between nitrone **25** and DMAD. When the two ortho positions of the *N*-phenyl ring are blocked by methyl groups, out of the two rotamers of the zwitterionic intermediate (**31a** and **31b**), we

observed the product formation only from **31b**. Blocking of both the ortho positions in **31a** disfavoured [3,3]-sigmatropic rearrangement. On the other hand rotomer **31b** undergoes intramolecular cyclisation to produce isoxazoline intermediate **33**, which readily rearranges to an aziridine intermediate **35**. Subsequently, **35** undergoes [3,3] sigmatropic rearrangement to generate a ring enlarged species **34** whereas its ring opening leads to the formation of dipolar species **29**. Compound **34** reacts with an additional molecule of DMAD in a Diels- Alder addition manner to give the 1:2 adduct **28**. The dipolar species **30** is generated from the rearrangement of **34** involving a C-N aryl migration (Scheme 5.6). Here we could observe an interesting *dichotomous behaviour* of the two ortho methyl substituents on the *N*-aryl group: with rotamer **31a** they block the [3,3] sigmatropic rearrangement while with the aziridine intermediate **35**, they do not. It is possible that the presence of ortho substituents alter the geometry of **31a**; in this case the *N*-aryl substituent is disposed orthogonal to the rest of the molecule whereby a [3,3] sigmatropic shift is rendered unviable. Though direct structural evidence for orthogonal disposition of the *N*-aryl substituent is unavailable, reported structure of the imine: *N*-(9H-fluoren-9-ylidene)-4-methoxyaniline (**36**), clearly indicates orthogonal positioning (68.08^{o} to be precise) of the *N*-aryl substituent with respect to the fluorenyl residue (Figure 5.11).[41] With **35**, the geometry is such that a rare [3,3] sigmatropic shift involving an aziridine ring, a carbonyl group and an aryl group is facilitated. Though Cope rearrangement of divninylcyclpropanes to the corresponding cycloheptadienes is well

documented in literature,[42] we could not find reported examples on Cope rearrangement in 2-arylaziridinylketones similar to **35**.[43] Mechanism for the rearrangement of **35** to **34** and failure of **31a** to undergo [3,3] shift were further investigated by geometry optimization studies and theoretical analysis of transition state geometry as described in the following section.



Scheme 5.6

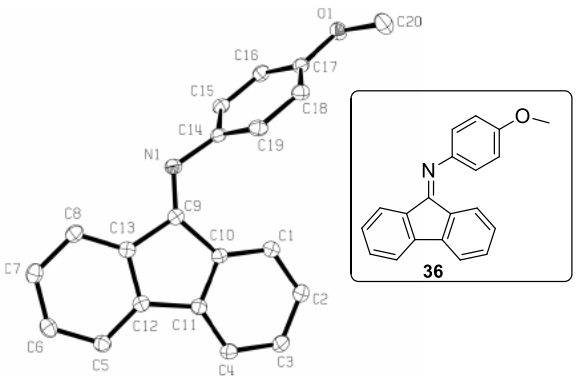


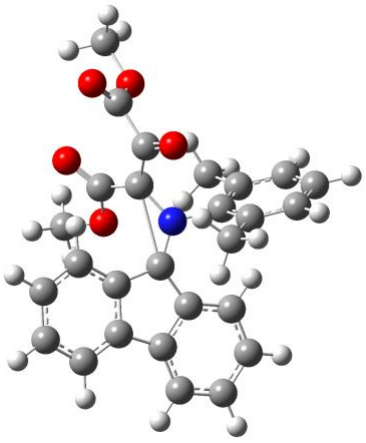
Figure 5.11 ORTEP diagram of **36**

5.3.3. The geometry optimization study of intermediates 34 and 35

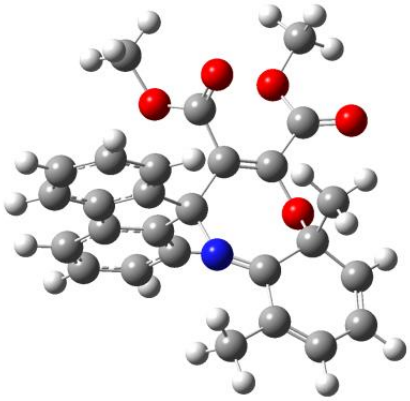
The geometry of the aziridine intermediate **35** and the ring enlarged product obtained by the [3,3] sigmatropic rearrangement (**34**) were optimized with Density Functional Theory (DFT) using B3LYP exchange correlation functional[44,45] and 6-31G(d) basis set. The stationary points are characterized by frequency analysis. The transition state was predicted using QST3 method and verified using frequency analysis and contains one imaginary frequency. The optimised geometry of **34**, **35** and that of the transition state **A** involved in the rearrangement of **35** to **34** are collected in Figure 5.12. Optimized geometry of **35** clearly indicates the positioning of the three two-electron components *viz.* aziridine ring, aryl substituent and the carbonyl group in a geometry suitable for the evolution of a chair-like transition state amenable for

[3,3]sigmatropic shifts. Geometry optimization studies revealed orthogonal disposition of the *N*-aryl substituent in intermediate **31a** and a proper transition state geometry for its rearrangement to **32** could not be generated.

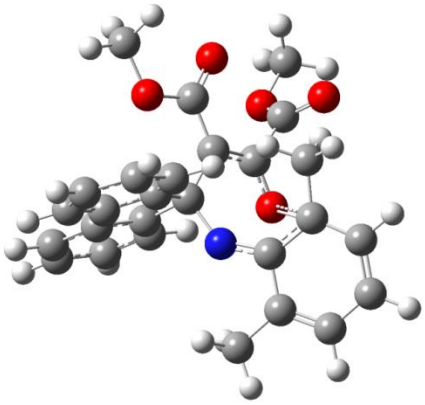
Optimised geometry of 35



Optimised geometry of 34



Optimised geometry of the transition state A



Colour codes

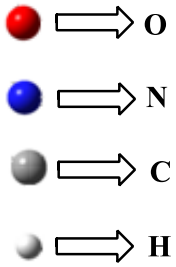
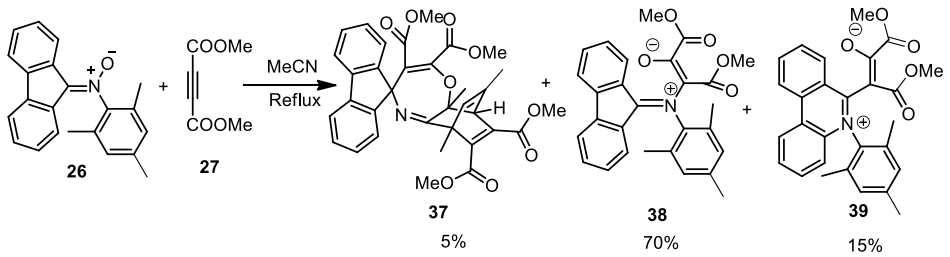


Figure 5.12

5.3.4. Reaction of *N*-(9*H*-fluoren-9-ylidene)-2,4,6-trimethylaniline oxide with DMAD

In continuation, we examined the reaction of a related *N*-aryl nitrone with DMAD. Reaction of *N*-(9*H*-fluoren-9-ylidene)-2,4,6-trimethylaniline oxide (**26**) with DMAD (**27**) furnished two 1:1 adducts and a 1:2 adduct (Scheme 5.7). All the products were analogous to the corresponding products obtained from the reaction of *N*-(9*H*-fluoren-9-ylidene)-2,6-dimethylaniline oxide (**25**) with DMAD and the reaction marked similar product distribution. By comparing the spectral and analytical data of the analogous compounds obtained from **25**, we assigned the structure **38** and **39** for the 1:1 adducts and structure **37** for the 1:2 adduct.



Scheme 5.7

5.3.5. Baldwin's mechanism revisited - isolation of intermediates involved

As discussed in the introduction, Baldwin *et al.* put forth a mechanism for 4-isoxazline-4-oxazoline rearrangement in the reaction of

N-(2,4,6-trimethylphenyl)nitrone with DMAD.[1] Though they could successfully isolate the aziridine intermediate, other intermediates along with the molecules of interest, *ie*. isoxazoline and oxazoline, were not isolated, but their existence was presumed through situational evidences. In our case also we could not identify the isoxazoline as well as oxazoline, instead we could isolate dipolar species **29** and **38** analogous to the intermediate **8** in the Baldwin's scheme. We could isolate additional products {two 1:1 adducts (**30** and **39**) and two 1:2 adducts (**28** and **37**)} which could be generated through an aziridine intermediate. We have direct evidence for the generation of zwitterionic intermediates such as **29**(isolated) and indirect evidence for the involvement of aziridine intermediate {as evidenced by isolation of products generated (presumably) thereof}. Our findings can hence be regarded as additional support for Baldwin's mechanism. The outcome of our work is shown in Table 5.1.

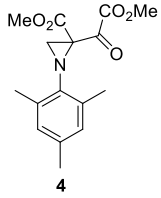
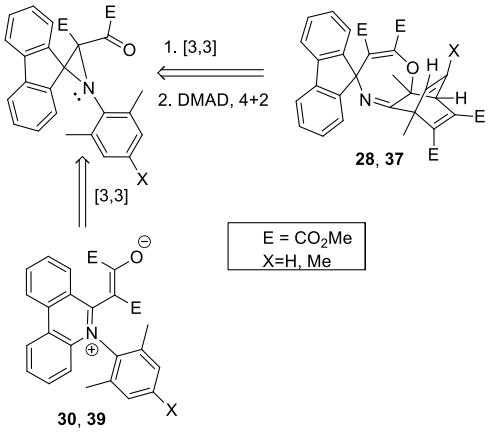
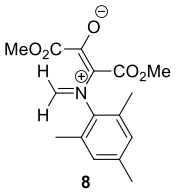
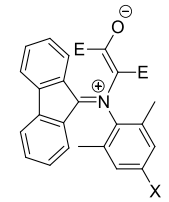
Intermediates	Baldwin's work	Our findings
Aziridine intermediate	**Isolated**  **4**	**Not isolated**  1. [3,3] 2. DMAD, 4+2 **28**, **37** [3,3] **30**, **39** E = CO_2Me X=H, Me
Zwitterionic intermediate	**Not isolated**  **8**	**Isolated**  E = CO_2Me X=H (**29**), Me (**38**)

Table 5.1

5.4. Experimental section

5.4.1. General techniques

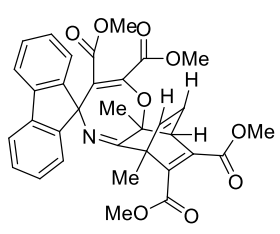
Described in Chapter 2 of this thesis.

5.4.2. General procedure for nitrone-DMAD reaction

A 1:1 mixture (100 mmol each) of respective nitrones and dimethylacetylenedicarboxylate (DMAD) in acetonitrile was stirred under reflux for 24 h. Solvent was evaporated off and the residue was column chromatographed over silica gel using mixtures of hexane and ethyl acetate. In both cases, small amount of nitrone precursor (~5%) remained unchanged and the last fraction eluted out with 10% methanol-ethyl acetate mixture.

5.4.3. Spectral and analytical data of significant compounds

5.4.3.1. 1:2 adduct 28



Off-white solid, 5%.

mp: 152 °C (d).

IR (KBr): 3053 cm^{-1} (=CH stretch), 1698 cm^{-1} (C=O stretch).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (q, J = 7.7 Hz, 2H), 7.35-7.40 (m, 2H), 7.21-7.30 (m, 4H), 6.66 (t, J = 6.8 Hz, 1H), 6.21 (dd, J = 1.6, 6.4 Hz, 1H),

4.40 (dd, J = 1.6, 6.4Hz, 1H), 3.84 (s, 3H), 3.70 (s, 6H), 3.06 (s, 3H), 1.87 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 166.5, 165.2, 164.1, 163.6, 150.0, 149.5, 145.5, 145.0, 141.5, 140.1, 137.0, 134.8, 134.7, 19.1, 128.5, 128.1, 127.3, 125.1, 124.7, 120.2, 119.7, 80.8, 55.3, 53.7, 52.0, 51.8, 49.5, 24.0, 14.7.

MS: *m/z* 583 (M^+), 584 (M+1).

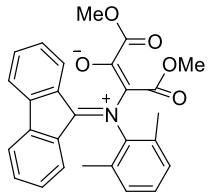
Elemental analysis calculated for $C_{33}H_{29}NO_9$: C: 67.92, H: 5.01, N: 2.40. Found: C: 67.97, H: 5.03, N: 2.43.

5.4.3.2. 1:1 adduct 29

Dark blue solid, 65%.

mp: 222-224 °C.

IR(KBr): 3052 cm^{-1} (=CH stretch), 1678 cm^{-1} (C=O stretch).



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06-7.50 (m, 9H), 3.88 (s, 3H), 3.52 (s, 3H), 2.27 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 168.0, 164.1, 162.5, 140.8, 134.6, 132.8, 130.2, 129.8, 127.5, 120.6, 106.6, 52.0, 50.7, 18.1.

MS: *m/z*441 (M^+), 442 (M+1).

Elemental analysis calculated for $C_{27}H_{23}NO_5$: C: 73.46, H: 5.25, N: 3.17.

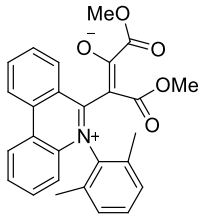
Found: C: 73.39, H: 5.21, N: 3.15.

5.4.3.3. 1:1 adduct 30

Dark red solid, 20%.

mp: 226-228 °C.

IR(KBr): 3062 cm^{-1} (=CH stretch), 1687 cm^{-1} (C=O stretch).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 8.4 Hz, 2H), 8.64 (d, J = 8 Hz, 1H), 8.05 (t, J = 7.6 Hz, 1H), 7.74-7.81 (m, 2H), 7.59 (t, J = 8.8 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.16-7.24 (m, 3H), 3.71 (s, 3H), 3.26 (s, 3H), 1.98 (s, 3H), 1.78 (s, 3H).

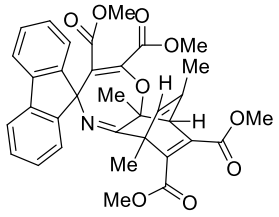
^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 169.1, 168.5, 166.8, 137.5, 136.4, 135.6, 135.4, 133.9, 130.9, 130.0, 129.9, 128.7, 127.5, 125.1, 123.8, 122.0, 51.7, 49.9, 18.0.

MS: *m/z* 441 (M^+), 442 (M+1).

Elemental analysis calculated for $C_{27}H_{23}NO_5$: C: 73.46, H: 5.25, N: 3.17. Found: C: 73.51, H: 5.27, N: 3.19.

5.4.3.4. 1:2 adduct 37

Off-white solid, 5%**.**



mp: 155 °C (d).

IR(KBr): 3052 cm^{-1} (=CH stretch), 1692 cm^{-1} (C=O stretch).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H7.68 (t, J = 8Hz, 2H), 7.34-7.39 (m, 2H), 7.19-

7.30 (m, 4H), 5.75 (s, 1H), 4.14 (s, 1H), 3.83 (s, 3H), 3.70 (s, 6H), 3.06 (s, 3H), 2.05 (s, 3H), 1.88 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 166.7, 165.2, 164.1, 163.7, 150.3, 150.1, 145.4, 145.2, 144.7, 141.5, 140.1, 134.7, 129.6, 129.0, 128.4, 128.2, 128.1, 127.3, 125.1, 124.7, 120.2, 119.6, 80.9, 54.6, 52.7, 52.4, 52.0, 51.8, 22.5, 20.8, 14.8.

MS: *m/z* 597 (M^+), 598 (M+1).

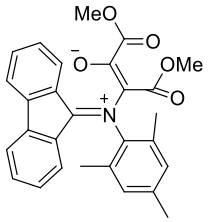
Elemental analysis calculated for $C_{34}H_{31}NO_9$: C: 68.33, H: 5.23, N: 2.34. Found: C: 68.31, H: 5.19, N: 2.27.

5.4.3.5. 1:1 adduct 38

Dark blue solid, 70%.

mp: 224-226 °C.

IR(KBr): 3056 cm^{-1} (=CH stretch), 1685 cm^{-1} (C=O stretch).



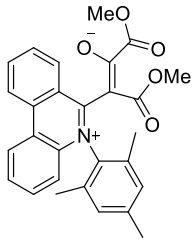
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96-7.49 (m, 8H), 3.87 (s, 3H), 3.53 (s, 3H), 2.36 (s, 3H), 2.22 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 168.0, 164.2, 162.8, 143.3, 140.3, 138.4, 135.3, 134.5, 132.8, 130.5, 129.3, 127.5, 120.6, 106.8, 52.0, 50.8, 21.2, 18.0.

MS: *m/z* 455 (M^+), 456 (M+1).

Elemental analysis calculated for $C_{28}H_{25}NO_5$: C: 73.83, H: 5.53, N: 3.08. Found: C: 73.87, H: 5.56, N: 3.11.

5.4.3.6. 1:1 adduct 39



Dark red solid, 15%.

mp: 230-232 °C.

IR(KBr): 3065 cm^{-1} (=CH stretch), 1691 cm^{-1} (C=O stretch).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (t, J = 8 Hz, 2H), 8.71 (d, J = 8.4 Hz, 1H), 8.13 (t, J = 7.6 Hz, 1H), 7.80-7.89 (m, 2H), 7.65 (t, J = 7.8 Hz, 1H), 7.21-7.24 (m, 2H), 3.80 (s, 3H), 3.34 (s, 3H), 2.39 (s, 3H), 2.09 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 169.6, 168.6, 167.0, 140.1, 136.3, 135.8, 135.4, 133.9, 130.8, 130.4, 130.0, 128.7, 125.0, 123.7, 122.0, 120.0, 51.7, 49.9, 21.2, 18.0.

MS: *m/z* 455 (M^+), 456 (M+1).

Elemental analysis calculated for $C_{28}H_{25}NO_5$: C: 73.83, H: 5.53, N: 3.08. Found: C: 73.88, H: 5.54, N: 3.12.

5.5 References

1. Natarajan, R.; Rappai, J. P.; Unnikrishnan, P. A.; Radhamani, S.; Prathapan, S. *Synlett* **2015**, *26*, 2467.
2. Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.***1968**, *90*, 5325.
3. Freeman, J. P. *Chem. Rev*. **1983**, *83*, 241.
4. El-Din, A. M. N.; El- Said Mourad, A. F.; Mekamer, R. *Heterocycles***1985**, *23*, 1155.
5. Liguori, A.; Ottana, R.; Romeo, G.; Sindona, G.; Uccella, N. *Heterocycles* **1988**, *27*, 1365.
6. Radhamani, S.; Natarajan, R.; Unnikrishnan, P. A.; Prathapan, S.; Rappai, J. P. *New J. Chem.* **2015**, *39*, 5580.
7. Gree, R.; Carrie, R. *J. Am. Chem. Soc.***1977**, *99*, 6667.
8. Adachi, I.; Harada, K.; Kano, H. *TetrahedronLett*. **1969**, 4875.
9. Huisgen, R.; Niklas, K. *Heterocycles* **1984**, *22*, 21.
10. Albert Padwa, A.; George, S. K.; Wong, G. S. K. *J. Org. Chem.***1986**, *51*, 3125.
11. Chukanov, N. V.; Reznikov, V. A. *Russ. Chem. Bull*. **2011**, *60*, 379.
12. Huisgen, R.; Seheer, W.; Huber, H. *J. Am. Chem.* Soc.**1967**, *89*, 1753.
13. Padwa, A.; Eisenhardt, W. *Chem. Commun.* **1968**, 380.
14. Winterfeldt, E.; Krohn, W.; Stracke, H. U. *Chem. Ber*. **1969**,*102*, 2346.
15. Adachi, I.; Harada, K.; Kano, H. *Tetrahedron Lett.* **1969**, 10, 4875.
16. Schmidt, G.; Stracke, H. U.; Winterfeldt, E. *Chem. Ber.***1970**, *103*, 3196.
17. Padwa, A.; Dean, D.; Oine, T. *J. Am. Chem.* Soc. **1975**, *97*, 2822.
18. Wenkert, D.; Ferguson, S. B.; Porter, B.; Qvarnstrom, A. *J. Org. Chem.* **1985**, *50*, 4114.

19. Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc*. **1986**, *108*, 6433.
20. Padwa, A. Wong, G. S. K. *J. Org.Chem.* **1986**, *51*, 3125.
21. Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc*. **1988**, *110*, 3238.
22. Mullen, G. B.; Georgiev, V. S. *J. Org. Chem.***1989**, *54*, 2476.
23. Bennet, G. A.; Mullen, G. B.; Georgiev, V. S. *Helv. Chim. Acta* **1989**, *72*, 1718.
24. Yu, Y.; Ohno, M.; Eguchi, S. *Tetrahedron* **1993**, *49*, 823.
25. Zhao, B. X.; Yu, Y.; Eguchi, S. *Tetrahedron* **1996**, *52*, 12049.
26. Friebolin, W.; Eberbach, W. *Tetrahedron* **2001**, *57*, 4349.
27. Tomioka, Y.; Nagahiro, C.; Nomura, Y.; Maruoka, H. *J. Heterocycl. Chem.* **2003**, *40*, 121.
28. Murray, W. V.; Francois, D.; Maden, A.; Turchi, I. *J. Org. Chem.* **2007**, *72*, 3097.
29. Diev, V. V.; Stetsenko, O. N; Tung, T. Q.; Kopf, J.; Kostikov, R. R.; Molchanov, A. P. *J. Org. Chem.* **2008**, *73*, 2396.
30. Lopez-Calle, E.; Keller, M.; Eberbach, W. *Eur. J. Org. Chem.* **2003**, 1438.
31. Mullen, G. B.; Bennett, G. A.; Georgiev, V. S. *Liebigs Ann.Chem.* **1990**, 109.
32. Gayon, E.; Debleds, O.; Nicouleau, M.; Lamaty, F.; van der Lee, A.; Vrancken, E.; Campagne, J-M. *J. Org. Chem*. **2010**, *75*, 6050.
33. Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2006**, 2873.
34. Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2010**, 3363.
35. Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev*. **2014**, *114*, 7954.
36. Jones, R. C. F.; Chatterley, A.; Marty, R.; Owton, W. M.; Elsegood, M. R. J. *Chem. Commun.* **2015**, *51*, 1112.

37. Boulton, A. J. and Katritzky, A. R., *Proc. Chem. Soc.* **1962**, 257.

38. Buscemi, S.; Vivona, N.; Caronna, T. *J. Org. Chem.* **1996**, *61*, 8397.

39. Neber, P. W.; Friedolsheim, A. V. *Justus Liebigs Ann. Chem*.**1926**, 449.

40. Sandhya, R. *Ph. D Thesis, CUSAT,* **2014**. http://dyuthi.cusat.ac.in/xmlui/handle/purl/3745

41. Glagovich, N.; Reed, E.; Crundwell, G.; Updergraff III, J. B.; Zeller, M.; Hunter, A. D. *Acta Cryst.* **2004**, *E60*, o623.

42. Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamsetti, K. G. *Org. React*. **1992**, *41*, 1.

43. Ohno, H in Aziridines and Epoxides in Organic Synthesis. Yudin, A. K (ed), Wiley-VCH Verlag GMBH & Co, KGaA, Weinheim, Germany **2006**.

44. Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648.

45. Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem*. **1994**, *98*, 11623.

OUTCOME

EXPANDING THE SCOPE OF THE NOVEL STRATEGY DEVELOPED IN-HOUSE FOR THE SYNTHESIS OF QUINOLINES AND INDOLES

As mentioned in the introduction of this thesis, our primary goal was to synthesise ester functionalised quinolines and indoles having predetermined substitution pattern. In order to validate the novel synthetic strategy, we have employed several *N*-arylnitrones and two ester functionalised acetylenes (DMAD and methyl propiolate). Detailed optimisation studies on the novel protocol was done in the synthesis of quinolines and the optimised condition turned out to be: reaction of a 1:1 mixture of *C*-fluorenylidenenitrone and DMAD (100 mM in each substrate) in acetonitrile at reflux for 4h; the same is applicable for indole synthesis using methyl propiolate as well.

We have successfully used our novel synthetic strategy in the synthesis of six quinoline derivatives and nine indole derivatives. In the quinoline synthesis, using DMAD, we could introduce a carbomethoxy group at the 4-position and substituents were introduced at 5-, 6-, 7- and 8- positions in a predetermined fashion by the choice of *N*-aryl substituents in the nitrone. Similarly, we have synthesised indole-3-carboxylates with pre-defined substituents at 4-, 5-, 6- and 7- positions by the reaction of different *N*-arylnitrones with methyl propiolate. However, using methyl phenylpropiolate in indole synthesis, contrary to our expectation, the reaction took a different course leading to an unexpected product. The product formation could be attributed to the

preferential intramolecular nucleophilic attack on to the ester carbonyl followed by the loss of methoxy group.

Since our strategy for quinolines and indoles requires at least one of the ortho positions in the *N*-phenyl ring of the nitrone to be free of substitution, we examined the reactions of *N*-(2,6-dimethylphenyl) and *N*-(2,4,6-trimethylphenyl)nitrones with DMAD to explore other reaction possibilities. By conducting these reactions we presumed to revisit the isoxazoline-oxazoline rearrangement proposed by Baldwin *et al.* with a similar nitrone. From the results obtained from these reactions, we could draw supportive evidences for Baldwin's proposal. We have direct evidence for the generation of zwitterionic intermediates involved in the mechanism and indirect evidence for the involvement of aziridine intermediate by isolating compounds generated thereof.

In summary, our findings reveal an attractive strategy for the synthesis of highly substituted quinolines and indoles. We have also contributed towards unravelling the mechanistic underpinnings of nitrone-acetylene reactions.

List of publications

1. A new method for the synthesis of 3-substituted indoles. **Rakesh Natarajan**, John P. Rappai, Peruparampil A. Unnikrishnan, Sandhya Radhamani and Sreedharan Prathapan, *Synlett* **2015**, *26*, 2467.

2. Diverse reactivity of nitrones towards electron deficient acetylenes. Sandhya Radhamani, **Rakesh Natarajan**, Peruparampil A. Unnikrishnan, Sreedharan Prathapan and John P. Rappai, *New J. Chem.* **2015**, *39*, 5580.

Oral and poster presentations in conferences

1. A new method for the synthesis of Indole-3-carboxylates. **N. Rakesh**, R. Sandhya, P.A. Unnikrishnan and S. Prathapan, an oral presentation at *National Symposium on Transcending Frontiers in Organic Chemistry-2014*, held at CSIR-NIIST, **2014**.

2. Development of a simple and efficient route for the synthesis of substituted benzoquinoline. **N. Rakesh**, P.A. Unnikrishnan and S. Prathapan, a poster presented at *Current Trends in Chemistry, CTriC-2014*, held at Cochin University of Science and Technology, **2014**.

3. Development of a simple and efficient route for the synthesis of substituted indoles. **N. Rakesh**, P.A. Unnikrishnan and S. Prathapan, a poster presented at Current *Trends in Chemistry, CTriC-2013*, held at Cochin University of Science and Technology, **2013**.

4. Cycloaddition reaction of nitrones followed by novel rearrangement of primary adducts. **N. Rakesh**, P.A. Unnikrishnan and S. Prathapan, a poster presented at *Current Trends in Chemistry, CTriC-2012*, held at Cochin University of Science and Technology, **2012**.